doi: 10.1111/obr.12442

Obesity Comorbidity/Prevention

Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials

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Received 17 February 2016; revised 5 May 2016; accepted 23 May 2016

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Summary

This study aimed to examine the effect of lifestyle intervention on the risk of gestational diabetes mellitus (GDM). We searched PubMed, Springer and other databases to retrieve articles published in English and Chinese up to 30 September 2015. The inclusion criteria were randomized controlled trials evaluating the effects of lifestyle intervention on risk of GDM. Exclusion criteria were studies with prepregnancy diabetes mellitus or interventions with nutrient supplements. Random-effect and fixed-effect model analyses were used to obtain pooled relative risks and 95% confidence intervals (CIs) of diet and physical activity on the risk of GDM. Subgroup analyses were performed to check the consistency of effect sizes across groups where appropriate. We identified 29 randomized controlled trials with 11,487 pregnant women, addressing the effect of lifestyle intervention on the risk of GDM. In the pooled analysis, either diet or physical activity resulted in an 18% (95%CI 5–30%) reduction in the risk of GDM ($P = 0.0091$). Subgroup analysis showed that such intervention was effective among women with intervention before the 15th gestational week (relative risk: 0.80, 95%CI 0.66–0.97), but not among women receiving the intervention afterwards. We conclude that lifestyle modification during pregnancy, especially before the 15th gestational week, can reduce the risk of GDM. © 2016 World Obesity

Keywords: gestational diabetes, lifestyle intervention, obesity, overweight.
obesity reviews (2016)

Introduction

Gestational diabetes mellitus (GDM) is prevalent, affecting about 16.4% of women globally and 25.0% in the South-east Asia region (1). GDM is associated with substantial adverse pregnancy outcomes such as macrosomia, primary Caesarean delivery and neonatal hypoglycaemia (2) and also associated with increased risks of diabetes in later life in the mothers (3) and childhood obesity (4) and cardiovascular disease (5) in the offspring. Major randomized controlled trials (RCTs) demonstrated that lifestyle intervention in GDM aiming at normalizing glucose levels can improve pregnancy outcomes, including macrosomia and pregnancy-induced hypertension (6,7) and reduced insulin resistance in the female offspring around 5 years of age (8). On the other hand, the key issue of whether GDM can be prevented by lifestyle modification during early pregnancy or before pregnancy remains unanswered.

Although prepregnancy obesity is a strong risk factor for GDM (9), pregnancy itself represents a state of insulin resistance, and GDM occurs when insulin secretion fails to counterbalance the increased insulin resistance during pregnancy. Measures targeting insulin resistance have the potential to reduce the risk of GDM. Indeed, prospective cohort studies consistently showed a positive result of lifestyle intervention during pregnancy on reducing the risk of GDM

(10,11). On the other hand, there are inconsistent findings from RCTs regarding the effect of lifestyle intervention during pregnancy on the risk of GDM. In this regard, some reported that such interventions were effective for prevention of GDM (12,13), while others reported the contrary (14). Indeed, the effect of lifestyle intervention during pregnancy on GDM remained unanswered.

We performed a systematic review and meta-analysis of RCTs to address the efficacy of lifestyle intervention during pregnancy, i.e. diet and physical activity, on the risk of GDM.

Methods

Search strategy and selection criteria

We performed literature searches using 10 mainstream electronic databases (PubMed, Cochrane Library, Web of Science, SpringerLink, JAMA, Ovid, Sino Med, Wiley Online Library, Science Direct and Embase) and 7 other databases (Clinicaltrials.gov, *Lancet*, *Nature*, *Science*, the *New England Journal of Medicine*, BioMedNet and Google Scholar) for studies published in English and Chinese.

The following Medical Subject Heading terms, words and combinations of words were used in constructing the systematic search: 'pregnan* OR pregnan* complications OR pregnan* outcome OR prenatal care', 'prenatal OR antenatal', 'intervention', 'randomized controlled trial', 'lifestyle', 'early intervention (education)', 'health education', 'patient education', 'exercise therapy', 'health promotion', 'diet', 'carbohydrate-restricted diet', 'fat-restricted diet', 'diet therapy', 'physical activity', 'behaviour intervention', 'nutrition OR nurture', 'Gestational diabetes mellitus OR GDM', 'diabetes mellitus OR T2DM', 'Impaired fasting glucose OR IFG' and 'Impaired glucose tolerance OR IGT'. The searches were unlimited by time up to 1 October 2015 and limited to human studies and RCTs. The details of the search with PubMed are shown in Table 1. We supplemented this strategy with manual searches of the reference lists of included studies and relevant reviews.

Two investigators reviewed the retrieved articles independently in three phases. Firstly, we assessed the relevance of the studies in the primary pool by the title and abstract as well as full text when needed. Secondly, we read the full text and references of papers selected from the first stage and supplemented some potential studies that were not included in the primary pool. Finally, the study content, methodology and appropriateness for inclusion were performed and recorded. Any disagreement about whether having met the inclusion was resolved by group discussions.

The inclusion criteria included RCTs that only evaluated lifestyle interventions during the first two trimesters of pregnancy with an outcome measure of GDM; and the exclusion criteria were having either type 1 or type 2 diabetes mellitus before pregnancy or having existing GDM. Studies on interventions with only nutrient supplements were excluded. Inclusion of trials was not restricted by publication date, nationality or country. Systematic reviews, meta-analysis, observational studies, study protocol and pilot study (15) were all excluded. We carefully checked the quality against the criteria set by the Preferred Reporting Items Systematic Reviews and Meta-Analyses guidelines (16) and Cochrane Library and excluded 33 non-RCTs, 21 reviews, 16 meta-

Table 1 Search strategy for PubMed and other database

Batch	Search term	Combinations	Results
1	Pregnan* Complications/OR Pregnan*/OR Pregnan* Outcome/OR Pregnan*, High Risk		213,396
2	Prenatal Care/OR Antenatal		40,668
3	Gestation*		193,724
4		1 or 2 or 3	392,603
5	Nutrition*/OR Nurture/OR Diet/OR Dietary/OR Dietary, Fat-Restricted /OR Diet, Protein-Restricted/OR Diet, Carbohydrate-Restricted/OR Diet, Reducing/OR Diet Therapy		794,962
6	Lifestyle/OR Behavio(u)r Intervention/OR Behavio(u)r Therapy		1,978,388
7	Health Education/OR Patients Educations/OR Health Promotion		508,316
8	Exercise/OR Physical Activity		497,281
9		5 or 6 or 7 or 8	3,276,701
10	Gestational Diabetes Mellitus/OR GDM/OR Diabetes Mellitus/OR T2DM		383,691
11	Impaired Fasting Glucose/OR IFG		8,939
12	Impaired Glucose Tolerance/OR IGT		22,644
13		10 or 11 or 12	396,904
14		4 and 9 and 13	4,909
15		LIMIT 14 to ([humans] and [clinical trial])	436

GDM, gestational diabetes mellitus; T2DM, type 2 diabetes; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

analysis and 43 other studies, to ensure the quality of the studies included in the meta-analysis. The flow chart of the article screening process was shown in Fig. 1.

Data extraction

Two independent reviewers assessed the quality of each study and extracted the data with pre-designed forms. We recorded design methods, sample size, ethnicity or country, outcomes, participant characteristics, interventions, GDM criteria, conclusions and 95% confidence intervals (CIs) of the relative risks (RRs) of the intervention and its components for GDM. A summary of the included studies was listed in Table S1.

Statistical analysis

STATA/SE 11.2 for Windows was used to analyse the data unless specified. χ^2 and I^2 were calculated to assess the statistical heterogeneity among included trials. Heterogeneity graded by I^2 was set as low (<25%), medium (25–75%) and high (≥75%). Fixed-effect and random-effect model analyses were performed to obtain unadjusted RRs with 95%CI when the heterogeneity was low and medium–high, respectively, and visualized by forest plots. Standard errors and 95%CI were estimated by Woolf's method. A P value of <0.1 was deemed significant in the pooled estimate. Funnel plot and Egger regression asymmetry test were performed to check for potential publication bias.

The timing of the intervention may have a major impact on the effect size. To identify how early is early enough for the lifestyle intervention to result in a significant reduction in the risk of GDM, we also performed cumulative meta-analysis by gestational age of initiation of the intervention (Fig. S2). Then, we conducted subgroup analysis of the effect of lifestyle intervention before and after the identified gestational age. The mean gestational age at baseline in the intervention arm of the included RCTs was used as the intervention initiation time of the study concerned.

Prepregnancy obesity is a well-established risk factor for GDM, and the effect size may differ by the different diagnostic criteria for GDM. We therefore performed subgroup analyses by prepregnancy body mass index (BMI) with 25.0 kg m^{-2} as the cut-off point to check whether the intervention was particularly effective among pregnant women with prepregnancy obesity or overweight and by GDM cases defined by different diagnostic criteria for GDM to check specific benefits for GDM defined by different diagnostic criteria. Because weight gain before the first 15 gestational weeks was quite small and almost negligible (17), self-reported pregnancy body weight or measured body weight at the first prenatal care visit was used to calculate prepregnancy BMI. In addition, subgroup analysis based on maternal age was also performed to detect any subgroup effects by age. Pearson correlation analysis was conducted to estimate the trends of the effect size with gestational age at intervention, prepregnancy BMI and maternal age. Because of the possible heterogeneity of populations with different genetic predisposition and cultural settings, effect sizes may differ by different ethnicities. So we performed subgroup analysis by ethnicity to observe any ethnic-specific effects. In the 29 RCTs, the treatment that the control group received was different. We performed additional sensitivity analysis with inclusion of 23 RCTs whose control arm received standard, normal or usual care.

Post hoc power analysis was performed to estimate powers of the pooled analyses of individual intervention measures and in certain subgroup analyses with type I error set at 5% and use of weighted rates of GDM in the control arm and the detected effect sizes where appropriate.

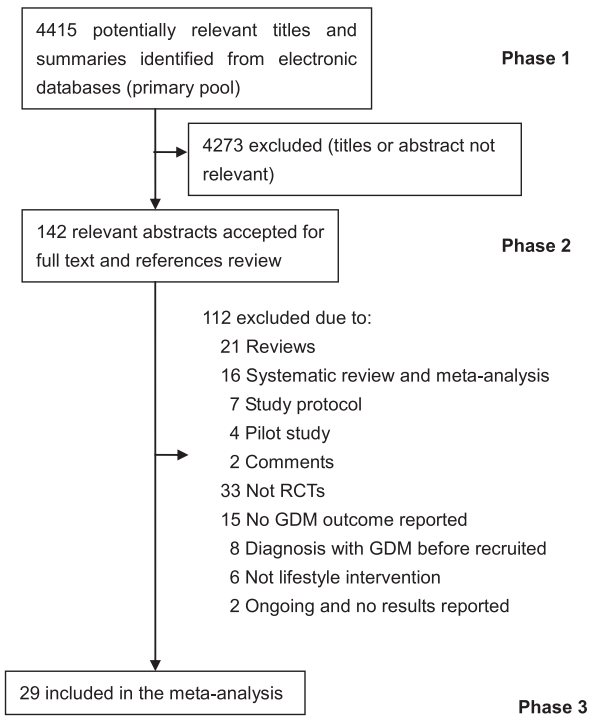

Figure 1 Flow chart of study selection of the meta-analysis. GDM, gestational diabetes mellitus; RCTs, randomized controlled trials. Solid lines with arrows stand for the process of study selection.

Results

Retrieval and screening of randomized controlled trials

The search approach retrieved a total of 4,415 articles. The three-phase screening identified 29 RCTs with 11,487 pregnant women, which were included in this study (Fig. 1).

Characteristics of the included studies

The 29 identified RCTs were conducted in 13 countries, with six RCTs in the USA (18–23), five in Spain (24–28), three in Australia (29–31), three in Finland (32–34), three in Denmark (35–37), two in Canada (38,39), one respectively in Belgium (40), Norway (41), the Netherlands (42), Italy (43), India (44), Ireland (45) and the UK (12) (Table S1).

The interventions were categorized into three groups: physical activity (PA) only, diet only and PA and diet mixed intervention. Of the 28 RCTs reporting the gestational age at recruitment, 20 RCTs initiated the intervention in the intervention arm at or before the 15th gestational week and 8 after the 15th gestational week. Of the 29 RCTs, 8 were conducted among pregnant women with prepregnancy BMI $<25.0\,kg\,m^{-2}$, 18 among pregnant women with prepregnancy BMI $\geq 25.0\,kg\,m^{-2}$ and 3 among pregnant women who gave no description.

Twenty-one RCTs reported the diagnosis criteria: six RCTs used the International Association of Diabetes and Pregnancy Study Group's (IADPSG) criteria (2010) (12,27,30,43,45,46), four used the American Diabetes Association's criteria (2004) (22,32,34,44), three used the World Health Organization's criteria (1999) (27,31,41,43), two used the Canadian Diabetes Association's criteria (38,47), two used Carpenter–Coustan's criteria (24,45), two used the European Association for the Study of Diabetes's criteria (36,37), two used the Australasian Diabetes in Pregnancy Society's criteria (30,40) and one RCT each used the National Diabetes Data Group's criteria (25), the modified 4th International Workshop Conference's criteria (33) and the South Australian Perinatal Practice Guidelines (29). In estimating pooled effect sizes of the 29 RCTs, the results of IADPSG's criteria were used for the three RCTs (27,30,45) that also used another GDM diagnostic criteria (Table S1).

Of the 29 RCTs, 12, 16 and 1 were conducted in pregnant women with mean ages of <30 years old, ≥30 years old and not reported, respectively. Details of the included trials including population representativeness, study design, analysis principle and outcome measures were available in Table S2.

Effects of the lifestyle intervention

The pooled analysis of the 29 RCTs with 11,487 participants showed that lifestyle intervention of diet, PA or both resulted in an 18% (95%CI 5–30%) reduction in the risk of GDM ($P = 0.0091$, power = 54.5%) (Fig. 2) with an acceptable publication bias ($P = 0.0944$) (Fig. S1).

However, the pooled effects of PA plus diet (RCT = 14, $n = 6{,}047$), diet only (RCT = 5, $n = 1{,}279$) and PA only (RCT = 10, $n = 4{,}161$) on the risk of GDM did not reach statistical significance although they all showed a tendency of protection (RR of PA plus diet: 0.85, 95%CI 0.70–1.03, $P = 0.0922$; diet only: 0.80, 95%CI 0.58–1.10, $P = 0.1658$; PA only: 0.77, 95%CI 0.54–1.09, $P = 0.1456$) (Fig. S2). The powers of diet plus PA, PA only and diet only were 15.4%, 65.9% and 22.7%, respectively.

Effects of the lifestyle intervention by subgroups

There was a trend with an increased effect size at an earlier initiation of the intervention during pregnancy and a cut-off of 15 gestational weeks was indicated by cumulative meta-analysis (Fig. S3). Lifestyle intervention of diet, PA or both before the 15th gestational week (RCT = 20, $n = 7{,}159$) was highly effective in reducing the risk of GDM (the pooled RR: 0.78, 95%CI 0.64–0.96, $P = 0.0187$, power = 39.1%) (Fig. 3), with an acceptable publication bias (Fig. S4). Lifestyle intervention initiated at or after the 16th gestational week (RCT = 8, $n = 4{,}204$) was not able to reduce the risk of GDM (the pooled RR: 0.97, 95%CI 0.82–1.13, $P = 0.6633$, power = 19.2%) (Fig. 3).

The pooled effects of PA plus diet (RCT = 10, $n = 3{,}931$), diet only (RCT = 5, $n = 1{,}155$) and PA only (RCT = 8, $n = 2{,}073$) initiated before 15 gestational weeks on the risk of GDM did not reach statistical significance (RR of PA plus diet: 0.82, 95%CI 0.68–1.03, $P = 0.1579$; diet only: 0.80, 95%CI 0.56–1.08, $P = 0.2391$; PA only: 0.64, 95%CI 0.36–1.12, $P = 0.1205$) (Fig. S5). The powers of diet plus PA, PA only and diet only were 15.4%, 20.3% and 72.0%, respectively.

The effect sizes were similar among women with prepregnancy overweight or obesity (RCT = 18, $n = 7{,}040$) and those with normal prepregnancy body weight (RCT = 8, $n = 3{,}962$) (the pooled RR in overweight/obesity: 0.83, 95%CI 0.69–1.00, $P = 0.0523$, power = 31.3%; and in normal body weight: 0.82, 95%CI 0.62–1.10, $P = 0.1983$, power = 51.5%) (Fig. S6).

Three pooled RRs from studies using different diagnostic criteria, including 1999 World Health Organization's ($n = 1{,}254$), 2010 IADPSG's ($n = 2{,}693$) and 2004 American Diabetes Association's criteria ($n = 974$) did not reach statistical significance, although all these effect sizes tended to favour the intervention (Figs S7–S9). The powers using the three sets of criteria were 37.4%, 8.1% and 8.1%, respectively.

There was a significant effect identified if we limit it to women aged ≥30 years (RCT = 16, $n = 5{,}936$) for the risk of GDM (the pooled RR: 0.79, 95%CI 0.64–0.97, $P = 0.0263$, power = 65.9%), but the effect did not reach significance among women <30 years of age (the pooled RR: 0.88, 95% CI 0.70–1.11, $P = 0.2831$, power = 9.6%; RCT = 12, $n = 5{,}300$) (Fig. S10).

The effect sizes were similar in Caucasian-dominated populations (pooled RR: 0.80, 95%CI 0.60–0.1.06, $P = 0.1187$, power = 39.3%) and non-Caucasian-dominated populations (pooled RR: 0.84, 95%CI 0.71–1.00, $P = 0.0542$, power = 34.1%) although non-significant. The effect size with

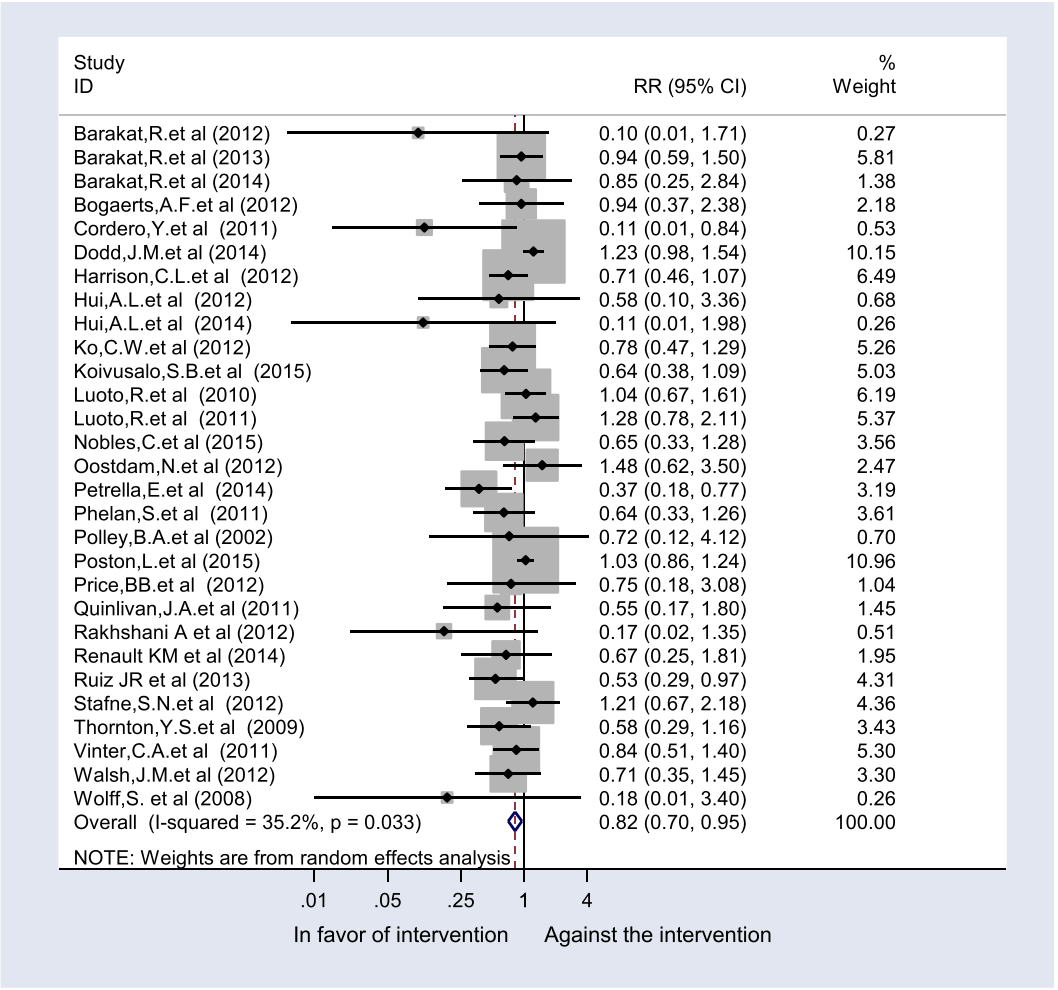

Figure 2 Forest plot of meta-analysis with 29 randomized controlled trials (RCTs). There was a significant overall effect of diet, physical activity or both for the risk of gestational diabetes mellitus [relative risk (RR): 0.82, 95% confidence interval (CI) 0.70–0.95]. The heterogeneity of the 29 RCTs included was moderate ($\chi^2 = 43.191$, $P = 0.0333$, $\tau^2 = 0.0445$, $I^2 = 35.17\%$). Results screened by the International Association of Diabetes and Pregnancy Study Group criteria (2010) of Barakat *et al.* (2013) and Walsh *et al.* (2012) were used in this pooled estimate.

only inclusion of the RCTs whose control arm received a standard, normal or usual care did not reach statistical significance (pooled RR: 0.92, 95%CI 0.82–1.02, $P = 0.1011$, power = 38.7%).

Discussion

Our meta-analysis of 11,487 pregnant women enrolled in 29 RCTs demonstrates that lifestyle modification during pregnancy can achieve an 18% reduction in the risk of GDM, mainly driven by lifestyle intervention initiated before the 15th gestational week. The observed effectiveness seemed to be similar among women with different prepregnancy obesity/overweight status and among women who had different maternal ages.

Although there are three meta-analyses conducted in the past decade in an attempt to address the issue of efficacy of lifestyle intervention on the risk of GDM, these meta-analyses failed to generate consistent findings probably because of the small sample size prior to the recent RCTs (12,22,25). Indeed, this issue remains unanswered by individual RCTs and meta-analyses of these RCTs. Most of the meta-analyses of observational studies reported a positive effect of lifestyle intervention on the risk of GDM (14,48). On the other hand, meta-analyses of RCT data failed to find a protective effect of lifestyle intervention on the risk of GDM (49–53). More recent meta-analyses of RCT data also reported mixed and, sometime, confusing conclusions. In this regard, Russo *et al.* (54) analysed the data of 10 RCTs of 3,401 pregnant women and found a slightly protective effect of physical activity on the risk of

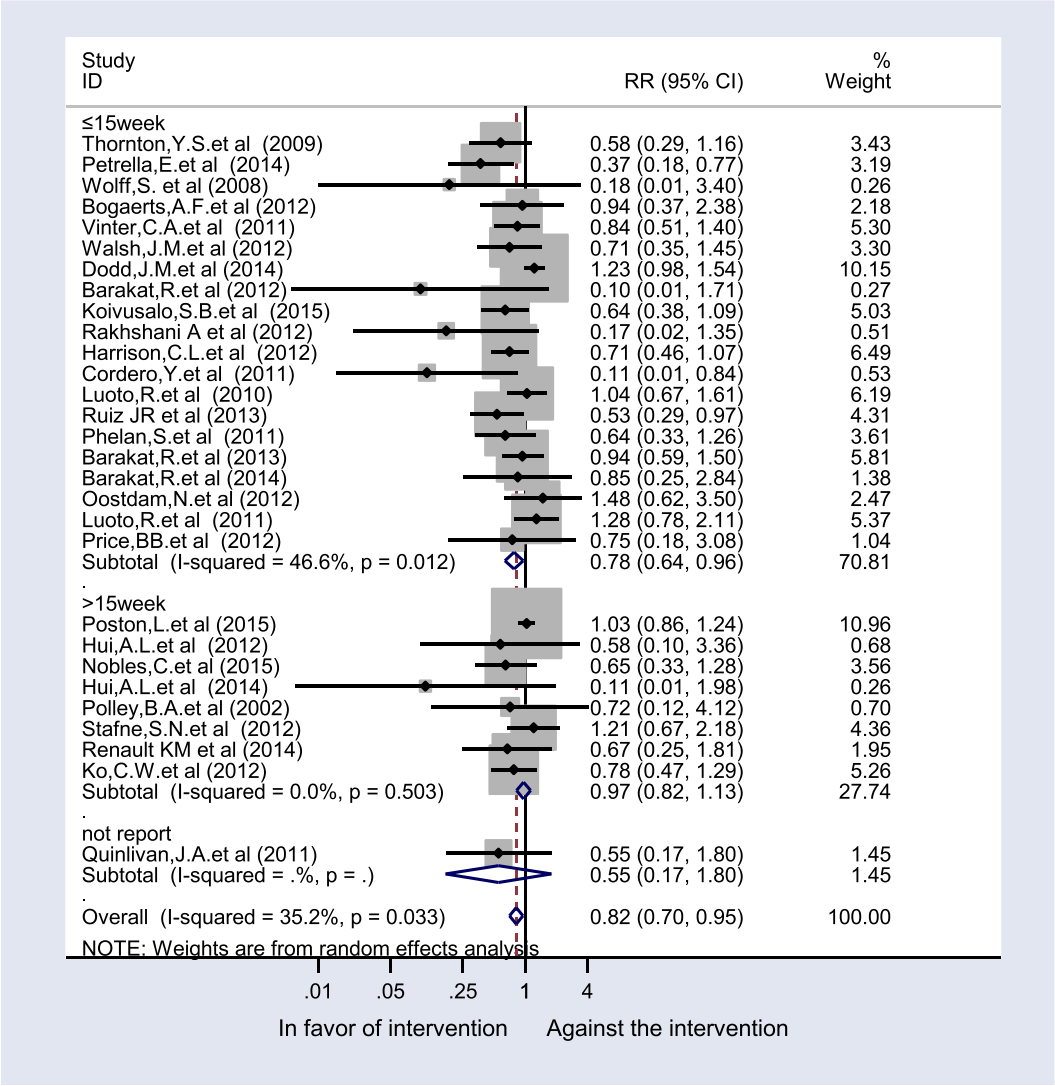

Figure 3 Forest plot of meta-analysis with subgroups by gestational age. There was a significant overall effect of diet, physical activity or both for the risk of gestational diabetes mellitus with randomized controlled trials (RCTs) initiating the intervention at or before the 15th gestational week [relative risk (RR): 0.78, 95% confidence interval (CI) 0.64–0.96]. The heterogeneity of the 20 RCTs included was moderate ($\chi^2 = 35.560$, $P = 0.0119$, $\tau^2 = 0.0807$, $I^2 = 46.6\%$). There was no significant overall effect of diet, physical activity or both for the risk of gestational diabetes mellitus with RCTs initiating the intervention after the 16th gestational week (RR: 0.97, 95%CI 0.82–1.13). The heterogeneity of the eight RCTs included was low ($\chi^2 = 6.320$, $P = 0.5028$, $I^2 = 0.0\%$).

GDM while Rogozinska *et al.* (*55*) analysed the data of 20 RCTs of 6,444 pregnant women and found that diet-based intervention could reduce the risk of GDM but diet and PA mixed intervention had no effects on GDM. Several major limitations in these meta-analyses are noticed: (1) biases in observational studies are possible and evidence from meta-analysis of observational studies is unlikely to be strong or conclusive; (2) unavailability of recent RCTs, especially the recent three large RCTs, may render these meta-analyses underpowered to address the efficacy of lifestyle intervention on the risk of GDM; and (3) gestational age when the intervention started may be a critical factor for the benefits. Nevertheless, all these meta-analyses of RCT data did not take into consideration the timing of the intervention. In this regard, our meta-analysis included more recent RCTs and only those studies that used an RCT design, thus having larger power and more likely free of biases inherent in observational studies. More importantly, we performed a cumulative meta-analysis of the included RCTs by gestational age, suggesting a trend of the effects of lifestyle intervention with the timing of the intervention during pregnancy, i.e. the earlier the intervention, the larger the intervention's effect is. If we used a cut-off point of 15 gestational weeks, the intervention before that time was able to achieve a 22% (95%CI 4–36%) reduction in the risk of development of GDM, and presumably, adverse pregnancy complications as suggested by Catalano *et al.*

(56). On the other hand, the effect size may not differ among women with different BMIs before pregnancy and at different maternal ages.

The increasing prevalence of overweight, obesity and maternal age at pregnancy over time may account for part of the rapid secular increase in the prevalence of GDM. For example, our data showed that in Tianjin, China, prepregnancy BMI increased from 21.2 to 22.3 $kg\,m^{-2}$ and age at pregnancy increased from 26.3 to 28.3 years over a 12-year time span, which was accompanied by an increase in the prevalence of GDM from 2.3% to 8.1% (57). In other words, prepregnancy obesity or insulin resistance may contribute to, at least, part of the secular increase in the prevalence of GDM, although genetic predisposition to GDM may also play a role in the development of GDM (58). In this connection, our subgroup analysis by prepregnancy BMI showed that the effect of lifestyle intervention did not have greater benefits among women who were overweight or obese prior to pregnancy. Pregnancy is a state of insulin resistance that starts in the 12th to 14th gestational weeks advancing throughout the pregnancy (59). Undue weight gain is a well-established risk factor for GDM (60). The increasing insulin resistance during pregnancy originating from undue weight gain may, presumably, contribute to the increased risk of GDM. Our findings suggest that women at high risk of GDM because of risk factors other than obesity prior to pregnancy may also benefit from lifestyle intervention: the critical issue may be to start the intervention before pregnancy-induced insulin resistance is well developed, e.g. before the 15th gestational week. Of note, many women with unintended pregnancy are hard to reach and manage, and our data did not support that intervention later in pregnancy could reduce the risk of GDM. Nevertheless, those women at high risk of GDM may also benefit from lifestyle intervention as many trails (7) including ours (61) had showed that lifestyle intervention can improve pregnancy outcomes in GDM.

It is also interesting to note that the effect sizes of intervention were similar in overweight/obesity women and normal-weight women although both did not reach statistical significance because of shortfall of power. Prepregnancy obesity or insulin resistance may contribute to the increased risk of GDM when it is recognized for the first time during pregnancy (62). Because pregnancy is a state of insulin resistance (59) and GDM is characterized by more pronounced insulin resistance than non-GDM (59,63), our findings seem to support the notion that lifestyle intervention in early pregnancy is effective for undue pregnancy-induced insulin resistance.

Our study has strong public health implications. GDM is a prevalent metabolic disease, with adverse pregnancy outcomes and long-term adverse health impacts on the mothers and their offspring (58). Many women become pregnant in an unplanned manner. So it is critically important to know whether or not GDM can be prevented once individuals are already pregnant. The findings that there was a similar effect size in overweight/obese and normal-body-weight women before pregnancy suggest that we need to identify the high-risk group in early pregnancy, not only owing to overweight/obesity and advanced maternal age but also by other factors. A risk score approach will serve the purpose well, which can be used to define a group of women at high risk for GDM who may benefit from early intervention.

Our study has several limitations. First, we searched for the studies published in English and Chinese only because of the language barrier, so studies published in other languages would be omitted. Second, most of these trials in favour of the intervention were conducted in developed countries except one in India (44), as our findings cannot be directly extrapolated to the settings of developing countries. Third, our study was underpowered to address the relative efficacies of individual components of lifestyle intervention, i.e. diet or PA, on the risk of GDM because of the relatively small sample sizes. Fourth, we could not explore the dose–response relationship between lifestyle intervention and the risk of GDM because of heterogeneity among the included studies. Fifth, meta-regression may be helpful in exploring sources of heterogeneity among studies included. However, because of the dispersion and missing confounders in the included studies, this effort was unsuccessful.

In conclusion, our meta-analysis provides evidence that lifestyle modification, in particular, before the 15th gestational week, can reduce the risk of GDM. The benefit of such interventions may not be limited to women with prepregnancy overweight or obesity. Given the increasing prevalence of GDM in many parts of the world, our findings highlight an urgent need to develop a risk score to identify women at high risk for GDM in early pregnancy, so that lifestyle intervention can be initiated among women who may benefit most from the intervention. Further well-designed RCTs in early pregnancy, especially in developing countries such as China, are urgently needed to address the effectiveness and cost-effectiveness of lifestyle modifications for GDM.

Conflicts of interest statement

All the authors declared no conflicts of interest.

Author contributions

X. Y. conceived the research question and supervised the process of the meta-analysis and edited the manuscript; C. S. and J. Li searched the published studies, selected articles, extracted information from each included study and performed the data analysis; C. S. and X. Y. wrote the first draft. J. Leng and R. M. gave critical comments. All authors were involved in editing the manuscript and agreed to submit it for publication.

Acknowledgements

The authors would like to express their thanks to Dr Jonatan R. Ruiz (University of Granada, Spain), Dr Alexis Shub (University of Melbourne Mercy Hospital for Women, Australia) for providing additional data regarding their trial.

Funding sources

None.

Supporting Information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12442

Figure S1. Funnel plot of the meta-analysis with 29 RCTs. Legends: This meta-analyses with 29 RCTs had an acceptable publication bias (Begg's Test with continuity correction, $P = 0.0944$).

Figure S2. Forest plot of the meta-analysis with subgroups by intervention methods. Legends: There were no significant effects of physical activity, diet, and physical activity plus diet for the risk of gestational diabetes mellitus (RR: 0.77, 95%CI 0.54-1.09; RR: 0.80, 95%CI 0.58-1.10; RR: 0.85, 95%CI 0.70-1.03).

Figure S3. Forest plot of the cumulative meta-analysis by gestational age of initiation of the intervention. Legends: We performed this cumulative meta-analysis by descending gestational age of initiation of the intervention. From this plot, we can see that the pooled RRs were nearly the same after including Renault, K.M., Wolff, S. and Bogaerts, A. R.'s trials and the corresponding gestational age was just 15th week. So we use the 15th week as the cut-off to identify the impact of initiation timing on the effect size

Figure S4. Funnel plot of the meta-analysis with RCTs initiating the intervention at or before 15th gestational weeks. Legends: This meta-analysis with initiating the intervention at or before 15th gestational weeks had an acceptable publication bias (Begg's Test with continuity correction, $P = 0.1978$).

Figure S5. Forest plot of the meta-analysis with subgroups by intervention methods initiated at or before 15th gestational weeks. Legends: There were no significant effects of physical activity, diet, and physical activity plus diet for the risk of gestational diabetes mellitus initiated at or before 15th gestational weeks (RR: 0.64, 95%CI 0.36-1.12; RR: 0.80, 95% CI 0.56-1.16; RR: 0.82, 95%CI 0.63-1.08).

Figure S6. Forest plot of the meta-analysis with subgroups by prepregnancy BMI. Legends: There was significant effect identified with RCTs including women with mean prepregnancy BMI $\geq 25\,kg\,m^{-2}$ for the risk of gestational diabetes mellitus (RR: 0.83, 95%CI: 0.68-1.00). The heterogeneity of the 18 RCTs included was medium ($\chi^2 = 29.473$, $P = 0.0304$, $\tau^2 = 0.0523$, $I^2 = 42.32\%$). No effect was identified with RCTs including women with mean prepregnancy BMI $< 25\,kg\,m^{-2}$ for the risk of gestational diabetes mellitus (RR: 0.82, 95%CI 0.60-1.11).

Figure S7. Forest plot of the meta-analysis with RCTs using IADPSG's criteria (2010). Legends: There was no significant effect identified with RCTs using IADPSG's criteria (2010) for the risk of gestational diabetes mellitus (RR: 0.80, 95%CI: 0.59-1.09, $P = 0.1624$). The heterogeneity of the 5 RCTs included was medium ($\chi^2 = 8.983$, $P = 0.0615$, $\tau^2 = 0.0620$, $I^2 = 55.47\%$).

Figure S8. Forest plot of the meta-analysis with RCTs using ADA criteria (2004). Legends: There was no significant effect identified with RCTs using ADA's criteria (2004) for the risk of gestational diabetes mellitus (RR: 0.76, 95%CI: 0.45-1.27, P=). The heterogeneity of the 4 RCTs included was medium ($\chi^2 = 6.593$, $P = 0.0861$, $\tau^2 = 0.1405$, $I^2 = 54.50\%$). The diagnosis criteria of GDM recommended by ADA was the same from 2004 to 2010 until 2011 adopting the IADPSG's criteria (2010).

Figure S9. Forest plot of the meta-analysis with RCTs using WHO's criteria (1999). Legends: There was no significant effect identified with RCTs using WHO's criteria (1999) for the risk of gestational diabetes mellitus (RR: 0.83, 95%CI: 0.62-1.10, $P = 0.0321$). The heterogeneity of the 3 RCTs included was low ($\chi^2 = 2.537$, $P = 0.2812$, $I^2 = 21.18\%$). Both the WHO's criteria (1999) and IADPSG's criteria (2010) were used in the Barakat, R.'s trial (2013).

Figure S10. Forest plot of the meta-analysis with subgroups by maternal age. Legends: There was significant effect identified with RCTs including women $\geq$30 years old for the risk of gestational diabetes mellitus (RR: 0.79, 95%CI 0.64-0.97). No effect was identified with RCTs including women $<$30 years old for the risk of gestational diabetes mellitus (RR: 0.88, 95%CI 0.70-1.11).

Table S1. Characteristics of the studies included in the meta-analysis

Table S2. Details on the quality of trials included in the meta-analysis

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