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Diet and exercise for preeclampsia prevention in overweight and obese pregnant women: systematic review and meta-analysis

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ABSTRACT

Objective: To investigate the effect of diet and/or exercise in overweight or obese pregnant women on the risk of preeclampsia.

Methods: We performed a systematic review and meta-analysis of randomized controlled trials examining the effect of diet and/or exercise interventions in overweight and obese pregnant women on the risk of PE and hypertensive disorders. We completed a literature search through PubMed, Embase, Cinahl, Web of science, Cochrane CENTRAL Library from their earliest entries to November 2017 and from references of other systematic reviews. No language restrictions were applied. Relative risks with random effect were calculated with their 95% confidence intervals.

Results: There were 23 eligible trials (7,236 participants), including 11 (5,023 participants) investigating the effect of diet and 3 (387 participants) investigating the effect of exercise on risk of preeclampsia, 14 (4,345 participants) investigating the effect of diet, 5 (884 participants) investigating the effect of exercise and 1 (304 participants) investigating the effect of diet and exercise on risk of hypertensive disorders. Most studies were considered to be at low risk of bias for random sequence allocation and incomplete outcome data but at high risk of bias for blinding of participant and personnel. The heterogeneity of the studies on preeclampsia was low (I^2 =0%-11%), but the heterogeneity of the studies on hypertensive disorders was variable (I^2=0%-53%). In women randomized to diet and/or exercise, compared to expectant management, there was no significant difference in the risk of preeclampsia (relative risk 1.01, 95% confidence interval 0.80 to 1.27; p=0.96) or hypertensive disorders of pregnancy (relative risk 0.87, 95% confidence interval 0.70 to 1.06; p=0.17). In the intervention group, compared to expectant management, gestational weight gain was significantly lower (-1.47 kg, 95% confidence interval -1.97 to -0.97; p<0.00001). Meta-regression weighted by the size of the studies showed no significant association between gestational weight gain and the risk of preeclampsia or hypertensive disorders (p=0.314 and p=0.124, respectively).

Conclusions: Diet and exercise in overweight or obese pregnant women are beneficial in reducing gestational weight gain. However, these interventions do not reduce the risk of preeclampsia or hypertensive disorders of pregnancy.

Key words: Diet, exercise, preeclampsia, hypertensive disorders, obese, overweight, systematic review, meta-analysis, randomized controlled trial

Introduction

Obesity has been described as a global pandemic with increasing prevalence in both developed and developing countries [1]. It is estimated that more than 50% of pregnant women in Europe are overweight, with a body mass index (BMI) ≥25 kg/m^2 or obese with a BMI ≥30 kg/m^2 [2,3].Increased maternal BMI is associated with substantial increase in adverse pregnancy outcomes, including development of preeclampsia (PE) and gestational hypertension [4-6].

Diet and/or exercise in pregnancy have the potential to reduce weight gain and therefore the associated risk of developing PE. Several randomized trials investigating the effect of diet and/or exercise in reducing gestational weight and adverse pregnancy outcomes have been conducted; the majority of these trials have shown a beneficial effect on gestational weight gain, but they reported contradictory results on the effect of reducing the risk of PE. A recent meta-analysis examining the effect of aerobic exercise in pregnant women irrespective of their BMI concluded that this intervention was associated with a 30% reduction in risk of hypertensive disorders of pregnancy [7].

This review examines whether diet and/or exercise can prevent PE in overweight or obese pregnant women.

Methods

This is a systematic review and meta-analysis of randomized controlled trials evaluating the effect of dietary or exercise interventions in overweight or obese pregnant women on the risk of PE. No ethical approval was required. A priori protocol was performed and registered in PROSPERO (CRD42018086408).

Research strategy

We searched PubMed, Embase, Cinhal, Web of Science and Cochrane CENTRAL from their earliest entries to November 2017 using MeSH terms and keywords (obese, overweight, obesity, weight gain, lifestyle, diet, exercise, behavioural, nutritional, physical activity, dietary counselling, dietary, nutrition, preeclampsia, pre-eclamspia, eclampsia, hypertension, hypertensive disorders, gestational hypertension, pregnancy induced hypertension, PIH, GH, SGA, small for gestational age, macrosomia, LGA, large for gestational age, complication, gestational weight gain, gestational diabetes, pregnancy, pregnant, prenatal, antenatal) and from references or other systematic reviews. No language restriction was applied.

Selection of articles

All citations were examined to identify potentially relevant studies; the abstracts were revised by two independent reviewers (AS and MSC) who selected eligible studies for full assessment of the complete article. Any disagreements were resolved by discussion with a third party (KN). The inclusion criteria were randomized controlled trials evaluating the effect of diet and/or exercise on the risk of PE and hypertensive disorders of pregnancy, as a composite of either PE or gestational hypertension. Only studies providing results on overweight or obese women were included.

The trials were classified according to the intervention into: diet alone, exercise alone or a combination of diet and exercise. Trials in which both diet and exercise were used but the latter was not structured or was unsupervised with only recommendations for increasing walking or developing a more active lifestyle were classified into the dietary intervention group.

Outcome measures

The main outcome measure was PE. Secondary outcome measure was hypertensive disorders of pregnancy. We also examined these outcomes in relation to gestational weight gain. The definitions for PE, hypertensive disorder of pregnancy and gestational weight gain varied between studies and we accepted the definition used in each study.

Quality evaluation

PRISMA tool was used to assess the quality of the study and the Cochrane Handbook criteria were used to assess the risk of bias [8.9].

Statistical analyses

Relative risks (RR) and mean differences were calculated with their 95% confidence intervals (CI) using random effects [10]. Subgroup analyses were performed to evaluate the effect of the type of intervention: diet only, exercise only or diet and exercise together. Meta-regression weighted by the size of the studies was performed to evaluate the association of gestational weight gain and the risk of PE and hypertensive disorder. Heterogeneity was measured using Higgin's I^2 and considered high if over 50% [11,12]. Visual inspection of funnel plot was performed to evaluate the risk of publication bias [13]. Analyses were carried out with Review Manager 5.3 software (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) and Stata release 14.0 (StataCorp, College Station, Tex).

Results

The literature search identified 4,717 potentially appropriate trials, but only 23 trials (7,236 participants) were considered to be eligible for analysis (Figure 1). These included 11 trials (5,023 participants) investigating the effect of diet [14-24]and 3 (387 participants) investigating the effect of exercise [25-27]on risk of PE, 14 (4,345 participants) investigating the effect of diet [15-21,24,28-32], 5 (884 participants) investigating the effect of exercise [26,27,33-35]and 1 (304 participants) investigating the effect of diet and exercise [36] on risk of hypertensive disorders. Details of individual studies are provided in Table s1.

Characteristics of studies

In total, 13 studies included overweight and obese women and 10 studies included only obese women. The definition of overweight and obese was BMI of $\geq$25 kg/m^2 and $\geq$30 kg/m^2, respectively. However, in one study overweight was defined as BMI $\geq$24kg/m^2, in two studies obese was defined as BMI $\geq$29 kg/m^2 and in another study obese was defined as BMI $\geq$28kg/m^2. The definition of PE and/or gestational hypertension were provided in 10 of the 23 studies. Gestational weight gain was provided by 18 studies but the definitions varied from self-reported weight before pregnancy, measured weight in early pregnancy or at randomization to measured weight at a prespecified gestational age or the last visit before delivery or at delivery. Randomization was at <21 weeks' gestation in 22 studies and at 8-35 weeks in one study. The primary outcome of the trials was gestational weight gain in 13 studies, GDM in 3, perinatal outcome in 2, birth weight in 2, and 1 each for hypertensive disorder, need for insulin therapy and time spent undertaking physical activity at 36 weeks' gestation.

Most studies were considered to be at low risk of bias for random sequence allocation and incomplete outcome data but at high risk for blinding of participant and personnel (Figure 2). Analysis of the funnel plots suggests the possibility of publication bias or low methodological quality of smaller studies because small asymmetry of the right (Figure s1). The heterogeneity of the studies on PE was low (I^2 =0%-11%), but the heterogeneity of the studies on hypertensive disorders was variable (I^2=0%-53%)

Outcome measures

In women randomized to diet and/or exercise, compared to expectant management, there was no significant difference in the risk of PE (RR 1.01, 95% CI 0.80 to 1.27; p=0.96) or hypertensive disorders of pregnancy (RR 0.87, 95% CI 0.70 to 1.06; p=0.17) (Figures 3, and s2).

In the intervention group, compared to expectant management, gestational weight gain was significantly lower (-1.47 kg, 95% CI -1.97 to -0.97; p<0.00001, Figure s3). Meta-regression weighted by the size of the studies showed no significant association between gestational weight gain and the risk of PE or hypertensive disorder (p=0.314 and p=0.124, respectively; Figure s4).

Discussion

Principal findings of this study

This systematic review and meta-analysis of 23 trials on a combined total of 7,236 overweight or obese pregnant women, demonstrated that diet and/or exercise initiated at <21 weeks' gestation reduce gestational weight gain but have no effect on the risk of PE or hypertensive disorders of pregnancy.

Previous studies have reported that the risk of PE increases with both starting BMI and gestational weight gain [4-6,37-40].It is possible that the observed reduction in gestational weight gain in overweight or obese women treated with diet and/or exercise was not sufficient to have an effect on risk of PE. In the meta-regression analysis there was a non-significant trend between gestational weight gain and risk of PE.

Strengths and limitations of the study

The strengths of this meta-analysis are first, the large number of participants included, second, the focus on only overweight and obese women who are at higher risk for PE compared to normal BMI women and third, the low heterogeneity across the included studies for the primary outcome.

This meta-analysis has certain limitations. Firstly, the definition of the intervention varied across the trials and we took the pragmatic approach of accepting the definition used in each study. Secondly, only one of the included trials was powered to examine the effect of diet and/or exercise in reducing the risk of PE; in all other trials PE was a secondary rather than primary outcome. An essential element in randomised trials is the adherence to the study intervention and unlike interventions such as supervised exercise, interventions focused on diet cannot provide information to allow assessment of the influence of adherence on the potential beneficial effect of diet on pregnancy outcome. Similarly, the extent to which stricter diets can affect pregnancy outcome remains unclear.

Comparison with previous studies

Several meta-analyses have been conducted to evaluate the effect of diet and/or exercise on adverse pregnancy outcomes but most of them have included all BMI groups. There were four meta-analyses that were confined to overweight or obese women but none of these had PE as a primary outcome measure; however, their results were consistent with our finding that diet and/or exercise do not reduce the risk of PE [41-44]. The largest of the four previous meta-analyses was conducted 7 years ago and included 10 trials on a combined population of 1,434 participants, which is considerably lower than the 7,236 participants included in our study [44].

Clinical implications of the study

High BMI is an important risk factor for the development of PE [6]. As demonstrated in this meta-analysis, the risk of PE is not reduced by diet and/or exercise initiated in the first half of the index pregnancy.

Recent evidence suggests that an effective approach for reduction in risk of PE is first-trimester screening by a combination of maternal characteristics, including weight and height, with previous obstetric history, medical history and biomarkers and treatment of the high-risk group with aspirin (150 mg/day from the first- to the third-trimester of pregnancy); such intervention reduced the overall risk of PE by about 30% and the risk of preterm-PE by >60% [45]. Subgroup analysis of the ASPRE trial demonstrated that there was no evidence of difference in the effect of aspirin on incidence of preterm-PE in subgroups defined by BMI of <25 and ≥25 kg/m^2[46].

There is contradictory evidence concerning the value of metformin in obese women in reducing the risk of PE. One trial (EMPOWaR) reported that metformin (2.5 g/day from 16-18 weeks' gestation to delivery) in 449 non-diabetic women with BMI >30 kg/m^2 had no significant effect on gestational weight gain or risk of PE [47]. In contrast, another trial (MOP) reported that metformin (3.0 g/day from 12-18 weeks' gestation to delivery) in 400 non-diabetic women with BMI >35 kg/m^2 was associated with significant reduction in gestational weight gain and risk of PE (odds ratio 0.24, 95% CI 0.10-0.61) [37].

Conclusions

Diet and exercise in overweight or obese pregnant women are beneficial in reducing gestational weight gain. However, these interventions do not reduce the risk of PE or hypertensive disorders of pregnancy.

Figure legends

Figure 1. Flow chart for the systematic review.

Figure 2. Summary of the quality of included studies.

Figure 3. Forest plots of the risk of preeclampsia: comparison between interventions vs. control groups.

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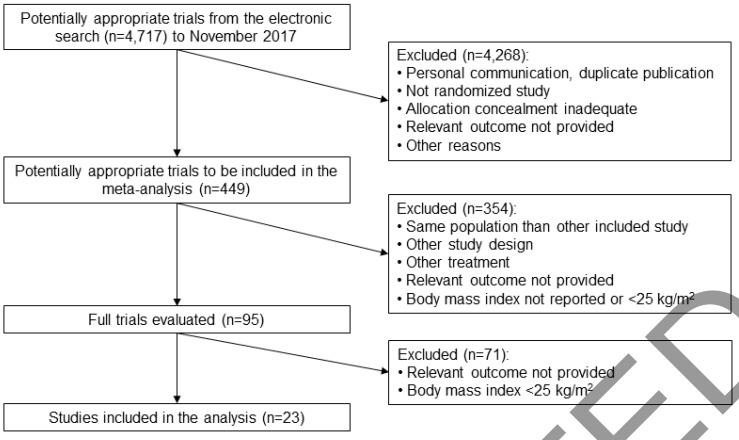

Figure 1

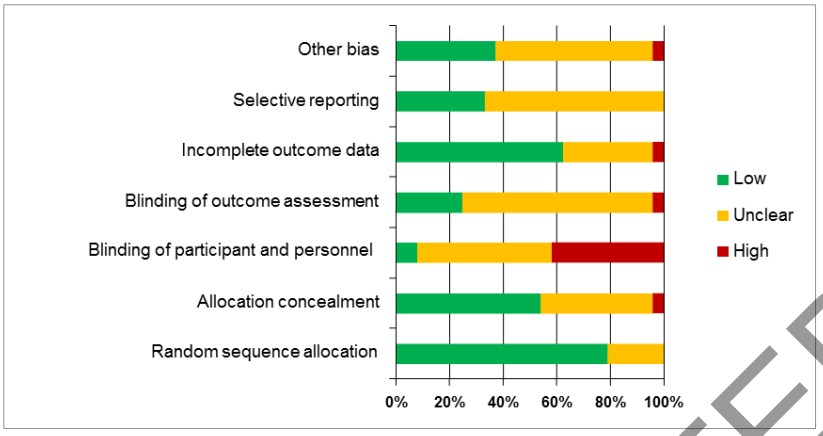

Figure 2

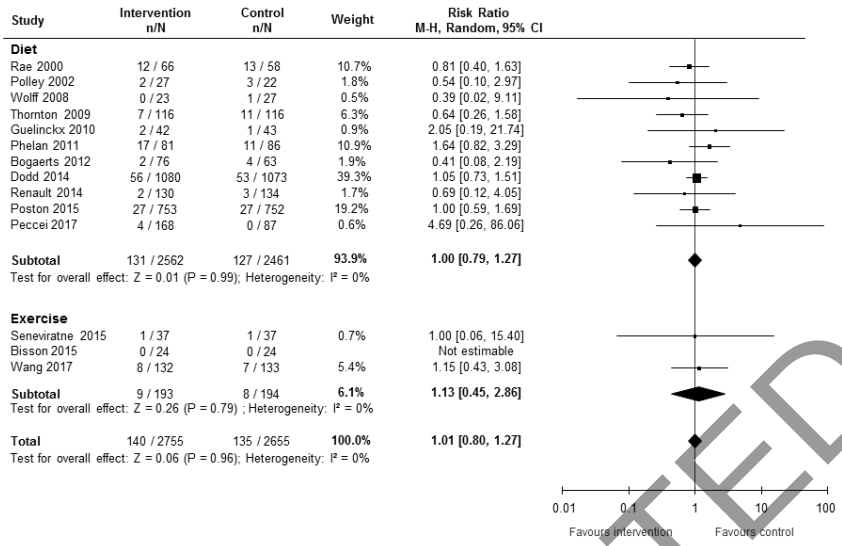

Figure 3