ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

Η ΔΙΑΤΡΟΦΗ ΣΤΗΝ ΥΓΕΙΑ ΚΑΙ ΣΤΗ ΝΟΣΟ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Ο ρόλος των παρεμβάσεων τρόπου ζωής κατά τη διάρκεια της κύησης για την πρόληψη του σακχαρώδους διαβήτη κύησης σε γυναίκες υψηλού κινδύνου: μία συστηματική ανασκόπηση και μετα-αναλύσεις των δημοσιευμένων τυχαιοποιημένων κλινικών δοκιμών

Τσιρονίκος Γεώργιος

Ιατρός, MD, MSc

ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

Μπαργιώτα Αλεξάνδρα, Αναπληρώτρια Καθηγήτρια Παθολογίας-Ενδοκρινολογίας, Τμήμα Ιατρικής Πανεπιστημίου Θεσσαλίας, Επιβλέπουσα Καθηγήτρια

Ποταμιάνος Σπυρίδων, Ομότιμος Καθηγητής Γαστρεντερολογίας, Τμήμα Ιατρικής Πανεπιστήμιου Θεσσαλίας, Μέλος Τριμελούς Επιτροπής

Τατσιώνη Αθηνά, Αναπληρώτρια Καθηγήτρια Γενικής Ιατρικής, Τμήμα Ιατρικής Πανεπιστημίου Ιωαννίνων, Μέλος Τριμελούς Επιτροπής

Λάρισα, 2023

UNIVERSITY OF THESSALY

SCHOOL OF HEALTH SCIENCES

FACULTY OF MEDICINE

POSTGRADUATE STUDIES PROGRAM

NUTRITION IN HEALTH AND DISEASE

DIPLOMA THESIS

Effectiveness of lifestyle interventions during pregnancy on preventing gestational diabetes mellitus in high-risk women: a systematic review and meta-analyses of published RCTs

Contents

Abstract

Background

Until now, it is uncertain whether lifestyle interventions during pregnancy could prevent gestational diabetes mellites (GDM) in both general population, and high-risk pregnant women.

Objective

This study aims at investigating the effectiveness of dietary interventions, or exercise interventions, or both of them during pregnancy on preventing GDM in high-risk pregnant women.

Materials and Methods

Eligible randomized controlled trials (RCTs) were selected after a search in CENTRAL, Scopus, and PubMed. Synthesis was performed for the GDM's outcome for women with any identified risk factor. Separate meta-analyses (MA) were performed to assess the efficacy of interventions of nutrition, or physical activity (PA), or both of them compared to standard prenatal care on preventing GDM. Data were combined through random effect (RE) model. Heterogeneity and variability across studies were evaluated with Cochran's Q statistic, and I^2 calculations, respectively. Subgroup and sensitivity analyses, as well as meta-regressions against OR were performed to assess potentional heterogeneity. Overall quality, quality of RCTs, and publication bias were also evaluated.

Results

A total of 13524 participants high-risk pregnant women in eligible RCTs were analyzed for GDM. 3109 out of them high-risk pregnant women received only dietary intervention for preventing GDM. 553 (17.8%) of them developed GDM [241 (15.7%) in intervention group, and 312 (19.7%) in control group]. Women receiving nutrition intervention during pregnancy were less likely to experience GDM compared to women following standard prenatal care; however, the result of MA was marginally not significant (OR 0.73, 95%CI 0.51, 1.03; P-value 0.07), [Q 21.29, P-value 0.01; I^2 58% (95%CI 10, 78%)]. On the opposite, subgroup analyses demonstrated an effect for studies not including BMI as GDM risk factor (OR 0.57; 95%CI 0.36, 0.93; P-value 0.02), and for studies including patterns of Mediterranean diet as intervention's component (OR 0.61; 95%CI 0.46, 0.81; P-value 0.0006). Among 2742 high-risk pregnant women being analysed for GDM's outcome after intaking only exercise intervention, 461 (16.8%) [192 (14%) in experimental group, and 269 in comparator group (19.7%)] were diagnosed with GDM. Women after receiving PA intervention were less possible to develop GDM (OR 0.64, 95%CI 0.51, 0.80; P-value < 0.0001), [Q 11.27, P-value 0.51; I^2 0% (95%CI 0, 99%)]. 1308 (17%) [622 (16.1%) in intervention, and 686 (18%) in control group] cases of GDM were diagnosed among 7673 high-risk pregnant women undergoing both diet and PA intervention. Women in the group of mixed lifestyle intervention had a significant reduction in incidence of GDM (OR 0.70, 95%CI 0.55, 0.90; P-value 0.005), [Q 50.32, P-value < 0.0001, I^2 66%, (95% CI 44, 79%)].

Conclusions

The results of this study could support the efficacy of lifestyle interventions during pregnancy on preventing GDM in high-risk women, if an exercise content is included as an intervention arm, either alone, or combined with diet. Nutrition interventions in high-risk women without obesity, or the implementation of Mediterranean diet approach may also have a protective effect. Future research is needed to strengthen these findings.

Key words

diet, nutrition, exercise, PA, GDM

Introduction

According to the latest guideline of the American Diabetes Association (ADA) GDM is a type of diabetes mellitus (DM) that is not pregestational, and is recognized after the trimester of pregnancy, [1, 2]. It is the most common gestational and childbirth complication [3, 4]. Independently of the applied diagnostic criteria, incidence of GDM is increasing in worldwide [5, 6]. It is an important disease that affects pregnancies [7], increasing the incidence of short-term and long-term unfavorable health circumstances [8].

Main identified risk factors for GDM include nonwhite race–ethnicity [9], advanced maternal age (≥ 35 years) [8, 10], westernized diet [11], sedentary lifestyle [9, 12], pre-pregnancy overweight or obesity [13, 14], excessive gestational weight gain (GWG) [5, 11, 15], family history of first-degree relatives with DM [8, 11, 12], history of GDM [11, 12], and history of macrosomia (birthweight ≥ 4000 g) [8, 12].

Although PA may be protective against T2DM, the data regarding PA and GDM are less extensive and less convincing [16]. Several interventions to mitigate hyperglycemia have been suggested, the main ones being pharmacological, PA and lifestyle counseling [17]. Lifestyle interventions do not have enough evidence to on preventing GDM [18]. The research question of whether GDM could be prevented by interventions during pregnancy or before pregnancy remains unanswered [19, 20].

According to a recent SR and MA, any intervention of diet, or PA, or both of them, succeeded significantly less occurrences of GDM [21]. Additionally, a recent network MA demonstrated that GDM could be prevented with the implementation of exercise plus probiotic interventions, whereas dietary only, or dietary plus PA interventions did not alter the GMS' incidence [1]. However, a previous SR and MA did not found benefit with diet, or exercise, or a mix approach of them on reducing GDM's risk [22]. In the same line, three SR and MA assessing lifestyle interventions during pregnancy including

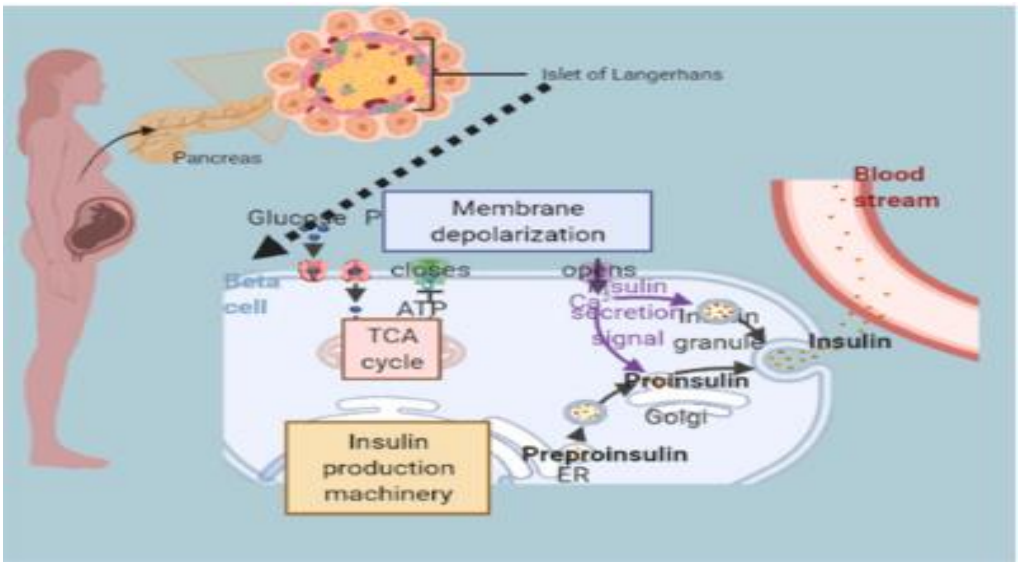
diet and PA reported no effect on decreasing GDM's outcome in obese or overweight women [20, 23, 24].

Pregnancy may represent a good time period for lifestyle changes as pregnant women have strong willingness to improve the health benefits for them and for their offsprings [23]. Preventing GDM is a priority in pregnancy [17]. This study aims at investigating the efficacy any lifestyle interventions, including only nutrition intervention, or only PA intervention, or diet plus exercise intervention implemented in gestational period on preventing GDM among high-risk women.

General Part

GDM is the result of glucose and carbohydrate metabolism disorder diagnosed during pregnancy [25]. It is a heterogenous disorder stemming from genetic, environmental and physiological risk factors [6, 11]. Pregnancy creates a diabetogenic condition similar to T2DM [25]. GDM is characterized by impaired pancreatic function of β-cells, and resistance in insulin, due to the physiological, metabolic and endocrine changes of local and placental hormones during pregnancy in order to reach the continuously fetus demands of nutrient and oxygen [6, 11, 25]. An unbalance between insulin secretion and resistance promotes the symptoms of GDM [25] (Figure (Fig) 1 [26]). The management of GDM requires initial treatment with nutrition medical therapy, PA and weight control according to pregestational weight [27]. Should glycaemic targets not be achieved after lifestyle modifications, pharmaceutical agents including insulin and metformin should be used, with insulin as first-line option [27].

Figure 1. Mechanism of Insulin secretion in the pancreas of woman with GDM



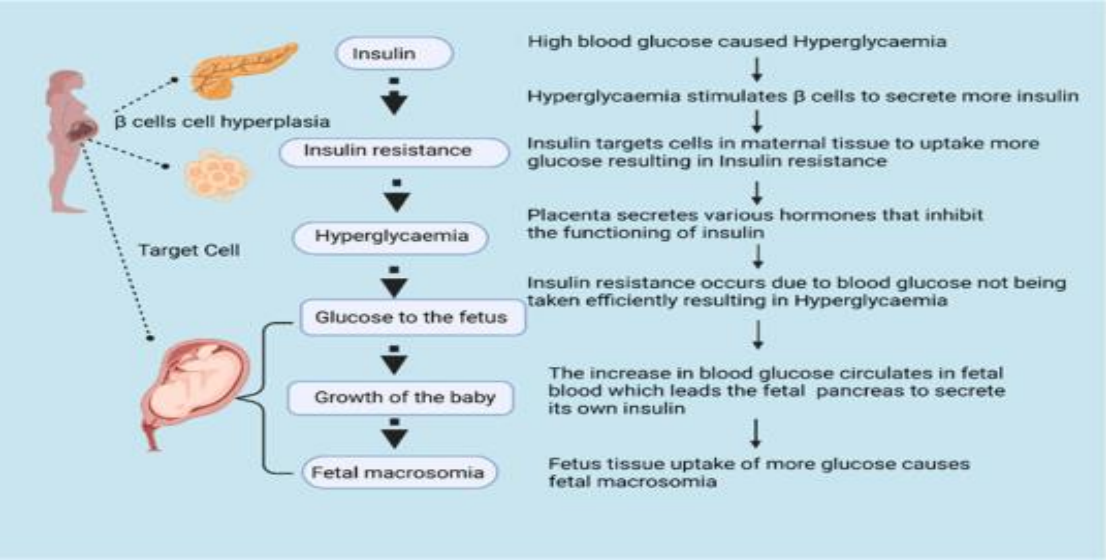
Gestational diabetes consists the most frequent health problem of pregnancy and childbirth [3, 4]. According to the 2019 International Diabetes Atlas estimates, GDM affects about 17.1 million of births annually [28]. Independently of the applied diagnostic criteria, incidence of GDM is increasing globally [5, 6]. Taking into account the the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, 14.7% of pregnancies across world are complicated by GDM [11]. According to the International Diabetes Federation (IDF) GDM's prevalence in the world was 16.7% in 2021 [2]. In the United States of America (US) GDM's prevalence has been leveled since 2017, after a continuous and nearly doubled increase between 2006 and 2016 [29]; however, its prevalence in Europe may touch 24% [4].

GDM is an important disease [7]. GDM enhances short-term and long-term maternal and children's complications [7, 8]. The negative effects may produce vicious cycles across generations [30]. The fetuses are also in a hyperglycemic status, and they need to secrete more insulin to absorb the maternal glucose [18]. GDM's complications are associated with maternal glucose in a linear manner [5]. GDM pregnancies are at high perinatal morbidity risk [31, 32], and increased perinatal mortality [9].

Short-terms unfavorable results include gestational hypertension (HY) [8], preeclampsia (PE) [20] and neonatal hypertensive disorders [14], fetal hypoglycemia [11], neonatal hypoglycaemia [18, 33], neonatal hypocalcemia [18], congenital malformation [18] and impaired development [4], fetal death [18], polyhydramnios [8], fetal hyperinsulinemia [25], overweight fetus [18], abnormal infant birth weight [4], large-for-gestational-age neonates [9], macrosomia [8, 18] (Fig 2 [26]), shoulder dystocia [33], respiratory distress syndrome [18, 33], asphyxia [33], infant hyperbilirubinemia [27] and perinatal jaundice [11, 18], increased birth weight [34], birth injuries [11], antepartum and postpartum hemorrhage [28], preterm birth [8], induction of labor [28], cesarean section [8, 31], infections [35], and admission to a neonatal care unit [25, 34].

Long-term consequences include overweight or obesity, T2DM, metabolic syndrome, cardiovascular disease (CVD), and neuropsychological deficits for both mothers and their offspring [8, 20, 35]; delayed neurocognitive development [2], and T1DM for children [32]; chronic kidney disease [2], cancer [2], psychological burden [28], and depression for mothers [36]. Two or more GDM pregnancies may increase overall risk of breast cancer (BC), and especially oestrogen receptor-positive BC [37]. Additionally, cardiovascular risk is increasing in offspring of mothers with metabolic risk factors in pregnancy, including obesity, HY, and hyperlipidaemia [38].

Fig 2. Pathway of fetal macrosomia



GDM is a well-established predictor of future DM [6]. Women with GDM as well as next generations have an increased risk of developing T2DM [14, 39]. Particularly, women with GDM may develop T2DM until 70% in later life [15]. T2DM is diagnosed soon after delivery up to 10% of women with previous GDM [6], and its prevalence may approach 38% within first postpartum year [7]. The percentage of T2DM is increasing up to 50% within five years after delivery [40]; up to 70% in a 10-year duration of follow-up [6]; and 60% in the 16th postpartum year [7]. At a 15-year follow-up duration, weight and body mass index (BMI) are significant T2DM risk factors in addition to GDM history [40].

Risk factors for GDM include nonwhite race–ethnicity [9], Hispanic, Middle Eastern, Southern Asian, Polynesian, and African ethnic groups [3, 11, 13], low-middle income and low education level [41], advanced maternal age (≥ 35 years) [8, 10], maternal smoking [25], westernized diet [11], diets with low fibre concentrations and with a high glycaemic load (GL) [9,12], diets with increased consumption of saturated fats and decreased consumption of polyunsaturated fats [5], physical inactivity [9, 12], increasing and high parity [9,12], pre-existent overweight or obesity [13, 14], excessive gestational weight gain (GWG) [5, 11, 15], maternal adiposity [15], family history of first-degree relatives with DM [8, 11, 12], maternal high or low birth weight [9], history of GDM [11, 12], history of macrosomia (birthweight ≥ 4000 g) [8, 12], history of congenital abnormalities [28], history of abortion [28] or recurrent abortions [25], history of preterm delivery [28], previous fetal death [33], previous stillbirth [25], polycystic ovarian syndrome (PCOS) [11, 12], history of HY or pregnancy associated high blood pressure [25], abnormal lipid metabolism [8], and persistent glucosuria [25]. Previous obesity, HY or hypertriglyceridaemia increase metabolic risk in pregnancy [38].

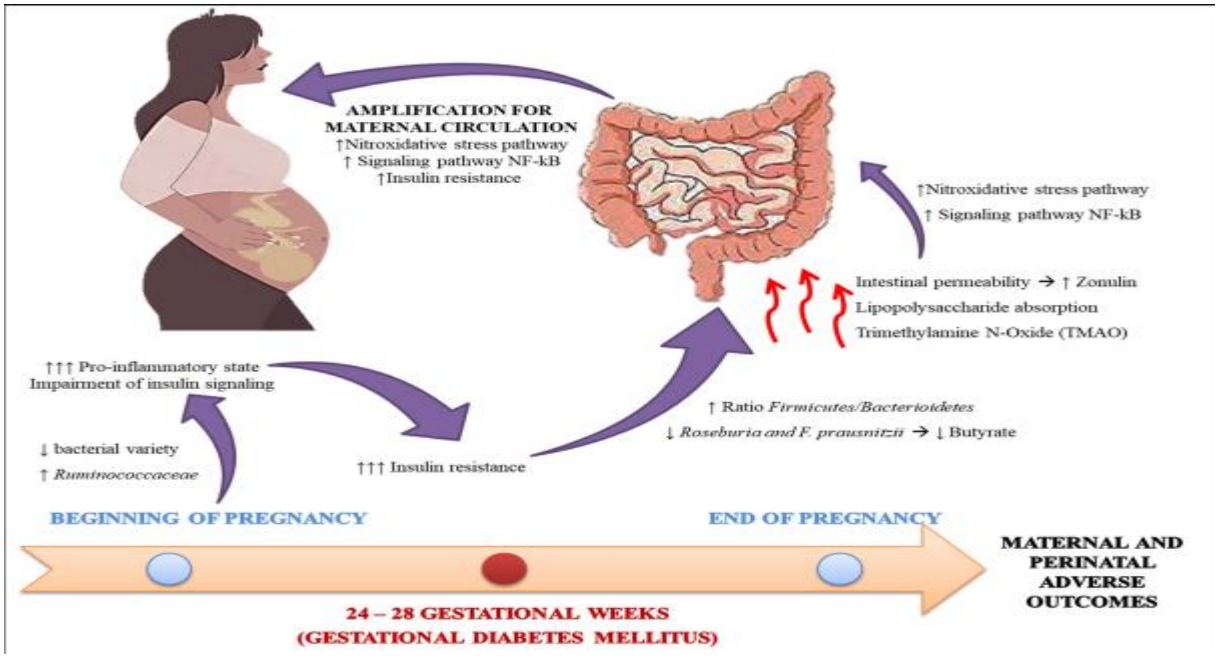
Overweight and obesity are serious problems for public health globally, increasing morbidity and mortality [42, 43]. Apart from GDM, prevalence of obesity and DM are increasing, as well [10]. During last decades overweight and obesity incidence has been importantly increased [44]. Currently,

obesity is epidemic [17], and the most common medical condition in the world [21]. Overweight and obesity prevelance reached 38.0% in women, and 36.9% in men globally, in 2013 (29.8% in women, and 28.8% in men, in 1980). [45]. At the moment, about 40% of adults are considered overweight or obese [46].

Woman obesity is more widespread in high-income countries (HIC), with its prevelance at 34% in the US, and 25% in the United Kingdom (UK) [47]. The percentage of woman overweight or obesity in reproductive age is up to 60% in HIC [6], and in the US approximately the two-thirds of them [48]. Pre-pregnancy overweight or obesity has almost doubled since the last three decades [49]. About a half of women are already overweight or obese in the beginning of pregnancy [50, 51], reaching at an alarming level [52]. This percentage varies across world; 60% in the US, 30% in Europe, and 10% in Asia [53]. It is estimated that women's BMI category of childbearing age is increased every five years, gaining about 700 g annually [42]. Furthermore, 25% of women start pregnancy with preexisting HY or hypertriglyceridaemia in addition to obesity [38, 54]. Still, about 25% of women remain overweight after childbirth [55].

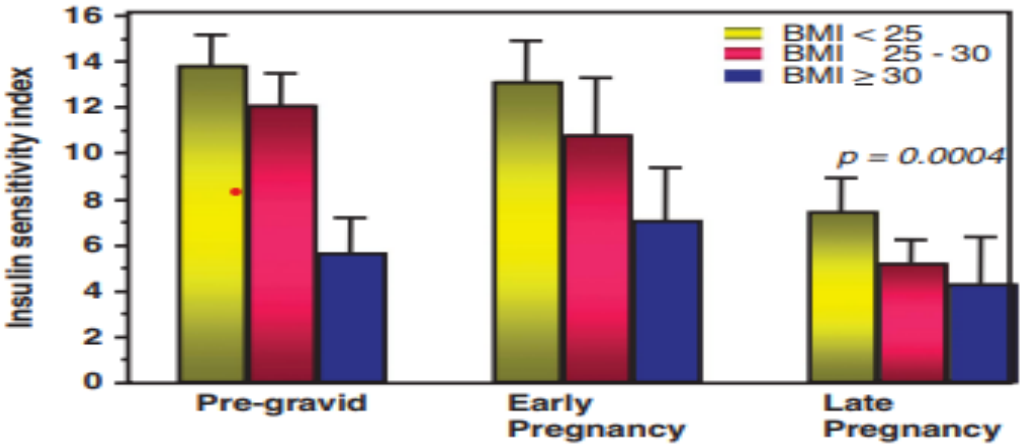
Obesity in pregnancy expands the risk of inflammation [45], and the metabolic risk of insulin resistance and elevated plasma glucose [56]. During pregnancy oxidative stress, as well as antioxidant enzymes activation, are normally increased, facilitating metabolic functions related to the placental and fetal development [57]. Pregnancies with obesity and GDM are also at a moderate inflammation status, in addition to the normal maternal metabolism changes, high oxidative stress, insulin resistance, and dyslipidemia [58]. Elevated inflammatory factors may contribute to insulin resistance and GDM [14] (Fig 3 [59]). Furthermore, oxidative stress is involved in GDM's occurrence [57]. Moreover, an unbalanced antioxidant, and lipid peroxidation status during pregnancy may play a role in GDM's circumstances [57].

Fig 3. Interaction between intestinal microbiota, inflammation, oxidative stress and GDM



High maternal weight and associated risks during pregnancy are well studied, and increasing according to BMI [50]. Pre-pregnancy overweight and obesity are highly and strongly related with GDM [6, 13, 14]. A 10% pre-pregnancy increased BMI is corelated with a 10% increased GDM's, and PE's risk [56]. The risk of GDM may be increased by maternal overweight and obesity at 2.4–3.5 times [7]. Particularly, GDM's risk in overweight women (BMI 25–30) is 6.5-fold increased, and in obese women is higher, approximately at 17%, compared to 1–3% of normal weighted women [60]. Higher obesity of mothers leads to an elevated GDM's risk by two-, four-, and 8-fold in overweight, obese, and extremely obese, respectively [25, 61]. However, obesity may cause adverse maternal and neonatal outcomes, either short-term or long-term, independent to glucose tolerance [6, 62]. Moreover, combined overweight or obesity and GDM magnify the negative effects in pregnancy caused by either disease separately [63]. (Fig 4 [64])

Fig 4. Pregravid, early pregnancy and late pregnancy changes in insulin sensitivity according to weight



Obesity in pregnancy increases maternal, fetus and neonatal morbidity and mortality [45, 65]. In the UK about 50% of women dying during pregnancy or postpartum, are overweight or obese [66]. Except for GDM, it may cause insulin resistance [56], excessive GWG [56], gestational HY and PE [50], neural tube defects [65], congenital anomaly[65, 67], intrauterine fetal death [52], stillbirth [45, 47], fetal growth disorders [63], high weight or macrosomic infant [50], neonatal hypoglycaemia [13], large-for-gestational-age infants [68], shoulder dystocia [23], clotting disorders [60], thromboembolic diseases [52, 65], miscarriage [13], preterm birth (< 37 weeks of gestation (GW)) [67], intrapartum interventions [60], labor induction and caesarean section [50, 65], postoperative complications [63], infections [52], would infections [60], urinary tract infection and endometritis [65], post-partum hemorrhage [52], anaemia [65], stress [65], urinary incontinence [65], depression [65], longer hospitalization [45,49], neonatal intensive care unit admission [45], difficulties with breast feeding [65], and lower ratio of breast feeding influencing infant's growth [45].

Independently of offspring's birth weight [39,50], maternal obesity may lead to infant, childhood, young adults' and future generations obesity [49, 67], development of T2DM [67], metabolic syndrome [49, 65], CVD [45], and cardiovascular events, as well as premature mortality in later life [49]. Regarding long-term adverse consequences for themselves, obese women are at a lifetime increased risk for T2DM, CVD, depression, orthopedic diseases, and specific types of cancer, as reproductive [69].

GWG is the calculated difference of weight after delivery and in the beginning of pregnancy [70]. Extreme GWG is a growing epidemic globally [53]. The percentage of a larger GWG than suggested in the US and in Europe is 20–40% [66]. Excessive GWG is more common in obese women [68], and may affect up to 64% of overweight or obese pregnant women [71]. Adverse effects of GWG in mothers and their offspring may be short-term and long-term [62], similar to maternal obesity [68], irrespective to maternal obesity progression [13], even in normal weight women [67].

Irrespective to pre-pregnancy BMI, excessive GWG is correlated with higher fat accretion, leading to endothelial dysfunction and elevating the risk factor of glucose intolerance, GDM, and PE [56]. Thereby, GWG may itself increases the GDM's risk [60]. Pre-pregnancy BMI and GWG are two of the most important GDM's risk factors [14], and the two many causes of large-for-gestational-age infant [48]. Additionally, they raise the risk of HY, fetal growth malformations, premature birth, cesarean delivery, deep vein thrombosis, and would infections [7]. Combined maternal obesity and GWG can synergistically increase incidence of GDM, large-for-gestational-age newborn, postpartum weight retention, and childhood obesity [53]. Postpartum weight retention risk doubles after excessive GWG [42]. Normal weight mothers gaining excessive weight in pregnancy have been estimated that they retain more than five kilograms (kg) one year after birth at a percentage greater than 70% [42].

GWG can also independently increase adolescence and early adulthood obesity, and further woman obesity, as well [32]. A birthweight above four kg is well documented with childhood obesity [42]. Furthermore, extreme GWG in the first gestational period is strongly corelated with later-life obesity [39]. Every gained kg during pregnancy elevates at 1.08-fold the risk of early childhood obesity [42]. Significantly lower fecundity after years in women having experienced an excessive GWG, has been estimated [69].

PCOS is an endocrine disease involving extend ovaries with numerous cysts and irregular menstruation [69]. It affects up to 18% of women in fertile age, and consists a leading cause of infertility [69]. Overweight or obesity can also coexist with PCOS at high prevalence [71]. Central adiposity elevates the risk of PCOS, and promotes insulin resistance, hyperinsulinemia, and hyperandrogenemia leading to anovulation [69]. PCOS is associated with pre-pregnancy HY, and GDM, PE, preterm birth, and perinatal mortality during pregnancy [71]. Furthermore, obese women with PCOS may have intracellularly deficient of inositol, a second messenger of insulin [72].

Another identified GDM risk factor is advanced maternal age (≥ 35 years) [8, 10]. Older parturient pregnant women are those with maternal age ≥ 35 years old [73]. The number of them is growing every year, increasing scientifically the probability of gestational complications [71].

Studying a cohort in Spain, it was found that consumption of nuts, high-glucose-load cereals, refined rice, bread, paste, juices, sweetened drinks, cookies and pastries during pregnancy may be associated with GDM adopting IADPSG diagnostic criteria [74]; however, those nutritional patterns were not associated with GDM according to Carpenter-Coustan criteria (CC) [74]. Additionally, two MA of observational studies reported that vitamin (vit) D deficiency is pregnancy may be linked with GDM [33, 75]. An RCT investigating the serum levels of adipocytokines among high-risk GDM pregnant women identified that certain adipocytokines (i.e. adiponectin, omentin-1, and interleukin-6 were corelated with GDM's occurrence [76]. Their real-life utilization as GDM predictor biomarker toll in high-risk pregnant women might be challenging [76].

Pregnant women cardiovascular system's changes occur to adapt to the needs of the fetus [77]. They include higher myocardial work, leading to increased volume of blood in the beginning of pregnancy, and increased peripheral resistance in the last weeks of pregnancy [77]. These adaptions may cause some reversible after delivery cardiac remodeling, affecting rarely left ventricular (LV) function [77]. However, the pregnancy may aggravate preexisting unfavorable conditions or may be the period of CVD's initiation, particularly in pre-existing risk factors including obesity, DM, HY, smoking, and advanced age [77]. Women without established risk factors before pregnancy developing gestational disorders including GDM, HY, excessive GWG, and psychological disorders are also at high-risk [77]. Physical inactivity is common during pregnancy and it is another identified CVD risk factor [77].

The IADPSG criteria have been adopted by the World Health Organization (WHO) for GDM diagnosis [35]. These criteria implement lower thresholds for several glucose indices than previously accepted, yielding, therefore, more gestational diabetes occurrences [35]. The diagnostic modalities and positive results include 1-hour (h) 75 gram (g) oral glucose tolerance test (OGTT) ≥ 10.0 mmol/l, or 2-h 75-g OGTT ≥ 8.5 mmol/l, and fasting blood glucose (FBG) ≥ 5.1 mmol/l. The IADPSG criteria recommend a 2-h 75-g OGTT for all women in pregnancy without known diabetes [33]. The International Federation of Gynecology and Obstetrics and the local guidelines of many countries recommend 2-h 75 g OGTT between 24- and 28-GW for all pregnants [2]. Instead, there is lack of consensus on screening and diagnostic tests for GDM across world [33], and several guidelines support an OGTT should there be one or more predicting factors for GDM [33].

Preventing GDM in pregnancy is a priority [17]. Several RCTs attempting to reduce the incidence of GDM, including interventions during pregnancy of diet, PA, a combination of them, or medication, reported contentious results [20]. Despite extensive research, overall efficacy of diet or exercise or both of them on GDM's prevention and treatment is still controversial [46]. Indeed, the preventive action for GDM of lifestyle intervention in pregnancy is unclear [19]. GDM, also, offers a good opportunity for DM prevention, as T2DM is increasing among the young [78], and history of GDM consists T2DM risk factor [19]. However, preventing the progression of GDM to T2DM through lifestyle interventions is doubtable [19, 20]. Three SR and MA exploring the preventive role of lifestyle interventions after pregnancy in women who had GDM did not report differences in T2DM risk [40, 77, 79]. On the opposite, a subsequent SR and MA demonstrated significant findings for T2DM should lifestyle interventions be initiated early in women with GDM [80].

The nutritional demands during pregnancy are increased, and they are often followed by a higher food intake [67]. Traditional cultural beliefs of "eating for two" may lead to an exceed of ordinary calories needs [67]. The lack of awareness of nutritional and blind consumption of supplementation can result in nutritional imbalances and obesity, adding unfavorable gestational risks [55]. Over-nutrition, and under-nutrition during pregnancy increase adverse short-term perinatal, and long-term later-life

circumstances [81]. Negative short-term pregnancy outcomes include GDM, PE, impaired or excessive fetal growth, and preterm birth [81]. On the opposite, an appropriate diet during pregnancy, and a limited GWG improve gestational outcomes [81]. Consequently, pregnant women should be advised to keep the appropriate balance between energy intake and expenditure in order to avoid unwishful GWG [67].

International and national clinical practice guidelines for nutrition in pregnancy recommend rich dehydration; according to two of them the amount should be 2-2.5 liters (l) of water daily [81]. Most guidelines do not quantify the consumption of fat, carboxylate, and protein [81]. However, one of them supports an uptake of > 175 g of fat daily [81]. Moreover, three guidelines recommend additionally 700 – 1400 mg/week of docosahexaenoic acid (DHA) [81]. Three of the guidelines suggest 175 g of carboxylates daily [81]. Other three guidelines recommend 10 – 71 g of protein daily [81]. Fiber consumption is advocated by two guidelines, particularly between 28 and 35 g daily [81]. The suggested amount of micronutrition's intake is notably varied [81]. The daily dose of folic acid ranges from 200 mcg to 800 mcg, of iron from ≤ 30 to 60 mg, of vit B12 from 2.6 mcg to 80 mg per day, of vitD from ≤ 50 mcg to 1.8 mg per day, of calcium from 5 mcg to 1.3 g, and of iodine from 150 mcg to 1.7 mg when its administration is suggested [81].

Diet is a cornerstone in GDM management [4]. However, optimal diet on treating or preventing GDM remains debatable [4, 82]. Exploring the efficacy of diet intervention during pregnancy on preventing GDM in the general population, one systematic review (SR) and MA reported significant results for the Mediterranean diet [54]. On the other hand, a previous SR and MA did not find significant reduce of GDM applying any pattern of nutrition intervention [67]; however, total GWG reduction was significant [67]. In the same line, a subsequent SR and MA demonstrated marginally non-significant results [83]; however, a protective effect on GDM is potentional with diet interventions in complicated pregnancies by obesity [83]. Additionally, preconception weight loss among obese women implementing a very low-energy diet for six to 12 months did not succeed in reducing GDM in an RCT [84].

According to an SR and MA, FBG, and serum insulin were improved in GDM pregnancies with supplementation of omega-3, magnesium, vitD, zinc and probiotics [85]. Furthermore, the promising act of probiotics on GDM metabolic control is strengthened by four MA [86, 87, 88, 89]. Another MA found that probiotics may be efficient on lowering FPG in pregnancy, especially in women without GDM [18]. A recent network MA supported reduced incidence of GDM with probiotic plus exercise intervention [1]. On the opposite, a previous SR and MA demonstrated that probiotics were not effective on preventing GDM; additionally, they increased the risk of PE and, probably, pregnancy hypertensive disorders [90]. Moreover, a network MA evaluating different interventions for GDM's prevention in overweight or obese pregnants reported no effect with probiotics [91].

As previously reported, vitD deficiency may be associated with GDM [33,75]. Regarding vitD supplementation, an SR and MA reported possible significant effect on GDM prevention [22]. Additionally, an SR and MA evaluating the effect of vitD supplementation on glucose and lipid metabolism in gestational diabetes reported important decrease of and LDL-cholesterol, and important improvement of insulin sensitivity; however, it did not reveal an improvement of FPG, hemoglobin A1C (HBA1C), total- and HDL-cholesterol, and triglycerides [92]. Furthermore, a network MA found that vitD was not superior compared to placebo on preventing GDM in obese pregnant women [91].

Supplementation of myo-inositol may significantly decrease the incidence of GDM, in compliance with two SR and MA [2, 22]. Contrariwise, a network MA assessing a combination of them with diet and PA intervention did not found any change on GDM's risk [1]. One RCT investigating the outcome of GDM in high risk obese pregnant women having consumed myo-inositol supplementation in addition to folic acid, found significant reduced GDM's rates compared to the standard consumption of folic acid [72]. For the same population, the consumption of dietary blueberry and soluble fiber increased significantly antioxidant capacity and decreased adipocyte disfunction, and insulin resistance, as reported another RCT [57].

Two SR and MA studying omega-3 supplementation in pregnancy resulted in no significant reduction of metabolic markers (i.e. FPG, insulin resistance, total cholesterol, LDL-cholesterol, triglycerides), and of GDM's outcome, respectively [22, 58]. However, omega-3 increased significantly HDL-cholesterol and reduced C-reactive protein (CRP) [58]. Two MA reported no effect on preventing GDM with fish oil supplementation as well [93, 94].

In accordance with an SR and MA, the pharmacological effect of metformin might be beneficial on preventing GDM in high-risk obese pregnants [22]. Contrarily, two MA did not confirm the success of the medication approach [20, 91]. Controversial is also the act of metformin, concerning GWG in overweight and obese women; an SR and MA showed an effect [43], whereas a recent SR and MA demonstrated no effect on restricting GWG [20].

The interest in the possible beneficial effect of exercise during pregnancy for both mothers and offspring has been grown through the last two decades [32]. Traditional cultural beliefs of reducing PA or stop working to prevent obstetric complications have been abandoned [32]. PA during pregnancy has minimal risk [95]. Previous SR and MA demonstrated safety of exercise during pregnancy, concerning miscarriage, perinatal mortality, congenital anomalies and mother hyperthermia [96, 97].

PA has important advantages for pregnant women without complications [95]. Exercise during pregnancy increases cardiorespiratory fitness, and decreases GWG [98]. Training regularly during pregnancy promotes the expression of the endothelial nitric oxide synthetase (eNOS), nitric oxide (NO), and oxygen metabolism in placenta, probably reducing the likelihood of GDM, and HY [99]. PA can improve quality of life (QUALY) of pregnant women [100]. Two SR and MA reported that both prenatal

[101] and postnatal exercise [102] may decrease postpartum depression. Further benefits include reduced preterm labor, fitness, less back pain, better sleep, and reduced anxiety [95]. Offspring complications of the autonomous nervous system development, growth, and weight may be avoided [100].

PA is recommended in pregnancy guidelines [95]. The WHO recommends continuous workout in pregnancy including aerobic exercise (i.e. walking, swimming), and anaerobic exercise (i.e. strength training) [100]. The American College of Obstetricians and Gynecologists (ACOG) emphasizes on the importance of restricting excessive GWG [103]. According to the ACOG 2020 guidelines, healthy pregnant women should accumulate moderate to vigorous exercise, preferably aerobic or combined aerobic and anaerobic, at least 30 minute (min) daily, 3–4 times weekly [43]. In compliance with the U.S. Department of Health and Human Services PA 2008 guidelines, healthy American pregnants should exercise moderately for 150 min weekly spread throughout the week, [48]. The PA recommendation for during overweight and obese pregnancies are not clear [43]. PA benefits in this population remain uncertain [98]. However, there is an expert consensus that obese pregnant women could have long-term benefits for their children through PA before and/or during pregnancy [49].

Seven SR and MA evaluating RCTs implementing exercise intervention to prevent GDM in general population during pregnancy revealed significant results [9, 32, 35, 100, 104, 105, 106]. Two of them showed an effect on preventing hypertensive disorders [100, 104], especially with aerobic exercise [104]. However, another MA did not demonstrate decrease of PE [105]. Furthermore, a significant reduction of GWG was reported in two of them [35, 100]. Additionally, an SR and MA investigating the effect of exercise intervention before pregnancy and in early pregnancy found a protective effect in decreasing GDM [16]. Conversely to this trend, a previous SR and MA found no significant difference for the risk of GDM with exercise intervention [107].

The results of SR and MA assessing the efficacy of PA on preventing GDM in overweight and obese high-risk pregnant women subject to controversary. Three SR and MA advocated the preventive role of PA for GDM [43, 44, 45], especially of aerobic exercise [43]. Additionally, one of them showed significant limitation of GWG [45]. In opposition, three SR and MA reported no effect of exercise for GDM [25, 55, 56]. In spite of non-significant findings for GDM, two of them showed significant lower GWG [55, 56]. In addition, one of them found significant gestational HY decrease [55], whereas the other one reported no difference for the outcome of HY [56]. Neither exercise intervention nor pharmacological interventions of probiotics, vitD, and metformin were eligible to reduce GDM, according to a network MA [91]; however, PA and metformin reduced GWG [91]. Two MA evaluating exercise during pregnancy in high-risk pregnant women, irrespective to obesity, revealed significant results for GDM's prevention [17, 41]; one of them with intervention's initiation before the 20GW, and

if delivered in the healthcare facility [17], and the subsequent independent to the starting time period or the way of delivery [41].

The research interest about appropriate interventions able to limit excessive GWG is increasing and consists priority for many healthcare organizations [108]. According to the Institute of Medicine (IOM) 2009 guidelines, diet and PA during pregnancy for weight balance are very important [62]. The IOM recommended ideal GWG is based on pregestational BMI [62]. Particularly, during pregnancy, women with pregestational BMI ≥ 30 should gain from 5.0 to 9.0 kg [20, 39, 67]; with pregestational BMI 25.0-29.9 from 7 to 11.5 kg [67]; with pregestational BMI 18.5-24.9 from 11.5 to 16.0 kg [20, 67]; and with pregestational BMI ≤ 18.5 from 12.5 to 18 kg [20, 109]. Meanwhile, pregnancy for most women is associated with greater GWG than recommended [32]. Moreover, overweight and obese pregnants are twice possible to overlook recommendations compared to normal weight pregnant women [109]. Further investigation is necessary to determine effective measures for improvement of GWG in high-risk population of overweight and obesity [24].

The Academy of Nutrition and Dietetics demonstrated its position for woman obesity in reproductive age including behavioral counseling of diet and PA in the preconception period, during pregnancy, and postpartum for at least 12 to 18 months [69]. Moreover, lifestyle interventions to moderate GWG during pregnancy and reduce weight retention postpartum are suggested [69].

An SR and MA synthesizing any type of lifestyle intervention designed to limit GWG reported a significant reduction of GDM's incidence with either diet or exercise intervention alone, and no benefit with the mixed approach of them [110]. However, a previous MA assessing the associations between excessive GWG and adverse pregnancy events after lifestyle interventions did not found differences for the GDM's outcome [111].

Regarding studies evaluating lifestyle interventions attempting to prevent GDM and optimize GWG, among other outcomes, there have been heterogenous findings. Most of them support a preventive effect for GWG; however, the results for GDM are conflicting. A previous MA exploring the effect of diet and/or PA in pregnancy found that only dietary's intervention was beneficial in reducing significantly GDM [66]. Additionally, any intervention minimized GWG [66]. Another SR and MA for the US Preventing Service Task Force (USPSTF) evaluating active lifestyle interventions during pregnancy administrating the IOM's guidelines supported that women were less likely to develop GDM [70]. An achievement of a healthy GWG was also demonstrated [70]. In accordance with a recent SR and MA, any intervention of diet or PA or both of them overall succeeded significantly less GDM and GWG, as well [21]; however, mixed interventions were only associated with decreased GWG [21].

On the other hand, a previous MA including RCTs of dietary and lifestyle interventions to reduce GWG advocated non-significant difference in GDM's occurrence, although the limitation of GWG was significant [42]. In total compliance between them, three SR and MA assessing lifestyle

interventions during pregnancy including diet and PA in overweight and obese women reported no prevention for GDM, despite the significant differences in lowering excessive GWG [20, 23, 24]. In the same line, a multicenter RCT conducted in 9 European countries revealed no effect for either diet, or PA, or both of them on GDM's occurrence, whereas GWG was lower significantly in the group of complex intervention [112].

The efficacy of lifestyle interventions in normalizing GWG is strengthened by another SR and MA supporting benefit of either diet, or exercise, or both of them [113]. However, the International Weight Management in Pregnancy (i-WIP) Collaborative Group performing a MA found no significant reduction of maternal GWG neither with diet or PA interventions separately, nor with combined interventions, or overall effect of lifestyle interventions [108]; even so, an effect of exercise interventions, and an overall effect of lifestyle interventions was revealed on reducing GDM [108].

Regarding studies aiming at primary preventing GDM, there are also varied supports. A MA reported that either diet or exercise interventions during pregnancy could prevent GDM [19]. Particularly, a subsequent MA revealed beneficial effect for exercises-only interventions arm [114]. Additionally, according to a recent network MA, GDM could be prevented with the implementation of exercise plus probiotic intervention, whereas dietary only, or dietary plus PA interventions did not alter the GMS' incidence [1]. On the opposite, a previous MA reported no differences for GDM's outcome with applying both dietary based, and dietary plus lifestyle interventions [115]. In the same line, a following SR and MA did not demonstrate benefit with diet or exercise or a combination of them on preventing GDM [22]. Investigating the effectiveness of mixed diet and PA interventions for reducing gestational diabetes, a MA revealed a preventive role of the mixed diet and PA approach [116]. However, two previous SR and MA identifying also mixed nutrition and PA interventions did not recognize beneficial action on GDM's prevention [12, 117].

Main Part

Aim

This study aims at systematically appraising RCTs evaluating the effectiveness of diet interventions, or PA intervention, or both diet plus PA interventions in pregnancy on preventing GDM. Eligible trials included high-risk pregnant women at any risk factor for GDM, assessing any type of lifestyle intervention, compared to standard prenatal care. The total effect of each intervention's category was synthesizing through MA.

Materials and methods

This systematic review was performed according to PRISMA extension for complex interventions guidelines [118].

Search Strategy

PubMed, Cochrane Library Central Register of Controlled Trials (CENTRAL), and Scopus were searched (from inception to August 2022). The search strategy for Pubmed included keywords related to diet, nutrition, exercise, PA, and GDM combined with the Cochrane Collaboration search algorithm for RCTs. CENTRAL and Scopus were searched systematically using the same keywords. Based on title and/or abstract, the full text was retrieved for unclear items or potentially eligible. (Supplementary material; Table S1)

Eligibility Criteria

PICO (population, intervention, comparator, and outcome) approach was used for selecting eligible trials. RCTs in English language, including high-risk pregnant women for GDM were accepted. Factors increasing diabetes risk during pregnancy have been determined in general part. RCTs appraising any type of active lifestyle intervention of diet alone, or exercise alone, or both of them during pregnancy compared to standard antenatal care were included. Trials involving GDM's outcome diagnosed by any recommended modality were considered as eligible.

If an RCT was multiply publicated with demonstrated results in different follow-up periods, the publication with the largest sample size was accepted. Protocol of RCTs, pilot RCTs, and abstracts from conference proceedings were excluded.

Data extraction

Extracted items were first author's name, publication's year, country of performance, type of RCT, number of centers for multicentered trials, study duration, drop-out rate, sample size, women's mean age, women with low education level, GDM risk factors, the type of intervention and the care for provided in the control group, as well as any potential reported side-effects for both experimental, and comparator group. The Consensus on Exercise Reporting Template (CERT) tool for complex interventions was used to evaluate exercise programs in RCTs applying only PA in the intervention arm [119]. Finally, the number of GDM diagnosed by any method was captured as outcome, separately in any group.

Quality assessment of the studies and rating of overall evidence

Evaluating the quality of eligible RCTs, the risk of bias tool proposed by the Cochrane Collaboration was used [120]. In addition, overall evidence was rated through the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework (GRADEpro, Version 3.6.1. McMaster University, 2011) [121].

Statistical Analysis

The main analyses included all available data. The significance level for all analyses, except for Cochran's Q statistic, was set at P-value < 0.05. SPSS 22.0 (SPSS, Inc., Chicago, Illinois, USA), Stata Statistical Software 10.1 (Stata, College Station, TX, USA), and Review Manager 5.4.1 (Cochrane Collaboration, UK) were used for analyses.

Both fixed effects (FE) and RE MA were performed to combine the GDM's events. Heterogeneity between studies was assessed by Cochran's Q statistic (statistically significant level for P-value < 0.10) [122]. Heterogeneity was measured with the I^2 index (< 25%, low; 25–49%, moderate; 50–74%, large; > 75%, very large) [122]. In case of large heterogeneity, the results were reported synthesized by RE (odds ratio (OR) with 95% CI) [123].

Separate analyses were performed for studies including women participants with low education level at a percentage set more than 10%, and until 10%; studies including increased BMI as a GDM risk factor, and studies not considering overweight or obesity; studies with intervention duration more than 20 weeks, and studies with intervention duration until 20 weeks; trials including Mediterranean diet as a component of dietary interventions, and trials not considering Mediterranean diet; trials including a motivation component in the intervention, and trials not including motivation [124]. The effect of the RCTs with the largest sample size was also estimated by its exclusion in sensitivity analyses [124]. Additionally, sensitivity analyses were also performed for studies with low attrition bias. Meta-regression analyses on GDM OR were conducted with the effect of baseline risk, and study duration as covariates [124, 125]. Publication bias was assessed via the visual analysis of funnel plot [126]. The statistical test of Egger was also performed for publication bias assessment [127].

Results

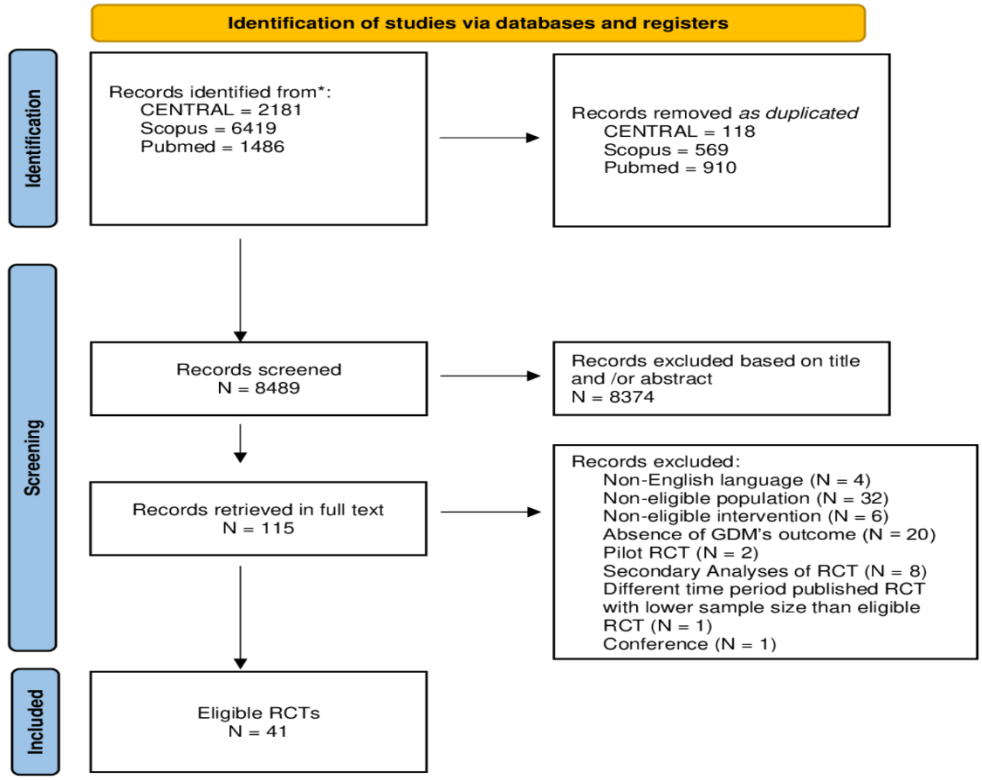
Eligible studies

The search yielded 10086 items (2181 in CENTRAL, 6419 in Scopus, and 1486 in PubMed). 1519 items were excluded as duplicated. Out of the 8489 remaining items, 8347 were excluded as non-relevant based on the title, or abstract. Thus, 115 papers were retrieved in full text. Out of the 115 articles, 74 were excluded; one study was published in non-English language; 32 studies did not include

an eligible population; six studies included a non-eligible intervention; 20 trials did not report the onset of GDM as an outcome; two papers reported a pilot RCT; 8 papers included secondary analyses of RCTs; one RCT with lower sample size than eligible RCT was published in a different time period; and one paper was retrieved from conference. Finally, this study included 41 eligible published RCTs. Particularly, 10 of them reported diet only intervention, 13 exercise only intervention, and 18 diet plus exercise intervention. (Fig 5)

Fig 5. Flow chart of procedures of selecting studies

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Characteristics of eligible studies

10 eligible RCTs were identified with intervention of diet only. They were published between 2011 and 2022. Four of them were conducted in Europe [3, 38, 82, 128] (one in Spain; one in UK; one in Finland; one in Ireland), other three in Oceania [51, 60, 68] (two in Australia; one in New Zealand),

two in China [14, 129], and one study in US [4]. Two trials were multi-centered [38, 129] (two and five recruited centers, respectively), and the study design was parallel, except for one crossover RCT [68]. Studies' duration ranged from 10 to 48 months, whereas the duration was not reported in two studies [60, 82]. All RCTs had a drop-out ratio below 30%. (Table 1a)

Table 1a. Characteristics of eligible trials with dietary intervention

Name of first author, year of publication	**Country**	**Number of participated centers**	**Study design**	**Study duration, mo**	**Drop-out rate n (%)**
Korpi-Hyövälti, 2011	Finland	1	Parallel	ND	6 (10.0)
Quinlivan, 2011	Australia	1	Parallel	ND	8 (6.1)
Walsh, 2012	Ireland	1	Parallel	48	41 (5.1)
McCarthy, 2016	Australia	1	Parallel	20	11 (2.9)
Yi Zhang,2019	China	2	Parallel	40	31 (10.2)
Al Wattar, 2019	UK	5	Parallel	17	67 (5.3)
Okesene-Gafa, 2019	New Zealand	1	2 x 2Factorial	26	6 (2.6)
Melero, 2020	Spain	1	Parallel	12	25 (8.8)
Basu, 2021	USA	1	Parallel	23	11 (24.4)
Dong-Yao Zhang, 2022	China	1	Parallel	10	6 (5.8)

ND, no data

13 RCTs with exercise intervention alone, were considered as eligible. They were published between 2011 and 2022. Six trials were conducted in Europe [31, 61, 77, 103, 109, 130] (three in Spain, one in Ireland, one in Norway, and another one in the Netherlands), four in America [65, 98 131, 132] (two in US, one in Brazil, one in Canada), two in Oceania [34, 49] (one in Australia, and the other in New Zealand), and one in China [63]. All of them had a parallel design and two of them were multicentered [103, 130] (three, and five centres, respectively). The duration of studies varied between 19 and 60 months. Their drop-out ratio was less than 20%, except for two trials [77, 131] with an estimated drop-out ratio at 31.9% [131], and 41.1% [77]. (Table 1b)

Table 1b. Characteristics of eligible trials with exercise intervention

Name of first author, year of publication	**Country**	**Number of participated centers**	**Study duration, mo**	**Drop-out rate n (%)**
Do Nascimento, 2011	Brazil	1	19	2 (2.4)

Oostdam, 2012	Netherlands	5	48	22 (18.2)
Price, 2012	USA	1	45	29 (31.9)
Barakat, 2013	Spain	1	40	82 (16)
Ruiz, 2013	Spain	3	40	138 (14.3)
Nobles, 2015	USA	1	60	39 (13.4)
Bisson, 2015	Canada	1	25	5 (10.0)
Seneviratne, 2015	New Zealand	1	19	1 (1.3)
Perales, 2016	Spain	1	49	99 (41.1)
Krohn Garnæs, 2016	Norway	1	22	17 (18.7)
Guelfi, 2016	Australia	1	37	3 (1.7)
Wang, 2017	China	1	20	35 (11.7)
Daly, 2017	Ireland	1	41	2 (2.3)

18 eligible trials implemented a complex intervention of diet and exercise. Their publication year is from 2011 to 2022. Seven were performed in Europe [5, 6, 15, 39, 47, 62, 133] (two in Finland; two in Italy; one in Ireland; one in Denmark; one in UK), seven in Asia [7, 8, 10, 11, 28, 71, 73] (six in China; one in UAE), two Australia [13, 50], and two in America [53, 134] (one in US; one in Canada). Seven of them recruited participants on a multi-centered way [5, 6, 13, 39, 47, 50, 53] (number of centers from 2 to 14), and 11 of them were single-centered [7, 8, 10, 11, 15, 28, 62, 71, 73, 133, 134]. Their design was parallel, apart from a cluster RCT [5]. The duration of them ranges between five and 71 months. All trials had a drop-out ratio less than 30%, apart from one trial with an estimated drop-out ratio at 31.4% [133]; one trial did not provide data [73].

Table 1c. Characteristics of eligible trials with dietary plus exercise intervention

Name of first author, year of publication	**Country**	**Number of participated centers**	**Study design**	**Study duration, mo**	**Drop-out rate n (%)**
Luoto, 2011	Finland	14	Cluster	14	43 (9.7)
Vinter, 2011	Denmark	2	Parallel	36	56 (15.5)
Harrison, 2013	Australia	3	Parallel	ND	25 (10.1)
Petrella, 2013	Italy	1	Parallel	6	0 (0)
Dodd, 2014	Australia	3	Parallel	30	70 (3.2)
Hui, 2014	Canada	1	Parallel	28	0 (0)
Poston, 2015	UK	8	Parallel	62	275 (17.7)
Koivusalo, 2015	Finland	4	Parallel	71	24 (8.2)

Bruno, 2016	Italy	1	Parallel	16	60 (31.4)
Kennelly, 2018	Ireland	1	Parallel	35	67 (11.8)
Chan, 2018	China	1	Parallel	24	63 (27.5)
Ferrara, 2020	USA	5	Parallel	42	4 (1)
Lin, 2020	China	1	Parallel	5	23 (7.6)
Li, 2021	China	1	Parallel	10	ND
Liu, 2021	China	1	Parallel	27	58 (15.1)
Ding, 2021	China	1	Parallel	10	15 (6.5)
Deng, 2022	China	1	Parallel	11	10 (10.6)
Sadiya, 2022	UAE	1	Parallel	22	7 (11.1)

ND, no data

A total of 3690 (1841 in intervention group, and 1849 in control group) high risk pregnant women for GDM participated in the eligible trials of only dietary intervention arm. Their mean age varied from 31.7 to 21.7 years for women in the intervention group, and from 36.9 to 22.0 years for women in the control group. One study reported the mean age without standard deviation (SD) [60], and another one did not report data regarding age [82]. Three trials provided data about education level [3, 51, 68]. The percentage of women with low education level ranges between 10.5% and 30.2% in experimental group, and between 7.8% and 29.8% in comparator group. Overweight or obesity is a GDM risk factor identified in 8 RCTs [4, 14, 38, 51, 60, 68, 82, 129]. Family history of DM or history of GDM are included in two RCTs [4, 82]. Two RCTs involve also the history of previous macrosomia [82, 128]. Advanced maternal age is mentioned in one RCT [82]. Hispanic origin is examined in one trial [3]. Chronic HY or abnormal lipid metabolism are appraised in another study [38]. (Table 2a)

Table 2a. Characteristics of participants in studies with dietary intervention

Name of first author, year of publication	**Sample size (intervention / control)**	**Mean age (SD), yr intervention / control**	**Low education level, n (%) intervention / control**	**Risk factors for GDM**
Korpi-Hyövälti, 2011	60 (30 / 30)	ND	ND	At least one of: (1) advanced maternal age (> 40 years), (2) overweight or obesity (BMI > 25), (3) family history of DM, (4) history of GDM or history of macrosomia

Quinlivan, 2011	132 (67 / 65)	28.3 / 29.5	ND	Overweight (BMI 25 – 29.9) or obesity (BMI > 29.9)
Walsh, 2012	800 (394 / 406)	32.0 (4.2) / 32.0 (4.2)	ND	History of macrosomia
McCarthy, 2016	382 (190 / 192)	31.9 (4.6) / 31.8 (4.6)	20 (10.5) / 15 (7.8)	Overweight or obesity (BMI ≥ 25)
Yi Zhang,2019	400 (200 / 200)	28.1 (3.6) / 28.0 (3.7)	ND	Overweight or obesity (BMI ≥ 24)
Al Wattar, 2019	1252 (627 / 625)	31.4 (5.2) / 30.9 (5.2)	ND	At least one of: (1) obesity (BMI ≥ 30), (2) raised serum triglycerides (≥ 1.7 mmol/L), (3) chronic HY (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg)
Okesene-Gafa, 2019	230 (116 / 114)	29.8 (5.7) / 27.8 (5.5)	35 (30.2) / 34 (29.8)	Obesity (BMI ≥ 30)
Melero, 2020	285 (143 / 142)	31.7 (5.4) / 31.3 (5.6)	18 (12.6) / 28 (19.7)	Hispanic origin
Basu, 2021	45 (22 / 23)	27.0 (5.3) / 27.0 (5.0)	ND	Obesity (BMI ≥ 30) AND at least one of: (1) family history of DM, (2) history of GDM
Dong-Yao Zhang, 2022	104 (52 / 52)	31.1 (4.2) / 30.0 (4.0)	ND	Overweight or obesity (BMI ≥ 24)

ND, no data; BMI, body mass index, DM; diabetes mellitus; GDM, gestational diabetes mellitus; HY, hypertension

3073 (1532 in intervention group, and 1541 in control group) high-risk pregnant women for GDM participated in studies implementing only exercise. The mean age ranges from 22.9 to 38 years in the intervention group, and from 20.3 to 37.7 years in the control group. One study reported only the range of age of participated women (18 – 40 years) [132]. Women's percentage of low education level varies between 2.3% and 40% in intervention group, and between 7% and 36% in control group. Four trials did not mention to women's [34, 49, 61, 131], and one trial reported percentages of women who did not receive university education [103]. Overweight or obesity are reported as risk factors for GDM in 8 RCTs [49, 61, 63, 65, 98, 109, 130, 132], a sedentary way of life in four RCTs [31, 77, 103, 131], family history of diabetes and previous gestational diabetes in two RCTs [130, 140], and history of macrosomia in one RCT [130]. (Table 2b)

Table 2b. Characteristics of participants in studies with exercise intervention

Name of first author, year of publication	**Sample size (intervention / control)**	**Mean age (SD), yr intervention / control**	**Low education level, n (%) intervention / control**	**Risk factors for GDM**
Do Nascimento, 2011	82 (40 / 42)	29.7 (6.8) / 30.9 (5.9)	6 (15) / 10 (23.8)	Overweigh (BMI 26.0 – 29.9) or obesity (BMI ≥ 30.0)
Oostdam, 2012	121 (62 / 59)	30.1 (4.5) / 30.8 (5.2)	16 (34) / 17 (34.7)	Overweigh (BMI ≥ 25) or obesity (BMI ≥ 30.0) AND at least one of: (1) family history of DM, (2) history of GDM, (3) history of macrosomia

Price, 2012	91 (43 / 48)	30.5 (5) / 27.6 (7.3)	ND	Sedentary lifestyle; no aerobic exercise more than once per week for at least the past six months
Barakat, 2013	510 (255 / 255)	31 (3) / 31 (4)	54 (24.7) / 75 (34.4)	Sedentary lifestyle; not exercising more than 20 min on more than 3 days/week
Ruiz, 2013	962 (481 / 481)	31.6 (6.4) / 31.9 (4)	211 (43.9) / 183 (38.3) *	Sedentary lifestyle; not exercising more than 20 min on more than three days/week
Nobles, 2015	290 (143 / 147)	Range 18 – 40	26 (22.2) / 31 (27.4)	One of: overweigh or obesity (BMI ≥ 25) AND family history of DM, (2) history of GDM
Bisson, 2015	50 (25 / 25)	30.5 (3.7) / 31.0 (4.0)	10 (40) / 9 (36)	Obesity (BMI ≥ 30.0)
Seneviratne, 2015	75 (38 / 37)	ND	ND	Overweigh or obesity (BMI ≥ 25)
Perales, 2016	241 (120 / 121)	31 (4) / 31 (4)	29 (24) / 30 (25)	Sedentary lifestyle; not exercising regularly more than 30 min on three days/week
Krohn Garnæs, 2016	91 (46 / 45)	31.3 (3.8) / 31.4 (4.7)	1 (2.3) / 3 (7.0)	Overweigh or obesity (BMI ≥ 28.0)
Guelfi, 2016	172 (85 / 87)	33.6 (4.1) / 33.8 (3.9)	ND	History of GDM
Wang, 2017	300 (150 / 150)	32.1 (4.6) / 32.5 (4.9)	31 (20.7) / 40 (26.7)	Overweigh or obesity (BMI ≥ 24.0)
Daly, 2017	88 (44 / 44)	30.0 (5.1) / 29.4 (4.8)	ND	Obesity (BMI ≥ 30.0)

ND, no data; BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; min, minutes; * no university education

8532 (4317 in intervention group, and 4215 in control group) high-risk pregnant women for GDM participated in RCTs applying both diet and exercise intervention. The mean age of them varies between 23.9 and 41 years in experimental group, and between 20 and 40.5 years in comparator group. One trial reported mean age of 29 years with ranges for both intervention and control arms [39]. The percentage of low education level of women ranges from 2.7% to 40.6%, and from 2.2% to 47.7%, for intervention and control group, respectively.8 studies do not report data regarding women's education level [7, 8, 28, 47, 50, 71, 73, 134]. The most frequently appeared GDM's risk factor is overweight or obesity being reported in any of 18 eligible trials, except for one trial [73]. Next, history of GDM is included in six trials [5, 6, 8, 10, 11, 28], as well as family history of diabetes is evaluated in five trials [5, 8, 10, 11, 28]. Furthermore, advanced maternal age is revealed in five trials [5, 8, 10, 28, 73]. Moreover, history of macrosomia is located in four trials [5, 8, 10, 11], and history of PCOS is assessed in three studies [11, 28, 71]. Finally, high-risk ethnicities are identified in two trials [11, 13], and history of abnormal lipid metabolism, and elevated FPG in early pregnancy are investigated in one study [8]. (Table 2c)

Table 2c. Characteristics of participants in studies with dietary plus exercise intervention

Name of first author, year of publication	Sample size (intervention / control)	Mean age (SD), yr intervention / control	Low education level, n (%) intervention / control	Risk factors for GDM
Luoto, 2011	442 (246 / 196)	29.5 (4.8) / 30.0 (4.7)	73 (33.8) / 59 (33.7)	At least one of: (1) advanced maternal age (≥ 40 years), (2) overweight or obesity (BMI ≥ 25), (3) family history of DM, (4) history of GDM or history of macrosomia
Vinter, 2011	360 (180 / 180)	29 (Range 27 – 32) / 29 (Range 26 – 31)	39 (26.0) / 54 (35.0)	Obesity (BMI 30.0 – 45)
Harrison, 2013	228 (121 / 107)	32.4 (4.6) / 31.7 (4.5)	20 (16) / 12 (11)	Overweight (BMI ≥ 25 or ≥ 23 if high-risk ethnicity; Polynesian, Asian, African) or obesity (BMI ≥ 30.0)
Petrella, 2013	61 (33 / 28)	31.5 (4.2) / 32.4 (5.9)	11 (33.3) / 13 (43.3)	Overweight or obesity (BMI ≥ 25)
Dodd, 2014	2202 (1105 / 1097)	29.3 (5.4) / 29.6 (5.6)	ND	Overweight or obesity (BMI ≥ 25)
Hui, 2014	113 (57 / 56)	31.0 (4.0) / 32.0 (5.0)	ND	Overweight or obesity (BMI ≥ 25)
Poston, 2015	1555 (783 / 772)	30.5 (5.5) / 30.4 (5.6)	ND	Obesity (BMI ≥ 30.0)
Koivusalo, 2015	293 (155 / 138)	32.3 (4.9) / 32.6 (4.5)	4 (3) / 3 (2)	At least one of: (1) obesity (BMI ≥ 30.0), (2) history of GDM
Bruno, 2016	191 (96 / 95)	31.5 (5.0) / 30.8 (5.5)	39 (40.6) / 35 (35.9)	Overweight or obesity (BMI ≥ 25)
Kennelly, 2018	565 (278 / 287)	32.8 (4.6) / 32.1 (4.2)	7 (2.7) / 6 (2.2)	Overweight or obesity (BMI 25.0 – 39.9)
Chan, 2018	229 (118 / 111)	33.2 (4.4) / 33.1 (4.1)	31 (38.8) / 41 (47.7)	At least one of: (1) advanced maternal age (≥ 35 years), (2) overweight or obesity (BMI ≥ 25), (3) family history of DM, (4) history of GDM or history of macrosomia
Ferrara, 2020	398 (200 / 198)	32.4 (4.1) / 32.6 (4.3)	10 (5) / 12 (6)	Overweight or obesity (BMI 25.0 – 40.0)
Lin, 2020	304 (152 / 152)	31.4 (4.9) / 31.8 (5.1)	ND	At least one of: (1) advanced maternal age (≥ 35 years), (2) overweight or obesity (BMI ≥ 25), (3) family history of DM, (4) history of GDM (5) history of PCOS
Li, 2021	820 (410 / 410)	37.5 (3.5) / 38 (2.5)	ND	Older pregnant women
Liu, 2021	384 (192 / 192)	31.8 (3.4) / 32.3 (3.8)	ND	Overweigh or obesity (BMI ≥ 25) AND history of PCOS
Ding, 2021	230 (114 / 116)	30.6 (2.8) / 30.1 (2.7)	ND	Overweigh or obesity (BMI ≥ 24)
Deng, 2022	94 (47 / 47)	29.6 (3.9) / 29.6 (3.4)	ND	At least one of: (1) advanced maternal age (≥ 35 years), (2) overweight or obesity, (3) family history of DM, (4) history of GDM, (5) history of macrosomia, (6) history of PCOS, (7) history of abnormal lipid metabolism, (8) elevated FPG in early pregnancy (FPG ≥ 5.1 mmol/L)

Sadiya, 2022	63 (30 / 33)	32.8 (4.1) / 30.8 (5.2)	3 (10) / 6 (18)	High-risk ethnic group (Middle Eastern, Southern Asian) AND at least two of: (1) obesity (BMI ≥ 30), (2) family history of DM, (3) history of GDM, (4) history of macrosomia, (5) history of PCOS

ND, no data; BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome; FPG, fasting plasma glucose

Dietitians were the providers of dietary intervention in five eligible RCTs [3, 14, 82, 128, 129], and especially one trial reported clinical nutritionist as provider [82]. In addition, in three RCTs dietitians were assisted from nurse practitioner [4], trained researchers [38], and health workers [68]. Midwifes [51], and a food technologist [60] provided the nutrition intervention in the rest two RCTs [51, 60]. One trial reported an exact time period of intervention of 10 weeks [38]. The mean intervention's duration in ascending order of weeks in the rest trials is: 17.7 (15.4 – 20) [14], 19 (16 – 22) [128], 25.5 (22.4 – 28) [68], 28 [82], and 30 (28 – 32) [3]. Three RCTs reported mean intervention's duration in weeks > 14 [4], > 16 [51], and ≥ 19 [129]. One trial provided no data on duration of intervention [60]. A vary of nutritional interventions with delivery, components, motivation, assessment, and side effects / adverse events are described in detail. (Table 3a)

Table 3a. Eligible studies with dietary intervention

Name of first author, year of publication	**Provider**	**Duration of intervention**	**Description of dietary intervention**	**Side effects /adverse events (intervention /control)**
Korpi-Hyövälti, 2011	Clinical nutritionist	From GW 8–12 until 36–40	Delivery: Individual dietary advice, four times in the first and second trimesters, and two times in the third trimester. Components: Food record before the first appointment at GW 8–12, and basis for dietary advice during the first session according to baseline four-day (four consecutive days, one weekend day). Repetition of food record procedure before fifth and sixth appointment at GW 26–28, and 36–40, respectively. Nutrition rich in fruits, vegetables, and berries, consumption of fat-free and low-fat dairy products, low-fat meat, soft margarines, vegetable oils, and whole-grain products. Daily energy intake of 126 kJ/kg and 105 kJ/kg for normal-weight, and for overweight women, respectively, divided into carbohydrate 50–55 E%, fat 30 E%, saturated fat < 10 E%, protein 15–20 E%, and dietary fibre at least 15 g / 4184 kJ (1000 kcal). Motivation: Informative. Assessment: Questionnaires, nutrient calculation software, food records analyses.	ND
Quinlivan, 2011	Food technologist	ND	Delivery: Dietary intervention at antenatal visits with weighing, and continuous care provider. Components: Increasing consumption of fresh vegetables, fresh fruit, home-cooked main meal, and water; decreasing consumption of carbonated drinks, sports drinks, commercial fruit juices, and fresh fast foods. Motivation: Psychological assessment and intervention if necessary.	Preterm delivery (1 /1), acute polyhydramnios (0 / 1)

			Assessment: ND	
Walsh, 2012	Dietitian	From GW 15 ± 3 until 34	Delivery: Dietary sessions in a group of two to six women, lasting 2-h. Components: Firstly, general advices on guidelines of healthy eating during pregnancy. Recommended low GI eucaloric diet, and not reducing total caloric intake. Focus of education sessions on the GI. Encouragement of choosing many low GI foods instead high GI. Motivation: Answers at any dietary queries of participants, written information regarding low GI nutrition. Assessment: Food diaries for estimation of the GI, questionnaires for assessment of adherence to the low GI diet.	Stillbirths (1 / 0)
McCarthy, 2016	Midwifes	From GW < 20 until 36	Delivery: Individual sessions provided by research midwife of approximately 30 min at subsequent antenatal appointments. Components: Nutrition advices, encouragement of recording weight, and discussing weight gain with doctors and/or midwives. Motivation: N/a Assessment: Self-weight record in light indoor clothing, questionnaires	Early pregnancy loss (2 / 1)
Yi Zhang,2019	Dietitians	From GW ≤ 16 until 34–36	Delivery: Individualized dietary consultation by separate dietitians on a different day. Components: Individualized diet planning for achievement of a low GI goal with consideration of individual food preference. Participants nutrition assessment through 24-h food recall intake of the nearest working day about daily consumption of total provided energy, protein, fat, and carbohydrate intake based on. Also, diet GI and GL calculations in the diet assessment. Equipment of a mobile phone app DietGI with the function of calculating GI and GL for every selected food. Motivation: Counseling about substituting high GI with low GI foods, cooking techniques, and combining foods in meals. Assessment: Worksheet for diet records, and customized excel worksheet for calculation of GI and GL.	Miscarriage (5 / 4)
Al Wattar, 2019	Dietitian, trained researchers	From GW 18 until 28	Delivery: Three sessions; a personalised session at GW 18, and two sessions in a group at GW 20 and 28, using presentations. In addition, permission of presence women's spouses. Components: Firstly, 24-h food recall consumption identifying any possible participants' changes needed to follow a Mediterranean pattern of diet. A book providing cooking advice on Mediterranean diet and community teams. Diet key components of increased consumption of fruit, vegetables, non-refined grains, legumes, nuts, and EVOO; moderate to high fish intake; low to moderate poultry and dairy products consumption; low red and processed meat intake; and avoidance of sugary drinks, fast food, and animal fat. Provision of mixed nuts (30 g/day of walnuts, hazelnuts, and almonds) and EVOO (0.5 L/week) as main sources of fat. Motivation: Follow-up telephone calls Assessment: Number of attended sessions, questionnaires	None reported
Okesene-Gafa, 2019	Dietitian, community health workers	From GW 12^{+0}–17^{+6} until delivery	Delivery: Four education sessions at home. Development of a manual provided by a dietitian. Components: A HUMBA handbook with advices on healthy nutritious foods, unhealthy drinks, and recipes. Behavioral changes techniques promoting healthy diet, and setting SMARTER goals. Motivation: Feedback, positive reinforcement for goals achieved, motivational text messages Assessment: A personal pregnancy weight-gain chart, number of attended sessions, questionnaires.	Fetal death (1 / 3)

Melero, 2020	Dietitian	From GW 8–12 until delivery	Delivery: Four clinic-based visits of participants. Components: Counseling on Mediterranean diet, and increased consumption of EVOO and nuts; daily consumption of EVOO ≥ 40 mL, and pistachios 25–30 g for at least 3 days weekly. Free provision of 10 L of EVOO, and 2 Kg of pistachios during the first and second visit. Advices against consumption of alcohol and juices. Motivation: Free of cost supplies Assessment: Questionnaires, MEDAS for assessment adoption of Mediterranean Diet; MEDAS score 0 – 12 points, without consideration of alcohol and juice.	ND
Basu, 2021	Dietitian, nurse practitioner	From GW < 20 until 32–36	Delivery: Three clinic-based visits of participants, one at baseline; GW < 20 and, at two subsequent in the second, and third trimesters; GW 24–28, and 32–36, respectively. Components: Maintenance of habitual diet throughout the study (280 g daily food intake of 160 kcal divided into 38 g total carbohydrates, 8 g total fiber, 8 mg vit C, 3 mg sodium, 168 mg K, 1600 mg total polyphenols, and 700 mg anthocyanins). Consumption of two cups of frozen blueberries in mid-morning, or afternoon, or evening as a snack by itself and not in combination with any other food items. Intake of 12 g soluble fiber daily from meals (soups, gravies, and shakes). No consumption of fruit juice. Motivation: Free of cost food supplies, education, telephone calls Assessment: Return of any unconsumed supplementation, 24-h food recalls, nutrition calculation software.	Miscarriage (1 / 1)
Dong-Yao Zhang, 2022	Nutritionists	From GW 20^{+0}–24^{+6} until delivery	Delivery: Dietary education and advice according the Chinese Dietary Guidelines for pregnancy. Components: Participants recalls of amount and frequency consumption of each food in the last five weeks, at GW 20 and 25. In addition to the above Guidelines, consumption of soluble powder of fiber twice daily in total amount of 12 g (energy, 51.93 kcal; carbohydrates, 3.31 g; fiber, 9.78 g). Motivation: Presentations Assessment: Questionnaires, Chinese Food Composition Table for evaluation of mean daily total energy intake	Dietary fiber intolerance (2 / 0), loss of pregnancy (0 / 1)

GW, gestational week; E%, energy percent; kJ, kilo joule; kcal, kilocalories; L, liter; mL, milliliter; kg, kilogram; g, gram; GI, glycaemic index; GL, glycemic load; min, minute; i.e., id est; eg, for example; K, potassium; vit, vitamin; EVOO, extra virgin olive oil; app, application; SMARTER, specific, measurable, action-oriented, realistic, timed, evaluated, and reviewed; HUMBA, Healthy Mums and Babies Study; MEDAS, Mediterranean Diet Adherence Screener; ND, no data; N/a, not applicable; h, hour

Exercise was the exclusive intervention in 13 eligible trials. Researchers were the providers of the exercise in four studies [61, 63, 103, 131], physiotherapist in three studies [65, 109, 130], and exercise physiologist in two trials [34, 49]. In the rest studies, the intervention's providers were fitness instructors [77], kinesiologists [98], health educators [132], and fitness specialist in assistant of an obstetrician [31]. The duration of exercise varies across studies. According to the RCTs reporting an exact period of intervention's duration in weeks, the increasing order is: 10 [132], 12 [98], 14 [34], 15 [49], and 25 [130]. Reporting the means of intervals of exercise intervention in weeks, the increasing order is: 17 (12 – 22) [65], 23 (22 – 28) [131], 24.5 (21 – 28) [109], 26.4 (25 + 1/7 – 27 + 4/7) [61], 27 (25 – 29) [63], 27.5 (26 – 29) [31], 28.5 (27 – 30) [77], 29.5 (29 – 30) [103]. One trial reported addition PA until sixth week postpartum [61]. The core of exercise programs at each eligible trial included

aerobic PA. Exercise programs, providers, delivery, components, motivation, assessment, and potential side effects are being reported. (Table 3b)

Table 3b. Eligible studies with exercise intervention

Name of first author, year of publication	Provider	Duration of intervention	Description of exercise intervention	Side effects /adverse events (intervention /control)
Do Nascimento, 2011	Physiotherapist	From GW 14–24 until 36	Delivery: Individualized or in a group, supervised exercise program of weekly classes. Components: PA of light to moderate intensity with HR less than 140 beats per min, according to the ACOG recommendations (2002). Total duration of 40 min; stretching for 10 min, strengthen exercises including lower and upper limb muscles for 22 min, and relaxing for 10 min. In addition, home-based exercise for five times weekly, or walking. Motivation: Counselling Assessment: Self-reported exercise journal	None reported
Oostdam, 2012	Physiotherapist	From GW 15 until delivery	Delivery: Individualized, supervised exercise program. Components: Light intensity beginning with a warm-up period for 5–10 min. Next, program's core for 40 min consisting of aerobic and strength exercises. Finally, a cool-down period for 5–10 min. Motivation: Information about the benefits of exercise in pregnancy. Assessment: Accelerometer for moderate and vigorous activity, METs with cut-off values from the ACSM statement	None reported
Price, 2012	Researchers	From GW 12–14 until 36 or to delivery if participants wished	Delivery: Both individualized and in a group, supervised exercise program performed four times per week. Components: Aerobic PA of moderate intensity for of 45–60 min, according to the ACOG guidelines. Particularly, on the first day performance of step aerobics, on the second day walking in a group over hilly terrain, on the third day training circularly, and on the fourth day individual walking for 30 to 60 min. Substitution with weight training for 1–10 min, after performing aerobic exercise with an equal time interval. End of sessions with stretches of lower limbs' muscles for 5 min. Motivation: N/a Assessment: Questionnaires, RPE on the Borg Scale, produced power during the timed walking, documentation of temperature, sit-and-reach test.	Anxiety with exercise (1 / 0), history of preterm pregnancy (1 / 0), pain from leiomyomas (1 / 0)
Barakat, 2013	Fitness specialist; obstetrician	From GW 10–12 until 38–39	Delivery: In a group of 10–12 women, supervised exercise program at three sessions per week (Monday, Wednesday, and Friday). Components: Aerobics, strength and flexibility exercises for 50–55 min, according to the ACOG guidelines. A gradual warm-up and a cool-down period preceding and following main part, respectively, both for 10–12 min. Sessions' main part for 25–30 min, including resistance exercises of moderate intensity. In addition, aerobic dance at one session per week, in sections of three to four min with one min breaks including stretching and relaxation activities. Motivation: Sessions accompanied with music, and performance in an airy, well-lighted exercise room at the Hospital. Assessment: HR monitors during the training sessions, Borg's Scale.	Premature labour (5 / 3), pregnancy-induced HY (5 / 4), persistent bleeding (3 / 0), molar pregnancy (0 / 3)
Ruiz, 2013	Researchers	From GW 9 until 38–39	Delivery: In a group of 8–10 women, supervised exercise program of three times a week (Monday, Wednesday, and Friday).	Threat of premature delivery (14 /

			Components: Aerobic and unaerobic PA of light to moderate intensity for 50-55 min per session. In the beginning, a warm-up period of light intensity for 10-min. Afterward, main part for 25 to 30 min, including aerobic exercises once a week (usually on Friday), and resistance exercises twice a week (usually on Monday and Wednesday). In the end, a cool-down period of light intensity for 10-min. Motivation: N/a Assessment: HR monitors, RPE on the Borg Scale	11), persistent bleeding (7 / 9)
Nobles, 2015	Health educators	10 GW on avarage	Delivery: N/a both design (individualized or in a group), and guidance. Performance on most days of the week. Components: Self-selected specific activities (i.e. dancing, walking, and yard work) of moderate-intensity, for 30 min at least. Motivation: Telephone calls, emails Assessment: Questionnaires, and responses-based individual manual.	Medical contraindication (3 / 1), miscarriage or termination (1 / 2)
Bisson, 2015	Kinesiologists	From GW 15 until 27	Delivery: Individualized, supervised exercise program, three times weekly. Components: Consistent with the ACSM Guidelines, moderate-intensity exercise program, and duration of 1-h per session. Session's content: a warm-up period on a stationary ergocycle for 5–10 min, treadmill walk for 15–30 min, strength PA for 20 min, and finally, relaxing. Motivation: Pamphlet, kinesiologists always available for counselling, modification of the resistance exercises, counselling Assessment: Number of completed sessions, HR monitors, exercise log, RPE on the Borg Scale, accelerometer, questionnaires, METs	None reported
Seneviratne, 2015	Exercise physiologist	From GW 20 until 35	Delivery: Individualized, unsupervised home-based exercise program. Varied frequency and duration, according to stage of pregnancy, between three and five sessions per week, and 15 and 30 min per session, respectively. Components: Home-based exercise sessions of moderate intensity. A warm-up and a cool-down period of low intensity for 5 min, and stationary cycling as main session's part of moderate intensity. Motivation: Support by an available exercise physiologist. Assessment: HR monitors	None reported
Perales, 2016	Fitness instructors	From GW 9–11 until 38–39	Delivery: In a group of 8–10 women, supervised exercise program, sessions thrice weekly (Monday, Wednesday, and Friday). Components: Session's duration of 55–60 min. Same structure of all sessions; in the beginning a warm-up period for 5 to 7 min, next aerobic and resistance PA of moderate intensity for 25–30 min, and finally a cool-down period for 5 to 10 min. Motivation: N/a Assessment: HR monitors, resting HR values.	Risk of preterm delivery (4 / 5), obstetric complications (3 / 4)
Krohn Garnæs, 2016	Physiotherapist	From GW 12–19 until delivery	Delivery: In a group, supervised exercise sessions, thrice weekly. Components: PA program for 60 min; aerobic PA of moderate intensity for 35 min, and strength PA for 25 min. Additionally, home-based exercise program at least once weekly for 50 min; endurance training for 35 min, and strength exercises for 15 min. Motivation: Encouragement, and motivational interview individually or in a group. Assessment: Self-reporting in a training diary, Borg Scale, and individually adjusted resistance training.	None reported
Guelfi, 2016	Exercise physiologist	From GW 14 until 28	Delivery: Individualized, supervised sessions of stationary cycling at home, three times per week. Components: Beginning with a warm up period for 5 min. Main part of session with periods of continuous cycling of moderate intensity for 5 min, and periods of interval cycling for 5 min; two types of intervals: an increase in pedaling rate for 15 sec, and an increase in cycling resistance for 30 sec repeated every 2 min. Finish with a cool-down period for 5 min.	Pregnancy loss (1 / 2)

			Motivation: N/a Assessment: Accelerometer, questionnaires	
Wang, 2017	Researchers	From GW < 12^{+6} until 36–37 (27 ± 2 weeks)	Delivery: Supervised cycling program, at least three times per week. Components: Progressively increased PA according to individual ability. Exercise of low intensity in the beginning of the intervention, cycling for 30 min. Continuous increase of the duration until 45-60 min by adding 5 min to the cycling phases of moderate intensity or to the intervals of cycling. A warm-up and cool-down period for 5 min of each one, in the beginning, and in the end of sessions, respectively. Motivation: N/a Assessment: Questionnaires, RPE on the Borg Scale, records	Cervical length < 25 mm (1 / 5), low-lying placenta (1 / 0), ankle sprain (1 / 0), malformation (0 / 1), fetal death in utero (0 / 1)
Daly, 2017	Researchers	From GW 13 $^{+4/7}$ ± $1^{+2/7}$ until 6 weeks postpartum	Delivery: In a group, supervised exercise program, on a choice of performance day and h. Components: Exercise program for 50–60 min with a warm-up period for 10 min, aerobic resistance exercise both for 15–20 min, and a cool-down period for 10 min. Motivation: Secret Facebook group, SMART goal-setting, classes in a group, journaling, choice of day and h, variance of classes each day, and assurance of childcare during classes. Assessment: HR monitoring, and Borg Scale, according to the ACOG guidelines.	None reported

GW, gestational week; IOM, International Institute of Medicine; ACOG, American College of Obstetricians and Gynecologists; ACSM, American College of Sports Medicine; GWG, gestational weight gain; SMART, specific, measurable, action-oriented, realistic, timed; PA, physical activity; MET, metabolic equivalent task;VO2, volume of oxygen; RPE, perceived exertion; HY, hypertension; HR, heart ratio; HRR, HR reserve; min, minute; sec, second; ND, no data; N/a, not applicable; h, hour

18 eligible RCTs involved exercise in addition to dietary interventions. Dietitians provided the combined intervention in six of them [11, 53, 62, 71, 133, 134], researchers in three of them [15, 28, 73], health trainers in other two [13, 47], and nurses in one of them [5]. In six studies, the dietitians provided the intervention in collaboration with physiotherapists [39], trained research assistants [50], study nurses [6], exercise instructor [10], clinical nutritionist [7], exercise experts and nurses [8]. Intervention's duration of studies from lower to largest time period reported exactly in weeks is: 8 [47], 12 [11], 20 [62]. Intervention's duration reported in means ranges in weeks at increasing order is:12 (10 – 14) [8], 13 (12 – 14) [13], 13 (10 – 16) [134], 13.1 (12.2 – 14) [53], 19.5 (17 – 22) [15], 21.7 (19.8 – 23.6) [6], 23 (20 – 26) [39], 23 (20 – 26) [50], 25.5 (24 – 27) [133], 27 (25 – 29) [5], 30 (28 – 32) [71].One trial reported an intervention period > 12 weeks [10], another study > 14 [7], and another one >18 [28]. One trial did not report data on study duration [73]. Any intervention included a motivation arm. Details on the dietary, and the exercise arms of interventions, as well as potential side effects are being reported. (Table 3c)

Table 3c. Eligible studies with dietary plus exercise intervention

First author, publication year	Provider	Duration of intervention	Description of diet intervention	Description of exercise intervention	Side effects /adverse events (intervention /control)

Luoto, 2011	Nurses	From GW 8–12 until 37	Delivery: Dietary counseling session at four visits. Components: Advise on consuming vegetables, fruits, and berries, preferably at least five portions (400 g) a day; selecting mostly high fiber bread (> 6 g fiber / 100 g) and other whole-meal products; selecting mostly fat-free or low-fat versions of milk and milk products and of meat and meat products; eating fish at least twice per week (excluding the fish species not recommended for pregnant women); using moderate amounts of soft table spreads on bread, oil-based salad dressing in salad, and oil in cooking and baking; consuming seldom and only in small portions foods high in fat; and consuming seldom and only in small-portions snacks containing high levels of sugar and/or fat Motivation: Counseling cards Assessment: Participants' notebooks, questionnaires	Delivery: Monthly thematic exercise program in a group Components: Progressively increase of minimum weekly leisure time PA dose at 800 MET min, including light-intensity PA. Maximum of 750 MET min of moderate-intensity PA. Motivation: PA counseling Assessment: Self-reports, questionnaires, METs	Miscarriages (6 / 8)
Vinter, 2011	Dietitians, physiotherapists	From GW 10–14 until 34–36	Delivery: Dietary counseling on four sessions, at GW 15, 20, 28, and 35. Components: Dietary advice based on the official Danish recommendations; individually estimated energy participant's requirements, according to weight and level of activity. Motivation: Encouragement Assessment: Online computer program	Delivery: In a group, supervised exercise program of 1-h weekly. Components: Aerobic; low-step, resistance; light weights, elastic bands, and balance exercises. In addition, advise of being moderately physically active 30–60 min daily. Motivation: Encouragement, free full-time membership in a fitness center Assessment: Bench platform, pedometer, online computer program	Missed abortion (1 / 4)
Harrison, 2013	Health trainer	From GW 14–16 until 28	Delivery: Four sessions of individually participants' determined goals. Components: Reduced consumption of high fat or convenience foods, and increase consumption of fruit and vegetable intake Motivation: Lifestyle messages Assessment: Self-monitor based on IOM recommendations	Delivery: Individualised exercise program. Components: Moderate and vigorous activity of daily walking. Motivation: Lifestyle messages Assessment: Self-monitor, pedometers, questionnaires, METs	Miscarriages-termination (1 / 2), premature delivery (3 / 1)
Petrella, 2013	Dietitian	From GW 16 until 36	Delivery: 1-h counseling session Components:1500 kcal / day, divided at three main meals, and three snacks; due to PA program, an addition of 200 kcal / day for obese, and 300 kcal/day for overweight women. Macronutrient diet's target composition of 55% carbohydrate at least of 225 g/day to prevent ketosis (80% complex low GI, 20% simplex), 20% protein (50% animal, 50% vegetable), and 25% fat (12% mono-insatured, 7% poli-insatured, and 6% satured) with moderately low saturated fat levels. Motivation: Counseling Assessment: Questionnaires, urine exams (ketonuria)	Delivery: PA program at least thrice a week Components: 30 min of moderate intensity activity Motivation: Exercise and lifestyle surveys Assessment: Pedometers, talk test	ND
Dodd, 2014	Dietician, trained research assistants	From GW 10–16 until 36	Delivery: A planning session with a research dietician Components: Nutrition counselling according to Australian standards for a balanced consumption of carbohydrates, fat, and protein. Consumption of two servings of fruit, five servings of vegetables, and three servings of dairy each day, and reduced intake	Delivery: Generic Components: PA advices on primarily increasing walking and incidental activity.	Stillbirths (5 / 5), miscarriages (25 / 25); neonatal deaths (4 / 1), maternal

			of foods high in refined carbohydrates and saturated fats, while increasing intake of fibre and Motivation: Encouragement, supporting, individualized facilitators, telephone calls Assessment: Self-monitoring, work book	Motivation: Encouragement, supporting, individualized facilitators, telephone calls Assessment: Self-monitoring, work book	deaths (1; motor vehicle collision) / (1; ruptured maternal splenic artery aneurysm)
Hui, 2014	Dietitians	From GW 20–26 until 36	Delivery: A personalized, individualized nutrition consultation, with the assistance of FCM interview tool (possibility of receiving a complete intake weekly, and decision make for food choices). Components: Nutritional recommendations based on the dietary intake analysis and Health Canada guidelines for food intake in pregnancy with considerations on personal food preference, food beliefs, and food budgeting. Motivation: Food stickers on a magnetic board, nutritional information on the food sticker scanned into the computer, instant analyse of daily calorie intake and macronutrients Assessment: Self-reported food intake records, software containing Canadian Food Database	Delivery: In a group or individualized PA program in a group or at home, 3–5 times weekly. Components: Aerobic exercise, strength exercise, and stretching of mild to moderate intensity, in a group or at home according to the exercise DVD instruction, for 30–45 min. Motivation: DVD, exercise logbook Assessment: Questionnaires	ND
Poston, 2015	Health trainer	From GW $20^{+6/7}$ until $28^{+6/7}$	Delivery: 8 health trainer-led group or individual sessions of 1-h duration once a week for 8 weeks. Components: Promotion of a healthy pattern of eating but not necessarily restriction of energy intake. Recommendations tailored to the woman's habitual diet and cultural preference. Suggested exchanging carbohydrate-rich foods with a medium-to-high GI for those with a lower GI to reduce the GL, and restricting dietary intake of saturated fat Motivation: Telephone calls, emails, SMART goals, handbook counseling, encouragement Assessment: Self-monitoring, log book, dietary data, GWG, anthropometry, questionnaires, and nutrition calculation software.	Delivery: 8 health trainer-led group or individual sessions of 1-h duration once a week for 8 weeks Components: Walking at a moderate, progressively increased intensity, tailored to women's pre-existing activities. Additional PA options for previously active women. Motivation: SMART goals, handbook, counseling, encouragement, DVD Assessment: Pedometer, log book, PA scores, GWG, anthropometry, questionnaires, METs	Loss of pregnancy (14 / 14), miscarriages (6 / 2), fetal deaths in utero (2 / 4), termination (1 / 3)
Koivusalo, 2015	Dietitians, study nurses	From GW 13.3 (12–14.6) until 35.1 (34.4–35.6)	Delivery: In the beginning, counseling session in a group led by a dietitian. After enrollment, three sessions of individualized counseling according to the stage of the pregnancy, led by the study nurses. Components: Dietary advice based on contemporary Nordic Nutrition Recommendations 2004. Focus on optimizing participants' consumption of vegetables, fruits and berries, whole-grain products rich in fiber, low-fat dairy products, vegetable fats high in unsaturated fatty acids, fish, and low-fat meat products, and a lower intake of sugar-rich foods. Motivation: Counseling Assessment: Questionnaires, questionnaires-based dietary index	Delivery: In a group or individualized, supervised exercise program. Components: PA of moderate-intensity, at least for 150 min weekly. Motivation: Free access to public swimming pools. Assessment: Self-reporting	Miscarriages or termination of pregnancy (7 / 6)
Bruno, 2016	Dietitian	From GW 9–12 until 36	Delivery: At enrolment, a counselling session lasting approximately 1-h with a dietitian prescribing a personalized dietary intervention. Four additional follow-up sessions.	Delivery: In a group exercise program, at least three times a week. Components: PA of moderate intensity for 30 min at each time, according with	Miscarriages (7 / 6)

			Components: Decreased intake of foods with a high GI and a high saturated fat content and replacement of them with healthier nutrition based on the taste and preferences. A diet based on the high consumption of plant foods, cereals, legumes and fish, with olive oil as the main source of fat, and moderate to no consumption of red wine. A low-glycaemic, low saturated fat diet with a total intake of 1500 kcal/day divided into three main meals, and three snacks; additionally, daily intake of 300 kcal, and 200 kcal for overweight and obese participants, respectively, due to PA program. Target at daily dietary macronutrients' composition at 55% carbohydrates at least 225 g (ketosis prevention) divided into 80% complex carbohydrates with low GI, and 20% simple carbohydrates with high GI; 20% protein divided into 50% animal, and 50% vegetable; 25% fat, divided into 12% mono-unsaturated, 7% polyunsaturated, 6% saturated; and low intake of saturated fat. Motivation: Telephone calls, counseling Assessment: Questionnaires	the ACOG 2002 and the ACSM guidelines. Motivation: Telephone calls, counseling Assessment: Pedometer, talk test	
Kennelly, 2018	Researchers	From GW 12–17 until 34	Delivery: Face-to-face education sessions individually or in pairs, smartphone application, emails every two weeks of SMART goals. Components: Healthy recommended approximately eucaloric diet in pregnancy, changes of GI foods for low GI. Motivation: Food diaries quantifying GI and GL, smartphone application, encouragement. Assessment: Self-reported, food diaries, and nutrition calculation software.	Delivery: Exercise program between five and seven days per week. Components: Exercise of moderate intensity for 30 min divided into three or two periods of 10 or 15 min, respectively, according to the ACOG guidelines. Motivation: Smartphone application Assessment: Self-reported; pregnancy exercise and lifestyle surveys	Miscarriages (1 / 0), congenital anomaly (3 / 1), pretern delivery and neonatal death (1 / 0), maternal parvovirus infection (0 / 1), hyperemesis gravidarum (0 / 1)
Chan, 2018	Dietitian, exercise instructor	From GW ≤ 12 until 24	Delivery: Bi-weekly face-to-face or phone consultations in the first two months, and monthly face-to-face consultations afterwards till the end of the intervention. Components: An individualized menu plan aiming at achieving a varied balanced diet with an emphasis on fruit and vegetables consumption, and intake of moderate-carbohydrate, low-fat, low GI and low-caloric products in appropriate portions. Also, advices on the use of dietary supplements and managing pregnancy discomforts. Motivation: Telephone calls, advises, booklet, emails Assessment: Food records, questionnaires, nutrition calculation software, diet adherence score.	Delivery: A supervised exercise program at least three times a week. Components: Based on international guidelines; a session of 30-min of easy to moderate intensity of low impact aerobics PA. Motivation: Support Assessment: Questionnaires, number of accomplished exercise sessions, PA adherence score	Miscarriages (13 / 13), pretern delivery (1 / 1)
Ferrara, 2020	Dietitians	From 14.3 GW (13.3–15.1)	Delivery: Core of the intervention of 13 weekly individual sessions. First and last sessions in person, and 11remaining by telephone. Components: Eating healthy foods in appropriate portion sizes, total caloric intake, and calories from fat. Motivation: Motivational interviewing techniques, a step-wise, phased approach to behaviour change.	Delivery: Exercise program weekly. Components:150 min per week of moderate-intensity to vigorous intensity PA	Pregnancy loss (5 / 4)

		until 27.3	Assessment: Workbook, personalised graphs, 24-h dietary recalls	Motivation: Motivational interviewing techniques, a step-wise, phased approach to behaviour change. Assessment: Accelerometer	
Lin, 2020	Researchers	From GW < 8 until 24–28	Delivery: One face-to-face education session with an interventionist at the onset of intervention and continuous educational messages delivered via a WeChat public account at a frequency of twice per week. Components: Encouragement of consuming vegetables, fruits, high-fiber wholegrain products, low-fat dairy products, and avoiding foods rich in sugar and saturated fatty acids, among other guidance. Motivation: Encouragement, messages Assessment: N/a	Delivery: Exercise program at a frequency of three to four times per week. Components: Approximately 30 min of moderate-intensity PA Motivation: Encouragement, messages Assessment: N/a	Early pregnancy loss (5 / 4)
Li, 2021	Researchers	ND	Delivery: Individualized medical nutrition guidance Components: Instruction of choosing appropriate foods, and preparation methods for each meal (including vegetables, fruits, and meat). Recommendation of eating less at each meal, and more often at a frequency of six daily meals (three main meals and three additional meals). Energy distribution per each meal category as 15% to 20% for breakfast, 20% to 30% for lunch, 20% to 30% for dinner, and 15% to 30% for extra meals. Calculation of total energy intake of each according to pre-pregnancy BMI; increasement of the average daily energy intake by 200 kcal on this basis during the second and third trimester of pregnancy, including 50% to 55% carbohydrate, 25% to 30% fat, and 15% to 20% protein. Motivation: Choice of foods Assessment: Food record, anthropometry	Delivery: Individualized exercise program Components: Walking for 15 – 20 min after meals. Continued engaged pre-pregnancy aerobic activities (i.e. swimming, yoga), according to individual's preferences and physical condition for 30 – 40 min. Motivation: Continuation of preferable activities Assessment: Anthropometry	ND
Liu, 2021	Dietitian	From GW 8–12 until delivery	Delivery: Individual sessions of face-to face instruction and video teaching for 1-h every 2–4 weeks from the first intervention until the end of pregnancy. Components: A hypocaloric, low-glycemic, low-saturated fat diet with a sample meal plan and recipes. Individualized diet according to pre-pregnancy BMI and PA. For overweight with light PA, recommended 25–30 kcal/kg of ideal body weight (IBW); for obese women with light PA, recommended 20–25 kcal/kg of ideal body weight. Distribution of the daily energy intake as carbohydrate 50–55%, protein 15–20%, and fat 25–30%. Suggested energy for the first trimester not below 1500 kcal/day, and for the second trimester not less than 1600 kcal/day. Motivation: Follow-up through WeChat for unavailable participants for meetings with the dietitian. Assessment: Dietary log	Delivery: Individualized exercise guidance, at least five days each week. Components: Moderate-intensity PA with brisk walking, swimming, dancing, pregnancy yoga, or other aerobic exercises for at least 30 min a day. Motivation: WeChat Assessment: Exercise log, HR monitoring by talking pulse	Miscarriages (19 / 32)
Ding, 2021	Dietitian, clinical nutritionist	From GW < 12 until 24–28	Delivery: Personalized dietary and exercise guidelines based on the guide of diagnosis and treatment of GDM2014, social media platform, personalized nutrition care Components: IBW energy requirement calculator, and consideration of pregnancy stage. For BMI 24–27.9 and early pregnancy EER 25–	Delivery: Daily exercise program Components: Walk for at least 6000 steps per day Motivation: An available dietitian, counseling, social media platform	Early spontaneous abortion (6 / 5)

			30 kcal/kg; for BMI 24–27.9 and mid-pregnancy pregnancy EER 200 kcal in addition to previous intake; for BMI ≥ 28 and early pregnancy EER 20–25 kcal/kg; and for BMI ≥ 28 and mid-pregnancy EER 200 kcal in addition to previous intake. Minimum energy intake not less than 1500 kcal at early pregnancy, and 1800 kcal at mid-pregnancy. Daily macronutrient components of healthy recommended diet: 50–60% carbohydrate, < 30% fat, and 1.0–1.3 g/kg protein. Motivation: An available dietitian, counseling, social media platform Assessment: Dietary surveys, questionnaires	Assessment: Smartphone's data, questionnaires	
Deng, 2022	Nutritionist, exercise experts, nurses	From GW 14 until 24–28	Delivery: One-on-one explanation with an average of 20 minutes per person, educational manuals Components: Per capita calculation of daily intake of various foods, daily energy intake, daily intake of the three major nutrients, and energy ratio. Energy requirements individually calculated, with 50% to 60% of E% coming from carbohydrates, 20 to 30 E% from fats and 15 to 20 E% from protein. Encouragement of selecting high-fiber bread, whole-meal products or multigrain rice as staple food, intaking more vegetables and fewer high-sugar fruits, selecting fat-free or low-fat versions of milk and milk products, and using moderate amounts of oil in cooking and baking. Presentation of sample meals and food model samples to the women at enrollment. Advise on choosing the favorite food of the same kind through food exchange. Motivation: Advice, social media platform Assessment: Diaries, questionnaires	Delivery: Exercise program at least five days a week. Components: According to the recommendations of ACOG (2015);20–30 min of moderate-intensity exercise including walking, yoga, and gestational gymnastics designed by exercise experts; in situ steps, upper limb and shoulder back training, and hip 3D exercises. Motivation: Advice, social media platform Assessment: Diaries, questionnaires	None reported
Sadiya, 2022	Dietitians	From GW ≤ 12; 12 GW	Delivery: Face-to-face individualized dietary consultations. Components: Increased consumption of whole grains, vegetables, fruits, and lower intake of processed food, and simple carboxylates, according to ADA recommendations. Target at macronutrient composition: 50-55% carbohydrates, 25-30% fat, and 20% protein. Motivation: Telephone calls, motivational interviewing, SMART goals Assessment: Food recalls, questionnaires, food log	Delivery: An available choice of a weekly or daily exercise program. Components: Weekly moderate-intensity PA of 150 min or a daily minimum of 10000 steps; 1-h and 40min daily activity. Motivation: Telephone calls, motivational interviewing, SMART goals Assessment: Self-monitoring, smartphone pedometer application	Miscarriages (2 / 2)

GDM, gestational diabetes mellitus; GW, gestational week; IOM, Institute of Medicine; ACOG, American College of Obstetricians and Gynecologists; ACSM, American College of Sports Medicine; ADA, American Diabetes Association; BMI, body mass index; GWG, gestational weight gain; IBW, ideal body weight; SMART, specific, measurable, action-oriented, realistic, timed; EER, estimated energy requirement; E, total energy; FCM, food choice map; kcal, kilocalories; kg, kilogram; g, gram; GI, glycaemic index; GL, glycaemic load; PA, physical activity; MET, metabolic equivalent task; HR, heart ratio; min, minute; DVD, digital video disk; 3D, three dimensional; ND, no data; N/a, not applicable; h, hour

Description of exercise intervention of eligible trials

Exercise is being reported based on CERT tool for eligible trials implementing only exercise intervention [119]. One trial did not report any equipment type used during exercise [65]. One other trial did not mention the provider [103]. Two studies did not describe whether PA was performed individually or in a group [63,132], and one of them did not demonstrate existence of supervision or not [132]. All trials reported measures of adherence. No data regarding motivation component of intervention were found in five RCTs [34, 63, 77, 103, 131]. One trial did not introduce decision rules for progressing exercise program [65]. Two trials provided description of the exercise, capable of replication and reproduction [49, 77]. Four trials included exercise home component [34, 49, 65, 109]. Four studies involved additionally non-exercise components [61, 65, 131, 132]; particularly advises on GWG and nutrition in one of them [65], counseling of diet in another one [131], counseling of IOM guidelines for GWG and diet in another trial [132], and advises of lifestyle including local dietary guidelines during pregnancy in one other [61]. All trials provided documentation or management of possible adverse events. The location of exercise was not clarified in one trial [131]. All the 13 RCTs described PA dosage. The intervention of exercise was tailored to individual in seven trials [34, 49, 63, 98, 103, 109, 130], and generic in the rest six RCTs [31, 61, 65, 77, 131, 132]. Seven out of 13 studies did not determine decision rules for the starting level of exercise [31, 34, 49, 65, 77, 103, 109]. Finally, all trials reported measures of how well the intervention was delivered. (Table S2)

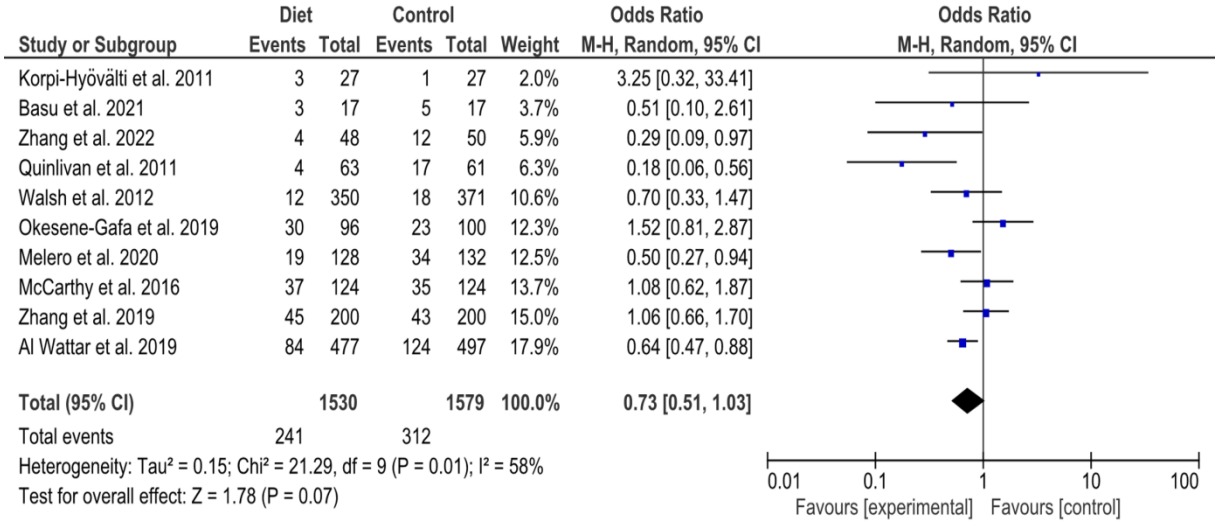
Effectiveness of lifestyle interventions during pregnancy

A total of 3109 (1530 in intervention, and 1579 in control group) high-risk pregnant women receiving dietary intervention were analysed for GDM outcome. Among them, 553 (17.8%) developed GDM [241 (15.7%) in intervention group, and 312 (19.7%) in control group]. Combining studies, heterogeneity across them was significant (Q 21.29, P-value 0.01), as well as variability was large [I^2 58% (95%CI 10, 78%)]. Therefore, RE model was selected for synthesizing the effect of dietary interventions. Women receiving nutrition intervention during pregnancy were less likely to develop GDM compared to women following standard prenatal care; however, the result of MA was marginally not significant (OR 0.73, 95%CI 0.51, 1.03; P-value 0.07). (Fig 6a)

Contrariwise to summary OR, a significant effect was shown when analyses were limited to studies where BMI was not including among GDM risk factors (OR 0.57, 95%CI 0.36, 0.93; P-value 0.02), and to studies including patterns of Mediterranean diet as intervention's component (OR 0.61 95%CI 0.46, 0.81; P-value 0.0006).The test of difference was significant for those subgroup analyses; P-value 0.049, and P-value < 0.001, respectively. In addition, the test of difference was significant for subgroup analyses based on low education level; P-value < 0.001, and motivation component in the intervention; P-value 0.0076. On the opposite, the test of difference was not statistically significant for analyses based on study duration; P-value 0.14 (Table S3a). In sensitivity analysis evaluating the effect

of the RCT with the largest sample size [38], the OR remained non-significant (OR 0.73; 95%CI 0.48, 1.13; P-value 0.16) (Table S3a). Due to small number of trials, and potentional variability among studies in subgroup analyses, significant results should be interpreted cautiously. Meta-regression analyses with baseline risk, and study duration as covariates did not show a statistically significant effect on the summary OR (Table S3b).

Fig 6a. Dietary intervention and the risk of gestational diabetes mellitus in high-risk pregnant women. Studies' presentation by weight contributing to the meta-analysis, in odds ratio (OR) estimates corresponding to their 95% confidence interval (95% CI). Summary OR by random effect model demonstration, as well as metrics of heterogeneity.

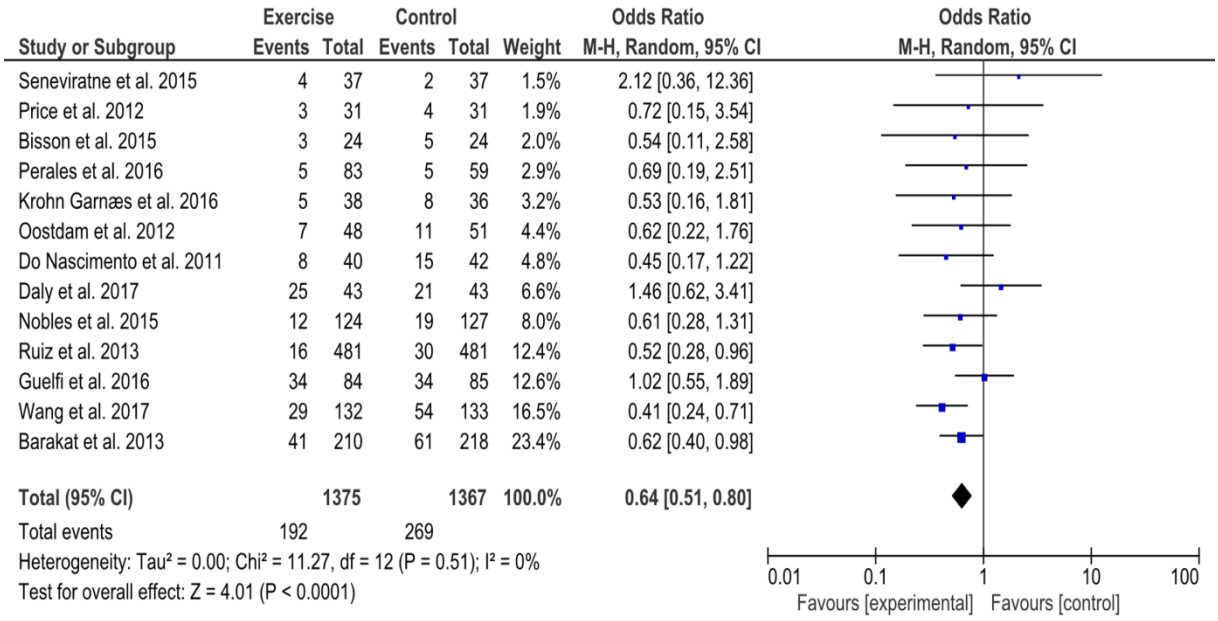


Trials involving exercise intervention reported 461 (16.8%) [192 (14%) in the intervention group, and 269 in the control group (19.7%)] diagnosed occurrences with GDM among 2742 (1375 in intervention group, and 1367 in control group) high-risk pregnant women analysed for gestational diabetes outcome. Heterogeneity across studies is non-significant (Q 11.27, P-value 0.51); however, variability could not be excluded as [I^2 0% (95%CI 0, 99%)], and upper limit for I^2 is greater than 75%. Thereby, the results of synthesis are being presented through FE model. The result of MA revealed a significant reduce of GDM's outcome for women participating in the group of exercise intervention, compared to them participating in the group of standard care (OR 0.64, 95%CI 0.51, 0.80; P-value < 0.0001). (Fig 6b)

Based on subgroup analyses the summary OR remained significant for studies including participant women with low education level at a percentage more than 10%; for studies applying an intervention lasting more than 20 weeks; for studies independently to considering of overweigh or obesity as a GDM risk factor; and for studies irrespective to applying a motivational component in the exercise intervention. However, no effect was revealed when analyses were limited to studies with a

percentage of participants with low education level below 10% (OR 0.53, 95%CI 0.16, 1.81; P-value 0.31); and to studies with duration of exercise intervention below to 20 weeks (OR 0.77, 95%CI 0.51, 1.15; P-value 0.20). The tests of difference were significant for any subgroup analysis (P-value < 0.01) (Table S4a). Investigating the effect of the RCT with the largest sample size [103], and the RCT with high attrition bias [77] (drop-out ratio 41.1%) in sensitivity analyses, the summary OR remained significant; (OR 0.66, 95%CI 0.52, 0.80; P-value 0.0005), and (OR 0.64, 95%CI 0.51, 0.80; P-value 0.0001), respectively (Table S4a). Baseline risk, and study duration as covariates in meta-regression analyses did not have a significant effect on the summary OR (Table S4b).

Fig 6b. Exercise intervention and the risk of gestational diabetes mellitus in high-risk pregnant women. Meta-analysis of eligible studies with fixed effect model. Presentation of studies according to their weight contributing to the synthesis. Estimates of odds ratio (OR) with 95% confidence interval (95% CI) of each trial, and overall OR with measures of heterogeneity.



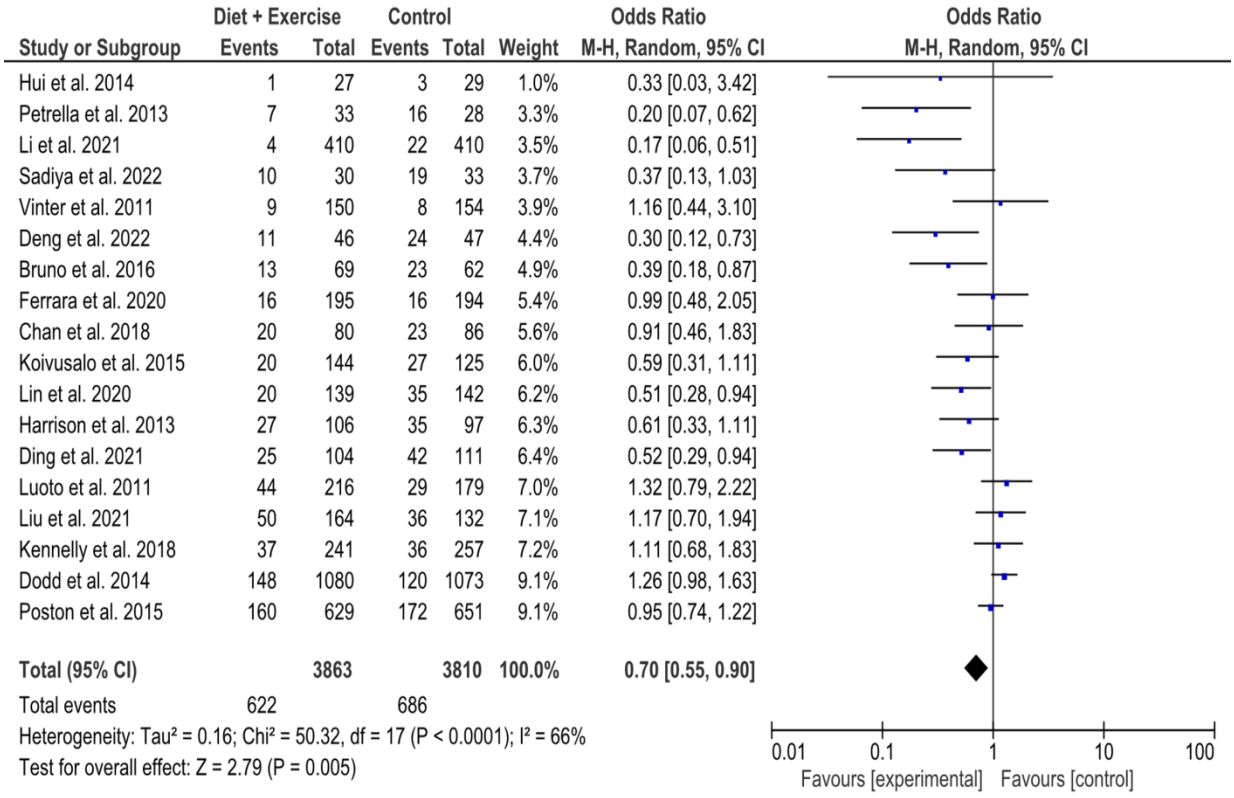
Among 7673 (3863 in experimental group, and 3810 in comparator group) high-risk pregnant women analyzed for GDM undergoing both diet and exercise intervention, 1308 (17%) [622 (16.1%) in intervention group, and 686 (18%) in control group] cases were diagnosed with diabetes of pregnancy. Studies' combination was performed through MA with RE in the presence of significant heterogeneity (Q 50.32, P-value < 0.0001, and large variability [I^2 66%, (95% CI 44, 79%)]. Women in the group of mixed lifestyle intervention had a significant reduction in GDM's incidence (OR 0.70, 95%CI 0.55, 0.90; P-value 0.005). (Fig 6c)

The summary OR remained significant when separate analyses were limited to studies including interventions lasting less than 20 weeks. On the opposite, no effect was found when separate analyses

were limited to studies based on percentage of participant women with low education level; low education level more than 10% of participating women (OR 0.64, 95%CI 0.40, 1.03; P-value 0.07), and up to 10% of participating women (OR 0.89, 95%CI 0.60, 1.32; P-value 0.56); studies with intervention duration more than 20 weeks (OR 0.97, 95% CI 0.68, 1.36; P-value 0.84); and studies without a motivation component in the intervention (OR 1.16, 95%CI 0.44, 3.10; P-value 0.76). The test of difference was significant only for subgroup analysis based on low education level, and intervention duration; P-value < 0.001 in both of them. The test of difference for subgroup analyses based on increased BMI as a GDM risk factor, and intervention motivation component was non-significant; P-value 0.23, and P-value 0.19, respectively (Table S5b).

Based on sensitivity analyses, the summary OR remained statistically significant evaluating the effect of the RCT with the largest sample size [50] (OR 0.67, 95%CI 0.52, 0.86; P-value 0.002), and the RCT with high attrition bias [133] (drop-out ratio 31.4%) (OR 0.73, 95%CI 0.57, 0.93; P-value 0.01) (Table S5a). Meta-regression analyses with covariates of baseline risk, and study duration did not prove an effect on the summary OR (Table S5b).

Fig 6c. Diet plus exercise intervention and the risk of gestational diabetes mellitus in high-risk pregnant women. Metrics of RCT in odds ratio (OR) with 95% confidence interval (95% CI). Performance of meta-analysis with random effect model. Presentation of studies in ascending order of weight.



Quality of reporting, potential bias, and quality of evidence

Assessing the quality of RCTs with dietary intervention, some of them were considered dubious on specific quality reports. Particularly, three trials did not provide information on both participants and personnel blinding [3, 14, 128]; in addition, one of them did not declare allocation concealment [3]. Also, other three trials did not mention to participants blinding [51, 60, 82]. Four studies were considered of being at high-risk regarding blinding of participants and personnel [4, 38, 68, 129]; specifically, three of them were unblinded for participants [4, 38, 68], and one of them was unblinded for personnel [129]. (Table 4a)

Based on the funnel plot assessment via visualization, studies did not have a close distribution around the summary effect estimate [126] (Fig 6a). Egger's test of small study effects had a P-value of 0.726.

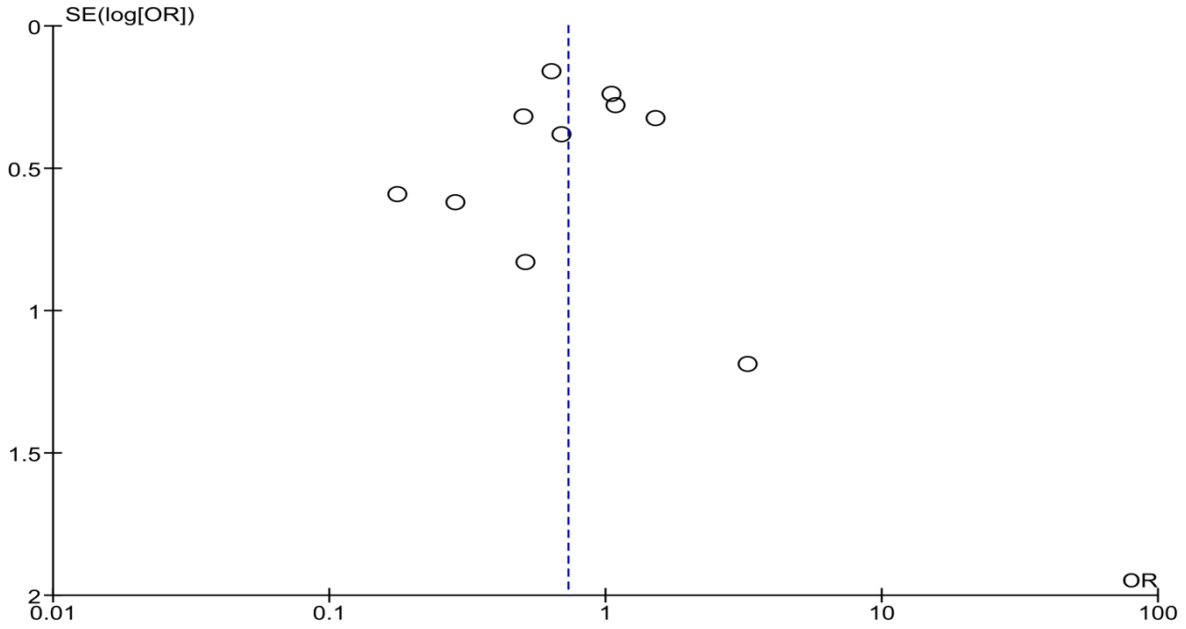
Performance bias was potential in four out of 10 RCTs, and unclear in the rest six out of them. Overall quality of evidence was moderate for dietary interventions during pregnancy compared to standard prenatal care for preventing GDM in high-risk pregnant women. (Table S6a)

Table 4a. Quality of reporting for eligible studies with dietary intervention

First author, publication year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Korpi-Hyövälti, 2011	L	L	?	L	L	L	L
Quinlivan, 2011	L	L	?	L	L	L	L
Walsh, 2012	L	L	?	L	L	L	L
McCarthy, 2016	L	L	?	L	L	L	L
Yi Zhang, 2019	L	L	H	L	L	L	L
Al Wattar, 2019	L	L	H	L	L	L	L
Okesene-Gafa, 2019	L	L	H	L	L	L	L
Melero, 2020	L	?	?	L	L	L	L
Basu, 2021	L	L	H	L	L	L	L
Dong-Yao Zhang, 2022	L	L	?	L	L	L	L

H, high risk; L, low risk; ?, unclear

Fig 6a. Funnel plot including all studies comparing diet intervention vs. standard prenatal care for gestational diabetes prevention among high-risk pregnant women [P-value 0.684 in the weighted regression of ln(OR) against the standard error]



Evaluating the quality of RCTs with exercise intervention, some concerns were also prompted on performance bias. Three studies did not report to blinding of either participants, or personnel [65, 103, 131]. Still, performance bias was considered unclear in five more RCTs [34, 98, 109, 130, 132]; three of them did not report information on participants blinding [98, 109, 130], and two of them on personnel blinding [34, 132]. A detection bias could not be excluded in two trials with unclear performance bias [34, 131], as information on recording data were not provided. Performance bias was judged as high in five studies [31, 49, 61, 63, 77]; one of them was unblinded for both participants and personnel [63], and four of them were unblinded for participants only [31, 49, 61, 77]. In addition, one trial reported a drop-out participants' rate at 41% [77]. (Table 4b)

Visualizing funnel plot, there was a variation in the standard error of the studies with exercise intervention. Small studies are placed narrow to the summary effect estimate [126] (Fig 6b). However, Egger's test of small study effects had a P-value of 0.399.

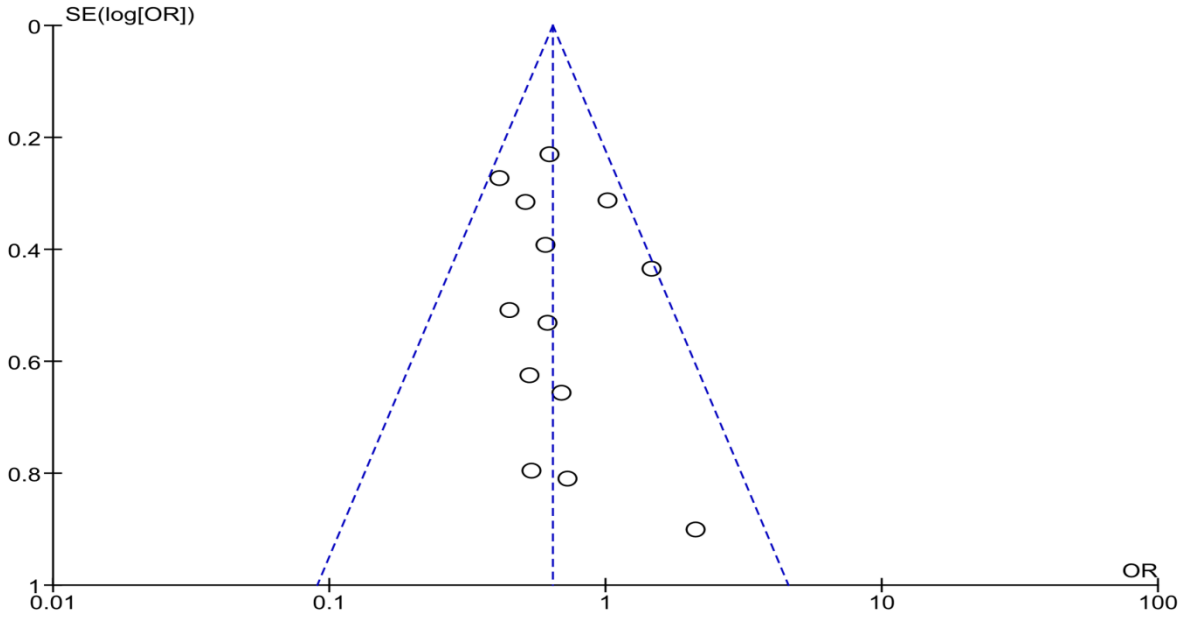
Totally, five out of 13 RCTs had potentional performance, or attrition bias. The other 8 RCTs were unclear about blinding. Overall quality of evidence was moderate for exercise interventions during pregnancy compared to standard prenatal care for preventing GDM in high-risk pregnant women. (Table S6b)

Table 4b. Quality of reporting for eligible studies with exercise intervention

First author, publication year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Do Nascimento, 2011	L	L	?	L	L	L	L
Oostdam, 2012	L	L	?	L	L	L	L
Price, 2012	L	L	?	?	L	L	L
Barakat, 2013	L	L	H	L	L	L	L
Ruiz, 2013	L	L	?	L	L	L	L
Nobles, 2015	L	L	?	L	L	L	L
Bisson, 2015	L	L	?	L	L	L	L
Seneviratne, 2015	L	L	H	L	L	L	L
Perales, 2016	L	L	H	L	H	L	L
Krohn Garnæs, 2016	L	L	?	L	L	L	L
Guelfi, 2016	L	L	?	?	L	L	L
Wang, 2017	L	L	H	L	L	L	L
Daly, 2017	L	L	H	L	L	L	L

H, high risk; L, low risk; ?, unclear

Fig 6b. Funnel plot including all studies comparing exercise intervention vs. standard prenatal care for gestational diabetes prevention among high-risk pregnant women [P-value 0.110 in the weighted regression of ln(OR) against the standard error]



Similar to quality assessment of RCTs with only dietary, and only exercise intervention, some uncertain is risen on RCTs with a combined intervention of diet and exercise. Performance bias was assessed as unclear in half of them; particularly, three of them did not give information on both participants and personnel blinding [28, 39, 73], and six of them only on participants blinding [6, 13, 50, 53, 62, 133]. In addition, an RCT had a participants' drop-out rate at 31.4% [132]. The performance bias was judged as high in the other half studies; specifically, seven out of them were unblinded for participants and personnel [5, 7,8, 15, 47, 71, 134], and two out of them were unblinded for participants [10, 11].

Studies with exercise intervention form an asymmetry by optically evaluating funnel plot [126] (Fig 6c). Similarly, Egger's test of small study effects had a P-value of 0.001.

In summary,10 out of 18 RCTs had a potential performance or attrition bias, and 9 out of them were unclear about blinding. Overall quality of evidence was low for dietary plus exercise interventions during pregnancy compared to standard prenatal care for preventing GDM in high-risk pregnant women. (Table S6c)

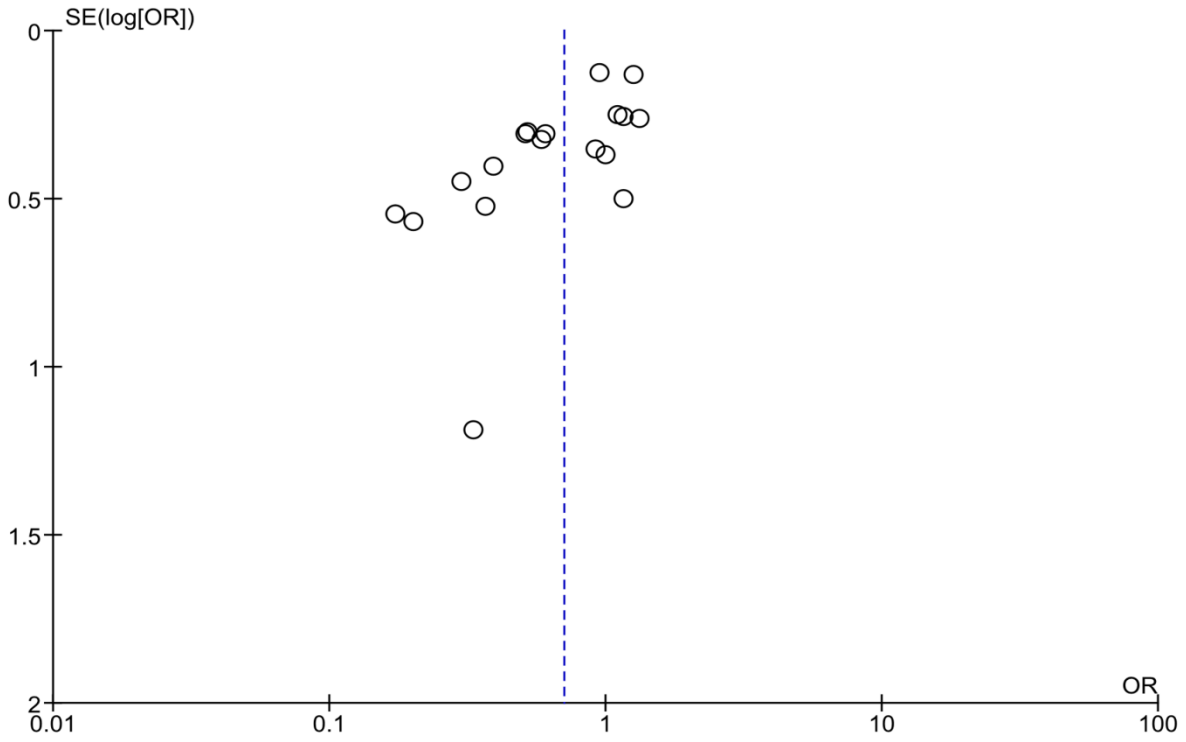
Table 4c. Quality of reporting for eligible studies with diet plus exercise intervention

First author, publication year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Luoto, 2011	L	L	H	L	L	L	L

Vinter, 2011	L	L	?	L	L	L	L
Harrison, 2013	L	L	?	L	L	L	L
Petrella, 2013	L	L	?	L	L	L	L
Dodd, 2014	L	L	?	L	L	L	L
Hui, 2014	L	L	H	L	L	L	L
Poston, 2015	L	L	H	L	L	L	L
Koivusalo, 2015	L	L	?	L	L	L	L
Bruno, 2016	L	L	?	L	H	L	L
Kennelly, 2018	L	L	H	L	L	L	L
Chan, 2018	L	L	H	L	L	L	L
Ferrara, 2020	L	L	?	L	L	L	L
Lin, 2020	L	L	?	L	L	L	L
Li, 2021	L	L	?	L	L	?	L
Liu, 2021	L	L	H	L	L	L	L
Ding, 2021	L	L	H	L	L	L	L
Deng, 2022	L	L	H	L	L	L	L
Sadiya, 2022	L	L	H	L	L	L	L

H, high risk; L, low risk; ?, unclear

Fig 6c. Funnel plot including all studies comparing diet plus exercise intervention vs. standard prenatal care for gestational diabetes prevention among high-risk pregnant women [P-value 0.983 in the weighted regression of ln(OR) against the standard error]



Discussion

High-risk pregnant women for GDM undergoing lifestyle interventions during pregnancy may have benefit on preventing GDM. The effectiveness of dietary interventions only was marginally non-significant. Heterogeneity between studies was large. In subgroup analyses it was found that dietary interventions in high-risk pregnant women for GDM not being overweight or obese, or nutrition interventions with Mediterranean diet may have benefit on preventing GDM. PA interventions decreased significantly the incidence of GDM. Non-significant heterogeneity across studies could not be excluded. Contrary to significant effect, the summary OR of exercise interventions changed when analyzing separately studies with a percentage of participants with low education level below 10%, and studies with a duration of intervention less than 20 weeks. A combination of diet plus exercise interventions during pregnancy on high-risk GDM pregnant women may also lead to less GDM occurrences. Heterogeneity across studies is significant. Contrariwise to overall benefit, subgroup analyses revealed that there was no effect for mixed interventions when analyses were limited to studies based on percentage of participant women with low education level (more or less than 10%), and studies with intervention duration more than 20 weeks.

Previous studies evaluating the preventive role of lifestyle interventions in pregnancy on preventing GDM in high-risk women demonstrated dubious results. An SR and MA evaluating dietary interventions for preventing GDM reported a possible effect in obese pregnant women [83], and marginally non-significant results in general population [83]. According to three SR and MA,

overweight and obese pregnant women may have also benefit on preventing GDM with PA interventions during pregnancy [43, 44, 45]. Moreover, evaluating overall high-risk GDM pregnant women, independently to obesity, two MA reported significant results on preventing GDM with exercise during pregnancy [17, 41]. However, three SR and MA evaluating lifestyle interventions during pregnancy including diet and PA among overweight and obese pregnant women revealed no prevention for GDMs' outcome [20, 23, 24]. As far as is known this is the first study of appraising systematically the effect of lifestyle interventions during pregnancy on preventing GDM among pregnant women with any risk factor for GDM.

An SR identified intrapersonal themes as the most frequently reported barriers and enablers to PA during pregnancy [95]. Moreover, obese women are less active compared to normal weight [98], and their adherence to exercise programs is low [98]. Overweight and obese pregnant women change their lifestyle habits with difficulty, probably lacking of motivation [15], or believing of not being at risk [13]. Furthermore, the efficacy of exercise interventions during pregnancy addressing this population is not often measured [98]. The dosage of PA in obesity is unknown, although most guidelines suggest exercising through obese pregnancy [98]. The lack of success of some RCTs on preventing GDM may have been attributed to the lack of statistical power and poor adherence to study protocols [64]. In addition, the main issue of performing RCTs with lifestyle interventions concerns performance bias, as blinding either participants, or personnel might be difficult due to the nature of interventions [5, 15]. Moreover, the possibility of preventing DM after GDM experience through lifestyle interventions is unclear [19, 20]. Specifically, previous MA reported non-significant reduction of T2DM risk for GDM women after lifestyle interventions [40, 77, 79]; however, a subsequent MA reported significant findings for T2DM after an early initiation of lifestyle interventions in GDM women [80].

Women of childbearing age have been highlighted as a target group for prevention of obesity, according to the WHO [42]. Those strategies may include a limitation of gained weight in pregnancy, and postpartum [42]. Pre-pregnancy time period could be ideal regarding the implementation of interventions aiming at weight loss [23]. However, this is difficult to achieve because many pregnancies are unplanned (i.e. 50% of pregnancies in the UK), and only a small percentage of women planning pregnancy follow nutrition and lifestyle recommendations [23]. Thus, a pre-pregnancy intervention may reach only a small proportion of the intended women [23].

The antenatal period is considered an ideal time to intervene as mothers are motivated to make changes that could optimise their outcome and that of the baby, with opportunities for regular contact with health care professionals [66]. Trials of lifestyle interventions demonstrating safety and efficacy for both the mother and her offspring, could be performed before gestational metabolic changes during the first trimester of pregnancy [64]. Social support also may have an enabling role [95]. Person-centred

strategies using behaviour change techniques should be used to address intrapersonal and social factors to translate pregnant women's positive attitudes into increased PA participation [95]. Targeted and well-designed exercises programmes are needed for obese pregnant women [98]. Furthermore, studies on bariatric surgery prior to pregnancy suggest that interventions targeting maternal obesity can also improve short- and long-term offspring health [49].

The prevelance of obesity and diabetes is increasing as well as their complications in public health, the cost for patients and health care systems, representing a crisis [135]. Obese individuals have been calculated as having medical costs 30% higher, on average, than normal-weight individuals [45]. Particularly, obesity costs the UK National Health Service (NHS) around £0.5 bn a year and the UK economy a further £2.3 bn in indirect costs [66], and the global health care cost associated with diabetes is totally estimated at least 490 billion U.S. dollars [6]. Additionally, GDM represents a heavy economic burden on patients and societies due to the diagnosis and treatment [8]. In China, it has been found that GDM diagnosis and treatment, delivery, and the management of mother's and neonatal complications of the last trimester of pregnancy have a cost of $1,929.87 on avarage per woman more than a non-GDM pregnant woman [8]. In Australia, the cost for women with GDM not needing insulin is AUD$ 2026, AUD$ 2534 for women needing insulin, and AUD$ 3826 if fetal heart rate is being monitored via cardiotocography [136]. In Australia, also, according to previous estimations, $53,985 additional direct costs were incurred for every 100 women with a singleton pregnancy and receiving treatment for mild GDM in addition to routine obstetric care, $6,521 additional charges were incurred by women and their families, $27,503 was the incremental cost per additional serious perinatal complication prevented, $60,506 per perinatal death prevented, and $2,988 per discounted life-year gained [137].

Preventing GDM could have economic and health benefits rather than treatment [1]. It is likely that additional health service and personal monetary charges for GDM's prevention in general population of HIC would find reductions in perinatal mortality and in serious perinatal complications sufficient to be satisfied [137]. Lifestyle interventions aiming to prevent excessive GWG and GDM were found to be neutral and possible cost effective for the health care system of Australia [138]. The cost-effectiveness evaluation of the multicenter RCT conducted in Europe including diet only or exercise only or a combined approach of them for pregnant women at increased risk of GDM found that a promotion of healthy eating and PA was the preferred strategy for limiting GWG, and for QUALY after delivery; however, the mixed approach of lifestyle interventions was not cost-effective for FBG [139]. Another assessment of cost efficacy of lifestyle intervention for preventing GDM at high-risk pregnant women in Finland showed that interventions were not cost-effective for neonatal birth weight [140]. In addition, an analysis of cost of exercise intervention in high-risk pregnant women in Holland reported no significant results for GDM prevention, FBG, insulin sensitivity, infant birth weight and maternal QUALY [141].

This study has several limitations. RCTs were considered as eligible if they recruited only high-risk GDM pregnant women. Thus, the results cannot be generalized to general population. However, not only women who were overweight or obese were included in investigated population; in addition, women with any risk factor for GDM including ethnicity, medical, and family history, and sedentary lifestyle were evaluated, trying to broaden the criteria of the population under assessment. Furthermore, this study included only trials that evaluated lifestyle interventions with initiation during pregnancy; thereby, their findings cannot be generalized to lifestyle interventions that may begin in preconception period.

Conclusion

Compared to usual prenatal care, this study could support the effectiveness of lifestyle interventions during pregnancy on preventing GDM in high-risk pregnant women including an exercise arm separately, or combined with diet. Nutrition interventions alone appeared narrowly insufficient on preventing GDM. However, dietary interventions in pregnant women at risk for GDM except for overweight or obesity, or nutrition interventions during pregnancy including Mediterranean diet could also contribute to protective effect. Future, large, high-quality RTCs are necessary to confirm the protective effect.

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Supplementary material

Table S1. Search Strategy

PubMed	((diet OR nutrition) OR (exercise OR "physical activit*" OR workout)) AND (diabetes AND (gestational OR pregnancy)) AND ("Clinical Trials as Topic"[Mesh] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab]) with PubMed publication date Between Jan 1950 and Aug 2022
CENTRAL	((diet OR nutrition) OR (exercise OR "physical NEXT activit*" OR workout)) AND (diabetes AND (gestational OR pregnancy)) with Cochrane Library publication date Between Jan 1950 and Aug 2022 (Word variations have been searched)
Scopus	TITLE-ABS-KEY ((diet OR nutrition) OR (exercise OR "physical activit*" OR workout) AND (diabetes AND (gestational OR pregnancy))) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Female") OR LIMIT-TO (EXACTKEYWORD , "Pregnancy")) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (PUBYEAR , 2023)

TableS2. Assessment of the exercise intervention based on CERT tool

First author, Publication year, Country	1) Equipment	2) Provider	3) Performance	4) Supervision	5) Adherence	6) Motivation	7) Progressing	8) Description, reproduction	9) Home component	10)Non exercise components	11) Adverse events; documentation and management	12) Location	13) Dosage	14) Tailoring to individual	15) Starting level	16) How well
Do Nascimento, 2011, Brazil	ND	Physiotherapist	In a group or individually	Supervised	Exercise journal	Counseling	ND	ND	Five times weekly	Counseling on GWG, nutrition	None reported	Prenatal Outpatient Clinic of the Women's Integral Healthcare Centre (CAISM-UNI-CAMP)	ACOG (2002); strengthen program of 40 min, light- to moderate-intensity, weekly	Generic	ND	62.5% adherence and 60% 9 – 16 weeks home PA
Oostdam, 2012, Netherlands	Cycle ergometers, treadmills, cross-trainers, stationary rowing machines, free weights, accelerometer	Physiotherapist	Individually	Supervised	Accelerometer, MET from the ACSM	Counseling	Number of repetitions, talk test", Borg Scale until 12	ND	ND	ND	None reported	Department of Physiotherapy in the participating hospitals	Light intensity warming-up for 5–10 min., such as slow cycling at a level of 50 Watt. 40 min of 1 or 2 aerobic exercises and 4 to 6 strength exercises. Cool-down for 5–10 min by slowly reducing the activity.	Training intensity carefully and individually controlled.	Maximal muscle strength and aerobic capacity, Valsalva maneuver during resistance exercise, one Repetition Maximum (1RM; the heaviest weight that can be lifted once) predicted from the Oddvar	Close supervision of a physiotherapist under the guide of ACOG

															Holten diagram.	
Price, 2012, USA	Treadmills, elliptical trainers, stationary bicycles, weight machines, exercise balls	Researchers	Both in a group and individually	Supervised	Borg Scale, temperature and humidity rates, sit-and-reach test, questionnaire	ND	A program at moderate intensity (12 – 14 on Borg Scale)	ND	ND	Dietary advice	Intervention Group: anxiety with exercise (n = 1), preterm pregnancy (n = 1), pain from leiomyomas (n = 1)	ND	ACOG; aerobic training of 45 – 60 min, 4 times per week, at moderate intensity. Step aerobics on the 1st day, walked as a group on the 2nd day, and circuit training on a 3rd day, of 1–10 min of aerobic exercise, alternating with an equal time interval of weight training, using a weight that allowed one set of 20 repetitions. End with 5 min of hamstring, quadriceps, and calf stretching. Also, a brisk walk individually, 30- to 60-min, once weekly.	Generic	Aerobic fitness test, submaximal strength assessment by lifting a 7-kg medicine ball from floor to waist high as many times possible within 1 min	Author's log of exercise activities and attendance
Barakat, 2013, Spain	Bar-bells, therabands, HR monitor	Fitness specialist, obstetrician	In a group	Supervised	HR monitor, Borg Scale	Music, and airy, well-lighted exercise room at the Hospital	Moderate exercise intensity	ND	ND	ND	Under medical follow-up	Exercise room at the Hospital	3 days/week, 50–55 min/ session. Warm-up and cool-down period, both of 10–12 min; walking and light, static stretching of most muscle group. Main part of 25–30 min; moderate-intensity resistance exercises at full range of major muscle groups motion. One set of pelvic tilting in standing position and exercises using bar bells or low-to-medium resistance elastic bands (Therabands). In addition, one session/week of aerobic choreography dance in sections of 3–4 min with 1 min breaks of stretching and relaxation activities.	One size fit all	ND	Training sessions in a group of 10–12 women, carefully supervised by qualified fitness specialist with the assistance of an obstetrician.
Ruiz, 2013, Spain	Bar-bells (3 kg), bench, elastic bands (therabands), HR monitor	ND	In a group	Supervised	HR monitors, and Borg conventional	ND	Light to moderate exercise intensity	ND	ND	ND	Intervention Group: threat of prematurity (n=14), persistent bleeding (n=7); Control group: threat of	Hospital Universitario de Fuenlabrada, Madrid, Spain	Light to moderate-intensity aerobic and resistance exercise, 3 times a week, 50-55 min per session. Start and finish with 10-min warm-up and 10-min cool-down, respectively, with same exercises of light intensity walking and static stretching of most muscle groups, plus relaxation and	HR consistently less than 60% of age predicted maximum HR (208 - [0.7 * age in years]),	ND	Total pleasure with the intervention, adherence> 97%, intention to be physically active during future

											prematurity (n=11), persistent bleeding (n=9)		pelvic floor exercises at cool-down period. Core section of 25 to 30 min of moderate intensity aerobic exercises once a week; low-impact aerobic dance activities for 3 to 4 min with 1-min breaks, with stretching and relaxation of upper and lower limbs. Resistance exercises twice a week; performance through the full range of motion, engaging major muscle groups, strengthening the muscles used in labor and the pelvic floor (3rdtrimester), and supine position on the floor exercises up to 2 min.	and rate of RPE n range from 10 to 12 (fairly light to somewhat hard, respectively).		pregnancies.
Nobles, 2015. USA	Digital pedometer	Health educators	ND	ND	Questionnaires, manuals	Booster telephone calls, mailed tip sheets	Safe progress toward the overall PA goal; weekly increasement by 10% of spent time at moderate intensity PA	ND	ND	Counseling of IOM guidelines for appropriate nutrition and GWG.	Medical records	ambulatory obstetric practices of Baystate Medical Center, western Massachusetts	≥ 30 min of moderate-intensity PA on most days of the week. Specific self-selected activities including dancing, walking, and yard work.	Generic	Tailoring questionnaire	62.1% of participants meting the College' s guidelines for PA, adherence as returning completed questionnaires, 95% of participants satisfied with information received
Bisson, 2015, Canada	Stationary ergocycle, treadmill, exercising balls, strength equipment, HR monitors, accelerometer	Kinesiologists	Individually	Supervised	Self-monitoring with HR monitors, Borg Scale, exercise log, accelerometry, questionnaire, MET	Counseling, modification of PA, pamphlet	Targets at 70% of peak HR (fitness test), progressively increasement PA from 15 min of 1st week to 30 min by the end of the 1st month.	ND	ND	ND	None reported	Pavillon de prévention des maladies cardiaques (PPMC, Institut Universitaire de Cardiologie et Pneumologie de Québec)	ACSM guidelines; moderate-intensity exercise sessions of 1h, 3 times weekly. Warm-up 5–10 min on a stationary ergocycle. 15–30 min treadmill walk. 20 min muscular work-out with dynamic exercises for both lower and upper limbs using the participant's own body weight, small weights, exercising balls and strength equipment with selective charge. Cool-down period.	Intensity adjusted to participants' tolerance level.	Cardiorespiratory testing in obese pregnant women. Assessment for PA, anthropometry, fitness and fetal growth. Start with 1 set of 10–15 repetitions per exercise and progressed to 2 sets of 15 repetitions.	Documentation of PA at GW 36. Participants' percentages and accomplished level of prescribed sessions : 60% ≥ 50%, and 20% ≥ 75%.
Seneviratne, 2015, New Zealand	Magnetic stationary bicycles, HR monitors	Exercise physiologist	Individually	Unsupervised	HR monitors	An available exercise physiologist for	HR in exercise sessions at moderat	Written program	Home-based cycling program	ND	None reported	At home	5-min warm-up and cool-down period at low intensity. Frequency varying between three and five sessions per week, and	According to stage of pregnancy	ND	Download of HR monitor data

						help with exercise-related problems.	e intensity	of prescription					duration of moderate-intensity exercise between 15 and 30 min per session, according to stage of pregnancy.			
Perales, 2016, Spain	HR monitors, light weights, fit ball, dumbbells	Fitness instructors	In a group	Supervised	HR monitors	ND	Narrow HR target at high end of moderate–intensity; 55%–60% of HRR	Visualization techniques	ND	ND	Intervention Group: risk of prematurity(n=4), obstetric complications (n=3); Control Group: risk of prematurity (n=5), obstetric complications(n=4)	Hospital Universitario de Fuenlabrada, Madrid, Spain	Three aerobic and strength training sessions per week, of 55–60 min per session. Constant duration and structure. Start with a 5- to 7-min warm-up consisting of walking at different intensities, mild static stretching of most muscle groups, joint mobility exercises, and locomotion games. Aerobic activities for 25–30 min of different exercises and music choreographies. Next, the strength part of the session, engaging major muscles groups with the aim of improving general muscle strength and preventing common muscle imbalances during pregnancy (low back pain, sciatica, and kyphosis), and improving balance, pelvis mobility, and body awareness, as well as pelvic floor muscle exercises for prevention of urinary incontinence. End with a 5- to 10-min cool-down period including relaxing exercises, static stretching, and partner massages.	Generic	ND	HR values every 2, 15 min after of sitting while taking deep breaths.
Krohn Garnæs, 2016, Norway	Treadmill	Physiotherapist	In a group	Supervised	Training diary, Borg Scale	Motivational interview session, and encouragement	Endurance exercise at 80% of the maximum capacity, according to the Borg Scale 12-15.	ND	50 min at least one weekly (35 min of endurance training and 15 min of strength exercises), and daily pelvic floor muscle exercises	ND	None reported	St. Olvas Hospital	Three times a week, 35 min of moderate-intensity endurance exercise and 25 min of strength training.	Adjustment to each woman's strength level.	ND	Late pregnancy: physically active ≥ 30 min/day 61%, and regular exercise training 77%
Guelfi, 2016, Australia	Upright cycle ergometer, accelerometer	Exercise physiologist	Individually	Supervised	Accelerometer, questionnaire	ND	Progressively increased session's duration	ND	Home-based stationary cycling program	ND	Intervention Group: pregnancy loss (n=1); Control Group: pregnan	At home	Sessions three times each week. Start with a 5-min warm up consisting of pedaling at an intensity equated to 55–65% of age-predicted maximum HR and a rating of 9–11 on the Borg Scale. Subsequent period	Tailored to the individual	ND	Supervised sessions by an exercise physiologist monitoring the duration

							by 5-min every 2–3 weeks, from 20 to 30 min to a max of 60 min. Degree of progression according to the baseline fitness level and ongoing pregnancy symptoms.				cy loss (n=2)		divided into 5-min periods of continuous moderate-intensity cycling, alternating with 5-min periods of interval cycling; two types of intervals: an increase in pedaling rate for 15 seconds (sec), and an increase in cycling resistance for 30 sec repeated every 2 min. End with 5-min cool-down by light stretching.			and intensity of exercise.
Wang, 2017, China	Stationary bike	Researchers	ND	Supervised	Questionnaires, Borg Scale assessing the RPE score, records based on the RPE score	ND	Progressive increase of the exercise duration to 45-60 min, adding 5 min to the intervals or the continuous phases of cycling, based on individual abilities	ND	ND	ND	Standard prenatal care for all women. Recording and review of cervical length at each examination and exclusion of women with a cervical length <25 mm.	Peking University First Hospital	Exercise at the beginning of the intervention at the lower calculated limit, based on the maximum predicted HR for age, progressively increased with the progress of the program, at least 3 days a week.	Tailored to the individual	Measurements of each participant's height to the nearest 0.5 cm without shoes, weight accurate to 0.1 kg with light clothing, and BMI calculation as kg/m².	Questionnaire, metabolic equivalents of task min/week
Daly, 2017, Ireland	Weights	Researchers	In a group	Supervised	HR monitoring, Borg Scale	Secret Facebook group goal-setting, class in a group, journaling, taught weekly, on a choice of days, and h, varied each day, and a "kids' corner" with	According to the ACOG	ND	ND	Facebook group lifestyle advice, pamphlet with information on healthy eating during pregnancy based on national guidelines	None reported	Coombe Women and Infants University Hospital, Dublin, Ireland	50–60 min of exercise sessions; 10-min warm-up focused on core and pelvic floor exercises; 15–20 min of resistance or weights working important muscle groups for a healthy pregnancy and birth recovery (lower limb, upper limb, back, and core muscle groups); 15–20 min of aerobic exercises; and 10-min cool-down.	Exercises scaled according to the ability, SMART personal goals	ParMed-X for pregnancy form to rule out contraindications to exercise in pregnancy	Attendance recorded by both participants and researchers

						toys and a mat and playpen.										

ND, no data; h, hour

Table S3a. Subgroup and sensitivity analyses for dietary intervention

Factor	Subgroup	Number of studies	Odds Ratio (95% CI)	P-value	Cochran's Q statistic	I^2 (95%CI)	Test of difference P-value
Subgroup analyses							
Low education level	More than 10% of participating women	2	0.87 (0.29, 2.59)	0.81	5.95	83% (54,94%)	<0.001
	Up to 10% of participating women	1	1.08 (0.62, 1.87)	0.78	n/a	n/a	
Increased BMI as a risk factor	Included	8	0.77 (0.50, 1.18)	0.23	19.38	64% (0, 95%)	0.049
	Not included	2	0.57 (0.36, 0.93)	0.02	0.43	0% (n/a)	
Intervention duration	More than 20 weeks	3	1.04 (0.39, 2.79)	0.94	7.14	72% (20, 90%)	0.14
	Up to 20 weeks	2	0.51 (0.22, 1.17)	0.11	1.48	33% (n/a)	
Mediterranean diet	Included	2	0.61 (0.46, 0.81)	0.0006	0.48	0% (n/a)	< 0.001
	Not included	8	0.78 (0.49, 1.25)	0.30	16.71	58% (48, 65%)	
Motivation component in the intervention	Included	9	0.68 (0.46, 1.00)	0.05	19.40	59% (17, 79%)	0.0076
	Not included	1	1.08 (0.62, 1.87)	0.78	n/a	n/a	
Sensitivity analyses							
Effect of RCT with the largest sample size	Lower sample size	9	0.73 (0.48, 1.13)	0.16	19.67	59% (19, 79%)	n/a

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; n/a, not applicable

Table S3b. Meta-regression for GDM OR in dietary intervention

Covariate	Number of studies	Coefficient b (95% CI)	SE	P-value	t
Baseline risk of GDM	10	-0.5189 (-5.69526, 4.65746)	2.641	0.085	-1.965
Study duration (months)	8	0.019 (-0.00844, 0.04644)	0.014	0.228	1.342

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; SE, standard error

Table S4a. Subgroup and sensitivity analyses for exercise intervention

Factor	Subgroup	Number of studies	Odds Ratio (95% CI)	P-value	Cochran's Q statistic	I^2 (95%CI)	Test of difference P-value
Subgroup analyses							
Low education level	More than 10% of participating women	7	0.54 (0.42, 0.70)	< 0.00001	1.82	0% (0, 57%)	< 0.001
	Up to 10% of participating women	1	0.53 (0.16, 1.81)	0.31	n/a	n/a	
Increased BMI as a risk factor	Included	8	0.62 (0.43, 0.89)	0.01	8.39	17% (0, 72%)	0
	Not included	5	0.68 (0.50, 0.92)	0.01	2.56	0% (0, 69%)	
Intervention duration	More than 20 weeks	8	0.59 (0.46, 0.77)	< 0.0001	6.42	0% (0, 64%)	< 0.001
	Up to 20 weeks	5	0.77 (0.51, 1.15)	0.20	3.73	0% (0, 78%)	
Motivation component in the intervention	Included	8	0.68 (0.51, 0.92)	0.01	5.81	0% (0, 60%)	0
	Not included	5	0.60 (0.41, 0.88)	0.009	5.05	21% (0, 84%)	
Sensitivity analyses							

Effect of RCT with the largest sample size	Lower sample size	12	0.66 (0.52, 0.83)	0.0005	10.75	0% (0, 70%)	n/a
Attrition bias	Low	12	0.64 (0.51, 0.80)	0.0001	11.25	2% (0, 71%)	n/a

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; n/a, not applicable

Table S4b. Meta-regression for GDM OR in exercise intervention

Covariate	**Number of studies**	**Coefficient b (95% CI)**	**SE**	**P-value**	**t**
Baseline risk of GDM	13	-0.108 (-2.0484, 1.8324)	0.999	0.916	-0.108
Study duration (months)	13	0.001 (- 0.001156, 0.003156)	0.011	0.949	0.066

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; SE, standard error

Table S5a. Subgroup and sensitivity analyses for diet plus exercise intervention

Factor	**Subgroup**	**Number of studies**	**Odds Ratio (95% CI)**	**P-value**	**Cochran's Q statistic**	**I^2 (95%CI)**	**Test of difference P-value**
Subgroup analyses							
Low education level	More than 10% of participating women	7	0.64 (0.40, 1.03)	0.07	15.80	62% (20, 82%)	< 0.001
	Up to 10% of participating women	3	0.89 (0.60, 1.32)	0.56	2.53	21% (0, 97%)	
Increased BMI as a risk factor	Included	17	0.75 (0.60, 0.95)	0.02	41.45	(36, 81%)	0.23
	Not included	1	0.17 (0.06, 0.51)	0.001	n/a	n/a	
Intervention duration	More than 20 weeks	6	0.97 (0.68, 1.36)	0.84	11.86	58% (2, 82%)	< 0.001

	Up to 20 weeks	8	0.64 (0.43, 0.94)	0.02	17.85	61% (51, 69%)	
Sensitivity analyses							
Effect of RCT with the largest sample size	Lower sample size	17	0.67 (0.52, 0.86)	0.002	40.16	60% (34, 76%)	n/a
Attrition bias	Low	17	0.73 (0.57, 0.93)	0.01	46.33	65% (42, 79%)	n/a

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; n/a, not applicable

Table S5b. Meta-regression for GDM OR in diet plus exercise intervention

Covariate	**Number of studies**	**Coefficient b (95% CI)**	**SE**	**P-value**	**t**
Baseline risk of GDM	18	-1.754 (-3.41412, -0.09388)	0.847	0.055	-2.071
Study duration (months)	17	0.016 (0.00032, 0.03168)	0.008	0.065	1.991

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; SE, standard error

Table S6a. GRADE evaluation of overall evidence for dietary intervention

Diet for GDM prevention

Patient or population: pregnant women with high risk for GDM
Settings: outpatient
Intervention: Diet

Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Control**	Corresponding risk **GDM**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
GDM	**Study population**		**OR 0.73** (0.51 to 1.03)	3109 (10 studies)	⊕⊕⊕⊖ **moderate**[1]	
	198 per 1000	**152 per 1000** (112 to 202)				
	Moderate					
	245 per 1000	**192 per 1000** (142 to 251)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Significant level of heterogeneity

Table S6b. GRADE evaluation of overall evidence for exercise intervention

Exercise for GDM prevention

Patient or population: pregnant women with high risk for GDM
Settings: outpatient
Intervention: Exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **GDM**				
GDM	**Study population**		**OR 0.64** (0.51 to 0.8)	2742 (13 studies)	⊕⊕⊕⊖ **moderate**	
	197 per 1000	**136 per 1000** (111 to 164)				
	Moderate					
	216 per 1000	**150 per 1000** (123 to 181)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table S6c. GRADE evaluation of overall evidence for diet plus exercise intervention

Diet plus exercise for GDM prevention

Patient or population: pregnant women with high risk for GDM
Settings: outpatient
Intervention: Diet plus exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **GDM**				
GDM	**Study population**					

	180 per 1000	**133 per 1000** (108 to 165)			
	Moderate		**OR 0.7** (0.55 to 0.9)	7673 (18 studies)	⊕⊕⊖⊖ **low**[1,2]
	255 per 1000	**193 per 1000** (158 to 236)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Significant level of heterogeneity
[2] Existence of publication bias