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DOCTORAL THESIS

Gestational Diabetes Mellitus: From classic to new risk factors. The role of physical activity behaviour and Persistent Organics Pollutants.

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Gestational Diabetes Mellitus: From classic to new risk factors. The role of physical activity behaviour and Persistent Organics Pollutants.

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Doctoral thesis presented by Malak Kouiti in the framework of cotutelle to obtain the degree of Doctor in Clinical Medicine and Public Health with international mention from the University of Granada (UGR) and the degree of Doctor in Biology, Health and Environment from the University Hassan 1th (UH1).

Based on the collaboration agreement signed between the UGR and the UH1 of Settat, research periods at the UGR were financed by the Center for Development Cooperation Initiatives (CICODE) in the framework of the UGR Development Cooperation Fund. The mobility period between April and June 2022 in the University of Birmingham was funded by the UGR international mobility program for doctoral students in the framework of the Erasmus+ scholarships.

PREAMBLE

This doctoral thesis was conducted in the Doctoral Programme Biology, Health and Environment and the Doctoral Programme Clinical Medicine and Public Health, within the framework of the cotutelle between the University Hassan 1th and the University of Granada.

The initial research project, "Exposure to Persistent Organic Pollutants (POPs) in Moroccan pregnant women and neonatal health" established in collaboration between the two universities aims to: 1) describe the level of exposure to POPs in Settat area, 2) analyse the factors associated with a high level of exposure, 3) assess the association between the levels of POPs in women of childbearing age and anthropometric measurements of the new-born. Unfortunately, this project was suspended due to the prolongation of the COVID-19 pandemic and the restriction of access to hospital units. As a consequence, the thesis had to be modified and a second project titled "Gestational Diabetes Mellitus: From classic to new risk factors. The role of physical activity behaviour and Persistent Organics Pollutants" was initiated.

This new proposal maintains the interest in maternal and child health with a focus on Gestational Diabetes Mellitus (GDM). The project consists of three axes. The first two axes analyse the role of physical activity in reducing the risk of GDM. And the third axe evaluate the role of new risk factors, such as the exposure to POPs.

In loving memory of my father,
who left us too soon, but never be forgotten…

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ABREVIATURS

ACOG American College of Obstetrics and Gynaecologists

ADA American Diabetes Association

BMI Body Mass index

CDA Canadian Diabetes Association

CI Confidence Interval

FBS Fasting Blood Glucose

GCT Glucose Challenge Test

GDM Gestational Diabetes Mellitus

GPAQ Global Physical Activity Questionnaire

IADPSG International Association of Diabetes and Pregnancy Study Groups

IDF International Diabetes Federation

IOTF International Obesity Task Force

IQR Interquartile Range

KPAS Kaiser Physical Activity Survey

LOD Limit of Detection

LOQ Limit of Quantification

NDDG National Diabetes Data Group

OGTT Oral Glucose Tolerance Test

OR Odds Ratio

PAFQ Physical Activity Frequency Questionnaire

PAS Physical Activity Survey

POP Persistent Organic Pollutants

PPAQ Pregnancy Physical Activity Questionnaire

RR Relative Risk

SPGC Society of Obstetricians and Gynaecologists of Canada

SD Standard Deviation

QUIPS Quality in Prognosis Studies scale

WHO World Health Organisation

ABSTRACT

Introduction. Gestational diabetes mellitus (GDM) is a public health problem due to being the most common metabolic disorder during pregnancy and being associated with a number of long- and short-term health consequences for both mother and child. Although several epidemiological studies aimed to analyse and investigate associated factors to GDM, such as lifestyle, the results are not constantly consistent. Furthermore, as a multifactorial disease, other determinants like environmental pollution, and in particular exposure to endocrine disruptors such as persistent organic pollutants (POPs), may also increase prevalence of GDM.

Objectives. The research carried out in this thesis aims to:

1) Evaluate the effects of dietary and/or physical activity interventions during pregnancy to prevent GDM.
2) Estimate the effect of replacing 1 hour per week of watching TV with 1 hour per week of light to moderate or vigorous physical activity before and during pregnancy on the risk of GDM.
3) Estimate the strength of the association between the exposure to POPs and GDM.

Methods. Different types of epidemiological studies were conducted to answer these questions. 1) An umbrella review including systematic reviews of randomised clinical trials that analyse the effects of physical activity and dietary interventions before and during pregnancy. 2) The isotemporal substitution model was used to calculate the effect of replacing 1 hour/week of watching TV with the same duration of physical activity on a case-control study involving 290 women with GDM (cases) and 1175 healthy women (controls). And 3) A systematic review with meta-analysis of observational studies that analyse the association between the exposure to POPs measured early in the pregnancy and the risk of GDM.

Results. Physical activity and dietary interventions may reduce the risk of developing GDM when provided separately. However, combined intervention

involving both physical activity and diet do not seem to significantly reduce the risk of GDM.

On the other hand, the pregnant women in our case-control study have a high level of sedentary behaviour. The incidence of GDM was higher in women who spend more time watching TV and did less physically active during pregnancy.

Finding obtained using the isotemporal substitution model showed that pregnant women would reduce the risk of GDM to 34% simply by replacing one hour per week of watching TV with one hour per week of pregnancy-appropriate vigorous physical activity.

Regarding the association between the exposure to POPs and the risk of GDM, our results showed a small mean difference was observed for PFHpA 0.26 (95% CI 0.17 to 0.35, I^2=0.0%), PCB180 0.37 (95% CI 0.19 to 0.56; I2=25.3%), BDE47 0.23 (95% CI, 0.0 to 0.45, I^2=0%), BDE99 0.36 (95% CI 0.14 to 0.59; I2=0%), BDE100 0.42 (95% CI 0.19 to 0.64; I2=0%) and (HCB) 0.22 (95% CI 0.01to 0.42, I2=39.6%). No considerable difference was observed for the rest of POPs.

Conclusion. GDM is a multifactorial disease associated with several health determinants. Simple lifestyle changes, such as replacing one hour per week of watching TV with one hour per week of vigorous physical activity, would reduce the risk of GDM. Other factors, such as the exposure to some POPs, may increase the risk of GDM. However, evidence show mostly moderate quality and results were heterogeneous to establish a clear association for POPs. Improving the methodology is needed to assess POPs and GDM risk.

RÉSUMÉ

Introduction. Le diabète gestationnel (DG) est un problème de santé publique. C'est la maladie métabolique la plus fréquente pendant la grossesse. Le DG a été associer aux plusieurs complications de santé chez la mère et l'enfant, à court y long terme. Bien que de nombreuses études épidémiologiques s'intéressent à analyser les différents facteurs responsables d'augmenter l'incidence du DG, tels que le mode de vie, les résultats ne sont pas toujours cohérents. En outre, comme il s'agit d'une maladie multifactorielle, d'autres déterminants de santé tels que la pollution environnementale et en particulier l'exposition à des perturbateurs endocriniens comme les polluants organiques persistants (POPs) peuvent également augmenter le risque de DG.

Objectifs. A travers des travaux de recherche menés dans le cadre de cette thèse doctoral, nous visons à :

1) Évaluer les effets des interventions basés sur le régime alimentaire et/ou l'activité physique pendant la grossesse pour prévenir le DG.
2) Estimer l'effet de remplacer une heure hebdomadaire de télévision par une heure hebdomadaire d'activité physique légère à modérée ou vigoureuse avant et pendant la grossesse sur le risque de DG.
3) Estimer la magnitude l'association entre l'exposition aux POPs et le DG.

Méthodes. Pour répondre à ces questions, différents types d'études épidémiologiques ont été menés. 1) Une revue umbrella des revues systématiques menées avec des essais cliniques randomisés analysant l'effet des interventions basées sur l'activité physique et le régime alimentaire avant et pendant la grossesse. 2) Le modèle de substitution isotemporelle a été utilisé pour calculer l'effet du remplacement d'une heure/semaine passée devant la télévision par la même durée d'activité physique dans une étude de cas-témoins portant sur 290 femmes atteintes de DG (cas) et 1 175 femmes en bonne santé (témoins). Et 3) Une revue systématique avec méta-analyse d'études observationnelles examinant l'association entre l'exposition aux POPs mesurée au début de la grossesse et le développement de DG.

Résultats. Les interventions basées sur l'activité physique et le régime alimentaire peuvent réduire le risque de DG lorsqu'elles sont menées séparément. Cependant, les interventions combinant activité physique et régime alimentaire ne semblent pas réduire de manière significative le risque de DG.

D'autre part, les femmes enceintes de notre étude cas-témoins se caractérisent par un niveau élevé de sédentarité. Les femmes qui passent plus de temps à regarder la télévision et moins de temps à être physiquement actives ont tendance à avoir un risque plus élevé de développer le DG. Les résultats obtenus à l'aide d'un modèle d'analyse isotemporelle montrent que les femmes enceintes peuvent réduire le risque de DG de 34 % simplement en remplaçant une heure par semaine passée devant la télévision par une heure par semaine d'activité physique vigoureuse approprié.

Quant aux résultats relatifs à l'exposition aux POPs en tant que facteur de risque de DG. Nos résultats montrent une petite variance dans la concentration du PFHpA 0.26 (95% CI 0.17 to 0.35, I2=0.0%), PCB180 0.37 (95% CI 0.19 to 0.56; I2=25.3%), BDE47 0.23 (95% CI, 0.0 to 0.45, I2=0%), BDE99 0.36 (95% CI 0.14 to 0.59; I2=0%), BDE100 0.42 (95% CI 0.19 to 0.64; I2=0%) et (HCB) 0.22 (95% CI 0.01to 0.42, I2=39.6%) entre les cas de DG et le groupe control concernant. Aucune différence considérable n'a été observée pour les autres POP.

Conclusion. Le DG est une maladie multifactorielle liée à différents déterminants de la santé. De simples changements de mode de vie, tels que le remplacement d'une heure de télévision hebdomadaire par une activité physique rigoureuse, peuvent réduire le risque de la maladie. En outre, l'exposition à certains POPs peuvent augmenter le risque de DG. Cependant, les preuves scientifiques sont pour la plupart de qualité moyenne et les résultats sont hétérogènes, ce qui ne permet pas d'établir un lien clair avec les POP. Il est nécessaire d'améliorer la méthodologie pour évaluer l'association entre l'éxpositio aux POPs et le risque de diabète gestationnel.

RESUMEN

Introducción. La Diabetes Gestacional (DG) es un problema de salud pública por ser la enfermedad metabólica más frecuente durante el embarazo, y por ser responsable de la aparición de deferentes condiciones en la salud de la madre y el niño a largo y corto plazo, como las la diabetes tipo 2, las enfermedades cardiovasculares y los traumas en el momento del parto. A pesar de que muchos estudios epidemiológicos se interesaron a analizar y estudiar los diferentes factores responsables del aumento de la incidencia de DG como el estilo de vida, los resultados no son siempre consistentes. Además, debido que es una enfermedad multifactorial, otros determinantes como la contaminación ambiental y especialmente la exposición a distruptores endocrinos como los Contaminantes Orgánicos Persistentes (COPs) pueden ser responsable también del aumento de la prevalencia de la DG.

Objetivos. A través de los trabajos de investigación realizado en esta tesis doctoral se pretende:

1) Evaluar los efectos de las intervenciones de dieta y/o actividad física durante el embarazo para prevenir la DG.
2) Estimar el efecto de reemplazar 1 hora por semana de ver televisión con 1 hora por semana de actividad física ligera a moderada o vigorosa antes y durante el embarazo sobre el riesgo de DG.
3) Estimar la fuerza de la asociación entre la exposición a COP y DMG en una revisión sistemática con meta-análisis

Métodos. Para responder a estas preguntas, diferentes tipos de estudios epidemiológicos se llevaron a cabo. 1) Una revisión umbrella de revisiones sistemáticas realizadas con ensayos clínicos aleatorizados que analizan el efecto de intervenciones basadas en la actividad física y la dieta antes y durante el embarazo. 2) Se utilizó el modelo de sustitución isotemporal para calcular el efecto de sustituir 1 hora/semana de ver la televisión por la misma duración de actividad física sobre en un estudio de caso-control que incluye 290 mujeres con DG (casos) y 1175 mujeres sanas (controles). Y 3) Una revisión sistemática con meta-análisis de

estudios observacionales que analizan la asociación entre la exposición a COPs medida al principio del embarazo y el desarrollo de la DG.

Resultados. Las intervenciones basadas en la actividad física y la dieta pueden reducir el riesgo de padecer la DG cuando se realizan de forma separada. Sin embargo, las intervenciones combinadas de actividad física y dieta no parecen reducir el riesgo de desarrollar la DG de forma destacable.

Por otro lado, las mujeres embarazadas de nuestro estudio de caso-control se caracterizan con alto nivel de sedentarismo. Las mujeres que pasan más tiempo viendo la televisión y menos tiempo realizando actividad física tienden a tener más riesgo de desarrollar la DG. Los resultados obtenidos mediante el modelo de análisis isotemporal mostraron que las mujeres embarazadas pueden reducir hasta 34% su riesgo de DG, simplemente reemplazando una hora por semana de televisión por una hora por semana de actividad física vigorosa apropiada al embarazo.

En cuanto a los resultados relacionados con la exposición a COPs como factor de riesgo de la DG. Nuestros hallazgos mostraron una pequeña varianza en la concentración del PFHpA 0.26 (95% CI 0.17 to 0.35, I2=0.0%), PCB180 0.37 (95% CI 0.19 to 0.56; I2=25.3%), BDE47 0.23 (95% CI, 0.0 to 0.45, I2=0%), BDE99 0.36 (95% CI 0.14 to 0.59; I2=0%), BDE100 0.42 (95% CI 0.19 to 0.64; I2=0%) et (HCB) 0.22 (95% CI 0.01to 0.42, I2=39.6%) entre los casos de DG y el grupo control. No se observaron diferencias considerables para el resto de los COPs. Sin embargo, la evidencia actual no parece lo suficientemente sólida como para sacar conclusiones firmes.

Conclusión. La DG es una enfermedad multifactorial relacionada con diferentes determinantes de salud. Simples cambios en el estilo de vida como el hecho de reemplazar una hora semanal de ver la televisión con una actividad física rigurosa puede reducir el riesgo de esta enfermedad. Otros factores como la exposición a algunos COPs pueden aumentar el riesgo de la DG. Sin embargo, la evidencia científica muestra en su mayoría una calidad moderada y los resultados fueron

heterogéneos para establecer una asociación clara para los COPs. Es necesario mejorar la metodología para evaluar los COPs y el riesgo de DMG.

INTRODUCTION

1. Gestational Diabetes Mellitus

1.1 Definition, aetiology and diagnosis

Gestational Diabetes Mellitus (GDM) is defined as a carbohydrate intolerance, first detected during pregnancy, and results in hyperglycaemia (1). As the most common metabolic disorder of pregnancy, the aetiology of GDM remains unknown. However, some theories suggest a role for placental hormones such as kisspeptin in altering beta-cell receptors, which may be associated with insulin resistance and hyperglycaemia (2–4).

As GDM is a non-symptomatic pregnancy outcome, the American Diabetes Association (ADA) recommends a systematic screening on pregnant women without diabetes (5). In general, for women without high risk factors such as obesity and a history of GDM, screening is scheduled for the second visit at 24 gestational weeks. Different criteria were used to define GDM as not standardized form was established. In 1973 O' Sullivan et al., published the first diagnostic criteria for GDM (6). Since then, different organizations such as the WHO, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), and the Canadian Diabetes Association (CDA) have developed their own criteria. Regardless of the cut-off point established by each organisation, two main strategies have been used to screen for GDM.

- One step strategy: Consist on a 75-g OGTT, GDM diagnosis cut-off point was established for a plasma
- glucose measurement greater than or equal at least one of the following values 5.1 mmol/L at fasting, 10.0 mmol/L at 1h or 8.5 mmol/L at 2h (5).
- Two step strategy: start with standardized non-fasting 50-g glucose challenge screening test (GCT), if the value is <7.8 mmol/L, no

further testing is required and if the value of the GCT is ≥11.1 mmol/L, gestational diabetes mellitus is diagnosed (Table 1).

However, to standardise the definition of GDM, the WHO recommends the use of the IADPSG criteria for a universal screening at the first antenatal visit at 24-28 weeks (1). In addition, the International Diabetes Federation (IDF) confirms that the IADPSG has the highest prevalence of GDM compared to other screening criteria (7,8).

Table 1. *GDM screening criteria*

Criteria	Glucose Challenge	Fasting blood glucose mmol/l	1-h plasma glucose mmol/l	2-h plasma glucose mmol/l	3-h plasma glucose mmol/l	Abnormal value mmol/l
Who, 1999 (9)	75g OGTT	≥ 7.0	Not required	7.8	Not required	≥ 1
Who, 2006 (10)	75g OGTT	≥ 7.0	Not required	≥ 11.1	Not required	≥ 1
Who, 2013 (11)	75g OGTT	≥ 5.1-6.9	≥ 10	≥8.5-11.0	Not required	≥ 1
Carpenter & Coustan (12)	100g OGTT	5.3	10.0	8.6	7.8	≥2
NDDG (13)	100g OGTT	5.9	10.6	9.2	8.0	≥2
IADPSG (14)	75g OGTT	≥ 5.1	≥ 10.0	≥ 8.5	Not required	≥ 1
Canadian Diabetes Association (15)	100g OGTT	≥ 5.3	≥ 10.6	≥ 8.9	Not required	≥ 1
SOGC (16)	100g OGTT	≥ 5.3	≥ 10.6	≥ 9.0	Not required	≥ 1

WHO: World health organization, IADPSG: International Association of Diabetes and Pregnancy Study Groups, NDDG: National Diabetes Data Group, SOGC: Society of Obstetricians and Gynaecologists of Canada.

1.2 Epidemiology and risk factors

In a recent meta-analysis, the IDF provided the first standardised global estimate of the prevalence of GDM 14.0% (95% CI 13.97-14.04%). The highest prevalence of hyperglycaemia was 28.0%, registered in South-East Asea region. And the lowest level was registered in Middle East & North Africa 8.6 % (Figure 1). Moreover, 16% of live birth are affected by hyperglycaemia during pregnancy, 80.3% of cases due to GDM (17).

Several factors were associated to highest levels of GDM. Which fall into two categories: 1) Unmodifiable risk factors such as age, genetic predisposition, belonging to a high-risk ethnic group, diabetes mellitus family antecedents, GDM antecedents and macrosomia antecedents (18–22). And 2) Modifiable risk factors, susceptible to change and whose modification may increase or decrease the risk of GDM, such as high body mass index (BMI), low physical activity practice, sedentary behaviour and unhealthy diet (18,23,24). These factors are of high public health interest as a key of primary prevention. However. RCTs are needed to confirm their effectiveness (See GDM prevention and treatment).

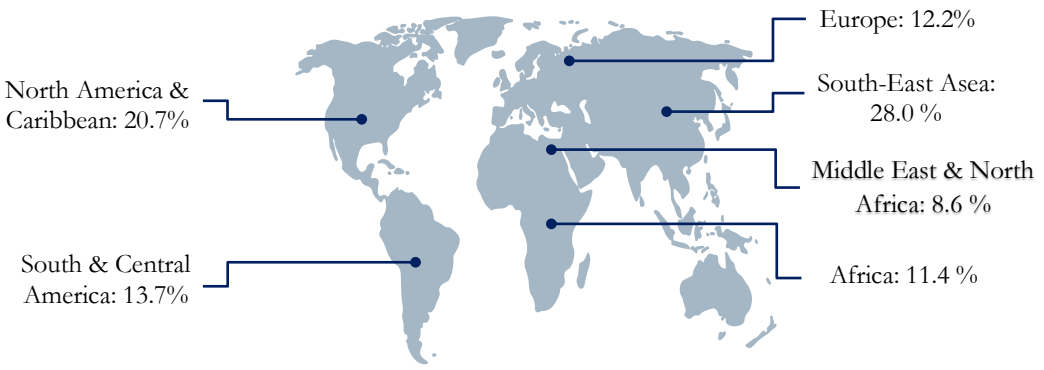


Figure 1. *Hyperglycaemia in pregnancy (20–49 years) by IDF Region, ranked by 2021 age-adjusted comparative prevalence estimates. Source: Adapted from IDF ATLAS 10th edition (17)*

1.3 Implication for maternal and new born health

Although GDM is not a chronic disease, epidemiological studies raise the association between GDM and developing multiple gynaeco-obstetrical complications. Several outcomes were observed during the embryonic and foetal stage as congenital malformation, growth retardation, abortion, macrosomia, respiratory complications and hypoglycaemia. Preterm birth and Complications during delivery were stressed as pelvic-foetal incidence and disproportion, premature rupture of membranes and caesarean (25,26).

At long term, women with GDM may develop diverse complications. Recent cohort studies affirm that GDM increase the risk of cardiovascular diseases such as coronary artery disease, myocardial infarction, ischemic stroke, peripheral artery disease, heart failure, mitral regurgitation and atrial fibrillation/flutter and metabolic morbidity (27,28). 5.7% of women with GDM develop diabetes mellitus type 2 in the next 3–6 years (29).

1.4 GDM Prevention and treatment

The increasing prevalence of GDM and the serious repercussions on maternal and neonatal health call for the development and implementation of preventive strategies. In public health the prevention of GDM is based on the control of modifiable risk factors. Several epidemiological studies have emphasised the importance of improve healthy diet and physical activity, and reduce sedentary behaviour to control blood glucose levels during pregnancy and reduce the risk of GDM. Dietary interventions based on a reduced carbohydrate and high fibre intake, or a high adherence to the Mediterranean diet help to prevent GDM (30,31). Similarly, physical activity intervention has been shown a preventive effect against GDM in several clinical trials (32).

Treatment of GDM aims to control blood glucose levels. As with prevention, the treatment strategy is generally based on dietary modification, adapted physical activity and follow-up (33). However, in some cases of GDM, pharmacotherapy may be required and a medical treatment such as insulin, metformin, or glyburide has been prescribed (34,35).

2. Physical activity

2.1 Importance of physical activity for health

Physical activity, as defined by the WHO, can be any muscular movement that requires the expenditure of energy. Physical activity is not limited to sport, as any moderate or vigorous activity performed in leisure time or for recreation and relaxation may be sufficient to improve health (36).

Physical activity is one of the most important lifestyle determinants of human health and its prognosis. Regular physical activity, such as walking, cycling, dancing and sports, helps to prevent and control chronic diseases such as cardiovascular disease, metabolic syndrome, as well as improving mental health and well-being, as confirmed by several studies and RTCs (37–39). During pregnancy, physical activity has been associated to multiple outcomes. Women with high levels of physical activity have a lower incidence of caesarean section, lower gestational weight gain, lower gestational hypertensive disorders, lower preterm birth and lower birth weight (40).

Considering that physical activity can be a low-cost and accessible solution to many health problems, such as obesity, and a preventive factor for others. Health policies should focus more on improving physical activity among the general population at different ages and for vulnerable groups.

2.2 Physical activity recommendations

The WHO provide physical activity recommendations for each age group (36):

- Children under 5: should get at least 180 min/day of physical activity and screen time is not recommended. Children under one year of age

should not be restrained for more than one hour in a pram/stroll, chair or other device.

- Children and adolescents aged 6-17 years: should be physically active for at least 60 minutes/day, including vigorous activities such as aerobic and muscle-strengthening exercises at least 3 times/week. Sedentary time needs to be limited, especially screen time.
- Adults aged 16-64 should get at least 150-300 min/week of moderate physical activity or at least 75-150 min/week of vigorous physical activity. In addition, muscle-strengthening activities were recommended at least twice a week.
- Older people aged 65 and over: Have the same recommendation as adults aged 16-64. However, in addition, they should improve functional capacity through strength training at moderate or higher intensity and emphasise functional balance through specific physical activities.
- Pregnant women with no contraindications should get at least 150 min/week of moderate-intensity exercise, including aerobic and muscle-strengthening activities. Sedentary time, especially screen time, should be replaced by physical activity of any intensity (36). The safety and appropriateness of various exercises for pregnant women, such as walking, stationary cycling, aerobic exercise, dance resistance exercise (using weights and elastic bands), stretching and aqua aerobics, have been confirmed (41).

2.3 Physical activity strategies

The WHO invite countries to implement policies and develop strategies appropriate to the characteristics of their population and their culture. The principal recommendations should insure (36):

1) The accessibility and safety of non-motorized transport as walking and cycling.

2) Create adapted workspace that encourage employees to be physically active during the work day.

3) Promote adapted space for active leisure time in educational establishments.

4) Provide physical activity education in primary and secondary schools to improve active routines at long term.

5) Establishing adapted physical activity programs and schedules for the community and school.

6) The accessibility and facility to participate in recreational physical activity events and sports.

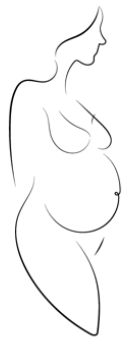
7) Health professionals encourage patients to be physical active and provide adapted advice according.

2.4 Evaluation of physical activity. Surveys and scales

Several questionnaires have been developed to measure the level of physical activity practice in different population. Up to 85 versions of questionaries can be listed (42). The WHO proposes the Global Physical Activity Questionnaire (GPAQ) to help countries in the monitor of physical activity (36,43). Other instruments have usually been used by scientists, such as the Physical Activity Frequency Questionnaire (PAFQ), Physical Activity Survey (PAS), Paffenbarger questionary (44–46). For pregnant women the Pregnancy Physical Activity Questionnaire (PPAQ) has been developed and other instruments such as Kaiser Physical Activity Survey (KPAS) and Paffenbarger questionary was adapted (47–49).

2.5 Isotemporal substitution model to analyse physical activity

In 2009, Mekary et al. developed the isotemporal substitution model to analyse the relationship between physical activity and health outcomes, considering the differences that may occur when other behaviours are removed or reallocated. The ISM is based on the fact that a day is limited to 24 hours, implying that time spent in one activity substitutes for time spent in another. The magnitude of the effect of physical activity may vary depending on the activity that is substituted (50). If 1h of watching TV is substituted by 1h of running, the inactive behaviour is reduced at the same time as the physical activity is increased. In this example, if 1h of running replaces 1h of walking, the effect may not be of the same magnitude as for watching TV.



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3. Persistent Organic Pollutants

3.1 POPs definition and types

Persistent Organic pollutants (POPs), are very lipophilic pollutants and persistent to degradation. Polychlorinated biphenyl (PCBs), Per-and polyfluoroalkyl substances (PFAS), Polybrominated diphenyl ethers (PBDE) and organochlorine pesticides (OCPs) were classified as POPs due to their persistence and bio-accumulation nature. 12 principal POPs are listed in the Stockholm Convention, identified in three categories:

- Pesticides: aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene (HCB), Hexachlorocyclohexanes (HCH) including several forms α-, β-, δ-, and γ, mirex, toxaphene.
- Industrial chemicals: hexachlorobenzene, polychlorinated biphenyls (PCBs).
- By-products: hexachlorobenzene; polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), and PCBs.

3.2 Contamination sources

Human exposure to POPs results from daily activities. The main pathway is dietary intake. Some foods, especially fish, meat and animal products such as milk and eggs, have often been a high source of contamination due to the lipophilic nature of these contaminants, which favours their accumulation in animal fat. The persistence of high levels of POPs even after their banning was justified by the persistence of food contamination (51).

Occupational exposure and indoor inhalation can also be alternative pathways of contamination. People living in industrial areas, working in a contaminated environment such as construction or building, or handling

contaminated materials such as cables, transformers and paints, as well as agricultural workers, are highly exposed to POPs (52–54).

3.3 POPs and health outcomes

The exposure to POPs can be a risk for human health due to their toxicity and persistence in human tissue and blood. Several health outcomes were associated to high contamination such as cardiovascular diseases, reparatory complications, carcinogenic, neurological, endocrine diseases, immunodeficiency and metabolic conditions such as obesity and diabetes (55,56). Hexachlorobenzene (HCB), dichlorodiphenyl-dichloroethylene (p,p'-DDE), and PCBs have been described as potential risk factors for diabetes mellitus type 2 (57,58).

Epidemiological studies suggest that early life is most vulnerable to the effect of POPs. At these most vulnerable stages, some OCPs, PCBs and HCBs appear to be a potential risk for developing neurotoxicity and altering foetal growth. In pregnant women, some studies suggest an association between pregnancy outcomes such as GDM, miscarriage, preterm birth and other adverse effects. (59–61) (Figure 2).

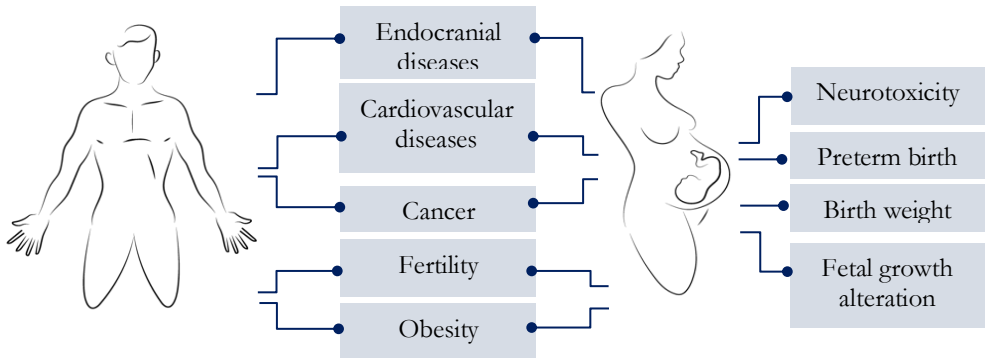

Figure 2. *Health outcomes associated to GDM*

3.4 Stockholm convention

The first text of the Stockholm convention was adopted in April 2001 and entered into vigour in 2004. Since then, it has been updated at the biennial Conferences. This convention aims to protect human health and the environment from POPs. The Stockholm convention lists 29 regulated POPs and proposes control measures to prohibit and/or limit their production and use, and to restrict their import and export. Furthermore, Stockholm convention also requires countries to develop a national plan to comply with these measures.

In Morocco, the first national plan for the implementation of the Stockholm Convention was established in 2006. A second national plan was adopted in 2019. The measures adopted are relate to three main axes: 1) regulatory and institutional measures; 2) technical and management aspects and 3) training and awareness-raising (62).

In Spain, the first national plan to implement the Stockholm Convention was adopted in 2005 and the second in 2019. The main actions were related to: 1) production, use and marketing; 2) improvement of techniques and practices; 3) management of waste and contaminated sites; 4) monitoring of POPs concentrations and evaluation of the effectiveness of the measures taken; and 5) information and awareness-raising (63).

JUSTIFICATION & HYPOTESIS

1. Justification

GDM is a serious public health problem as is the most frequent disease during pregnancy and its positive association with several health outcomes at short and long term. From a preventive perspective, GDM are closely related the mother lifestyle such as sedentary and dietary pattern. These risk factors are susceptible to change and may be the key to controlling the incidence of GDM. In this sense, several epidemiological studies have been interested in analysing the benefit of interventions that aim to promote physical activity and healthy diet on reducing GDM risk. However, some systematics reviews stress the presence of discrepancies between studies and the lack of clarity about the most effective physical activity strategies in terms of type, frequency and intensity to achieve the preventive effect (64,65). Moreover, benefit that can be achieved depend not only on the activities that are added to the woman's routine, but also on the activities that are eliminated.

On the other hand, gestational diabetes is a multifactorial obstetric complication. Analysing and intervening exclusively at the lifestyle level may not be sufficient to reach the desired prevention. Other risk factors especially those related to environmental contamination are less investigated. The exposure to some pollutants especially those with the particularity to being an endocrine disruptor such as POPs may play a role in increasing the risk of GDM.

2. Hypothesis

Therefore, this work has therefore been developed based on the following hypotheses:

- Physical activity and dietary intervention early in pregnancy help prevent GDM.
- Sedentary behaviour before and during pregnancy increase the risk of GDM.
- Pregnant women who engage in leisure-time physical activity before and during pregnancy may have a lower risk of developing GDM.
- Replacing 1 hour per week of television with 1 hour per week of light to moderate physical activity or vigorous physical activity before and during pregnancy may reduce the risk of GDM.
- Exposure to persistent organic pollutants may be another risk factor for developing GDM.

OBJECTIVES

4. General objective

Analyse the role of physical activity behaviour in the prevention of gestational diabetes mellitus and persistent organic pollutants as a new potential risk factor.

5. Specific objectives

1- Evaluate the effects of dietary and/or physical activity interventions during pregnancy on the prevention of gestational diabetes mellitus.
2- Estimate the effect of replacing 1 hour/week of TV watching with 1 hour/week of light to moderate or vigorous physical activity before and during pregnancy on the risk of gestational diabetes mellitus.
3- Estimate the strength of the association between the exposure to persistent organic pollutants and gestational diabetes mellitus.

METHODS

First objective

Evaluate the effects of dietary and/or physical activity interventions during pregnancy on preventing gestational diabetes mellitus.

Second objective

Estimate the effect of replacing 1 hour/week of watching TV with 1 hour/weekof light to moderate or vigorous physical activity before and during pregnancy on the risk of GDM.

Third objective

To estimate the strength of the association between the exposure to POPs and GDM in a systematic review with meta-analysis.

1. First objective

To evaluate the effects of dietary and/or physical activity interventions during pregnancy on the prevention of gestational diabetes mellitus an umbrella review of systematic reviews/meta-analysis was conducted according to the following PICOS statement:

- **P**opulation: Healthy pregnant women.
- **I**ntervention: Dietary and physical activity interventions before and/or during pregnancy.
- **C**omparison: Pregnant woman receiving routine care.
- **O**utcomes: Gestational diabetes mellitus.
- **S**tudy design: Systematic reviews/meta-analysis of randomized controlled studies.

1.1 Protocol & registration

A protocol was prospectively registered in PROSPERO under the reference (www.crd.york.ac.uk/PROSPERO, CRD42021237895).

1.2 Search strategy

A systematic search was done in major biomedical sources: PubMed, Scopus, Web of Science and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Methodology Register). To reduce selection bias, a hand-search on the reference of included studies was done. Additionally, automatics alerts in each data base were activated.

The search was performed combining the following terms: Gestational diabetes mellitus, gestational diabetes, Activit*, physical activity, exercise, sport, training, fitness, eating behaviors, feeding behaviors, eating habits, food habits, dietary habits, feeding patterns, dietary pattern, diet, systematic review, meta-

analysis, diabetes mellitus type 1, diabetes mellitus type 2, T2D, DM2, treatment (Table 2).

Table 2. *Search strategy*

Search	Query
#1	"Gestational diabetes mellitus" OR "gestational diabetes"
#2	"physical activity" OR Activit* OR exercise OR sport OR training OR fitness
#3	"eating behaviors" OR "feeding behaviors" OR "eating habits" OR "food habits" OR "dietary habits" OR "feeding patterns" OR "dietary pattern" OR diet
#4	"systematic review" OR metaanalysis
#5	"diabetes mellitus, type 1" [Mesh] OR "diabetes mellitus, type 2"[Mesh]
	(#1 AND (#2 OR #3) AND #4) NOT #5

1.3 Study selection

Study selection was independently conducted by two reviewers (MK and CHM), and discrepancies were resolved by a third researcher (JJJM). An initial screening based on title and abstract assessment was done. Systematic reviews and meta-analyses that met the following inclusion and exclusion criteria were then selected for full-text screening:

→ Inclusion criteria:

a) Systematic reviews and meta-analysis based on randomized controlled trials.
b) Evaluating diet and physical activity interventions, separately or in combination.
c) Including GDM as a primary or secondary outcome.

d) Published in English, Spanish, French or Arabic from the inception of the databases used for researching until December 2021.

→ Exclusion criteria

a) Reviews involving study designs other than RCTs.
b) Reviews including original studies with participants suffering GDM, diabetes mellitus type 1 or 2, or multiple pregnancy.
c) Gray literature, communications, conferences, congresses, and scientific meetings were excluded.

1.4 Data extraction

The following information was extracted individually and independently by the same two reviewers using a previously developed database containing the relevant information to be extracted from each systematic review:

- General information: First author, year of publication, title, and purpose.
- Information related to the design of the review and the original studies included: Selection criteria, number of studies included, sample size, characteristics of participants.
- Information related to the intervention and its characteristics.
- Risk of bias information: quality assessment of the original studies and the tool used (Cochrane Handbook, Jadad scale or GRADE), assessment of heterogeneity and publication bias, funding details.
- Outcome information: Measures of association (relative risk, odds ratio, risk difference).

1.5 Quality assessment

Similarly, the methodological quality of the included systematic reviews was assessed independently by two reviewers using a measurement tool to assess systematic reviews (AMSTAR-2), and discrepancies were resolved by a third reviewer.

The AMSTAR-2 tools determine the methodological quality of systematic reviews and meta-analyses of RCTs by assessing sixteen domains related to the purpose of the study, protocol and registration, search strategy, study selection, description of included studies, risk of bias and heterogeneity assessment, data combination and synthesis and the presence of conflicts of interest. The compliance of domains is considered as "yes", "partially yes" or "no", and the final score depends mainly on meeting the following seven domains considered as critical:

- Item 2: use of a previously registered protocol.
- Item 4: adequacy of the bibliographic search (use of at least two databases, definition of the search strategy and keywords, search of grey literature, and search performed within 24 months of the protocol conception and no later than 6 months before the acceptance of the manuscript.
- Item 7: information on excluded studies and the reasons for their exclusion.
- Item 9: assessment the risk of bias, such as those related to blinding and randomisation, using appropriate tools.
- Item 11: adequacy of the statistical combination on the meta-analysis using a random-effect model and considering heterogeneity.

- Item 13: the quality and risk of bias of the included studies and was considered in the interpretation of the results.
- Item 15: publication bias was assessed and results were clearly reported.

The following cut-off point were used to define the quality level of included systematic reviews:

1) Critically low quality: do not meets any critical item, regardless of meeting or not no-critical items.
2) Quality low quality: meets one critical item or less, regardless of meeting or not the no-critical items.
3) Moderate quality: meets all critical items and more than one non-critical item.
4) High quality: meets all critical item and meets at least eight of the nine no-critical items (66).

1.6 Strategy of data synthesis

The overlap between selected systematic reviews was assessed for each intervention (physical activity, diet and combined interventions), and by population characteristics (healthy pregnant women and high-risk pregnant women). In addition, systematic reviews were grouped by year of publication (before and after 2015), as systematic reviews were considered to be out of date after 5.5 years.

The overlap level was estimated as a percentage calculated using the Corrected Covered area (CCA) methods. CCA is: (N-r)/(rc-r); Where **"N"** (grand total) is the value that includes the number of primary studies evaluated in each of the systematic reviews included, **"R"** (rows) is the number of rows of the primary

studies investigated in the systematic reviews; **"C"** (columns) is the number of columns corresponding to the systematic reviews included in the overlap assessment. Very high overlap between systematic review was considered at CCA>15%, high at CCA between 11 and 15%, moderate at CCA between 6 and 10%, and low at CCA between 0-5% (67).

The characteristics of each intervention (physical activity, diet and combined intervention) were assessed and summarised. The descriptive synthesis of the results was done in a narrative way. The results of the association measures were used to compare the magnitude of the effect of each intervention on reducing the risk of GDM. In addition, a forest plot was created to summarise the results of the meta-analysis.

2. Second objective

To estimate the effect of replacing 1 hour/week of TV watching with 1 hour/week of light to moderate or vigorous physical activity before and during pregnancy on the risk of GDM, a case control study was conducted according to the following PECOS statement:

- **P**opulation: Pregnant women.
- **E**xposure: Hours/week of light to moderate or vigorous physical activity.
- **C**omparison: Hours/week of watching TV.
- **O**utcomes: Gestational diabetes mellitus.
- **S**tudy design: A case-control study of pregnant women with GDM (cases) and healthy pregnant women (controls).

2.1 Sitting

This study was conducted using a database collected previously for the project of Excellence of the Junta de Andalucía CTS 05/942 realized in the catchment area of Virgen de las Nieves University Hospital (VNUH) of Granada, Spain. This project was approved by the Ethics and Research Committees of VNUH and the University of Granada.

2.2 Target population

The population of interest was pregnant women resident in the area covered by VNUH. One in five women who attend to the hospital for the second pregnancy visit scheduled in the 20th gestational week was invited to participate in the study (Figure 3).

2.3 Eligible population

Women from the target population must meet the inclusion and exclusion criteria to be eligible for the study. Pregnant women diagnosed with GDM were allocated to cases group and healthy pregnant women to control group.

→ Inclusion criteria:

1) Spanish women aged 18 years or older, with a singleton pregnancy,
2) Residents in the area covered by the VNUH,
3) Attend to VNUH for the second visit programmed in pregnancy follow-up,
4) Included in the Andalusian Program of Infant–Maternal Health.

→ Exclusion criteria:

1) Pregnant women with metabolic disease diagnosed before pregnancy or in early gestational weeks, and who require a change in dietary pattern or physical activity during pregnancy,
2) Pregnancy with complications requiring a change in dietary pattern or physical activity during pregnancy,
3) High risk pregnancy transferred to the VNUH.

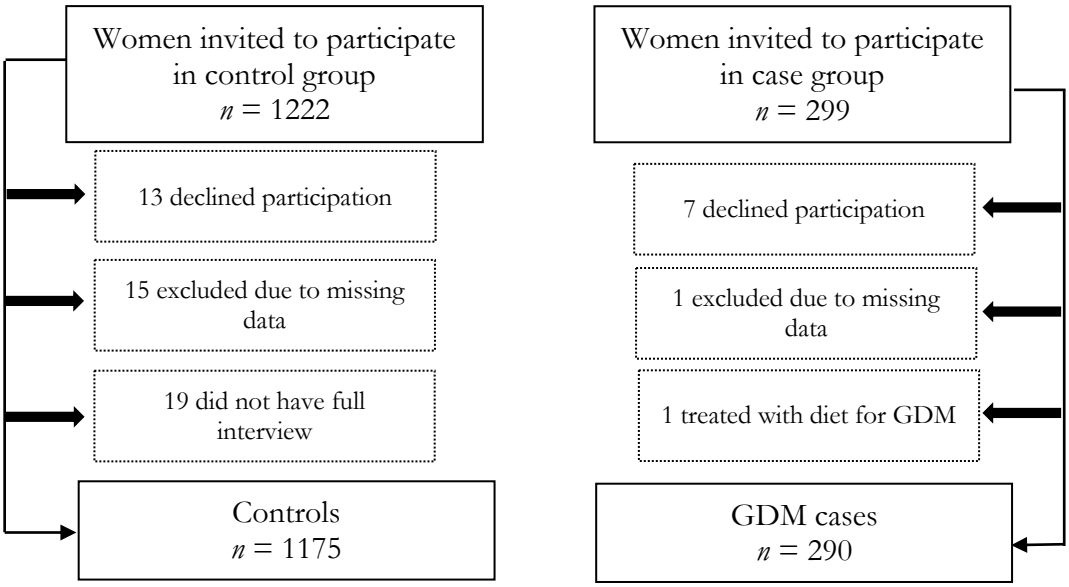

Figure 3. *Participant flowchart*

2.4 Physical activity and TV–watching assessment

Information related to time, frequency and intensity of physical activity realized on leisure time, displacement, work and house hold was collected using Paffenbarger Physical Activity Questionnaire, validated for Spanish pregnant women (49,68). Additionally, information related to sedentary behaviour such watching TV was collected.

Leisure time physical activities were classified in two categories according to the intensity provided in Ainsworth´s Compendium of Physical Activity (69):

→ Light to moderate physical activity (LMPA), including activities < 6 METs: walking, gym, swimming, and gardening.

→ Vigorous physical activity (VPA), including activities ≥ 6 METs: cycling, aerobics activities, dancing, and mountain hiking.

Then, the time (hours/week) of LMPA, VPA and TV–watching was calculated. LMPA, VPA and watching TV were divided into categories using cut-off points based on the control group physical activity and watching TV levels.

2.5 Outcome assessment

GDM cases was identified as two or more glucose test measurements equal or exceed the cut-off point of National Diabetes Data Group (NDDG) criteria. The cut-off points were: 105 mg/dL at fasting, 190 mg/dL at 1 hour, 2 hours at 165 mg/dL, and 145 mg/dL at 3 hours (13).

2.6 Confounder factors assessment

To avoid risk of bias in the association between physical activity and GDM, information related to possible confounders was collected:

- Sociodemographic characteristics such as employment, income and education level.
- Lifestyle habits including smoking, alcohol consumption and energy intake. In addition, dietary pattern was assessed using a validated food frequency questionnaire in Spanish population (70), and the adherence to Mediterranean diet was identified through the score proposed by Trichopoulous (71).
- Anthropometrics data such as wights and height. The BMI was calculated according to the equation weight (kg)/height square (m^2) and categorised according to the cut-off points established by the International Obesity Task Force (IOTF): underweight, normal weight, overweight and obesity.
- Obstetrics data such as history of pregnancies, abortions, gestational weight gain and GDM antecedents.

Participants characteristics were reported as measures of central tendency and dispersion. To compare variables between GDM cases and control group, the Chi-squared and T-Student were used as appropriate.

The odds ratio (OR) and 95% CI for the association between physical activity practice identified as LMPA and VPA, and watching TV with GDM was estimated using logistic regression model. For the adjusted model, the following

confounder were considered: maternal age, body mass index, educational level, smoking, GDM antecedent, Mediterranean diet adherence and energy intake. Additionally, light to moderate and vigorous physical activity was adjusted by watching TV and watching TV by both intensities of physical activity.

Then, joint effect of LMPA–watching TV and VPA–watching TV with GDM was estimated considering the following combination:

a) High LMPA/VPA–low watching TV.
b) High LMPA/VPA–high watching TV.
c) Low LMPA/VPA –low watching TV.
d) Low LMPA/VPA –high watching TV.

Subsequent, the effect of replacing 1 hour/week of watching TV with 1 hour/week of LMPA or VPA was estimated as the difference between β coefficient of both activities (LMPA/VPA and TV–watching). Time spent in other activities (Occupation, displacement and house hold physical activities) was considered in the statistical model. Additionally, multivariable adjustment model was conducted using the confounder factors mentioned above. Result was exponentiated and OR with 95% CI obtained reflects the prevalence reduction obtained if the participants increase the time spent in physical activity (LMPA or VPA) by 1 hour/week and reduced likewise watching–TV.

Statistical analysis was performed using STATA 15.0. All statistical tests were two-sided and statistical significance was set at $p < 0.05$.

3. Third objective

To analyse the strength of the association between the exposure to persistent organic pollutant and the risk of gestational diabetes mellitus, a systematic review and meta–analysis was conducted according to the following PECOS statement:

- **P**opulation: Healthy women of childbearing age or with sample pregnancy, whose exposure to POPs has been assessed during the year prior to the pregnancy or at the beginning of pregnancy (First trimester).
- **E**xposure: Polyfluoroalkyl substances (PFAS), Polychlorinated biphenyl (PCB), Polybrominated diphenyl ethers (PBDEs). And Organochlorine pesticides (OCPs), including Hexachlorobenzene (HCB), Dichloro-Diphenyl-Trichloroethane (DDT) and its metabolites.
- **C**omparison: Exposure reference level to POPs.
- **O**utcomes: Gestational diabetes mellitus.
- **S**tudy design: Cohort studies, case-control studies, and hybrid studies (nested case-control studies and case-cohort studies).

3.1 Protocol & registration

Protocol was prospectively registered in PROSPERO under the reference (CRD42022303450), disponible at https://www.crd.york.ac.uk/prospero/.

3.2 Search strategy

A systematic search was done in major biomedical sources: PubMed, Scopus, Web of Science and Wen of Science. To reduce selection bias, a hand-search on the reference of included studies was done. Additionally, automatics alerts in each data base were activated.

The search was performed combining the following terms: Organochlorinate, organochlorine, chlorinated, Persistent organic pollutant, POP, persistent pesticides, persistent toxic substances, Per-and polyfluoroalkyl substances, PFAs, Polybrominated diphenyl ethers, PBDEs, Polychlorinated biphenyls, PCBs, Hexachlorobenzene, HCB, Dichlorodiphenyltrichloroethane, DDT, p,p'DDT, Dichlorodiphenyldichloroethylene, DDE, p,p'DD, Dichlorodiphenyldichloroethane, DDD, p,p'DDD, Gestational diabetes mellitus, gestational diabetes, GDM.

3.3 Study selection

To be selected, studies should meet the following criteria:

a) Cohort, case-control studies, and hybrid studies (nested case-control studies and case-cohort studies).
b) Based on women of childbearing age
c) Identifying exposure level by biomonitoring at the beginning of pregnancy and analysing the relationship between the individual contamination levels of POPs and the incidence of GDM
d) Published from the inception of the database used for the search until June 2022.

All cross-sectional studies, book chapters, and conference communications were excluded.

3.4 Data extraction

The following data was extracted by two authors independently from included studies:

a) Basic data: Authors, publication year, study period, country, and research funding.

b) Study characteristics: type of study design, sample method, sample size, selection criteria, characteristics of the participants, and compliance with ethical principles.
c) Exposure data: type of examined POPs, biomarkers used to assess contamination level, gestational age for the sample collection, analytic methodology, limit of detection (LOD) or limit of quantification (LOQ), unit of measurement for POPs, and lipid adjustment for the final determinations.
d) Outcome data: The criteria used for the diagnosis of GDM were collected (National Diabetes Data Group criteria, Carpenter-Coustan criteria, International Association of Diabetes and Pregnancy Study Groups criteria, and World Health Organization criteria).
e) Descriptive measurements of POPs by comparison groups and analytic results: mean and Standard Deviation (SD), median and Interquartile Range (IQR) or geometric mean to describe the levels of POPs; and Relative Risk (RR), Odds Ratio (OR) and their 95% Confidence Interval (CI) as association measures.

3.5 Quality assessment

The methodological quality of selected studies was assessed by two authors using Quality in Prognosis Studies scale (QUIPS) (72). This assessment tool contains 32 items, categorised into six domains related to the sampling, exposure factors measurement, outcome measurement, confounding factors and statistical methods, report and risk of bias of was evaluated. The overall quality was defined according the risk of bias of each domain as follow:

- Low risk of bias: ≥ five domains judged as low risk of bias.
- Moderate risk of bias: five domains judged as low risk of bias plus one as high risk of bias. Or if two domains had moderate risk of bias.

- High risk of bias: Two items judged as moderate risk of bias
- moderate risk of bias and high risk of bias. Weighted kappa coefficient (Kw) for the six domains was measured to assess inter-rater reliability (73). Disagreement and doubt were solved through discussion with senior reviewers (JJJM and JZ).

3.6 Strategy of data synthesis and meta-analysis

A pooled standardized mean difference (SMD) was estimated separately for each type of POPs. A random effect model was used and heterogeneity was assessed using chi-square test. Publication bias was evaluated using a funnel plot and Egger's lineal regression asymmetry tests. Significance was considered at p value < 0.05. Analyses were conducted using STATA software version 14.0.

RESULTS

The results of this doctoral thesis will be presented separately for each of the objectives that have been established.

1. **First objective: Evaluate the effect of diet and/or physical activity interventions during pregnancy on preventing GDM.**

The results of the first objective are detailed bellow and were published on May 14, 2022 in Nutrient (*Impact Factor: 5.9; Percentile: 81.3*) as a review titled "Preventing Gestational Diabetes Mellitus by Improving Healthy Diet and/or Physical Activity during Pregnancy: An Umbrella Review."

1.1 Literature search and study characteristics

The search strategy yielded a total of 693 studies (PubMed n = 222; Web of Science n = 209; Scopus n = 150; and Cochrane Library n = 112). After removing duplicates, a total of 452 records were excluded by title and abstract screening and 56 were selected for full-text assessment. Five studies were excluded for not being systematic reviews (74–78), eleven for including designs other than RCTs (79–88), and six for analysing an outcome other than GDM or women was already diagnosed with GDM (89–94). Therefore, left 34 records that met the selection criteria. In addition, one review was identified by the alert activated in the databases used. Finally, a total of 35 records were included in our umbrella review (Figure 4).

The main characteristics of the 35 included systematic reviews are summarised on Table 3 to 6. The selected systematic reviews were classified according to the type of intervention analysed. Sixteen reviews aim to analyse exclusively the preventive effect of physical activity interventions on reducing the risk of GDM (64,95–109), nine analyse only dietary interventions (110–113) and fifteen reviews analyse both physical activity such as dietary interventions (114–128). Only three reviews do not include a meta-analysis (97,110,125). The number

of RCTs included for GDM analysis as principal outcome varied from 2 to 27. The association measurement was reported mostly as relative risk and odds ratio. The risk difference was reported one time (128).

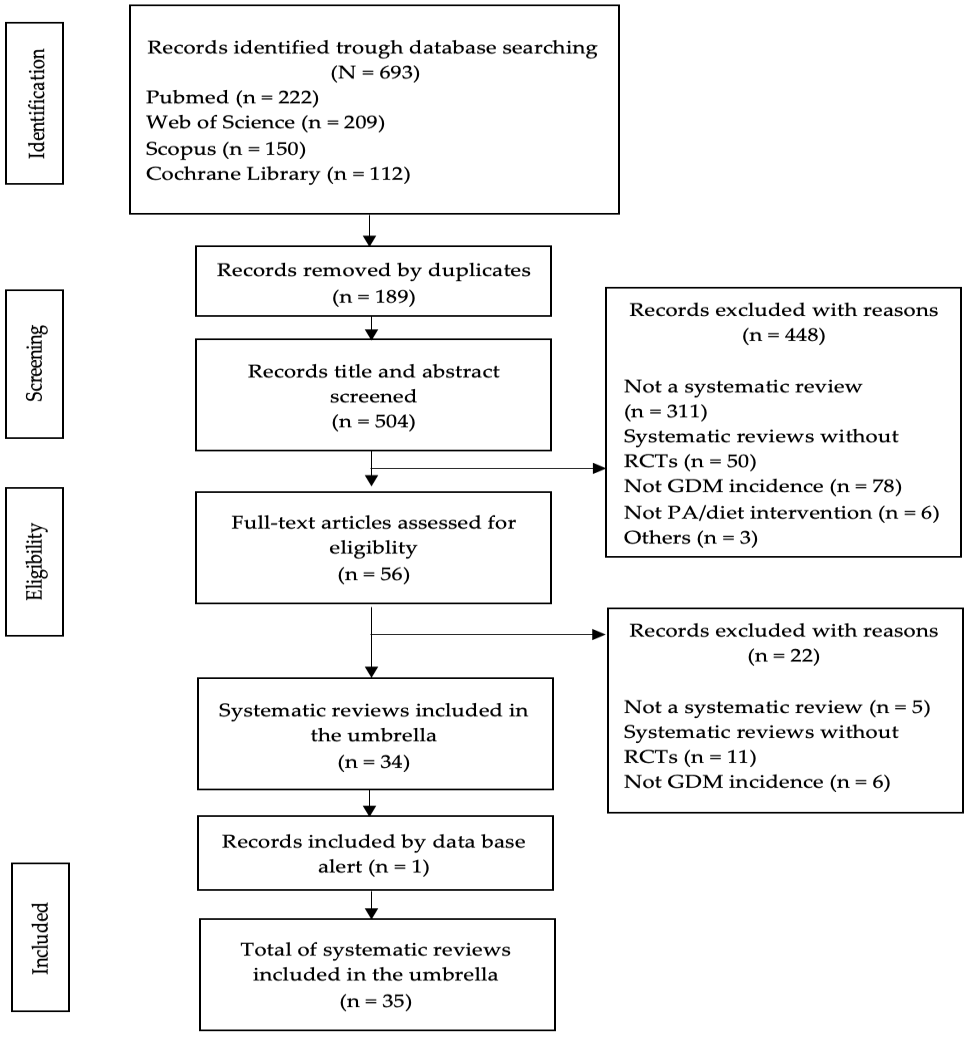

Figure 4. *Flow diagram for the search criteria.*

RCTs: Randomized controlled trials; GDM: Gestational Diabetes Mellitus and PA: Physical Activity

Table 3. *Systematic reviews and meta-analysis of randomised control trials of physical activity intervention*

Study ID	RCTs number	Sample IG/CG	Association measurement	I^2 (P)
Oostdam et al. 2011 (128)	3	125/113	RD -0.05 (-0.20—0.10)	66 (0.05)
Han et al. 2012 (108)	5	437/389	RR 1.10 (0.66 – 1.84)	0 (0.37)
Yin et al, 2014 (107)	6	-	RR 0.91 (0.57 – 1.77)	26 (0.25)
Russo et al. 2015 (106)	10	569/520	RR 0.74 (0.57 – 0.97)	12 (0.33)
Sanabria-Martínez et al. 2015 (105)	8	-	RR 0.69 (0.52 – 0.91)	0 (0.614)
Madhuvrata et al. 2015* (122)	3	76/76	OR 0.77 (0.33 – 1.79)	0 (0.53)
Aune et al, 2016 (102)	12	9804	RR 0.69 (0.50 – 0.96)	30.2 (0.15)
Song et al, 2016 (118)	-	-	RR 0.77 (0.54 – 1.09)	-
Da Silva et al. 2017 (104)	10	1883/1907	RR 0.67 (0.49 – 0.92)	33 (0.135)
Zheng et al. 2017 (109)	7	550/ 563	OR 0.62 (0.43 – 0.89)	37 (0.19)
Ming et al 2018* (103)	9	1472/ 1509	RR 0.58 (0.37 – 0.90)	46 (0.07)
Davenport 2018 (116)	27	7568/ 7198	OR 0.62 (0.52 – 0.75)	0 (0.51)
Bennett et al. 2018 (115)	12	-	RR 0.62 (0.50 – 0.78)	0 (0.909)
Yu et al. 2018 (99)	6	651/ 719	RR 0.59 (0.39 – 0.88)	46 (0.11)
Chatzakis et al. 2019* (100)	14	575/ 589	RR 0.80 (0.60 - 1.07)	30
Du et la 2019* (98)	13	550/ 572	RR 0.71 (0.57 - 0.89)	0 (0.52)
Makaruk et al. 2019 (97)	10	1747/ 2013	-	-
Nasiri-Amiri fatemeh et al. 2019* (96)	8	727/ 714	RR 0.76 (0.65 - 1.08)	50 (0.05)
Guo et al. 2019 (114)	19	5883	RR 0.70 (0.59 - 0.84)	-
Doi et al. 2020* (95)	11	722/ 745	RR 0.69 (0.51 - 0.94)	23.2 (0.015)

*Population= women at high risk; IG: intervention group; CG: control group; OR= odds ratio; RR= relative risk; RD= risk difference; N= exposed simple size; n= no exposed simple size; I^2(P) = heterogeneity test (P-value).

Table 4. *Systematic reviews and Meta-analysis of randomised control trials of dietary intervention*

Study ID	RCTs number	Sample IG/CG	Association measurement	I^2(P)
Oostdam et al. 2011 (128)	7	449/ 364	RD -0.05 (-0.10 - -0.01)	41 (0.12)
Madhuvrata et al. 2015* (122)	3	202/ 207	OR 0.33 (0.14 - 0.76)	26 (0.26)
Rogozińska et al. 2015 (129)	6	725/ 754	RR 0.67 (0.38 - 1.15)	52 (0.06)
Song et al. 2016 (118)	5	1279	RR 0.80 (0.58 - 1.10)	-
Tieu et al. 2017 (111)	11	628/ 652	RR 0.60 (0.35 - 1.04)	56 (0.07)
Bennett et al. 2018 (115)	9	3388	RR 0.56 (0.36 - 0.87)	53 (0.03)
Lamminpää et al. 2018 (110)	15	-	-	-
Guo et al. 2019 (114)	11	2838	RR 0.75 (0.59 - 0.95)	-
Zhang et al, 2020** (112)	2	911/ 937	OR 0.66 (0.52 - 0.82)	0 (0.85)

*Population= women at high risk; **Mediterranean diet; IG: intervention group; CG: control group, OR= odds ratio; RR= relative risk; N= exposed simple size; n= no exposed simple size; I^2(P) = heterogeneity test (P-value).

Table 5. *Systematic reviews and Meta-analysis of randomised control trials of mixed intervention including both physical activity and diet*

Study ID	Number RCTs	Sample IG/CG	Association measurement	I^2(P)
Bain et al. 2015 (124)	13	1903/1841	RR 0.92 (0.68 - 1.23)	43.13 (0.06)
Madhuvrata et al. 2015* (122)	-	1470	OR 1.44 (0.96 - 2.14)	0 (0.39)
Rogozińska et al. 2015 (129)	12	4745	RR 0.95 (0.76 - 1.18)	23 (0.21)
Song et al. 2016 (118)	14	4161	RR 0.85 (0.70 - 1.03)	- (0.092)
Shepherd et al. 2017 (117)	19	6633	RR 0.85 (0.71 - 1.01)	42 (0.03)
Davenport 2018 (116)	22	-	OR 0.90 (0.74 - 1.10)	30 (0.09)
Bennett et al. 2018 (115)	22	7274	RR 0.90 (0.77 - 1.05)	33 (0.072)
Guo et al. 2019 (114)	18	7024	RR 0.86 (0.71 - 1.04)	-

*Population= women at high risk; **Mediterranean diet; IG: intervention group; CG: control group; OR= odds ratio; RR= relative risk; N=exposed simple size; n= no exposed simple size; I^2(P) = heterogeneity test (P-value).

Table 6. *Systematic reviews and Meta-analysis of randomised control trials including GDM as a secondary outcome*

	Number RCTs	Sample IG/CG	Association measurement	I^2(P)
Physical actvivity				
Magro-Malosso et al 2016* (101)	7	623 / 727	RR 0.61 (0.41 - 0.90)	-
Díaz-Burrueco et al 2021 (64)	5	782/1091	OR 0.68 (0.39 - 1.19)	-
Diet				
Thangaratinam et al 2012 (127)	3	409	RR 0.39 (0.23 - 0.69)	21 (0.001)
Mixed intervention				
Rogozińska et al 2021(120)	31	5710 / 5408	OR 0.77 (0.63 - 0.94)	38 (0.02)
O'brien et al 2015(121)	2	243	RR 1.02 (0.41 - 2.57)	-
Thangaratinam et al 2012 (127)	6	1233	RR 1.18 (0.78 - 1.77)	0 (0.44)
Oteng-Ntim Et al 2012*(126)	6	526 / 491	OR 0.80 (0.58 - 1.10)	62 (0.002)

* Pregnant women at high risk; IG: intervention group; CG: control group.

1.2 Interventions characteristics

The definition of lifestyle interventions based on both physical activity and diet, as well as the interventions based on a mixed approach that include both activities, varied widely between the different RCTs included in the systematic reviews selected for this umbrella. Mostly, the interventions started early in pregnancy, before 24 gestational weeks. Pregnant women received the intervention up to 34-37 gestational weeks or up to delivery. A variety of guidelines were used to develop the interventions and advice. These include the Institute of Medicine (IOM) guidelines (117,129), the American College of Obstetricians and Gynaecologists guidelines for gestational weight gain (117), Health Canada guidelines (125,129), prenatal nutrition guidelines, official national dietary recommendations (122,125,129) and Danish recommendations (122,129,130).

Pregnant women were most likely to receive physical activity interventions in a group session, and less often at home. The interventions consisted of sessions or recommendations that included different types of exercise, such as aerobic, muscle-strengthening, resistance and balanced exercises. Cycling, swimming and pelvic floor exercises were also recommended in some RCTs. Each session included a warm-up and a cool-down, both based on walking and stretching. The intensity of the exercise was mostly light to moderate or moderate. The frequency of sessions was around three times a week, sometimes up to five times a week. The duration of each session can vary from 35 to 60 minutes.

In the dietary intervention, a dietitian or food technologist provides advice and recommendations on healthy eating, in particular by reducing energy intake, limiting high glucose intake and encouraging high fibre intake. In one of the trials, the intervention consists of the promotion of a Mediterranean diet (112). Pregnant women received the intervention in a face-to-face session. In contrast to physical activity, group sessions were less frequently used to deliver the intervention. When it was, the intervention was supported by a telephone call and/or written support. The frequency of sessions varied widely between RCTs, ranging from three to ten sessions per participant.

In the combined intervention, pregnant women received advice on physical activity and diet at the same time. Interventions were provided by informed personnel such as nutritionists or dieticians, sometimes accompanied by food technologists, physiotherapists or nurses. The frequency and types of interventions are similar to those mentioned above for physical activity and diet separately. In some trials, the interventions were supplemented by individual follow-up and personalised monitoring (ANNEX 1).

1.3 Risk of bias of included studies

The methodological quality of the 35 selected systematic reviews assessed by AMSTAR 2 is shown in Figure 5. 54.2% (n=19) of the reviews were rated as critically low quality, 38.6% (n=10) as low quality and 8.57% (n=3) as moderate quality. A similar number of reviews had of high quality. Most systematic reviews used an appropriate statistical method for meta-analyses and assessed how the risk of bias might affect the results, 84.4% (n=27) and 93.3% (n=31) respectively. In terms of risk of bias, defined by AMSTAR 2 as critical items, only 25.7% of included systematic reviews have a protocol registered before the review is conducted, and 54.3% (n=19) do not provide the list of studies likely to meet the selection criteria that were excluded by full-text reading, or the reason for exclusion. Regarding non-critical issues, less than 45% of reviews do not explain the decision on which study designs to include in the review and less than 10% report the source of funding for the included RCTs.

1.4 Overlapping assessment

The overlapping between included systematic reviews ranged from 19.3% and 37.5% (Table 7). Although this overlap is considered as very high, all systematic reviews was maintained as no systemic review covers all RCTs retrieved. For example, for the 11 systematic reviews assessed on physical activity interventions in general pregnant women published since 2015, 35 original RCTs studies were included. However, ten RCTs of the 35 were included only once time, and 13 RCTs of the 35 were used in the half of the included systematic reviews. In addition, our umbrella review does not provide a pooled effect of the meta-analysis, therefore the risk related to considering an RCTs multiple times is not conceivable.

Table 7. *Corrected Covered Area for the overlapping assessment between included systematic reviews*

Overlapping	N	CCA	Classification
Physical activity as only intervention			
Reviews of RCTs with pregnant women in general published since 2015	11	26.28%	Very high
Reviews of RCTs with high-risk women published since 2015	6	19.26%	Very high
Reviews of RCTs with pregnant women in general published before 2015	3	37.5%	Very high
Diet as only intervention	4	25.39%	Very high
Mixed intervention	5	36.49%	Very high

N = Number of reviews included in the overlapping assessment; CCA = Corrected Covered Area

1.5 Synthesis of results

Most of systematic reviews and meta-analysis found an inverse association between physical activity interventions and the risk of GDM. This association was not significant in five studies (100,107,108,118,122). Among the four meta-analysis that include women at high risk, three report a significative inverse association (100) (Figure 5. A). Regarding dietary interventions, four meta-analyses found a reduction on GDM incidence. Meanwhile, results were not statistically significant in three meta-analyses (Figure 5. B). When the participants receive a mixed intervention that includes both physical activity and diet simultaneously, the preventive effect is less clear. Regardless of the quality of the systematic reviews, the CI for ORs and RRs include the value 1 in all meta-analyses (Figure 5. C). Similar results were founded on systematic reviews and meta-analysis analysing GDM as secondary outcome (64,101,121,126,127,129).

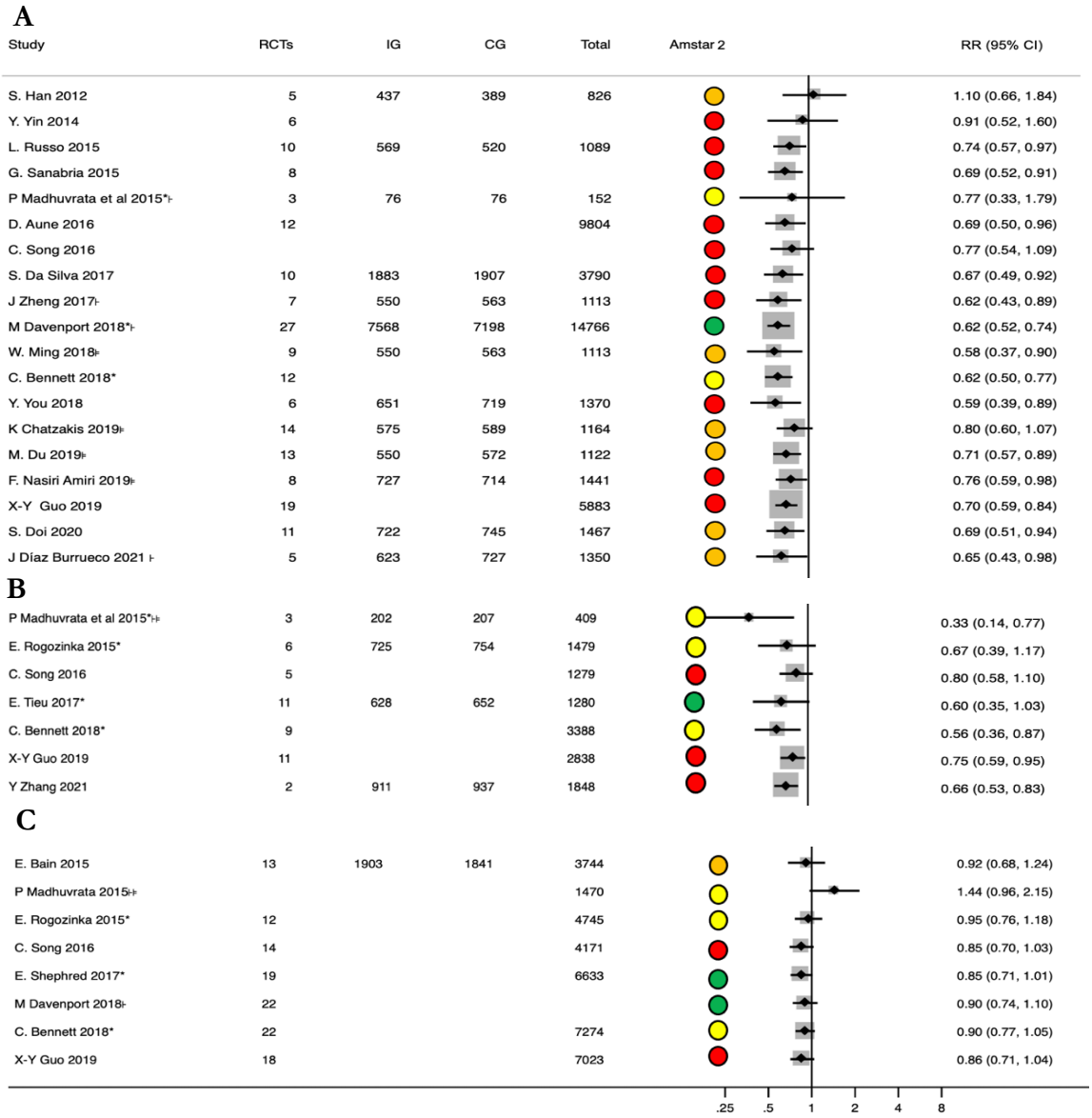

Figure 5.*Forest plot for the association of lifestyle interventions and the risk of GDM. (A) physical activity intervention. (B) Diet intervention. (C) Mixes intervention*

IG: Intervention group, CG: Control group
⊢: odds ratio and ⊨: women at high risk.

Critically low quality Low quality Moderate quality High quality

2. **Second objective: Estimate the effect of replacing 1 hour/week of watching TV with 1 hour/week of light to moderate or vigorous physical activity before and during pregnancy on the risk of GDM.**

The results of the second objective are detailed bellow and were published on October 2023 in the International Journal of Gynecology & Obstetrics (*Impact Factor: 3.9; Percentile: 74.7*) as an original article titled: "Replacement of TV watching with physical activity and change in Gestational Diabetes Mellitus risk: a case-control study".

2.1 Demographic characteristics

The sociodemographic and anthropometric characteristics of the women with GDM and the control group are summarised in Table 7. All parameters measured showed significant differences between the two groups, with the exception of educational level. In comparison with control group, women with GDM were more likely to be older, had a higher baseline BMI, gained more weight during pregnancy and had a history of GDM ($p<0.001$).

Differences in lifestyle between controls and GDM cases are shown in Table 8. Both groups were inactive and spent little time on physical activity. Before pregnancy, women with GDM had a higher energy intake ($p=0.040$) and spent less time in vigorous physical activity (0.52 vs 0.76 hours/week). During pregnancy, women with GDM spend less time on vigorous physical activity (0.06 vs 0.15 hours/week, $p=0.025$) and more time watching TV (16.01 vs. 13.97 hours/week, $p=0.002$).

***Table 8**. Baseline characteristics of control group and GDM cases*

	Controls *n* = 1175	GDM Cases *n* = 290	*p*-value
Maternal age (years), mean (SD)	29.80 (5.14)	33.49 (5.51)	<0.001
<25	178 (15.1)	18 (6.2)	
25–29	345 (29.4)	49 (16.9)	
30–34	436 (37.1)	91 (31.4)	<0.001
35–39	199 (16.9)	95 (32.8)	
≥40	17 (1.5)	37 (12.7)	
Educational level			
Primary	478 (40.7)	136 (46.9)	0.157
Secondary	339 (28.8)	74 (25.5)	
University	358 (30.5)	80 (27.6)	
BMI			
Normal weight	786 (67.0)	117 (40.3)	<0.001
Overweight	267 (22.8)	80 (27.6)	
Obesity	120 (10.2)	93 (32.1)	
Missing	2	-	
Gestational weight gain (Kg), mean (SD)	3.71 (3.51)	5.41 (5.13)	<0.001
Previous abortion			
0	933 (79.4)	202 (69.3)	<0.001
1	199 (16.9)	68 (23.4)	
≥2	43 (3.7)	21 (7.3)	
Pregnancies			
0	555 (47.2)	106 (36.5)	
1	365 (31.1)	89 (30.7)	<0.001
2	168 (14.3)	56 (19.3)	
3	61 (5.2)	22 (7.6)	
≥4	26 (2.2)	17 (5.9)	
GDM antecedents			
No	1152 (98.0)	233 (80.3)	<0.001
Yes	23 (2.0)	57 (19.7)	
Family diabetes mellitus antecedents			
No	875 (74.5)	156 (53.8)	<0.001
Yes	300 (25.5)	134 (46.2)	

Data are n (%) except if mean (SD) is indicated. GDM, Gestational Diabetes Mellitus; SD, standard deviation.

Table 9. *Lifestyle behaviors before and during pregnancy of control group and GDM cases*

	Before pregnancy			During pregnancy		
	Controls *n* = 1175	GDM Cases *n* = 290	*p*-value	Controls *n* = 1175	GDM Cases *n* = 290	*p*-value
Smoking						
Never	504 (42.9)	110 (37.9)		504 (42.9)	110 (37.9)	
Ex-smoker	242 (20.6)	72 (24.8)	0.188	242 (20.6)	71 (24.8)	0.207
Quit Smoking	–	–		209 (17.8)	59 (20.3)	
Smoker	429 (36.5)	108 (37.2)		220 (18.7)	49 (16.9)	
Alcohol consumption (g), mean (SD)	2.41 (4.24)	2.61 (4.14)	0.460	0.10 (0.67)	0.06 (0.32)	0.306
Energy intake (Kcal/day), mean (SD)	2593.69 (808.75)	2706.64 (959.79)	0.040	2563.27 (779.98)	2494.84 (834.20)	0.187
Mediterranean diet adherence						
Low	725 (61.7)	171 (59.0)		446 (38.0)	112 (38.6)	
Medium	377 (32.1)	102 (35.2)	0.604	512 (43.6)	131 (45.2)	0.663
High	73 (6.2)	17 (5.87)		217 (18.5)	47 (16.2)	
LMPA (hours/week), mean (SD)	2.60 (3.75)	2.38 (3.59)	0.372	2.73 (3.39)	2.73 (3.76)	0.984
VPA (hours/week), mean (SD)	0.76 (2.03)	0.52 (1.41)	0.058	0.15 (0.67)	0.06 (0.27)	0.025
Watching TV (hours/week), mean (SD)	12.95 (9.13)	13.95 (9.69)	0.100	13.97 (9.76)	16.01 (10.93)	0.002

Data are n (%) except if mean (SD) is indicated. GDM, Gestational Diabetes Mellitus; LMPA, light to moderate physical activity; SD, standard deviation; VPA, Vigorous Physical Activity.

2.2 Association between leisure-time physical activity and watching TV before and during pregnancy on the risk of GDM

During pregnancy, the risk of GDM increase with each hour of watching TV aOR= 1.02 (95% CI 1.00-1.03) and decrease with each hour of vigorous physical activity aOR=0.71 (95%CI 0.48–1.06). The comparison between the lowest and highest quartile of watching TV show an increase in the risk of developing GDM aOR= 1.51 (95% CI 1.93-2.45). When the joint effect of light to moderate physical activity, vigorous physical activity, and watching TV was analysed, results show that women who spent less time in light to moderate physical activity and more time on watching TV, as well as women who spent less time in vigorous physical activity and more time on watching TV, were more likely to develop GDM during pregnancy, aOR=1.76 (95%CI 1.14-2.71) and aOR=1.62 (95%CI 0.86-3.05), respectively (Table 9). This approach allows us to understand that the prevention of gestational diabetes depends not only on introducing physical activity interventions into the routine of pregnant women, but also on eliminating sedentary behaviour.

2.3 Substitution of watching TV by light to moderate and vigorous physical activity before and during pregnancy.

The replacement of 1 hour/week of watching TV by 1 hour/week of vigorous physical activity during pregnancy was associated with an aOR=0.66 (95%CI 0.43–1.00, p=0.049) in the multivariable adjusted model. Replace 1 hour/week TV watching by light to moderate physical activity did not seem to decrease the risk of GDM (Table 10). Sensitivity analyses were conducted for women with BMI <30, and women without family diabetes mellitus antecedents, no substantial change was observed (Table 11).

Table 10. *Association between leisure time physical activity, watching TV before and during pregnancy on the risk of GDM.*

	Before pregnancy		During pregnancy	
	Controls/GDM cases	aOR (95%CI)[a]	Controls/GDM cases	aOR (95%CI)[b]
LMPA (hours/week)				
For each hour		0.97 (0.93–1.02)		1.00 (0.96–1.05)
0	389/112	Reference	310/85	Reference
>0 – ≤ 1	214/38	0.58 (0.37–0.92)	278/44	0.58 (0.38–0.91)
>1 – ≤ 3.75	284/78	0.85 (0.58–1.24)	319/90	0.97 (0.66–1.42)
>3.75	288/62	0.60 (0.40–0.90)	268/71	0.94 (0.62–1.42)
VPA (hours/week)				
For each hour		0.95 (0.87–1.05)		0.71 (0.48–1.06)
0	855/222	Reference	1065/270	Reference
> 0 – ≤ 2.5	196/49	1.02 (0.68–1.51)	90/21	1.03 (0.59–1.80)
≥ 2.5	124/20	0.82 (0.47–1.40)	20/0	–
Watching TV (hours/week)				
For each hour		1.00 (0.99–1.02)		1.02 (1.00–1.03)
≥ 0 – ≤ 6	209/54	Reference	426/77	Reference
>6 – ≤ 12.25	356/75	0.88 (0.56–1.38)	422/106	0.90 (0.55–1.47)
>12.25 – ≤ 14	333/78	0.95 (0.61–0.50)	56/13	1.05 (0.64–1.70)
>14	277/84	1.10 (0.69–1.77)	271/94	1.51 (1.93–2.45)
Joint effect LMPA–watching TV				
High LMPA–low watching TV	451/108	Reference	429/103	Reference
High LMPA–high watching TV	121/32	0.98 (0.59–1.66)	158/43	1.15 (0.72–1.84)
Low LMPA–low watching TV	447/98	1.09 (0.77–1.54)	419/80	0.84 (0.58–1.21)
Low LMPA–high watching TV	156/52	1.45 (0.91–2.29)	169/64	1.76 (1.14–2.71)
Joint effect VPA–watching TV				
High VPA–low watching TV	266/57	Reference	89/17	Reference
High VPA–high watching TV	54/12	0.86 (0.39–1.90)	217/4	0.77 (0.19–3.11)
Low VPA–low watching TV	632/149	0.99 (0.67–1.44)	759/166	0.99 (0.54–1.80)
Low VPA–high watching TV	223/72	1.24 (0.78–1.97)	306/103	1.62 (0.86–3.05)

GDM, Gestational Diabetes Mellitus; LMPA, light to moderate physical activity; VPA, Vigorous Physical Activity.
[a]Adjusted for maternal age, BMI, educational level, smoking before pregnancy, GDM antecedent, Mediterranean diet adherence before pregnancy and energy intake before pregnancy. Additionally, light to moderate and vigorous physical activity was adjusted by watching TV and watching TV by both intensities of physical activity.
[b]Adjusted for maternal age, BMI, educational level, smoking during pregnancy, GDM antecedent, Mediterranean diet adherence and energy intake during pregnancy. Additionally, light to moderate and vigorous physical activity was adjusted by watching TV and watching TV by both intensities of physical activity.

Table 11. *Substitution of 1 hour/week of watching TV with 1 hour/week of physical activity for GDM.*

	Before pregnancy		During pregnancy	
	aOR 95%CI[a]	*p*-value	aOR 95%CI[b]	*p*-value
LMPA replacement	0.97 (0.93–1.02)	0.227	0.99 (0.95–1.04)	0.724
VPA replacement	0.95 (0.87–1.05)	0.328	0.66 (0.43–1.00)	0.049

LMPA, light to moderate physical activity; VPA, Vigorous Physical Activity.
[a]Adjusted for maternal age, BMI, education level, smoking before pregnancy, GDM antecedents, Mediterranean diet adherence and energy intake before pregnancy.
[b]Adjusted for maternal age, BMI, education level, smoking during pregnancy, GDM antecedents, Mediterranean diet adherence and energy intake during pregnancy.

Table 12. *Sensitivity analysis for the substitution of 1 hour/week of watching TV with 1 hour/week of light to moderate or vigorous physical activity for GDM risk*

	Controls/GDM cases		Before pregnancy		During pregnancy	
			OR 95%CI[a]	*p*–value	OR 95%CI[b]	*p*–value
Excluding women with family antecedents of diabetes mellitus	875/156	LMPA replacement	1.01 (0.96–1.07)	0.673	1.04 (0.98–1.10)	0.161
		VPA replacement	0.95 (0.83–1.09)	0.482	0.73 (0.44–1.20)	0.222
Excluding women with BMI ≥ 30	1053/198	LMPA replacement	0.99 (0.94–1.04)	0.779	1.00 (0.95–1.05)	0.902
		VPA replacement	0.96 (0.87–1.06)	0.440	0.63 (0.39–1.00)	0.053

GDM, Gestational Diabetes Mellitus; LMPA, Light to moderate Physical activity; VPA, Vigorous Physical Activity

[a]Adjusted for potential confounders maternal age, BMI, educational level, smoking before pregnancy, GDM antecedent, Mediterranean diet adherence and energy intake before pregnancy.

[b]Adjusted for potential confounders maternal age, BMI, educational level, smoking during pregnancy, GDM antecedent Mediterranean diet adherence and energy intake during pregnancy.

3. Third objective. Estimate the strength of the association between POPs exposure and GDM in a systematic review with meta-analysis.

The results of this objective are detailed bellow and were accepted on An International Journal of Obstetrics & Gynaecology *(Impact Factor: 5.8; Percentile 88)* as a review titled "Persistent Organic Pollutant exposure as a risk factor of Gestational Diabetes Mellitus: A systematic review and meta-analysis."

3.1 Literature search and study characteristics

The initial database search yielded 161 studies (PubMed n = 48; Web of Science n = 69; Scopus n = 44). A total of 78 duplicate records were removed. Accordingly, 83 studies were assessed for eligibility by title and abstract screening and 19 were selected for full text assessment. Six studies were excluded for the following reasons: the outcome was not GDM (n=3) (131–133), the assessed exposure was not POPs (n=1) (134), the exposure was not measured at the beginning of pregnancy (n=1) (135), and women already diagnosed with GDM (n=1) (136). Thus, 13 studies that met the inclusion criteria were selected and one additional study was identified by hand searching reference lists. Two records were added after the last update (137,138). Finally, 17 records were included in this systematic review (Figure 6).

Of the 16 included studies, 75% (n=12) had a cohort design while 18.75% (n=3) were nested case-control studies. Eight studies were performed in China, five in the United States, and one in Spain, Greece, and Canada. Four studies were derived from the Xicheng hospital cohort (139–142) and three from the Life cohort (143–145). The sample size median and interquartile rang was of cases and control groups was 77 (53 to 135) and 258 (154 to 1161) respectively. The exposure level of POPs was measured mostly on serum samples 68.75% (n=11)

(137–147), the plasma was used in 25% of studies (n=4),(148–151) and only one study used two types of biological samples; serum such as plasma (152).

Different criteria were employed for GDM screening. In eight studies. (137–142,146,148), Carpenter and Coustan in three studies (147,149,150). The National Diabetes Data Group was used only one time (151). One study screened GDM using two criteria; Canadian Diabetes Association and Society of Obstetricians and Gynecologists of Canada (152). Whereas, GDM diagnostic was self-reported in the three studies from Life cohort (144,145,153). GDM diagnosis was self-reported (143–145). The association between POPs and GDM was reported on different scales; OR, log transformed OR, log10-unit change OR, ln-unit change OR, risk ratio per each unit of increase of SD and OR across quartiles and terciles categories (Table 12).

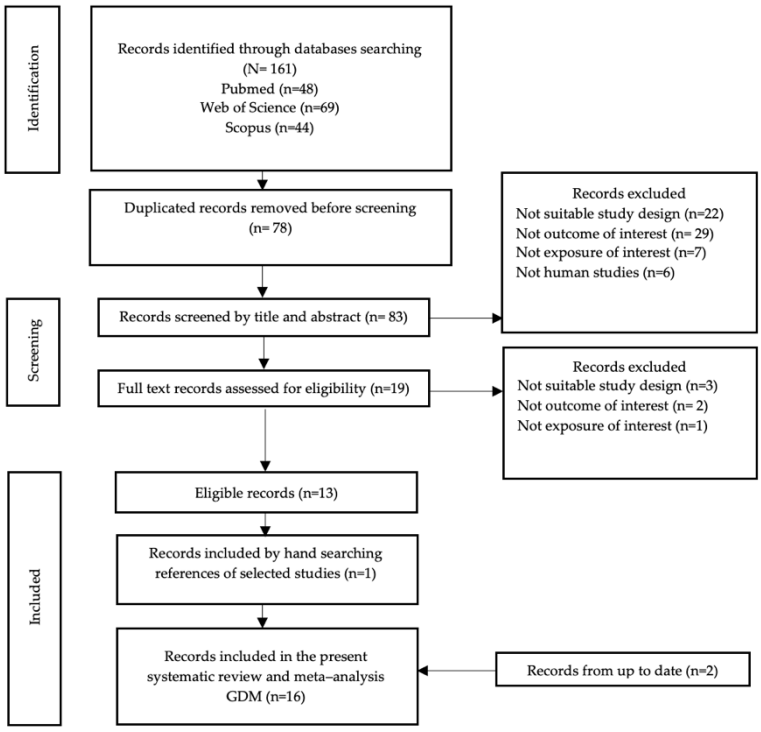

Figure 6. *Flow diagram for the search criteria*

Table 13. *Characteristics of the included studies assessing the association between different POPs and GDM.*

Article ID and country	Study design	Sample size	Bio specimen	GDM screening	Eligibility criteria	Participant characteristics	POPs categories	Measurement techniques	Adjusting variables	Exposure contrast
Zhang et al., 2023	Case control	204	Serum	OGTT (IADPSG)	Pregnant women were screened for GDM at 24–28 weeks of gestation, without a history of diabetes mellitus or pre-existing chronic medical conditions: chronic hypertension, hypothyroidism, and chronic kidney disease	Age mean±SD for GDM, 34.4 ± 4.6 years and non-GDM 30,9 ± 4,6 years. Pre-pregnancy BMI for GDM: 26.8 ± 4.2 kg/m2 and non-GDM 30,4 ± 2,9kg/m2. Primiparous: GDM, 103 (76,3%) and non-GDM 54 (78,3%)	PFAS (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDoA, PFTrA, PFTeA, PFBS, PFHxS, PFOS, 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFOSA)	Liquid chromatography Waters ACQUITY UPLC system/ tandem mass spectrometry MS/MS; XEVO_TQS	Maternal age, weeks of gestation at delivery, BMI, pregnancy times, parity, educational level, career type, blood lipids, smoking and alcohol consumption during pregnancy, fetal sex, and fetal weight.	OR (95% CI) per tercils
Zang et al., 2023	Nested case-control	590	Serum	OGTT (IADPSG)	Age ≥ 20 years, planned to seek antenatal care and planned to deliver at the study hospital. Excluded women with pre-pregnancy diabetes mellitus, history of related diseases or family history of diabetes	Age mean±SD for GDM 31.6 (3.77) and non-GDM, 31.5 (3.65) years. Pre-pregnancy BMI for GDM range (<18.5) 59.7% and non-GDM 73.6%.	PFAS (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFBS, PFPeS, PFHxS, PFHpS, PFOS, 6:2 PFESA, 8:2 PFESA)	High-performance liquid chromatography-isotope dilution tandem mass spectrometry UPLC-MS/MS	Maternal age, pre-pregnancy BMI, education, smoking, alcohol drinking, previously spontaneous abortion, pregnancy mode, ethnicity, parity, sampling time, and serum lipids	OR (95% CI) per quartiles

									(triglyceride and total cholesterol)	
Yu et al., 2021 (China) (148)	Cohort (Shangai birth cohort)	2747	Plasma	OGTT (IADPSG)	Age ≥ 20 years, without previous GDM, registered Shanghai resident, planned to seek prenatal care and give birth at the collaborative hospitals	Age mean±SD, 29.1±3.7; 63.7% Pre-pregnancy BMI (18.5-23.9); 80% nulliparous	PFAS (PFOS, PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFDoA, PFBS, PFHpA, PFOSA)	High-performance liquid chromatography/tandem mass spectrometry HPLC/MS-MS	Maternal age, pre-pregnancy BMI, maternal education, smoking status, parity, physical activity, and economic status	OR (95% CI) per log-transformed concentration
Liu et al., 2021 (China) (139)	Nested case-control study (Xicheng hospital cohort)	231	Serum	OGTT (IADPSG)	Healthy pregnant women, without prediabetes or familiar history of diabetes	Age GM and range, GDM: 28.8 (23.0-37.0) and non-GDM: 28.8 (21.0-37.0); GM and range Pregnancy BMI, GDM: 22.2 (17.3-29.4) and non GDM: 21.6 (15.6-32.4)	PFAS (PFOS, PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFHxA, PFBA, PFHpA, PFPeA), PBDE (#28, 47, 99, 100, 153, 154, 183), PCB (#28, 52, 101, 138, 153, 180)	Ultra-performance liquid chromatography tandem triple-quadrupole mass spectrometry	Pregnancy BMI, serum triglyceride and total cholesterol, (Maternal age was used as a matched pair factor)	OR (95% CI) per WQS (sum of Weighted Quartile Index for 24 POPs components)
Preston et al., 2020 (USA) (149)	Cohort (Project Viva)	1540	Plasma	GCT (Carpenter and Coustin)	Singleton pregnancy, at 22 weeks gestation or less at the time of enrollment, spoke English and without prior history of type 1 or type 2 diabetes mellitus	Age mean±SD: 31.9±5.1, prepregnany BMI mean±SD: 25.0±5.5, 50% nulliparous and 68% never Smook	PFAS (PFOS, PFOA, PFHxS, PFNA, EtFOSAA, MeFOSAA, FOSA)	High performance liquid chromatography (HPLC)	Maternal age, pre-pregnancy BMI, prior history of GDM/parity, race/ethnicity, smoking, and education	OR (95% CI) per quartiles

Xu et al., 2020 (China) (146)	Nested case-control study	495	Serum	OGTT (IADPSG)	Healthy pregnant women, without history of diabetes mellitus, multiple birth or chronic disease	Age mean±SD, GDM: 29.7±3.1 and non-GDM: 29.4±3.0; IMC ≥ 24, GDM: 10.9% and non-GDM: 7.9%	PFAS (PFOA, PFOS, PFBS, PFDoA, PFUA, PFDA, PFHpS, PFNA, PFHxS, PFDS, PFHpA, PFOSA)	Ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry	Maternal age, sampling time, parity, BMI, educational level, and serum lipids (tri-glyceride and total cholesterol)	OR (95% CI) per log-transformed concentration and per quartiles
Rahman et al., 2019 (USA) (150)	Cohort	2292	Plasma	GCT/ OGTT (Carpenter and Coustin)	Age 18-40 years. < 13 GW, Singleton pregnancy. Women with IMC > 30kg/m2, Smoking the past 6 months, consuming alcohol, and with past pregnancy complications or others medical conditions were excluded	Low risk women, Age mean±SD 28.2±5.5; 30 > IMC ≥ 25: 752 (32.8%); Nulliparous 1129 (49.3%)	PFAS (PFDA, PFDoDA, PFHpA, PFHxS, PFNA, PFOA, PFOS,PFUnDA) PCBs (Di-PCB, Tri-CB, Tetra-CB, Penta-CB, Hexa-CB, Hepta-CB, Octa-CB, Nona-CB, Deca-CB)[a], PBDE (#28, 47, 99, 100, 153, 154, 209), OCPs (γ-HCH, HCB, DDTs, Oxychlordane, Transchlordane, Transnanochlor, Mirex)	OCPs (GC-DFS)[b] /PBDEs (GC-MSD)[c]/ PCBs (HRGC-MS)[d]/ PFAS (UPLC-MS)[e]	Maternal age, BMI, education, parity, race/ethnicity, family history of DM2, serum cotinine level, and serum total lipids. (PFAS were not adjusted for serum total lipids)	RR (95% CI) for each unit of increase of SD
Liu et al., 2019	Cohort (Xicheng	189	Serum	OGGT/ PFB (IADPSG)	Pregnant women in the 1th trimester of pregnancy, without	Age mean±SD 29.3±2.9; pregnancy	PFAS (PFOS, PFOA, PFNA, PFBA, PFPeA,	Ultra-performance liquid	BMI in early pregnancy, fetal sex, and serum	OR (95% CI) per ln-unit

(China) (140)	hospital cohort)				previous history and a family history of diabetes	BMI mean±SD: 21.9±2.8	PFHxA, PFHpA)	chromatography tandem triple-quadrupole mass	triglyceride and total cholesterol (pair matched design by maternal age)	change and tercile level
Liu et al., 2018 (China) (141)	Cohort (Xicheng hospital cohort)	231	Serum	OGGT/ PFB (IADPSG)	Primipara healthy pregnant women at 1th trimester of pregnancy, without previous history and a family history of diabetes	Age mean±SD, GDM: 28.9 ±4.6, non-GDM: 28.9±2.8; BMI > 24 kg/m2, GDM: 26%, non GDM: 15.6%	PBDE (#28, 47, 99, 100, 153, 154, 183)	Gas chromatography high resolution mass spectrometry (GC-HRMS)	Pregnancy BMI, serum triglycerides and total cholesterol. (Age are matched between cases and controls)	OR (95% CI) for log-transformed concentration in a single and multiple model. OR (95% CI) per quantiles
Zhang et al., 2018 (China) (142)	Cohort (Xicheng hospital cohort)	154	Serum	OGTT (IADPSG)	Primiparous healthy pregnant women at 1th trimester of pregnancy, without previous history and a family history of diabetes	Median (IQR), age: 29.0 (27.0,31.0). BMI GDM: 21.6 (20-24.1) and BMI non-GDM :21.3 (19.8,23.1)	PCBs (#28, 52, 101, 138, 153, 180)	Gas chromatography high resolution mass spectrometry (GC-HRMS)	BMI in early pregnancy, ethnic group, parity, maternal drinking, tobacco usage during pregnancy, and serum levels of lipids. (Pair matched design by age)	OR (95% CI)

Santander et al., 2017 (Spain) (151)	Cohort (INMA)	1214	Plasma	OGTT (NDDG)	Age ≥16 years, no assisted reproduction, a singleton pregnancy, intention to deliver at the reference hospital, and no communication handicap.	Age mean±SD: 31.9±4.0; 60.7% had none Breastfeeding history; normal weight Prepreganacy BMI: 69.2%; Overweight Prepreganacy BMI: 18.5%	PFAS (PFAS, PFOS, PFOA, PFNA, PFHxS)	Column-switching high-performance liquid chromatography (HPLC) coupled to mass spectrometry (LC/MS/MS)	Country of birth, age, pre-pregnancy BMI, parity, previous breastfeeding duration, gestational week at blood extraction, physical activity, relative Mediterranean Diet Score.	OR (95% CI) per log10 unit increase and per quartiles
Vafeiadi et al., 2017 (Greece)(147)	Cohort (Rhea)	939	Serum	OGTT (Carpenter and Coustan)	Age ≥ 16 years. Understanding of the Greek language. Without prior history of diabetes.	Age mean±SD, GDM: 31±4.6 and non-GDM: 29.3±SD 5.1 (0.001); Pre-pregnancy BMI mean±SD: GDM 26.2±6.2 and non-GDM 24.2±4.7, (0.001)	PCBs (#118, 138, 153, 156, 170, 180), BDE-47, OCPs (HCB, p,p'-DDT and p,p'-DDE)	Gas chromatograph triple quadrupole mass spectrometer (GC-MS/MS)	Gestational, maternal age, pre-pregnancy BMI, parity, maternal educational level, smoking during pregnancy, gestational weight gain and maternal serum triglycerides and cholesterol	OR (95% CI) per log10 unit increase and per contamination terciles defined as (low, middle and high)
Shapiro et al., 2016	Cohort (MIREC)	1146	Urine sample for OCPs	OGTT/ GCT	Age ≥ 18 years, ability to consent and communicate in English	Age ≥ 35: 40.4%, age 30-34: 35%; BMI	PFAS (PFOA, PFOS, PFHxS), (PCBs (#118,	PCBs and OC (Gas chromatograp	Maternal age, race, pre-pregnancy BMI	OR (95% CI) per quartiles

(Canada) (152)			(DDTs and HCB) measurement. Plasma sample for PCBs	(CDA and SPGC)	or French, < 14 GW, without fetal abnormalities antecedents or history of medical complications. Planning on delivering at a local hospital.	< 25: 59%, BMI ≥ 30: 15%	138, 153, 180), OCPs (p,p'DDE, oxychlordane, trans-nonachlor DEP, DMP, DMTP)	hy mass spectrometry)/ PFAS (Waters Acuity UPLC-MS-MS)	and education; analyses for organophosphorus pesticide metabolites are additionally adjusted for urinary specific gravity; analyzes for PCBs and organochlorine pesticides are additionally adjusted for total lipids.		
Jaacks et al., 2016 (USA) (153)	Cohort (Life)	258	Serum	Self report	Age 18-49, married or in a committed relationship, self-reported menstrual cycles within the range of 21-42 days, no hormonal birth control injections in the past months, and English or Spanish speaking	Pre-pregnancy age mean±SD, GDM: 30.2±2.9 and non-GDM: 29.6±3.8; Pre-pregnancy BMI mean±SD GDM: 27.0±4.6 and non-GDM 26.1±6.4	PCBs (#153, 28, 44, 66, 74, 99, 101, 105, 110, 114, 118, 138, 146, 153, 146, 153, 156, 157, 167, 170, 172, 177, 178, 178, 180, 183, 187, 194, 195, 196, 201, 206, 209), PBB 153	High-performance gas chromatography high resolution mass spectrometry	Total serum lipids, age, and waist-to-height ratio	OR (95% CI) between maternal serum POPs and GDM	
Smarr et al., 2016 (USA) (144)	Cohort (Life)	258	Serum	Self report	Age 18-40; no physician diagnosis of infertility/sterility; menstrual cycles between 21 and 42 days	Age mean±SD 29.68±3.70, BMI mean±SD 26.17±6.29. Difference was not	OCPs (HCB, HCH, o,p'-DDT, p,p'-DDE, p,p'-DDT, Mirex,	Isotope dilution gas chromatography high resolution	Serum lipids, age, BMI, non-white race, smoking, and the sum of	OR (95% CI) between maternal serum POPs and GDM	

					consistent with use of a fertility monitor to help achieve pregnancy. Have not received injectable hormonal contraceptive, Ability to communicate in English or Spanish	significant between cases and controls.	Oxychlordane, trans-Nonachlor), PBDEs (#17, 28, 47, 66, 85, 99, 100, 153, 154, 183)	mass spectrometry	remaining chemicals in the relevant class of compounds	
Zhang et al., 2015 (USA) (145)	Cohort (Life)	258	Serum	Self report	Age 18-40 years, in a committed relationship, menstrual cycle length between 21-42 days, no injectable contraceptives within 12 months, 5) off contraception for < 2 months, no physician diagnosed infertility and able to communicate in English or Spanish	Age mean±SD 29.7±3.7. BMI (18.5,24.9): 52.3% and BMI (25.0,29.9): 27.5%	PFOS (PFOA, PFOS, PFDeA, PFNA, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH)	Isotope dilution high-performance liquid-chromatography-tandem mass spectrometry	Age, BMI, parity conditional on gravidity, race/ethnicity, and smoking	OR (95% CI) between maternal serum POPs and GDM

3.2 Risk of bias of included studies

The methodological quality of the studies included in this systematic review and meta-analysis was assessed by two authors independently using the QUIPS risk of bias assessment tool (72). Accordingly, only one study showed a low risk of bias, 68.75% (n=11) were classified as moderate risk of bias and 25% (n=4) were at high risk of bias.

The Figure 7 show the estimated risk of bias for each of the domains assessed by QUIPS. Weaknesses were related to limited reporting of study attrition details in 81.25% (n=13), exposure factor measurement in 31.25% (n=5), outcome measurement in 25% (n=4), and study confounding in 12% (n=3).

A weighted kappa was calculated for the six domains, and inter-rater agreement was substantial (weighted kappa=0.75).

Publication bias results was reported on figure 8-10.

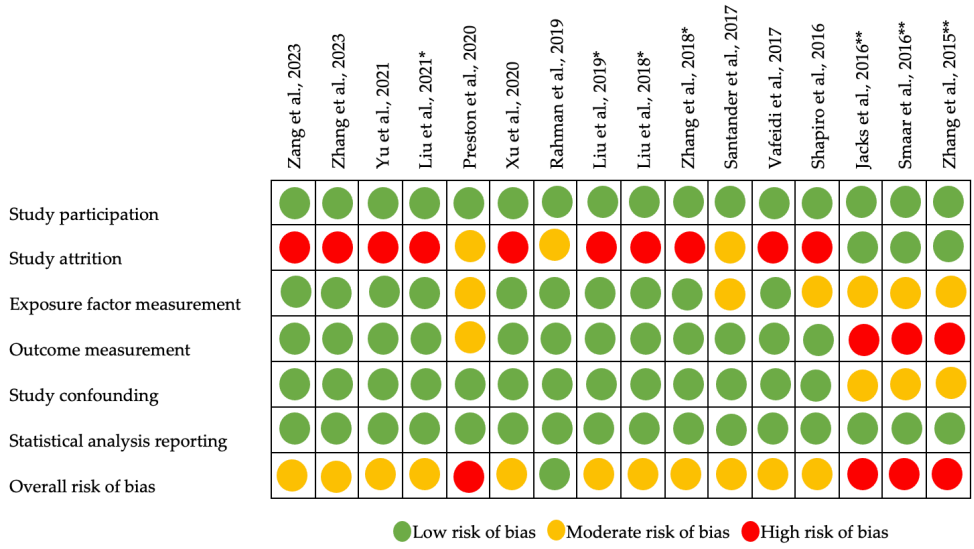

Figure 7. *Summary of QUIPS assessment applied to the cohort and nested case-control studies included in the systematic review and meta-analysis.*
* Manuscript derived from Xicheng hospital cohort
** Manuscript derived from life cohort.

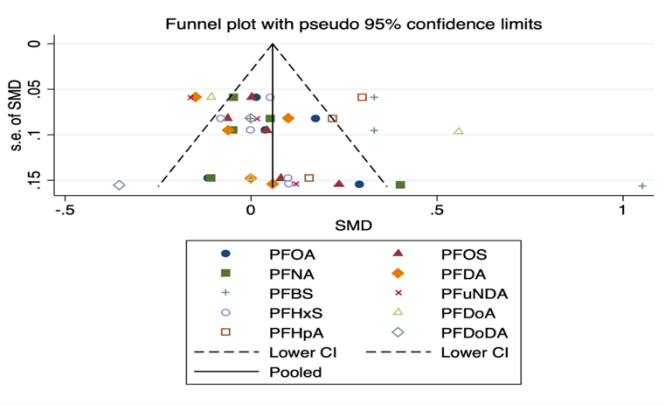

Figure 8. *PFAS funnel plot*

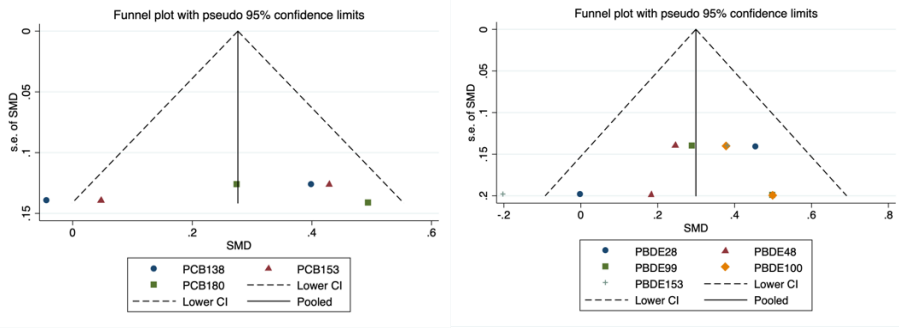

Figure 9. *PCBs and PBDE funnel plot*

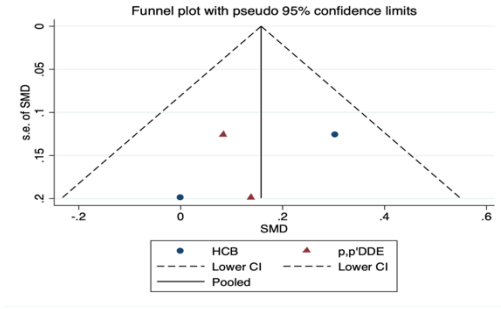

Figure 10. OCPs funnel plot

3.3 Synthesis of results

A total of 33 POPs including ten PFAS (140,145,146,148–152), sixteen PCBs (142,143,147,150,152), and three OCPs (144,147,150,152) were summarized (Table 13-15). The pooled SMD and 95% CI between GDM cases and control group was estimated where sufficient combinable data are available for the same type of POPs (Figure 11-14).

Association between PFAS exposure and GDM risk

A total of eight studies provided risk estimates for PFAS exposure (137,138,140,145,146,148–152) (Table 13). Some PFAS such as PFBS, PFDoA, PFHpA have been positively associated with the risk of GDM. However, this association has been reported in individual studies (146,148). Our meta-analysis based on continuous data show a small variance on the PFHpA exposure between GDM cases and controls, SMD=0.26 (95% CI 0.17 to 0.35, I2=0.0%) and no considerable variance was observed for the rest of PFAS (Figure 11).

Association between PCBs and GDM risk

The association between PCBs and GDM was reported on five studies. Some PCBs such as PCB 138-153, PCB 156, PCB 167, PCB 170, PCB 180, PCB 194 show an inverse association with GDM (142,143,147,150,152). However, these results were reported only on individual studies (Table 14). Our results show a small variance on the PCB180 exposure between GDM cases and controls, SMD=0.37 (95% CI 0.19 to 0.56, I2=25.3%). High heterogeneity was observed for PCB 138 and PCB 153 (Figure12).

Association between PBDE and GDM risk

The association between PBDE exposure and GDM was reported in three studies. Two studies showed a possible association between BDE-47 and BDE-154 and GDM (141,150). Individual studies stress an association between BDE-153, BDE 183 (Liu 2018), BDE 154 and GDM (150) (Table 15). Our meta-analysis shows a small variance on the BDE47, BDE99 and BDE100 exposure between GDM cases and control, 0.23 (95% CI 0.00 to 0.45, I2=0%), 0.36 (95% CI 0.14 to 0.59, I2=0%) and 0.42 (95% CI 0.19 to 0.64, I2= 0%) (Figure13).

Association between OCPs and GDM risk

A total of four studies provided risk estimates for OCPs exposure (144,147,150,152) (Table 16). Meta-analysis results between HCB and GDM show a small variance on the standardized mean difference between cases and controls 0.22 (95% CI 0.01 to 0.42, I2=39.6%). No considerable difference was observed for p,p'DDE (Figure14).

Table 14. *Summarized results of the association between PFAS and GDM*

Exposure (records number)		Article ID	Case/control sample size	Median (IQR) GDM cases	Median (IQR) control group	Adjusted exposure contrast (95% CI)
PFAS (n=10)	PFOA	Zhang et al., 2023	135/69	5.22 (2.06-7.01) ng/ml	5.03 (4.00-7.84) ng/ml	T2 1.68 (1.31-3-47) T3 3.38 (2.16-6.89) 1.84 (1.26-3.51)[d]
		Zang et al., 2023	259/259	10.3 (7.94-14.4) ng/ml	9.52 /7.04-12.6) ng/ml	Q2 1.58 (0.89-2.80) Q3 2.34 (1.32-4.16) Q4 2.37 (1.32-4.26) 1.68 (1.10-2.57)[a]
		Yu et al., 2021	325/2422	11.62±5.60 ng/ml	11.55 (5.93) ng/ml	1.11 (0.83,1.50)
		Xu et al., 2020	165/330	8.19 (3.55-13.19) ng/ml	7.91 (3.51-12.90) ng/ml	Q2 1.05 (0.45-2.04) Q3 1.12 (0.46-2.20) Q4 1.20 (0.28-2.21) 1.51 (0.63-3.84) [a]
		Preston et al., 2020	1284/85	NA	NA	Q2 1.1 (0.5-2.3) Q3 1.3 (0.6-2.8) Q4 1.4 (0.7-2.9)
		Rahman et al., 2019	1792	NA	NA	0.70 (0.43-1.14) [b]
		Liu et al., 2019	63/126	2.47 (1.88-3.27) ng/ml	2.19 (1.71-2.96) ng/ml	NA
		Matilla santander et al., 2017	53/1161	2.31 (1.71) [c] ng/ml		Q2 1.28 (0.55-3.02) Q3 1.35 (0.56-3.23) Q4 1.25 (0.50-3.13) 1.20 (0.61-2.30) [d]
		Shapiro et al., 2016	44/1102	1.64 (1.64) e µg/l	1.68 (1.80) e µg/l	Q2 0.9 (0.4-2.1) Q3 1.0 (0.4-2.2)

					Q4 0.9 (0.3-2.3)
	Zhang et al., 2015	28/230	3.94 (3.15-4.93) f ng/ml	3.07 (2.83-3.32) f ng/ml	1.86 (1.14-3.02) g
PFOS	Zhang et al., 2023	135/69	7.53 (5.00-9.98) ng/ml	7.44 (6.7.70-8.52) ng/ml	T2 0.47 (0.20-1.80) T3 1.60 (0.64-3.99) 1.37 (0.19-3.78) [d]
	Zang et al., 2023	259/259	6.11 (4.15-9.50) ng/ml	6.38 (4.07-10.4)	Q2 1.34 0.79-2.25) Q3 1.21 (0.73-1.99) Q4 0.82 (0.46-1.43) 1.02 (0.78-1.35)[a]
	Yu et al., 2021	325/2422	9.41±7.32 ng/ml	9.40 (6.90) ng/ml	1.10 (0.88,1.36)
	Xu et al., 2020	165/330	6.69 (3.24-9.42) ng/ml	6.45 (3.11-9.20) ng/ml	Q2 0.69 (0.34-2.07) Q3 0.72 (0.48-1.90) Q4 1.07 (0.51-1.32) 0.61 (0.42-1.65) [a]
	Preston et al., 2020	1284/85	NA	NA	Q2 1.1 (0.5-2.4) Q3 1.0 (0.5-2.2) Q4 1.5 (0.7-3.0)
	Rahman et al., 2019	1792	NA	NA	0.86 (0.60,1.23) b
	Liu et al., 2019	63/126	4.70 (3.01-6.34) ng/ml	4.15 (2.71-6.37) ng/ml	NA
	Matilla santander et al., 2017	53/1161	5.77 (1.61) a ng/ml		Q2 1.89 (0.77-4.64) Q3 1.54 (0.61-3.87) Q4 2.07 (0.93-6.18) 2.40 (0.93-6.18) d

	Shapiro et al., 2016	44/1102	4.74 (1.67) e μg/l	4.85 (1.81) e μg/l	Q2 0.6 (0.3-1.6) Q3 1.1 (0.5-2.5) Q4 0.7 (0.3-1.7)
	Zhang et al., 2015	28/230	13.10 (10.52-16.33) f ng/ml	12.04 (11.12-13.05) f ng/ml	1.13 (0.75-1.72) g
PFNA	Zang et al., 2023	259/259	6.11 (4.15, 9.50) ng/ml	6.38 (4.07-10.4)	Q2 1.34 (0.79-2.25) Q3 1.21(0.73-1.99) Q4 0.82 (0.46-1.43) 1.02 (0.78-1.35)[a]
	Yu et al., 2021	325/2422	1.61±1.08 ng/ml	1.65 (1.07) ng/ml	1.03 (0.81, 1.30)
	Xu et al., 2020	165/330	0.77 (0.20-1.91) ng/ml	0.83 (0.21-1.94) ng/ml	Q2 1.01 (0.57-2.04) Q3 1.14 (0.60-1.90) Q4 0.71 (0.43-1.35) 1.11 (0.49-2.85) [b]
	Preston et al., 2020	1284/85	NA	NA	Q2 1.4 (0.8-2.6) Q3 0.8 (0.4-1.9) Q4 1.0 (0.5-2.0)
	Rahman et al., 2019	1792	NA	NA	0.80 (0.50-1.27) [b]
	Liu et al., 2019	63/126	0.50 (0.37-0.59) ng/ml	0.43 (0.32-0.57) ng/ml	NA
	Matilla santander et al., 2017	53/1161	0.64 (1.75) [a] ng/ml		Q2 1.01 (0.62-2.23) Q3 1.27 (0.59-2.73) Q4 0.70 (0.28-1.75) 0.85 (0.40-1.80) [d]
	Zhang et al., 2015	28/230	1.23 (0.99-1.52) [f] ng/ml	1.20 (1.12-1.30) [f] ng/ml	1.06 (0.70-1.60) [g]

PFDA	Zhang et al., 2023	135/69	0.48 (0.33-0.57) ng/ml	0.48 (0.35-0.62) ng/ml	T2 0.86 (0.39-1.59) T3 1.29 (0.41-2.71) 1.07 (0.32-1.63)[d]
	Zang et al., 2023	259/259	1.31 (0.94,2.03) ng/ml	1.27 (0.87-1.84) ng/ml	Q2 0.91 (0.53-1.56) Q3 1.40 (1.84-2.32) Q4 1.20 (0.69-2.06) 1.13 (1.86-1.48) [a]
	Yu et al., 2021	325/2422	1.56±1.30 ng/ml	1.71 (1.38) ng/ml	0.95 (0.78-1.16)
	Xu et al., 2020	165/330	1.46 (0.90-2.27) ng/ml	1.53 (0.93-2.31) ng/ml	Q2 0.71 (0.29-1.46) Q3 1.01 (0.42-2.71) Q4 1.14 (0.53-2.07) 0.81 (0.21-2.01) [a]
	Rahman et al., 2019	1792	NA	NA	0.72 (0.39-1.32) [b]
	Liu et al., 2019	63/126	0.36 (0.29-0.51) ng/ml	0.35 (0.25-0.48) ng/ml	NA
PFBS	Zhang et al., 2023	135/69	0.36 (0.26-0.48) ng/ml	0.36 (0.31-0.51) ng/ml	T2 0.64 (0.34-1.41) T3 1.28 (0.69-2.12) 1.54 (0.19-3.04) [d]
	Zang et al., 2023	259/259	1.03 (0.64-1.71) ng/ml	0.95 (0.64-1.69) ng/ml	Q2 0.18 (0.68-2.02) Q3 1.09 (0.65-1.82) Q4 1.03 (0.61-1.73) 1.03 (0.82-1.29)[a]
	Yu et al., 2021	325/2422	0.045±0.05 ng/ml	0.035 (0.05) ng/ml	1.23 (1.05-1.44)

	Xu et al., 2020	165/330	0.17 (0.09-0.26) ng/ml	0.13 (0.07-0.24) ng/ml	Q2 1.23 (1.02-1.99) Q3 1.30 (1.25-2.17) Q4 1.97 (1.09-3.42) 1.69 (1.20-2.01) [a]
	Liu et al., 2019	63/126	0.005 (<lod-0.006) ng/ml	0.005 (<lod-0.006) ng/ml	NA
PFUnDA	Zang et al., 2023	259/259	0.02 (0.01-0.04) ng/ml	0.02 (0.01-0.04) ng/ml	Q2 0.98 (0.57-1.69) Q3 1.35 (0.79-2.30) Q4 0.90 (0.52-1.54) 1.12 (0.84-1.49)[a]
	Yu et al., 2021 Rahman et al., 2019 Liu et al., 2019	325/2422 1792 63/126	1.27±1.03 ng/ml NA 0.33 (0.26-0.50) ng/ml	1.40 (1.10) ng/ml NA 0.31 (0.21-0.43) ng/ml	0.91 (0.74-1.12) 0.66 (0.37-1.19) [b] NA
PFHxS	Zhang et al., 2023	135/69	0.45 (0.40-0.58)	0.43 (0.26-0.65)	T2 2.09 (0.91-4.85) T3 3.46 (1.64-6.30) 1.33 (1.72-3.48)[d]
	Zang et al., 2023	259/259	0.87 (0.56,1.37) ng/ml	0.86 (0.58-1.40) ng/ml	Q2 0.83 (0.50-1.39) Q3 0.90 (0.53-1.52) Q4 0.95 (0.56-1.60) 1.02 (0.81-1.29)[a]
	Yu et al., 2021	325/2422	0.54±0.25 ng/ml	0.53 (0.26) ng/ml	1.15 (0.86-1.54)
	Xu et al., 2020	165/330	1.33 (0.40-1.95) ng/ml	1.33 (0.41-1.98) ng/ml	Q2 0.71 (0.25-1.65) Q3 0.90 (0.39-2.04) Q4 0.81 (0.21-1.64) 1.09 (0.49-3.01) [a]

	Rahman et al., 2019	1792	NA	NA	0.87 (0.52-1.31) [b]
	Liu et al., 2019	63/126	0.30 (0.20-0.46) ng/ml	0.28 (0.17,0.45) ng/ml	NA
	Matilla santander et al., 2017	53/1161	0.55 (1.96) [a] ng/ml		Q2 1.25 (0.51-3.03) Q3 1.81 (0.76-4.28) Q4 1.15 (0.42-3.12) 1.58 (0.73-3.44) [d]
	Shapiro et al., 2016	44/1102	1.05 (20.3) [e] μg/l	1.02 (2.31) [e] μg/l	Q2 1.6 (0.7-3.8) Q3 1.4 (0.6-3.5) Q4 1.2 (0.4-3.5)
PFDoA	Yu et al., 2021	325/2422	0.14±0.11 ng/ml	0.15 (0.13) ng/ml	0.99 (0.78-1.26)
	Xu et al., 2020	165/330	0.19 (0.04-0.33) ng/ml	0.08 (0.02,0.28) ng/ml	Q2 0.77 (0.50-1.78) Q3 1.99 (1.10-3.23) Q4 13.02(4.71-27.28) 2.49 (1.07-3.72) [a]
PFDoDA	Zang et al., 2023	259/259	0.08 (0.06-0.09) ng/ml	0.08 (0.05-0.11) ng/ml	Q2 0.98 (0.58-1.65) Q3 1.05 (0.61-1.81) Q4 0.96 (0.57-1.62) 0.99 (0.76-1.30)[a]
	Rahman et al., 2019	1792	NA	NA	0.37 (0.12-1.10) [b]
	Liu et al., 2019	63/126	0.05 (0.02-0.07) ng/ml	0.04 (0.01,0.06) ng/ml	NA
PFHpA	Zhang et al., 2023	135/69	0.07 (0.03-0.11) ng/ml	0.07 (0.03-0.12) ng/ml	NA
	Zang et al., 2023	259/259	0.05 (0.02,0.09) ng/ml	0.04 (0.02,0.08) ng/ml	Q2 1.18 (0.70-1.99) Q3 1.05 (0.62-1.78)

					Q4 1.27 (0.76-2.11) 1.10 (0.89-1.37)[a]
	Yu et al., 2021	325/2422	0.061±0.06 ng/ml	0.054 (0.04) ng/ml	1.25 (1.07-1.46)
	Rahman et al., 2019	1792	NA	NA	0.99 (0.75-1.31)
	Liu et al., 2019	63/126	0.02 (<lod-0.03) ng/ml	0.01 (<lod-0.03) ng/ml	NA

NA: not available. Q: quartile. T: tertile

[a] Odds ratio per each log PFAS exposure.

[b] Participant without family history of T2D, RR for each unit of increase of SD.

[c] Geometric mean (Geometric standard deviation) PFOS concentration for all pregnant women in INMA birth cohort.

[d] Odds ratio per log10-unit increase.

[e] Geometric mean (SD).

[f] Geometric mean (95% CI).

[g] Odds ratio per unit of increase of SD (0.43- 0.32 and 0.55 for PFOA- PFNA and PFOS, respectively).

Table 15. *Summarized results of the association between PFAS and GDM*

Exposure (records number)		Article ID	Case/control sample size	Median (IQR) GDM cases	Median (IQR) control group	Adjusted exposure contrast (95% CI)
PCBs (n=5)	PCB28	Zhang et al., 2018	77/154	12.2 (9.8-16.9) pg/ml	11.5 (8.8-15.6) pg/ml	1.86 (1.05-3.27) [a]
		Jaack et al., 2016	258	NA	NA	0.90 (0.24-1.49)
	PCB44	Rahman et al., 2019	1792	NA	NA	1.03 (0.77-1.39) [b]
		Jaack et al., 2016	258			0.88 (0.24-3.23)
	PCB99	Rahman et al., 2019	1792	NA	NA	1.02 (0.79-1.31) [b]
		Jaack et al., 2016	258	NA	NA	0.78 (0.48-1.29)
	PCB101	Zhang et al., 2018	77/154	1.4 (1.0-1.8) pg/ml	1.0 (0.7-1.6) pg/ml	1.85 (1.22-2.82) [a]
		Jaack et al., 2016	258	NA	NA	1.00 (0.69-1.47)
	PCB110	Rahman et al., 2019	1792	NA	NA	1.07 (0.75-1.52) [b]
		Jaack et al., 2016	258	NA	NA	0.82 (0.46-1.46)
	PCB118	Vafeiadi et al., 2017	68/871	19.8±12.1 pg/ml	16.0 (11.8) pg/ml	NA
		Shapiro et al., 2016	44/1102	0.014 (2.091) [c] µg/l	0.014 (2.057) [c] µg/l	Q2 1.0 (0.4-2.6) Q3 0.9 (0.3-2.5) Q4 1.4 (0.5-3.5)
		Jaack et al., 2016	258	NA	NA	0.81 (0.51-1.29)
	PCB138	Zhang et al., 2018	77/154	11.2 (8.5-11.7) pg/ml	11.4 (7.2-14.5) pg/ml	1.51 (0.90-2.53) [a]
		Vafeiadi et al., 2017	68/871	143.0 (97.6) pg/ml	113.7 (91.7) pg/ml	NA
		Shapiro et al., 2016	44/1102	0.02 (2.22) [c] µg/l	0.02 (2.12) [c] µg/l	Q2 1.8 (0.7-4.8) Q3 1.3 (0.5-3.8) Q4 1.5 (0.5-4.2)

	Jaack et al., 2016	258	NA	NA	0.53 (0.29-0.99)
PCB153	Rahman et al., 2019	1792	NA	NA	1.01 (0.77-1.32) [b]
	Zhang et al., 2018	77/154	15.1 (10.5-24.5) pg/ml	14.7 (10.2-19.9) pg/ml	1.45 (0.88-1.88) [a]
	Vafeiadi et al., 2017	68/871	75.0±46.3 pg/ml	60.5 (50.3) pg/ml	NA
	Shapiro et al., 2016	44/1102	0.04 (2.21) [c] µg/l	0.047 (2.13) [c] µg/l	Q2 1.9 (0.7-4.8) Q3 1.0 (0.3-3.0) Q4 1.4 (0.5-4.1)
	Jaack et al., 2016	258	NA	NA	0.48 (0.24-0.98)
PCB156	Rahman et al., 2019	1792	NA	NA	0.97 (0.64-1.46) [b]
	Vafeiadi et al., 2017	68/871	7.3±8.4 pg/ml	6.0 (6.7) pg/ml	NA
	Jaack et al., 2016	258	NA	NA	0.42 (0.21-0.87)
PCB167	Rahman et al., 2019	1792	NA	NA	1.00 (0.78-1.29) [b]
	Jaack et al.- 2016	258	NA	NA	0.42 (0.21-0.84)
PCB170	Rahman et al., 2019	1792	NA	NA	1.04 (0.82-1.32) [b]
	Vafeiadi et al., 2017	68/871	36.3±30.4	30.2 (29.5)	NA
	Jaack et al., 2016	258	NA	NA	0.40 (0.18-0.88)
PCB177	Rahman et al., 2019	1792	NA	NA	1.00 (0.84-1.20) [b]
	Jaack et al., 2016	258	NA	NA	0.46 (0.17-1.25)
PCB180	Rahman et al., 2019	1792	NA	NA	1.08 (0.83-1.39) [b]
	Zhang et al., 2018	77/154	7.7 (5.1-10.3) pg/ml	6.6 (4.4-4.7) pg/ml	1.25 (0.83-1.88)
	Vafeiadi et al., 2017	68/871	71.6 (57.7) pg/ml	59.9 (57.4) pg/ml	NA
	Shapiro et al., 2016	44/1102	0.029 (2.470) [c] µg/l	0.030 (2.371) [c] µg/l	Q2 1.5 (0.6-3.8) Q3 0.7 (0.2-2.2)

					Q4 1.3 (0.5-3.5)
	Jaack et al., 2016	258	NA	NA	0.41 (0.19-0.87)
PCB194	Rahman et al., 2019	1792	NA	NA	1.03 (0.79-1.35) [b]
	Jaack et al., 2016	258	NA	NA	0.50 (0.27-0.95)
PCB206	Rahman et al., 2019	1792	NA	NA	1.07 (0.96-1.20) [b]
	Jaack et al., 2016	258	NA	NA	0.72 (0.41-1.27)
PCB209	Rahman et al., 2019	1792	NA	NA	1.01 (0.96-1.11) [b]
	Jaack et al., 2016	258	NA	NA	0.92 (0.91-1.13)

NA: not available. Q: quartile

[a] Odds ratio not adjusted.

[b] Participant without family history of T2D, RR for each unit of increase of SD.

[c] Geometric mean (SD).

Table 16. *Summarized results of the association between PBDE and GDM*

Exposure (records number)		Article ID	Case/control sample size	Median (IQR) GDM cases	Median (IQR) control group	Adjusted exposure contrast (95% CI)
PBDE (n=5)	BDE28	Rahman et al., 2019	1792	NA	NA	1.08 (0.94-1.23) [a]
		Liu et al., 2018	77/154	1.66 (1.15-2.46) pg/g wet weight	1.26 (0.87-2.00) pg/g wet weight	1.30 (0.89-1.91)
		Smarr et al., 2016	28/230	0.01 (0.004-0.01) ng/g serum	0.01(0.003-0.01) ng/g serum	
	BDE47	Rahman et al., 2019	1792	NA	NA	1.18 (1.08-1.29) [a]
		Liu et al., 2018	77/154	30.45 (22.35-47.29) pg/g wet weight	26.36 (18.03-39.07) pg/g wet weight	1.67 (1.00-2.77)
		Smarr et al., 2016	28/230	0.13 (0.06-0.19) ng/g serum	0.11 (0.06-0.21) ng/g serum	
	BDE99	Rahman et al., 2019	1792	NA	NA	1.04 (0.92-1.18) [a]
		Liu et al., 2018	77/154	30.92 (21.18-41.72) pg/g wet weight	26.85 (19.57-37.5) pg/g wet weight	1.43 (0.86,2.40)
		Smarr et al., 2016	28/230	0.03 (0.01-0.04) ng/g serum	0.02 (0.01-0.04) ng/g serum	
	BDE100	Rahman et al., 2019	1792	NA	NA	0.90 (0.49,1.66) [a]
		Liu et al., 2018	77/154	4.99 (3.36-6.34) pg/g wet weight	4.07 (2.60-6.02) pg/g wet weight	1.62 (0.98,2.61)
		Smarr et al., 2016	28/230	0.03 (0.01-0.04) ng/g serum	0.02 (0.01-0.04) ng/g serum	
	BDE153	Rahman et al., 2019	1792	NA	NA	0.64 (0.26,1.27) [a]

	Liu et al., 2018	77/154	8.24 (6.72-10.44) pg/g wet weight	7.21 (5.05-8.63) pg/g wet weight	4.04 (1.92,8.52)
	Smarr et al., 2016	28/230	0.03 (0.02-0.10) ng/g serum	0.04 (0.02-0.09) ng/g serum	
BDE154	Rahman et al., 2019	1792	NA	NA	1.23 (1.12,1.34) [a]
	Liu et al., 2018	77/154	2.41 (1.61-3.22) pg/g wet weight	1.79 (1.28-2.94) pg/g wet weight	1.88 (1.15,3.09)
	Smarr et al., 2016	28/230	0.003 (<lod-0.005) ng/g serum	<lod (<lod-0.004) ng/g serum	NA
BDE183	Liu et al., 2018	77/154	2.08 (1.44-3.28)	1.42 (0.90-2.18)	1.91 (1.31,2.80)
	Smarr et al., 2016	28/230	<lod	<lod	NA

NA: not available.

[a]Participant without family history of T2D, RR for each unit of increase of SD.

Table 17. *Summarized results of the association between OCPs and GDM*

Exposure (records number)		Article ID	Case/control sample size	Median (IQR) GDM cases	Median (IQR) control group	Adjusted exposure contrast (95% CI)
OCPs (n=5)	HCB	Rahman et al., 2019	1792	NA	NA	0.96 (0.89-1.04) [a]
		Vafeiadi et al., 2017	68/871	92.4±76.1 pg/ml	80.2 (52.3) pg/ml	1.06 (0.26-4.37) [b]
		Smarr et al., 2016	28/230	0.05 (0.04-0.06) ng/g serum	0.05 (0.04-0.06) ng/g serum	NA
	p,p'DDT	Rahman et al., 2019	1792	NA	NA	0.65 (0.23-1.86) [a]
		Smarr et al., 2016	28/230	<lod (<lod-0.02) ng/g serum	<lod (<lod-0.02) ng/g serum	NA
	p,p´DDE	Rahman et al., 2019	1792	NA	NA	1.01 (0.93-1.09) [a]
		Vafeiadi et al., 2017	68/871	2181.6±1843.4 pg/ml	2030.4 (2466.1) pg/ml	0.59 (0.23-1.51) [b]
		Smarr et al., 2016	28/230	0.60 (0.47-0.97) g/g serum	0.56 (0.38-0.77) ng/g serum	
		Shapiro et al., 2016	44/1102	0.32 (1.95) [c] µg/l	0.36 (2.36) [c] µg/l	Q2 1.4 (0.6-3.5) Q3 0.5 (0.2-1.6) Q4 1.1 (0.4-2.9)

NA: not available. Q: quartile

[a] Participant without family history of T2D RR for each unit of increase of SD.

[b] Odds ratio HCB and p,p'-DDE $\log_{10}$ pg/ml.

[c] Odds ratio HCB and p,p'-DDE $\log_{10}$ pg/ml.

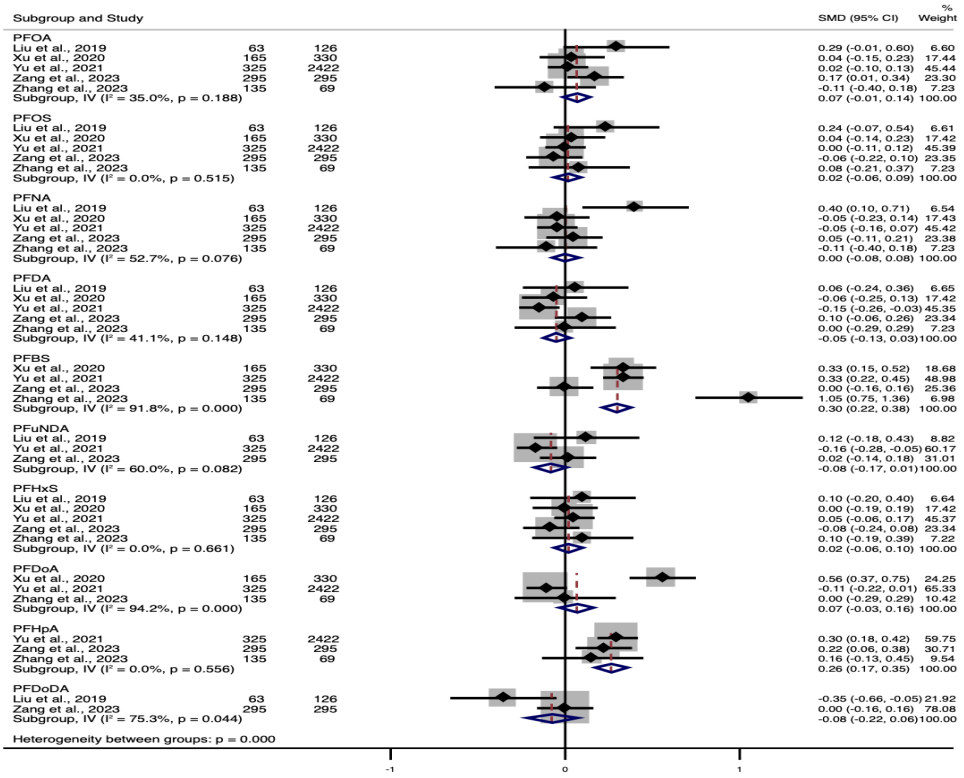

Figure 11. *Meta-analysis of the association between PFAS and the risk of GDM. Weights are from random-effects analysis.*

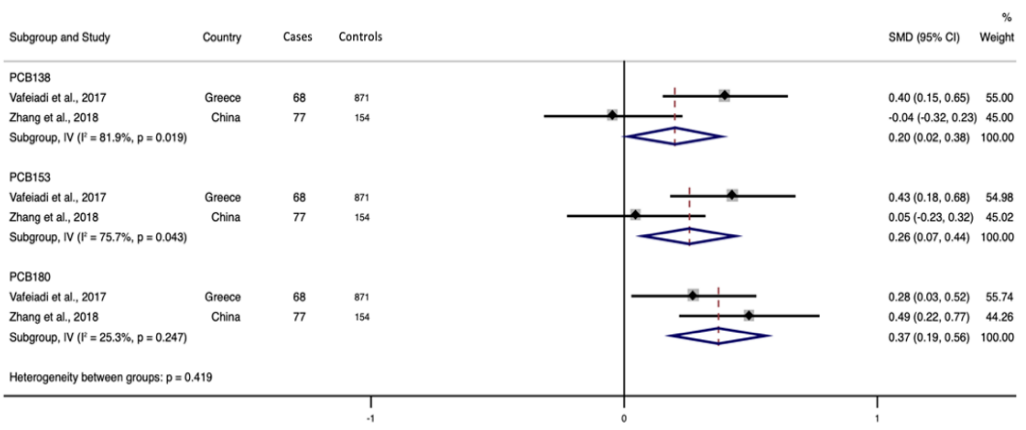

Figure 12. *Meta-analysis of the association between PCBs and the risk of GDM. Weights are from random-effects analysis.*

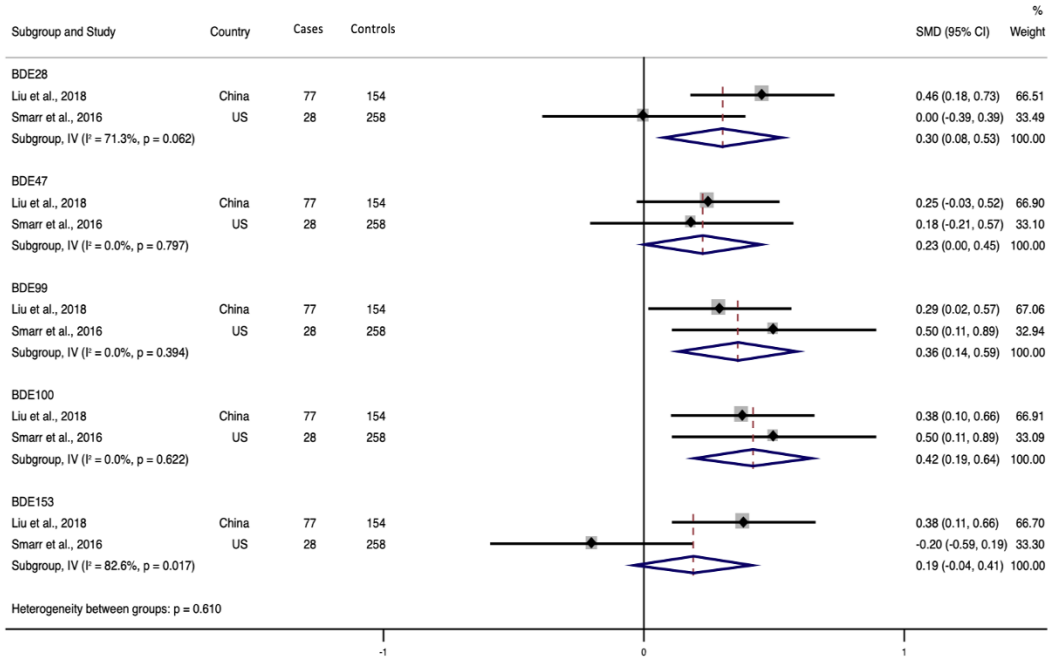

Figure 13. *Meta-analysis of the association between PBDE and the risk of GDM. Weights are from random-effects analysis.*

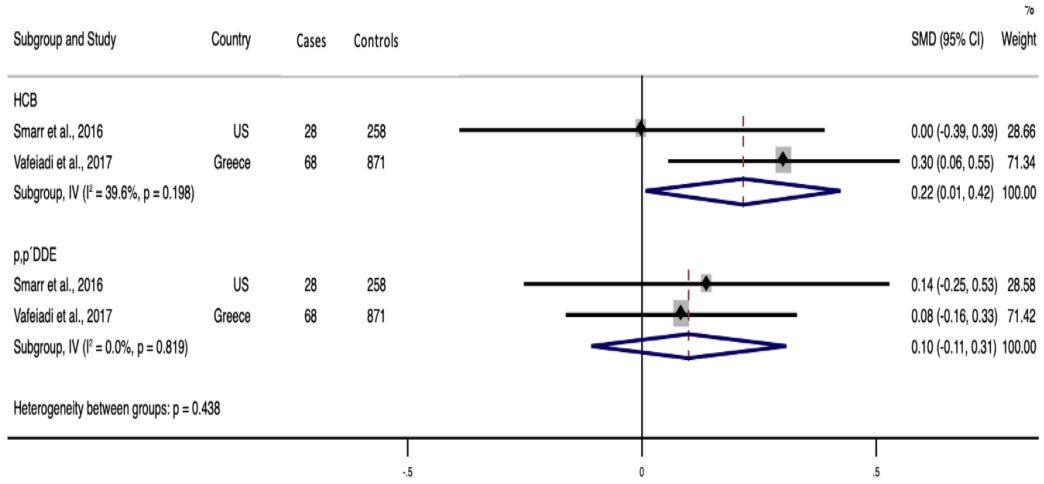

Figure 14. *Meta-analysis of the association between PBDE and the risk of GDM. Weights are from random-effects analysis.*

DISCUSSION

1. Discussion of the methodology and results of the first objective.

Evaluate the effects of diet and/or physical activity interventions during pregnancy on preventing gestational diabetes mellitus.

An umbrella review was realized on systematic review of randomized clinical trials proposing an intervention based on diet and/or physical activity. The protocol was previously registered in PROSPERO (www.crd.york.ac.uk/PROSPERO, CRD42021237895).

1.1 Principal finding

The results of our umbrella review show that systematic reviews, although variable, tend to defend the protective role of physical activity and dietary interventions. However, high variability was observed in the definition of interventions to determine a dose-effect relationship. The protective benefits of a mixed intervention, including both physical activity and diet, are not entirely clear. In addition, there is not enough high-quality evidence to determine whether combined interventions have a protective effect.

In several reviews the reduction in the risk of GDM depend on the accomplishment of certain criteria such as: starting the intervention early in the pregnancy (97), receiving supervised exercise (95), achieving at least 600 MET-min/week of moderate-intensity (116) or water exercise practice (64). However, such as the type of interventions varied widely identifying the most effective physical activity on type, intensity, frequency and duration was not feasible. Regarding dietary intervention, results reveal that low calories intake could decrease the risk of GDM. Curiously, when the intervention includes both physical activity and diet simultaneously, the results were not at all clear and the preventive effect cannot be confirmed. The presence of discrepancies in results can be

explained by the presence of differences on the population characteristics, interventions properties and circumstances such as the follow-up time, sample size, physical activity and nutritional education, the presence of not measured residual confounders and the quality of RCTs included. In addition, other factors, such as inadequate information from healthcare professionals and low motivation to prioritize lifestyle changes among participants, may increase this gap.

Although overviews are limited, several previous systematic reviews of lifestyle interventions based on physical activity and dietary intervention found similar difficulties to ours in terms of performing a dose-response analysis and drawing firm conclusions about the most effective type of physical activity intervention (110,114,125).

In line with our finding a recent umbrella suggests that single exercise intervention reduce the incidence of GDM. In contrast, another overview finding suggests a possible preventive effect for combined physical activity and diet intervention, and now effect when their provided separately. This difference may can be explained by the fact that this overview was limited to Cochrane reviews. Therefore, only 11 systematic reviews were included (65).

1.2 Methodology: strengths and limitations

Limitation of the systematic reviews included in our umbrella may hinder our ability to draw concrete recommendation about dietary pattern or physical activity in terms of type, duration of intervention, frequency and intensity. There was heterogeneity across systematic reviews and original studies in the definitions of physical activity and dietary interventions and the description provided was limited. Moreover, methodological quality was relatively low and high risk of bias was observed.

On the other hand, the main of this umbrella review strengths lay in:

1) Being one of the few works that provide an exhaustive analysis of the three types of interventions "physical activity", "diet" or "mixed intervention" in the prevention of GDM.

2) Developed according to the protocol previously registered in PROSPERO (CRD42021237895).

3) Performed an exhaustive search in the four main electronic databases without date restrictions.

4) All major steps, such as selection of systematic reviews, data extraction, quality assessment and measurement of overlap, were performed independently by two investigators to reduce potential bias.

1.3 Clinical practice

Our umbrella review supports current recommendations for lifestyle modification, particularly diet and physical activity, in pregnant women. However, there are still inconsistencies in the currently available scientific evidence, and the best strategies to promote the preventive effect remain unclear. Therefore, we will emphasise the need for clinical trials with appropriate methodology to analyse dose-effects and differences in effects between different dietary and physical activity interventions.

On the other hand, physical activity and dietary programmes should be promoted in primary care. Primary care providers responsible for monitoring pregnant women are not specifically trained to provide personalised physical activity and dietary interventions to pregnant women. It will therefore be necessary to train current providers and to strengthen these services with specialist staff such as dieticians, nutritionists and antenatal physical activity trainers.

2. Discussion of the methodology and results of the second objective.

Estimate the effect of replacing 1 hour/week of watching TV with 1 hour/weekof light to moderate or vigorous physical activity before and during pregnancy on the risk of GDM.

A case-control study was carried out, including a total of 290 women with GDM (cases) and 1175 controls (healthy women). Physical activity was assessed using Paffenbarger questionary validated for Spanish pregnant women.

2.1 Principal finding

During pregnancy, women with GDM spent less time in vigorous physical activity and more time watching TV than controls ($p<0.05$). Therefore, each hour of TV watching during pregnancy could slightly increase the risk of GDM, ORa= 1.02 (95% CI 1.00-1.03). The results of the isotemporal substitution model show that replacing one hour of TV per week with one hour of vigorous physical activity could reduce the risk of developing GDM by 34%, aOR=0.66 (95%CI 0.43-1.00).

Several epidemiological studies suggest an inverse association between physical activity and the prevention of GDM. However, the specific type of physical activity, in terms of frequency, duration and intensity that guarantees a preventive effect against GDM has not yet been fully identified (154,155). In difference to the statistical approaches traditionally used to analyse the association between physical activity and GDM, this study uses an isotemporal substitution model, which estimates the magnitude of the effect obtained by substituting one behaviour for another. The main findings stress the low level of physical activity among pregnant women with GDM compared with healthy pregnant women. Vigorous physical activity during pregnancy seems to reduce the risk of GDM, while watching TV increases the likelihood. Results from the isotemporal

substitution model support this association, suggesting that replacing 1 hour/week of TV with 1 hour/week of vigorous physical activity during pregnancy could reduce the risk of GDM by about 30%.

No studies were used previously the isotemporal substitution model, however, other studies that analyse the association between different intensities of physical activity and GDM risk tend to show inverse association for vigorous physical activity and nit for light to moderate physical activity. Regarding to watching TV, results are more controversial such some studies suggest that Watching TV could increase GDM risk whereas other don't report any association.

2.2 Methodology: strengths and limitations

This study was designed as a prospective cohort study. Follow-up took place between 20th and 24th gestational weeks until the end of pregnancy. In this design, the exposure (physical activity level) was assessed before the occurrence of the outcome (GDM) is the first study analysing the association between physical activity, watching TV, and GDM risk using an isotemporal substitution model. Our sample was representative of the area covered by the HUVN, as one in five women attending the hospital for the programmed visit received the invitation to participate. The participation rate was high, as only 13 women renegued the participation. In terms of external validity, our sample has similar characteristics to other healthy Spanish pregnant women. Therefore, we consider that results obtained can be extrapolated to other populations with the same characteristics. To improve internal validity, several potential risks of bias related to physical activity and dietary patterns were identified.

First, residual confounder factors such as energy intake and the adherence to Mediterranean diet was analysed, because physical activity cannot be analysed without taking in consideration the dietary pattern such as very associated factors. Second, the risk of bias due to cultural differences was reduced by including only Spanish women. Third, both the FFQ and the Paffenbarger questionnaire used to assess diet and physical activity were validated in the Spanish population and in pregnant women (49,68,156). Fourth, risk of bias related to diet and physical activity may be introduced by health conditions that require a specific diet or physical activity intervention was controlled by excluding women with metabolic disease or whether condition that requires this change.

Finally, recall bias related to lifestyle during pregnancy was reduced by assessing diet and physical activity during the first 24 weeks of pregnancy. However, it was not possible to control for this bias risk on lifestyle before pregnancy. Moreover, information related to health conditions and obstetric antecedents collected using the medical history of the participants.

On the other hand, some limitations should be taken into account when interpreting our results. Although the FFQ and Paffenbarger are the most widely used instruments in the world, they are based on self-reported data. Therefore, potential bias in the assessment of diet and physical activity was reduced. In addition, more data on sedentary behaviours other than TV watching may allow more precise analysis. Regarding dietary assessment, the Mediterranean diet adherence index used in our analysis has been validated for the general population, but not specifically for pregnant women.

2.3 Clinical practice

Our study supports the importance of reducing television watching time during pregnancy and replacing it with physical activity. A simple substitution of one hour per week of TV viewing for one hour per week of appropriate vigorous physical activity interventions in women without contraindications, such as aerobic and arm exercises and reducing sedentary behaviours, can reduces considerably the risk of GDM.

Introduce physical activity interventions in the pregnancy follow up program can be helpful to prevent pregnancy complications. However, the general recommendations given by health care providers in primary care may not be sufficient to achieve the desired effect. There is a lack of qualified physical activity specialists in primary care. Therefore, it may be necessary to involve physical activity specialists in order to provide personalized intervention adapted to each woman.

3. Discussion of the methodology and results of the third objective.

To estimate the strength of the association between POPs exposure and GDM in a systematic review with meta-analysis.

A systematic review and meta-analysis was realized on observational studies analysing the relationship between the individual contamination levels of POPs and the incidence of GDM. The protocol was previously registered in PROSPERO (www.crd.york.ac.uk/PROSPERO, CRD42022303450).

3.1 Principal finding

In this systematic review and meta-analysis, the pooled effect of standardised mean difference between GDM cases and controls of 20 POPs was estimated. Small variance was observed for PFHpA, PCB 180, BDE 47, BDE99, BDE100 and HCB. No considerable difference was observed for the rest of POPs

Epidemiological studies analysing the effect of POPs on GDM show diverse finding as the statistically significant results were not always observed in the same POPs. The systematic review published by wang et al in 2022, including four types of PFAS (PFOS, PFOA, PFHxS, PFNA). However, only PFOA seem to increase the risk of GDM (OR = 1.27, 95% CI: 1.02–1.59) I^2=0% (157). In other meta-analysis only dos POPs seem increase the risk of GDM; PBDE 154 (OR= 1.23, 95% CI: 1.13–1.35) I^2=0% and PFOA (OR= 1.23, 95% CI: 1.13–1.35) I^2=19.5%, no association statistically different was observed for the rest of PFAS, PCBs or PBDE or high heterogeneity was observed such for PFBS (I^2=76.4%) (158). This discrepancy is further observed when exposure levels are measured after the outcome has occurred in the original studies.

Inconsistency in findings regarding the association between different types of POPs and gestational diabetes may be due to using different ways to combine

results from individual studies, the use of different scale to estimate the magnitude of this association, selection criteria established in each systematic review, exposure measurement issues, residual confounder associated to GDM such as gestational weight gain, diabetes mellitus antecedents and GDM antecedents.

In studies where exposure was measured after the outcome occurred, there was further inconsistency. PBDE and PCB show an inverse relationship with GDM in a Spanish cohort of 86 participants (159). In a case control study of 140 Iranian women Ln PCB 28 was inversely associated to GDM, while Ln PCB 187, Ln PCB 118 and Ln PBDE 99, Ln PBDE 28 could increase the risk of GDM (136).

In our systematic review, we did not consider the combined effect of the sum of the different types of POPs, as the correlation between different POPs is not at all clear. In addition, some of the elements have an opposite effect on each other.

3.2 Methodology: strengths and limitations

Our results may be limited by the quality of the included studies. In addition, our ability to perform dose-response analysis, subgroup analysis, and publication bias assessment was hindered by the small amount of data that could be combined. On the other hand, confounding factors closely related to GDM, such as physical activity and dietary patterns, as well as exposure to other pollutants, were not measured in most of the selected studies.

The principal strengths of this systematic review and meta-analysis lay in the following:

1) Been the first systematic review and meta-analysis including exclusively prospective studies assessing the association of several POPs and risk of GDM.
2) Reducing possible bias due to study design and estimate a possible causal effect association between exposure and outcome by including only prospective cohort and case-control studies in which exposure was measured at the beginning of pregnancy.
3) Using strengths algorithm for research that included the different possible nominations of included POPs.
4) Including only exposures measured in biospecimens.
5) Adhere to the previously published protocol cycle and follow the PRISMA 2020 guidelines.

3.3 Clinical practice

At the clinical level, our results suggest that some types of POPs are likely to increase the risk of GDM. However, the scarcity of available combinable data may hinder the correct estimation of the association. The establishment of a standardized form for the analysis of POPs and the creation of a consortium with individual data are needed to draw stronger and more precise conclusions.

CONCLUSIONS

1- Physical activity and dietary interventions would decrease the risk of GDM. However, the most effective physical activity pattern in terms of type, frequency and intensity are not at all clear. In contrast, there is not enough evidence with sufficient quality to determine the role of a combined intervention involving both physical activity and diet in preventing GDM.

2- Spanish pregnant women are more likely to have a sedentary lifestyle and a lower level of physical activity, both before and during pregnancy.

3- Women with higher levels of physical activity during pregnancy tend to have a lower risk of GDM. The joint effect between light to moderate and vigorous physical activity with watching TV show that women with higher levels of vigorous physical activity and lower levels of watching TV are less likely to develop GDM.

4- Pregnant women can reduce their risk of GDM up to 34% simply by replacing one hour per week of watching TV with one hour per week of VPA.

5- The exposure to contaminants such as POPs may increase the risk of GDM. However, the current evidence does not seem robust enough to draw firm conclusions. The analysis of POPs requires the establishment of standardised forms to facilitate the combination and analysis of data.

REFERENCES

1. Word Health Organization. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. 2013.
2. Bowe JE, Hill TG, Hunt KF, Smith LIF, Simpson SJS, Amiel SA, et al. A role for placental kisspeptin in β cell adaptation to pregnancy. JCI Insight. 2019 Oct 17;4(20).
3. Salazar-Petres ER, Sferruzzi-Perri AN. Pregnancy-induced changes in β-cell function: what are the key players? Journal of Physiology. 2022;600(5):1089–117.
4. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci. 2018;19(11):1–21.
5. American diabetes association. Classification and diagnosis of diabetes. Diabetes Care. 2017;40(January):S11–24.
6. O'Sullivan JB, Mahan CM, Charles D, Dandrow R V. Screening criteria for high risk gestational diabetic patients. Am J Obstet Gynecol. 1973 Aug;116(7):895–900.
7. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, et al. IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. Diabetes Res Clin Pract. 2022;183:109050.
8. Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, Ramezani Tehrani F. The impact of diagnostic criteria for gestational diabetes on its prevalence: A systematic review and meta-analysis. Diabetol Metab Syndr. 2019;11(1):1–18.
9. Word Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. 2nd ed. Geneva; 1999.
10. Word Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. RepoRt of a WHo/IDf ConsultatIon. Geneva; 2006.
11. WHO/NMH/NMD. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in PregnancyNo Title. 2013.
12. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982 Dec;144(7):768–73.
13. National Diabetes Data Group. Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance. Diabetes. 1979 Dec 1;28(12):1039–57.
14. Metzger BE. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care. 2010 Mar 1;33(3):676–82.
15. Canadian Diabetes Association. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. 2008. S172 p.

16. Berger H, Gagnon R, Sermer M. Guideline No. 393-Diabetes in Pregnancy. Journal of Obstetrics and Gynaecology Canada. 2019;41(12):1814-1825.e1.
17. IDF. IDF Diabetes Atlas. 10th ed. 2021.
18. Amiri FN, Faramarzi M, Bakhtiari A, Omidvar S. Risk Factors for Gestational Diabetes Mellitus: A Case-Control Study. Am J Lifestyle Med. 2021;15(2):184–90.
19. Kouhkan A, Najafi L, Malek M, Baradaran HR, Hosseini R, Khajavi A, et al. Gestational diabetes mellitus: Major risk factors and pregnancy-related outcomes: A cohort study. Int J Reprod Biomed. 2021;19(9):827–36.
20. Cao M, Zhang L, Chen T, Shi A, Xie K, Li Z, et al. Genetic Susceptibility to Gestational Diabetes Mellitus in a Chinese Population. 2020;11(April):1–9.
21. Hedderson MM, Darbinian JA, Ferrara A. Disparities in the risk of gestational diabetes by race-ethnicity and country of birth. Paediatr Perinat Epidemiol. 2010;24(5):441–8.
22. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia : a systematic review and meta-analysis. 2018;1–20.
23. Wagnild JM, Hinshaw K, Pollard TM. Associations of sedentary time and self-reported television time during pregnancy with incident gestational diabetes and plasma glucose levels in women at risk of gestational diabetes in the UK. BMC Public Health. 2019 May 15;19(1).
24. Fuller H, Id JBM, Iles MM, Id MAZ. PLOS GLOBAL PUBLIC HEALTH Ethnic-specific associations between dietary consumption and gestational diabetes mellitus incidence : A meta-analysis. 2022;1–13.
25. Grupo CTO. Manual CTO de enfermería-Tomo I. 6th ed. 2013. 318 p.
26. Malaza N, Masete M, Adam S, Dias S, Nyawo T, Pheiffer C. A Systematic Review to Compare Adverse Pregnancy Outcomes in Women with Pregestational Diabetes and Gestational Diabetes. Int J Environ Res Public Health. 2022;19(17).
27. Lee SM, Shivakumar M, Park JW, Jung YM, Choe EK, Kwak SH, et al. Long-term cardiovascular outcomes of gestational diabetes mellitus: a prospective UK Biobank study. Cardiovasc Diabetol. 2022;21(1):1–14.
28. Christensen MH, Rubin KH, Petersen TG, Nohr EA, Vinter CA, Andersen MS, et al. Cardiovascular and metabolic morbidity in women with previous gestational diabetes mellitus: a nationwide register-based cohort study. Cardiovasc Diabetol. 2022;21(1):1–13.
29. Song C, Lyu Y, Li C, Liu P, Li J, Ma RC, et al. Long-term risk of diabetes in women at varying durations after gestational diabetes: a systematic review and meta-analysis with more than 2 million women. Obesity Reviews. 2018 Mar;19(3):421–9.
30. Olmedo-Requena R, Gómez-Fernández J, Amezcua-Prieto C, Mozas-Moreno J, Khan KS, Jiménez-Moleón JJ. Pre-Pregnancy Adherence to the

Mediterranean Diet and Gestational Diabetes Mellitus: A Case-Control Study. Nutrients. 2019 May 1;11(5):1003.
31. Raghavan R, Dreibelbis C, Kingshipp BL, Wong YP, Abrams B, Gernand AD, et al. Dietary patterns before and during pregnancy and maternal outcomes: A systematic review. Vol. 109, American Journal of Clinical Nutrition. 2019. p. 705S-728S.
32. Doi SAR, Furuya-Kanamori L, Toft E, Musa OAH, Mohamed AM, Clark J, et al. Physical activity in pregnancy prevents gestational diabetes: A meta-analysis. Diabetes Res Clin Pract. 2020;168.
33. American Diabetes Association. Gestational Diabetes. Treatment & Perspective [Internet]. Available from: https://diabetes.org/diabetes/gestational-diabetes/how-to-treat-gestational-diabetes#:~:text=Treatment for gestational diabetes aims,glucose testing and insulin injections.
34. Pilszyk A, Niebrzydowska M, Pilszyk Z, Wierzchowska-Opoka M, Kimber-Trojnar Ż. Incretins as a Potential Treatment Option for Gestational Diabetes Mellitus. Int J Mol Sci. 2022;23(17).
35. Lende M, Rijhsinghani A. Gestational diabetes: Overview with emphasis on medical management. Int J Environ Res Public Health. 2020;17(24):1–12.
36. Word Health Organization. Physical activity. 2020 [cited 2021 Oct 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/physical-activity
37. Hejazi K, Mohammad Rahimi GR, Rosenkranz SK. Effects of Exercise Training on Inflammatory and Cardiometabolic Risk Biomarkers in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biol Res Nurs. 2023;25(2).
38. Wood G, Taylor E, Ng V, Murrell A, Patil A, van der Touw T, et al. Estimating the Effect of Aerobic Exercise Training on Novel Lipid Biomarkers: A Systematic Review and Multivariate Meta-Analysis of Randomized Controlled Trials. Sports Med. 2023;53(4).
39. Arsh A, Afaq S, Carswell C, Bhatti MM, Ullah I, Siddiqi N. Effectiveness of physical activity in managing co-morbid depression in adults with type 2 diabetes mellitus: A systematic review and meta-analysis. J Affect Disord. 2023 May 15;329:448–59.
40. The american college of obstetrician and gynecologists. Physical Activity and Exercise During Pregnancy and the Postpartum Period. 2020;804.
41. Berghella V, Saccone G. Exercise in pregnancy! Am J Obstet Gynecol. 2017 Apr;216(4):335–7.
42. Mireille N.M. van Poppel, Mai J.M. Chinapaw, Lidwine B. Mokkink W van M and CBT. Physical Activity Questionnaires for Adults. A systematic Review of Measyrement Properies. Sports Medicine. 2010;40(7):565–600.

43. Armstrong T, Bull F. Development of the World Health Organization Global Physical Activity Questionnaire (GPAQ). J Public Health (Bangkok). 2006;14(2):66–70.
44. Bernstein M, Sloutskis D, Kumanyika S, Sparti A, Schutz Y, Morabia A. Data-based Approach for Developing a Physical Activity Frequency Questionnaire. Am J Epidemiol. 1998 Jan 15;147(2):147–54.
45. AADAHL M, J??RGENSEN T. Validation of a New Self-Report Instrument for Measuring Physical Activity. Med Sci Sports Exerc. 2003 Jul;35(7):1196–202.
46. PAFFENBARGER, RALPH S. JR.; BLAIR, STEVEN N.; LEE, I-MIN; HYDE RT. Measurement of physical activity to assess health effects in free-living populations. Med Sci Sports Exerc. 1993;25:60–70.
47. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a pregnancy physical activity questionnaire. Med Sci Sports Exerc. 2004;36(10):1750–60.
48. SCHMIDT MD, FREEDSON PS, PEKOW P, ROBERTS D, STERNFELD B, CHASAN-TABER L. Validation of the Kaiser Physical Activity Survey in Pregnant Women. Med Sci Sports Exerc. 2006 Jan;38(1):42–50.
49. Fernandez-Martinez O, Bueno-Cabanillas A, Martinez-Martinez M, Jimenez-Moleon JJ, de la Higuera MJL. Validez y fiabilidad de un cuestionario de actividad física para mujeres embarazadas. Archivos de Medicina. 2008;4(5):0–7.
50. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. Am J Epidemiol. 2009;170(4):519–27.
51. Arrebola JP, Fernández MF, Martín-Olmedo P, Molina-Molina JM, Sánchez-Pérez MJ, Sánchez-Cantalejo E, et al. Adipose tissue concentrations of persistent organic pollutants and total cancer risk in an adult cohort from Southern Spain: Preliminary data from year 9 of the follow-up. Science of The Total Environment. 2014 Dec;500–501:243–9.
52. Word Health Organization. Food safety: Persistent organic pollutants (POPs) [Internet]. 2020. Available from: https://www.who.int/news-room/questions-and-answers/item/food-safety-persistent-organic-pollutants-(pops)
53. Malisch R, Kotz A. Dioxins and PCBs in feed and food — Review from European perspective. Science of The Total Environment. 2014 Sep 1;491–492:2–10.
54. Hu J, Zheng M, Liu W, Li C, Nie Z, Liu G, et al. Occupational exposure to polychlorinated dibenzo-p-dioxins and dibenzofurans, dioxin-like polychlorinated biphenyls, and polychlorinated naphthalenes in workplaces of secondary nonferrous metallurgical facilities in China. Environ Sci Technol. 2013;47(14):7773–9.

55. Lim J eun, Park SH, Jee SH, Park H. Body concentrations of persistent organic pollutants and prostate cancer: a meta-analysis. Environmental Science and Pollution Research. 2015;22(15):11275–84.
56. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A Review of the Pathways of Human Exposure to Poly- and Perfluoroalkyl Substances (PFASs) and Present Understanding of Health Effects. J Expo Sci Environ Epidemiol. 2019; 29(2):131.
57. Barrios-Rodríguez R, Pérez-Carrascosa FM, Gómez-Peña C, Mustieles V, Salcedo-Bellido I, Requena P, et al. Associations of accumulated selected persistent organic pollutants in adipose tissue with insulin sensitivity and risk of incident type-2 diabetes. Environ Int. 2021; 155:106607.
58. Tornevi A, Sommar J, Rantakokko P, Åkesson A, Donat-Vargas C, Kiviranta H, et al. Chlorinated persistent organic pollutants and type 2 diabetes - A population-based study with pre- and post- diagnostic plasma samples. Environ Res. 2019 Jul 1;174:35–45.
59. Gao X, Ni W, Zhu S, Wu Y, Cui Y, Ma J, et al. Per- and polyfluoroalkyl substances exposure during pregnancy and adverse pregnancy and birth outcomes: A systematic review and meta-analysis. Vol. 201, Environmental Research. Academic Press Inc.; 2021. p. 111632.
60. Kappil MA, Li Q, Li A, Dassanayake PS, Xia Y, Nanes JA, et al. In utero exposures to environmental organic pollutants disrupt epigenetic marks linked to fetoplacental development. Environ Epigenet. 2016; 2(1).
61. Dwivedi N, Mahdi AA, Deo S, Ahmad MK, Kumar D. Assessment of genotoxicity and oxidative stress in pregnant women contaminated to organochlorine pesticides and its correlation with pregnancy outcome. Environ Res. 2022;204(PB):112010.
62. Secrétariat d'Etat auprés du Ministre de l'Energie des Mines et du Développement Durable. Deuxieme Plan National De Mise En Œuvre De La Convention De Stockholm Sur Les Polluants Organiques Persistants. 2019.
63. Ministerio para la Transición Ecológica y el Reto Demográfico. Plan Nacional de Aplicación de COP. Red Nacional de Vigilancia Ambiental de COPicono barra herramientas.
64. Díaz-Burrueco JR, Cano-Ibáñez N, Martín-Peláez S, Khan KS, Amezcua-Prieto C. Effects on the maternal-fetal health outcomes of various physical activity types in healthy pregnant women. A systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology [Internet]. 2021; 262:203–15.
65. Griffith RJ, Alsweiler J, Moore AE, Brown S, Middleton P, Shepherd E, et al. Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2020(9):CD012394.
66. Shea A. AMSTAR-2: herramienta de evaluación crítica de revisiones sistemáticas de estudios de intervenciones de salud. BMJ. 2017; 21.

67. Pieper D, Antoine SL, Mathes T, Neugebauer EAM, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014; 67(4):368–75. Available from: https://www.sciencedirect.com/science/article/pii/S08954
68. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, et al. A collection of Physical Activity Questionnaires for health-related research. Med Sci Sports Exerc. 1997; 29(6 Suppl):S1-205.
69. Ainsworth Be, Haskell Wl, Herrmann Sd, Meckes N, Bassett Dr, Tudor-Locke C, et al. 2011 Compendium of Physical Activities. Med Sci Sports Exerc. 2011 Aug;43(8):1575–81.
70. Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol. 1993; 22(3):512–9.
71. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean Diet and Survival in a Greek Population. New England Journal of Medicine. 2003 Jun 26;348(26):2599–608.
72. Group CCPM. Review Tools. 2018. The Cochrane Collaboration Prognosis Methods GroupNo Title.
73. Graham P, Jackson R. The analysis of ordinal agreement data: beyond weighted kappa. J Clin Epidemiol. 1993;46(9):1055–62.
74. Juan J, Yang H. Prevalence, Prevention, and Lifestyle Intervention of Gestational Diabetes Mellitus in China. Int J Environ Res Public Health. 2020; 17(24):9517.
75. Šćepanović, DŠćepanović, D., & Hrvatin, I. (2020). The effect of maternal exercise on maternal and foetal health in obese pregnant women. Zdravniski Vestnik, 89(3–4) 223–234.
76. Mottola Mf, Artal R. Role of Exercise in Reducing Gestational Diabetes Mellitus. Clin Obstet Gynecol. 2016;59(3):620–8.
77. Zhang C, Rawal S, Chong YS. Risk factors for gestational diabetes: is prevention possible? Diabetologia. 2016; 59(7):1385–90.
78. Halperin IJ, Feig DS. The Role of Lifestyle Interventions in the Prevention of Gestational Diabetes. Curr Diab Rep. 2014;14(1):452.
79. Egan AM, Bogdanet D, Griffin TP, Kgosidialwa O, Cervar-Zivkovic M, Dempsey E, et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. Diabetologia. 2020; 63(6):1120–7.
80. Hasbullah FY, Mohd Yusof BN, Shariff ZM, Rejali Z, Yong HY, Mitri J. Factors associated with dietary glycemic index and glycemic load in pregnant women and risk for gestational diabetes mellitus. Int J Food Sci Nutr. 2020 May 18;71(4):516–24.
81. Carolan-Olah M, Duarte-Gardea M, Lechuga J. A systematic review of interventions for Hispanic women with or at risk of Gestational diabetes mellitus (GDM). Sexual & Reproductive Healthcare. 2017 Oct;13:14–22.

82. Donazar-Ezcurra M, López-del Burgo C, Bes-Rastrollo M. Primary prevention of gestational diabetes mellitus through nutritional factors: a systematic review. BMC Pregnancy Childbirth. 2017;17(1):30.
83. Mijatovic-Vukas J, Capling L, Cheng S, Stamatakis E, Louie J, Cheung N, et al. Associations of Diet and Physical Activity with Risk for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. Nutrients. 2018; 30;10(6):698.
84. Raghavan R, Dreibelbis C, Kingshipp BL, Wong YP, Abrams B, Gernand AD, et al. Dietary patterns before and during pregnancy and maternal outcomes: a systematic review. Am J Clin Nutr. 2019; 109:705S-728S.
85. Morales-Suárez-Varela M, Clemente-Bosch E, Peraita-Costa I, Llopis-Morales A, Martínez I, Llopis-González A. Maternal Physical Activity During Pregnancy and the Effect on the Mother and Newborn: A Systematic Review. J Phys Act Health. 2021;18(1):130–47.
86. Tieu J, Shepherd E, Middleton P, Crowther CA. Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews. 2017;(8).
87. Dietary Intake and Physical Activity Predictors of Gestational Diabetes: A Systematic Review | Request PDF [Internet]. [cited 2023 Apr 13]. Available from: https://www.researchgate.net/publication/334821450_233-LB_Dietary_Intake_and_Physical_Activity_Predictors_of_Gestational_Diabetes_A_Systematic_Review
88. Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. Physical Activity Before and During Pregnancy and Risk of Gestational Diabetes Mellitus. Diabetes Care [Internet]. 2011 Jan 1;34(1):223–9. Available from: https://diabetesjournals.org/care/article/34/1/223/27804/Physical-Activity-Before-and-During-Pregnancy-and
89. Yaping X, Huifen Z, Chunhong L, Fengfeng H, Huibin H, Meijing Z. A meta-analysis of the effects of resistance training on blood sugar and pregnancy outcomes. Midwifery. 2020; 91:102839.
90. Li N, Yang Y, Cui D, Li C, Ma RCW, Li J, et al. Effects of lifestyle intervention on long-term risk of diabetes in women with prior gestational diabetes: A systematic review and meta-analysis of randomized controlled trials. Obesity Reviews. 2021;22(1):1–8.
91. Xu J, Ye S. Influence of low-glycemic index diet for gestational diabetes: a meta-analysis of randomized controlled trials. Journal of Maternal-Fetal and Neonatal Medicine. 2020;33(4):687–92.
92. Laredo-Aguilera JA, Gallardo-Bravo M, Rabanales-Sotos JA, Cobo-Cuenca AI, Carmona-Torres JM. Physical activity programs during pregnancy are effective for the control of gestational diabetes mellitus. Int J Environ Res Public Health. 2020;17(17):1–14.

93. Bao H, Yu P, Song X, Zhou Y, Zhu Y, Xu X. The influence of home-based exercise on gestational diabetes: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med. 2020;33(13):2300–5.
94. Bielefeld D, Grafenauer S, Rangan A. The Effects of Legume Consumption on Markers of Glycaemic Control in Individuals with and without Diabetes Mellitus: A Systematic Literature Review of Randomised Controlled Trials. Nutrients. 2020;12(7):2123.
95. Doi SAR, Furuya-Kanamori L, Toft E, Musa OAH, Mohamed AM, Clark J, et al. Physical activity in pregnancy prevents gestational diabetes: A meta-analysis. Diabetes Res Clin Pract. 2020 Oct;168:108371.
96. Nasiri-Amiri F, Sepidarkish M, Shirvani MA, Habibipour P, Tabari NSM. The effect of exercise on the prevention of gestational diabetes in obese and overweight pregnant women: a systematic review and meta-analysis. Diabetol Metab Syndr. 2019;11:72.
97. Makaruk B, Galczak-Kondraciuk A, Forczek W, Grantham W, Charmas M. The Effectiveness of Regular Exercise Programs in the Prevention of Gestational Diabetes Mellitus-A Systematic Review. Obstet Gynecol Surv. 2019;74(5):303–12.
98. Du MC, Ouyang YQ, Nie XF, Huang Y, Redding SR. Effects of physical exercise during pregnancy on maternal and infant outcomes in overweight and obese pregnant women: A meta-analysis. Birth. 2019;46(2):211–21.
99. Yu Y, Xie R, Shen C, Shu L. Effect of exercise during pregnancy to prevent gestational diabetes mellitus: a systematic review and meta-analysis. Vol. 31, Journal of Maternal-Fetal and Neonatal Medicine. 2018. p. 1632–7.
100. Chatzakis C, Goulis DG, Mareti E, Eleftheriades M, Zavlanos A, Dinas K, et al. Prevention of gestational diabetes mellitus in overweight or obese pregnant women: A network meta-analysis. Diabetes Res Clin Pract. 2019;158:107924.
101. Magro-Malosso E, Saccone G, Di Mascio D, Di Tommaso M, Berghella V. Exercise during pregnancy and risk of preterm birth in overweight and obese women: A systematic review and meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand. 2017;96(3):263–73.
102. Aune D, Sen A, Henriksen T, Saugstad OD, Tonstad S. Physical activity and the risk of gestational diabetes mellitus: a systematic review and dose-response meta-analysis of epidemiological studies. Eur J Epidemiol. 2016 Oct;31(10):967–97.
103. Ming WK, Ding W, Zhang CJP, Zhong L, Long Y, Li Z, et al. The effect of exercise during pregnancy on gestational diabetes mellitus in normal-weight women: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018 Nov;18(1):440.
104. da Silva SG, Ricardo LI, Evenson KR, Hallal PC. Leisure-Time Physical Activity in Pregnancy and Maternal-Child Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Cohort Studies. Sports Medicine. 2017;47(2):295–317.

105. Sanabria-Martínez G, García-Hermoso A, Poyatos-Leõn R, Álvarez-Bueno C, Sánchez-Lõpez M, Martínez-Vizcaíno V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: A meta-analysis. Vol. 122, BJOG: An International Journal of Obstetrics and Gynaecology. 2015. p. 1167–74.
106. Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus a systematic review and meta-analysis. Obstetrics and gynecology. 2015;125(3):576–82.
107. Yin Y nan, Li X lian, Tao T jun, Luo B ru, Liao S juan. Physical activity during pregnancy and the risk of gestational diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2014;48(4).
108. Han S, Middleton P, Crowther CA. Exercise for pregnant women for preventing gestational diabetes mellitus. Cochrane Database of Systematic Reviews. 2012;(7).
109. Zheng J, Wang H, Ren M. Influence of exercise intervention on gestational diabetes mellitus: a systematic review and meta-analysis. Vol. 40, Journal of Endocrinological Investigation. 2017. p. 1027–33.
110. Lamminpää R, Vehviläinen-Julkunen K, Schwab U. A systematic review of dietary interventions for gestational weight gain and gestational diabetes in overweight and obese pregnant women. Eur J Nutr. 2018;57(5):1721–36.
111. Tieu J, Shepherd E, Middleton P, Crowther CA. Dietary advice interventions in pregnancy for preventing gestational diabetes mellitus. Cochrane Database of Systematic Reviews. 2017 Jan 3;2017(1).
112. Zhang Y, Xia M, Weng S, Wang C, Yuan P, Tang S. Effect of Mediterranean diet for pregnant women: a meta-analysis of randomized controlled trials. The Journal of Maternal-Fetal & Neonatal Medicine. 2021 Feb 25;1–11.
113. Tieu J, Crowther CA, Middleton P. Dietary advice in pregnancy for preventing gestational diabetes mellitus. In: Tieu J, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2008.
114. Guo XY, Shu J, Fu XH, Chen XP, Zhang L, Ji MX, et al. Improving the effectiveness of lifestyle interventions for gestational diabetes prevention: a meta-analysis and meta-regression. BJOG [Internet]. 2019 Feb;126(3):311–20. Available from: https://doi.org/10.1111/1471-0528.15489.
115. Bennett CJ, Walker RE, Blumfield ML, Gwini SM, Ma J, Wang F, et al. Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. Diabetes Res Clin Pract. 2018;141:69–79.
116. Davenport MH, Ruchat SM, Poitras VJ, Garcia AJ, Gray CE, Barrowman N, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. Br J Sports Med. 2018; 52(21).

117. Shepherd E, Gomersall JC, Tieu J, Han S, Crowther CA, Middleton P. Combined diet and exercise interventions for preventing gestational diabetes mellitus. Vol. 2017, Cochrane Database of Systematic Reviews. 2017.
118. Song C, Li J, Leng J, Ma RC, Yang X. Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials. Obesity Reviews. 2016;17(10):960–9.
119. Rogozinska E, Marlin N, Betran AP, Astrup A, Bogaerts A, Cecatti JG, et al. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. BMJ. 2017;358:j3119.
120. Rogozińska E, Marlin N, Jackson L, Rayanagoudar G, Ruifrok AE, Dodds J, et al. Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation. Health Technol Assess. 2017;21(41):1–158.
121. O'Brien CM, Grivell RM, Dodd JM. Systematic review of antenatal dietary and lifestyle interventions in women with a normal body mass index. Acta Obstet Gynecol Scand. 2016;95(3):259–69.
122. Madhuvrata P, Govinden G, Bustani R, Song S, Farrell TA. Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: a systematic review and meta-analysis of randomised trials. Obstet Med. 2015 Jun;8(2):68–85.
123. Rogozinska E, Chamillard M, Hitman GA, Khan KS, Thangaratinam S. Nutritional Manipulation for the Primary Prevention of Gestational Diabetes Mellitus: A Meta-Analysis of Randomised Studies. PLoS One. 2015;10(2):e0115526.
124. Bain E, Crane M, Tieu J, Han S, Crowther CA, Middleton P. Diet and exercise interventions for preventing gestational diabetes mellitus. Vol. 2015, Cochrane Database of Systematic Reviews. 2015.
125. Skouteris H, Morris H, Nagle C, Nankervis A. Behavior Modification Techniques Used to Prevent Gestational Diabetes: A Systematic Review of the Literature. Curr Diab Rep. 2014;14(4):480.
126. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Med. 2012 Dec 10;10(1):47.
127. Thangaratinam S, Rogozińska E, Jolly K, Glinkowski S, Duda W, Borowiack E, et al. Interventions to reduce or prevent obesity in pregnant women: A systematic review. Vol. 16, Health Technology Assessment. 2012. p. 1–191.
128. Oostdam N, van Poppel MNM, Wouters MGAJ, van Mechelen W. Intervention for preventing Gestational Diabetes Mellitus: A systematic Review and Meta-analysis. J Womens Health. 2011;20(10):1551–63.
129. Rogozinska E, Chamillard M, Hitman GA, Khan KS, Thangaratinam S. Nutritional Manipulation for the Primary Prevention of Gestational Diabetes Mellitus: A Meta-Analysis of Randomised Studies. PLoS One. 2015 Feb;10(2).

130. Bennett CJ, Walker RE, Blumfield ML, Gwini SM, Ma J, Wang F, et al. Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. Diabetes Res Clin Pract. 2018;141:69–79.
131. Neblett MF, Curtis S, Gerkowicz S, Spencer JB, Terrell ML, Jiang VS, et al. Examining polychlorinated biphenyl exposure and reproductive health outcomes. Fertil Steril [Internet]. 2018 Sep;110(4):e171.
132. Valvi D, Oulhote Y, Weihe P, Dalgård C, Bjerve KS, Steuerwald U, et al. Gestational Diabetes and Offspring Birth Size at Elevated Environmental Pollutant Exposures. Environ Int. 2017;107:205.
133. Jensen RC, Glintborg D, Timmermann CAG, Nielsen F, Kyhl HB, Andersen HR, et al. Perfluoroalkyl substances and glycemic status in pregnant Danish women: The Odense Child Cohort. Environ Int. 2018;116:101–7.
134. Liu X, Zhang L, Li J, Wang J, Meng G, Chi M, et al. Relative Effect Potency Estimates for Dioxin-Like Compounds in Pregnant Women with Gestational Diabetes Mellitus and Blood Glucose Outcomes Based on a Nested Case-control Study. Environ Sci Technol. 2019;53(13):7792–802.
135. Arrebola JP, González-Jiménez A, Fornieles-González C, Artacho-Cordón F, Olea N, Escobar-Jiménez F, et al. Relationship between serum concentrations of persistent organic pollutants and markers of insulin resistance in a cohort of women with a history of gestational diabetes mellitus. Environ Res [Internet]. 2015;136:435–40.
136. Eslami B, Naddafi K, Rastkari N, Rashidi BH, Djazayeri A, Malekafzali H. Association between serum concentrations of persistent organic pollutants and gestational diabetes mellitus in primiparous women. Environ Res. 2016;151:706–12.
137. Zhang Y, Chen R, Gao Y, Qu J, Wang Z, Zhao M, et al. Human serum poly- and perfluoroalkyl substance concentrations and their associations with gestational diabetes mellitus. Environmental Pollution. 2023;317:120833.
138. Zang L, Liu X, Xie X, Zhou X, Pan Y, Dai J. Exposure to per- and polyfluoroalkyl substances in early pregnancy, risk of gestational diabetes mellitus, potential pathways, and influencing factors in pregnant women: A nested case-control study. Environmental Pollution. 2023;326:121504.
139. Liu X, Zhang L, Chen L, Li J, Wang J, Zhao Y, et al. Identification and prioritization of the potent components for combined exposure of multiple persistent organic pollutants associated with gestational diabetes mellitus. J Hazard Mater. 2021;409.
140. Liu X, Zhang L, Chen L, Li J, Wang Y, Wang J, et al. Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women. Environ Int. 2019; 127:85–93.

141. Liu X, Zhang L, Li J, Meng G, Chi M, Li T, et al. A nested case-control study of the association between exposure to polybrominated diphenyl ethers and the risk of gestational diabetes mellitus. Environ Int. 2018;119(7):232–8.
142. Zhang L, Liu X, Meng G, Chi M, Li J, Yin S, et al. Non-dioxin-like polychlorinated biphenyls in early pregnancy and risk of gestational diabetes mellitus. Environ Int. 2018; 115:127–32.
143. Jaacks LM, Barr DB, Sundaram R, Maisog JM, Zhang C, Buck Louis GM. Pre-pregnancy maternal exposure to polybrominated and polychlorinated biphenyls and gestational diabetes: A prospective cohort study. GDM: A Global Access Science Source. 2016;15(1).
144. Smarr MM, Grantz KL, Zhang C, Sundaram R, Maisog JM, Barr DB, et al. Persistent organic pollutants and pregnancy complications. Science of the Total Environment. 2016; 551–552:285–91.
145. Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Buck Louis GM. A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. Fertil Steril. 2015; 103(1):184–9.
146. Xu H, Zhou Q, Zhang J, Chen X, Zhao H, Lu H, et al. Exposure to elevated per- and polyfluoroalkyl substances in early pregnancy is related to increased risk of gestational diabetes mellitus: A nested case-control study in Shanghai, China. Environ Int. 2020;143.
147. Vafeiadi M, Roumeliotaki T, Chalkiadaki G, Rantakokko P, Kiviranta H, Fthenou E, et al. Persistent organic pollutants in early pregnancy and risk of gestational diabetes mellitus. Environ Int. 2017; 98:89–95.
148. Yu G, Jin M, Huang Y, Aimuzi R, Zheng T, Nian M, et al. Environmental exposure to perfluoroalkyl substances in early pregnancy, maternal glucose homeostasis and the risk of gestational diabetes: A prospective cohort study. Environ Int. 2021;156:106621.
149. Preston E v., Rifas-Shiman SL, Hivert MF, Zota AR, Sagiv SK, Calafat AM, et al. Associations of Per- And Polyfluoroalkyl Substances (PFAS) with Glucose Tolerance during Pregnancy in Project Viva. Journal of Clinical Endocrinology and Metabolism. 2020;105(8):E2864–76.
150. Rahman ML, Zhang C, Smarr MM, Lee S, Honda M, Kannan K, et al. Persistent organic pollutants and gestational diabetes: A multi-center prospective cohort study of healthy US women. Environ Int. 2019 Mar 1;124:249–58.
151. Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, Manzano-Salgado CB, Ballester F, Ibarluzea J, et al. Exposure to Perfluoroalkyl Substances and Metabolic Outcomes in Pregnant Women: Evidence from the Spanish INMA Birth Cohorts. Environ Health Perspect. 2017;125(11):1–11.
152. Shapiro GD, Dodds L, Arbuckle TE, Ashley-Martin J, Ettinger AS, Fisher M, et al. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC Study. Environ Res. 2016; 147:71–81.

153. Jaacks LM, Boyd Barr D, Sundaram R, Grewal J, Zhang C, Buck Louis GM. Pre-Pregnancy Maternal Exposure to Persistent Organic Pollutants and Gestational Weight Gain: A Prospective Cohort Study. Int J Environ Res Public Health. 2016; 13:905.
154. Kouiti M, Hernández-Muñiz C, Youlyouz-Marfak I, Salcedo-Bellido I, Mozas-Moreno J, Jiménez-Moleón JJ. Preventing Gestational Diabetes Mellitus by Improving Healthy Diet and/or Physical Activity during Pregnancy: An Umbrella Review. Nutrients. 2022; 14(10):2066.
155. Amezcua-Prieto C, Olmedo-Requena R, Jímenez-Mejías E, Hurtado-Sánchez F, Mozas-Moreno J, Lardelli-Claret P, et al. Changes in leisure time physical activity during pregnancy compared to the prior year. Matern Child Health J. 2013; 17(4):632–8.
156. de la Fuente-Arrillaga C, Vázquez Ruiz Z, Bes-Rastrollo M, Sampson L, Martinez-González MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr. 2010 Sep 28;13(9):1364–72.
157. Wang J, Zhang J, Fan Y, Li Z, Tao C, Yan W, et al. Association between per- and polyfluoroalkyl substances and risk of gestational diabetes mellitus. Int J Hyg Environ Health. 2022 Mar 1;240.
158. Yan D, Jiao Y, Yan H, Liu T, Yan H, Yuan J. Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: a systematic review and meta-analysis. Environmental Health. 2022; 21(1):1–24.
159. Alvarez-Silvares E, Fernández-Cruz T, Domínguez-Vigo P, Rubio-Cid P, Seoane-Pillado T, Martínez-Carballo E. Association between placenta concentrations polybrominated and polychlorinated biphenyls and gestational diabetes mellitus: a case-control study in northwestern Spain. 2021; 28, pages10292–10301.

ANNEXES

ANNEX I. INTERVETNIONS CARACTERISTICS

Table 1. Description of physical activity interventions from the included systematic reviews

1th authors, year	Start and end of intervention	Type of intervention	Intensity	Frequency	Duration
Díaz-Burrueco et al. 2021	Interventions started between 8-18 GW, and x2 RCTs at 36- 38 GW. The end was generally between 35-39 gestational weeks, x1 to delivery, x1 6 weeks post-partum	x6 supervised exercise including (aerobic, strengthening, stretching guided exercises), x3 Cycling program, x1 water exercise, x1 walking		The frequency was 3 times/ week in 10 studies, in one was 3-5 times/week	in 6 RCTs the duration was 60 min, x1 50-55min, x1 55min, x1 20-60min., x1 15-30min, x1 30 min
Doi et al. 2020	5/11 RCTs health care facility supervised exercise program. 6/11 supervised facility outside health care facility. In 7 studies, recruitment was prior to the 16 gestational weeks. In 4 studies have been up to 20 weeks. Intervention continued till approximately 36 weeks.				
Guo et al. 2019	Interventions started from 7 to 20 weeks of gestation				
Nasiri-Amiri fatemeh et al. 2019	In 2 studies, exercise began in the first trimester and continued until delivery. In three studies, exercise activities began in the second trimester and lasted until 34–37 weeks of gestation. In two studies, exercise activities started less than 17 weeks and continued up to 6 weeks after delivery.	Studies included aerobic exercise (x3), aerobic and resistance (x1), aerobic and strength (x1), only resistance (x1), pelvic floor exercise (x1).	The intensity level of exercise activities was low to moderate in two studies, moderate to high in three studies, and moderate in a study.	In 1 study exercise was repeated 2x/week. In 4 was repeated 3x/week. In 1 study was daily repeated during a week. In 1 study repeated 3-5x/ week.	In all studies the duration was between 15-60min.

Makaruk et al. 2019	Interventions started between 6-22 gestational week, and continued till 34-delivery	The most frequent exercise was aerobic, resistance and strength exercise. And less frequently pelvic floor exercise and balancing exercise. For warm-up and the cool-down walking, stretching was the most frequent. Cycling and swimming was performed less frequently	Mostly the intervention was moderate	The frequency was 3 times/week. Except in one trial it was 2 times/ week.	In 5 studies the duration of the mean part of exercise sessions was between 20-35, and in 5 studies was between 40-50 min. And in 1 study, between 30-60min (individually prescribed)
Du et al. 2019	In five studies, the mean gestational age at recruitment was 11.4 ± 2.7 week. Three recruited women before 20 weeks. In three, the recruitment of women was realized before 20 weeks, 1 at 18 weeks, one before 16 weeks28; two at 12 weeks, and one at 11-14 weeks of gestation. In seven studies the intervention was continued until delivery, four studies to the 32-36 week's gestation, and two ended the intervention at the 28 week's gestation.	In three studies, the exercise program was "stationary cycling". In another three studies the program was "aerobic strength and muscle exercises". In two studies the activity was "walking for 11 000 steps or at least 30 minutes daily". Three studies had a "mixed method of stationary cycling, treadmill walk, and muscle exercise". And two studies used a "personalized exercise plan".		The frequency of the "stationary cycling" program was 3/week. The frequency of "aerobic strength and muscle exercises" was 2-3 times/week. For the mixed method was 1-3 times/week	The duration of the "stationary cycling" program was 30min/session. Duration of "aerobic strength and muscle exercises was 60 min/ session. And for the mixed method was about 50min/ session
You et al. 2018		Three studies reported a supervised cycling program. The intervention was based on the American college of obstetricians and gynecologists' guidelines in another three studies.		The cycling program was realized 3 times/ week.	
Bennett et al. 2018	Recruitment was realized mostly < 12-20 gestational week.	Intervention consisted of group exercise classes, including aerobic, muscle strength, flexibility, toning, and resistance exercises. An aquatic	The intensity was light-moderate (x1), moderate exercise	The frequency is mainly 3 times/week.	The duration of exercise ranged from 35 to 60 min per session

		session and light resistance activity was mentioned (x1) and an unsupervised walking program (x1).	(x2), light resistance activity (x1)		
Davenport et al. 2018		Seven RCTs with exercise the only intervention including aerobic exercise alone, two resistance training alone, one pelvic floor muscle training alone, and 11 RCTs including various types of exercise.		Frequency of exercise ranged from 1 to 7 days/week.	The duration of exercise ranged from 10 to 90 min per session
Ming et al. 2018	Seven trials started in the first trimester and continued to the end of the third trimester. Only one trial spanned the 20th through 36th weeks of gestation	Only one study includes aerobic exercise alone as the intervention, two studies included two types of interventions ("aerobic and resistance exercise"; and "two on land and one as aquatic exercise"). The rest of the studies included 3 types of exercise of the following (aerobics, stretching, resistance, mobilization, toning, flexibility, and muscle strength.)	light to moderate intensity	3 times/ week except in one study was 1 / week	the period ranged from 35-60min
Zheng et al. 2017		Physical activity based on American College of Obstetricians and Gynecologists (ACOG) guidelines. In two studies the intervention was a supervised cycling program	The intensity of exercise in the included studies were different	The frequency of the supervised cycling program was 3 times/ week	The duration time of exercise in the included studies were different
Da Silva et al. 2017	Nine studies started between the 6-10 gestational week. And six studies started as minimum in the 12 gestational weeks. Two studies were continued to delivery, eight in the third trimester, one between the 20-36 week's gestation, and three did not mention the end's intervention date.	All interventions comprised a structured exercise program. The majority of trials included aerobic exercises and muscle resistance or strength training. Other types of activities like walking or stretching were reported.	Most included moderate-intensity physical activities: five trials reported a light to moderate intensity, seven moderate, and one moderate to vigorous. Intensity	3 times/ week reported in 11 of studies, in 4 studies the frequency was. 1h, 2h and 4h per week.	The duration of sessions varied between 20 and 70 min. Only one study reported less than 30 min.

			was not reported in two studies.		
Madhuvrata et al. 2015	Started between 12-36 week's gestation	Individualized exercise programs with an energy expenditure. Session of aerobic and strength exercises under supervision of trained physiotherapist. 10 weeks of home-based supervised cycling exercise	Started with a 50–60% Hr_{max} and progress to 60–70%,	2-3 times/week	25-60min (data provided for 2 trials)
Sanabria-Martínez et al. 2015	Programs were conducted throughout pregnancy in 7 studies, and from the second trimester to the end of pregnancy in 6 studies	Supervised interventions consist in aerobic exercises (x11) resistance, toning, flexibility, and strength exercises (x7) weight training (x2). Strength exercises with muscles of the pelvic floor (x4).	In the majority of trials (x8) the intensity was moderate, and in four studies was light to moderate.	The frequency in the majority of trials (nine studies) was three times/week. In two trials was five times/ week. The minimum was two sessions in one trial.	Sessions lasted between 15 and 60 minutes.
Russo et al. 2015	The majority of studies enrolling participants at less than 16 weeks of gestation. With a variability between 6-8 and 18-22 weeks.	The intervention consisted of a group exercise session, except in four trials. All of the interventions included an aerobic component (walking, land or water aerobics or both, cycling), and four included an anaerobic component (strength training and balance exercises)		Mostly the frequency was about 3 times/ week	Duration of exercise ranged from 35-60 min
Yin et al. 2014	Beginning gestation weeks (6–18 weeks)	Individualized plan, regular exercise advice and paper-based instructions. (x1) included aerobic exercise, resistance exercise, aerobic sessions, aquatic activities, stretching, and balance exercises. (x1) included a yoga session.	(x1) was based on light intensity.	3-4 times/ week	35-45

Han et al. 2012	6-9 GW to 38-39 GW, 12-week gestation.	Home-based supervised exercise (x2) including supervised sessions, individualized exercise plan (by face-to-face visits and phone calls), and paper-based diaries, 2 home exercises, and one group session. Interventions was provided by fitness specialist and obstetrician, physiotherapist. Exercises consist of: aerobic (x4) sessions, cycling (x2), strength training, balance exercise, and aquatic activities. (x1 provided dietary recommendation and pelvic floor muscle exercise to both groups intervention and control)	Light-moderate (x2)	3-5 times/ week	35-60 min

Table 2. Description of dietary interventions from the included systematic reviews

1th authors, year	Start and end of intervention	Type of intervention	Visits	Service provider	Guide and recommendations	Personalized recommendations
Zhang et al. 2020		In two studies, this consisted of high consumption of fruits and vegetables, nuts, less intake of meat and moderate to high on fish. All studies include virgin olive oil, and two include nuts,				
Guo et al. 2019	Interventions started from 7 to 20 weeks of gestation					Individual dietary advice (x1), individual dietary assessment (x1)
Bennett et al. 2018	recruitment was realized mostly < 12-20 gestational week.	Intervention consisted of dietary advice for healthy eating. The recommendation mostly favored a balanced diet with a percentage recommendation for each nutrient, low-GI and energy-restricted diet was encouraged. And	Counseling usually performed in an individual session (3-10 visits). One trial completed the face-to-face visit by 1 phone call, and one trial relied on group education sessions. In	dietitian (x2)	Australian Guide to Healthy Eating was used in two trials, Danish dietary recommendations, IOM recommendations, Chinese Society of Nutrition Pregnancy Guidelines.	A personalized intervention is provided in most studies: individualized intake restrictions, women provided with food products, diet-based on the participant's weight, counseling according to their baseline nutritional status.

		trials encouraging self-weighing.	other trials, monitoring was realized every 4 weeks, and more frequently for some participants.			
Lamminpää et al. 2018	-	-	-	-	-	-
Tieu et al. 2017		Four studies compared low-glycemic index (GI) with moderate- to high-GI dietary advice; and one compared specific (high-fiber focused) with standard dietary advice.	The frequency was very different between studies. Some made 10 one-hour consultations. Others, 3 times during pregnancy. And two hours sessions	Interventions were conducted mainly by dietitian, and also by research dietitian and food technologist.	Different guidelines were used: Danish dietary recommendation, Nordic nutrition recommendation, general healthy eating guidelines, Australian guidelines from the National Health and Medical Research Council, Conventional nutrition guidelines,	Energy intake was restricted based on individually estimation

Table 3. Description of mixed interventions from the included systematic reviews

1th Authors, year	started and end of intervention	type of intervention	intensity	Frequency/visit	duration	services provider	guide
Guo et al. 2019	Interventions started from 7 to 20 weeks of gestation					trained graduate, dietitian	
Bennett et al. 2018	recruitment was realized mostly < 12-20 gestational week.	Advice regarding physical activity and diet was realized through regular clinic visits often supported by phone calls. **Exercise:** Interventions consisted of sessions at the gym (x3), physical activity DVD, recommendation to increase physical activity to 11000 steps/day, walking. **Diet:** Nutritional education sessions, brochure regarding diet, group session recording energy intake and intake recommendation, meal plans, recipes, and snack ideas were provided, individual change behavior session, balanced diet, energy-restricted diet, encouraging low-GI diet, and reduced saturated fat. Dietary advice included portion sizes, regular meals, snacking, increasing	Moderate (x2)	3-5 sessions plus 4-6 phone calls. **Exercise:** Recommendation of physical activity frequency is around 3 times/week **Diet:** 3-6 face-to-face consultation plus phone calls. Counseling varied between every two weeks alternating outpatient and phone calls and 4 dietary counseling sessions. Two trials reported the duration (one hour counseling and 1.5 nutrition education lecture).	30-60 min	Mostly the intervention was realized by dietitians (5 studies), in 4 studies was realized by dietitians and gynecologists or trained trials nurses or graduate students. In other studies, was realized by exercise physiologist, 1 trained graduate student, nurse and physiotherapist, masters and doctoral with nutritional training, health trainer, trained researchers.	DASH diet.

		intake of water, fruit and vegetables. cooking class.					
Shepherd et al. 2017	One study mentioned that the interventions started at 22 week's gestation to 36 week's gestation. In other studies, the intervention was initiated in the first trimester. In one study, the intervention began at 19 weeks' gestation	**Exercise:** The intervention in the majority of studies consisted of an intensive lifestyle intervention, or intensive exercise program. One study consisted of a recommendation that women increase activity to walking 5000 steps daily. Four studies recommended min 30 min daily walking or the most frequent possible. And in one study, women received a free six-month gym membership. **Diet:** The most frequent intervention was a hypocaloric or low-glycemic diet. The intervention was conducted in different ways: phone calls that provided diet advice or structured meal plans, written education materials/reminders, notebook for monitoring and exercise recommendation.	Seven studies included moderate-intensity exercise, one mild exercise, and one mild to moderate	**Exercise:** The frequency varied between 3 -7 times per week. 3 times a week was the most frequent in the recommendation. **Diet:** The majority of intervention was realized in one-on-one visit (x9). 6 studies one-on-one visit with a weekly or monthly group session, phone session, or distribution of digital scales.	Session's duration recommended is generally 30 min with some variation that can reach 40-45 min in some intervention		Frequently the interventions are based on some guide: Institute of Medicine (IOM) guidelines (x4) and American College of Obstetricians and Gynecologists guidelines for gestational weight gain,
Song et al. 2016	20 Trials initiated the intervention at or before 15 gestational week, and 8					dietitian,	

	after the 15th gestational week.						
Rogozińska et al. 2015	All the interventions were commenced before 28 weeks at varied time points in the first or second trimester.	**Exercise:** Recommendation to increase the amount of walking and incidental activity, two trials just recommended walking, and trials recommend different types of activities: swimming, aerobic, stretching, strength exercise. One trial conducted an indoor training with light weights, elastics band, balance, and aerobics exercises. **Diet:** Change of habitual diet in interventions groups more frequently by recommendations for a healthy and balanced diet. Increase fiber, increase low-GI food. A study used a simple behavioral change using a social cognitive theory.	Intensity was reported as moderate in just one trial.	**Exercise:** 3-5 times/ week. **Diet:** Different type of visit was reported in 3 trials: one-to-one contact session, four sessions of behavioral change and lifestyle interventions. A session every 2 weeks.	The duration was reported for two studies, 30-45 min, and 30-60 min, respectively.	A dietitian and nutritionist mostly provided the sessions. Many times accompanied by physiotherapists, or nurses. Masters and doctoral level staff with training in nutrition or clinical psychology.	The most mixed approach intervention was based on the official National Dietary Recommendations. The Institute of Medicine (IOM) guidelines and Danish recommendation were also used.
Madhuvrata et al. 2015	15-35 week's gestation	**Exercise:** In general, intervention was based on encouraging physical activity by aerobic and aquafit classes provided by a specialist and written and oral instruction, or encouraging walking. A study provided free membership to a fitness center for 6 months with closed training classes 1h	Moderate exercise recommended in two trials	**Diet:** 3 group sessions (5 women/1h), one face-to-face	30 min most days	Nurse (x3) or doctor, Licensed fitness trainers and registered dietician, Masters or Doctoral students, food technologist and clinician physiologist, study coordinator, exercise physiologist,	Official National Dietary recommendation, Danish recommendations.

		every week and use of a pedometer. **Diet:** Phone calls, brochure which provided advice on nutrition, balanced healthy diet, recommendation for energy intake, automated postcards that promote healthy eating.			trained dietitian, and primary care provider.	
Skoutris et al. 2014	8-12 at 20-28 gestational week	Individual session in most trials, the intervention consisted of verbal counseling with written support education in some trials. **Exercise:** Seven studies encouraged physical activity, one mentioned pelvic floor exercises as a specific exercise. **Diet:** Food Choice map, Information, and recommendation on healthy eating.			Mostly dietitian (x5), clinic nurse, nutritionist	Health Canada guidelines, Prenatal nutrition guidelines
Oostdam et al. 2011	Varying start dates	**Exercise:** Supervised exercise, group session, or brochure recommendation consist in encouraging physical activity especially toning exercise, cycling (data presented separately) brochure and active counseling session, or phone calls consist in the promotion of balanced diet recommendation, high dietary	Moderate exercise, light resistance	3-5 times/ week		

	fiber, and low intake of sucrose, restricted energy diet LGI diet, one trials consist in self-monitoring	

ANNEX II: QUESTIONNAIRE FOR INFORMATION COLLECTION

Número de Registro |__||__||__||__| Fecha |__||__| |__||__| |__||__|

Número de Historia |__||__||__||__||__||__| SS |__||__||__||__||__||__||__||__|

DATOS DE FILIACIÓN

Apellidos y NombreDomicilio Habitual

Teléfono |__||__||__|-|__||__||__||__||__||__| Móvil |__||__||__||__||__||__||__||__||__|Fecha de Nacimiento |_||_| |_||_| |_||_|

1) ¿Nacionalidad española? (1. Sí; 2. No) |___| Sólo para mujeres extranjeras:

¿Nacionalidad?

¿Desde qué año reside en España? |_| |__| |__| |__|

2) ¿Cuál es el máximo nivel de estudios que ha completado? 1. Sin estudios (no sabe leer ni escribir)

2. Primarios incompletos
3. Estudios primarios o EGB hasta 5º
4. Graduado escolar (EGB hasta 8º ó ESO)
5. Bachiller superior (BUP, FP o similar)
6. Estudios Universitarios de Primer ciclo
7. Estudios Universitarios de Segundo ciclo
9. No sabe/ No contesta

3) ¿Está casada? (1. Sí; 2. No; 3. NC) |__|

Si la respuesta es "No", ¿con quién vive actualmente?

4) ¿Usted trabaja fuera de casa? (1. Sí; 2. No; 3. NC) |__|

¿En qué trabaja?

¿Ha dejado de trabajar durante el embarazo? (1. Sí; 2. No; 3. NC) |_|Situación laboral actual 1. Trabajo a tiempo completo

2. Trabajo a tiempo parcial
3. Ama de casa
4. Paro
5. Jubilada por incapacidad
6. Baja relacionada con embarazo
7. Excedencia o asuntos propios

Si la contestación ha sido "3" pase a la pregunta número "5", si no conteste las dos cuestionessiguientes:

¿Es usted autónoma? (1. Sí; 2. No; 3. NC) |__|

Código de Extracción:

_____

¿Cuál es o era su situación de empleo en esa ocupación?

1. Trabajadora por cuenta propia, sin asalariados
2. Trabajadora por cuenta propia, con menos de 10 asalariados
3. Trabajadora por cuenta propia, con 10 ó más asalariados
4. Gerente de una empresa con 10 ó más asalariados
5. Gerente de una empresa con menos de 10 asalariados
6. Capataz, supervisora o encargada
7. Otros asalariados

5) Asistencia durante el embarazo (1. Pública; 2. Mixta; 3. NC) |__|

6) Centro de Salud de Referencia C.P.E. de Referencia

8) Seguimiento del embarazo actual
1. Coordinado entre atención primaria y especializada
2. Sólo atención especializada por embarazo de alto riesgo
3. Sólo atención especializada por decisión personal
4. NS/NC

ANTECEDENTES FAMILIARES Y PERSONALES DE INTERÉS

1) ¿Algún miembro de su familia padece o ha padecido diabetes? (1. Sí; 2. No; 9. NC) |__| Si la respuesta es "Sí", ¿cuántos? |_|

Señale quién o quiénes:
1. Padre
2. Madre
3. Hermanos
4. No sé

2) ¿Es fumadora? |__|

(1. Sí; 2. No, lo he dejado durante el embarazo; 3. No, lo dejé antes del embarazo; 4. Nunca he fumado; 9. NC)

Si ha contestado "1", "2" ó "3" (fuma o ha fumado) conteste las siguientes preguntas:

¿A qué edad comenzó a fumar? |__||__|
¿Cuántos cigarrillos fumaba al día antes del embarazo? |__||__|
¿Cuántos cigarrillos fuma al día durante el embarazo? |__||__|
Si lo ha dejado, ¿hace cuánto tiempo? |__||__| años |__||__| meses

3) ¿Consume alcohol durante el embarazo? (1. Sí; 2. No; 9. NC) |__| Frecuencia_____
¿Consumía alcohol antes de estar embarazada? (1. Sí; 2. No; 9. NC) |__| Frecuencia_____

4) Según su actividad física diaria usted considera su estilo de vida antes del embarazo como:

1. Sedentario |__|
2. Intermedio |__|
3. Activo |__|
4. NS/NC |__|

¿Y durante el embarazo? |__|

¿Limita de alguna manera su embarazo la actividad física diaria? 1. Sí; 2. No; 9. NC) |_|

Si la respuesta es "SÍ", ¿Por qué?_____

En su tiempo libre, ¿cuántas veces realiza ejercicio físico de forma reglada a la semana? |_|

Si la respuesta es "Sí", ¿qué tipo de ejercicio realiza?: _____

5) Si le preguntasen por su dieta habitual, usted la consideraría tipo:	1. Mediterránea	|__|	|__|*
	2. Americana	|__|	
	3. Mixta	|__|	
	4. NS/NC	|__|	
En cuanto a la cantidad que consume usted diría que es:	1. Excesiva	|__|	|__|*
	2. Adecuada	|__|	
	3. Insuficiente	|__|	
Y en cuanto a su consumo de grasas, ¿cómo lo consideraría?	1. Excesivo	|__|	|__|*
	2. Adecuado	|__|	
	3. Insuficiente	|__|	
Usted diría que su consumo proteico (carnes, pescados...) es:	1. Excesivo	|__|	|__|*
	2. Adecuado	|__|	
	3. Insuficiente	|__|	

*¿Y antes del embarazo?

6) ¿Presenta algún tipo de patología crónica? (1. Sí; 2. No; 9. NC) |_|

Si la respuesta es "Sí", ¿cuál?: _____

¿Qué tratamiento toma? _____

Como consecuencia de su patología, ¿sigue una dieta especial? (1. Sí; 2. No; 9. NC) |__|

¿Qué tipo de dieta? _____

¿Le han recomendado modificar su actividad física habitual? (1. Sí; 2. No; 9. NC) |__|

¿Qué le han recomendado? _____

ANTECEDENTES OBSTÉTRICOS DE INTERÉS

1) Fórmula obstétrica (No considerar el embarazo actual) |__||__||__||__||__|

(nº embarazos; nº abortos; nº partos; nº R.N. vivos; vivos actualmente)

2) Antecedente de diabetes mellitus gestacional (1. Sí; 2. No; 3. No estoy segura; 9. No sabe) |__|

Si la respuesta ha sido "Sí"

- ¿qué tratamiento recibió? (1. Dieta; 2. Dieta + Insulina) |__|
- ¿le realizaron una sobrecarga después del parto? (1. Sí; 2. No; 9. No sabe) |__|
- ¿cuál fue el resultado? (1. Diabetes; 2. Intolerancia H-C; 3. Normal) |__|

3) Antecedente de macrosomía (recién nacidos de 4 kilos ó más) (1. Sí; 2. No; 9. NC) |__|

¿Cuántos hijos ha tenido de más de 4 kilos al nacer? |__|

¿Recuerda cuál fue su peso? 1º hijo |__||__||__||__|
2º hijo |__||__||__||__|
3º hijo |__||__||__||__|

4) ¿Presentó problemas de hipertensión en embarazos anteriores? (1. Sí; 2. No; 9. NC) |__|

Si ha contestado "Sí" ¿podría señalar qué tipo? 1. Hipertensión inducida por el embarazo
2. Preclampsia
3. Eclampsia
4. No recuerdo

VARIABLES ANTROPOMÉTRICAS

1) Talla* |__|.|__||__|

2) Peso antes embarazo* |__||__||__|.|__|

3) Peso en la primera visita* |__||__||__|.|__| Semana gestacional |__||__|.|__|

4) Último peso conocido* |__||__||__|.|__| Semana gestacional |__||__|.|
| (*Si es posible esta información debería recogerse siempre a partir de la Cartilla Maternal)

5) ¿Cuánto peso ha ganado desde que se quedó embarazada? |__||__|.|__|

6) ¿Ha ganado peso desde que tuvo su primer hijo? (1. Sí; 2. No; 9. No sabe) |__|

Si la respuesta ha sido Sí, ¿cuánto pesaba antes del primer embarazo? |__||__||__|.|__|

¿Cuántos años han pasado desde el primer embarazo hasta la fecha? |__||__|

EMBARAZO ACTUAL

1) Semana gestacional de la primera visita |__|.|__||__|

2) Número de visitas realizadas en A.P. |__||__|

3) Número de visitas realizadas en A.E. |__||__|

4) Número de visitas realizadas en consultas privadas |__||__|

5) Número total de visitas |__||__|

6) ¿Ha estado ingresada durante el embarazo? (1. Sí; 2. No) |__|

Si la respuesta ha sido "Sí", ¿cuál fue el motivo de ingreso? _____

7) Semana de gestación en que se realiza el cribado o test de O' Sullivan |__| |__|

Glucemia basal |__||__||__| Glucemia 1 hora después |__||__||__|

8) ¿Se realizó sobrecarga oral con 100 g glucosa? (1. Sí; 2. No) |__|

Glucemia basal |__||__||__| Glucemia 1 h |__||__||__|

Glucemia 2 h |__||__||__| Glucemia 3 h |__||__||__|

Si no se completa la SOG especificar la causa (vómitos, ausencia de la mujer, hipotensión...) _____

9) Diagnóstico definitivo (1. Diabetes gestacional; 2. Intolerancia H-C; 3. Normal) |__|

10) ¿El embarazo es de Alto Riesgo Obstétrico? (1. Sí; 2. No) |__|

Motivo del ARO_____|__||__||__|

PREGUNTAS COMPLEMENTARIAS (marido y nivel de ingresos de la pareja)

¿Cuál es el máximo nivel de estudios que ha completado su marido?

1. Sin estudios (no sabe leer ni escribir)
2. Primarios incompletos
3. Estudios primarios o EGB hasta 5º
4. Graduado escolar (EGB hasta 8º ó ESO)
5. Bachiller superior (BUP, FP o similar)
6. Estudios Universitarios de Primer ciclo
7. Estudios Universitarios de Segundo ciclo
9. No sabe/ No contesta

¿Cuál es la ocupación que desempeña actualmente o la última que ha desempeñado? _____

¿Cuál es su situación laboral actual?

1. Trabajo a tiempo completo
2. Trabajo a tiempo parcial
3. Paro
4. Jubilado por incapacidad
5. Otros (indicar cuál) _____

¿Cuál es o era su situación de empleo en esa ocupación?

1. Trabajador por cuenta propia, sin asalariados
2. Trabajador por cuenta propia, con menos de 10 asalariados
3. Trabajador por cuenta propia, con 10 ó más asalariados
4. Gerente de una empresa con 10 ó más asalariados
5. Gerente de una empresa con menos de 10 asalariados
6. Capataz, supervisor o encargado
7. Otros asalariados

¿En qué banda situaría usted los ingresos mensuales medios de su hogar (suyos y de su marido)?

1. Menos de 500 euros (menos de 83.000 Ptas.)
2. De 501 a 1.000 euros (de 83.000 a 166.000 Ptas.)
3. De 1.001 a 1.500 euros (166.000-250.000 Ptas.)
4. De 1.501 a 2.000 euros (250.000-333.000 Ptas.)
5. De 2.001 a 2.500 euros (333.000-417.000 Ptas.)
6. De 2.501 a 3.000 euros (417.000-500.000 Ptas.)
7. Más de 3.000 euros (más de 500.000 Ptas.)
8. No sabe / No contesta

Número de Registro |__||__|| **Fecha** |__||__| |__||__|

CUESTIONARIO DE FRECUENCIA DE ALIMENTOS

INSTRUCCIONES. El presente cuestionario pretende recoger el consumo medio de alimentos por persona durante el embarazo y en el último año anterior al mismo. Está basado en el "Food Frequency Questionnaire" utilizado en el estudio de las enfermeras americanas realizado en la Universidad de Harvard y validado en España por Martín-Moreno et al.

Para cada alimento debe señalar su frecuencia de consumo por término medio durante el embarazo y en el último año. Para facilitar la recogida de información debería considerar:

1) Que cada mes consta de 4 semanas y el objetivo del cuestionario es recoger la variación verano/invierno, de tal forma que si usted en verano consume helados un día a la semana durante todas las semanas (de 12 a 15 semanas), su ingesta media será de un helado al mes.
2) Si un alimento lo consume menos de una vez al mes (por ejemplo, sólo en tres ocasiones al cabo del año) considere que lo consume "Nunca o Casi Nunca".
3) Para que le sea más fácil contestar lea el nombre del alimento y piense si lo consume todos los días o no. Si es así se centrará en el consumo diario y descartará todos los demás. Si no lo consume todos los días plantee la misma cuestión para una semana o un mes dependiendo del caso.

Si tiene cualquier duda pregúntela sin ningún tipo de compromiso a la encargada de recoger la información y que le ha suministrado el cuestionario inicialmente.

I-CONSUMO DE LÁCTEOS

LÁCTEOS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**									
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Leche entera (1 taza, 200 cc																					
Leche semidesnatada (1 taza, 200 cc)																					
Leche desnatada (1 taza, 200 cc)																					
Leche condensada (1 cucharada)																					
Nata o crema de leche (1/2 taza)																					
Batidos de leche (1 vaso, 200 cc)																					
Yogurt entero (1, 125 g)																					
Yogurt descremado (1, 125 g)																					
Petit suisse (1, 100 g) **¿100 ó 50?**																					
Requesón o cuajada (1/2 taza)																					
Queso en porciones o cremoso (1 porción)																					
Queso blanco o fresco (Burgos, cabra…) (50 g)																					
Quesos curados/semicurados (Manchego, Bola, Emental, Camembel…) (50 g)																					
Natillas, flan, puding (1 taza, 200 cc)																					
Helados (uno)																					

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

II-CONSUMO DE HUEVOS y CARNES (Se refiere a un plato o ración de 100 a 150 gramos excepto cuando se indique otra cosa entre paréntesis)

HUEVOS y CARNES	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**								
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Huevos (uno)																					
Pollo o pavo CON piel																					
Pollo o pavo SIN piel																					
Carne de ternera MAGRA																					
Carne de ternera GRASA																					
Carne de cerdo MAGRA																					
Carne de cerdo GRASA																					
Carne de cordero																					
Conejo o liebre																					
Hígado																					
Otras vísceras (sesos, corazón, mollejas...)																					
Jamón serrano o paletilla																					
Jamón cocido, jamón york (50 gr)																					
Embutidos (chorizo, salchichón, mortadela, 50g)																					
Morcilla (50 gr)																					
Sobrasada (50 gr)																					
Tocino, bacon, panceta (50 gr)																					
Salchichas (50 gr)																					
Patés, foie-gras (25 gr)																					
Hamburguesa (50 gr)																					

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

III-CONSUMO DE PESCADO (Se refiere a un plato o ración de 100 a 150 gramos excepto cuando se indique otra cosa entre paréntesis)

PESCADOS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**								
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Pescado blanco: merluza, pescadilla, mero, lenguado, rape... (1 plato, pieza o ración)																					
Pescado azul: boquerones, sardinas, atún, bonito, salmón, caballa...(1 plato, pieza o ración)																					
Bacalao																					
Pescados salados y/o ahumados: arenques, salmón, mojama, anchoas...																					
Ostras, almejas, mejillones... (6 unidades)																					
Gambas, langostinos, cigalas...																					
Pulpo, calamares, chipirones, jibia...																					

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

IV. VERDURAS Y HORTALIZAS (un plato o ración de 250 gramos excepto cuando se indique otra cosa entre paréntesis)

VERDURAS Y HORTALIZAS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**									
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Acelgas, espinacas																						
Col, coliflor, brócoles																						
Lechuga, endibias, escarola																						
Tomate (1, 150 gr)																						
Zanahoria, calabaza																						
Judías verdes																						
Berenjenas, calabacines, pepinos																						
Pimientos																						
Espárragos																						
Patatas fritas (1 ración 150 grs)																						
Patatas asadas o cocidas (1 ración 150 grs)																						
Gazpacho																						
Porra antequerana, salmorejo																						
Ensalada de verduras																						

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

V. FRUTAS (Una pieza o ración salvo cuando se indique entre paréntesis el número de unidades)

FRUTAS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**									
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Naranja (1), pomelo (1), mandarina (2)																						
Plátano																						
Manzana, pera																						
Fresas, fresones (6 unidades)																						
Melocotón, albaricoque, nectarina																						
Cerezas, picotas, ciruelas (1 plato de postre)																						
Higos, brevas																						
Higos chumbos																						
Sandía (1 tajada, 200-250 gr)																						
Melón (1 tajada, 200-250 gr)																						
Uvas (1 racimo o plato de postre)																						
Frutas en almíbar (2 unidades)																						
Frutas en su jugo, macedonia (2 unidades)																						
Dátiles, higos secos, pasas, ciruelas-pasas (150 grs)																						
Almendras, cacahuetes, avellanas, nueces (frutos secos, 50 grs)																						
Aguacates																						
Kiwi																						
Mango, papaya																						
Aceitunas (10 unidades)																						

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

VI. LEGUMBRES Y CEREALES (Un plato o bien una ración de 60 gramos en seco)

LEGUMBRES Y CEREALES	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**									
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Lentejas																					
Garbanzos																					
Alubias (pintas, blancas o negras)																					
Guisantes																					
Pan blanco (3 rodajas, 60 gramos)																					
Pan integral (3 rodajas, 60 gramos)																					
Pan de molde (1 rebanada)																					
Pan de molde integral (1 rebanada)																					
Cereales en desayuno (30 gramos en seco)																					
Arroz																					
Pasta (fideos, macarrones, espaguetis...)																					
Pizza (1 ración, 200 gr)																					

VII. ACEITES Y GRASAS (Una cucharada o porción individual)

ACEITES Y GRASAS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										**		**CONSUMO MEDIO DURANTE EL AÑO PASADO**								
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Mantequilla (1 porción individual = 2 rebanadas)																					
Margarina (1 porción individual = 2 rebanadas)																					
Aceite de oliva																					
Aceite de girasol o soja																					
Otros (especificar) _____																					
Otros (especificar) _____																					
¿Con qué frecuencia consume alimentos fritos:																					
En CASA?																					
Fuera de CASA?																					

En su casa utiliza para freír: 1. Aceite de oliva 2. Aceite de girasol
3. Aceite de soja 4. Mantequilla
5. Margarina 6. Otros (especificar) _____

VIII. BOLLERÍA Y PASTELERÍA

BOLLERÍA Y PASTELERÍA	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**								
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Galletas tipo María (4-6 unidades, 50 g)																					
Galletas con chocolate (4-6 unidades, 50 g)																					
Magdalenas (1-2 unidades)																					
Donuts (1)																					
Bollería industrial: ensaimada, croissant... (1)																					
Repostería casera (bizcocho, tarta de queso...)																					
Pasteles (1, 50 gramos)																					
Churros, porras y similares (ración, 100 grs)																					
Chocolate y bombones (30 gramos)																					
Turrón (1/8 barra)																					
Pastas de té, mantecados, mazapán (ración, 90 gramos)																					

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

IX. OTROS ALIMENTOS

OTROS ALIMENTOS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**								
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Croquetas, buñuelos, empanadillas																					
Palitos de merluza, pescado empanado																					
Sopas y cremas de sobre																					
Mostaza (1 cucharadita)																					
Mayonesa (1 cucharadita)																					
Salsa de tomate, tomate frito, ketchup																					
Picante: tabasco, pimienta																					
Sal (añadida a las comidas ya cocinadas)																					
Azúcar (1 cucharadita)																					
Mermelada (1 cucharadita)																					
Otros alimentos de consumo frecuente:																					

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

X. BEBIDAS

BEBIDAS	**CONSUMO MEDIO DURANTE EL EMBARAZO**										******		**CONSUMO MEDIO DURANTE EL AÑO PASADO**								
		DÍA				**SEMANA**			**MES**			**AÑO**	**DÍA**				**SEMANA**			**MES**	
	Nunca o casi nunca	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 a sem**	**5-6 sem**	**2-3 mes**	**1 al mes**		**Nunca o casi nunca**	**1 día**	**2-3 día**	**4-6 día**	**Más de 6 al día**	**1 semana**	**2-4 sem**	**5-6 sem**	**2-3 al mes**	**1 al mes**
Vino tinto (1 vaso 100 cc) (en total)																					
Vino tinto sólo en las comidas (1 vaso 100 cc)																					
Vino dulce (1 vaso 100 cc) (en total)																					
Otros vinos (blanco, rosado...) (en total)																					
Cerveza (1 vaso 250 cc)																					
Licores, destilados: whisky, coñac, ginebra, anís ... (1 copa, 50 cc)																					
Bebidas carbonatadas azucaradas (Fanta, Coca –Cola...; 1 vaso, 200 cc)																					
Bebidas carbonatadas bajas en calorías (Fanta Free, Coca–Cola Light...; 1 vaso, 200 cc)																					
Zumo de naranja natural (1 vaso 200 cc)																					
Zumos naturales de otras frutas (1 vaso 200 cc)																					
Zumos de frutas en botella o enlatados (200 cc)																					
Café descafeinado (1 taza 50 cc)																					
Café (1 taza 50 cc)																					

** ¿Ha modificado su consumo durante el embarazo? Indique si ha aumentado con el símbolo "↑"; ha disminuido con el símbolo "↓" o continua igual con el símbolo "="

¿ESTÁ TOMANDO VITAMINAS Y/O MINERALES DURANTE EL EMBARAZO O LOS TOMÓ DURANTE EL AÑO ANTERIOR A QUEDARSE EMBARAZADA?

Sí; 2. No; 3. NS/NC

Si la respuesta ha sido Sí:

MARCAS DE LOS SUPLEMENTOS VITAMÍNICOS O MINERALES (Nº pastillas/día)	CONSUMO MEDIO DURANTE EL EMBARAZO											CONSUMO MEDIO DURANTE EL AÑO PASADO									
		DÍA				SEMANA			MES			AÑO	DÍA				SEMANA			MES	
	Nunca o casi nunca	1 día	2-3 día	4-6 día	Más de 6 al día	1 semana	2-4 a sem	5-6 sem	2-3 mes	1 al mes		Nunca o casi nunca	1 día	2-3 día	4-6 día	Más de 6 al día	1 semana	2-4 sem	5-6 sem	2-3 al mes	1 al mes

IMPRESIÓN PERSONAL SOBRE DIETA Y EMBARAZO		**¿Y antes del embarazo?**
1) ¿Procura tomar mucha fibra? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
2) ¿Procura tomar mucha fruta? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
3) ¿Procura tomar mucha verdura? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
4) ¿Procura tomar mucho pescado? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
5) ¿Suele comer entre comidas (picotear)? (1. Sí; 2. No; 9. NS/)	|__|	|__|
6) ¿Evita el consumo de mantequillas? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
7) ¿Procura reducir el consumo de grasa? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
8) ¿Qué hace con la grasa de la carne? (1. La como; 2. Se la quito)	|__|	|__|
9) ¿Limita la sal en las comidas? (1. La como; 2. Se la quito)	|__|	|__|
10) ¿Procura reducir el consumo de dulces? (1. Sí; 2. No; 9. NS/NC)	|__|	|__|
11) ¿Cuántos días toma fruta a la semana como postre?	|__|	|__|

ACTIVIDAD FÍSICA HABITUAL EN EL TIEMPO LIBRE Y GENERAL

	DURANTE EL EMBARAZO				**ANTES DEL EMBARAZO**		
ACTIVIDADES REALIZADAS EN SU TIEMPO LIBRE	**DIAS A LA SEMANA**	**TIEMPO DEDICADO AL DIA (HORAS O MINUTOS)**	**ESFUERZO REALIZADO (L, M, I)**		**DÍAS A LA SEMANA**	**TIEMPO DEDICADO AL DIA (HORAS O MINUTOS)**	**ESFUERZO REALIZADO (L, M, I)**
Andar o pasear fuera de casa							
Bicicleta (incluyendo estática)							
Nadar							
Aeróbic							
Baile, danza							
Excursiones en la montaña							
Gimnasia de mantenimiento							
Cuidado del jardín, piscina (meses*)							
OTROS:							

DESPLAZAMIENTOS							
Bicicleta							
Andar de casa al trabajo/ trabajo a casa							
OTROS:							

ACTIVIDAD FÍSICA HABITUAL EN EL TIEMPO LIBRE Y GENERAL

	DURANTE EL EMBARAZO				ANTES DEL EMBARAZO		
ACTIVIDADES DEL HOGAR	**DIAS A LA SEMANA**	**TIEMPO DEDICADO AL DIA (HORAS O MINUTOS)**	**ESFUERZO REALIZADO (L, M, I)**		**DÍAS A LA SEMANA**	**TIEMPO DEDICADO AL DIA (HORAS O MINUTOS)**	**ESFUERZO REALIZADO (L, M, I)**
Trabajo de casa ligero:							
• Cocinar							
• Planchar							
• Lavar los platos							
• Cuidar a los niños							
• Otros:							
Trabajo de casa intenso:							
• Fregar los suelos							
• Andar con bolsas pesadas de la compra)							
• Otros:							

	DURANTE EL EMBARAZO				ANTES DEL EMBARAZO		
ACTIVIDAD EN EL TRABAJO	**DIAS A LA SEMANA**	**TIEMPO DEDICADO AL DIA (HORAS O MINUTOS)**	**ESFUERZO REALIZADO (L, M, I)**		**DÍAS A LA SEMANA**	**TIEMPO DEDICADO AL DIA (HORAS O MINUTOS)**	**ESFUERZO REALIZADO (L, M, I)**
Trabajo ligero (sentada, de pie y con escaso movimiento)							
Trabajo intenso (transportando objetos pesados en el trabajo, etc.)							

OTRAS ACTIVIDADES							
Ver televisión - video							
Sentada ante la pantalla del ordenador							
Conduciendo							
Estar sentada							
Dormir por las noches							
Dormir la siesta							
Salir con su pareja, familiares o amigos							
De pie							
Leyendo							
Otros:							

¿Podemos contactar con usted para conocer cuál ha sido la evolución de su embarazo? SI NO

FIRMA:

DG: Efectos sobre la madre y el recién nacido

Señale con una X las fuentes de información utilizadas

Libro de partos ☐
Historia digital ☐
Entrevista ☐
Historia clínica ☐

Registro:
Nº Historia Clínica:
Apellidos y Nombre:
Teléfono:
Fecha Nacimiento:

1) Ganancia de peso durante el embarazo (k)

1. Incremento total ☐☐.☐
2. Peso primera visita ☐☐☐.☐ Semana de Gestación (SG) ☐☐
3. Peso última visita ☐☐☐.☐ Semana de Gestación (SG) ☐☐

2) Complicaciones del embarazo

1. Aborto tardío (<22 SG/500 g) (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
2. Muerte Fetal ante parto (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
3. HT Inducida por Embarazo ☐ SG☐☐
   (0. No, 1. Leve; 2. Grave >160/110; 9. No sabe)
4. Preeclampsia ☐ SG☐☐
   (0. No, 1. Leve; 2. Grave >160/110; 9. No sabe)
5. Eclampsia (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
6. Amenaza de Parto Prematuro (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐*
   *Semana de gestación del primer episodio
   Número de Episodios ☐☐
7. Rotura Prematura Membranas (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
8. Polihidramnios (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
9. Oligoamnios (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
10. Crec. Intrauterino Retardado (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐
11. Malformaciones Fetales (0. No, 1. Sí; 9. No sabe) ☐ SG☐☐*
    *Semana de gestación del diagnóstico inicial
    Tipo:
12. Infecciones Tracto Urinario (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    12.1 Bacteriuria asintomática (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    12.2 Cistitis (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    12.3 Pielonefritis (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
13. Vulvovaginitis candidiásica (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
14. Infección puerperal (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    14.1 Fiebre puerperal sin foco (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    14.2 Infección tracto urinario (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    14.3 Endometritis (0. No, 1. Sí; 9. No sabe) ☐
    14.4 Mastitis (0. No, 1. Sí; 9. No sabe) ☐ Número☐☐
    14.5 Infección herida quirúrgica (0. No, 1. Sí; 9. No sabe) ☐

15. Número de Visitas ☐☐
    15.1 Atención Primaria ☐☐
    15.2 Atención Pública Especializada ☐☐
    15.3 Consultas en urgencias HMI ☐☐
16. Número de ingresos ☐☐
    16.1 Días de ingreso (1º) ☐☐
    16.1' Motivo ingreso (1º) Codificación ☐☐
    16.2 Días de ingreso (2º) ☐☐
    16.3 Motivo de ingreso (2º) ☐☐
    16.3 Días de ingreso (3º) ☐☐
    16.3' Motivo de ingreso (3º) ☐☐
20. Otras complicaciones: _____

3) Parto y características

0. Fecha del parto ☐☐☐☐☐☐, Fecha alta puerperal ☐☐☐☐☐☐
1. Motivo ingreso Codificación ☐☐☐
2. Días de gestación ☐☐☐
3. Bolsa rota (0. Intraparto;1. Anteparto; 9. NS) ☐
4. Riesgo obstétrico Codificación ☐☐☐
5. EGB vaginorectal (0. Negativo, 1.Positivo, 2. Desconocido) ☐
6. Episiotomía (0. No, 1. Sí; 9. No sabe) ☐
7. Presentación ☐
   1. Cefálica; 2. Cefálica reflexionada; 3. Nalgas; 4. Transversa; 9. No sabe
8. Comienzo ☐.☐
   1. Espontáneo; 2. Inducido Oxitocina; 3. Ind. PG; 4. Ind. PG + Oxitocina; 5. Cesárea electiva; 9. No sabe
9. Terminación ☐
   1. Espontáneo; 2. Espátulas; 3. Ventosa; 4. Fórceps; 5. Cesárea; 6. Cesárea + histerectomía; 9. No sabe
10. Indicación inducción Codificación ☐☐☐
11. Indicación Op. Vaginal ☐
    1. Acortamiento expulsivo; 2.Estancamiento expulsivo; 3. Riesgo pérdida bienestar fetal, 4.No sabe
12. Indicación Cesárea Codificación ☐☐☐
13. Lesión canal del parto ☐
    1. No; 2; Desgarro I grado; 3. Desgarro II grado; 4. Desgarro III grado; 5. Desgarro IV grado;
    6. Prolongación episiotomía; 7. Desgarro cervical; 8. Rotura vesical; 9. Rotura uterina; 99. No sabe

4) Resultados neonatales

1. Apellidos
2. Peso en gramos ☐☐☐☐
3. Sexo (0. Mujer; 1. Varón) ☐
4. Apgar 1 ☐☐
5. Apgar 5 ☐☐
6. pH arterial
7. pH venoso
8. Líquido amniótico ☐
   1. Claro; 2. Meconio; 3. Sanguinolento; 4. Ausente
9. Mortalidad (0. No, 1. Sí) ☐
   Causa

10. Morbilidad (0. No, 1. Sí; 9. No sabe) ☐
11. Hipoglucemia neonatal (0. No, 1. Sí; 9. No sabe) ☐
12. Hipocalcemia neonatal (0. No, 1. Sí; 9. No sabe) ☐
13. Hiperbilirrubinemia (0. No, 1. Sí; 9. No sabe) ☐
14. Traumatismos parto (0. No, 1. Sí; 9. No sabe) ☐
    Tipo:
15. Poliglobulia (0. No, 1. Sí; 9. No sabe) ☐
16. Malformaciones congénitas (0. No, 1. Sí; 9. No sabe) ☐
    Tipo:
17. EGB (0. Negativo; 1. Positivo; 2. Desconocido) ☐
18. Destino del recién nacido ☐

    0. Con la madre partos; 1. Madre planta; 2. Cuidados mínimos; 3. Cuidados medios; 4. Intensivos; 5. Prematuros; 6. Éxitus

19. Fecha alta del recién nacido (unidad neonatal) ☐☐☐☐☐☐

5) **Lactancia materna** (0. No, 1. Sí) ☐ Meses (nº)

APPENDIX. SCIENTIFIC PUBLICATIONS

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SYSTEMATIC REVIEW

Persistent organic pollutant exposure as a risk factor of gestational diabetes mellitus: A systematic review and meta-analysis

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Abstract

Background: Findings related to the association between persistent organic pollutants (POPs) and gestational diabetes mellitus (GDM) are inconclusive.

Objectives: To estimate the strength of the association between POP exposure and GDM in a systematic review with meta-analysis.

Search strategy: MEDLINE, Scopus and Web of Science were searched until July 2023.

Selection criteria: Cohort and case–control studies analysing the association between POPs and GDM.

Data collection and analysis: We assessed the risk of bias using the Quality in Prognosis Studies scale (QUIPS). Standardised mean differences were pooled using random-effect models.

Main results: Sixteen articles including 12 216 participants were selected. The risk of bias was high in four articles (25%), moderate in 11 (68.75%) and low in one (6.25%). Small mean difference between GDM cases and controls was observed for PFHpA (0.26, 95% confidence interval [CI] 0.1–0.35, $I^2 = 0.0\%$), PCB180 (0.37, 95% CI 0.19–0.56; $I^2 = 25.3\%$), BDE47 (0.23, 95% CI 0.0–0.45, $I^2 = 0\%$), BDE99 (0.36, 95% CI 0.14–0.59; $I^2 = 0\%$), BDE100 (0.42, 95% CI 0.19–0.64; $I^2 = 0\%$) and HCB (0.22, 95% CI 0.01–0.42, $I^2 = 39.6\%$). No considerable difference was observed for the rest of POPs.

Conclusion: Small mean differences between GDM cases and controls were observed for some POPs. However, evidence shows mostly moderate quality and results were heterogeneous. Improved research methodology is needed to assess POPs and GDM risk.

KEYWORDS
exposure, gestational diabetes mellitus, meta-analysis, persistent organic pollutants, risk factor, systematic review

1 | INTRODUCTION

Persistent organic pollutants (POPs), such as Per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and organochlorine pesticides (OCPs) are highly lipophilic compounds and are peculiarly persistent and resistant to biodegradation. Due to their long half-life, POPs have the ability to bioaccumulate in the environment, food and organisms.[1] The principal pathway for human exposure to

Javier Zamora and José Juan Jiménez-Moléon contributed equally to this work.

most POPs is through dietary intake. However, occupational exposure, indoor inhalation and inadvertent ingestion of dust are important sources of exposure for some POPs.[2–4] Chronic exposure to POPs can be related to ill health, even in low doses.[5] In adults, high specimen POPs levels were associated with a high risk of carcinogenic, neurological, endocrine and metabolic conditions.[6–9] Several POPs, such as hexachlorobenzene (HCB), dichlorodiphenyldichloroethylene (p,p′-DDE) and PCBs have been described as potential risk factors for diabetes mellitus type 2.[10,11]

During pregnancy, POPs exposure increases the risk of several outcomes such as miscarriage, preterm birth and low birthweight.[12–14] However, findings related to gestational diabetes mellitus (GDM) tend to show more discrepancies.[12,15,16] Zhang et al.[17] describe a positive association between PCB 52 and GDM, and no association for PCB 138, 153 and 180. However, Jaack et al.'s[18] cohort study shows a negative association between PCB 138, 15, and 180 with GDM. Regarding PFAS, Yan et al.'s[19] systematic review supports that PFAS increase the risk for GDM;in contrast, no association was affirmed by Gao et al.[12] This disparity may be caused by population characteristics and selection biases, small sample sizes, lipid adjustment, POPs measurement procedures, the use of different definitions for GDM, and methodological issues related to the adjustment for confounding factors. Furthermore, it would be necessary to ensure that exposure assessment precedes the outcome's occurrence to reduce possible bias, especially as blood concentrations of POPs may change throughout pregnancy.[20,21] We found one systematic review based on follow-up studies, but this review focused only on the relation between DDT and GDM.[15]

Therefore, we aimed to explore comprehensively the association between POPs and GDM using a systematic review with a meta-analysis of cohort and case–control studies.

2 | METHODS

This systematic review and meta-analysis protocol has been registered previously in PROSPERO (www.crd.york.ac.uk/PROSPERO, CRD42022303450). It was reported according to the 2020 update of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[22] Patients were not involved in the development of the research and ethical approval was not required due to the study design.

2.1 | Eligibility criteria

Eligibility criteria were defined a priori according to the PECOS statement (P: population, E: exposure, C: comparators, O: outcome, S: study design). More information about these criteria are provided in Table S1. The selection criteria were: (1) cohort, case–control studies and hybrid studies (nested case–control studies and case–cohort studies); (2) studies based on women of childbearing age; (3) studies analysing the relation between the individual contamination levels of POPs and the incidence of GDM; (4) published studies from the inception of the database used for the search until July 2023. All cross-sectional studies, book chapters and conference communications were excluded.

2.2 | Information source and research strategy

A systematic search was conducted in March 2022, and then updated every 6 months. The last update was realised on July 2023, and two additional records were included in our systematic review.[23,24] Terms were searched on PubMed Central, Web of Science via Clarivate, and Scopus via Elsevier. The updated version of each platform was used. Free keywords were combined on a search equation according to each database's recommendations (Appendix S1).

The following terms were used for the searches: organochlorinate, organochlorine, chlorinated, persistent organic pollutant, POP, persistent pesticides, persistent toxic substances, per- and polyfluoroalkyl substances, PFAs, polybrominated diphenyl ethers, PBDEs, polychlorinated biphenyls, PCBs, hexachlorobenzene, HCB, dichlorodiphenyltrichloroethane, DDT, p,p′DDT, dichlorodiphenyldichloroethylene, DDE, p,p′DDE, dichlorodiphenyldichloroethane, DDD, p,p′DDD, gestational diabetes mellitus, gestational diabetes, GDM.

Additionally, the reference lists of selected reviews were hand-searched. Details of search results are provided for each data resource in Appendix S1. Two investigators (MK and MACH) independently conducted the search and identified the eligible articles. After duplicated articles were removed, a first screening by title and abstract was done. Articles that met inclusion criteria were assessed by reading the full text. Disagreement or uncertainties in the selection of studies was resolved through discussion with senior reviewers (JJJM and JZ).

2.3 | Data extraction and quality assessment

Selected articles were reviewed by MK and MACH independently. From each article the following information was extracted in a standardised form:

Basic data: authors, publication year, study period, country and research funding.

Study characteristics: type of study design, sample method, sample size, selection criteria, characteristics of the participants and compliance with ethical principles.

Exposure data: type of examined POPs, biomarkers used to assess contamination level, gestational age for the sample collection, analytic methodology, limit of detection (LOD) or limit of quantification (LOQ), unit of measurement for POPs and lipid adjustment for the final determinations.

Outcome data: criteria used for the diagnosis of GDM were collected from the National Diabetes Data Group criteria, Carpenter–Coustan criteria, International Association of Diabetes and Pregnancy Study Groups criteria, World Health Organization criteria, Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada).

Descriptive measurements of POPs by comparison groups and analytic results: mean and standard deviation (SD), median and interquartile range (IQR) or geometric mean (GSD) to describe the levels of POPs; and relative risk (RR), odds ratio (OR) and their 95% confidence interval (CI) as association measures. Confounding factors used for adjustment analyses were also collected. The authors were contacted by email in the case of missing information.

Risk of bias and methodological quality of each included study in the systematic review were evaluated independently by two researchers (MK and MACH) using the Quality in Prognosis Studies scale (QUIPS).[25] The following describes the six domains with their respective issues and cut-off points to consider for judging the risk of bias in QUIPS:

Study participation, including factors such as the source of the target population, method/s used to identify the population, recruitment period, inclusion and exclusion criteria, adequate study participation and baseline characteristics. The risk of bias was classified as low (5–7 items), moderate (3, 4) and high (1, 2).

Study attribution, related to strategies to avoid losses, the reasons for the losses, and the potential impact of subjects lost to follow-up on the results based on outcome and prognostic factor/s information on those lost to follow-up. The risk of bias was categorised as low (met 5 items), moderate (3, 4) and high (1, 2).

Appropriate definition of the following: the exposure and measurement methods, the same method and setting for all study participants, exposure measurement available for adequate sample proportion, and appropriate methods of imputation. The cut-off points for the risk of bias were: low (met 5 items), moderate (3, 4) and high (1, 2).

Outcomes: outcome measurement collection, definition of the outcome (gestational diabetes or not), valid and reliable measurement of outcome, method and setting of outcome measurement were assessed. These were classified as low (met 3 items), moderate (2) and high (1) risk of bias.

Collection of confounding factors and their characteristics: definition of confounding factor, methods, setting, validity and reliability of the measurements, methods used for missing data, and appropriate strategies to avoid the effect of confounding factors. The risk of bias was classified as low (met 5–7 items), moderate (3, 4) and high (1, 2) risk of bias.

Statistical analysis and reporting: the analytical strategy, models of development strategy, and reporting of results were assessed. The risk of bias was classified as low (met 4 items), moderate (2, 3) and high (1).

In addition to the guidelines provided by the QUIPS scale to judge the risk of bias in each item, supplementary comments were developed to facilitate the consensus. Studies were classified as follows:

- low risk of bias, requires at least five domains judged as low risk of bias and none classified as high risk of bias;
- moderate risk of bias for those cases with (1) five items classified as low risk of bias and one item judged as high risk of bias, or (2) two items evaluated as moderate risk of bias;
- high risk of bias for those cases with at least two items judged as high risk of bias or at least three items evaluated as moderate risk of bias.

The weighted kappa coefficient (Kw) for the six domains was measured to assess inter-rater reliability.[26] Disagreements and uncertainties were solved through discussion with senior reviewers (JJJM and JZ).

2.4 | Data synthesis and meta-analysis

To determine the method to combine individual studies data in the meta-analysis, the characteristics and the results of each included study were assessed. To combine the information from every study, the exposed levels of POPs expressed as continuous data in groups of GDM and non-GDM pregnant women was used. Studies that only showed association measurements (e.g. OR, log OR, ln-OR per-unit increment, RR per unit of increase of SD, terciles, quartiles and quintiles) were excluded from meta-analyses. Mean values and standard deviations were used when provided. If not provided, the median as a mean approximation was used, and SD was estimated using the IQR according to the formula: (SD = IQR/1.35). The standardised mean difference was interpreted according to the following cut-off point: 'Small standardised mean difference: 0.2–0.5, medium 0.5–0.8 and large >0.8'.[27] A random-effects meta-analysis was conducted separately for each exposure according to POP type. Heterogeneity was assessed using the I^2 test. Publication bias was evaluated using a funnel plot and Egger's lineal regression asymmetry tests. Significance was considered at a P-value <0.05. Analyses were conducted using STATA software version 14.0.

3 | RESULTS

3.1 | Literature search and study characteristic

From 161 identified studies, 78 duplicated records were removed, and 83 screened by title and abstract. Accordingly, 19 studies were selected for full-text screening after our initial search for studies, and 13 records met the selection criteria (Figure 1). One additional article was identified by hand searching references[28] and two records were added after the last update using alerts for the identification of new studies.[23,24] Excluded records are provided in Table S2.

Of the 16 articles finally included in our systematic review, 75% ($n = 12$) were cohort studies, 18.75% ($n = 3$) nested

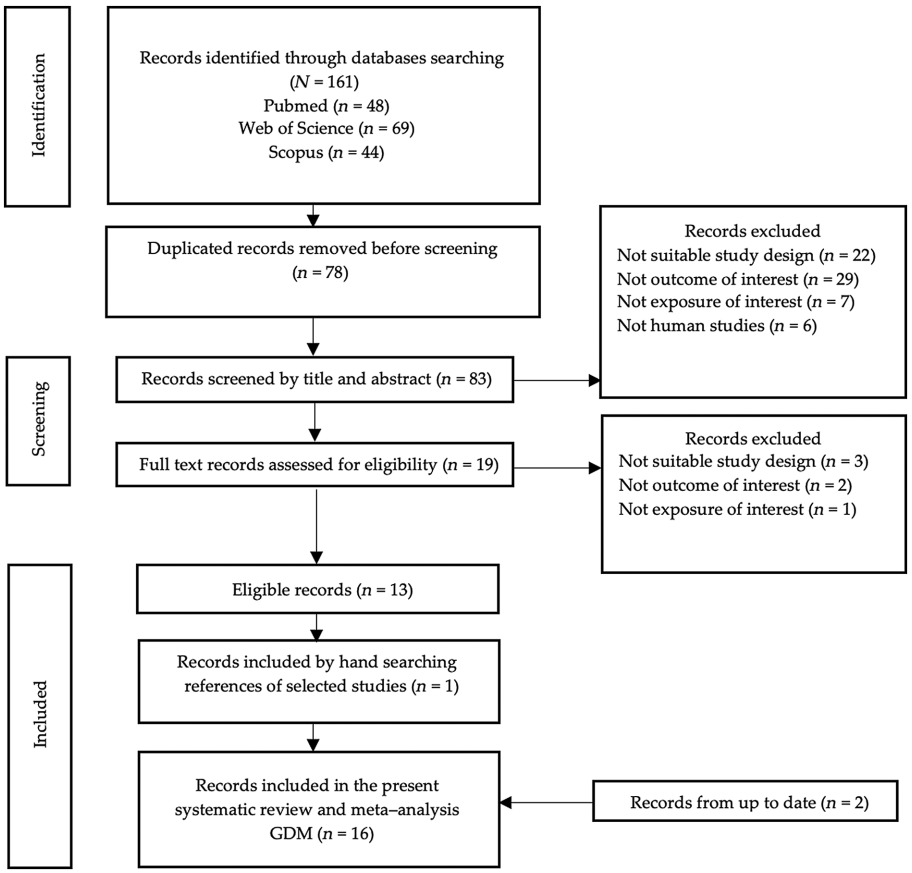

FIGURE 1 Flow chart diagram: study selection process.

case–control studies and 6.25% ($n = 1$) a case–control study. Eight studies were conducted in China, five in the USA, and one each of the following countries: Spain, Greece and Canada. Four studies were derived from the Xicheng hospital cohort[17,29–31] and three from the Life cohort.[28,32,33] Total sample size ranged from 154 to 2747 pregnant women;[34] sample size median (IQR) of the cases and controls was 77 (53–135) and 258 (154–1161), respectively. In most of the studies included in the systematic review, women were aged ≥18 years, except for two studies which included women aged ≥16 years.[35,36]

Serum was used as a biological sample in most studies 68.75% ($n = 11$),[17,23,24,28–33,36,37] plasma was used in 25% ($n = 4$)[16,34,35,38] and only one study also combined two types of biological sample (urine and plasma).[39] GDM was screened using the International Association of Diabetes and Pregnancy Study Groups criteria in eight studies[17,23,24,29–31,34,37] and the Carpenter–Coustan criteria in three studies.[16,36,38] The National Diabetes Data Group criteria were used only once.[35] One study screened GDM using two criteria: Canadian Diabetes Association and Society of Obstetricians and Gynaecologists of Canada.[39] GDM diagnosis was self-reported in the three studies from the Life cohort[18,28,33] (Table S3). In all studies, regression analysis was adjusted by at least maternal age and body mass index (BMI), except for Xicheng hospital cohort studies, where age was used for a paired matched design.[17,29–31] Exposure contrast was provided in different scales, and some studies supply two different measures.[31,35–37,40] Three studies log-transformed the exposure level to estimate odds ratios,[31,34,37] two studies presented $\log_{10}$-unit change OR,[35,36] one study provided ln-unit change OR[30] and one study provided risk ratio per each unit of increase of SD.[16] Exposure levels were categorised as quartiles in five studies[24,35,37–39] and terciles in three.[23,30,36]

3.2 | Study quality assessment

Risk of bias was moderate in most of studies 68.75% ($n = 11$), high in 25% ($n = 4$) and low in one study. Weaknesses were related to limited reporting of study attrition details in 81.25% ($n = 13$), exposure factor measurement in 31.25% ($n = 5$), outcome measurement in 25% ($n = 4$) and study confounding in 12% ($n = 3$) (Appendix S2). A weighted Kappa was calculated of the six domains and agreement was substantial between raters (weighted Kappa = 0.75).

3.3 | Data synthesis

3.3.1 | PFAS exposure and GDM risk

Findings regarding 10 PFAS were reported in eight studies.[16,23,24,28,30,34,35,37–39] Results are summarised in

Table S4. The approaches to measure the exposure to PFAS were very variable and were reported as per unit of increase of SD, per unit of increase according to a log scale or categorised from the original data. The Liu et al.[29] study estimated the association between dioxin-like compounds using total toxic equivalent (TEQ); this was estimated only in this study. Their results showed a TEQ of 0.025 versus 0.015 ng/ml in cases and controls, respectively ($P = 0.020$).[29] For most PFAS, such as PFBS, PFDoA and PFHpA, the association was isolated and reported in a specific study with moderate risk of bias (Table S4).[34,37] Our meta-analysis based on continuous data shows a small mean difference on the PFHpA exposure between GDM cases and controls (SMD = 0.26, 95% CI 0.17–0.35, $I^2 = 0.0\%$) and no considerable mean difference was observed for the rest of the PFAS (Figure 2).

3.3.2 | PCB exposure and GDM risk

Five studies[16,17,32,36,39] analysed the association between 16 PCBs and risk of GDM (Table S5). Only two studies with low and moderate risk of bias[16,17] reported a positive association between some PCBs, such as PCB18 and PCB101, and GDM (Table S5). Additionally, TEQs of PCB101 were 1.40 versus 0.99 pg/g in cases and controls respectively ($P = 0.005$).[29] Although Jaack et al.[32] stressed an inverse association between PCB (#138–153, 156, 167, 170, 180, 194) and GDM (Table S5), the risk of bias in their results was classified as high. The pooled standardised mean difference for three PCBs (PCB138, PCB153 and PCB180) was estimated. Our results show a small mean difference on the PCB180 exposure between GDM cases and controls (SMD = 0.37, 95% CI 0.19–0.56, $I^2 = 25.3\%$). High heterogeneity was observed for PCB 138 and PCB 153 (Figure 3).

3.3.3 | PBDE exposure and GDM risk

Results related to seven PBDE were summarised from three studies (Table S6).[16,31,33] The association between PBDE and GDM was positive or negative, depending on the type of PBDE. Two studies, with moderate quality, describe a higher risk of GDM for BDE47, 54 and 183.[29,31] In contrast, our meta-analysis show a small mean difference for BDE47, BDE99 and BDE100 exposure between GDM cases and control: respectively 0.23, 95% CI 0.00–0.45, $I^2 = 0\%$; 0.36, 95% CI 0.14–0.59, $I^2 = 0\%$; and 0.42 (95% CI 0.19–0.64, $I^2 = 0\%$) (Figure 3).

3.3.4 | OCP exposure and GDM risk

Findings related to three OCPs were reported in four studies (Table S7).[16,33,36,39] Meta-analysis results between HCB and GDM show a small mean difference on the standardised mean difference between cases and controls (0.22, 95% CI 0.01–0.42, $I^2 = 39.6\%$). No considerable difference was observed for p,p′DDE (Figure 4).

Publication bias results are reported in Appendix S3.

4 | DISCUSSION

4.1 | Main findings

In this systematic review and meta-analysis, the pooled effect of the standardised mean difference between GDM cases and controls of 20 POPs was estimated. Generally, the associations found were for isolated POPs subtypes and were based on a small number of studies. Small mean differences were observed for PFHpA, PCB 180, BDE 47, BDE99, BDE100 and HCB. No considerable difference was observed for the rest of POPs.

4.2 | Strengths and limitations

Our systematic review and meta-analysis have several strengths. First, to our knowledge this is the first systematic review with meta-analysis including exclusively prospective studies assessing the association of several POPs and risk of GDM (prospective studies based on the measurement of the level of POPs exposure prior to the diagnosis of GDM). Secondly, we used a strengths algorithm for research that included the different possible names of included POPs. Moreover, only exposures measured in biospecimens were included. Thirdly, to reduce possible bias due to the design of studies and estimate a possible causal effect association between the exposure and the outcome, only prospective cohort and case–control studies where the exposure was measured at the beginning of or before pregnancy were included. However, we cannot be sure that no cases of gestational diabetes appeared at the beginning of pregnancy, even if diagnosed later. And finally, this systematic review was conducted according to the protocol previously registered in PROSPERO and was reported according to PRISMA recommendations.

Our findings may be limited by the quality of included studies and therefore should be interpreted with caution. Furthermore, owing to the limited data combinable for each exposure, we were unable to conduct a dose–response analysis, assess the sources of heterogeneity by subgroup analysis, or analyse the publication of bias. However, the risk of bias of each study was assessed by two authors independently using an adapted and strong instrument (QUIPS). Another limitation may be related to residual confounders. Information related to diet and physical activity, factors closely associated with GDM, and the possible effect of not measured contaminants, such as metals and non-organic pollutants, was missed in most studies.

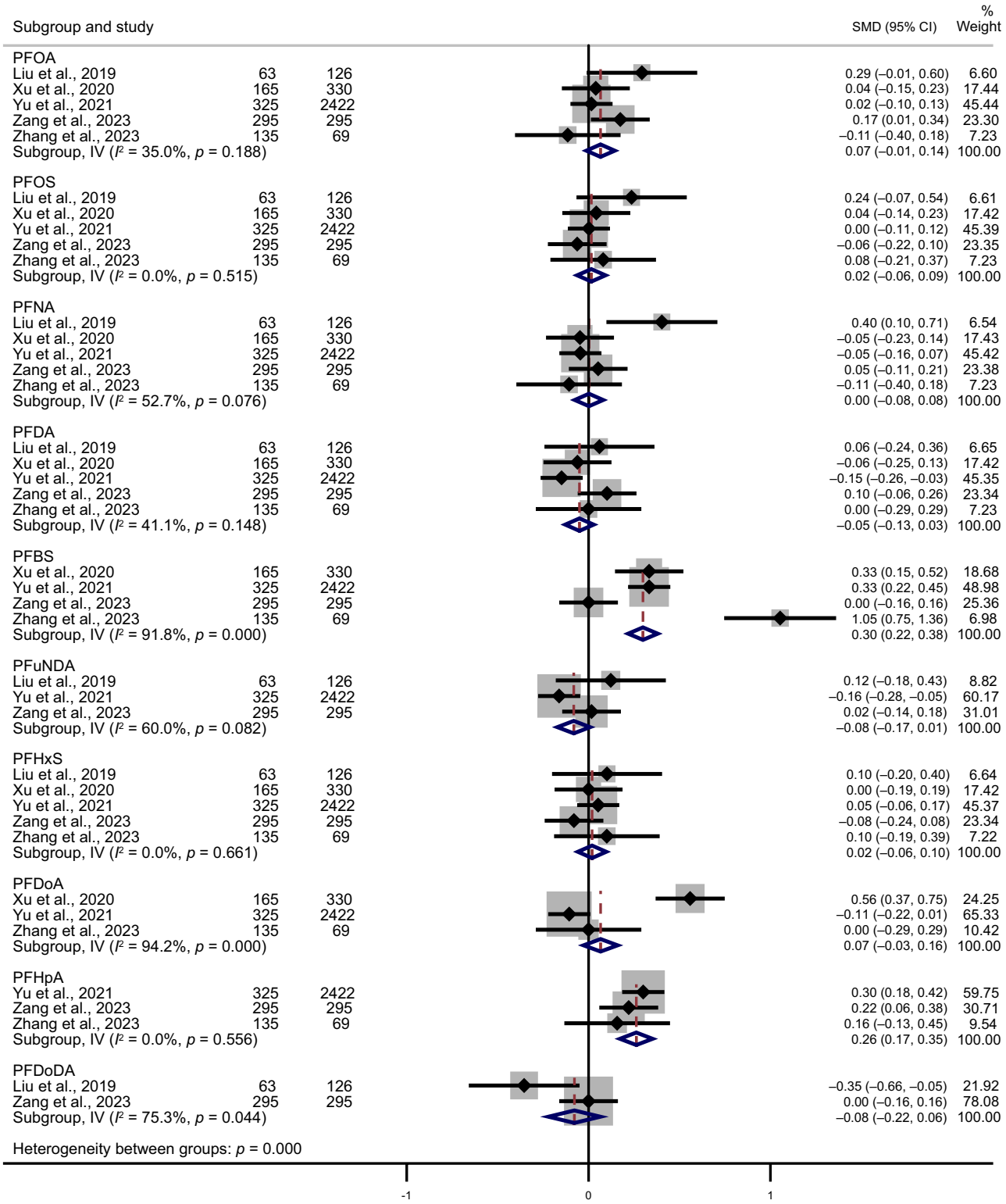

FIGURE 2 Pooled estimate of SMD with 95% CI of PFAS and gestational diabetes mellitus cases versus controls.

4.3 | Interpretation

POPs have been defined as endocrine disruptors; they affect glucose metabolism by reducing insulin secretion and disrupt glucose homeostasis,[41,42] and have been associated in several studies with a high risk of diabetes mellitus type 2 and other metabolic diseases. On this basis, we hypothesised the existence of an association between POPs and GDM.[10]

The systematic review by Wang et al.[43] suggested a significant association between PFOA and GDM, while no

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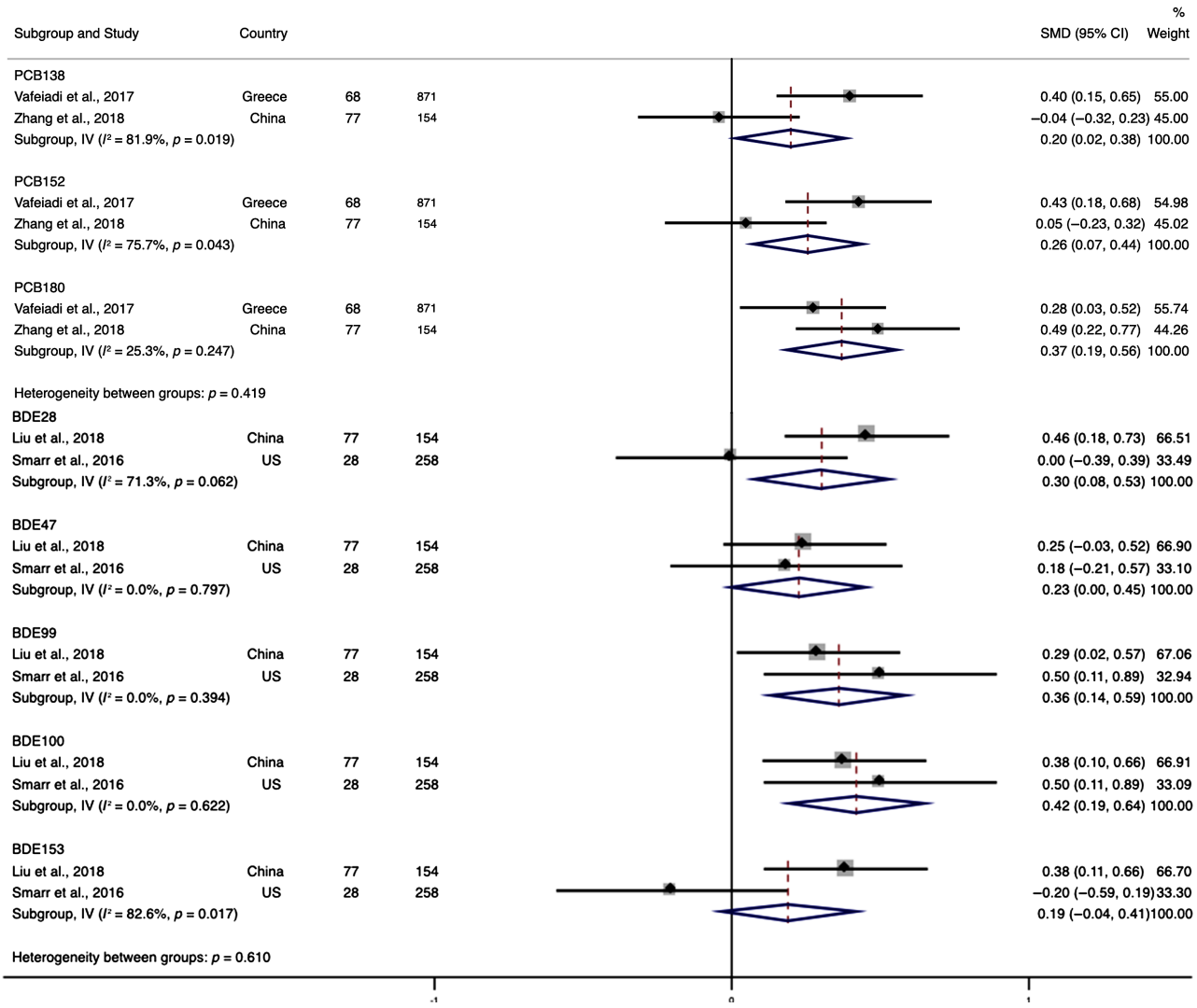

FIGURE 3 Pooled estimate of SMD with 95% CI of PCBs and PBDE with gestational diabetes mellitus cases versus controls.

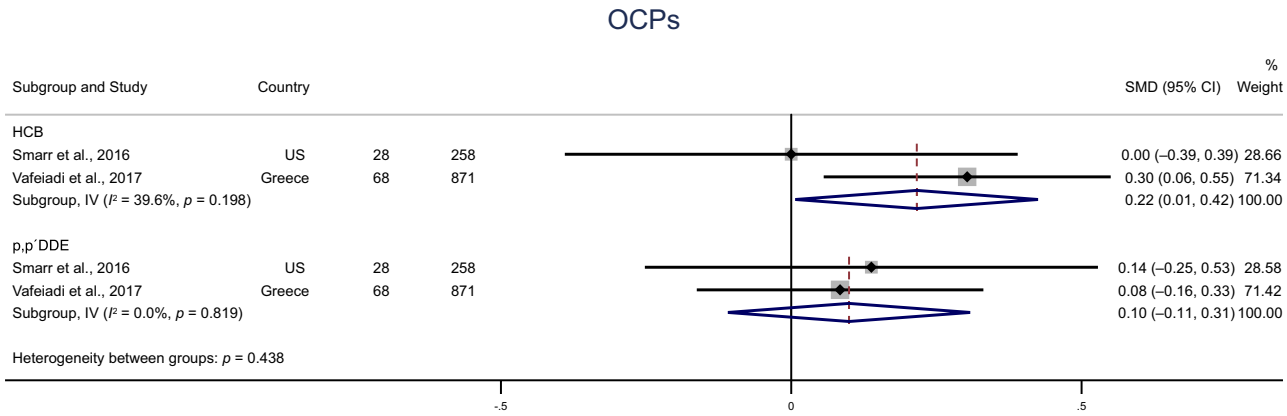

FIGURE 4 Pooled estimate of SMD with 95% CI of OCPs and gestational diabetes mellitus cases versus controls.

association was observed for the rest of PFAS. A recent systematic review found a significant association with GDM estimated for the sum of subgroups POPs; ∑PCB congeners, ∑PBDE compounds and ∑PFAS chemicals, and when most of these exposures were analysed separately. Meanwhile, high heterogeneity was observed in all meta-analyses, including the sum for each POP categories, and in most meta-analyses analysing POPs separately.[19] Discrepancies between

systematic reviews can be explained by the differences in the way the individual studies were combined. These systematic reviews combined different scales of measurement of association in the same meta-analysis. Another factor influencing the results could be the selection criteria established in each systematic review.

Although several studies consider that the sum of POPs may increase the risk of GDM, interpreting these results is challenging, as the correlation between the different compounds is unclear, and different congeners can have opposite effects.[17,30] For example, when the association between a PFAS exposure and GDM was controlled by other PFAS, it appears that the PFOS, PFNA and PFHpA are the main contributors to this association.[34] This is why the results of the overall effect for ∑PFAS, ∑PCBs, ∑PBDE and ∑OCPs are not provided in our meta-analysis.

When exposure was measured after the occurrence of the outcome, the association was less clear. A cohort analysing placental samples of 86 participants showed a negative association between PCBs and PBDE and GDM.[44] A case–control study of 86 participants showed an inverse association between PCBs and PBDE with GDM.[44] Another case–control study of 140 participants, showed a positive association between Ln PCB 187, 118 and Ln PBDE99 with GDM, and an inverse association with Ln PCB28.[45] Results from Valvi et al., 2017 suggest a significative association between DDE and GDM, while the association with PCBs congeners and PFAS was not significant.[46] Several factors closely associated with GDM, such as gestational weight gain, diabetes mellitus and GDM history, may be responsible for these differences.

Our results suggest a possible association between some types of POPs and GDM. Data with better quality and homogeneity are required to carry out stronger reviews and more consistent and concise conclusions. In this systematic review, we join other authors in stressing the need for a standardised approach to studying and analysing POPs and the creation of a consortium with individual data.[15,47]

5 | CONCLUSION

This systematic review and meta-analysis of prospective studies provides a synthesis of the possible effect of POPs exposure in increasing the risk of GDM. There are insufficient data to analyse each exposure with more consistency and conduct a dose-response analysis. To confirm our results and draw stronger conclusions, further research is needed to ensure that the effects measured are due to a specific pollutant or the entire sub-category. In particular, a standardised method of studying POPs is required to make combining results more consistent.

AUTHOR CONTRIBUTIONS

This work was conceptualised and supervised by J.J.J.-M., J.Z., R.O.-R. and M.K. The methodology was developed by J.J.J.-M., J.Z., M.K., M.A.C.-H., I.Y.-M. and R.O.-R. All analyses and data curation were performed by M.K. and M.A.C.-H., and supervised by J.Z., J.J.J.-M., R.O.-R. and I.Y.-M. The interpretation of data was realised by all authors. The original draft was written by M.K. and J.J.J.-M. Critical review and editing of the article was provided by J.J.J.-M., M.K., J.Z., I.Y.-M., S.T., K.S.K., M.A.C.-H. and R.O.-R. All other authors provided final approval of this manuscript. K.S.K. is a distinguished investigator at the University of Granada funded by the Beatriz Galindo (senior modality) programme of the Spanish Ministry of Education.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

All necessary data to replicate the analysis can be found in this article.

ETHICS APPROVAL

This study involved only literature review of previously published studies and the contained data. It involved no primary research on human or animal subjects, or medical records. As such, this work was considered exempt from ethical review.

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REFERENCES

1. Stockholm Convention. What are POPs? 2001. [cited 2023 Sep 10]. Available from: http://www.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx
2. Word Health Organization. Food safety: Persistent organic pollutants (POPs). 2020. [Cited 2023 sep 10]. Available from: https://www.who.int/news-room/questions-and-answers/item/food-safety-persistent-organic-pollutants-(pops)
3. Malisch R, Kotz A. Dioxins and PCBs in feed and food—review from European perspective. Sci Total Environ. 2014;491–492:2–10.
4. Hu J, Zheng M, Liu W, Li C, Nie Z, Liu G, et al. Occupational exposure to polychlorinated dibenzo-p-dioxins and dibenzofurans, dioxin-like polychlorinated biphenyls, and polychlorinated naphthalenes in workplaces of secondary nonferrous metallurgical facilities in China. Environ Sci Technol. 2013;47(14):7773–9.
5. Thompson LA, Darwish WS. Environmental chemical contaminants in food: review of a global problem. J Toxicol. 2019;2019:1–14.
6. Lim J, Park SH, Jee SH, Park H. Body concentrations of persistent organic pollutants and prostate cancer: a meta-analysis. Environ Sci Pollut Res. 2015;22(15):11275–84.
7. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly- and

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perfluoroalkyl substances (PFASs) and present understanding of health effects. J Expo Sci Environ Epidemiol. 2019;29(2):131–47.
8. Davidsen N, Lauvås AJ, Myhre O, Ropstad E, Carpi D, de Gyves EM, et al. Exposure to human relevant mixtures of halogenated persistent organic pollutants (POPs) alters neurodevelopmental processes in human neural stem cells undergoing differentiation. Reprod Toxicol. 2021;100:17–34.
9. Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L. Association of exposure to persistent organic pollutants with mortality risk: an analysis of data from the Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS) Study. JAMA Netw Open. 2019;2(4):e193070.
10. Barrios-Rodríguez R, Pérez-Carrascosa FM, Gómez-Peña C, Mustieles V, Salcedo-Bellido I, Requena P, et al. Associations of accumulated selected persistent organic pollutants in adipose tissue with insulin sensitivity and risk of incident type-2 diabetes. Environ Int. 2021;155:106607.
11. Tornevi A, Sommar J, Rantakokko P, Åkesson A, Donat-Vargas C, Kiviranta H, et al. Chlorinated persistent organic pollutants and type 2 diabetes – a population-based study with pre- and post-diagnostic plasma samples. Environ Res. 2019;174:35–45.
12. Gao X, Ni W, Zhu S, Wu Y, Cui Y, Ma J, et al. Per- and polyfluoroalkyl substances exposure during pregnancy and adverse pregnancy and birth outcomes: a systematic review and meta-analysis. Environ Res. 2021;201:111632.
13. Kappil MA, Li Q, Li A, Dassanayake PS, Xia Y, Nanes JA, et al. In utero exposures to environmental organic pollutants disrupt epigenetic marks linked to fetoplacental development. Environ Epigenet. 2016;2(1):dvv013.
14. Dwivedi N, Mahdi AA, Deo S, Ahmad MK, Kumar D. Assessment of genotoxicity and oxidative stress in pregnant women contaminated to organochlorine pesticides and its correlation with pregnancy outcome. Environ Res. 2022;204(Pt B):112010.
15. Hernández-Mariano JÁ, Baltazar-Reyes MC, Salazar-Martínez E, Cupul-Uicab LA. Exposure to the pesticide DDT and risk of diabetes and hypertension: systematic review and meta-analysis of prospective studies. Int J Hyg Environ Health. 2022;239:1438–4639.
16. Rahman ML, Zhang C, Smarr MM, Lee S, Honda M, Kannan K, et al. Persistent organic pollutants and gestational diabetes: a multicenter prospective cohort study of healthy US women. Environ Int. 2019;124:249–58.
17. Zhang L, Liu X, Meng G, Chi M, Li J, Yin S, et al. Non-dioxin-like polychlorinated biphenyls in early pregnancy and risk of gestational diabetes mellitus. Environ Int. 2018;115:127–32.
18. Jaacks LM, Boyd Barr D, Sundaram R, Grewal J, Zhang C, Buck Louis GM. Pre-pregnancy maternal exposure to persistent organic pollutants and gestational weight gain: a prospective cohort study. Int J Environ Res Public Health. 2016;13:905.
19. Yan D, Jiao Y, Yan H, Liu T, Yan H, Yuan J. Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: a systematic review and meta-analysis. Environ Health. 2022;21(1):1–24.
20. Glynn A, Larsdotter M, Aune M, Darnerud PO, Bjerselius R, Bergman Å. Changes in serum concentrations of polychlorinated biphenyls (PCBs), hydroxylated PCB metabolites and pentachlorophenol during pregnancy. Chemosphere. 2011;83(2):144–51.
21. Adetona O, Horton K, Sjodin A, Jones R, Hall DB, Aguillar-Villalobos M, et al. Concentrations of select persistent organic pollutants across pregnancy trimesters in maternal and in cord serum in Trujillo, Peru. Chemosphere. 2013;91(10):1426–33.
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
23. Zhang Y, Chen R, Gao Y, Qu J, Wang Z, Zhao M, et al. Human serum poly- and perfluoroalkyl substance concentrations and their associations with gestational diabetes mellitus. Environ Pollut. 2023;317:120833.
24. Zang L, Liu X, Xie X, Zhou X, Pan Y, Dai J. Exposure to per- and polyfluoroalkyl substances in early pregnancy, risk of gestational diabetes mellitus, potential pathways, and influencing factors in pregnant women: a nested case-control study. Environ Pollut. 2023;326:121504.
25. Group CCPM. The Cochrane collaboration prognosis methods group. Review Tools. 2018. [cited 2022 Jul 17]. Available from: https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/uploads/QUIPS%20tool.pdf
26. Graham P, Jackson R. The analysis of ordinal agreement data: beyond weighted kappa. J Clin Epidemiol. 1993;46(9):1055–62.
27. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Lawrence Erlbaum Associates, Publishers – References – Scientific Research Publishing; 1988.
28. Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Buck Louis GM. A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. Fertil Steril. 2015;103(1):184–9.
29. Liu X, Zhang L, Chen L, Li J, Wang J, Zhao Y, et al. Identification and prioritization of the potent components for combined exposure of multiple persistent organic pollutants associated with gestational diabetes mellitus. J Hazard Mater. 2021;409:124905.
30. Liu X, Zhang L, Chen L, Li J, Wang Y, Wang J, et al. Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women. Environ Int. 2019;127:85–93.
31. Liu X, Zhang L, Li J, Meng G, Chi M, Li T, et al. A nested case-control study of the association between exposure to polybrominated diphenyl ethers and the risk of gestational diabetes mellitus. Environ Int. 2018;119(7):232–8.
32. Jaacks LM, Barr DB, Sundaram R, Maisog JM, Zhang C, Buck Louis GM. Pre-pregnancy maternal exposure to polybrominated and polychlorinated biphenyls and gestational diabetes: a prospective cohort study. Environ Health. 2016;15(1):11.
33. Smarr MM, Grantz KL, Zhang C, Sundaram R, Maisog JM, Barr DB, et al. Persistent organic pollutants and pregnancy complications. Sci Total Environ. 2016;551–552:285–91.
34. Yu G, Jin M, Huang Y, Aimuzi R, Zheng T, Nian M, et al. Environmental exposure to perfluoroalkyl substances in early pregnancy, maternal glucose homeostasis and the risk of gestational diabetes: a prospective cohort study. Environ Int. 2021;156:106621.
35. Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, Manzano-Salgado CB, Ballester F, Ibarluzea J, et al. Exposure to perfluoroalkyl substances and metabolic outcomes in pregnant women: evidence from the Spanish INMA birth cohorts. Environ Health Perspect. 2017;125(11):1–11.
36. Vafeiadi M, Roumeliotaki T, Chalkiadaki G, Rantakokko P, Kiviranta H, Fthenou E, et al. Persistent organic pollutants in early pregnancy and risk of gestational diabetes mellitus. Environ Int. 2017;98:89–95.
37. Xu H, Zhou Q, Zhang J, Chen X, Zhao H, Lu H, et al. Exposure to elevated per- and polyfluoroalkyl substances in early pregnancy is related to increased risk of gestational diabetes mellitus: a nested case-control study in Shanghai, China. Environ Int. 2020;143:105952.
38. Preston EV, Rifas-Shiman SL, Hivert MF, Zota AR, Sagiv SK, Calafat AM, et al. Associations of per- and polyfluoroalkyl substances (PFAS) with glucose tolerance during pregnancy in project viva. J Clin Endocrinol Metabol. 2020;105(8):E2864–76.
39. Shapiro GD, Dodds L, Arbuckle TE, Ashley-Martin J, Ettinger AS, Fisher M, et al. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: the MIREC study. Environ Res. 2016;147:71–81.
40. Liu X, Chen D, Wang B, Xu F, Pang Y, Zhang L, et al. Does low maternal exposure to per-and polyfluoroalkyl substances elevate the risk of spontaneous preterm birth? A nested case–control study in China. Environ Sci Technol. 2020;54:8259–68.
41. Zhang Z, Sun ZZ, Xiao X, Zhou S, Wang XC, Gu J, et al. Mechanism of BDE209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. Arch Toxicol. 2013;87(8):1557–67.

42. Birru RL, Liang HW, Farooq F, Bedi M, Feghali M, Haggerty CL, et al. A pathway level analysis of PFAS exposure and risk of gestational diabetes mellitus. Environ Health. 2021;20(1):1–16.
43. Wang J, Zhang J, Fan Y, Li Z, Tao C, Yan W, et al. Association between per- and polyfluoroalkyl substances and risk of gestational diabetes mellitus. Int J Hyg Environ Health. 2022;240:113904.
44. Alvarez-Silvares E, Fernández-Cruz T, Domínguez-Vigo P, Rubio-Cid P, Seoane-Pillado T, Martínez-Carballo E. Association between placenta concentrations polybrominated and polychlorinated biphenyls and gestational diabetes mellitus: a case-control study in northwestern Spain. Environ Sci Pollut Res Int. 2021;28:10292–301.
45. Eslami B, Naddafi K, Rastkari N, Rashidi BH, Djazayeri A, Malekafzali H. Association between serum concentrations of persistent organic pollutants and gestational diabetes mellitus in primiparous women. Environ Res. 2016;151:706–12.
46. Valvi D, Oulhote Y, Weihe P, Dalgård C, Bjerve KS, Steuerwald U, et al. Gestational diabetes and offspring birth size at elevated environmental pollutant exposures. Environ Int. 2017;107:205–15.
47. Peinado FM, Artacho-Cordón F, Barrios-Rodríguez R, Arrebola JP. Influence of polychlorinated biphenyls and organochlorine pesticides on the inflammatory milieu. A systematic review of in vitro, in vivo and epidemiological studies. Environ Res. 2020;186:109561.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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CLINICAL ARTICLE

Obstetrics

Replacement of watching television with physical activity and the change in gestational diabetes mellitus risk: A case–control study

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Abstract

Objective: To evaluate the effect of replacing 1 h/week of watching television with 1 h/week of light to moderate (LMPA) or vigorous physical activity (VPA) before and during pregnancy on the risk of gestational diabetes mellitus (GDM).

Methods: A case–control study was conducted in pregnant women. Physical activity and television watching before and during pregnancy were assessed using the Paffenbarger Physical Activity Questionnaire. Each type of activity was classified according to intensity (metabolic equivalent of task; MET): less than 6 METs is LMPA, 6 METs or more is VPA. The duration of physical activity and watching television was calculated, and logistic regression models were used to estimate adjusted odds ratios (aOR) and 95% confidence intervals for their association with GDM risk. The isotemporal substitution model was used to calculate the effect of replacing 1 h/week of watching television with the same duration of physical activity.

Results: The GDM cases ($n = 290$) spent less time performing VPA than controls without GDM ($n = 1175$) and more time watching television during pregnancy ($P < 0.05$). During pregnancy, the risk of GDM increased for each hour of watching television (aOR = 1.02; 95% confidence interval 1.00–1.03). Women who spent more time watching television during pregnancy were likely to develop GDM ($aOR_{>14\,h/week\ vs.\ 0–6\,h/week} = 2.03$; 95% confidence interval 1.35–3.08). Replacing 1 h/week of watching television with 1 h/week of VPA during pregnancy could decrease the chance of developing GDM (aOR = 0.66; 95% confidence interval 0.43–1.00).

Conclusions: A simple change of 1 h/week of watching television for 1 h/week of VPA in pregnant women may reduce the risk of GDM considerably.

Alfredo Gea and José J. Jiménez-Moleón contributed equally.

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KEYWORDS
case–control studies, gestational diabetes mellitus, Isotemporal substitution model, physical activity, pregnancy, watching television

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is the most frequent pregnancy complication, representing 75%–90% of cases of hyperglycemia during pregnancy.[1] Furthermore, GDM is associated with a high risk of cesarean, preterm delivery, and macrosomia.[2] In the long term, women with GDM antecedents show an increased incidence of type 2 diabetes mellitus, cardiovascular diseases, and kidney diseases.[3,4] Epidemiological studies affirm the importance of regular physical activity and little sedentary behavior to prevent pregnancy complications such as GDM, gestational weight gain, preterm birth, and some neonatal outcomes, like macrosomia and birth trauma.[5–9] In particular, high sedentary behavior can increase the risk of maternal and fetal health outcomes.[7,10] In this sense, WHO recommends that pregnant women replace sedentary behaviors with any intensity of physical activity.[11]

Although it is known that physical activity prevents GDM,[12] results related to the most effective type of physical activity and intervention strategies for preventing GDM remain inconclusive.[13,14] This may be because previous intervention studies did not reach the minimum level of physical activity necessary to reduce GDM.[15] In addition, we must consider that a day is limited to 24 h and spending time on one activity may substitute the realization of another.[16] In this way, the behavior replaced shows an influence over the magnitude of the effect on other pathologies such as depression and type 2 diabetes.[17,18] Although a traditional model does not consider possible differences produced by removing or reallocating other behaviors, the isotemporal substitution model allows us to evaluate the effect of behavior replacement.[16] To our knowledge, this is the first study to assess the effect of replacing time spent watching television with physical activity on the risk of GDM.

Considering all of the above and that pregnant women tend to reduce their physical activity practice and spend more time in sedentary behaviors during pregnancy,[10,19–22] we aimed to estimate the effect of replacing 1 h/week of watching television with 1 h/week of light to moderate (LMPA) or vigorous physical activity (VPA) before and during pregnancy on the risk of GDM.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

This case–control study consisted of pregnant women with GDM (cases) and pregnant women without GDM (controls). It was conducted in the catchment area of Virgen de las Nieves University Hospital of Granada, Spain (Project of Excellence of the Junta de Andalucía CTS 05/942). This project was approved by the Ethics Committee of the University of Granada and Virgen de las Nieves Hospital.

All women included met the following inclusion criteria: (1) age equal to or older than 18 years; (2) Spanish nationality; (3) singleton pregnancy; (4) pregnancy without complications, and (5) included in the Andalusian Program of Infant–Maternal Health, with universal and public coverage. In addition, cases had to be diagnosed with GDM, as described below. One in five women who attended the programmed visit at 20–22 weeks of gestation were systematically informed about the study; informed consent was obtained for participation. The study methodology has been described in detail previously.[23]

2.2 | Outcome assessment

Cases of GDM were identified weekly among the pregnant women interviewed by consulting the 50 g glucose and oral glucose tolerance test results (24–28 weeks of gestation). In this way, GDM was diagnosed according to the National Diabetes Data Group criteria. Cut-off points were determined for the time points, fasting, 1, 2, and 3 h, as 105, 190, 165, and 145 mg/dL, respectively. Participants were attributed to the case group if at least two measurements equaled or exceeded the cut-off point. The control group had a negative 50 g glucose challenge test (<140 mg/dL) or a positive 50 g glucose test (≥140 mg/dL) and a negative diagnostic oral glucose tolerance test.[27]

In total, 1222 controls and 299 cases were initially invited to participate. The final sample for this analysis comprised 1175 healthy pregnant women and 290 pregnant women diagnosed with GDM (Figure 1).

2.3 | Physical activity and television-watching assessment

Information on physical activity and television watching were collected for 1 year before and during pregnancy using the Paffenbarger Physical Activity Questionnaire, validated for Spanish pregnant women.[24,25] Physical activity was differentiated as: leisure-time physical activity, including walking, cycling, swimming, aerobic activity, dancing, mountain excursions, gym, and gardening. Frequency (days per week) and duration (minutes per session) were collected for each activity. Leisure-time physical activities were categorized as: (1) LMPA, including walking, gym, swimming, and gardening

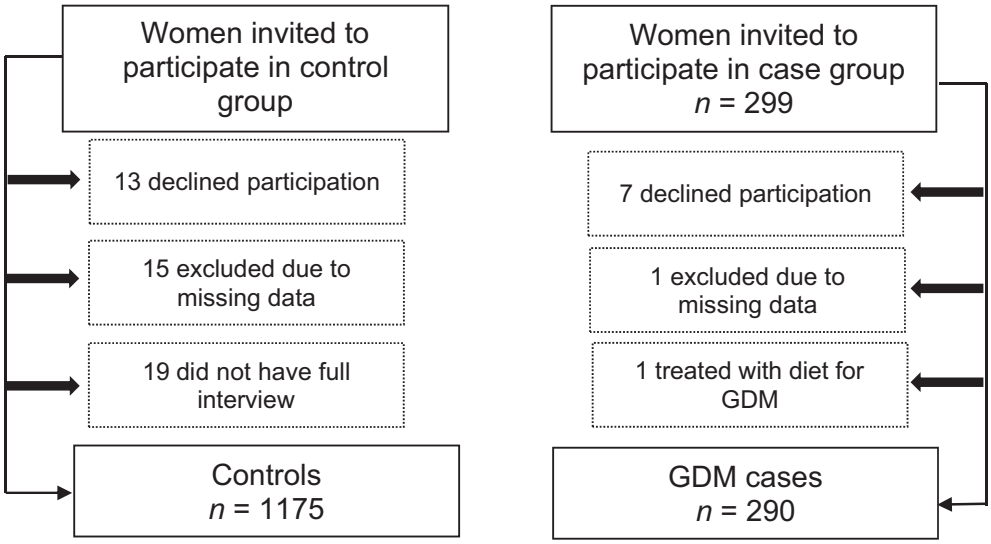

FIGURE 1 Participant flowchart.

(metabolic equivalent of task [MET] <6); and (2) VPA, including cycling, aerobics activities, dancing, and mountain hiking (METs ≥ 6) according to Be et al.[26]

Other physical activities and information related to occupational, household, and displacement activities were collected.

In this way, the time (h/week) of LMPA, VPA, and watching television before and during pregnancy was calculated. These variables were categorized based on the distribution of controls (LMPA 0; >0–≤1; >1–≤3.75; >3.75 h/week; VPA 0; >0–≤2.5; >2.5 h/week; watching television ≥0–≤6; >6–≤ 2.25; >12.25–≤14; >14 h/week).

In addition, the joint effect of LMPA–watching television and VPA–watching television before and during the pregnancy was evaluated from the median of the control group. Thus, four categories were derived by combining low or high LMPA with low or high watching television. Similarly, the combined effect of VPA–watching television was analyzed.

2.4 | Covariate assessment

Sociodemographic characteristics, lifestyle habits, anthropometrics, antecedents, and obstetrics data were requested. In addition, information on diet was collected using an adapted and validated food frequency questionnaire.[28] Using this, the adherence to a Mediterranean diet was classified using the Mediterranean Diet score proposed by Trichopoulou et al.[29] as: low (0–3 points), medium (4–5 points), and high adherence (≥6 points).

2.5 | Statistical analysis

Participant characteristics were reported as mean and standard deviation for quantitative variables, and percentages for categorical variables. The comparison between GDM cases and controls was performed using the χ^2 or Student *t*-test for categorical and continuous variables, respectively.

Logistic regression models were used to estimate the odds ratio and 95% confidence interval for the association between leisure-time physical activity (LMPA and VPA), watching television, and the joint effect of LMPA–watching television and VPA–watching television before and during pregnancy on the GDM risk. The following confounder factors were used for adjustment: maternal age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), educational level, smoking, GDM antecedent, Mediterranean diet adherence, and energy intake. Additionally, the logistic regression models used to evaluate the association between GDM and physical activity (LMPA and VPA) were adjusted by watching television and watching television models by LMPA and VPA.

The effect produced by replacing 1 h/week watching television with 1 h/week of LMPA or VPA on the risk of GDM was analyzed through isotemporal substitution models. Odds ratios and 95% confidence interval were estimated as the difference between the beta coefficient of the two activities studied and then exponentiated. The odds ratio reflects the reduction in GDM risk that is observed when the mean time spent in LMPA or VPA increased by 1 h/week because the mean time spent watching television decreased by 1 h/week.

We also conducted sensitivity analyses by rerunning the isotemporal substitution model, excluding women with family diabetes mellitus antecedents, those with a BMI of 30 or more, those older than 35 years, and with two or more pregnancies (see Table S1).

The statistical analysis was performed using STATA 15.0 (StataCorp LLC, College Station, TX, USA). All statistical tests were two-sided, and statistical significance was set at *P* less than 0.05.

3 | RESULTS

3.1 | Study population

Cases with GDM were older, most often had obesity, and gained more weight during pregnancy until recruitment than the controls. In addition, the cases with GDM more often had a history of abortion, were more likely to be multiparous, and more frequently had GDM and diabetes mellitus family antecedents ($P < 0.001$) (Table 1). Lifestyle habits, including smoking, alcohol consumption, energy intake, Mediterranean diet adherence, leisure-time physical activity, and watching television before and during pregnancy of cases and controls, are shown in Table 2. GDM cases consumed more energy before pregnancy than controls ($P = 0.040$). Regarding leisure-time physical activity and watching television, differences between GDM cases and controls were observed during pregnancy; GDM cases spent less time performing VPA than controls (0.06 vs 0.15 h/week) and more time watching television (16.01 vs 13.97 h/week).

3.2 | Association between leisure-time physical activity and watching television before and during pregnancy on the risk of GDM

Table 3 shows the association between leisure-time physical activity, watching television, the joint effect of LMPA–watching television and VPA–watching television on the GDM risk. During pregnancy, for each hour of VPA performed, the probability of GDM

TABLE 1 Sociodemographic, anthropometric, antecedent, and obstetric characteristics of gestational diabetes mellitus (GDM) cases and controls.

	Controls ($n = 1175$)	GDM cases ($n = 290$)	*P*-value
Maternal age (years), mean (SD)	29.80 (5.14)	33.49 (5.51)	<0.001
<25	178 (15.1)	18 (6.2)	<0.001
25–29	345 (29.4)	49 (16.9)	
30–34	436 (37.1)	91 (31.4)	
35–39	199 (16.9)	95 (32.8)	
≥40	17 (1.5)	37 (12.7)	
Educational level			0.157
Primary	478 (40.7)	136 (46.9)	
Secondary	339 (28.8)	74 (25.5)	
University	358 (30.5)	80 (27.6)	
Body mass index[a]			<0.001
Normal weight	786 (67.0)	117 (40.3)	
Overweight	267 (22.8)	80 (27.6)	
Obesity	120 (10.2)	93 (32.1)	
Missing	2	-	
Gestational weight gain (kg), mean (SD)	3.71 (3.51)	5.41 (5.13)	<0.001
Previous abortion			<0.001
0	933 (79.4)	202 (69.3)	
1	199 (16.9)	68 (23.4)	
≥2	43 (3.7)	21 (7.3)	
Pregnancies			<0.001
0	555 (47.2)	106 (36.5)	
1	365 (31.1)	89 (30.7)	
2	168 (14.3)	56 (19.3)	
3	61 (5.2)	22 (7.6)	
≥4	26 (2.2)	17 (5.9)	
GDM antecedents			<0.001
No	1152 (98.0)	233 (80.3)	
Yes	23 (2.0)	57 (19.7)	
Family diabetes mellitus antecedents			<0.001
No	875 (74.5)	156 (53.8)	
Yes	300 (25.5)	134 (46.2)	

Note: Data are *n* (%) except if mean (SD) is indicated.

Abbreviation: SD, standard deviation.

[a]Calculated as weight in kilograms divided by the square of height in meters.

TABLE 2 Lifestyle behaviors before and during pregnancy of cases and controls.

	Before pregnancy			During pregnancy		
	Controls ($n=1175$)	GDM cases ($n=290$)	*P*-value	Controls ($n=1175$)	GDM cases ($n=290$)	*P*-value
Smoking						
Never	504 (42.9)	110 (37.9)	0.188	504 (42.9)	110 (37.9)	0.207
Ex-smoker	242 (20.6)	72 (24.8)		242 (20.6)	71 (24.8)	
Quit smoking	–	–		209 (17.8)	59 (20.3)	
Smoker	429 (36.5)	108 (37.2)		220 (18.7)	49 (16.9)	
Alcohol consumption (g), mean (SD)	2.41 (4.24)	2.61 (4.14)	0.460	0.10 (0.67)	0.06 (0.32)	0.306
Energy intake (kcal/day), mean (SD)	2593.69 (808.75)	2706.64 (959.79)	0.040	2563.27 (779.98)	2494.84 (834.20)	0.187
Mediterranean diet adherence						
Low	725 (61.7)	171 (59.0)		446 (38.0)	112 (38.6)	0.663
Medium	377 (32.1)	102 (35.2)	0.604	512 (43.6)	131 (45.2)	
High	73 (6.2)	17 (5.87)		217 (18.5)	47 (16.2)	
LMPA (h/week), mean (SD)	2.60 (3.75)	2.38 (3.59)	0.372	2.73 (3.39)	2.73 (3.76)	0.984
VPA (h/week), mean (SD)	0.76 (2.03)	0.52 (1.41)	0.058	0.15 (0.67)	0.06 (0.27)	0.025
Watching television (h/week), mean (SD)	12.95 (9.13)	13.95 (9.69)	0.100	13.97 (9.76)	16.01 (10.93)	0.002

Note: Data are *n* (%) except if mean (SD) is indicated.

Abbreviations: GDM, gestational diabetes mellitus; LMPA, light to moderate physical activity; SD, standard deviation; VPA, vigorous physical activity.

reduced (adjusted odds ratio [aOR] = 0.72; 95% confidence interval 0.48–1.07), whereas for each hour watching television, the risk increased (aOR = 1.02; 95% confidence interval 1.00–1.03). In this way, those women who spent more time watching television during pregnancy were approximately twice as likely to develop GDM ($aOR_{>14\,h/week\ vs\ 0-6\,h/week} = 2.03$; 95% confidence interval 1.35–3.08). When combining LMPA–watching television, those women with low LMPA and high watching television during pregnancy presented the highest risk of GDM (aOR = 1.76; 95% confidence interval 1.14–2.71). A similar behavior was observed for the joint effect of VPA–watching television (aOR = 1.62; 95% confidence interval 0.86–3.05) for women with low VPA and high watching television.

3.3 | Substitution of watching television with LMPA and VPA before and during pregnancy

Replacing 1 h/week of watching television with 1 h/week of VPA during pregnancy may reduce the likelihood of developing GDM (aOR = 0.66; 95% confidence interval 0.43–1.00). However, no association was observed when replacing 1 h of watching television with 1 h of LMPA (Table 4). Sensitivity analysis performed excluding women at high risk of developing GDM did not show substantial changes with previous results (see Table S1).

4 | DISCUSSION

To our knowledge, this is the first study to assess the effect of replacing 1 h/week of watching television with 1 h/week of LMPA or VPA on the risk of GDM. Briefly, women with GDM performed less physical activity and spent more time watching television than controls during pregnancy. Performing VPA during pregnancy seems to reduce the probability of GDM. In addition, replacing 1 h/week of watching television with 1 h/week of VPA during pregnancy could reduce GDM risk by 34%.

The association between physical activity and GDM has been mainly studied using a traditional method based only on identifying associated factors (e.g. multivariant logistic regression). This approach does not consider possible differences due to the removal or reallocation of other behaviors, which can be analyzed using the isotemporal substitution model.

Our results suggest that performing VPA during pregnancy could reduce the probability of GDM, whereas watching television increases the likelihood of GDM. However, only 19.4% and 27.5% of participants met leisure-time physical activity recommendations before and during pregnancy, respectively, as described previously.[22] In line with our results, Oken et al.[30] did not report any association for LMPA, whereas VPA seemed to protect against GDM, although no statistically significant association was observed due to possible precision issues (only 91 cases of GDM and a cohort design). Likewise, a cohort study of 2388 American pregnant women showed that VPA improved maternal glucose metabolism.[31] In addition, the results of the Nurses Health Study II and Wagnild et al.[32] suggested that watching television could increase GDM, findings similar to ours.[33] In contrast, no association was observed between watching television and GDM in two cohorts conducted in Eastern and Singapore populations.[30,34] These last two cohorts were characterized by moderate to small sample sizes for cohort studies. These cohorts were realized with populations at high risk of GDM (e.g. in Padmapriya et al.,[34] the prevalence of GDM was 18.6%). In this type of population, it may be difficult to correctly

TABLE 3 Association between physical activity and watching television before and during pregnancy on the risk of gestational diabetes mellitus (GDM).

	Before pregnancy		During pregnancy	
	Controls/GDM cases	aOR (95% CI)[a]	Controls/GDM cases	aOR (95% CI)[b]
LMPA (h/week)				
For each hour		0.97 (0.93–1.02)		1.00 (0.96–1.05)
0	389 (33.1)/112 (38.6)	Reference	310 (26.4)/85 (29.3)	Reference
>0–≤1	214 (18.2)/38 (13.1)	0.58 (0.37–0.92)	278 (23.7)/44 (15.2)	0.58 (0.38–0.91)
>1–≤3.75	284 (24.2)/78 (26.9)	0.85 (0.58–1.24)	319 (27.1)/90 (31.0)	0.97 (0.66–1.42)
>3.75	288 (24.5)/62 (21.4)	0.60 (0.40–0.90)	268 (22.8)/71 (24.5)	0.94 (0.62–1.42)
VPA (h/week)				
For each hour		0.95 (0.87–1.05)		0.71 (0.48–1.06)
0	855 (72.8)/221 (76.2)	Reference	1065 (90.6)/269 (92.8)	Reference
>0–≤2.5	196 (16.7)/49 (16.9)	1.02 (0.68–1.51)	90 (7.7)/21 (7.2)	1.03 (0.59–1.80)
≥2.5	124 (10.5)/20 (6.9)	0.82 (0.47–1.40)	20 (1.7)/0 (0.0)	–
Watching television (h/week)				
For each hour		1.00 (0.99–1.02)		1.02 (1.00–1.03)
≥0–≤6	209 (17.8)/54 (18.6)	Reference	184 (15.7)/42 (14.5)	Reference
>6–≤12.25	356 (30.3)/74 (25.5)	0.88 (0.56–1.38)	331 (28.2)/64 (22.0)	0.90 (0.55–1.47)
>12.25–≤14	333 (28.3)/78 (26.9)	0.95 (0.61–0.50)	333 (28.3)/77 (26.5)	1.05 (0.64–1.70)
>14	277 (23.6)/84 (29.0)	1.10 (0.69–1.77)	327 (27.8)/107 (36.9)	1.51 (1.93–2.45)
Joint effect LMPA–watching television				
High LMPA–low watching television	451 (38.4)/108 (37.3)	Reference	429 (36.5)/103 (35.5)	Reference
High LMPA–high watching television	121 (10.3)/32 (11.0)	0.98 (0.59–1.66)	158 (13.4)/43 (14.8)	1.15 (0.72–1.84)
Low LMPA–low watching television	447 (38.0)/98 (33.8)	1.09 (0.77–1.54)	419 (35.7)/80 (27.6)	0.84 (0.58–1.21)
Low LMPA–high watching television	156 (13.3)/52 (17.9)	1.45 (0.91–2.29)	169 (14.4)/64 (22.1)	1.76 (1.14–2.71)
Joint effect VPA–watching television				
High VPA–low watching television	266 (22.6)/57 (19.7)	Reference	89 (7.6)/17 (5.9)	Reference
High VPA–high watching television	54 (4.6)/12 (4.1)	0.86 (0.39–1.90)	21 (1.8)/4 (1.4)	0.77 (0.19–3.11)
Low VPA–low watching television	632 (53.8)/149 (51.4)	0.99 (0.67–1.44)	759 (64.6)/166 (57.2)	0.99 (0.54–1.80)
Low VPA–high watching television	223 (19.0)/72 (24.8)	1.24 (0.78–1.97)	306 (26.0)/103 (35.5)	1.62 (0.86–3.05)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LMPA, light to moderate physical activity; VPA, vigorous physical activity.

[a]Adjusted for maternal age, body mass index (calculated as weight in kilograms divided by the square of height in meters), education level, smoking before pregnancy, GDM antecedents, Mediterranean diet adherence before pregnancy, and energy intake before pregnancy.

[b]Adjusted for maternal age, body mass index (calculated as weight in kilograms divided by the square of height in meters), education level, smoking during pregnancy, GDM antecedents, Mediterranean diet adherence during pregnancy, and energy intake during pregnancy.

estimate the magnitude of the effect of risk factors such as physical activity and sedentary behavior on the risk of GDM as a consequence of the presence of other risk factors.

Our findings related to the isotemporal substitution model show that replacing 1 h/week of watching television with 1 h/week of VPA during pregnancy could reduce the risk of GDM by 34%. These results cannot be compared with other literature, as no previous study has been found that used the isotemporal substitution model for GDM. Our study supports the importance of reducing the time spent watching television and instead performing physical activity, especially during pregnancy. A protective effect on GDM is observed when watching television is replaced by VPA. However, current guidelines recommend that pregnant women engage in moderate physical activity,[21,35] which might not be enough to protect against GDM.[15] Therefore, these results could have important clinical implications.

Until several decades ago, physical activity had been discouraged in pregnancy due to theoretical concerns of exercise-induced injury leading to adverse fetal and maternal outcomes.[36] However, some evidence from observational studies has suggested that the risk of GDM was decreased by 20%–55% among women with physical exercise of varying durations and intensity before or during pregnancy.[30,33,37] These studies support the performance of pregnancy-appropriate VPA as long as there is no prior contraindication for the woman. An example of exercise could be aerobic arm exercises or any other VPA that does not stimulate the production of uterine contractions.

TABLE 4 Substitution of 1 h/week of watching television with 1 h/week of physical activity on the risk for gestational diabetes mellitus (GDM).

	Before pregnancy		During pregnancy	
	aOR 95% CI[a]	*P*-value	aOR 95% CI[b]	*P*-value
LMPA replacement	0.97 (0.93–1.02)	0.227	0.99 (0.95–1.04)	0.724
VPA replacement	0.95 (0.87–1.05)	0.328	0.66 (0.43–1.00)	0.049

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LMPA, light to moderate physical activity; VPA, vigorous physical activity.

[a]Adjusted for maternal age, body mass index (calculated as weight in kilograms divided by the square of height in meters), education level, smoking before pregnancy, GDM antecedents, Mediterranean diet adherence, and energy intake before pregnancy.

[b]Adjusted for maternal age, body mass index (calculated as weight in kilograms divided by the square of height in meters), education level, smoking during pregnancy, GDM antecedents, Mediterranean diet adherence, and energy intake during pregnancy.

Some limitations should be considered when interpreting our findings. First, physical activity was derived from a self-reported questionnaire (based on the Paffenbarger questionnaire). This form of collecting information related to physical activity is the most frequently used in epidemiological studies. The questionnaire used in our study to assess physical activity has been used previously and validated for Spanish pregnant women.[25] We would have liked to analyze the role of physical activity in developing a hydrocarbon intolerance during pregnancy. This would have allowed us to analyze a possible dose–response effect. However, we used a case–control design and this relationship cannot be studied. On the other hand, our study has some strengths: (1) to our knowledge, it is the first study analyzing the association between physical activity, watching television, and GDM risk using an isotemporal substitution model; (2) a large sample size was included in our analyses; (3) our sample is representative of healthy Spanish women in the south of Spain. Furthermore, the loss of participants for not attending the programmed visits was minimal, as prenatal care protocol covers up to 99% of the population of pregnant women in the public hospital; (4) most GDM cases (97.0%) and controls (96.2%) had detailed information about physical activity; (5) residual confounders, such as Mediterranean diet adherence, smoking, GDM antecedents, and energy intake, were measured and adjusted for. However, we cannot rule out the absence of confounding by other exposures/agents related to physical activity, television watching, and GDM.

5 | CONCLUSIONS

A simple change of 1 h/week of watching television for 1 h/week of VPA in pregnant women may reduce the risk of GDM considerably. In this way, our finding reinforces the potential benefits of pregnancy-appropriate physical activity and reducing sedentary behaviors, specifically the time spent watching television, on GDM risk.

AUTHOR CONTRIBUTIONS

José J. Jiménez-Moleón designed the study. Malak Kouiti, Macarena Lozano-Lorca, and Carla González-Palacios Torres performed the analyses. José J. Jiménez-Moleón, Ibtissam Youlyouz-Marfak, Juan Mozas-Moreno, Rocío Olmedo-Requena, and Alfredo Gea verified the analyses. Malak Kouiti and Macarena Lozano-Lorca wrote the first draft of the manuscript. All authors have read, approved the content, and contributed to the work.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. The International Diabetes Federation (IDF). Diabetes Atlas. 10th ed. 2021. www.diabetesatlas.org
2. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2022;377:e067946. doi:10.1136/bmj-2021-067946
3. Shou C, Wei YM, Wang C, Yang HX. Updates in long-term maternal and fetal adverse effects of gestational diabetes mellitus. *Matern Med*. 2019;1:91-94. doi:10.1097/FM9.0000000000000019
4. Diaz-Santana MV, O'Brien KM, Park YM, Sandler DP, Weinberg CR. Persistence of risk for type 2 diabetes after gestational diabetes mellitus. *Diabetes Care*. 2022;45:864-870. doi:10.2337/dc21-1430
5. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am J Obstet Gynecol*. 2017;216:340-351. doi:10.1016/j.ajog.2017.01.037
6. da Silva SG, Ricardo LI, Evenson KR, Hallal PC. Leisure-time physical activity in pregnancy and maternal-child health: a systematic review and meta-analysis of randomized controlled trials and cohort studies. *Sport Med*. 2017;47:295-317. doi:10.1007/s40279-016-0565-2
7. Baena-García L, Ocón-Hernández O, Acosta-Manzano P, et al. Association of sedentary time and physical activity during pregnancy

with maternal and neonatal birth outcomes. The GESTAFIT project. *Scand J Med Sci Sport*. 2019;29:407-414. doi:10.1111/sms.13337
8. Sanabria-Martínez G, García-Hermoso A, Poyatos-León R, González-García A, Sánchez-López M, Martínez-Vizcaíno V. Effects of exercise-based interventions on neonatal outcomes. *Am J Health Promot*. 2016;30:214-223. doi:10.1177/0890117116639569
9. Physical Activity and Exercise During Pregnancy and the Postpartum Period: ACOG Committee Opinion, Number 804. *Obstet Gynecol*. 2020;135:e178-e188. doi:10.1097/AOG.0000000000003772
10. Fazzi C, Saunders DH, Linton K, Norman JE, Reynolds RM. Sedentary behaviours during pregnancy: a systematic review. *Int J Behav Nutr Phys Act*. 2017;14:32. doi:10.1186/s12966-017-0485-z
11. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451-1462. doi:10.1136/bjsports-2020-102955
12. Mijatovic-Vukas J, Capling L, Cheng S, et al. Associations of diet and physical activity with risk for gestational diabetes mellitus: a systematic review and meta-analysis. *Nutrients*. 2018;10:698. doi:10.3390/nu10060698
13. da Silva SG, Hallal PC, Domingues MR, et al. A randomized controlled trial of exercise during pregnancy on maternal and neonatal outcomes: results from the PAMELA study. *Int J Behav Nutr Phys Act*. 2017;14:1-11. doi:10.1186/s12966-017-0632-6
14. Kouiti M, Hernández-Muñiz C, Youlyouz-Marfak I, Salcedo-Bellido I, Mozas-Moreno J, Jiménez-Moleón JJ. Preventing gestational diabetes mellitus by improving healthy diet and/or physical activity during pregnancy: an umbrella review. *Nutrients*. 2022;14:2066. doi:10.3390/nu14102066
15. Šćepanović D, Šćepanović D, Hrvatin I. The effect of maternal exercise on maternal and foetal health in obese pregnant women. *Zdravniski Vestnik*. 2020;89(3–4):223-234. doi:10.6016/ZdravVestn.2944
16. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol*. 2009;170:519-527. doi:10.1093/aje/kwp163
17. Mekary RA, Lucas M, Pan A, et al. Isotemporal substitution analysis for physical activity, television watching, and risk of depression. *Am J Epidemiol*. 2013;178:474-483. doi:10.1093/aje/kws590
18. Llavero-Valero M, Martín JES, Martínez-González MA, Basterra-Gortari FJ, Gea A, Bes-Rastrollo M. Physical activity intensity and type 2 diabetes: isotemporal substitution models in the "seguimiento universidad de navarra" (sun) cohort. *J Clin Med*. 2021;10:2744. doi:10.3390/jcm10132744
19. Nascimento SL, Surita FG, Godoy AC, Kasawara KT, Morais SS. Physical activity patterns and factors related to exercise during pregnancy: a cross sectional study. *PloS One*. 2015;10:e0128953. doi:10.1371/journal.pone.0128953
20. Donofry SD, Germeroth LJ, Kolko Conlon RP, Venditti EM, Levine MD. Correlates of physical activity engagement among pregnant women with overweight and obesity. *Women's Heal Issues*. 2020;30:393-400. doi:10.1016/j.whi.2020.06.001
21. Word Health Organization. Physical activity. 2020. Accessed October 19, 2021. https://www.who.int/news-room/fact-sheets/detail/physical-activity
22. Amezcua-Prieto C, Olmedo-Requena R, Jímenez-Mejías E, et al. Changes in leisure time physical activity during pregnancy compared to the prior year. *Matern Child Health J*. 2013;17:632-638. doi:10.1007/s10995-012-1038-3
23. Olmedo-Requena R, Fernández JG, Prieto CA, Moreno JM, Bueno-Cavanillas A, Jiménez-Moleón JJ. Factors associated with a low adherence to a Mediterranean diet pattern in healthy Spanish women before pregnancy. *Public Health Nutr*. 2014;17:648-656. doi:10.1017/S1368980013000657
24. Pereira MA, FitzerGerald SJ, Gregg EW, et al. A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc*. 1997;29:S1-S205.
25. Fernandez-Martinez O, Bueno-Cabanillas A, Martinez-Martinez M, Jimenez-Moleon JJ, de la Higuera MJL. Validez y fiabilidad de un cuestionario de actividad física para mujeres embarazadas. *Arch Med*. 2008;4:1–8. doi:10.3823/011
26. Be A, Wl H, Herrmann S, et al. Compendium of physical activities. *Med Sci Sport Exerc*. 2011;2011(43):1575-1581. doi:10.1249/MSS.0b013e31821ece12
27. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28:1039-1057. doi:10.2337/diab.28.12.1039
28. Martin-Moreno JM, Boyle P, Gorgojo L, et al. Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol*. 1993;22:512-519. doi:10.1093/ije/22.3.512
29. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003;348:2599-2608. doi:10.1056/NEJMoa025039
30. Oken E, Ning Y, Rifas-Shiman SL, Radesky JS, Rich-Edwards JW, Gillman MW. Associations of physical activity and inactivity before and during pregnancy with glucose tolerance. *Obs Gynecol*. 2006;108:1200-1207.
31. McDonald SM, May LE, Hinkle SN, Grantz KL, Zhang C. Maternal moderate-to-vigorous physical activity before and during pregnancy and maternal glucose tolerance: does timing matter? *Med Sci Sports Exerc*. 2021;53:2520-2527. doi:10.1249/MSS.0000000000002730
32. Wagnild JM, Hinshaw K, Pollard TM. Associations of sedentary time and self-reported television time during pregnancy with incident gestational diabetes and plasma glucose levels in women at risk of gestational diabetes in the UK. *BMC Public Health*. 2019;19:19. doi:10.1186/S12889-019-6928-5
33. Zhang C, Solomon CG, Manson JAE, Hu FB. A prospective study of pregravid physical activity and sedentary behaviors in relation to the risk for gestational diabetes mellitus. *Arch Intern Med*. 2006;166:543-548. doi:10.1001/archinte.166.5.543
34. Padmapriya N, Bernard JY, Liang S, et al. Associations of physical activity and sedentary behavior during pregnancy with gestational diabetes mellitus among Asian women in Singapore. *BMC Pregnancy Childbirth*. 2017;17:17. doi:10.1186/S12884-017-1537-8
35. Colberg SR. Prescribing physical activity to prevent and manage gestational diabetes. *World J Diabetes*. 2013;4:256-262. doi:10.4239/wjd.v4.i6.256
36. Schlüssel MM, Souza EB d, Reichenheim ME, Kac G. Physical activity during pregnancy and maternal-child health outcomes: a systematic literature review. *Cad Saude Publica*. 2008;24:s531-s544. doi:10.1590/S0102-311X2008001600006
37. Dempsey JC. Prospective study of gestational diabetes mellitus risk in relation to maternal recreational physical activity before and during pregnancy. *Am J Epidemiol*. 2004;159:663-670. doi:10.1093/aje/kwh091

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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nutrients

MDPI

Review

Preventing Gestational Diabetes Mellitus by Improving Healthy Diet and/or Physical Activity during Pregnancy: An Umbrella Review

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Abstract: Several epidemiological studies have analyzed the effects of lifestyle modification on reducing the risk of gestational diabetes mellitus (GDM); however, their results remain inconsistent. This umbrella review aims to evaluate the effects of diet and/or physical activity interventions during pregnancy on preventing GDM. Systematic reviews and meta-analysis of randomized clinical trials reporting preventive effects of diet and/or physical activity in reducing the incidence of GDM were included from PubMed, Web of Science, Scopus and Cochrane library. Two authors independently assessed the overlapping and quality of the 35 selected reviews using AMSTAR 2. The results, although variable, tend to defend the protective role of diet and physical activity interventions separately and independently of each other in the prevention of GDM. However, the results for the combined interventions show a possible protective effect; however, it is not entirely clear because most of the analyzed meta-analyses tend to approach 1, and heterogeneity cannot be ruled out. Establishing conclusions about the most efficient type of intervention and a dose–effect relationship was not feasible given the low quality of systematic reviews (83% low to critically low) and the variability in reporting interventions. Therefore, more studies with better quality and definition of the interventions are required. The protocol was previously registered in PROSPERO as CRD42021237895.

Keywords: gestational diabetes mellitus; dietary intervention; physical activity intervention; randomized controlled clinical trials; experimental studies; systematic reviews; meta-analysis

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1. Introduction

Gestational Diabetes Mellitus (GDM) is the most frequent metabolic disease identified during pregnancy and is a growing public health problems. GDM has been associated with both short- and long-term adverse maternal and fetal health outcomes. Newborn complications, for example, include macrosomia, hypoglycemia and birth trauma [1–3]. For the mother, GDM increases the risk of developing diabetes mellitus type 2 and the risk of cardiovascular diseases [4–6]. Risk factors associated with GDM can be divided into non-modifiable and modifiable. Age, family history of diabetes, the genetic component and race have been described as non-modifiable risk factors of GDM [7–11].

However, among the main factors associated with a high risk of GDM is weight, concretely overweight, obesity and an excessive weight gain during the pregnancy, which

are factors that are potentially modifiable for GDM [9,12]. Thus, weight is very related to the diet type and the level of physical activity. In public health, factors susceptible to change improving lifestyle are very important for the prevention of diseases [13,14]. Sedentary behavior and diet with high caloric intake increase the risk of developing GDM [15,16]. In contrast, a Mediterranean diet pattern, for example, was associated with a lower risk of the disease [17].

Epidemiologic studies examining the effects of diet and physical activity on GDM prevention have increased in recent years. Several systematic reviews have been conducted regarding this subject [18–20]; however, their results are still inconsistent, and the most effective strategy remains unclear [21]. Some reviews defend that physical activity or diet reduces the risk of GDM [22,23]. Whereas other systematic reviews do not show a significant protective effect [24,25].

Several reasons may explain this lack of uniformity in the results of the systematic reviews conducted to date. The quality of the reviews, the characteristics of the evaluated diet and/or physical activity interventions, and the selection criteria used to select the studies, including the characteristics of the population selected, could help us to understand this heterogeneity. Therefore, we conducted an umbrella review to evaluate the effects of diet and physical activity interventions on the prevention of GDM, through an evidence synthesis of systematic reviews with or without meta-analysis of randomized clinical trials, evaluating the quality of the methodology of each systematic review.

2. Materials and Methods

An umbrella review of systematic reviews/meta-analysis was conducted in accordance with a previous protocol registered in PROSPERO (CRD42021237895).

2.1. Eligibility Criteria for the Selection of Systematic Reviews

The predefined inclusion criteria for our systematic review selection were: (1) Systematic reviews/meta-analysis based on randomized controlled trials. (2) Evaluating diet and physical activity interventions, separately or in combination. (3) Including GDM as a primary or secondary outcome. (4) Published in English, Spanish, French or Arabic from the inception of the databases used for researching until December 2021. All narrative reviews, gray literature, books and book chapters and communications at conferences were excluded.

Exposure was defined as those interventions aimed at modifying lifestyle by improving diet and/or physical activity before and during pregnancy to prevent GDM compared to the usual routine care. For data synthesis, studies were grouped according to the type of intervention conducted.

2.2. Information Sources and Search Strategy

A literature search was conducted using the major biomedical sources, including PubMed, Scopus, Web of Science and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Methodology Register). In addition, the research was completed by hand-searching the references included in each selected review, and alerts were activated in PubMed and ResearchGate to stay updated.

A primary search was performed in December 2020. The search was rerun in December 2021. No additional systematic review was included in the update as none met our inclusion criteria.

The following terms were combined when performing the search:

- Gestational diabetes mellitus, gestational diabetes.
- Activit*, physical activity, exercise, sport, training, fitness.
- Eating behaviors, feeding behaviors, eating habits, food habits, dietary habits, feeding patterns, dietary pattern, diet.
- Systematic review, meta-analysis.
- Diabetes mellitus type 1, diabetes mellitus type 2, T2D, DM2, treatment.

For example, in PubMed, a broad search was used combining natural language terms and MeSH terms, the following search equation was applied: ((“gestational diabetes mellitus” OR “gestational diabetes”) AND ((“physical activity” OR Activit* OR exercise OR sport OR training OR fitness) OR (“eating behaviors” OR “feeding behaviors” OR “eating habits” OR “food habits” OR “dietary habits” OR “feeding patterns” OR “dietary pattern” OR diet))) AND (“systematic review” OR meta-analysis) NOT (“diabetes mellitus type 1” [Mesh] OR “diabetes mellitus type 2” [Mesh]). The same keywords were used in all databases, adapting the equation to the form required in each. Further details about search strategy are provided in Supplementary Material, (Tables S1–S3).

2.3. Study Selection and Extraction Data

Two members of the research team (MK and CHM) performed the search and selection of systematic reviews and meta-analyses independently. By evaluating the title and the abstract, a first screening of the reviews that met the selection criteria was made. If there were any doubts or disagreements between the two researchers, the full text was read. Persistent disagreements were resolved through the advice of a third investigator (JJJM). Data extraction was conducted individually and independently by the same two researchers who conducted the first search and selection of systematic reviews with or without meta-analysis (MK and CHM). Information was stored in a structured way using a database.

The relevant information included was the following: author, publication year, journal and its impact factor according to Journal Citation Reports; number of studies included in its systematic reviews; databases used in the search; publication years included in the review; selection criteria of the systematic review; global sample size, characteristics of the interventions related to diet and physical activity as frequency, intensity and length of sessions; tools for evaluating the quality of the studies included in the reviews (Cochrane Handbook, Jadad scale and GRADE); analysis of heterogeneity of the studies included in the reviews, risk of publication bias assessment and review’s funding sources.

In the same way, the association measures used to evaluate the magnitude of the association were extracted and analyzed: total relative risk (RR), odds ratio (OR) estimated or risk difference (RD) and their 95% confidence intervals.

2.4. Quality Assessment

AMSTAR-2 was used to evaluate the quality of the systematic reviews included in the umbrella. AMSTAR is a specific tool developed by B.J. Shea et al. to assess the quality of systematic reviews of randomized controlled clinical trials for the evaluation of healthcare interventions [26,27]. AMSTAR-2 improves the characteristics of AMSTAR, allowing a deep evaluation of systematic reviews and both randomized and non-randomized studies.

The first items are dedicated to assessing the research question according to the PICO structure, the selection criteria, the existence of a previously registered protocol, and the justification of the type of design of the included studies in the systematic review. The remaining items attempt to assess methodological aspects related to the interpretation of the results and their discussion, in addition to the evaluation of the risks of bias and the analysis of heterogeneity [28]. Of the 16 items, seven are considered critical weaknesses: items 2, 4, 7, 9, 11, 13 and 15. The following describes how the evaluation of such items was conducted:

(1) Item 2: The systematic review must explicitly report the use of a previous protocol established before its implementation. If the protocol exists but has not been registered, the answer to this item is a “partial yes”.

(2) Item 4: Evaluates the study search conducted. An adequate bibliographic search must include at least the following criteria: use of at least two databases, reporting the search strategy, keywords and restrictions that have been applied in the databases. When these criteria are met, a “partial yes” evaluation is obtained. The “yes” rating requires searching in the references of the selected articles, the gray literature, consulting experts

and conducting the search within 24 months after the protocol and no more than 6 months prior to the acceptance of work.

(3) Item 7: The mention of excluded studies allows obtaining a "partial yes" and a "yes" requires explaining why they are excluded.

(4) Item 9: Assess the risk of bias of the selected studies (RCT) using adequate tools. Blinding and randomization masking are required at least for a 'partial yes' (Cochrane manual, GRADE or Jadad scale, for example). A "yes" qualification requires that the authors evaluate the generation of a random sequence to allocate the participants to the comparison groups.

(5) Item 11: Qualified as "yes" when the meta-analysis is justified, a random-effects model is used in the combination of data and adjusted for heterogeneity if necessary. Furthermore, the causes of heterogeneity are investigated.

(6) Item 13: Considering the risk of bias in the interpretation of results, including only studies with a low risk of bias or discussing the possible impact on the results, allows a "yes" classification.

(7) Item 15: It is evaluated as "yes" when the publication bias is explicitly reported using a funnel graph or the performance of the Egger test. AMSTAR-2 tool was applied by two researchers independently (MK and CHM). The doubts and disagreements that arose were discussed and resolved by a third investigator (JJJM).

After assessing the quality of the systematic reviews included in our umbrella, the results were stratified according to the following cut-off points for AMSTAR-2: (1) Critically low quality: the systematic review does not meet more than one critical item, regardless of the existence or not of non-critical weaknesses. (2) Low quality: the systematic reviews does not meet a critical weakness, meeting or not the rest of the items identified as non-critical weakness. (3) Moderate quality: the systematic review complies with all critical elements and does not meet more than one non-critical weakness. (4) High quality: when all critical elements are met, and there is only one non-critical weakness at most [28].

2.5. Overlapping Synthesis

When two or more systematic reviews investigated the same type of exposure and the risk of GDM, the primary studies included in each review should overlap for the coinciding time periods. In the present umbrella, the evaluation of the overlap was conducted according to the method described by Pieper and Okoth [29,30]. Examination of overlap was done for each intervention (physical activity, diet and mixed approach with both interventions).

In addition, reviews were distributed by year of publication (reviews published before 2015 and since 2015). To assess overlapping, the characteristics of the population were also considered (pregnant women in general and pregnant women at high risk of suffering GDM). For reviews that have an update, only the latest version was included in the overlap assessment [25,31]. In systematic reviews where overlapping was assessed, a 'Citation Matrix' was performed (Cross Tabulation Chart), including systematic reviews in columns, and primary studies in rows were performed [32].

This matrix of citations made it possible to measure the overlap value with a method called "Corrected Covered Area" (CCA) [30]. This procedure allows quantifying the percentage in degrees of overlap between two or more reviews, helping in the decision-making process on how to handle the overlap when it is present [30].

The equation to calculate the CCA is: (N-r)/(rc-r); Where "N" (grand total) is the value that includes the number of primary studies evaluated in each of the systematic reviews included, that is, the number of boxes selected in the citation matrix; "R" (rows) is the number of rows of the primary studies investigated in the systematic reviews; "C" (columns) is the number of columns corresponding to the systematic reviews included in the overlap assessment. The CCA expressed as a percentage allows a classification of the degree of the overlap as "very high" when the CCA is greater than 15%; "High" if the CCA has a value between 11% and 15%; "Medium" when the CCA obtains the value of 6–10%; and finally, "low" when the value is 0–5% [30].

2.6. Data Synthesis

Data from systematic reviews and meta-analyses that met the selection criteria were analyzed. A synthesis of the different interventions evaluated in the RCTs included in the systematic reviews was conducted.

3. Results

3.1. Literature Search

From the four bibliographic sources selected for searching, 693 articles were retrieved (PubMed n = 222; Web of Science n = 209; Scopus n = 150; and Cochrane library n = 112). A total of 189 articles were eliminated due to being duplicates, and 448 were definitively excluded after the title and abstract screening. Accordingly, the full text of 56 papers was evaluated. A final 34 systematic reviews met the selection criteria and were included in our umbrella. The reasons for the exclusion of the papers not selected by full-text assessment can be consulted in Supplementary Material, (Supplementary Table S4).

One review was identified thanks to the alerts activated in PubMed and the research social network ResearchGate. Thus, 35 systematic reviews were finally included in this umbrella review. All, except for three systematic reviews [33–35], also include a meta-analysis of the data of the individual clinical trials in each systematic review. Figure 1 summarizes the process applied for the selection of systematic reviews and meta-analyses included in this umbrella.

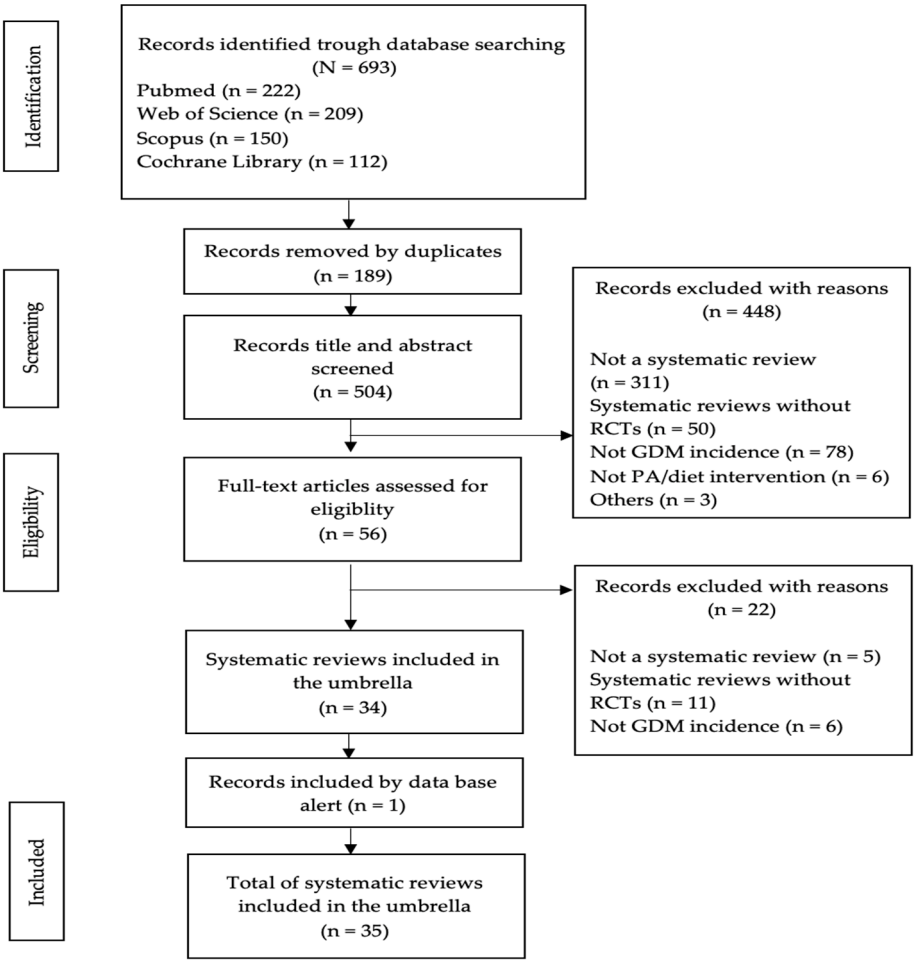


Figure 1. Flow chart: Systematic review selection process. RCTs: Randomized controlled trials; GDM: Gestational Diabetes Mellitus; and PA: Physical Activity.

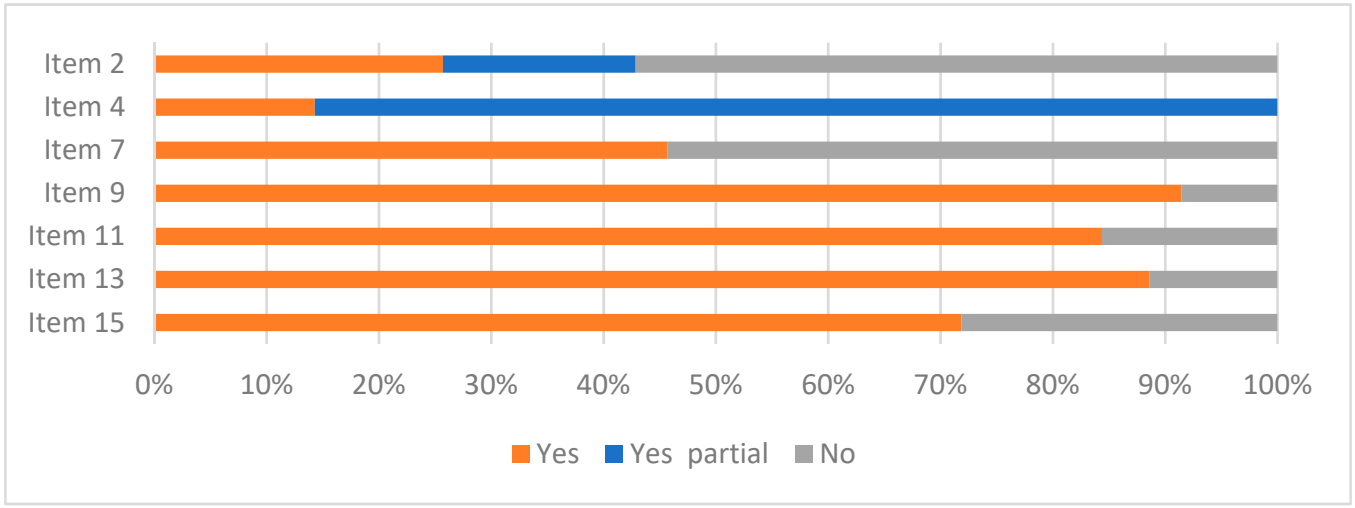
According to the intervention evaluated in each systematic reviews, the whole of the systematic reviews were classified into three groups: (a) systematic reviews about physical activity only: n = 16 (45.7%) [19,24,33,36–48]; (b) systematic reviews containing information about diet exclusively: n = 4 (11.4%) [25,34,49,50]; and (c) systematic reviews with information about both types of interventions, diet and physical activity: n = 15 (42.9%) [18,20,22,23,31,35,51–59].

3.2. Quality Assessment of the Systematic Reviews

Of the 35 systematic reviews selected for this umbrella, 19 (54.2%) were classified as critically low quality and 10 (28.6%) as low quality. The number of systematic reviews of medium and high quality was three for each category. More information about the quality evaluation can be consulted in, Supplementary Figure S1.

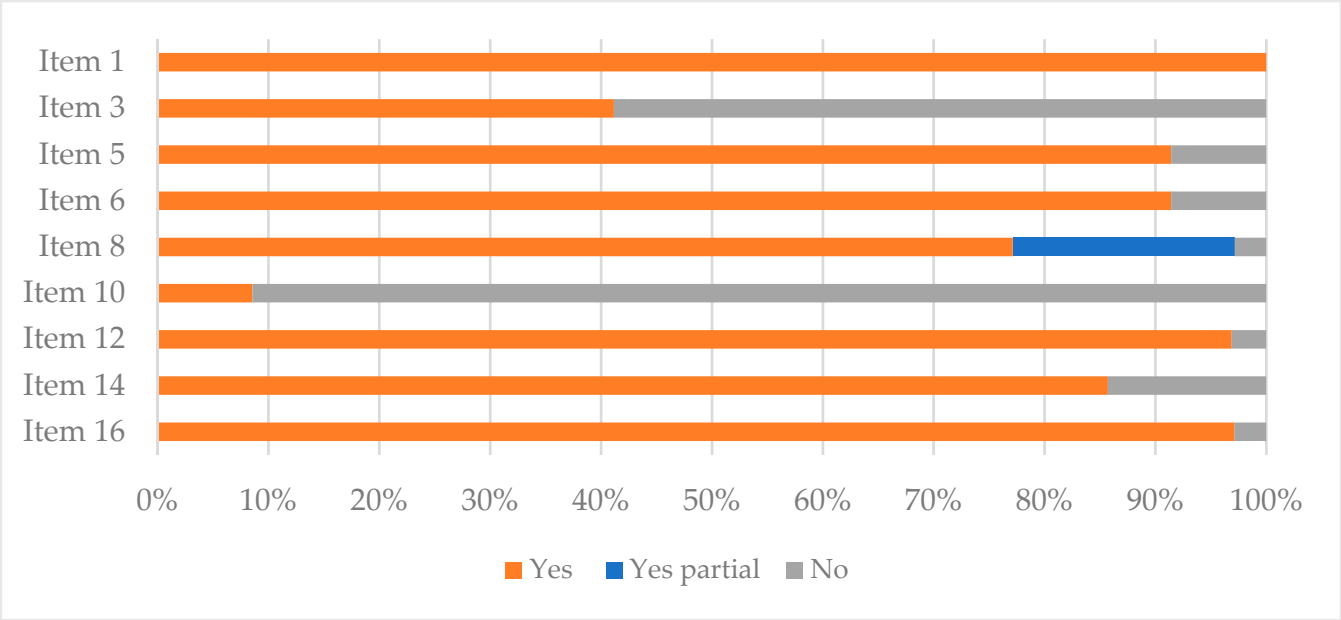
Three items were evaluated only in 32 systematic reviews that included a meta-analysis. Item 11: Appropriate meta-analysis methods; A total of 27 (84.4%) meta-analyses used an appropriate meta-analysis method for the statistic combination. Item 12: Assessing the potential impact of bias risk on results; 31 (93.3%) meta-analyses assessed the potential impact of bias risk on results. Item 15: Assessment of the presence and probable impact of publication bias; 23 (71.9%) meta-analyses investigated the presence of publication bias and assessed its possible impact. Only 25.7% of systematic reviews registered a protocol before conducting the systematic review (Item 2 from AMSTAR-2 tool), and 54.3% did not provide a list of the original studies excluded from the reviews as well as its justification (Item 7).

The presence and probable impact of the publication bias was not assessed in 28.1% of the systematic reviews included in this umbrella (Item 15). Figure 2A shows the results for the seven critical items from AMSTAR-2 tool. Regarding not critical items, the quality of the included systematic review was good except for the decision about study designs and the consideration of the sources of funding of the studies included in the reviews—items 3 and 10, respectively (Figure 2B).



(A)

Figure 2. *Cont.*



(B)

Figure 2. Accomplishment of systematic review with AMSTAR-2 items. (**A**) Critical items. (**B**) Non-critical items. Critical items: Item 2: Previous protocol review; Item 4: Adequate literature search; Item 7: Excluded studies justification; Item 9: Bias risk of individual studies included; Item 11: Appropriate meta-analysis methods; Item 13: Consideration of the bias risk in the interpretation of the review results; Item 15: Assessment of the presence and probable impact of publication bias. Non-critical items: Item 1: Research questions and inclusion criteria include PICO components; Item 3: Explaining decision about the study designs to include in the review; Item 5: Study selection performed in duplicate; Item 6: Data extraction performed in duplicate; Item 8: Describing included studies with sufficient detail; Item 10: Reporting the sources of funding for the studies included in the review; Item 12: Assessing the potential impact of bias risk on results; Item 14: Satisfactory explanation and discussing any observed heterogeneity in the review results; and Item 16: Potential sources of conflict including any funding received.

3.3. Overlapping between Reviews

Analysis of the overlapping was performed by groups of systematic reviews determined by: (a) The year of publication, differencing between systematic reviews published before 2015 and from 2015. (b) The type of the evaluated interventions: "physical activity", "diet" or "mixed interventions". (c) Characteristics of the study population according to risk pregnancy: "pregnant women at high risk" and "pregnant women in general".

The overlapping between systematic reviews was classified as very high for all the comparisons performed, with a CCA of 19.3% to 37.5% (See Table 1). Despite this, all 35 reviews have been maintained. This decision is explained by the high heterogeneity in the original studies included in each review. For example, for the 11 systematic reviews on physical activity interventions in general pregnant women published since 2015, 35 original RCTs studies were included. However, the 35 RCTs are not used in all 11 reviews; 10/35 were included only once, and 13/35 were used in half of the reviews. It should be noted that sometimes different articles from one study can be used. More details about the overlapping assessment are provided in Supplementary Material, (Tables S5–S9).

Table 1. Overlapping between reviews.

Overlapping	N	CCA	Classification
Physical activity as only intervention			
Reviews of RCTs with pregnant women in general published since 2015	11	26.28%	Very high
Reviews of RCTs with high-risk women published since 2015	6	19.26%	Very high
Reviews of RCTs with pregnant women in general published before 2015	3	37.5%	Very high
Diet as only intervention	4	25.39%	Very high
Mixed intervention	5	36.49%	Very high

(N = Number of reviews included in the overlapping assessment; CCA = Corrected Covered Area).

3.4. Main Results

3.4.1. Interventions

The beginning and the end of interventions differed between the RCTs involved in systematic reviews included in our umbrella. Nevertheless, lifestyle interventions mostly started before 20 week's gestation and lasted until 34–37 weeks of gestation or until delivery.

Generally, physical activity interventions consisted of educational recommendations on physical activity plus a group session or, less often, an in-home session. These interventions mainly include an aerobic activity, muscle strength exercise, resistance and balanced exercises. The warm-up and cool-down parts of a session usually consisted of walking and stretching activities. Cycling, swimming and pelvic floor exercise was recommended often as well. In most of interventions, the intensity of exercise was light to moderate or moderate. The frequency of sessions was around three times per week and sometimes reached five times per week. The duration of each session can vary from 35 min to 60 min [19,24,33,36–48].

Regarding diet, the interventions consisted of recommendations and advice made through face-on-face sessions and less frequently through group sessions, completed by a phone call and/or written support. The frequency of visits was very different between trials, with a fluctuation of three to ten visits per participant. Usually, the interventions were realized by a dietitian and sometimes by a food technologist. Regarding interventions related to diet, healthy eating was promoted, especially through reducing energy intake, restricting a high glucose intake, dietary conduct and encouraging a high fiber intake [22,23,25,51,52].

Except for Zhang et al., the recommendation was a Mediterranean diet with a sizeable intake of virgin olive oil, fruits and vegetables, nuts, moderate to high fish consumption and a low intake of meat [49]. Respecting combined interventions, advice provided during the visits was oriented to physical activity and diet simultaneously. Counseling was conducted mainly by a nutritionist or dietitian and sometimes accompanied or conducted by a food technologist, physiotherapists or nursing staff.

The details regarding the frequency of visits and physical activity sessions do not change from those mentioned above. The recommendations continue along the same lines: encouraging moderate physical activity at least three to five times/week and favoring a healthy and balanced diet with a low glucose intake and restricted energy consumption. In some trials, the interventions were completed by individual follow-up and personalized monitoring [23,31,59].

Different guidelines were used for elaborating interventions and advice. Those mentioned include the Institute of Medicine (IOM) guidelines, the American College of Obstetricians and Gynecologists guidelines for gestational weight gain, Health Canada guidelines, Prenatal nutrition guidelines, official National Dietary recommendation and Danish recommendations [22,23,31,35,55]. More details are provided in the Supplementary Material (Tables S10–S12).

3.4.2. Prevention of GDM

All the meta-analyses expressed the magnitude of the association between physical activity interventions, dietary interventions or mixed interventions and the risk of GDM as relative risk (RR) or odds ratio (OR), except for the meta-analysis of Oostdam et al. [59] that used a risk difference. To describe the results, we respected the measures used by each one of the systematic reviews.

(a) Physical activity intervention

Most reviews show a possible preventive effect of physical activity interventions in reducing the risk of GDM, although it does not always show a statistically significant effect [23,37,59]. Although systematic reviews with moderate to high quality, such as Davenport et al. (2018) and Bennett et al. (2018), highlight that it reduces the incidence of GDM [18,39] (Table 2 and Figure 3A).

Table 2. Systematic reviews finding including physical activity intervention in reducing GDM.

Systematic Review ID	RCTs Number	Participant Included in Intervention and Control Group (*N*/*n*)	Association Measurement	I^2 (*p*)	Quality (Amstar 2)
Oostdam et al., 2011 [59]	3	125/113	RD −0.05 (−0.20–0.10)	66 (0.05)	Critically low
Han et al., 2012 [47]	5	437/389	RR 1.10 (0.66–1.84)	0 (0.37)	Low
Yin et al., 2014 [46]	5	497/450	RR 0.91 (0.57–1.44)	26 (0.25)	Critically low
Russo et al., 2015 [45]	10	569/520	RR 0.74 (0.57–0.97)	12 (0.33)	Critically low
Sanabria-Martínez et al., 2015 [44]	8	N.A.	RR 0.69 (0.52–0.91)	0 (0.61)	Critically low
Madhuvrata et al., 2015 * [23]	3	76/76	OR 0.77 (0.33–1.79)	0 (0.53)	Moderate
Aune et al., 2016 [19]	12	9804 **	RR 0.69 (0.50–0.96)	30.2 (0.15)	Critically low
Song et al., 2016 [20]	10	4161 **	RR 0.77 (0.54–1.09)	N.A.	Critically low
Da Silva et al., 2017 [43]	10	1883/1907	RR 0.67 (0.49–0.92)	33 (0.14)	Critically low
Zheng et al., 2017 [24]	7	550/563	OR 0.62 (0.43–0.89)	37 (0.19)	Critically low
Ming et al., 2018 * [42]	9	1472/1509	RR 0.58 (0.37–0.90)	46 (0.07)	Low
Davenport et al., 2018 [18]	27	7568/7198	OR 0.62 (0.52–0.75)	0 (0.51)	High
Bennett et al., 2018 [22]	10	2981 **	RR 0.62 (0.50–0.78)	0 (0.90)	Moderate
Yu et al., 2018 [39]	6	651/719	RR 0.59 (0.39–0.88)	46 (0.11)	Critically low
Chatzakis et al., 2019 * [40]	14	575/589	RR 0.80 (0.60–1.07)	30	Low
Du et la., 2019 * [38]	13	550/572	RR 0.71 (0.57–0.89)	0 (0.52)	Low
Makaruk et al., 2019 [33]	10	1747/2013	N.A.	N.A.	Critically low
Nasiri-Amiri et al., 2019 * [37]	8	727/714	RR 0.76 (0.65–1.08)	50 (0.05)	Critically low
Guo et al., 2019 [51]	19	5883 **	RR 0.70 (0.95–0.84)	N.A.	Critically low
Doi et al., 2020 * [36]	11	722/745	RR 0.69 (0.51–0.94)	23.2 (0.02)	Low

* Population = women at high risk; ** Total sample size; N.A. = Not available; OR = odds ratio; RR = relative risk; RD = risk difference; *N* = exposed sample size; *n* = no exposed sample size; and I^2(*p*) = heterogeneity test (*p*-value).

(b) Diet intervention

The protective effects of only diet intervention were very variable between reviews. The Mediterranean diet can have a significant effect (OR 0.66, 95% CI 0.52–0.82, $I^2 = 0$) [49].

Diet as the lone intervention designed to reduce gestational weight gain also has a significant effect on the prevention of GDM but with a high degree of heterogeneity (RR 0.56, 95% CI 0.36–0.87, $I^2 = 53\%$; $p = 0.3$) [22] (Table 3 and Figure 3B). Other studies suggest that dietary consulting maybe reduce the risk of GDM in comparison with usual care, and no clear difference between low and moderate to high glycemic intake was observed [25,59]. One systematic review notes that diet had a significant protective effect only in obese and overweight pregnant women [55].

Table 3. Systematic reviews finding including diet intervention in reducing GDM.

Systematic Review ID	RCTs Number	Participant Included in Intervention and Control Group (*N*/*n*)	Association Measurement	I^2 (*p*)	Quality (Amstar 2)
Oostdam et al., 2011 [59]	7	449/364	RD −0.05 (−0.10–−0.01)	41 (0.12)	Critically low
Madhuvrata et al., 2015 * [23]	3	202/207	OR 0.33 (0.14–0.76)	26 (0.26)	Moderate
Rogozińska et al., 2015 [55]	6	725/754	RR 0.67 (0.38–1.15)	52 (0.06)	Moderate
Song et al., 2016 [20]	5	1279 **	RR 0.80 (0.58–1.10)	-	Critically low
Tieu et al., 2017 [25]	11	628/652	RR 0.60 (0.35–1.04)	56 (0.07)	High
Bennett et al., 2018 [22]	9	3388 **	RR 0.56 (0.36–0.87)	53 (0.03)	Moderate
Lamminpää et al., 2018 [34]	15	N.A.	N.A.	N.A.	Critically low
Guo et al., 2019 [51]	11	2838 **	RR 0.75 (0.59–0.95)	N.A.	Critically low
Zhang et al., 2020 *** [49]	2	911/937	OR 0.66 (0.52–0.82)	0 (0.85)	Critically low

* Population = women at high risk; ** Total sample size; *** Mediterranean diet; N.A. = Not available; OR = odds ratio; RR = relative risk; *N* = exposed simple size; *n* = no exposed simple size; and I^2(*p*) = heterogeneity test (*p*-value).

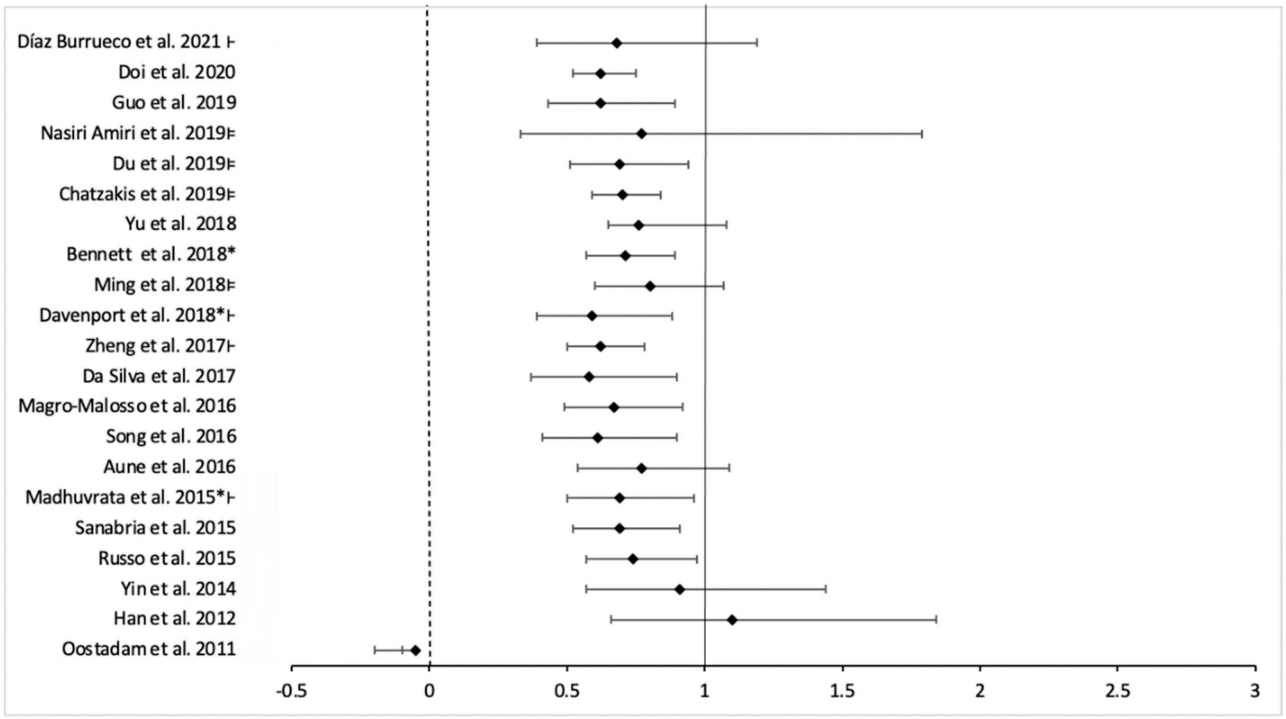
(c) Mixed intervention

When the participant received both interventions; diet and physical activity, four moderate to high-quality reviews showed a possible protective effect in reducing GDM risk (no statistically significant difference) although this effect is less clear (RR 0.90, 95% CI 0.77–1.05; I^2 = 33%; p = 0.072) [22], (OR 0.90, 95% CI 95% 0.74–1.10; I^2 = 30%; p = 0.09) [18], (RR 0.85, 95% CI 0.71–1.01; I^2 = 42%; p = 0.03) [31], (RR 0.95, 95% CI 0.76–1.18; I^2 = 23%; p = 0.21) [55]. Regardless of their quality, the CI for ORs and RRs include the value 1 in the most of the meta-analyses showing a moderate heterogeneity (Table 4 and Figure 3C).

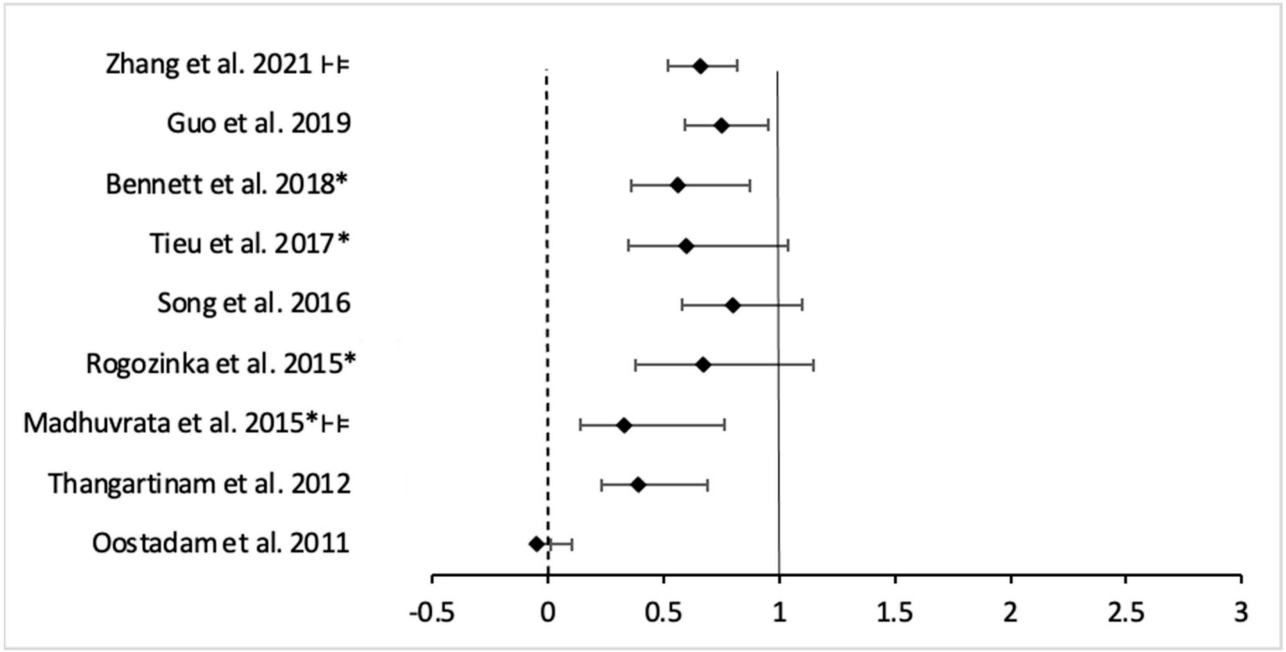
Table 4. Systematic reviews finding including mixed intervention in reducing GDM.

Study ID	RCTs Number	Participant Included in Intervention and Control Group (*N*/*n*)	Association Measurement	I^2(*p*)	Quality (Amstar 2)
Bain et al., 2015 [56]	13	1903/1841	RR 0.92 (0.68–1.23)	43.13 (0.06)	Low
Madhuvrata et al., 2015 * [23]	6	562/526	OR 1.44 (0.96–2.14)	0 (0.93)	Moderate
Rogozińska et al., 2015 [55]	12	2399/2346	RR 0.95 (0.76–1.18)	23 (0.21)	Moderate
Song et al., 2016 [20]	14	6047 **	RR 0.85 (0.70–1.03)	N.A.	Critically low
Shepherd et al., 2017 [31]	19	3353/3280	RR 0.85 (0.71–1.01)	42 (0.03)	High
Davenport et al., 2018 [18]	22	575/550	OR 0.90 (0.74–1.10)	30 (0.09)	High
Bennett et al., 2018 [22]	22	7274 **	RR 0.90 (0.77–1.05)	33 (0.072)	Moderate
Guo et al., 2019 [51]	18	7024 **	RR 0.86 (0.71–1.04)	N.A.	Critically low

* Population = women at high risk; ** Total sample size; N.A. = Not available; OR = odds ratio; RR = relative risk; N = exposed simple size; n = no exposed simple size; and I^2(*p*) = heterogeneity test (*p*-value).

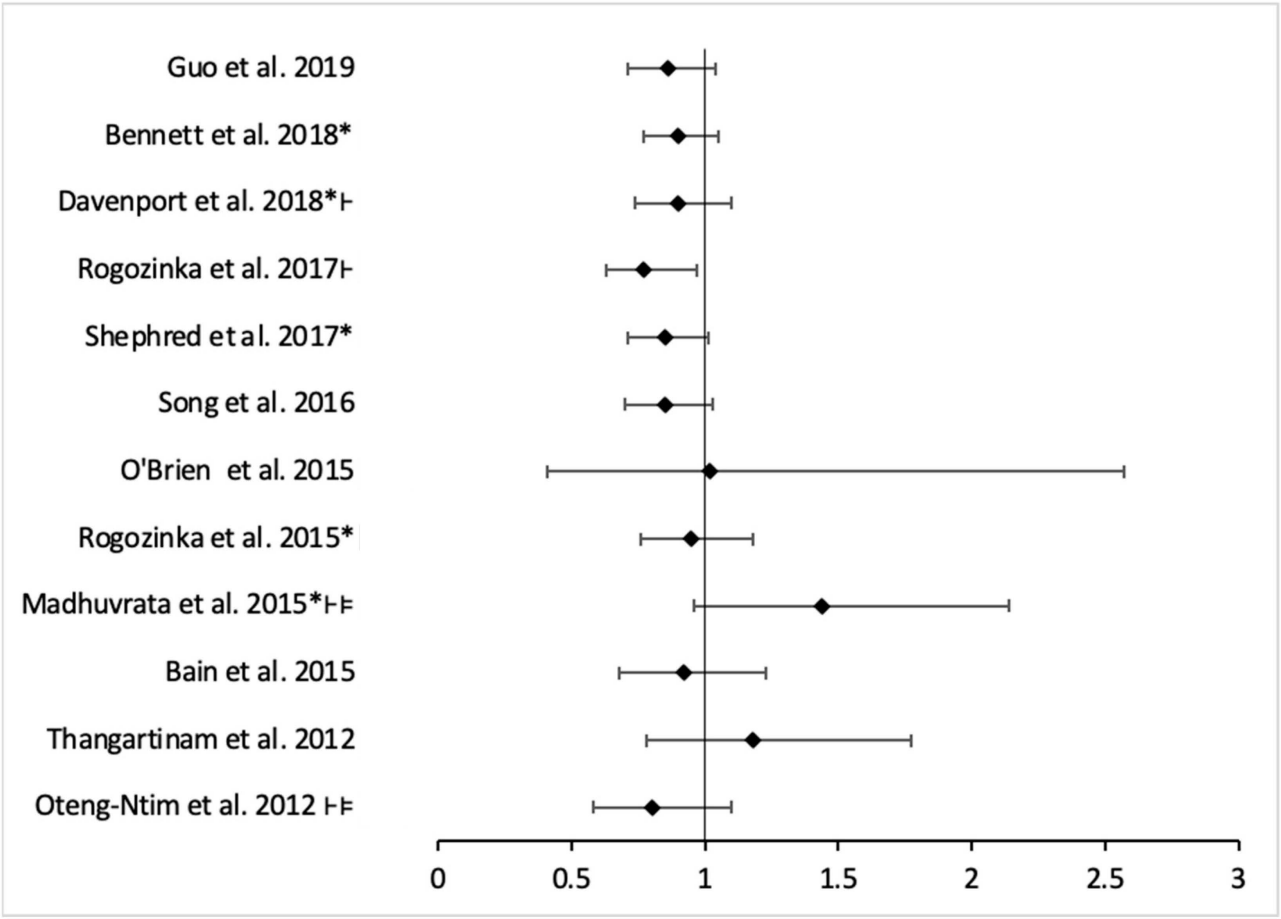


(**A**)



(**B**)

Figure 3. *Cont.*



(**C**)

Figure 3. Forest plot of association of lifestyle intervention in reducing the risk of GDM. (**A**) Physical activity intervention. (**B**) Diet intervention. (**C**) Mixed intervention. * Moderate to high-quality review; ⊢: Odds Ratio; and ⊨: Women at high risk.

3.5. Results from Studies with GDM as Not a Principal Outcome

We analyzed six reviews that show a possible protective effect in reducing the risk of GDM in each one of the interventions (Table 5). The results for these systematic reviews are very similar to those using GDM as the primary outcome. Regarding physical activity, a possible significant effect was observed (RR 0.61, 95% CI 0.41–0.90) [41]. Likewise, diet intervention based on a balanced nutritional regimen with a restriction of 2000 kcal/day (RR 0.39, 95% CI 0.23–0.69; I^2 = 21%; p = 0.001) [58]. When participants can receive both interventions, the effect of the intervention is less clear (RR 1.18, 95% CI 0.78–1.77; I2 = 0%; p = 0.04) [58] and (OR 0.80, 95% CI 0.58–1.10; I^2 = 62%; p = 0.002) [57].

Table 5. Systematic reviews finding including GDM as a secondary outcome.

Systematic Reviews with GDM as Not the Principal Outcome					
	RCTs Number	**Participant Included in Intervention and Control Group (*N*/*n*)**	**Association Measurement**	**I^2 (*p*)**	**Quality (Amstar 2)**
Physical activity					
Magro-Malosso et al., 2017 * [41]	7	623/727	RR 0.61 (0.41–0.90)	-	Critically low
Díaz-Burrueco et al., 2021 [48]	5	782/1091	OR 0.68 (0.39–1.19)	-	Low
Diet					
Thangaratinam et al., 2012 [58]	3	409 **	RR 0.39 (0.23–0.69)	21 (0.001)	Critically Low
Mixed intervention					
Rogozinska et al., 2017 [53]	31	5710/5408	OR 0.77 (0.63–0.94)	38 (0.02)	Low
O'brien et al., 2016 [54]	2	243 **	RR 1.02 (0.41–2.57)	-	Critically Low
Thangaratinam et al., 2012 [58]	6	1233 **	RR 1.18 (0.78–1.77)	0 (0.44)	Critically Low
Oteng-Ntim Et al., 2012 * [57]	6	526/491	OR 0.80 (0.58–1.10)	62 (0.002)	Critically Low

(* Pregnant women at high risk; and ** Total sample size).

4. Discussion

The present umbrella review proposes a synthesis of available scientific evidence on lifestyle modification through interventions based on diet and/or physical activity in the prevention of GDM using systematic reviews and meta-analyses of randomized controlled clinical trials.

Most reviews, regardless of their quality, tend to support that physical activity interventions can reduce the risk of GDM. The effectiveness of physical activity may be restricted by the accomplishment of some criteria: (a) delivering interventions in a healthcare facility [36]; (b) interventions took place early in pregnancy [33]; (c) achieving at least 600 MET-min/week of moderate-intensity [18]; or (d) only water exercise [48]. The incidence of GDM may decrease with diet intervention. However, establishing conclusions about the most effective dietary pattern can be difficult because of the differences in the dietary advice provided [34].

Contrary to expectations, the effect of the combined intervention is unclear or less effective than physical activity or diet alone. This may be because most meta-analyses analyzed tend to approach 1 (without showing significant statistical difference). This difference likely results from variability in the conception of interventions, their duration and other factors perhaps associated with the design of the studies and diet and physical activity patterns assessment. The quality of the RCTs included may also affect the results obtained, and this limitation cannot be discarded [48].

Variability in the descriptions of the interventions made it difficult to draw firm conclusions according to the most efficient type of activity. Similarly, in this research work, making clear recommendations and providing dose–effect analysis was not feasible for many reviews [34,35,51]. That is why it is important to establish, propose and investigate the types of interventions that are more efficient in order to have clear results.

To compare our results, only one overview was found. In contrast to our outcomes, their results show an unknown benefit for physical activity alone and diet alone interventions, although they also suggested a possible beneficial effect of combined diet and exercise [21]. It should be noted that their review was performed only for nine Cochrane reviews.

Regarding the strengths of this research: (1) To our knowledge, this umbrella is one of the few works that provide an exhaustive analysis of the three types of interventions "physical activity", "diet" or "mixed intervention" in the prevention of GDM. (2) It was developed according to the protocol previously registered in PROSPERO. (3) An exhaustive investigation was conducted in the four most important electronic databases without date restrictions. (4) To reduce the probable bias at the time of the search, the selection of the

articles, the data extraction (such as the quality assessment and the measurement of the overlap) were conducted independently by two investigators.

Regarding the limitations of the umbrella: (1) The variability, poor quality and lack of sufficient details describing intervention with respect to the type of diet, type of exercise, duration of the intervention and the intensity with which each intervention was conducted. This made it difficult to expose certain information regarding elements in the general review. This is a frequent weakness in systematic reviews that have been conducted in such a way that they focus on dietary intervention or are based on the promotion of physical activity without delving into the exact type of intervention. The effects of an intervention focused on caloric restriction do not have to be the same as those of an intervention aimed at promoting the Mediterranean diet.

(2) In relation to the above limitation, and as a limitation of the systematic reviews, we note the relatively low quality of systematic reviews conducted to date. For this reason, the interpretation of obtained results was conducted considering their quality.

Using the current findings, it is difficult to establish a well-defined protocol or provide practical recommendations to prevent GDM based on a comprehensive description of the type of physical activity and its intensity, as well as the type of diet and its main characteristics. Even so, it is clear that scientific evidence and WHO recommendations support the benefits of healthy lifestyles, improving physical activity and eating a balanced diet in the prevention of diseases, including GDM. However, this umbrella review of systematic reviews and meta-analyses provides scientific material that summarizes the current available data to facilitate its accessibility by practitioners and other scientists.

5. Conclusions

The previously available systematic reviews analyzing the relationship between physical activity and/or diet were of low quality. Moreover, the definitions of interventions were heterogeneous.

The results of the systematic reviews, although variable, tend to defend the protective role of diet, such as a Mediterranean diet and physical activity, such as three to five sessions a week of 30 min duration and moderate intensity, in preventing GDM. However, the protective effects of a mixed intervention with both are not completely clear. Furthermore, there is insufficient evidence of high quality to determine that combined interventions have a protective effect.

Establishing conclusions on the most efficient type of intervention and a dose–effect relationship has not been feasible given the high variability in the description of the interventions and the low quality of the revisions. Our results highlight the need to perform more clinical trials of better quality and approach interventions and systematic reviews with quality corresponding to the current standards.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu14102066/s1, Tables S1–S3: Search strategy, Table S4: Excluded studies and justification, Figure S1: Quality of included reviews assessed by Amstar 2, Tables S5–S9: Overlapping assessment, Table S10: Description of physical activity intervention in included systematic reviews, Table S11: Description of diet intervention in included systematic reviews, Table S12: Description of mixed intervention in included systematic review.

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References

1. He, X.-J.; Chao-Qing, T.; Hu, C.-L.; Zhu, M.; Tian, C.-Q.; Li, L. Is gestational diabetes mellitus an independent risk factor for macrosomia: A meta-analysis? *Arch. Gynecol. Obstet.* **2014**, *291*, 729–735. [CrossRef] [PubMed]
2. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care* **2021**, *44*, S15–S33. [CrossRef] [PubMed]
3. Billionnet, C.; Mitanchez, D.; Weill, A.; Nizard, J.; Alla, F.; Hartemann, A.; Jacqueminet, S. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia* **2017**, *60*, 636–644. [CrossRef] [PubMed]
4. Domínguez-Vigo, P.; Álvarez-Silvares, E.; Alves-Pérez, M.T.; Domínguez-Sánchez, J.; González-González, A. Incidencia y Factores Clínicos de Riesgo de Diabetes Mellitus En Mujeres Con Diabetes Gestacional Previa. *Ginecol. Obstet. Mex.* **2016**, *84*, 228–242. [PubMed]
5. Kramer, C.K.; Campbell, S.; Retnakaran, R. Gestational Diabetes and the Risk of Cardiovascular Disease in Women: A Systematic Review and Meta-Analysis. *Hormones* **2020**, *19*, 447–448. [CrossRef]
6. Nerenberg, K.; Daskalopoulou, S.S.; Dasgupta, K. Gestational Diabetes and Hypertensive Disorders of Pregnancy as Vascular Risk Signals: An Overview and Grading of the Evidence. *Can. J. Cardiol.* **2014**, *30*, 765–773. [CrossRef]
7. Xu, X.; Liu, Y.; Liu, D.; Li, X.; Rao, Y.; Sharma, M.; Zhao, Y. Prevalence and Determinants of Gestational Diabetes Mellitus: A Cross-Sectional Study in China. *Int. J. Environ. Res. Public Health* **2017**, *14*, 1532. [CrossRef]
8. Lin, P.-C.; Hung, C.-H.; Chan, T.-F.; Lin, K.-C.; Hsu, Y.-Y.; Tzeng, Y.-L. The risk factors for gestational diabetes mellitus: A retrospective study. *Midwifery* **2016**, *42*, 16–20. [CrossRef]
9. Li, F.; Hu, Y.; Zeng, J.; Zheng, L.; Ye, P.; Wei, D.; Chen, D. Analysis of risk factors related to gestational diabetes mellitus. *Taiwan. J. Obstet. Gynecol.* **2020**, *59*, 718–722. [CrossRef]
10. Petry, C.J. Gestational diabetes: Risk factors and recent advances in its genetics and treatment. *Br. J. Nutr.* **2010**, *104*, 775–787. [CrossRef]
11. American Diabetes Association. Available online: https://www.diabetes.org/diabetes/gestational-diabetes/how-will-this-impact-my-baby (accessed on 14 April 2021).
12. Kapustin, R.V.; Arzhanova, O.N.; Bespalova, O.N.; Pakin, V.S.; Ailamazyan, E.K. Abnormal Weight Gain as a Factor in the Development of Gestational Diabetes Mellitus: Systematic Review and Meta-Analysis. *Akusherstvo I Ginekol.* **2016**, *5*, 12–18. [CrossRef]
13. Montesi, L.; Moscatiello, S.; Malavolti, M.; Marzocchi, R.; Marchesini, G. Physical activity for the prevention and treatment of metabolic disorders. *Intern. Emerg. Med.* **2013**, *8*, 655–666. [CrossRef] [PubMed]
14. De la Iglesia, R.; Loria-Kohen, V.; Zulet, M.A.; Martinez, J.A.; Reglero, G.; Ramirez de Molina, A. Dietary Strategies Implicated in the Prevention and Treatment of Metabolic Syndrome. *Int. J. Mol. Sci.* **2016**, *17*, 1877. [CrossRef]
15. Wagnild, J.M.; Hinshaw, K.; Pollard, T. Associations of sedentary time and self-reported television time during pregnancy with incident gestational diabetes and plasma glucose levels in women at risk of gestational diabetes in the UK. *BMC Public Health* **2019**, *19*, 575. [CrossRef] [PubMed]
16. Zhang, C.; Rawal, S. Dietary iron intake, iron status, and gestational diabetes. *Am. J. Clin. Nutr.* **2017**, *106*, 1672S–1680S. [CrossRef]
17. Olmedo-Requena, R.; Gómez-Fernández, J.; Amezcua-Prieto, C.; Mozas-Moreno, J.; Khan, K.S.; Jiménez-Moleón, J.J. Pre-Pregnancy Adherence to the Mediterranean Diet and Gestational Diabetes Mellitus: A Case-Control Study. *Nutrients* **2019**, *11*, 1003. [CrossRef]
18. Davenport, M.H.; Ruchat, S.M.; Poitras, V.J.; Jaramillo Garcia, A.; Gray, C.E.; Barrowman, N.; Skow, R.J.; Meah, V.L.; Riske, L.; Sobierajski, F.; et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: A systematic review and meta-analysis. *Br. J. Sports Med.* **2018**, *52*, 1367–1375. [CrossRef]
19. Aune, D.; Sen, A.; Henriksen, T.; Saugstad, O.D.; Tonstad, S. Physical activity and the risk of gestational diabetes mellitus: A systematic review and dose–response meta-analysis of epidemiological studies. *Eur. J. Epidemiol.* **2016**, *31*, 967–997. [CrossRef]
20. Song, C.; Li, J.; Leng, J.; Ma, R.C.; Yang, X. Lifestyle intervention can reduce the risk of gestational diabetes: A meta-analysis of randomized controlled trials. *Obes. Rev.* **2016**, *17*, 960–969. [CrossRef]
21. Griffith, R.J.; Alsweiler, J.; Moore, A.E.; Brown, S.; Middleton, P.; Shepherd, E.; Crowther, C.A. Interventions to prevent women from developing gestational diabetes mellitus: An overview of Cochrane Reviews. *Cochrane Database Syst. Rev.* **2020**, *6*, CD012394. [CrossRef]

22. Bennett, C.J.; Walker, R.E.; Blumfield, M.L.; Gwini, S.-M.; Ma, J.; Wang, F.; Wan, Y.; Dickinson, H.; Truby, H. Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. *Diabetes Res. Clin. Pract.* **2018**, *141*, 69–79. [CrossRef] [PubMed]
23. Madhuvrata, P.; Govinden, G.; Bustani, R.; Song, S.; Farrell, T.A. Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: A systematic review and meta-analysis of randomised trials. *Obstet. Med.* **2015**, *8*, 68–85. [CrossRef] [PubMed]
24. Zheng, J.; Wang, H.; Ren, M. Influence of exercise intervention on gestational diabetes mellitus: A systematic review and meta-analysis. *J. Endocrinol. Investig.* **2017**, *40*, 1027–1033. [CrossRef] [PubMed]
25. Tieu, J.; Shepherd, E.; Middleton, P.; Crowther, C.A. Dietary advice interventions in pregnancy for preventing gestational diabetes mellitus. *Cochrane Database Syst. Rev.* **2017**, *1*, CD006674. [CrossRef] [PubMed]
26. Shea, B.J.; Grimshaw, J.M.; Wells, G.A.; Boers, M.; Andersson, N.; Hamel, C.; Porter, A.C.; Tugwell, P.; Moher, D.; Bouter, L.M. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med. Res. Methodol.* **2007**, *7*, 10. [CrossRef]
27. Shea, B.J.; Reeves, B.C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; Kristjansson, E.; et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **2017**, *358*, j4008. [CrossRef]
28. Shea, A. AMSTAR-2: Herramienta de Evaluación Crítica de Revisiones Sis- Temáticas de Estudios de Intervenciones de Salud. *BMJ* **2017**, *21*. [CrossRef]
29. Pieper, D.; Antoine, S.-L.; Mathes, T.; Neugebauer, E.A.; Eikermann, M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J. Clin. Epidemiol.* **2014**, *67*, 368–375. [CrossRef]
30. Okoth, K.; Chandan, J.S.; Marshall, T.; Thangaratinam, S.; Thomas, G.N.; Nirantharakumar, K.; Adderley, N.J. Association between the reproductive health of young women and cardiovascular disease in later life: Umbrella review. *BMJ* **2020**, *371*, m3502. [CrossRef]
31. Shepherd, E.; Gomersall, J.C.; Tieu, J.; Han, S.; Crowther, C.A.; Middleton, P. Combined diet and exercise interventions for preventing gestational diabetes mellitus. *Cochrane Database Syst. Rev.* **2017**, *11*, CD010443. [CrossRef]
32. Bougioukas, K.I.; Liakos, A.; Tsapas, A.; Ntzani, E.; Haidich, A.-B. Preferred reporting items for overviews of systematic reviews including harms checklist: A pilot tool to be used for balanced reporting of benefits and harms. *J. Clin. Epidemiol.* **2018**, *93*, 9–24. [CrossRef] [PubMed]
33. Makaruk, B.; Galczak-Kondraciuk, A.; Forczek, W.; Grantham, W.; Charmas, M. The Effectiveness of Regular Exercise Programs in the Prevention of Gestational Diabetes Mellitus—A Systematic Review. *Obstet. Gynecol. Surv.* **2019**, *74*, 303–312. [CrossRef] [PubMed]
34. Lamminpää, R.; Vehviläinen-Julkunen, K.; Schwab, U. A systematic review of dietary interventions for gestational weight gain and gestational diabetes in overweight and obese pregnant women. *Eur. J. Nutr.* **2018**, *57*, 1721–1736. [CrossRef] [PubMed]
35. Skouteris, H.; Morris, H.; Nagle, C.; Nankervis, A. Behavior Modification Techniques Used to Prevent Gestational Diabetes: A Systematic Review of the Literature. *Curr. Diabetes Rep.* **2014**, *14*, 480. [CrossRef] [PubMed]
36. Doi, S.A.; Furuya-Kanamori, L.; Toft, E.; Musa, O.A.; Mohamed, A.M.; Clark, J.; Thalib, L. Physical activity in pregnancy prevents gestational diabetes: A meta-analysis. *Diabetes Res. Clin. Pract.* **2020**, *168*, 108371. [CrossRef]
37. Nasiri-Amiri, F.; Sepidarkish, M.; Shirvani, M.A.; Habibipour, P.; Tabari, N.S.M. The effect of exercise on the prevention of gestational diabetes in obese and overweight pregnant women: A systematic review and meta-analysis. *Diabetol. Metab. Syndr.* **2019**, *11*, 72. [CrossRef] [PubMed]
38. Du, M.-C.; Ouyang, Y.-Q.; Nie, X.-F.; Huang, Y.; Redding, S.R. Effects of physical exercise during pregnancy on maternal and infant outcomes in overweight and obese pregnant women: A meta-analysis. *Birth* **2019**, *46*, 211–221. [CrossRef]
39. Yu, Y.; Xie, R.; Shen, C.; Shu, L. Effect of exercise during pregnancy to prevent gestational diabetes mellitus: A systematic review and meta-analysis. *J. Matern. Neonatal Med.* **2017**, *31*, 1632–1637. [CrossRef]
40. Chatzakis, C.; Goulis, D.G.; Mareti, E.; Eleftheriades, M.; Zavlanos, A.; Dinas, K.; Sotiriadis, A. Prevention of gestational diabetes mellitus in overweight or obese pregnant women: A network meta-analysis. *Diabetes Res. Clin. Pract.* **2019**, *158*, 107924. [CrossRef]
41. Magro-Malosso, E.R.; Saccone, G.; Di Mascio, D.; Di Tommaso, M.; Berghella, V. Exercise during pregnancy and risk of preterm birth in overweight and obese women: A systematic review and meta-analysis of randomized controlled trials. *Acta Obstet. Gynecol. Scand.* **2017**, *96*, 263–273. [CrossRef]
42. Ming, W.-K.; Ding, W.; Zhang, C.J.P.; Zhong, L.; Long, Y.; Li, Z.; Sun, C.; Wu, Y.; Chen, H.; Chen, H.; et al. The effect of exercise during pregnancy on gestational diabetes mellitus in normal-weight women: A systematic review and meta-analysis. *BMC Pregnancy Childbirth* **2018**, *18*, 440. [CrossRef] [PubMed]
43. Da Silva, S.G.; Ricardo, L.I.; Evenson, K.R.; Hallal, P.C. Leisure-Time Physical Activity in Pregnancy and Maternal-Child Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Cohort Studies. *Sports Med.* **2017**, *47*, 295–317. [CrossRef] [PubMed]
44. Sanabria-Martinez, G.; Garcia-Hermoso, A.; Poyatos-Leon, R.; Alvarez-Bueno, C.; Sanchez-Lopez, M.; Martinez-Vizcaino, V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: A meta-analysis. *BJOG* **2015**, *122*, 1167–1174. [CrossRef] [PubMed]

45. Russo, L.M.; Nobles, C.; Ertel, K.A.; Chasan-Taber, L.; Whitcomb, B.W. Physical Activity Interventions in Pregnancy and Risk of Gestational Diabetes Mellitus: A systematic review and meta-analysis. *Obstet. Gynecol.* **2015**, *125*, 576–582. [CrossRef] [PubMed]
46. Yin, Y.-N.; Li, X.-L.; Tao, T.-J.; Luo, B.-R.; Liao, S.-J. Physical activity during pregnancy and the risk of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. *Br. J. Sports Med.* **2014**, *48*, 290–295. [CrossRef] [PubMed]
47. Han, S.; Middleton, P.; Crowther, C.A. Exercise for pregnant women for preventing gestational diabetes mellitus. *Cochrane Database Syst. Rev.* **2012**, *7*, CD009021. [CrossRef] [PubMed]
48. Díaz-Burrueco, J.R.; Cano-Ibáñez, N.; Martín-Peláez, S.; Khan, K.S.; Amezcua-Prieto, C. Effects on the maternal-fetal health outcomes of various physical activity types in healthy pregnant women. A systematic review and meta-analysis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2021**, *262*, 203–215. [CrossRef]
49. Zhang, Y.; Xia, M.; Weng, S.; Wang, C.; Yuan, P.; Tang, S. Effect of Mediterranean diet for pregnant women: A meta-analysis of randomized controlled trials. *J. Matern. Neonatal Med.* **2020**, 1–11. [CrossRef]
50. Tieu, J.; Crowther, C.A.; Middleton, P. Dietary Advice in Pregnancy for Preventing Gestational Diabetes Mellitus. In *Cochrane Database of Systematic Reviews*; Tieu, J., Ed.; John Wiley & Sons, Ltd.: Chichester, UK, 2008; Volume 16.
51. Guo, X.Y.; Shu, J.; Fu, X.H.; Chen, X.P.; Zhang, L.; Ji, M.X.; Liu, X.M.; Yu, T.T.; Sheng, J.Z.; Huang, H.F. Improving the effectiveness of lifestyle interventions for gestational diabetes prevention: A meta-analysis and meta-regression. *BJOG* **2019**, *126*, 311–320. [CrossRef]
52. Rogozinska, E.; Marlin, N.; Betran, A.P.; Astrup, A.; Bogaerts, A.; Cecatti, J.G.; Devlieger, R.; Dodd, J.M.; El Beltagy, N.; Facchinetti, F.; et al. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: Meta-analysis of individual participant data from randomised trials. *BMJ* **2017**, *358*, j3119. [CrossRef]
53. Rogozinska, E.; Marlin, N.; Jackson, L.; Rayanagoudar, G.; Ruifrok, A.E.; Dodds, J.; Molyneaux, E.; Van Poppel, M.N.; Poston, L.; Vinter, C.A.; et al. Effects of antenatal diet and physical activity on maternal and fetal outcomes: Individual patient data meta-analysis and health economic evaluation. *Health Technol. Assess.* **2017**, *21*, 1–158. [CrossRef] [PubMed]
54. O'Brien, C.M.; Grivell, R.M.; Dodd, J.M. Systematic review of antenatal dietary and lifestyle interventions in women with a normal body mass index. *Acta Obstet. Gynecol. Scand.* **2016**, *95*, 259–269. [CrossRef] [PubMed]
55. Rogozińska, E.; Chamillard, M.; Hitman, G.A.; Khan, K.S.; Thangaratinam, S. Nutritional Manipulation for the Primary Prevention of Gestational Diabetes Mellitus: A Meta-Analysis of Randomised Studies. *PLoS ONE* **2015**, *10*, e0115526. [CrossRef] [PubMed]
56. Bain, E.; Crane, M.; Tieu, J.; Han, S.; Crowther, C.A.; Middleton, P. Diet and Exercise Interventions for Preventing Gestational Diabetes Mellitus. *Cochrane Database Syst. Rev.* **2015**, *5*. [CrossRef] [PubMed]
57. Oteng-Ntim, E.; Varma, R.; Croker, H.; Poston, L.; Doyle, P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: Systematic review and meta-analysis. *BMC Med.* **2012**, *10*, 47. [CrossRef] [PubMed]
58. Thangaratinam, S.; Rogozinska, E.; Jolly, K.; Glinkowski, S.; Duda, W.; Borowiack, E.; Roseboom, T.; Tomlinson, J.; Walczak, J.; Kunz, R.; et al. Interventions to reduce or prevent obesity in pregnant women: A systematic review. *Health Technol. Assess.* **2012**, *16*, 1–191. [CrossRef] [PubMed]
59. Oostdam, N.; Van Poppel, M.N.; Wouters, M.G.; Van Mechelen, W. Interventions for Preventing Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J. Women's Health* **2011**, *20*, 1551–1563. [CrossRef]

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