Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: Individual participant data (IPD) meta-analysis of randomised trials

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Complete List of Authors:	Rogozińska, Ewelina; Queen Mary University of London, Women's Health Research Unit Marlin, Nadine; Blizard Insitute, Queen Mary, University of London, Pragmatic Clinical Trials Unit Betrán, Ana Pilar; World Health Organization, Reproductive Health and Research Astrup, Arne; Copenhagen University, Dept of Nutrition, Exercise and Sports Barakat, Ruben; Universidad Politécnica de Madrid, Faculty of Physical Activity and Sports Sciences Bogaerts, Annick; Limburg Catholic University College, Healthcare Cecatti, Jose; University of Campinas, Obstetrics and Gynecology Devlieger, Roland; University Hospitals Leuven, Obstetrics and Gynaecology Dodd, Jodie; The University of Adelaide, Discipline of Obstetrics & Gynaecology El Beltagy , N; Alexandria University Faculty of Medicine Facchinetti , Fabio ; Azienda Ospedaliera Universitaria Policlinico di Modena, Obstetric Unit, Mother Infant Department Geiker, Nina; Copenhagen University Hospital Gentofte, Clinical Nutrition Guelfi , Kym; University of Western Australia, School of Sport Science, Exercise and Health Haakstad, Lene; Norges idrettshogskole, Department of Sports Medicine Harrison , Cheryce; Monash University, Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine Hauner , Hans; Klinikum rechts der Isar der Technischen Universitat Munchen, Else Kröner-Fresenius-Zentrum für Ernährungsmedizin Jensen, Dorte; Odense University Hospital, Department of Endocrinology Kinnunen, Tarja; Universtiy of Tampere, School of Health Sciences Khoury , Janette ; Oslo Universitetssykehus, Department of Obstetrics and Gynaecology Luoto, Riitta; UKK Institute for Health Promotion McAuliffe, Fionnuala; UCD Obstetrics and Gynaecology, School of Medicine

and Medical Science, University College Dublin, National Maternity Hospital
Motahari , Narges ; Mazandaran University of Medical Sciences, Department of Midwifery, School of Nursing and Midwifery
Morkved, Siv; Norwegian University of Science and Technology, Department of Public Health and General Practice
Owens, Julie; The University of Adelaide, Discipline of Obstetrics & Gynaecology
Perales, Maria; Universidad Politécnica de Madrid,
Petrella, Elisabetta; Azienda Ospedaliera Universitaria Policlinico di Modena
Phelan , Suzanne; California Polytechnic State University, Kinesiology Department
Poston, Lucilla; Kings College, London,
Rauh, Kathrin; Technische Universitat Munchen
Renault, Kristina; Odense University Hospital, University of Southern Denmark, Department of Obstetrics and Gynaecology; Hvidovre Hospital, University of Copenhagen, Department of Obstetrics and Gynaecology
Salvesen, Kjell; Trondheim University Hospital, Cardiovascular Medicine
Shen, Garry; University of Manitoba, Department of Internal Medicine
Shub, Alexis; University of Melbourne
Scudeller , Tania; Universidade Federal de Sao Paulo, Department of Management and Health Care
Surita, Fernanda; University of Campinas, Obstetrics & Gynecology
Stafne, Signe; Norwegian University of Science and Technology, Dep. of Public Health and General Practice
Teede, Helena; Monash University, School of Public Health and Preventive Medicine
Tonstad, Serena; Oslo University Hospital Ullevål, Oslo, Norway, Department of Preventive Cardiology
Van Poppel, Mireille; VU medisch centrum School of Medical Sciences, Department of Public and Occupational Health, EMGO Institute for Health and Care Research; Karl-Franzens-Universitat Graz, Institute of Sports Science
Vinter, Christina; Odense Universitetshospital, Department of Gynaecology and Obstetrics
Vistad, Ingvild; Rigshospitalet, Obstetric Clinic, JMC
Yeo, SeonAe; University of North Carolina at Chapel Hill, School of Nursing
Dodds, Julie; Barts and the London School of Medicine and Dentistry, Women's Health Research Unit
Kerry, Sally; Barts and the London SMD, Centre for Health Sciences
Jackson , Louise ; University of Birmingham, ealth Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences
Barton, Pelham; University of Birmingham, Health Economics Unit
Molyneaux, Emma ; King's College London, Section of Women's Mental Health, Health Service and Population Research Department, Institute of Psychiatry
Antequera, Alba; Hospital Ramon y Cajal (IRYCIS)
Rayanagoudar, Girish; Blizard Institute, Barts and The London School of Medicine and dentistry, Queen Mary University of London, Barts Health NHS Trust, Women's Health Research Unit
Ruifrok, Anneloes ; Universitair Medisch Centrum Groningen, Department of Obstetrics and Gynecology; VU medisch centrum School of Medical Sciences, Department of Obstetrics and Gynaecology, Faculty of Medicine
Roberts, Tracy; University of Birmingham, Health Economics Unit
de Groot, Christianne; VU University Medical Center,
Coomarasamy, Arri; University of Birmingham, School of Clinical and Experimental Medicine
Mol, Ben; University of Adelaide, School of Paediatrics and Reproductive Health
Zamora, Javier; Hospital Ramon y Cajal (IRYCIS),
Khan, Khalid; Queen Mary University of London
Riley, Richard; Keele University, Research Institute for Primary Care and

	Health Sciences Thangaratinam, Shakila; Queen Mary University of London, Women's Health Research Unit
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Rogozińska, Ewelina

Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Marlin, Nadine

Pragmatic Clinical Trials Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Betran, Ana Pilar

Department of Reproductive Health and Research, World Health Organization, Switzerland

Astrup, Arne

Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark

Barakat, Ruben

Facultad de Ciencias de la Actividad Fısica y del Deporte-INEF, Universidad Politecnica de Madrid, Spain

Bogaerts, Annick

Department of Development and Regeneration KULeuven, University of Leuven, Belgium.

Faculty of Medicine and Health Sciences, Centre for Research and Innovation in Care (CRIC), University of Antwerp, Belgium

Faculty of Health and Social Work, research unit Healthy Living, UC Leuven-Limburg, Belgium

Cecatti, Jose G

Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas, Brazil

Devlieger, Roland

Department of Obstetrics and Gynaecology, University Hospitals KULeuven, Belgium

Department of Obstetrics, Gynaecology and Fertility, GZACampus Sint-Augustinus, Belgium

Dodd, Jodie

The Robinson Research Institute, School of Medicine, Department of Obstetrics and Gynaecology, University of Adelaide, Australia

Women's and Children's Health Network, Women's and Babies Division, North Adelaide, Australia

El Beltagy Nermeen

Department of Obstetrics and Gynaecology, Faculty of Medicine Alexandria University, Egypt

Facchinetti, Fabio

Obstetrics and Gynecology Unit, Mother Infant Department, University of Modena and Reggio Emilia, Italy

Geiker, Nina RW

Clinical Nutrition Research Unit, Copenhagen University Hospital Gentofte, Denmark

Guelfi, Kim

School of Sport Science, Exercise and health, The University of Western Australia, Australia

Haakstad, Lene AH

Norwegian School of Sports Sciences, Department of Sports Medicine, Norway

Harrison, Cheryce

Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Australia

Hauner, Hans

Else Kröner-Fresenius-Zentrum für Ernährungsmedizin, Klinikum rechts der Isar, Technical University of Munich, Germany

Jensen, Dorte M

Department of Endocrinology, Gynaecology and Obstetrics, Odense University Hospital, University of Southern Denmark, Denmark

Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark

Kinnunen, Tarja I

Faculty of Social Sciences, University of Tampere, Tampere, Finland

Khoury, Janette

Department of Obstetrics and Gynaecology, Oslo University Hospital, Norway

Luoto, Riitta

Department of Health Sciences, University of Tampere, Tampere, Finland

UKK Institute for Health Promotion, Tampere, Finland

McAuliffe, Fionnuala

UCD Perinatal Research Centre, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland

Motahari, Narges

Department of Midwifery, Mazandaran University of Medical Sciences, School of Nursing and Midwifery, Iran

Mørkved, Siv

Department of Public Health and Nursing, Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Norway

Department of Clinical Service, St. Olavs Hospital, Trondheim University Hospital, Norway

Owens, Julie

The Robinson Research Institute, School of Medicine, Department of Obstetrics and Gynaecology, University of Adelaide, Australia

Perales, María

Facultad de Ciencias de la Actividad Fısica y del Deporte-INEF, Universidad Politecnica de Madrid, Spain

Petrella, Elisabetta

Obstetrics and Gynecology Unit, Mother Infant Department, University of Modena and Reggio Emilia, Italy

Phelan, Suzanne

Kinesiology Department, California Polytechnic State University, San Luis Obispo, USA

Poston, Lucilla

Division of Women's Health, Women's Health Academic Centre, King's College London, St. Thomas' Hospital, London, United Kingdom

Rauh, Kathrin

Else Kröner-Fresenius-Centre for Nutritional Medicine, Chair of Nutritional Medicine, Technische Universität München, Germany

Competence Centre for Nutrition (KErn), Germany

Renault, Kristina M

Department of Obstetrics and Gynaecology, Copenhagen University Hospital Hvidovre, Denmark

Obstetric Clinic, JMC, Copenhagen University Hospital Rigshospitalet, Denmark

Sagedal, Linda R

Department of Obstetrics and Gynecology, Sorlandet Hospital, Kristiansand, Norway

Salvesen, Kjell Å

Department of Obstetrics and Gynaecology, St. Olavs Hospital, Trondheim University Hospital, Norway

Department of Laboratory Medicine Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, Norway

Shen, Garry X

Department of Internal Medicine, University of Manitoba, Canada

Shub, Alexis

Department of Obstetrics and Gynaecology, University of Melbourne, Australia,

Department of Perinatal Medicine, Mercy Hospital for Women, Australia

Scudeller, Tânia

Department of Management and Health Care, São Paulo Federal University (UNIFESP), Brazil

Surita, Fernanda G

Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas, Brazil

Stafne, Signe N

Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Norway

Department of Clinical Service, St. Olavs Hospital, Trondheim University Hospital, Norway

Teede, Helena

Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Australia

Tonstad, Serena

Department of Obstetrics and Gynaecology, Oslo University Hospital, Norway

van Poppel, Mireille NM

Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Center, Netherlands

Institute of Sport Science, University of Graz, Austria

Vinter, Christina A

Department of Gynaecology and Obstetrics, Odense University Hospital, University of Southern Denmark, Denmark

Vistad, Ingvild

Department of Obstetrics and Gynecology, Sorlandet Hospital, Kristiansand, Norway

Yeo, SeonAe

School of Nursing, University of North Carolina at Chapel Hill, North Carolina, USA

Dodds, Julie

Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Kerry, Sally

Pragmatic Clinical Trials Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Jackson, Louise

Health Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Barton, Pelham

Health Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Molyneaux, Emma

Section of Women's Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

Martin, Alba A

Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS), Madrid, Spain

Rayanagoudar, Girish

Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Ruifrok, Anneloes E

Department of Obstetrics and Gynecology, Academic Medical Centre, The Netherlands

Department of Obstetrics and Gynaecology, Faculty of Medicine, VU University Medical Center, The Netherlands

Roberts, Tracy

Health Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Christine JM de Groot

Department of Obstetrics and Gynaecology, Faculty of Medicine, VU University Medical Center, The Netherlands

Coomarasamy, Arri

Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom

Mol, Ben W

Robinson Research Institute, School of Medicine, University of Adelaide

The South Australian Health and Medical Research Institute, Adelaide, Australia

Zamora, Javier

Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS) and CIBER Epidemiology and Public Health, Spain

Khan, Khalid S

Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Riley, Richard D

Research Institute for Primary Care and Health Sciences, Keele University, United Kingdom

Thangaratinam, Shakila

Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

for i-WIP (International Weight Management in Pregnancy) Collaborative Group

Corresponding author

Khalid S Khan

Women's Health Research Unit, Centre for Primary Care and Public Health,

Barts and The London School of Medicine and Dentistry,

Queen Mary University of London

Abstract

Objective

Policies and guidelines to tackle obesity and excess weight gain in pregnancy need to be underpinned by robust evidence. We synthesised the evidence on the overall, and differential effects of interventions based on diet and physical activity, primarily on gestational weight gain and composite maternal and offspring outcomes, according to women's body mass index, age, parity, ethnicity and pre-existing medical condition; and secondarily on individual complications.

Design

Systematic review and Individual Participant Data (IPD) meta-analysis

Data sources

Major electronic databases from inception to February 2017 without language restrictions.

Eligibility criteria for selecting studies

Randomised trials on diet and physical activity based interventions in pregnancy.

Data synthesis

Statistical models accounted for clustering of participants within trials and heterogeneity across trials, leading to summary mean difference or odds ratios with 95% confidence intervals for the effects overall, and in subgroups (interactions).

Results

We obtained IPD from 36 randomised trials (12,526 women). There was less weight gain in the intervention group than control (mean difference -0.70 kg; 95% CI -0.92 to -0.48, I^2=14.1%; 33 studies, 9,320 women). Though summary effect estimates favoured the intervention, the reductions in maternal (OR 0.90, 95% CI 0.79 to 1.03, I^2 = 26.7%; 24 studies, 8,852 women) and offspring (OR 0.94, 95% CI 0.83 to 1.08, I^2 = 0%; 18 studies, 7,981 women) composite outcomes were not significant. There was no evidence of differential intervention effects across subgroups, for either gestational weight gain or composite outcomes.

There was strong evidence that interventions reduced the odds of caesarean section (OR 0.91, 0.83 to 0.99, I^2= 0%; 32 studies, 11,410 women), but not for other individual complications in IPD meta-analysis. When IPD was supplemented with study-level data from studies that did not provide IPD, the overall effect was similar, with stronger evidence of benefit for gestational diabetes (OR 0.76, 95% CI 0.65 to 0.89, I^2= 36.8%; 59 studies, 16,885 women).

Conclusion

Diet and physical activity based interventions reduce gestational weight gain and lower the odds of caesarean section. There is no evidence that effects differ across subgroups of women.

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Introduction

Half of all women of childbearing age worldwide are overweight or obese.[1-3] Obesity and excessive gestational weight gain put mother and offspring at risk, both in pregnancy and in later life.[4-6] The resultant costs to the health service and society are considerable.[7,8] Increasingly, healthcare organisations and research funding bodies prioritise research on interventions and strategies to reduce maternal weight related adverse outcomes in pregnancy.[9-12]

Syntheses of study-level data on effects of diet and physical activity based interventions in pregnancy[13] have shown an overall benefit on limiting gestational weight gain, but the findings varied for their protective effect on maternal and offspring outcomes.[13,14] Importantly, the subgroups of women who may benefit the most from such interventions are not known.[15] For this, primary studies do not have sufficient power,[16,17] and study-level data meta-analyses are limited by the absence of published details of subgroup effects,[18] and by potential ecological bias.[19] These problems can be addressed by evidence synthesis using raw individual-level data from relevant studies.[20,21]

We undertook an Individual Participant Data (IPD) meta-analysis to assess the effects of diet and physical activity based interventions, primarily on gestational weight gain and on composite maternal and offspring outcomes, in subgroups defined by body mass index (BMI), age, parity, ethnicity and pre-existing medical condition. Furthermore, we assessed the overall effects, and those of individual interventions (diet, physical activity, mixed), on critically important maternal and offspring complications. In addition to using IPD, we also assessed the impact of incorporating study-level data from other studies not providing IPD.

Methods

The IPD meta-analysis was performed using a pre-specified protocol (PROSPERO CRD42013003804),[22] and was reported in line with The PRISMA-IPD (Preferred Reporting Items for Systematic reviews and Meta-Analysis of Individual Participant Data) recommendations.[23]

Literature search and study identification

We searched the major electronic databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and Health Technology Assessment Database (HTA) from October 2013 to March 2015 to update our previous search in this field for randomised trials on diet and physical activity based interventions in pregnancy.[13] The search was further updated twice; in January 2016, and in February 2017 to identify additional new studies. We searched the Internet by using general search engines including Google, and contacted researchers in the field to identify relevant trials. There were no language restrictions. The details of the search strategy are provided in Appendix 1.

Studies were selected in a two-stage process by two independent researchers (ER and NM/AM/EM). In the first step, potential citations were identified. Next, we did a detailed evaluation of the full manuscripts of potential papers and selected articles that fulfilled the eligibility criteria. We included randomised trials that assessed the effects of diet based, physical activity based, and mixed interventions in pregnancy, on maternal and offspring outcomes. As the mixed intervention we classified any complex, multi-component interventions targeting women's nutrition, level of physical activity, and associated with them habits and behaviour. We excluded studies that only included women with gestational diabetes at baseline, those that involved animals, trials reporting only non-clinical outcomes, and studies that were published before 1990.The primary outcomes were gestational weight gain, a composite of maternal, and a composite of offspring outcomes. The secondary outcomes were individual maternal and offspring complications. The components of the composite outcomes were determined by a two round Delphi survey of researchers in this field, and were considered to be critically important to clinical practice.[24] The maternal composite outcome included gestational diabetes mellitus, hypertensive diseases in pregnancy, preterm delivery and caesarean section. The offspring composite outcome included stillbirth, small-for-gestational age (SGA) fetus, large-for-gestational age (LGA) fetus, and admission of the newborn to the neonatal intensive care unit (NICU).

We defined gestational weight gain as the difference between maternal weight at booking and the last weight measured before delivery. We accepted the primary authors' definition and reporting of gestational diabetes mellitus, pregnancy induced hypertension, pre-eclampsia, caesarean section, stillbirth and admission to NICU. We defined preterm delivery as birth before 37 weeks of gestation, and SGA and LGA as babies with birth weight below the 10th and at or over 90th centile respectively, adjusted for mother's BMI, parity and gestational age at delivery.[25]

Establishment of IPD Collaborative Network and database

We established the International Weight Management in Pregnancy (i-WIP) IPD Collaborative Group by contacting researchers of eligible studies.[26] A bespoke database was developed, and we requested collaborators for relevant data in any format. We sent three reminders when there was no response.

Quality assessment of the included studies

The quality of the randomised trials was assessed by two independent reviewers using a risk of bias tool for sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias.[27] We considered a study to have a high risk of bias if it scored so in at least one of following domains: randomisation, allocation concealment, blinding of outcome assessment, or incomplete outcome data; all items should be scored as low risk for a study to be classified as low risk of bias.

Data extraction and assessment of IPD integrity

Two independent reviewers (ER, NM) undertook data extraction at study-level for inclusion and exclusion criteria, the characteristics of the intervention, and the reported outcomes. We sought to obtain IPD from relevant studies published until July 2015, which was the endpoint for IPD acquisition, to allow sufficient time for data cleaning, standardisation and amalgamation of datasets. We also extracted the published study-level data for all relevant studies published until February 2017, including those published beyond the individual data acquisition timeline, and those for which IPD were not provided by study authors.

We obtained IPD for individual maternal characteristics that were determined *a priori* such as BMI, age, parity, ethnicity, socioeconomic status, and pre-existing medical condition. Continuous variables were kept continuous, but some were also categorised when considered to be clinically useful. These included categorisations based on BMI (normal 18.5 - 24.9 kg/m², overweight 25 – 29.9 kg/m², obese ≥30 kg/m²), and age (cut off of 20 years). Mother's ethnicity was classified as Caucasian or non-Caucasian. The mother's educational status was used to indicate socioeconomic status. We defined the status to be "low" if the mother did not complete secondary education to A-level, "medium" if she completed secondary education (A-level equivalent) and "high" if she completed any further higher education. We defined the pre-existent medical condition as diabetes mellitus, early onset of gestational diabetes, or hypertension.

We considered participants to be adherent to the intervention based on the following criteria: completion of at least 70% of the intervention protocol, dataset provided information on adherence in a 'yes/no' format or was deemed to be adherent as per the study criteria. We performed range and consistency checks on all IPD and produced summary tables. The randomisation ratio, baseline characteristics and the method of analysis in the IPD dataset were compared with the published information. Any discrepancies, missing data, obvious errors, and inconsistencies between variables or outlying values were queried and rectified as necessary with input from the original authors.

Data synthesis

We undertook a two-stage IPD meta-analysis[21] for each primary outcome to obtain summary estimates (mean difference for gestational weight gain and odds ratios for binary outcomes) and 95% confidence intervals (CI) for the intervention effects. We assessed the effects across all interventions overall, and for individual interventions. A two-stage IPD meta-analysis was used to obtain summary estimates of the subgroup effects (interactions) of interest, which compared differential effects of interventions across the primary outcomes. We additionally evaluated whether there are any differential effects of interventions for individual complications, according to the BMI (normal, overweight, obese). All analyses were designed to preserve the intention-to-treat principle.

The two-stage meta-analysis was undertaken as follows. The first stage involved analysing the IPD in each trial separately, to account for the clustering of participants within trials, and to obtain the estimates of interest and their variances. For the cluster-randomised trials, we included a random intercept for a unit of randomisation to account for this further clustering. For the outcome of gestational weight gain, we used analysis of covariance in each trial to regress the final weight value against the intervention while adjusting for baseline weight and centres in cluster-randomised trials. For maternal and offspring outcomes, we used a logistic regression model for each trial separately, with the intervention as a covariate. We excluded women with confirmed glucose intolerance or hypertensive disorder at baseline, as defined by the primary authors, in the analysis of composite adverse pregnancy outcomes. To assess potential intervention effect modifiers, we extended the aforementioned models to include interaction terms between participant-level covariates and the intervention (i.e. treatment-covariate interaction terms).

In the second stage, we pooled the derived effect estimates (i.e. treatment effects or treatment-covariate interactions) across trials using a random effects model fitted using restricted maximum likelihood (REML). The random effects approach allowed us to account for unexplained between-study heterogeneity in effects across studies. This produced summary estimates and 95% confidence intervals for the intervention effects and the interactions (subgroup effects). The Hartung-Knapp correction was applied when subsequently deriving 95% confidence intervals (CI) for the true mean effect, to help account for the uncertainty of the estimate of between-study heterogeneity.[28,29]

We included studies that did not contribute IPD, by incorporating their extracted study-level data within the second stage of the IPD meta-analysis framework, to obtain summary estimates of intervention effects that combined IPD and non-IPD studies. Sensitivity analyses were also performed by excluding studies with high risk of bias, by analysing the primary outcomes separately for each intervention type (diet, physical activity and mixed), by excluding participants not adherent to the intervention, by analysing change in BMI instead of weight gain, and by excluding maternal weight gain estimates from pregnancies that ended before 37 completed weeks of gestation to avoid systematic differences.

Heterogeneity was summarised using the I-squared statistic, the estimated between-study variance ('tau-squared'),[30] and approximate 95% prediction intervals (PIs), which indicate the potential intervention (or interaction) effect in a new population similar to those included in the meta-analysis.[31]

Small-study-effects (potential publication bias) were investigated by using contour enhanced funnel plots alongside visual examination and statistical tests for asymmetry (Egger's test for continuous outcomes or Peter's test for binary outcomes).[32] We assessed for IPD availability bias by comparing the summary results when including non-IPD studies with those from IPD studies.[33] Further, we compared the symmetry of funnel plots before and after inclusion of non-IPD studies. All meta-analyses were undertaken using Stata software version 12.1 (StataCorp LP, College Station, TX, USA), and statistical significance was considered at the 5% level.

Results

Study selection

We identified 58 trials published up to June 2015, of which 36 studies (62%, 36/58) provided IPD, [16,17,34-67] that accounted for data from 80% of the participants (12,526/15,541); 22 studies (3,015 women) did not provide IPD (Fig 1).[68-88] A further 45 (9,945 women) trials[89-133] were identified after the IPD acquisition timeline until February 2017.

Characteristics of included studies and participants

IPD were available from 36 trials in 16 countries: 22 studies[17,34,36-39,41,42,47,48,51-53,56-63,67] were from Europe, four each from North America (the US and Canada),[44,54,65,66] Australia,[16,43,45,50] and South America (Brazil)[35,49,55,64], one study each from Egypt[40] and Iran.[46] Twenty-three IPD studies included women of any BMI,[34-38,42,44-48,52,54-56,58-61,64-67] seven included only obese women,[17,39-41,50,62,63] and six included obese and overweight women.[16,43,49,51,53,57] The interventions included those mainly based on diet (4 IPD studies),[47,61,62,64] mainly based on physical activity (16 IPD studies),[35-37,42,46,49-52,55,58,59,65,66,69] and those based on a mixed approach of diet, physical activity and/or behaviour modifying techniques (15 IPD studies)[16,17,34,39-41,43-45,48,53,54,56,60,63]. One study had a three-arm design with intervention arms being: physical activity only and a mixed approach.[57] The characteristics of all IPD studies, and also those that did not contribute IPD are provided in Appendix 2.

Over 80% of women in the IPD meta-analyses were of Caucasian origin, and at least half were classified as high socioeconomic status. Around 45% of women were nulliparous, 40% were obese, and a similar proportion was classified as having sedentary status with no exercise at baseline (Table 1). IPD were available to assess effects of interventions on gestational weight gain (33 studies, 9,320 women), composite maternal outcomes (24 studies, 8,852 women) and composite offspring outcomes (18 studies, 7,981 women). The largest IPD was available for the outcome of LGA fetus (34 studies, 12,047 women), followed by preterm delivery (32 studies, 11,676 women), SGA fetus (33 studies, 11,666 women), any caesarean section (32 studies, 11,410 women), hypertensive diseases in pregnancy (22 studies, 9,618 women), and gestational diabetes (27 studies, 9,427 women). We did not have access to IPD of 51% of all eligible women (13,023/25,549) from 67 studies (Fig. 1).

Quality of included studies

Overall, trials had a low risk of bias in random sequence generation (75%, 62/83). Over 90% (34/36) studies that contributed to the IPD were assessed as low risk of bias in this domain compared with to 58% of the non-IPD studies (28/67). Two IPD studies (2/36) and one non-IPD (3/67) were considered high risk for allocation concealment. Blinding of outcome assessment was appropriate in 44% (16/36) and 33% (22/67) of IPD and non-IPD studies respectively (Fig.

2). Fewer IPD studies (5/36) were assessed as high risk of bias for incomplete outcome data than non-IPD studies (15/67). The summary of the risk of bias estimates for all eligible studies and those that did, and did not contribute to IPD are provided in Fig 2. We did not encounter any issues that we were not able to clarify with the IPD contributor during the IPD integrity check.

Effects of interventions on pregnancy outcomes

Gestational weight gain

Based on IPD meta-analysis (33 studies, 9,320 women), diet and physical activity based interventions resulted in significantly less gestational weight gain compared to control (summary mean difference -0.70 kg; 95% CI -0.92 to -0.48 kg, I^2=14.1%), after adjusting for baseline weight and clustering. The approximate 95% prediction interval for the intervention effect in a new setting was -1.24 to -0.16 Kg. (Table 2)

Differential effects in subgroups

There was no strong evidence of a treatment-covariate interaction for baseline BMI when treated as a continuous covariate (-0.02 kg change in intervention effect per 1-unit increase in BMI, 95% CI -0.08 to 0.04), or when compared as overweight vs. normal (-0.11 kg, 95% CI -0.77 to 0.55), obese vs. normal (0.06 kg, 95% CI -0.90 to 1.01), and obese vs. overweight (-0.09 kg, 95% CI -1.05 to 0.86). We also did not observe evidence of a subgroup effect for age (-0.03 kg per 1-year increase in age, 95% CI -0.08 to 0.02), parity (0.10 kg change in effect for multiparity vs. nulliparity, 95% CI -0.39 to 0.60), ethnicity (0.05 kg change in effect for non-Caucasian vs. Caucasian, 95% CI -1.27 to 1.37), and underlying medical condition (1.51 kg change in effect for women with at least one condition vs. none, 95% CI -2.01 to 5.02). The findings were consistent when continuous covariates were analysed as categorical measures based on clinically relevant cut-points (Table 3).

Sensitivity analyses

The reduction in gestational weight gain due to the intervention was consistently observed when analysis was restricted to studies with low risk of bias (-0.67 kg, 95% CI -0.95 to -0.38; 15 studies, 5,585 women), women adherent to the intervention (-0.76 kg, 95% CI -1.00 to -0.52; 33 studies, 8,565 women), women followed up until over 37 weeks gestation (-0.91 kg, 95% CI -1.17 to -0.66; 28 studies, 5,324 women), and for BMI instead of maternal weight as an outcome (-0.30 kg/m^2, 95% CI -0.39 to -0.21; 31 studies, 9,238 women).

Addition of studies that did not contribute IPD

Meta-analysis undertaken by supplementing the IPD with study-level data from studies (48 studies, 8,210 women) that did not contribute IPD, we observed a larger beneficial intervention effect for weight gain (summary mean difference -1.1 kg; 95% CI -1.46 to -0.74; 81 studies, 17,530 women). The benefit was also consistently observed for individual interventions based on diet, physical activity or mixed approach (Table 2).

Composite maternal and offspring outcomes

In the IPD meta-analyses, the summary estimates favoured the intervention group for reduction in odds of composite maternal (OR 0.90, 95% CI 0.79 to 1.03, I^2 = 26.7%; 24 studies, 8,851 women) and offspring outcomes (OR 0.94, 95% CI 0.83 to 1.08, I^2 = 0%; 18 studies, 7,981 women), but were not statistically significant (Table 2).

Differential effects across subgroups

We observed no strong evidence of differential subgroup effects for either maternal composite outcome according to baseline BMI (treatment-covariate interaction 1.00, 95% CI 0.98 to 1.02), age (interaction 1.01, 95% CI 0.99 to 1.03), parity (interaction 1.03, 95% CI 0.75 to 1.39), ethnicity (interaction 0.93, 95% CI 0.63 to 1.37), and underlying medical condition (interaction 1.44, 95% CI 0.15 to 13.74) (Table 3).

A similar lack of differential effect was observed for composite offspring outcome in mothers grouped according to baseline BMI (interaction 0.98, 95% CI 0.95 to 1.00), age (interaction 1.01, 95% CI 0.98 to 1.04), parity (interaction 0.94, 95% CI 0.64 to 1.37), ethnicity (interaction 1.12, 95% CI 0.75 to 1.68), and underlying medical condition (interaction 0.58, 95% CI 0.03 to 9.81) (Table 2). The findings did not change for maternal and offspring outcomes when BMI and age were analysed as continuous instead of categorical variables.

Individual maternal outcomes

Overall, we observed a significant reduction in caesarean section (OR 0.91, 95% CI 0.83 to 0.99, I^2 = 0%; 32 studies, 11,410 women) with interventions compared to routine care, in the IPD meta-analysis. The reduction in other individual outcomes such as gestational diabetes (OR 0.89, 95% CI 0.72 to 1.10, I^2 = 23.8%; 27 studies, 9,427 women), hypertensive diseases in pregnancy (OR 0.95, 95% CI 0.78 to 1.16, I^2 = 24.2%; 22 studies, 9,618 women), and preterm delivery (OR 0.94, 95% CI 0.78 to 1.13, I^2 = 17.3%; 32 studies, 11,676 women) were not statistically significant in IPD meta-analyses (Table 2). We did not observe any differential effect according to baseline BMI category (normal, overweight, obese) for any of the individual maternal outcomes (Appendix 3). The findings were consistent when study-level data from non-IPD studies were meta-analysed with IPD, but with a stronger evidence of benefit for gestational diabetes. The reduction in gestational diabetes (OR 0.76, 95% CI 0.65 to 0.89, I^2 = 36.8%; 59 studies, 16,885 women) became significant (Table 2).

Amongst individual interventions, those based mainly on physical activity showed a reduction in gestational diabetes in both IPD (OR 0.67, 95% CI 0.46 to 0.99, I^2= 0%; 10 studies, 2,700 women) and in combined (IPD and non-IPD) meta-analyses (OR 0.66, 95% CI 0.53 to 0.83, I^2= 0%; 27 studies, 6,755 women). While the summary estimates for physical activity based interventions favoured caesarean section (OR 0.82, 95% CI 0.67 to 1.01, I^2= 0%; 13 studies, 3,046 women) and hypertensive diseases in pregnancy (OR 0.74, 95% CI 0.42 to 1.33, I^2= 6.0%; 7 studies, 2,565 women) in IPD meta-analyses, the addition of non-IPD studies resulted stronger evidence of benefit for these complications, with reduction in the respective odds by 17% (OR 0.83, 95% CI 0.73 to 0.95, I^2= 0%; 32 studies, 6,587 women) and 32% (OR 0.68, 95% CI 0.49 to 0.93, I^2= 0%; 20 studies, 5,125 women).

A strong effect was observed for preterm birth with diet based interventions in both IPD (OR 0.28, 95% CI 0.08 to 0.96, I^2= 0%; 4 studies, 1,344 women) and combined analyses (OR 0.32, 95% CI 0.14 to 0.70, I^2= 0%; 7 studies, 1,696 women), but the overall sample sizes were relatively small (Table 2). There was no evidence of benefit with mixed interventions for any maternal outcomes.

Individual offspring outcomes

There was no strong evidence that interventions had an effect on individual offspring outcomes such as stillbirth (OR 0.81, 95% CI <0.001 to 256.69, I^2 = 0%; 2 studies, 3,719 women), SGA fetus (OR 1.06, 95% CI 0.94 to 1.20, I^2 = 0%; 33 studies, 11,666 women), LGA fetus (OR 0.90, 95% CI 0.76 to 1.07, I^2 = 38.0%; 34 studies, 12,047 women) and admission to NICU (OR 1.01, 95% CI 0.84 to 1.23, I^2 = 0%; 16 studies, 8,140 women) based on the IPD meta-analyses. The significance of the findings did not change when non-IPD studies were added to the IPD meta-analyses (Table 2). The numbers of eligible participants for whom data were obtained, effect estimates and confidence intervals for all above analyses are available from the study authors on request. There was no differential effect for any individual offspring outcome according to the BMI category (Appendix 3).

Small-study effects

We found visual and statistical evidence (Egger's test p=0.04) of small study effects in the contour enhanced funnel plots for the IPD meta-analysis of the overall effect on gestational weight gain. The asymmetry of the plot was not improved by the addition of study-level data from non-IPD studies to the meta-analysis. When studies with high risk of bias were excluded from the analysis, the symmetry of the funnel plot improved (Egger's test p=0.61). We found significant evidence of small-study effects for the composite maternal (Peter's test p=0.04), but not for the offspring composite outcome (p=0.85) (Appendix 4).

Discussion

Statement of principal findings

Our large, collaborative IPD meta-analysis confirms that diet and physical activity based interventions in pregnancy reduce gestational weight gain. This beneficial effect was consistently observed irrespective of maternal BMI, age, parity, ethnicity or pre-existing medical condition; and held when studies at high risk of bias were excluded. The findings are generalisable, with the 95% prediction interval suggesting a beneficial effect on gestational weight gain when the intervention is applied in a new population or setting. There is no strong evidence that interventions reduce the risk of composite maternal and offspring outcomes, with no variation in effect observed across the subgroups.

For individual outcomes, interventions reduce caesarean section without a significant reduction in other maternal and offspring complications. The effects of interventions for individual maternal and offspring complications are consistent irrespective of the BMI of the mother. Addition of study-level data from non-IPD studies to the IPD meta-analysis increased the precision of estimates, without a change in the direction of effect, and showed additional benefit for gestational diabetes. Amongst individual interventions, those mainly based on physical activity lowered the odds of gestational diabetes.

Strengths and weaknesses of the study

This is the first IPD meta-analysis, to our knowledge, to assess the differential effects of diet and physical activity based interventions for important, clinically relevant outcomes, in subgroups of women who were identified *a priori*. Establishment of the i-WIP group facilitated the collaboration of key researchers in this area and provided access to the largest IPD in this field. This allowed us to extract data that were not published, with larger sample sizes for outcomes such as preterm birth, small and large for gestational age fetuses, and admission to the neonatal intensive care unit for IPD than study-level meta-analysis. Furthermore, we were able to minimise the heterogeneity in the population, by excluding individual women who did not fulfil the inclusion criteria. We compared the quality of studies that contributed to the IPD, which were generally of higher quality than those that did not contribute IPD.

Access to IPD provided us with substantially increased power (compared to individual trials) to robustly estimate treatment-covariate interactions, and to avoid the ecological bias observed in aggregate meta-regression of study-level covariates.[19,21] It also allowed us to adjust for baseline weight using analysis of covariance in each trial,[134] which is the best approach to analysing continuous outcomes,[135] though rarely used in individual trials. Our reporting of 95% prediction intervals for the overall, and differential effects of interventions, across subgroups, allowed us to quantify the range of effects across populations of interest.

The subgroups were chosen in response to the National Institute for Health and Care Excellence's (NICE) call for assessment of the effectiveness of lifestyle interventions in pregnancy, for specific groups of women considered to be at high risk of complications, such as teenagers, ethnic minorities, and women who enter pregnancy obese.[15] We assessed treatment covariate interactions for subgroups as both continuous and categorical variables. We chose 20 years to be the cut-off for age, as it allowed us to assess the effect of intervention in teenagers, where pregnancy may alter normal growth processes and increase their risk of becoming overweight or obese.[136] Adolescent mothers also retain more weight postpartum than mature control subjects.[136]

Due to the variation in reporting, we were only able to broadly classify the ethnicity of women as Caucasian or non-Caucasian. We combined diet based, physical activity based and mixed approach interventions to provide an overall estimate, and also reported their individual effects.[13,137] Since more than one clinical outcome is considered to be important to clinical care, we assessed the effects of interventions on maternal and offspring composite outcomes, whose individual components were identified through a robust Delphi process.[24] The varying definitions may have an impact on findings for gestational diabetes and pre-eclampsia, where the cut offs and the criteria for diagnosis differed. Another limitation is that the vast majority of our population has a medium-to-high education, a factor favouring compliance with interventions.

IPD repository

By establishing the i-WIP IPD live repository through the support of the individual research teams, we ensured that in addition to the standardisation, there was robust safeguarding of data. The continuing growth of the repository is crucial for future research in this area [138], and will accelerate update of the meta-analysis for the various relevant outcomes as new studies are published. We were successful in obtaining individual data from 80% of all participants within the IPD acquisition timeline. While every effort was made to include IPD from the latest studies identified in the updated search, we were limited by the considerable time needed to prepare the IPD datasets, which involved data access, setting up of institutional contracts, cleaning and formatting of accessed data, resolution of queries with individual researchers, and standardisation and merging of the data. This restricted our ability to include studies published after the agreed data acquisition time line in the IPD meta-analysis. In a high priority area such as obesity and weight gain in pregnancy, there has been a rapid increase in the number of published studies, with at least 10 trials published per year since 2011, and 16 published in 2016. We sought to maximise the information needed to inform the findings by combining study-level data from non-IPD studies to the IPD meta-analyses. The conclusions appeared to be robust for nearly all outcomes. Furthermore, the non-availability of IPD from these studies did not appear to contribute to the observed small study effects, since the asymmetry of the funnel plot was not altered when the non-IPD studies were added. Non-IPD studies were also generally at a higher risk of bias.

Gestational weight gain

Diet and physical activity based interventions reduce gestational weight gain. We have shown that this beneficial effect is observed in all women irrespective of maternal characteristics. The findings are consistent for any type of intervention, even when restricted to only high quality studies and to women adherent to the intervention, and when non-IPD are added to IPD. Mothers with excess weight gain in pregnancy are at increased risk of postpartum weight retention.[139] This increase in interpregnancy BMI may contribute to risks of entering subsequent pregnancies as overweight or obese, with adverse outcomes in subsequent pregnancy. [140] Furthermore, this may increase their risk of cardiovascular morbidity and mortality in later life.[141] Compared to published evidence to-date,[13] we identified a smaller reduction in gestational weight gain of 0.7 kg with interventions. The effect of such a reduction in gestational weight gain (compared to routine care) on post-partum weight retention and long-term outcomes is not known.

Maternal and offspring outcomes

Despite the summary effect estimates favouring the interventions for composite maternal and offspring outcomes, these were not significant. Interventions significantly reduced the odds of caesarean section. Previous systematic reviews showed a trend towards reduction in this risk overall, and for individual interventions (diet, physical activity, mixed), [13] but were limited by the small sample sizes and paucity of reporting, compared to the 11,000 women included in our IPD meta-analysis. Of the individual interventions, physical activity in pregnancy showed a trend towards reduction in caesarean section in IPD meta-analysis, which became significant, with minimal heterogeneity when non-IPD were added. The physical activity component in most studies involved a structured exercise of moderate intensity (aerobic classes, stationary cycling) with resistance training that varied in frequency (Appendix 5).

Although the direction of effect appeared to favour the intervention for other maternal outcomes, they were not significant. Addition of non-IPD to the IPD meta-analysis resulted in significant reduction in gestational diabetes. However, unlike our IPD analysis, we were not able to implement the strict inclusion and exclusion criteria, standardise the analysis strategy (e.g. adjust for baseline), and ascertain occurrence of outcome in the combined analysis with study-level data. Physical activity based interventions significantly reduced the odds of gestational diabetes in IPD meta-analysis, and also when combined with non-IPD. This benefit could be mediated through mechanisms that resulted in improved glycaemic parameters and outcomes in gestational diabetes and type 2 diabetes, through increased insulin sensitivity, and reduced oxidative stress. Exercise in pregnancy may also have a potential role in preventing hypertensive diseases in pregnancy. The effects of diet and physical activity on maternal and offspring outcomes did not vary according to the body mass index of the woman, highlighting the potential benefits for all and not selected groups of mothers.

Interventions based on diet showed a reduction in preterm birth, although the analysis included relatively small numbers of women. We did not identify any benefits with interventions in preventing any adverse offspring outcome, despite a sample size that was two to three folds more than published data for some outcomes, consistent with previous findings.[14] The lack of adverse effects such as small for gestational age and preterm birth with diet and physical activity in pregnancy, should reassure mothers who have traditionally been advised not to undertake structured exercise or manage their diet in pregnancy.

Implications for clinical practice

Currently in the UK, only obese women are offered access to dietician and specific antenatal classes for advice on diet and lifestyle, to minimise gestational weight gain. Based on our work, it is likely that women of all BMI groups could benefit with specific advice on diet and physical activity for weight gain, and some maternal outcomes. Healthcare professionals should avoid variations in care and lifestyle advice provided to mothers based on ethnicity, age and underlying medical conditions, since no differential effects were found.

Discussions about diet and physical activity in pregnancy, which are delivered as part of antenatal care, should incorporate specific estimates of benefit for caesarean section and gestational weight gain, and the likelihood of preventing gestational diabetes. Mothers should be reassured regarding the safety of the interventions, particularly on physical activity and structured exercise in pregnancy, by highlighting the benefits and lack of harm. This may improve engagement and compliance with the intervention. Importantly, such interventions in pregnancy could be considered in global efforts to reduce caesarean section in relevant populations.

Implications for further research

Whether the observed benefit in gestational weight gain with diet and physical activity translates to long-term benefits to the mother and child needs to be assessed. Evaluation of any differential effects according to the individual components of the intervention such as duration, frequency, provider, and setting, on individual outcomes is required to provide detailed recommendations.

The effects of these interventions on mothers in low- and middle-income countries, particularly in those countries with high rates of caesarean section and gestational diabetes, need to be ascertained with large randomised trials. There is a need to develop a harmonised core outcome set for future reporting of clinical trials in this area, to maximise the meaningful interpretation of published data. This is particularly relevant for rare but important outcomes such as shoulder dystocia, birth trauma and venous thromboembolic events.

Conclusion

Diet and physical activity based interventions in pregnancy limit gestational weight gain, with no evidence that this effect differs across subgroups defined by maternal characteristics. Caesarean section odds are also reduced.

What is already known

1. Increased weight gain in pregnancy is associated with maternal and fetal complications.
2. Interventions based on diet and/or physical activityin pregnancy minimise gestational weight gain.
3. Interventions based on diet and physical activity may have a potential role in preventing adverse pregnancy outcomes.

What this study adds

1. Diet and physical activity based interventions consistently reduce gestational weight gain across various subgroups of women categorised by age, parity, Body Mass Index (BMI), ethnicity and pre-existing medical condition.
2. The reduction in odds of composite adverse maternal and composite adverse offspring outcomes with diet and physical activity is not significant, and does not vary across various subgroups of women.
3. Interventions significantly lower the odds of caesarean section, and have no

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Contributors

ST, RR, CdG, AER and SK developed the protocol. JD overlooked the project and drafted the manuscript. ST, ER, NM conducted the review, drafted the manuscript and led the project. KSK, BWM provided input into the protocol development and the drafting of the initial manuscript. ER, EM, AM undertook the literature searches, study selection. AER, ER, ST, EM, GR acquired IPD. MvP, LP, CAV, FM, JMD, JO, RB, MP, JGC, FS, SY, AB, RD, HT, CH, LH, GXS, AS, NEB, NMo, JK, STo, RL, TIK, KG, FF, EP, SP, TTS, KR, HH, KMR, LRS, IV, SNS, SM, KAS, DMJ, MV, AA, NRWG contributed data to the project and provided input at all stages of the project. ER, GR and NM mapped the variables in the available datasets. ER and NM cleaned and quality checked data. NM harmonised the data. NM, SK, RR conducted the data analysis. TR, LJ, PB provided input into the protocol. APB provided input into the conduct of study. JZ provided methodological support. KSK, AC and BWM were involved in project development and provided input at all stages. All authors critical appraised the final draft of the report.

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Patient and Public Involvement

Patient and Public Involvement was obtained in interpretation of findings only.

Patient consent

Patient consent was not required for this study

Ethical approval

Ethical approval was not required for this study

Transparency

I, Ewelina Rogozińska, the lead author, affirs that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1. Baseline characteristics of women included in studies that contributed to the IPD meta-analysis on diet and physical activity based interventions in pregnancy

Baseline characteristics	**No. of studies**	**No. of women**	**Intervention Mean (SD) or N (%)** †	**Control Mean (SD) or N (%)** †
Age (yrs)	35	12,006	30.0 (5.1)	30.1 (5.2)
Normal weight (BMI 18.5 – 24.9)	34	12,031	1,974 (31.7%)	1,842 (31.8%)
Overweight (BMI 25 – 29.9)	34	12,031	1,578 (25.3%)	1,523 (26.3%)
Obesity (BMI ≥ 30)	34	12,031	2,680 (43.0%)	2,434 (42.0%)
Race/Ethnicity:	27	10,020		
Caucasian (incl Russia & Australia)			4,562 (88%)	4,217 (87.2%)
Asian			157 (3%)	156 (3.2%)
Black			292 (5.6%)	292 (6%)
Central/South American			67 (1.3%)	64 (1.3%)
Middle East (incl Iran&Turkey)			37 (0.7%)	37 (0.8%)
Other			71 (1.4%)	68 (1.4%)
Educational status of mother§:	29	8,914		
Low			722 (15.6%)	724 (16.9%)
Medium			1,372 (29.6%)	1,292 (30.2%)
High			2,536 (54.8%)	2,268 (52.9%)
Smoker	29	10,958	875 (15.4%)	865 (16.4%)
Parity:	33	11,805		
0			3,027 (49.5%)	2,692 (47.3%)
1			2136 (34.9%)	2083 (36.6%)
2			647 (10.6%)	634 (11.1%)
3			179 (2.9%)	165 (2.9%)
4+			129 (2.1%)	113 (2%)
No exercise or sedentary	27	7583	1,761 (44.6%)	1,731 (47.6%)
Pre-existing Diabetes mellitus	25	9589	6 (0.1%)	9 (0.2%)
Pre-existing Hypertension	23	5494	73 (2.5%)	54 (2.1%)

†Percentage refers to proportion out of observations in control or intervention arms respectively§ add definitions

Table 2. Effects of diet and physical activity based interventions on gestational weight gain and pregnancy outcomes summarised using Individual Participant Data (IPD) alone, and by supplementing IPD with study-level data from studies that did not contribute IPD

Outcome	**No. of studies (No. of women)**	**Intervention** Mean, SD Event/No-event	**Control** Mean, SD Event/No-event	**MD (95% CI) OR (95% CI)**	**I² (%)**
Gestational weight gain (Kg)					
Overall (IPD)	**33 (9,320)**	**10.1, 5.4**	**10.8, 5.4**	**-0.70 (-0.92 to -0.48)**	**14.1**

(IPD & non-IPD)	_81 (17,530)_	_10.6*_	_11.5*_	_-1.10 (-1.46 to -0.74)_	_73.8_
Diet	4 (1,168)	10.2, 4.4	11.0, 4.8	-0.72 (-1.48 to 0.04)	0.0
	_12 (2,017)_	_9.2*_	_11.7*_	_-2.84 (-4.77 to -0.91)_	_92.3_
Physical activity	15 (2,915)	9.8, 4.4	10.8, 4.8	-0.73 (-1.11 to -0.34)	0.0
	_37 (7,355)_	_11.3*_	_11.9*_	_-0.72 (-1.04 to -0.41)_	_45.4_
Mixed approach	15 (5,369)	10.2, 6.0	10.6, 5.9	-0.71 (-1.10 to -0.31)	34.9
	_35 (8,448)_	_10.3*_	_11.0*_	_-1.00 (-1.39 to -0.61)_	_54.6_
Maternal composite outcome					
Overall	**24 (8,851)**	**1,896/2,728**	**1,837/2,390**	**0.90 (0.79 to 1.03)**	**26.7**
Diet	3 (397)	42/137	84/134	0.60 (0.20 to 1.75)	0.0
Physical activity	9 (2,311)	346/850	367/748	0.81 (0.61 to 1.09)	10.8
Mixed approach	13 (6,259)	1,508/1,742	1,438/3,009	0.97 (0.84 to 1.12)	34.9
Gestational diabetes					
Overall	**27 (9,427)**	**584/4,333**	**571/3,939**	**0.89 (0.72 to 1.10)**	**23.8**
	_59 (16,885)_	_974/7,764_	_1,046/7,101_	_0.76 (0.65 to 0.89)_	_36.8_
Diet	4 (490)	13/208	19/250	1.03 (0.30 to 3.61)	0.0
	_8 (1,106)_	_57/476_	_75/498_	_0.79 (0.37 to 1.69)_	_0.0_
Physical activity	10 (2,700)	90/1300	121/1,189	0.67 (0.46 to 0.99)	0.0
	_27 (6,755)_	_240/3153_	_347/3,015_	_0.66 (0.53 to 0.83)_	_0.0_
Mixed approach	14 (6,355)	481/2825	441/2,608	1.02 (0.79 to 1.32)	35.2
	_27 (9,342)_	_677/4135_	_672/3,858_	_0.88 (0.72 to 1.07)_	_10.8_
Hypertensive diseases in pregnancy[#]					
Overall	**22 (9,618)**	**432/4,586**	**423/4,177**	**0.95 (0.78 to 1.16)**	**24.2**
	_45 (14,849)_	_559/7,130_	_592/6,568_	_0.85 (0.71 to 1.00)_	_21.5_
Diet[§]	3 (397)	18/161	39/179	0.59 (0.07 to 4.65)	35.8
	_5 (729)_	_23/322_	_49/335_	_0.57 (0.18 to 1.79)_	_38.0_
Physical activity	7 (2,565)	55/1,242	73/1,195	0.74 (0.42 to 1.33)	6.0
	_20 (5,125)_	_106/2,513_	_147/2,359_	_0.68 (0.49 to 0.93)_	_0.0_
Mixed approach	13 (6,797)	359/3,183	322/2,933	1.05 (0.86 to 1.28)	19.4
	_21 (9,136)_	_430/4,295_	_407/4,004_	_1.01 (0.87 to 1.17)*_	_16.3_
Preterm birth					
Overall	**32 (11,676)**	**332/5,713**	**345/5,286**	**0.94 (0.78 to 1.13)**	**17.3**
	_49 (14,339)_	_414/6,971_	_443/6,511_	_0.92 (0.79 to 1.08)_	_8.7_
Diet	4 (1,344)	9/647	35/653	0.28 (0.08 to 0.96)	0.0
	_7 (1,696)_	_13/819_	_45/819_	_0.32 (0.14 to 0.70)_	_0.0_
Physical activity	13 (3,249)	95/1541	73/1540	1.29 (0.90 to 1.85)	0.0
	_23 (5,149)_	_160/2,431_	_148/2,410_	_1.09 (0.84 to 1.41)_	_0.0_
Mixed approach	16 (7,219)	228/3525	243/3223	0.91 (0.73 to 1.12)	0.0
	_20 (7,630)_	_241/3721_	_256/3412_	_0.92 (0.75 to 1.12)_	_32.3_
Caesarean section					
Overall	**32 (11,410)**	**1,525/4,385**	**1,506/3,994**	**0.91 (0.83 to 0.99)**	**0.0**
	_66 (18,041)_	_2,373/6,860_	_2,440/6,368_	_0.89 (0.83 to 0.96)_	_16.2_
Diet	4 (1,340)	117/535	149/539	0.78 (0.50 to 1.22)	0.0
	_7 (1,732)_	_238/610_	_264/620_	_0.88 (0.65 to 1.17)_	_0.0_
Physical activity	13 (3,046)	306/1,230	349/1,161	0.82 (0.67 to 1.01)	0.0
	_32 (6,587)_	_648/2,646_	_746/2,547_	_0.83 (0.73 to 0.95)_	_0.0_
Mixed approach	16 (7,160)	1,102/2,620	1,059/2,379	0.95 (0.84 to 1.08)	17.6
	_28 (9,858)_	_1,487/3,604_	_1481/3,286_	_0.92 (0.80 to 1.06)_	_21.9_
Offspring composite outcome					
Overall	**18 (7,981)**	**1,007/3,172**	**951/2,851**	**0.94 (0.83 to 1.08)**	**0.0**
Diet	2 (346)	34/132	48/132	0.71 (0.03 to 18.23)	0.0

Physical activity	5 (1,274)	138/495	143/498	0.99 (0.67 to 1.46)	0.0
Mixed approach	12 (6,494)	835/2,545	797/2,317	0.95 (0.81 to 1.11)	4.7
Stillbirth[†]					
Overall	**2 (3,719)**	**9/1,858**	**11/1,841**	**0.81 (<0.01 to 256.69)**	**0.0**
	4 (4,534)	*12/2,261*	*14/2,247*	*0.85 (0.24 to 3.02)*	*0.0*
Small for gestational age					
Overall	**33 (11,666)**	**709/5,324**	**632/5,001**	**1.06 (0.94 to 1.20)**	**0.0**
	44 (12,937)	*773/6,018*	*685/5,461*	*1.05 (0.94 to 1.18)*	*0.0*
Diet	4 (1,337)	41/610	47/639	0.92 (0.45 to 1.88)	0.0
	6 (1,628)	*56/746*	*55/771*	*1.05 (0.62 to 1.77)*	*0.0*
Physical activity	14 (3,272)	243/1,402	232/1,395	1.05 (0.84 to 1.34)	12.3
	21 (3,955)	*274/1,740*	*271/1,670*	*1.01 (0.83 to 1.24)*	*51.7*
Mixed approach	16 (7,193)	425/3,312	370/3,086	1.08 (0.92 to 1.28)	0.0
	20 (7,670)	*443/3,532*	*386/3,309*	*1.08 (0.93 to 1.27)*	*0.0*
Large for gestational age					
Overall	**34 (12,047)**	**744/5,492**	**759/5,052**	**0.90 (0.76 to 1.07)**	**38.0**
	45 (13,348)	*820/6,185*	*833/5,510*	*0.86 (0.71 to 1.04)*	*41.0*
Diet	4 (1,408)	155/529	176/548	0.91 (0.60 to 1.37)	0.0
	6 (1,699)	*172/663*	*203/661*	*0.82 (0.54 to 1.22)*	*0.0*
Physical activity	15 (3,330)	121/1,557	124/1,528	0.96 (0.59 to 1.54)	34.3
	21 (3,930)	*159/1,842*	*161/1,768*	*0.96 (0.67 to 1.37)*	*6.9*
Mixed approach	16 (7,450)	468/3,406	481/3,095	0.89 (0.67 to 1.17)	51.0
	21 (8,040)	*489/3,680*	*523/3,348*	*0.83 (0.62 to 1.10)*	*4.3*
Admission to Neonatal Intensive Care Unit					
Overall	**16 (8,140)**	**302/3,973**	**279/3,586**	**1.01 (0.84 to 1.23)**	**0.0**
	21 (9,498)	*406/4,543*	*400/4,149*	*0.97 (0.82 to 1.14)*	*0.0*
Diet	1 (289)	3/137	13/136	*na*[#]	*na*
	2 (389)	*11/179*	*29/170*	*0.33 (<0.01 to 47.97)*	*0.0*
Physical activity	3 (1,166)	31/552	40/543	0.77 (0.21 to 2.81)	20.8
	4 (1,240)	*34/586*	*43/577*	*0.79 (0.35 to 1.78)*	*0.0*
Mixed approach	13 (6,818)	268/3,284	230/3,036	1.10 (0.89 to 1.35)	0.0
	15 (7,771)	*360/3,626*	*332/3,453*	*1.05 (0.88 to 1.25)*	*0.0*

*IPD & non-IPD – meta-analyses using combined IPD and non-IPD are provided in Italics. *recalculation using DerSimonian-Laird*

SD – standard deviation, MD – mean difference, OR – odds ratio, [#]standard deviations not possible to estimate, [§]no data from non-IPD studies, [†]For the outcome stillbirth all the data comes from the studies with mixed approach interventions

Table 3. Differential effects of diet and physical activity based interventions on gestational weight gain, composite maternal, and composite offspring outcomes in subgroups of pregnant women

Maternal characteristic	No. of studies	No. of women	Summary estimate	Treatment covariate interaction: Coeff. 95% CI (95% PI)	Treatment covariate interaction: I² (%)
GESTATIONAL WEIGHT GAIN			**MD* Kg (95% CI)**		
Baseline Body mass index					
Normal	21	3,376	-0.77 (-1.15 to -0.39)		
Overweight	28	2,574	-0.75 (-1.22 to -0.27)	-0.02; -0.08 to 0.04 *(-0.21 to 0.17)*[§1]	39.8
Obese	31	3,335	-0.85 (-1.41 to -0.29)		
Parity					
Nulliparous	27	4,513	-0.80 (-1.17 to -0.43)	0.10; -0.39 to 0.60	4.8

Multiparous	27	4,548	-0.62 (-0.88 to -0.37)	*(-0.83 to 1.04)*[§2]	
Ethnicity					
Caucasian	21	6,814	-0.74 (-1.07 to -0.42)	0.05; -1.27 to 1.37 *(-1.28 to 1.39)*[§3]	26.1
Non-Caucasian	15	621	-0.42 (-1.12 to 0.28)		
Age					
≥ 20 yrs	32	9,045	-0.72 (-0.95 to -0.50)	-0.03; -0.08 to 0.02 *(-0.14 to 0.09)*[§4]	25.9
< 20 yrs	13	232	0.05 (-1.34 to 1.44)		
Pre-existing medical condition[#]					
No medical condition	18	4,335	-0.62 (-0.90 to -0.34)	1.51; -2.01 to 5.02 *(-4.13 to 7.15)*[§5]	28.4
At least one medical condition	6	128	0.40(-1.92 to 2.71)		
MATERNAL COMPOSITE OUTCOME			**OR* (95% CI)**		
Baseline Body mass index					
Normal	12	2,445	0.91 (0.65 to 1.28)		
Overweight	19	2,222	1.04 (0.86 to 1.26)	1.00; 0.98 to 1.02 *(0.98 to 1.02)*[§1]	0
Obese	20	4,181	0.92 (0.80 to 1.05)		
Parity					
Nulliparous	21	4,613	0.87 (0.71 to 1.07)	1.03; 0.75 to 1.39 *(0.53 to 2.00)*[§2]	34.0
Multiparous	22	4,186	0.92 (0.78 to 1.07)		
Ethnicity					
Caucasian	15	6,510	0.92 (0.79 to 1.07)	0.93; 0.63 to 1.37 *(0.62 to 1.38)*[§3]	0
Non-Caucasian	11	917	0.86 (0.63 to 1.17)		
Age					
≥ 20 years	24	8,656	0.91 (0.81 to 1.02)	1.01; 0.99 to 1.03 *(0.99 to 1.03)*[§4]	0
< 20 years	9	172	1.57 (0.66 to 3.71)		
Pre-existing medical condition[#]					
No medical condition	15	3,135	0.85 (0.66 to 1.09)	1.44; 0.15 to 13.74 *(0.03 to 76.75)*[§5]	24.9
At least one medical condition	5	89	1.65 (0.36 to 7.51)		
OFFSPRING COMPOSITE OUTCOME					
Baseline Body mass index					
Normal	7	1,843	0.93 (0.60 to 1.43)		
Overweight	12	2,065	0.83 (0.61 to 1.13)	0.98; 0.95 to 1.00 *(0.94 to 1.02)*[§1]	18.5
Obese	13	4,327	0.92 (0.72 to 1.19)		
Parity					
Nulliparous	16	4,152	0.97 (0.80 to 1.17)	0.94; 0.64 to 1.37 *(0.39 to 2.28)*[§2]	35.5
Multiparous	15	4,048	0.91 (0.72 to 1.15)		
Ethnicity					
Caucasian	11	6,018	0.93 (0.79 to 1.08)	1.12; 0.75 to 1.68 *(0.74 to 1.69)*[§3]	0
Non-Caucasian	9	939	1.10 (0.78 to 1.54)		
Age					
≥ 20 yrs	16	8,061	0.95 (0.82 to 1.09)	1.01; 0.98, 1.04 *(0.97 to 1.05)*[§4]	4.1
< 20 yrs	7	162	1.01 (0.34 to 2.98)		
Pre-existing medical condition[#]					
No medical condition	12	3,407	0.89 (0.74 to 1.08)	0.58; 0.03, 9.81 *(<0.001, to 2440.15)*[§1]	0
At least one medical condition	3	63	0.54 (0.04 to 7.52)		

*Model accounted for baseline weight and clustering effect [#]diabetes mellitus or hypertension; [§1]per unit of Body Mass Index; [§2]Multipara vs. nullipara; [§3]Non-Caucasian vs. Caucasian; [§4]Per yr of age; [§5]At least one medical condition vs. none; CI: confidence interval; MD – mean difference; OR – odds ratio; PI: prediction interval

Table. Effects of diet and physical activity based interventions on gestational weight gain and pregnancy outcomes summarised using Individual Participant Data (IPD) alone, and by supplementing IPD with study-level data from studies that did not contribute IPD

Outcome	No. of studies (No. of women)	Intervention Mean, SD Event/ No-event	Control Mean, SD Event/ No-event	MD (95% CI) OR (95% CI)	I^2 (%)
MATERNAL					
Gestational weight gain (Kg)					
IPD	33 (9,320)	10.1, 5.4	10.8, 5.4	-0.70 (-0.9 to -0.48)	14.1
Combined IPD and non-IPD	*81 (17,530)*	*10.6**	*11.5**	*-1.10 (-1.46* to *-0.74)*	*73.8*
Maternal composite outcome[§]					
IPD	24 (8,851)	1,896/2,728	1,837/2,390	0.90 (0.79 to 1.03)	26.7
- **Gestational diabetes**					
IPD	27 (9,427)	584/4,333	571/3,939	0.89 (0.72 to 1.10)	23.8
Combined IPD and non-IPD	*59 (16,885)*	*974/7,764*	*1,046/7,101*	*0.76 (0.65 to 0.89)*	*36.8*
- **Hypertensive diseases in pregnancy**[#]					
IPD	22 (9,618)	432/4,586	423/4,177	0.95 (0.78 to 1.16)	24.2
Combined IPD and non-IPD	*45 (14,849)*	*559/7,130*	*592/6,568*	*0.85 (0.71 to 1.00)*	*21.5*
- **Preterm birth**					
IPD	32 (11,676)	332/5,713	345/5,286	0.94 (0.78 to 1.13)	17.3
Combined IPD and non-IPD	*49 (14,339)*	*414/6,971*	*443/6,511*	*0.92 (0.79 to 1.08)*	*8.7*
- **Caesarean section**					
IPD	32 (11,410)	1,525/4,385	1,506/3,994	0.91 (0.83 to 0.99)	0.0
Combined IPD and non-IPD	*66 (18,041)*	*2,373/6,860*	*2,440/6,368*	*0.89 (0.83 to 0.96)*	*16.2*
OFFSPRING					
Offspring composite outcome[§]					
IPD	18 (7,981)	1,007/3,172	951/2,851	0.94 (0.83 to 1.08)	0.0
- **Stillbirth**	-	-	-	-	-
IPD	2 (3,719)	9/1,858	11/1,841	0.81 (<0.01 to 256.69)	0.0
Combined IPD and non-IPD	*4 (4,534)*	*12/2,261*	*14/2,247*	*0.85 (0.24 to 3.02)*	*0.0*
- **Small for gestational age**					
IPD	33 (11,666)	709/5,324	632/5,001	1.06 (0.94 to 1.20)	0.0
Combined IPD and non-IPD	*44 (12,937)*	*773/6,018*	*685/5,461*	*1.05 (0.94 to 1.18)*	*0.0*
- **Large for gestational age**					
IPD	34 (12,047)	744/5,492	759/5,052	0.90 (0.76 to 1.07)	38.0
Combined IPD and non-IPD	*45 (13,348)*	*820/6,185*	*833/5,510*	*0.86 (0.71 to 1.04)*	*41.0*
- **Admission to Neonatal Intensive Care Unit**					
IPD	16 (8,140)	302/3,973	279/3,586	1.01 (0.84 to 1.23)	0.0
Combined IPD and non-IPD	*21 (9,498)*	*406/4,543*	*400/4,149*	*0.97 (0.82 to 1.14)*	*0.0*

MD – mean difference, SD – standard deviation, OR – odds ratio, CI – confidence intervals
[*] *standard deviations not possible to estimate,*
[#] For non-IPD data – for studies where pre-eclampsia and pregnancy-induced hypertension (PIH) were reported separately data for PIH were appended to IPD
[§] *no data from non-IPD studies,*

Print abstract

Study question

What are the effects of diet and physical activity based interventions on gestational weight gain and pregnancy outcomes, and do they differ according to women's body mass index, age, parity, ethnicity, and pre-existing medical condition?

Methods

We undertook an Individual Participant Data (IPD) meta-analysis of randomised trials on diet and physical activity based interventions in pregnancy on gestational weight gain, and composite maternal and offspring outcomes. Statistical models accounted for clustering of participants within trials and heterogeneity across trials, leading to summary mean difference or odds ratios with 95% confidence intervals for the effects overall, and in subgroups (interactions).

Study answer and limitations

Women gained less weight in the intervention group than control (mean difference -0.70 kg; 95% CI -0.92 to -0.48; 33 studies, 9,320 women); and the reductions in maternal (OR 0.90, 95% CI 0.79 to 1.03; 24 studies, 8,852 women) and offspring (OR 0.94, 95% CI 0.83 to 1.08; 18 studies, 7,981 women) composite outcomes were not significant. There was no differential intervention effect across subgroups, for gestational weight gain or composite outcomes. Interventions reduced the odds of caesarean section (OR 0.91, 95% CI 0.83 to 0.99; 32 studies, 11,410 women), but not other individual complications. When we supplemented IPD with study-level data from studies that did not provide IPD, the effect was similar, with stronger evidence

of benefit for gestational diabetes (OR 0.76, 95% CI 0.65 to 0.89; 59 studies, 16,885 women).

Studies varied in the components of interventions evaluated, such as intensity, setting, and frequency; and in the type and measurements of outcomes. The considerable time needed to obtain, and standardise IPD meant that we could not incorporate up-to-date published data in the IPD meta-analysis.

What this study adds

Diet and physical activity interventions minimise weight gain and reduce the odds of caesarean section, with no difference in effects across subgroups of women.

Systematic review registration CRD42013003804

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Competing interests: Hans Hauner and Ben W Mol reported other grants during the conduct of the study.

Data sharing: No additional data from the study are available.

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Appendix 5 Detailed characteristics of studies that provided Individual Participant Data

Study Year Language	Participants	Interventions	Control	Outcomes
Althuizen 2006 English	Inclusion criteria • First pregnancy • Ability to read, write and speak Dutch; • Gestational age less than 14 weeks Number of participants Intervention 123 Control 123	Two personal counsellors with a background in physical activity or remedial education provided 5 counselling sessions at 18, 22, 30, 36 weeks gestation and at 8 weeks postpartum. Principles of a psychological intervention method called 'problem-solving treatment for primary care' were used. Sessions lasted for 15 minutes except the first that lasted 30 minutes. A general information brochure was provided after the first session. The sessions were aimed at making the participants aware of issues related to weight gain in pregnancy including IOM guidelines. Weight gain charts specific to BMI categories with markings to show recommended weight gain (IOM guidelines) were provided. Dietary advice provide as per Dutch nutrition centre guidelines with emphasis on healthy eating, adjusting energy intake to activity levels and decreasing intake of high fat food. Physical activity was assessed by questionnaires and general information provided. Specific individualized activities were discussed in those not meeting physical activity guidelines. The American Centre for Disease Control and Prevention guidelines formed the basis for physical activity counselling. The last counseling session (telephone) focused on delivery, breast feeding, care of the new born along with physical activity and diet. The counselors were trained for the study by recording conversations with 10 pregnant women followed by feedback on performance by other members of the research team.	Standard Care	Primary • Change in body weight and body mass index (measured at 15, 25 and 35 weeks of pregnancy and at 7, 25 and 51 weeks postpartum) • Skin fold thickness and body fat percentage Secondary • Physical activity by Short Questionnaire to Assess Health enhancing physical activity (SQUASH) and accelerometer data • Questionnaire for nutrition and related behaviours (Dutch eating behavior questionnaire) • Leptin, ghrelin, fasting glucose, insulin, cortisol insulin growth factor 1, insulin growth factor binding proteins 1 and 3 from a subgroup of participants and cord blood.

Study Year Language	Participants	Interventions	Control	Outcomes
Barakat 2008 English	Inclusion criteria: • Singleton and uncomplicated pregnancy • Not at high risk for preterm delivery (no history of recurrent spontaneous preterm birth, i.e., number of previous preterm deliveries ≤1) • Age 25–35 years • Sedentary before gestation (not exercising > 20 min on > 3 days/week) Exclusion criteria: • Not being under medical follow-up throughout the entire pregnancy period • Women not planning to give birth in the same obstetrics hospital associated with the study • Women with any serious medical condition preventing them from exercising safely	The programme consisted of 35-40 minute sessions thrice weekly from 12-13 weeks gestation to end of pregnancy (38-39 weeks) with an estimated average of 80 sessions per participant). They were supervised by a trained fitness specialist with each group consisting of 10-12 women. The venue was spacious and well-lit with favourable conditions (altitude 600 m, temperature 19 – 21 degree C and humidity 50 – 60%). The sessions were accompanied by music. The exercise activity was of light to moderate intensity with a target heart rate of ≤ 80% of maximum predicted heart rate for age (220-age). All participants were provided heart rate monitors. Each session included warm-up (8 minutes), core session (20 minutes) and a cool-down period (8 minutes). Warm-up and cool-down components involved light stretching exercises for limbs, neck and trunk. Additionally, the cool-down period included relaxation exercises. The core portion involved toning and very mild resistance exercises.	The women were asked to maintain their level of activity	• Gestational weight gain (Weight before delivery minus weight before pregnancy) • Preterm deliveries • Birth weight • Macrosomia • Birth length • Head circumference • Ponderal index, • Apgar score 1 min, • Apgar score 5 min,

	Number of participants Intervention 80 Control 80	Toning included shoulder shrugs and rotations, arm elevations and leg lateral elevations, pelvic rocks and tilts. The resistance exercises included one set of (10–12 repetitions of each of i) abdominal curls and ii) the below exercises using barbells (3 kg/exercise) or low-to-medium resistance bands: biceps curls, arm side lifts and extensions, shoulder elevations, bench press, seated lateral row, leg circles and lateral leg elevations, knee (hamstring) curls and extensions, ankle flexions and extensions. Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided

Study Year Language	Participants	Interventions	Control	Outcomes
Barakat 2012 a English	Inclusion criteria • Healthy uncomplicated singleton pregnancy Exclusion criteria: • Absolute obstetrical contraindication to exercise [(as per American College of Obstetricians and Gynecologists (2002)] • Plans to deliver baby elsewhere • Not receiving antenatal care throughout the pregnancy • Participating in another physical activity program • Regular exercise before pregnancy (four or more times per week). Number of participants	The programme consisted of 40 - 45 minute sessions thrice weekly from 6-9 weeks gestation to end of pregnancy (38-39 weeks) with an estimated average of 85 sessions per participant). The participants were supervised by a trained fitness specialist with each group consisting of 10-12 women. The venue was spacious and well-lit with favourable conditions (altitude 600 m, temperature 19 – 21 degree C and humidity 50 – 60%). The sessions were accompanied by music. The exercise activity was of light to moderate intensity with a target heart rate of ≤ 70% of maximum predicted heart rate for age (220-age). All participants were provided heart rate monitors. Each session included warm-up (7-8 minutes), core session (25 minutes) and a cool-down period (7-8 minutes). Warm-up and cool-down components involved light stretching exercises for limbs, neck and trunk. The core portion included exercises for arms and abdomen and aerobic dance to improve posture, strengthen muscles of	Usual care	• Type of delivery (Normal, instrumental, Cesarean) • Gestational age at delivery • Preterm delivery (<37 weeks) • Maternal weight gain • Blood pressure • 1-hour glucose tolerance test • Gestational diabetes • Birth weight/length • pH of the umbilical cord blood • Apgar score

	Intervention 160 Control 160	labour and pelvic floor and prevent lower back pain. Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided. Supine exercises were limited to a maximum of 2 minutes and exercises involving Valsalva maneuver were avoided. Care was taken to ensure adequate nutrition prior to exercise sessions

Study Year Language	Participants	Interventions	Control	Outcomes
Dodd (LIMIT) 2011	Inclusion criteria: • Singleton, live gestation between 10 to 20 weeks gestation • Obese or overweight at their first antenatal visit. Exclusion criteria: • Multiple pregnancy • Pre-existing type 1 or 2 diabetes Number of participants Intervention 1108 Control 1104	Intervention: A combination of dietary, exercise and behavioural strategies, delivered by a research dietician and trained research assistants. Balanced diet containing carbohydrates, fat and protein was encouraged. They were asked to reduce refined carbohydrates and saturated fats, and increase intake of fibre, and consume two serves of fruit and five serves of vegetables each day. Women were encouraged to adopt a more active lifestyle, mainly by increasing the amount of walking. Interventions were tailored by stage theories of health decision making that suggests individuals' progress through a series of cognitive phases when undertaking behavioural change. Initially, as part of a planning session with a research dietician, women were given written dietary and activity information, tailored diet and physical activity plan, a diary and recipe book. Women were encouraged to set their own goals for lifestyle changes and monitor their progress with support from the research team. They were also asked to identify	Usual hospital guidelines, with no routine provision of dietary, lifestyle and behavioural recommendations.	Primary • Large for gestational age infant (birth weight ≥ 90th centile for gestational age). Secondary • Preterm birth (< 37 weeks gestation); • Mortality (stillbirth or infant death) • Death of a live born infant prior to hospital discharge, and excluding lethal congenital anomalies • Congenital anomalies; • Infant birth weight ≥ 4000 grams; • Hypoglycaemia requiring intravenous treatment • Admission to NICU or SCBU • Hyperbilirubinaemia requiring phototherapy; • Nerve palsy • Fracture • Birth trauma • Shoulder dystocia. • Maternal hypertension and pre-eclampsia • Maternal gestational Diabetes

	the barriers to achieving their goals. They were supported at regular intervals throughout their pregnancy, by the research dietician (at 28 weeks' gestation) and trained research assistants (telephone calls at 22, 24, and 32 weeks' gestation and a face-face interview at 36 weeks' gestation).	• Antenatal hospital stay • Antepartum haemorrhage requiring hospitalisation; • Preterm prelabour ruptured membranes; • Chorioamnionitis requiring antibiotic use during labour; • Need and reason for induction of labour • Any antibiotic use during labour • Caesarean section; • Postpartum haemorrhage (defined as blood loss $\geq$ 600 mL); • Perineal trauma • Wound infection; • Endometritis • Use of postnatal antibiotics • Length of postnatal hospital stay; • Thromboembolic disease • Maternal death.

Study Year Language	Participants	Interventions	Control	Outcomes
Guelinckx 2010 English	Inclusion criteria: • Obese (BMI >29.0, IOM criteria) • White women with gestational age less than 15 weeks consecutively attending the antenatal clinic Exclusion criteria: • Pre-existing diabetes or developing GDM • Multiple pregnancy • Gestational age > 15 weeks • Premature labour (< 37 weeks) • Special nutritional needs such as metabolic disorder, allergic conditions kidney problems and Crohn disease • Suboptimal knowledge of Dutch language Number of participants Intervention (Active)	Lifestyle intervention based on a brochure or on active education; Passive group: Provided with a brochure containing information on diet, physical activity and tips to limit gestational weight gain at the first antenatal consultation. Active group: Received same brochure and also actively counselled by a trained nutritionist (IG) in 3 group sessions at 15, 20, and 32 weeks gestation. The sessions had up to 5 women and lasted one hour each. Counselling on balanced diet was based on the official National Dietary Recommendations (Energy intake: 9 - 11% proteins, 30 -35% fat, and 50 - 55% carbohydrates). Aim was to limit intake of energy-dense foods, replacing with healthier alternatives such as fruits, increasing whole-wheat grains and low-fat dairy products, and reducing saturated fatty acids. General topics such as energy balance, body composition, food labels, and physical activity were discussed. Tips for behavioral modification to reduce emotional eating and binge eating, were provided. Total energy intake was	No intervention	• Pregnancy-induced hypertension, preeclampsia, chronic hypertension • GWG in accordance with IOM • GWG >11.2 kg, (weight gain from prepregnancy to 38 weeks) • Gestational age at delivery • Induction of labour • Caesarean section • Birth weight/length • Macrosomia (Birth weight>4000g) • Total physical activity score

65 Intervention (Passive) 65 Control 65	not restricted in any group but aimed to do so indirectly by limiting the intake of energy-dense foods. Nutritional data were obtained from 7-d dietary records. A Physical Activity score was calculated for each trimester of the pregnancy by using the Baecke questionnaire.

Study Year Language	Participants	Interventions	Control	Outcomes
Harrison 2013 English	Inclusion criteria: • Gestational age 12-15 weeks • Overweight (body mass index; BMI ≥ 25 or ≥ 23 kg/m2 if high-risk ethnicity [Polynesian, Asian, and African populations] or obese (BMI ≥ 30 kg/m2), • Increased risk of GDM as per a validated risk prediction tool. • Willing to complete an oral glucose tolerance test at 28 weeks gestation instead of the standard glucose challenge test at GDM screening Exclusion criteria: • Multiple pregnancies • Type 1 or 2 diabetes • BMI ≥ 45 kg/m2 • Preexisting	Individual four sessions behavior change lifestyle intervention in antenatal clinic setting at 14-16, 20, 24, and 28 weeks gestation. The intervention was based on the Social Cognitive Theory, adapted from the study group's earlier lifestyle intervention program (HeLP-her). The sessions were delivered by a health coach (exercise physiologist) Healthy eating and physical activity was encouraged along with specific dietary advice in pregnancy. Behavioral change strategies were aimed at identifying short-term goals and promoting self-efficacy and self-monitoring. Goals included lifestyle changes such as reducing high fat or convenience foods, increasing fruit/vegetable intake, and increasing frequency of physical activity. Participants themselves set goals. Pedometers and weight gain charts based on IOM recommendations were provided to monitor the progress. Written Australian dietary and physical activity	A single brief education session based on Australian Dietary and Physical Activity Guidelines was provided along with written versions of guidelines. GWG was not discussed	Primary • Gestational weight gain (weight was measured at baseline; 12, 16 and 28 weeks gestation Secondary • Diagnosis of GDM as per Australasian Diabetes in Pregnancy Society (ADIPS) criteria. IADPSG criteria were also evaluated • Physical activity using pedometer and International physical activity questionnaire (IPAQ) • Risk perception for GDM development and excess gestational weight gain (four-point Likert scale adapted from the theory of health Stage of Change was used)

	• chronic medical conditions • Non-English-speaking Number of participants Intervention 121 Control 107	guidelines and other resources to encourage optimal health, GWG, and lifestyle were provided

Study Year Language	Participants	Interventions	Control	Outcomes
Jeffries 2009 English	Inclusion criteria: Pregnant women with gestational age ≤ 14 weeks gestation Exclusion criteria: • Age <18 or >45 years • Non-English speaking • Multiple pregnancy • Type 1 or 2 diabetes mellitus Number of participants Intervention 148 Control 138	Women allocated to the intervention group were given personalized weight measurement card including information on optimal gestational weight gain (based on their BMI at the time of recruitment and the US Institute of Medicine guidelines) and were asked to record their weight at 16, 20, 24, 28, 30, 32, and 34 weeks' gestation. Patient was allowed to choose to measure weight at hospital or at home	No intervention	• Gestational weight gain- weekly and total from 11 weeks to delivery (and compliance with IOM recommendation) • Birth weight • SGA and LGA (weight< 10 centile and >90 centile) • Preterm delivery • Instrumental delivery • Caesarean delivery • Pre-eclampsia • Pregnancy-induced hypertension • Gestational Diabetes Mellitus • Apgar score <7 at 5 min • Hypoglycaemia • Shoulder dystocia • Gestational age at delivery

Study Year Language	Participants	Interventions	Control	Outcomes
Khoury 2005 English	Inclusion criteria: • Age 21 to 38 years • BMI of 19 to 32 kg/m2 • Non-smokers or ex-smokers (quit ≥ 5 years ago) • Not immigrants to Norway from non-Western countries • Single healthy fetus at 17-20 weeks gestation on ultrasound • No previous pregnancy complications • 1st, 2nd or 3rd pregnancy • Not vegetarian or following a Mediterranean-type diet Exclusion criteria: • High-risk pregnancies caused by: diabetes, endocrine disease, hypertension, drug abuse,	Diet/dietary advice – cholesterol-lowering diet from gestational week 17 to 20 to birth. Dietitian visits were arranged at inclusion, and at 24, 30, and 36 weeks gestation. Aims of dietary intervention were to: • Limit dietary cholesterol to 150 mg/day • Reduce the intake of saturated fat to 8% of dietary energy • Target total fat 32% of total energy intake (including 8%-9% of energy from polyunsaturated fat and 16%-17% from monounsaturated fat), protein 16% to 17% of energy, and carbohydrates 50% to 51% of energy. • Tailor energy intake for target at a weight gain of 8 to 14 kg from prepregnancy levels. • Encourage the intake of fatty fish, vegetable oils, mainly olive oil and rapeseed oil, nuts, nut butters, margarine based on olive- or rapeseed oil, • At least 6 a day of fresh fruits and vegetables was advised (at least 6 a day) • Prefer low-fat dairy products	Control group was advised to consume their usual diet, not to introduce more oils, low-fat meat and dairy products than usual; Target weight gain was 8-14 kg and energy intake breakdown of fats, carbohydrate and proteins was same as intervention group.	• Gestational age at delivery • Preterm delivery • Maternal weight gain between inclusion and week 30 • Preterm stillbirth • Intrauterine growth restriction • Hypertensive complications (pregnancy induced hypertension/ preeclampsia • Fetal distress • Birth weight • Maternal and neonatal lipid profile

	thromboembolic disease or significant cardiac, gastrointestinal, pulmonary, or hematologic disease • History of neonatal death, stillbirth, preterm delivery, or recurrent abortion (more than 3 previous spontaneous abortions) • Ongoing hyperemesis gravidarum or bleeding after gestational age of 12 weeks in the current pregnancy Number of participants Intervention 141 Control 149	Subjects were advised to have meat for a main meal twice a week and use legumes, fatty fish, poultry etc on other days. Cooking lessons were arranged for special foods. Coffee was limited to 2 cups/day.

Study Year Language	Participants	Interventions	Control	Outcomes
Nascimento 2011 English	Inclusion criteria: • Pregnancy • Pre-pregnancy overweight (BMI 26.0–29.9 kg/m2) or obesity (BMI ≥ 30.0 kg/m2) • Age ≥ 18 years • Gestational age 14 to 24 weeks Exclusion criteria: • Multiple pregnancy • Exercising regularly • Contraindications for exercise, such as cervical incompetence, severe hypertension, diabetes with vascular complications and risk of abortion. Number of participants Intervention 39 Control 41	Exercise protocol; Women performed exercise weekly under the guidance of a trained physical therapist. The exercises were light to moderate intensity exercises, with heart rates note exceeding 140 beats per minute. (ACOG recommendations). Standardised research protocol consisting of 22-exercise sequence was followed. Group or individual exercises lasted 40 minutes with 10 minutes of general stretching, 22 minutes of exercises to strengthen the limb muscles, and 10 minutes of guided relaxation. Home exercise counseling. Women were counseled on home exercise to be done 5 times/week, with exercises from the protocol or walking. They were required to note the details of daily exercise in a monthly exercise book.	Routine antenatal advice and standard nutritional counselling. They were not provided physical activity counselling	Primary • Gestational weight gain • Excessive maternal weight gain Secondary • Increased blood pressure • Perinatal outcomes – caeserian section, newborn weight, gestational age at delivery, preterm birth, Apgar scores at 1 and 5 minutes, LGA, SGA • Quality of life (WHOQOL – BREF questionnaire)
Ong 2009	Inclusion criteria:	Physical activity: home-based	No intervention	• Weight gain from 18 to 28

English	• Singleton pregnancy • Normal 18 week anatomy scan • No evidence of cardiovascular disease • No preexisting diabetes Number of participants Intervention 6 Control 6	exercise programme beginning at week 18 of gestation Three sessions per week of stationary cycling – home-based supervised exercise; Exercise training was performed at home on an upright stationary cycle ergometer provided to each participant for the study period. Each session consisted of a 10 min warm-up followed by one or two 15 min bouts of cycling (with rest periods if necessary). Exercise intensity was controlled by heart rate initially aimed at 50–60% HRmax and later increased to 60–70% HRmax. The duration was later increased to 40–45 min. Sessions ended with a 10 min cool-down period of slow pedalling.		weeks • Post-intervention glucose and insulin levels on oral glucose tolerance test

Study Year Language	Participants	Interventions	Control	Outcomes
Perales 2014 English	Inclusion criteria: • Pregnant women living in Madrid, Spain who underwent ultrasound examination within 12 weeks gestation Exclusion criteria: • Absolute obstetrical contraindication to exercise (as per American College of Obstetricians and Gynecologists (2002) • Plans to deliver baby elsewhere • Not receiving antenatal care throughout the pregnancy • Participating in another physical activity program • Regular exercise before pregnancy (four or more times per week).	The program consisted of three 55-60 minutes sessions thrice weekly from 9-12 weeks gestation to end of pregnancy (39-40 weeks gestation). Each session consisted of warm-up (5-8 minutes), aerobic dance and resistance exercises for muscle groups of legs, buttocks and abdomen to stabilize the lower back (25 minutes), balancing exercises (10 minutes), pelvic floor muscle training (10 minutes) and a cool-down (5-8 minutes). Exercises in supine position were limited to 2 minutes and extreme stretching, jumping, ballistic movements, overextension of joints and exercises involving valsalva maneuver were specifically avoided. The exercise intensity was light to moderate and was guided by the target heart rate (55-60% of maximum heart rate) for each participant displayed on a poster. All participants wore heart rate monitors during exercise sessions. Karvonen's formula based on trimester, physical condition and age was used to calculate maximum heart rate. Borg scale	Usual care	• Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire for depression at 9-12 weeks gestation and end of pregnancy • Gestational weight gain • Percentage of women with excessive weight gain (as per IOM guidelines) • Percentage of women with adequate weight gain (as per IOM guidelines) • Gestation age at delivery • Mode of delivery (Normal, instrumental, Caesarian section) • Birth weight • Birth length • Head circumference • APGAR score at 1 minute • APGAR score at 5 minutes

	Number of participants Intervention 101 Control 83	ratings were also used to adjust the intensity of exercise. Sessions had groups of 10-12 women and were supervised by a qualified fitness specialist and assisted by an obstetrician. The venue was a spacious well-lit room in a hospital (altitude 600 m, temperature 19–21 degrees C, and humidity 50 –60%) and sessions were accompanied by music. Care was taken to ensure adequate nutrition prior to exercise sessions.

Study Year Language	Participants	Interventions	Control	Outcomes
Petrella 2013 English	Inclusion criteria • Women with singleton pregnancies, • pre-pregnancy BMI ≥ 25 kg/m2 and age > 18 years were recruited during twelfth week of gestation from antenatal clinics. Exclusion criteria • Twin pregnancy • Chronic conditions such as diabetes mellitus, hypertension and untreated thyroid diseases • Other medical conditions known to affect body weight • Previous gestational diabetes mellitus • Smoking during pregnancy • Previous bariatric surgery	Diet: The intervention group diet was initiated at randomisation by a gynecologist and a dietitian who provided further 1-hour counseling on recommended weight gain in pregnancy for each BMI category. The calorie allowance was 1500 kcal/day with an extra 200 kcal/day for obese women and 300 kcal/day for overweight women to account for physical activity program. The target diet composition was 55% carbohydrate (80% complex, low-Glycemic Index), 20% protein (50% animal and 50% vegetable) and 25% fat (12% mono-unsaturated, 7% poly-unsaturated and 6% saturated fat) given as three main meals and three snacks. The last snack was 2 hours after dinner to prevent overnight hypoglycaemia. The minimum recommended intake of carbohydrates was 225 g/day. Urine was examined for ketonuria thrice during pregnancy. Exercise: The exercise intervention was in line with recommendations for the general population. Women were advised	The Control group received a simple nutritional booklet based on Italian guidelines for a healthy diet during pregnancy	Primary • Rate of women with weight gain exceeding the ranges recommended by IOM for each BMI category. Secondary • Diagnoses of gestational diabetes mellitus • Gestational hypertension • Rate of preterm delivery.

	• Women who just started regular physical activity, or used herbal products or dietary supplements known to affect body weight, • Not intending to deliver at the study centre Number of participants Intervention 33 Control 30	30 min of moderate intensity activity for a minimum of 3 days a week. Adherence was checked by a pedometer. Women were advised that the exercise intensity should allow them to maintain a conversation ('talk test')	

Study Year Language	Participants	Interventions	Control	Outcomes
Poston (UPBEAT trial) 2015 English	Inclusion criteria: Women with singleton pregnancy between 15 to 18^{+6} weeks gestation and BMI ≥ 30 at first antenatal appointment Exclusion criteria: • No informed consent • Outside 15 to 18^{+6} weeks gestation • Multiple pregnancy • Medical disorders including essential hypertension requiring treatment, pre-existing renal disease, systemic lupus erythematosus, sickle cell disease, antiphospholipid syndrome, thalassemia, coeliac disease, thyroid disease • Current psychosis • On metformin. Number of participants	One-to-one interview at baseline with a health trainer specifically trained for the study, followed by 8 weekly sessions of 1 to 1.5 hours each. Women are encouraged to attend all and strongly recommended to attend a minimum of 5 sessions with other sessions covered by phone or email. Health trainers cover specific goal setting, self-monitoring, and feedback on performance, problem solving and use of social support. Women were provided with handbook, DVD of recommended exercise regime, pedometer, logbook for recording weekly goals and steps achieved through pedometer. Exercise advice: to increase pedometer steps and daily activity incrementally; moderate activity in the form of walking encouraged in line with UKRCOG recommendations, with more options depending on baseline activity Diet: To promote healthier eating with no restriction of calories, substitute low-GI for medium/high-GI food, restrict sugar-sweetened beverages but	Routine antenatal care, explaining the risks of obesity, advising on healthy diet and safe levels of physical activity	Primary: • Diagnosis of gestational diabetes according to IADPSG criteria • Large for gestational age baby (>90th weight centile) Secondary: • Preeclampsia • Mode of delivery • Induction of labour • Blood loss at delivery • Inpatient nights • Gestational weight gain • Fasting glucose, insulin, Insulin resistance at 28 weeks gestation • Referral to antenatal clinic after OGTT • Foetal growth at 28 weeks • Insulin or metformin treatment in pregnancy • Quality of life • Anthropometry including mid-arm, hip, thigh circumference and skin-fold thickness • Fructosamine, lipid profile • Epigenetic, urinary and metabolomic biomarkers • Diet and physical activity • Depression • Smoking

	Intervention 783 Control 772	not fruit and reduce saturated fatty acid intake.	• Birthweight of baby • Gestational age at delivery • Neonatal death • Neonatal complications • Baby's anthropometry including head/abdominal circumference and skin-fold thickness • Epigenetic and other markers • Infant feeding habits and anthropometry at 6 months

Study Year Language	Participants	Interventions	Control	Outcomes
Rauh 2013 English	Inclusion criteria: • Age > 18 years • Singleton pregnancy • Gestational age < 18 weeks • BMI: ≥ 18.5 kg/m2 • Language skills: "sufficient" German. Exclusion criteria: • Contraindication to physical activity, such as cervical incompetence, placenta praevia, or persistent bleeding. • Prepregnancy diabetes • Uncontrolled chronic diseases affecting weight such as thyroid dysfunction or psychiatric diseases Number of participants Intervention 4 practices (167) Control 4 practices	The intervention group received two individual counseling modules at 20th and 30th weeks of gestation, the first session lasting 60 minutes and the second 30 minutes. General lifestyle advice including nutrition, physical activity and appropriate gestational weight gain was provided. Healthy nutrition and energy balance as per German Nutrition Society were explained. The dietary goals were to reduce the intake of high-fat and energy dense foods and increase the intake of low-fat foods and fruits, whole grain foods and vegetables. Women were encouraged to consume more fish and advised regarding appropriate fat/cooking oil/spreads. Physical activity equivalent to 30 minutes of moderate intensity exercises on most days was recommended. Non-weight bearing endurance exercises such as walking, swimming, aquatic exercises and cycling were suggested. Women were also provided with information on local antenatal exercise programs and encouraged to join them. The	Routine antenatal care including an information leaflet consisting of ten general statements on a healthy lifestyle during pregnancy not including advice on diet or gaining weight.	Primary: • Proportion of pregnant women exceeding IOM recommendations for weight gain Secondary: • Postpartum weight retention (Self-reported weight at 4 months postpartum minus prepregnancy weight) • Birth weight • Birth length • Gestational diabetes/ Impaired glucose tolerance • Mode of delivery (spontaneous, caesarian, vacuum) • Induction of labour • Preterm delivery • Infant sex • Large for gestational age • Small for gestational age

(83)	exercise recommendations were based on the guidelines of American College of Obstetricians and Gynecologists (ACOG) and Society of Obstetricians and Gynecologists (SOGC) of Canada. Women were provided with personalized weight charts as per BMI category including IOM recommendations for that category. They were asked to monitor their weights on a weekly basis. The individual counseling sessions also provided personalized feedback on diet and physical activity based on the 7-day records of diet and physical activity questionnaires

Study Year Language	Participants	Interventions	Control	Outcomes
Ruiz 2013 English	Inclusion criteria • Sedentary (not exercising > 20 min on > 3 days a week • Singleton • Uncomplicated pregnancy • Not at high risk of preterm delivery (≤ previous preterm delivery) • No participation in any other trial Exclusion criteria • Contraindication to exercise Number of participants Intervention 481 Control 481	The programme consisted of supervised 50-55 minute physical activity sessions thrice weekly from week 9 to weeks 38-39 with an estimated average of 85 sessions per participant. Each group consisting of 10-12 women. The exercise activity was of light to moderate intensity with a target heart rate of ≤ 60% of maximum predicted heart rate for age (208-[0.7 x age in years]). All participants were provided heart rate monitors. Intensity was also guided by Borg's conventional (6-20 point) scale with the rate of perceived exertion ranging from 10 to 12 ('fairly light' to 'somewhat hard'). Each session included warm-up (10 minutes), core session (25-30 minutes) and a cool-down period (10 minutes). Warm-up and cool-down components involved walking and light stretching exercises for limbs, neck and trunk. Additionally, the cool-down period included relaxation and pelvic floor exercises. The core portion involved moderate intensity aerobic exercises once weekly and	Usual care with regular scheduled visits to obstetricians and midwives. Information Healthcare professionals provided nutrition and physical activity counseling and they were not discouraged from exercising	Primary: • Gestational weight gain (Weight at last clinic visit before delivery minus weight at first antenatal weight) Secondary: • Gestational diabetes • Hypertension • Gestational age at delivery • Type of delivery (Natural, instrumental or cesarean) • Time of dilation, expulsion and childbirth • Birth weight • Low birth weight • Macrosomia

	resistance exercises twice a week. Aerobic dance took place for periods of 3 to 4 minutes with 1-minute breaks and included stretching and relaxation. Resistance exercises for pectoral muscles, back, shoulder, upper and lower limb muscles aimed to improve posture, strengthen muscles of labour and pelvic floor and prevent lower back pain. They involved exercises using barbells (3 kg/exercise) or low-to-medium resistance elastic and included biceps curls, arm side lifts and extensions, shoulder elevations, bench press, seated lateral row, leg circles and lateral leg elevations, knee (hamstring) curls and extensions, ankle flexions and extensions. Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided. Supine exercises were limited to a maximum of 2 minutes.	

Study Year Language	Participants	Interventions	Control	Outcomes
Stafne 2012 English	Inclusion criteria: • White women ≥ 18 years • Singleton live fetus. Exclusion criteria: • High-risk pregnancies • Diseases that could interfere with participation • Women who lived too far (more than 30-minute drive) from the hospitals Number of participants Intervention 375 Control 327	Standardized exercise program including aerobic activity, strength training, and balance exercises supervised by a physiotherapist. Training sessions in groups of 8–15 women offered once weekly for 12 weeks (between 20 to 36 weeks of gestation). Each session lasted 60 minutes. A written 45-minute home exercise program (30 minutes of endurance training and 15 minutes of strength/balance exercises) was recommended twice weekly and women were asked to record the exercise activities in personal training diaries. Physical activity was also assessed by questionnaires	Usual care, not discouraged from exercising. Written recommendatio ns on diet, pelvic floor exercises and pregnancy - related lumbo-pelvic pain	Primary: • Prevalence of GDM at 32-36 weeks gestation • Insulin resistance estimated by the homeostasis model assessment method Secondary: • Maternal weight at follow-up • Weight gain at follow-up • Body mass index at follow-up • Preeclampsia • Gestational hypertension • Caesarean delivery • Operative vaginal delivery • Gestational age at delivery • Birth weight • Birth weight at least 4000 g • Apgar score • Admission to NICU

Study Year Language	Participants	Interventions	Control	Outcomes

Vitolo 2011 Portuguese	Inclusion criteria • Pregnant women between 10 to 29 weeks gestation Exclusion criteria: • Positive HIV test • Previous diagnosis of diabetes • Hypertension • Anemia • Any conditions preventing women from undertaking exercise in pregnancy • Age above 35 years Number of participants Intervention 159 Control 162	Dietary counseling according to nutritional status. For pregnant women with low birth weight, was adopted as a priority to increase the energy density of the diet with the addition of a tablespoon of oil in the main meals, eat two snacks per day of high energy (with sample portions) 100 g kid once a week and fruit daily. For normal weight pregnant women, it was directed fractionate the power six times a day, daily servings of vegetables, legumes, fruit and water; restrict the consumption of foods high in fat and oil preparations. For pregnant women with excess weight, between meals (three to four hours) were prioritized; not repeat the food portions of meals and snacks; restrict daily consumption of soft drinks and sweets, processed foods high in fat and also oil preparations. They were determined daily servings of vegetables, vegetables and fruit. All guidance provided values and portion sizes.	The control group did not receive the dietary guidelines, but were informed about the nutritional status that had, and were asked to perform the prenatal care.	• Gestational weight gain • Diabetes • Preeclampsia • Infant birth weight • Prematurity
Walsh 2012 English	Inclusion criteria: • Secundigravid women with previous macrosomic infant (birthweight > 4 kg)	One two-hour dietary education session with the research dietitian in groups of two to six women. The diet was in line with current recommendations for pregnant	Routine antenatal care with no specific dietary recommendatio	Primary: • Mean birth weight centiles and ponderal indices at 14, 28 and 34 weeks gestation, at birth and 3 months post-partum

Number of participants Intervention 394 Control 406	were recruited at first antenatal consultation. Exclusion criteria: • Women with medical disorders including history of gestational diabetes, • those on any drugs, and those unable to give full informed consent were excluded. • Age less than 18 years • Gestational age greater than 18 weeks • Multiple pregnancy	women. General advice on healthy eating in pregnancy and following the food pyramid was provided. Women were taught about the rationale for having low glycaemic index food and encouraged to replace high glycaemic index carbohydrates for low glycaemic index alternatives. Written resources were provided after the education session. Women were not advised to reduce their total caloric intake. The research dietitian met again at 28 and 34 weeks' gestation to reinforce the advice and clarify any doubts. All women completed three food diaries of three days each—before dietary intervention, in the second and third trimesters of pregnancy. A questionnaire was provided at 34 weeks visit to assess adherence to the diet. It was based on a five point Likert-type scale (1="I followed the recommended diet all of the time"; 5="I followed the recommended diet none of the time").	n or advice about gestational weight gain.	Secondary: • Maternal weight gain at 14, 28 and 34 weeks gestation, at birth and 3 months post-partum • Adherence to IOM recommendations for gestational weight gain • Maternal glucose intolerance

Wolff 2008 English Number of participants Intervention 28 Control 38	Inclusion criteria: • Caucasian • BMI ≥30 kg/m 2 • Early pregnancy (15 ± 3 weeks of gestation) • Non-diabetic at inclusion Exclusion criteria: • Smoking • Age below 18 or above 45 years • Multiple pregnancy • Medical complications known to affect fetal growth adversely • Contraindication for limiting weight gain	10-h dietary consultations (healthy diet, restriction of energy intake): The intervention group received 10 consultations of 1 hour each with a trained dietitian during the pregnancy. Women were asked to eat a healthy diet according to the official Danish dietary recommendations [fat intake: max 30 energy percent (E%), protein intake: 15–20 E%, carbohydrate intake: 50–55 E%]. Energy intake was restricted on the basis of individually estimated energy requirements and estimated energy requirements of fetal growth (energy requirement=basal metabolic rate x 1.4 (physical activity level factor of 1.2 + 0.2 added to cover energetic cost of fetal growth).	No intervention	• Gestational diabetes mellitus • Gestational age at delivery • Pregnancy induced hypertension • Preeclampsia • Prolonged pregnancy • Cesarean delivery, • Total gestational weight gain (Weight at delivery minus self-reported pre-pregnancy weight) • Weight gain from 15 weeks to 36 week • Birth weight • Placental weight • Infant length • Head circumference • Abdominal circumference

Yeo 2000 English Number of participants Intervention 8 Control 8	Inclusion criteria: • ≥ 18 years old • High risk of gestational hypertensive disorders (Mild hypertension, history of gestational hypertensive disorders or family history of hypertensive disorders) Exclusion criteria: • Diabetes mellitus • Renal disease • Multiple pregnancies • Extremely vigorous exercisers (more than 3 times per week at a level above RPE 14 for longer than 30 min per session)	Exercise of moderate intensity. Exercise sessions of 30 minutes each were held in a laboratory three times a week A motorized treadmill and bicycle ergometer were alternated. Exercise consisted of a five-minute warm-up using the Branching protocol, followed by a 30-minute steady state, and ended with a 10 minute cool down. Steady state was defined as RPE 13, which was considered a moderate level of exercise.	No intervention	• Resting blood pressure before and after 10 weeks of exercise • Mean Percentage body fat of mother • Percentage of time/energy spent on light/moderate /heavy exercise

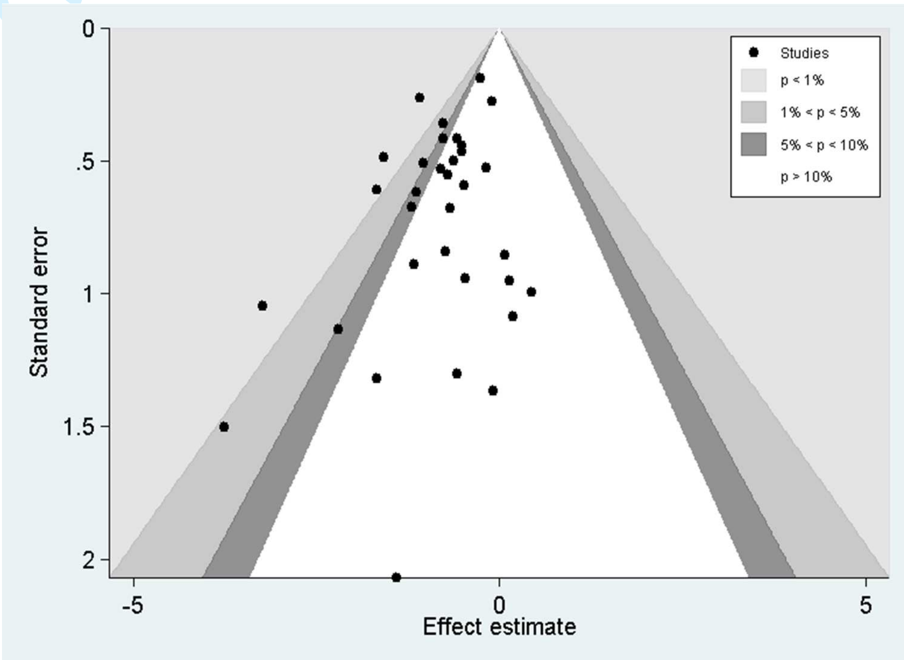
Yeo Unpublished (Protocol) English	Inclusion criteria Gestational age less than 12 weeks gestation plus one or more of the following: • History of preeclampsia • Type 2 diabetes • Chronic hypertension • BMI ≥ 30 kg/m2 either pre-pregnancy or at first visit in the first trimester for primiparous women • Diastolic blood pressure ≥ 90 mmHg before 12 weeks gestation Exclusion criteria: Any of the following conditions- • Multiple pregnancy • Vaginal bleeding • Diagnosed placenta previa • Antenatal care provider or primary care provider's objection to participation in the study • Any condition prohibiting regular	There are two intervention groups, walking exercise and stretching and the intervention runs for 10 weeks and involves 30 minute activity three times a week. The participants are free to choose the days of exercise provided they have a rest day between two exercise days. Research staff will train both groups for the first 2 weeks. Subsequently one session per week will be supervised and the remaining two unsupervised. Childcare facilities are arranged either onsite or by arranging exercise venues with child care arrangements. The Walking group: Walking exercise consists of 30 minutes moderate intensity walking in an environment (home, gym, workplace, neighborhood) agreed with the research staff. The exercise intensity is guided by a heart rate monitor and the Rate of Perceived Exertion (RPE). Women are advised to maintain the heart rate to 55-69% of age determined maximum heart rate (HR_{MAX}) and are guided by the digital screen on their wrists that senses information from the chest belts they wear. The suggested Rate of Perceived Exertion is 12	Research nurse visits for 30 minutes every other week to take measurements and is allowed to answer any queries related to healthy pregnancy and lifestyle	• Recruitment Rate - 15 subjects in 3 months • Feasibility of walking and stretching exercise: 85% of frequency and dropout rate within 5 weeks < 10% due to social and behavioral reasons (excluding obstetrical reasons) • Feasibility of collecting scheduled blood samples, and establishing a protocol for measuring superoxide dismutase • Sample size estimation for a larger study

	exercise (walking exercise and stretching) between 12 to 22 weeks gestation • Inability to complete questionnaires or communicate with research staff • Already exercising more thrice weekly during the first 11 weeks of pregnancy The women are divided into 3 groups: Walking, stretching, and standard care Data unpublished	or 13. If there is a discrepancy between heart rate and RPE, they are advised to keep both within/below the recommended limits. Stretching group: This consists of 30 minutes of stretching exercise thrice weekly without increasing the heart rate by more than 10% of the resting heart rate. The exercise involves slow muscle movements without aerobic or muscle resistance components, and participants are guided by a videotape showing recommended movements

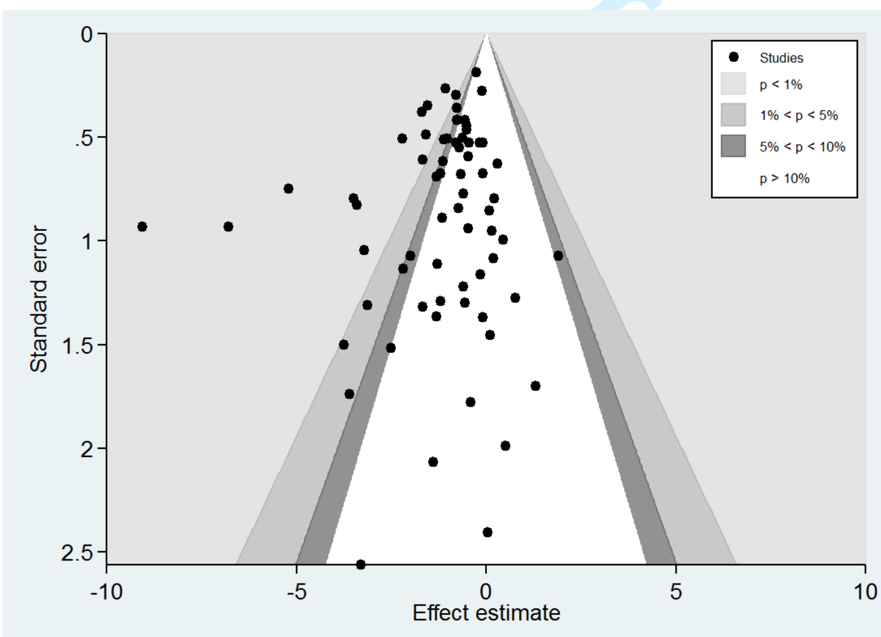
Appendix 3 Assessment of small study effects on trials in IPD meta-analysis of diet and physical activity based interventions in pregnancy

a. Gestational weight gain

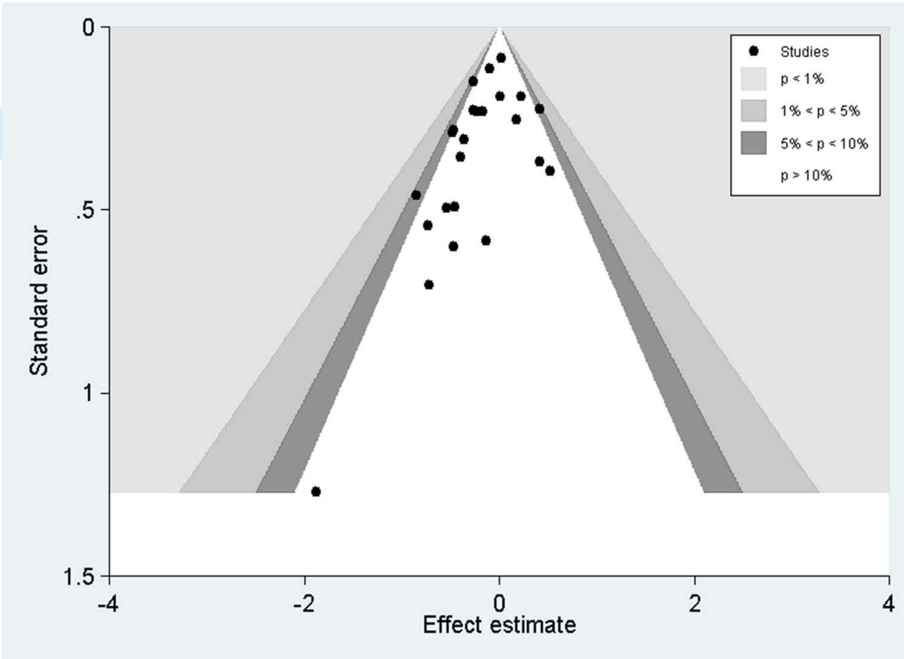
IPD studies



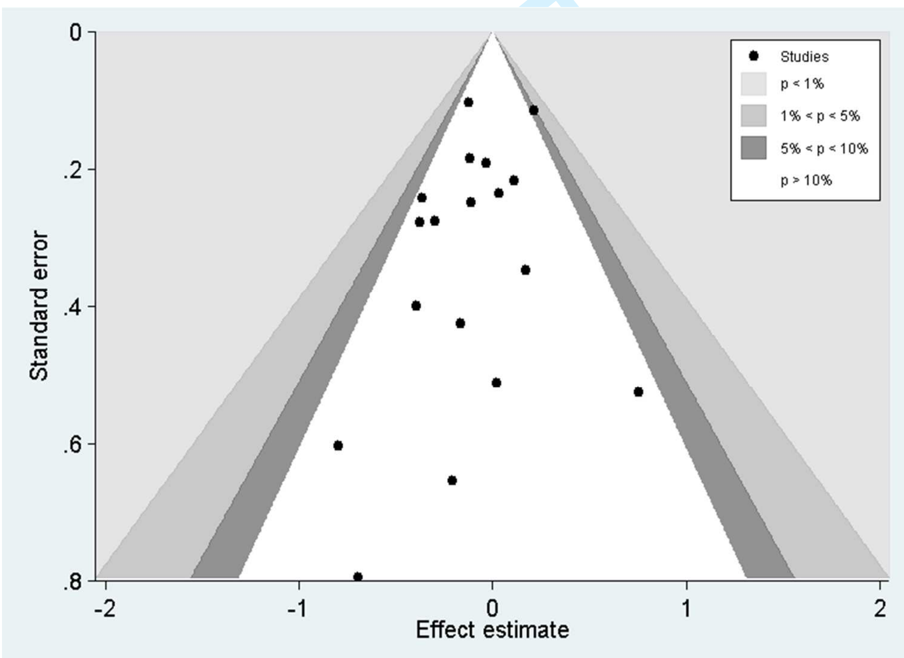
IPD and non-IPD studies



b. Maternal composite outcome



c. Offspring composite outcome



Appendix 3 Subgroup effects for effects of diet and physical activity based interventions, and interactions with the effect modifier baseline body mass index for individual complications

a. adverse maternal outcomes

Outcome	**Subgroup**	**No. of women (No. of studies)**	**Summary Odds Ratio, 95% CI**	**Pooled Treatment-covariate interaction*, 95% CI**	**95% Prediction interval**	**I^2**
Pre-eclampsia or Pregnancy Induced Hypertension	Normal weight	3,402 (6)	0.65 (0.23, 1.8)		(0.07, 6.02)	58.2%
	Overweight	6,181 (10)	0.91 (0.62, 1.32)		(0.62, 1.33)	0.0%
	Obese	7,749 (12)	1.14 (0.91, 1.42)		(0.91, 1.42)	0.0%
	Overweight vs normal	3,148 (8)		1.24 (0.46, 3.36)	(0.2, 7.64)	16.6%
	Obese vs normal	2,501 (8)		1.99 (0.71, 5.56)	(0.55, 7.26)	0.0%
	Obese vs overweight	4,531 (11)		1.35 (0.82, 2.21)	(0.81, 2.23)	0.0%
Gestational diabetes	Normal weight	3,805 (11)	0.99 (0.62, 1.58)		(0.42, 2.3)	18.3%
	Overweight	6,303 (14)	1.13 (0.74, 1.72)		(0.51, 2.51)	3.0%
	Obese	7,540 (16)	1.05 (0.87, 1.28)		(0.87, 1.28)	0.0%
	Overweight vs normal	3,503 (12)		0.92 (0.4, 2.1)	(0.17, 4.94)	16.4%
	Obese vs normal	2,849 (12)		1.05 (0.44, 2.51)	(0.24, 4.67)	1.6%
	Obese vs overweight	3,978 (13)		0.99 (0.6, 1.65)	(0.59, 1.66)	0.0%
Preterm delivery (<37 weeks)	Normal weight	4,411 (9)	1.08 (0.68, 1.72)		(0.67, 1.74)	0.0%
	Overweight	6,932 (12)	1.03 (0.67, 1.56)		(0.67, 1.57)	0.0%
	Obese	8,511 (14)	0.91 (0.61, 1.36)		(0.46, 1.83)	0.0%
	Overweight vs normal	2,660 (7)		1.11 (0.42, 2.93)	(0.4, 3.08)	0.0%
	Obese vs normal	2,143 (7)		0.8 (0.24, 2.63)	(0.23, 2.79)	0.0%
	Obese vs overweight	4,376 (11)		0.56 (0.3, 1.06)	(0.3, 1.07)	0.0%
Any Caesarean section	Normal weight	5,758 (18)	0.86 (0.7, 1.06)		(0.7, 1.06)	0.0%
	Overweight	9,064 (24)	0.99 (0.82, 1.2)		(0.82, 1.2)	0.0%
	Obese	10,643 (26)	0.92 (0.81, 1.05)		(0.81, 1.05)	0.0%
	Overweight vs normal	5,217 (19)		1.07 (0.76, 1.51)	(0.72, 1.6)	0.0%
	Obese vs normal	4,248 (19)		0.88 (0.55, 1.41)	(0.44, 1.79)	0.0%
	Obese vs overweight	6,131 (28)		0.91 (0.69, 1.2)	(0.69, 1.2)	0.0%

b. adverse offspring outcomes

Outcome	Subgroup	No. of women (No. of studies)	Summary Odds Ratio, 95% CI	Pooled Treatment-covariate interaction*, 95% CI	95% Prediction interval	I²
Small for gestational age fetus	Normal weight	6,001 (16)	1.14 (0.9, 1.46)		(0.9, 1.46)	0.0%
	Overweight	8,812 (21)	1.13 (0.81, 1.57)		(0.65, 1.96)	5.9%
	Obese	10,391 (23)	0.96 (0.74, 1.24)		(0.61, 1.51)	0.0%
	Overweight vs normal	5,271 (16)		1.01 (0.57, 1.81)	(0.3, 3.46)	7.5%
	Obese vs normal	4,265 (16)		0.68 (0.35, 1.31)	(0.35, 1.32)	0.0%
	Obese vs overweight	5,467 (20)		0.65 (0.42, 1.03)	(0.42, 1.03)	0.0%
Large for gestational age fetus	Normal weight	5,634 (14)	0.81 (0.63, 1.04)		(0.62, 1.05)	0.0%
	Overweight	8,715 (20)	0.92 (0.68, 1.25)		(0.56, 1.51)	26.2%
	Obese	10,328 (22)	0.96 (0.71, 1.32)		(0.48, 1.93)	32.6%
	Overweight vs normal	3,881 (12)		1.19 (0.7, 2.04)	(0.54, 2.65)	29.0%
	Obese vs normal	3,067 (12)		1.38 (0.79, 2.41)	(0.78, 2.43)	0.0%
	Obese vs overweight	5,956 (21)		1.04 (0.72, 1.5)	(0.72, 1.5)	0.0%
Admission to Neonatal Intensive Care Unit	Normal weight	2,736 (6)	0.96 (0.57, 1.63)		(0.54, 1.7)	0.0%
	Overweight	5,516 (10)	0.96 (0.52, 1.79)		(0.25, 3.64)	34.8%
	Obese	7,070 (11)	0.97 (0.73, 1.31)		(0.7, 1.35)	0.0%
	Overweight vs normal	2,501 (7)		0.83 (0.36, 1.92)	(0.26, 2.66)	0.0%
	Obese vs normal	1,982 (7)		1.45 (0.52, 4.08)	(0.49, 4.29)	0.0%
	Obese vs overweight	4,383 (11)		0.99 (0.35, 2.77)	(0.11, 9.24)	23.7%

*The number of studies included in subgroup and interaction analyses may not be the same. This can be due to lack of events within a BMI subgroup – the interaction between 2 subgroup can still be estimated but the subgroup effects cannot be calculated. Or, there may be no participants from a BMI subgroup in a study – allowing subgroup analysis for the other subgroups but not estimation of interactions.

Appendix 2 Characteristics of eligible randomised trials on diet and physical activity based interventions in pregnancy

a. Studies contributing IPD

Study ID	Country	Sample size*	Intervention	BMI group
Althuizen 2012	Netherlands	269	Mixed approach	All BMI groups
Baciuk 2008	Brazil	70	Physical activity	All BMI groups
Barakat 2008	Spain	140	Physical activity	All BMI groups
Barakat 2011	Spain	67	Physical activity	All BMI groups
Barakat 2012	Spain	279	Physical activity	All BMI groups
Bogaerts 2012	Belgium	197	Mixed approach (2 arms)	BMI ≥ 30
Dodd 2014	Australia	2,199	Mixed approach	BMI ≥ 25
El Beltagy 2013	Egypt	93	Mixed approach	BMI ≥ 30
Guelinckx 2010	Belgium	195	Mixed approach (2 arms)	BMI ≥ 30
Haakstad 2011	Norway	101	Physical activity	All BMI groups
Harrison 2013	Australia	238	Mixed approach	BMI ≥ 25
Hui 2011	Canada	183	Mixed approach	All BMI groups
Jeffries 2009	Australia	282	Mixed approach	All BMI groups
Khaledan 2010	Iran	39	Physical activity	All BMI groups
Khoury 2005	Norway	289	Diet	All BMI groups
Luoto 2011§	Finland	395	Mixed approach	All BMI groups
Nascimento 2011	Brazil	82	Physical activity	BMI ≥ 25
Ong 2009	Australia	13	Physical activity	BMI ≥ 30
Oostdam 2012	Netherlands	105	Physical activity	BMI ≥ 25
Perales 2014	Spain	165	Physical activity	All BMI groups
Perales 2016	Spain	163	Physical activity	All BMI groups
Petrella 2013	Italy	61	Mixed approach	BMI ≥ 25
Phelan 2011	USA	393	Mixed approach	All BMI groups
Poston 2015	UK	1,554	Mixed approach	BMI ≥ 30
Prevedel 2003	Brazil	39	Physical activity	All BMI groups
Rauh 2013§	Germany	244	Mixed approach	All BMI groups
Renault 2013	Denmark	425	Physical activity & Mixed approach (2 arms)	BMI ≥ 30
Ruiz 2013	Spain	927	Physical activity	All BMI groups
Sagedal 2016	Norway	600	Mixed approach	All BMI groups
Stafne 2012	Norway	854	Physical activity	All BMI groups
Vinter 2011	Denmark	304	Mixed approach	BMI ≥ 30
Vitolo 2011	Brazil	301	Diet	All BMI groups
Walsh 2012	Ireland	759	Diet	All BMI groups
Wolff 2008	Denmark	59	Diet	BMI ≥ 30
Yeo 2000	USA	16	Physical activity	All BMI groups
Yeo unpub	USA	18	Physical activity (2 arms)	All BMI groups

**Refers to sample size in IPD meta-analyses*
§Trials with randomisation by clUSAter

b. Studies that did not contribute IPD

Study ID	Country	Sample size*	Intervention	BMI group
Arthur 2016	Australia	400	Mixed approach	All BMI groups
Asbee 2009	USA	100	Mixed approach	All BMI groups
Aşcı 2016	Turkey	102	Mixed approach	All BMI groups
Badrawi 1993	Egypt	100	Mixed approach	BMI ≥ 30
Barakat 2012	Spain	83	Physical Activity	All BMI groups
Barakat 2013	Spain	428	Physical Activity	All BMI groups
Barakat 2014	Spain	200	Physical Activity	All BMI groups
Barakta 2015	Spain	765	Physical Activity	All BMI groups
Bisson 2015	Canada	45	Physical Activity	BMI ≥ 30
Blackwell 2002	USA	46	Diet	All BMI groups
Briley 2002	USA	20	Diet	All BMI groups
Brownfoot 2016	Australia	741	Mixed approach	All BMI groups
Bruno 2016	Australia			BMI ≥ 25
Clapp 2000	USA	46	Physical Activity	All BMI groups
Cordero 2014	Spain	247	Physical Activity	All BMI groups
Daley 2015	UK	68	Mixed approach	All BMI groups
Daly 2017	Ireland	88	Physical activity	BMI ≥ 30
Das 2015	USA	36	Diet	All BMI groups
de Oliveria Melo 2012	Brazil	171	Physical Activity	All BMI groups
Dekker 2015	USA	35	Physical Activity	BMI ≥ 30
Deveer 2013	Turkey	100	Diet	All BMI groups
Di Carlo 2014	Italy	120	Diet	All BMI groups
Garnæs 2016	Norway	91	Physical activity	BMI ≥ 25
Garshasbi 2005	Iran	212	Physical Activity	All BMI groups
Gesell 2015	USA	87	Mixed approach	All BMI groups
Gomez Tabarez 1994	Colombia	60	Diet	BMI ≥ 30
Hawkins 2015	USA	68	Mixed approach	BMI ≥ 25
Herring 2016	USA	56	Mixed approach	BMI ≥ 25
Hopkins 2010	New Zealand	84	Physical Activity	All BMI groups
Huang 2011	Taiwan	125	Mixed approach	All BMI groups
Hui 2014	Canada	113	Mixed approach	All BMI groups
Jackson 2010	USA	287	Mixed approach	All BMI groups
Jing 2015	China	221	Mixed approach	All BMI groups
Kihlstrand 1999	Sweden	258	Physical Activity	All BMI groups
Ko 2016	USA	1,124	Physical Activity	All BMI groups
Koivusalo 2015	Finland	269	Mixed approach	BMI ≥ 30
Kong 2014	USA	37	Physical Activity	BMI ≥ 25
Korpi-Hyovalti 2012	Finland	54	Diet	All BMI groups
Lee 1996	UK	353	Physical Activity	All BMI groups
Marquez 2000	USA	15	Mixed approach	All BMI groups
McCarthy 2016	Australia	371	Mixed approach	BMI ≥ 25
Mujsindi 2014	USA	79	Diet	BMI ≥ 25
Murtezani 2014	Republic of Kosovo	63	Physical Activity	All BMI groups

Study ID	Country	Sample size*	Intervention	BMI group
Parat 2015	France	268	Diet	BMI 25 – 29.9
Peaceman 2017	USA	281	Mixed approach	BMI ≥ 25
Perales 2016a	Spain	241	Physical activity	All BMI groups
Petrov Fieril 2015	Sweden	92	Physical activity	All BMI groups
Polley 2002	USA	110	Mixed approach	BMI ≤ 30
Price 2012	USA	62	Physical Activity	All BMI groups
Qiuling Li 2014	China	118	Mixed approach	All BMI groups
Quinlivan 2011	Australia	124	Diet	BMI ≥ 25
Rakhshani 2012	India	68	Physical activity	All BMI groups
Ramirez Velez 2011	Colombia	35	Physical Activity	All BMI groups
Ramirez Velez 2013	Colombia	20	Physical Activity	All BMI groups
Ronnberg 2014	Sweden	374	Physical Activity	All BMI groups
Santos 2005	Brazil	72	Physical Activity	BMI 25 – 29.9
Sedaghati 2007	Iran	90	Physical Activity	All BMI groups
Seneviratne 2015	New Zealand	74	Physical Activity	BMI ≥ 25
Simmons 2016	Europe	436	Mixed approach	BMI ≥ 30
Smith 2016	USA	45	Mixed approach	All BMI groups
Sun 2016	China	74	Mixed approach	All BMI groups
Thornton 2009	USA	232	Diet	BMI ≥ 30
Tomic 2013	Croatia	334	Physical Activity	All BMI groups
Toosi 2016	Iran	120	Physical Activity	All BMI groups
Vesco 2014	USA	114	Mixed approach	BMI ≥ 30
Wang 2016	China	300	Physical Activity	BMI ≥ 25
Willcox 2017	Australia	100	Mixed approach	BMI ≥ 25

**refers to number of participants that completed the study*

Appendix 1 Search strategy for identification of randomised trials on lifestyle interventions in pregnancy and maternal and offspring outcomes

Search strategy for Medline via Ovid

Item	Term
1	Pregnancy/
2	pregnan*.tw.
3	Gravidity/
4	gravid*.tw.
5	gestation*.tw.
6	Pregnant Women/
7	pregnant wom#n.tw.
8	(child adj3 bearing).tw.
9	childbearing.tw.
10	matern*.tw.
11	or/1-10
12	Weight Gain/ph [Physiology]
13	weight gain*.tw.
14	Weight Loss/ph [Physiology]
15	weight loss*.tw.
16	weight change*.tw.
17	Obesity/dh, me, ph, pc, px, th [Diet Therapy, Metabolism, Physiology, Prevention & Control, Psychology, Therapy]
18	obes*.tw.
19	Adiposity/ph [Physiology]
20	adipos*.tw.
21	Overweight/dh, me, ph, pc, px, th [Diet Therapy, Metabolism, Physiology, Prevention & Control, Psychology, Therapy]
22	overweight*.tw.
23	Body Mass Index/
24	bmi.tw.
25	or/12-24
26	exp Randomized Controlled Trial/
27	"randomized controlled trial".pt.
28	"controlled clinical trial".pt.
29	(random$ or placebo$).tw,sh.
30	((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.
31	single-blind method/
32	double-blind method/
33	or/26-32
34	11 and 25 and 33
35	exp Animals/
36	(rat$ or mouse or mice or hamster$ or animal$ or dog$ or cat$ or bovine or sheep or lamb$).af.
37	35 or 36
38	Humans/
39	human$.tw,ot,kf.
40	37 or 38
41	37 not (37 and 40)
42	34 not 41

Table 3. Differential effects of diet and physical activity based interventions on gestational weight gain, composite maternal, and composite offspring outcomes in subgroups of pregnant women

a) Gestational weight gain

Maternal characteristic	No. of studies	No. of women	MD* Kg (95% CI)	Treatment covariate interaction	
				Coeff.; 95% CI *(95% PI)*	I² (%)
Baseline Body mass index (BMI)					
Normal	21	3,376	-0.77 (-1.15, -0.39)		
Overweight	28	2,574	-0.75 (-1.22, -0.27)	-0.02; -0.08, 0.04 *(-0.21, 0.17)*[§1]	39.8
Obese	31	3,335	-0.85 (-1.41, -0.29)		
Parity					
Nulliparous	27	4,513	-0.80 (-1.17, -0.43)	0.10; -0.39, 0.60 *(-0.83, 1.04)*[§2]	4.8
Multiparous	27	4,548	-0.62 (-0.88, -0.37)		
Ethnicity					
Caucasian	21	6,814	-0.74 (-1.07, -0.42)	0.05; -1.27, 1.37 *(-1.28, 1.39)*[§3]	26.1
Non-Caucasian	15	621	-0.42 (-1.12, 0.28)		
Age					
≥ 20 yrs	32	9,045	-0.72 (-0.95, -0.50)	-0.03; -0.08, 0.02 *(-0.14, 0.09)*[§4]	25.9
< 20 yrs	13	232	0.05 (-1.34, 1.44)		
Pre-existing medical condition[#]					
No medical condition	18	4,335	-0.62; -0.90, -0.34	1.51; -2.01, 5.02 *(-4.13, 7.15)*[§5]	28.4
At least one medical condition	6	128	0.40; -1.92, 2.71		

* Model accounted for baseline weight and clustering effect [#]diabetes mellitus or hypertension; [§1]per unit of BMI, 31 studies (9,285 women); [§2]Multipara vs. nullipara, 24 studies (7,247 women); [§3]Non-Caucasian vs. Caucasian, 12 studies (4,439); [§4]Per yr of age 32 studies, (9,277 women); [§5]At least one medical condition vs. none, 5 studies (1,196 women); CI: confidence interval; MD – mean difference; PI: prediction interval

b) Maternal composite outcome

Maternal characteristic	No. of studies	No. of women	OR* (95% CI)	Treatment covariate interaction	
				Coeff.; 95% CI *(95% PI)*	I² (%)
Baseline Body mass index (BMI)					
Normal	12	2,445	0.91 (0.65, 1.28)		
Overweight	19	2,222	1.04 (0.86, 1.26)	1.00; 0.98, 1.02 *(0.98, 1.02)*[§1]	0
Obese	20	4,181	0.92 (0.80, 1.05)		
Parity					
Nulliparous	21	4,613	0.87 (0.71, 1.07)	1.03; 0.75, 1.39 *(0.53, 2.00)*[§2]	34.0
Multiparous	22	4,186	0.92 (0.78, 1.07)		
Ethnicity					
Caucasian	15	6,510	0.92 (0.79, 1.07)	0.93; 0.63, 1.37 *(0.62, 1.38)*[§3]	0
Non-Caucasian	11	917	0.86 (0.63, 1.17)		
Age					
≥ 20 years	24	8,656	0.91 (0.81, 1.02)	1.01; 0.99, 1.03 *(0.99, 1.03)*[§4]	0
< 20 years	9	172	1.57 (0.66, 3.71)		
Pre-existing medical condition[#]					
No medical condition	15	3,135	0.85 (0.66, 1.09)	1.44; 0.15, 13.74 *(0.03, 76.75)*[§5]	24.9
At least one medical condition	5	89	1.65 (0.36, 7.51)		

Model accounted for clustering effect; [#]diabetes mellitus or hypertension; [§1]per unit of BMI, 24 studies (8,848 women); [§2]Multipara vs. nullipara, 20 studies (8,053 women); [§3]Non-Caucasian vs. Caucasian, 9 studies (4,851); [§4]Per yr of age 24 studies, (8828 women); [§5]At least one medical condition vs. none, 4 studies (916 women); CI: confidence interval; MD – mean difference; PI: prediction interval

c) Offspring composite outcome

Maternal characteristic	No. of studies	No. of women	OR* (95% CI)	Treatment covariate interaction: Coeff.; 95% CI *(95% PI)*	Treatment covariate interaction: I² (%)
Baseline Body mass index (BMI)					
Normal	7	1,843	0.93 (0.60, 1.43)		
Overweight	12	2,065	0.83 (0.61, 1.13)	0.98; 0.95, 1.00 *(0.94, 1.02)* [§1]	18.5
Obese	13	4,327	0.92 (0.72, 1.19)		
Parity					
Nulliparous	16	4,152	0.97 (0.80, 1.17)	0.94; 0.64, 1.37 *(0.39, 2.28)* [§2]	35.5
Multiparous	15	4,048	0.91 (0.72, 1.15)		
Ethnicity					
Caucasian	11	6,018	0.93 (0.79, 1.08)	1.12; 0.75, 1.68 *(0.74, 1.69)* [§3]	0
Non-Caucasian	9	939	1.10 (0.78, 1.54)		
Age					
≥ 20 yrs	16	8,061	0.95 (0.82, 1.09)	1.01; 0.98, 1.04 *(0.97, 1.05)* [§4]	4.1
< 20 yrs	7	162	1.01 (0.34, 2.98)		
Pre-existing medical condition[#]					
No medical condition	12	3,407	0.89 (0.74, 1.08)	0.58; 0.03, 9.81*(0.00, 2440.15)*[§1]	0
At least one medical condition	3	63	0.54 (0.04, 7.52)		

* Model accounting for clustering effect; [#]diabetes mellitus or hypertension; [§1]per unit of BMI, 18 studies (7,978 women); [§2]Multipara vs. nullipara, 15 studies (7,295 women); [§3]Non-Caucasian vs. Caucasian, 9 studies (5,146); [§4]Per yr of age, 18 studies (7,965 women); [§5]At least one medical condition vs. none, 3 studies (925 women); CI: confidence interval; MD – mean difference; PI: prediction interval

Table 2. Summary estimates of effects of diet and physical activity based interventions on gestational weight gain and pregnancy outcomes using Individual Participant Data (IPD) alone, and by supplementing IPD with study-level data from studies that did not contribute IPD to the meta-analysis

a) Maternal outcomes

Outcome	No. of studies (No. of women)	Intervention Mean, SD	Control Mean, SD	MD (95% CI) (Kg)	I^2 (%)
Gestational weight gain					
Overall (IPD)	**33 (9,320)**	**10.1, 5.4**	**10.8, 5.4**	**-0.70 (-0.92, -0.48)**	**14.1**
(Combined IPD and non-IPD)	*81 (17,530)*	*10.6**	*11.5**	*-1.10 (-1.46, -0.74)*	*73.8*
Diet	4 (1,168)	10.2, 4.4	11.0, 4.8	-0.72 (-1.48, 0.04)	0.0
	12 (2,017)	*9.2**	*11.7**	*-2.84 (-4.77, -0.91)*	*92.3*
Physical activity	15 (2,915)	9.8, 4.4	10.8, 4.8	-0.73 (-1.11, -0.34)	0.0
	37 (7,355)	*11.3**	*11.9**	*-0.72 (-1.04, -0.41)*	*45.4*
Mixed approach	15 (5,369)	10.2, 6.0	10.6, 5.9	-0.71 (-1.10, -0.31)	34.9
	35 (8,448)	*10.3**	*11.0**	*-1.00 (-1.39, -0.61)*	*54.6*
	Overall number of studies (women)	**Intervention Event/ No-event**	**Control Event/ No-event**	**OR (95% CI)**	**I^2 (%)**
Maternal composite outcome					
Overall	**24 (8,851)**	**1,896/2,728**	**1,837/2,390**	**0.90 (0.79, 1.03)**	**26.7**
Diet	3 (397)	42/137	84/134	0.60 (0.20, 1.75)	0.0
Physical activity	9 (2,311)	346/850	367/748	0.81 (0.61, 1.09)	10.8
Mixed approach	13 (6,259)	1,508/1,742	1,438/3,009	0.97 (0.84, 1.12)	34.9
Gestational diabetes					
Overall	**27 (9,427)**	**584/4,333**	**571/3,939**	**0.89 (0.72, 1.10)**	**23.8**
	59 (16,885)	*974/7,764*	*1,046/7,101*	*0.76 (0.65, 0.89)*	*36.8*
Diet	4 (490)	13/208	19/250	1.03 (0.30, 3.61)	0.0
	8 (1,106)	*57/476*	*75/498*	*0.79 (0.37, 1.69)*	*0.0*
Physical activity	10 (2,700)	90/1300	121/1,189	0.67 (0.46, 0.99)	0.0
	27 (6,755)	*240/3153*	*347/3,015*	*0.66 (0.53, 0.83)*	*0.0*
Mixed approach	14 (6,355)	481/2825	441/2,608	1.02 (0.79, 1.32)	35.2
	27 (9,342)	*677/4135*	*672/3,858*	*0.88 (0.72, 1.07)*	*10.8*
Hypertensive diseases in pregnancy[1]					
Overall	**22 (9,618)**	**432/4,586**	**423/4,177**	**0.95 (0.78, 1.16)**	**24.2**
	45 (14,849)	*559/7,130*	*592/6,568*	*0.85 (0.71, 1.00)*	*21.5*
Diet[§]	3 (397)	18/161	39/179	0.59 (0.07, 4.65)	35.8
	5 (729)	*23/322*	*49/335*	0.57 (0.18, 1.79)	38.0
Physical activity	7 (2,565)	55/1,242	73/1,195	0.74 (0.42, 1.33)	6.0
	20 (5,125)	*106/2,513*	*147/2,359*	*0.68 (0.49, 0.93)*	*0.0*
Mixed approach	13 (6,797)	359/3,183	322/2,933	1.05 (0.86, 1.28)	19.4
	21 (9,136)	*430/4,295*	*407/4,004*	*1.01 (0.87, 1.17)**	*16.3*
Preterm birth					
Overall	**32 (11,676)**	**332/5,713**	**345/5,286**	**0.94 (0.78, 1.13)**	**17.3**
	49 (14,339)	*414/6,971*	*443/6,511*	*0.92 (0.79, 1.08)*	*8.7*
Diet	4 (1,344)	9/647	35/653	0.28 (0.08, 0.96)	0.0
	7 (1,696)	*13/819*	*45/819*	*0.32 (0.14, 0.70)*	*0.0*
Physical activity	13 (3,249)	95/1541	73/1540	1.29 (0.90, 1.85)	0.0
	23 (5,149)	*160/2,431*	*148/2,410*	*1.09 (0.84, 1.41)*	*0.0*
Mixed approach	16 (7,219)	228/3525	243/3223	0.91 (0.73, 1.12)	0.0
	20 (7,630)	*241/3721*	*256/3412*	*0.92 (0.75, 1.12)*	*32.3*

[1] For non-IPD data – for studies where pre-eclampsia and pregnancy-induced hypertension (PIH) were reported separately data for PIH were appended to IPD

	Overall number of studies (women)	Intervention Event/ No-event	Control Event/ No-event	OR (95% CI)	I² (%)
Caesarean section					
Overall	**32 (11,410)**	**1,525/4,385**	**1,506/3,994**	**0.91 (0.83, 0.99)**	**0.0**
	66 (18,041)	*2,373/6,860*	*2,440/6,368*	*0.89 (0.83, 0.96)*	*16.2*
Diet	4 (1,340)	117/535	149/539	0.78 (0.50, 1.22)	0.0
	7 (1,732)	*238/610*	*264/620*	*0.88 (0.65, 1.17)*	*0.0*
Physical activity	13 (3,046)	306/1,230	349/1,161	0.82 (0.67, 1.01)	0.0
	32 (6,587)	*648/2,646*	*746/2,547*	*0.83 (0.73, 0.95)*	*0.0*
Mixed approach	16 (7,160)	1,102/2,620	1,059/2,379	0.95 (0.84, 1.08)	17.6
	28 (9,858)	*1,487/3,604*	*1481/3,286*	*0.92 (0.80, 1.06)*	*21.9*

b) Offspring outcomes

	Overall number of studies (women)	Intervention Event/ No-event	Control Event/ No-event	OR (95% CI)	I² (%)
Offspring composite outcome					
Overall	**18 (7,981)**	**1,007/3,172**	**951/2,851**	**0.94 (0.83, 1.08)**	**0.0**
Diet	2 (346)	34/132	48/132	0.71 (0.03, 18.23)	0.0
Physical activity	5 (1,274)	138/495	143/498	0.99 (0.67, 1.46)	0.0
Mixed approach	12 (6,494)	835/2,545	797/2,317	0.95 (0.81, 1.11)	4.7
Stillbirth†					
Overall	**2 (3,719)**	**9/1,858**	**11/1,841**	**0.81 (0.00, 256.69)**	**0.0**
	4 (4,534)	*12/2,261*	*14/2,247*	*0.85 (0.24, 3.02)*	*0.0*
Small for gestational age					
Overall	**33 (11,666)**	**709/5,324**	**632/5,001**	**1.06 (0.94, 1.20)**	**0.0**
	44 (12,937)	*773/6,018*	*685/5,461*	*1.05 (0.94, 1.18)*	*0.0*
Diet	4 (1,337)	41/610	47/639	0.92 (0.45, 1.88)	0.0
	6 (1,628)	*56/746*	*55/771*	*1.05 (0.62, 1.77)*	*0.0*
Physical activity	14 (3,272)	243/1,402	232/1,395	1.05 (0.84, 1.34)	12.3
	21 (3,955)	*274/1,740*	*271/1,670*	*1.01 (0.83, 1.24)*	*51.7*
Mixed approach	16 (7,193)	425/3,312	370/3,086	1.08 (0.92, 1.28)	0.0
	20 (7,670)	*443/3,532*	*386/3,309*	*1.08 (0.93, 1.27)*	*0.0*
Large for gestational age					
Overall	**34 (12,047)**	**744/5,492**	**759/5,052**	**0.90 (0.76, 1.07)**	**38.0**
	45 (13,348)	*820/6,185*	*833/5,510*	*0.86 (0.71, 1.04)*	*41.0*
Diet	4 (1,408)	155/529	176/548	0.91 (0.60, 1.37)	0.0
	6 (1,699)	*172/663*	*203/661*	*0.82 (0.54, 1.22)*	*0.0*
Physical activity	15 (3,330)	121/1,557	124/1,528	0.96 (0.59, 1.54)	34.3
	21 (3,930)	*159/1,842*	*161/1,768*	*0.96 (0.67, 1.37)*	*6.9*
Mixed approach	16 (7,450)	468/3,406	481/3,095	0.89 (0.67, 1.17)	51.0
	21 (8,040)	*489/3,680*	*523/3,348*	*0.83 (0.62, 1.10)*	*4.3*
Admission to Neonatal Intensive Care Unit					
Overall	**16 (8,140)**	**302/3,973**	**279/3,586**	**1.01 (0.84, 1.23)**	**0.0**
	21 (9,498)	*406/4,543*	*400/4,149*	*0.97 (0.82, 1.14)*	*0.0*
Diet	1 (289)	3/137	13/136	*na#*	*na*
	2 (389)	*11/179*	*29/170*	*0.33 (0.00, 47.97)*	*0.0*
Physical activity	3 (1,166)	31/552	40/543	0.77 (0.21, 2.81)	20.8
	4 (1,240)	*34/586*	*43/577*	*0.79 (0.35, 1.78)*	*0.0*
Mixed approach	13 (6,818)	268/3,284	230/3,036	1.10 (0.89, 1.35)	0.0
	15 (7,771)	*360/3,626*	*332/3,453*	*1.05 (0.88, 1.25)*	*0.0*

*Combined IPD and non-IPD analysis are provided in Italics. *recalculation using DerSimonian-Laird*
SD – standard deviation, N – number of women, OR – odds ratio, #standard deviations not possible to estimate, §no data from non-IPD studies, †For the outcome stillbirth all the data comes from the studies with mixed approach interventions

Table 1. Baseline characteristics of women included in studies that contributed to the IPD meta-analysis on diet and physical activity based interventions in pregnancy

Baseline characteristics	**No. of studies**	**No. of women**	**Intervention Mean (SD) or N (%)** †	**Control Mean (SD) or N (%)** †
Age (yrs)	35	12,006	30.0 (5.1)	30.1 (5.2)
Normal weight (BMI 18.5 – 24.9)	34	12,031	1,974 (31.7%)	1,842 (31.8%)
Overweight (BMI 25 – 29.9)	34	12,031	1,578 (25.3%)	1,523 (26.3%)
Obesity (BMI ≥ 30)	34	12,031	2,680 (43.0%)	2,434 (42.0%)
Race/Ethnicity:	27	10,020		
Caucasian (incl Russia & Australia)			4,562 (88%)	4,217 (87.2%)
Asian			157 (3%)	156 (3.2%)
Black			292 (5.6%)	292 (6%)
Central/South American			67 (1.3%)	64 (1.3%)
Middle East (incl Iran&Turkey)			37 (0.7%)	37 (0.8%)
Other			71 (1.4%)	68 (1.4%)
Educational status of mother§:	29	8,914		
Low			722 (15.6%)	724 (16.9%)
Medium			1,372 (29.6%)	1,292 (30.2%)
High			2,536 (54.8%)	2,268 (52.9%)
Smoker	29	10,958	875 (15.4%)	865 (16.4%)
Parity:	33	11,805		
0			3,027 (49.5%)	2,692 (47.3%)
1			2136 (34.9%)	2083 (36.6%)
2			647 (10.6%)	634 (11.1%)
3			179 (2.9%)	165 (2.9%)
4+			129 (2.1%)	113 (2%)
No exercise or sedentary	27	7583	1,761 (44.6%)	1,731 (47.6%)
Pre-existing Diabetes mellitus	25	9589	6 (0.1%)	9 (0.2%)
Pre-existing Hypertension	23	5494	73 (2.5%)	54 (2.1%)

†*Percentage refers to proportion out of observations in control or intervention arms respectively*§ *add definitions*

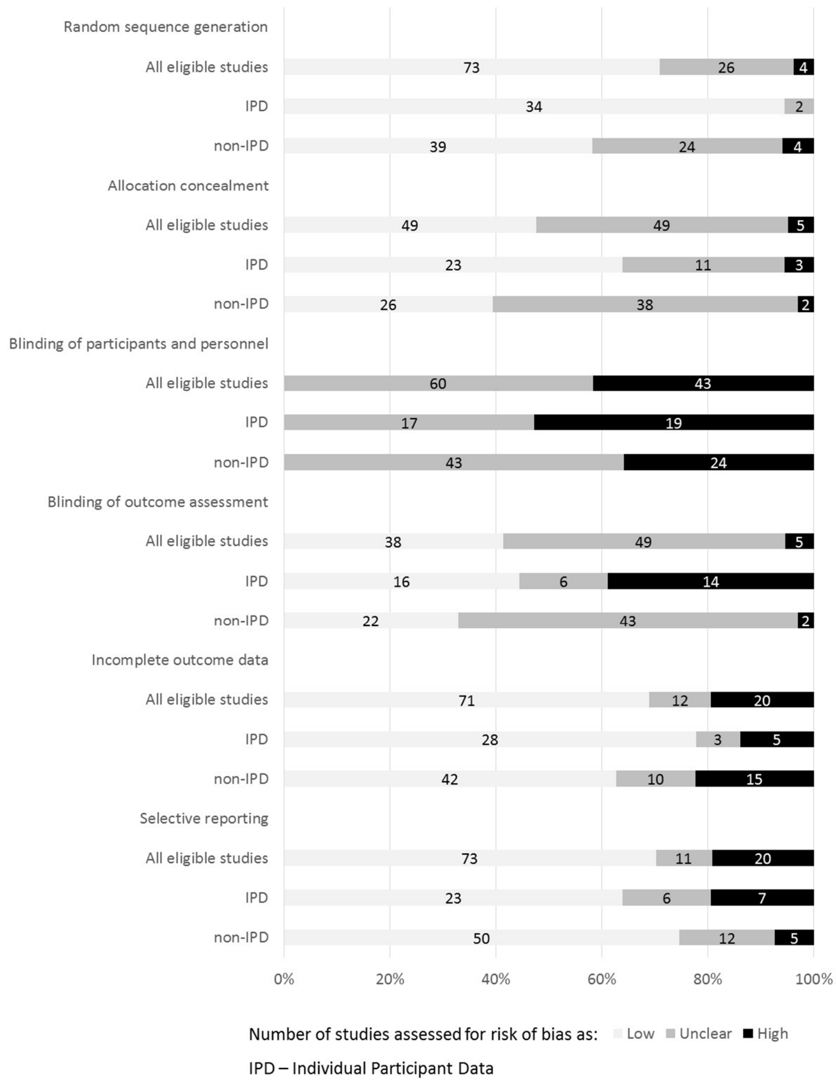
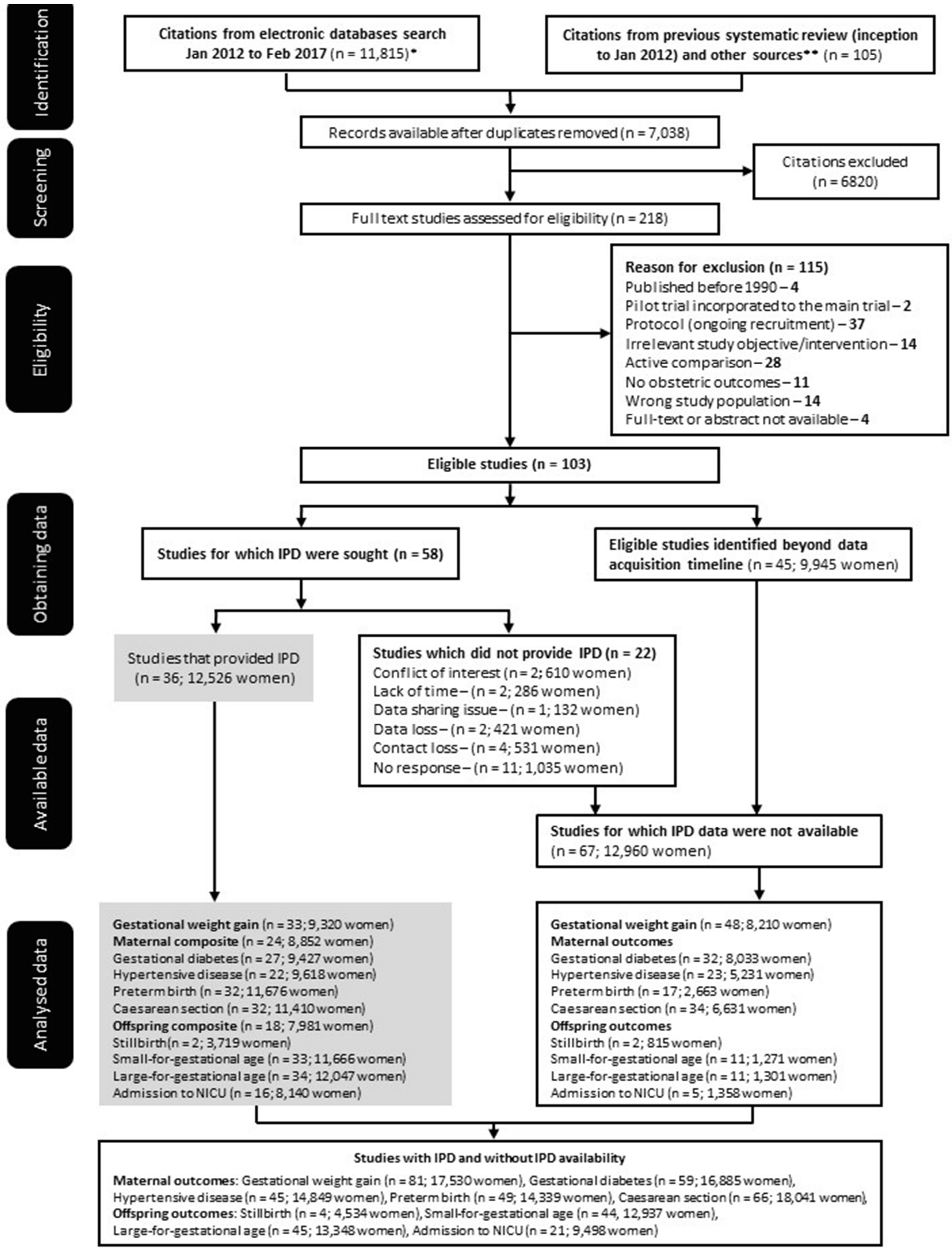


Fig 2. Assessment of risk of bias in all eligible studies (N = 103), studies with IPD (N = 36), and studies without access to IPD (N = 67)

Fig 2

338x451mm (96 x 96 DPI)

Fig 1 Identification and selection of studies in Individual Participant Data (IPD) meta-analysis of diet and physical activity based interventions on gestational weight gain pregnancy outcomes



** Database search was updated three times: in October 2013 (9,359 records), March 2015 (3,551 records), Jan 2016 (1,379 records) and Feb 2017 (1,547 records);*
*** Other sources: reference search, personal communication, and Google search;*
IPD: individual participant data, NICU: Neonatal Intensive Care Unit

Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: Individual participant data (IPD) meta-analysis of randomised trials

Rogozińska, Ewelina
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom
Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Marlin, Nadine
Pragmatic Clinical Trials Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Betran, Ana Pilar
Department of Reproductive Health and Research, World Health Organization, Switzerland

Astrup, Arne
Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark

Barakat, Ruben
Facultad de Ciencias de la Actividad Fısica y del Deporte-INEF, Universidad Politecnica de Madrid, Spain

Bogaerts, Annick
Department of Development and Regeneration KULeuven, University of Leuven, Belgium.
Faculty of Medicine and Health Sciences, Centre for Research and Innovation in Care (CRIC), University of Antwerp, Belgium
Faculty of Health and Social Work, research unit Healthy Living, UC Leuven-Limburg, Belgium

Cecatti, Jose G
Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas, Brazil

Devlieger, Roland
Department of Obstetrics and Gynaecology, University Hospitals KULeuven, Belgium
Department of Obstetrics, Gynaecology and Fertility, GZACampus Sint-Augustinus, Belgium

Dodd, Jodie
The Robinson Research Institute, School of Medicine, Department of Obstetrics and Gynaecology, University of Adelaide, Australia

Women's and Children's Health Network, Women's and Babies Division, North Adelaide, Australia

El Beltagy Nermeen
Department of Obstetrics and Gynaecology, Faculty of Medicine Alexandria University, Egypt

Facchinetti, Fabio
Obstetrics and Gynecology Unit, Mother Infant Department, University of Modena and Reggio Emilia, Italy

Geiker, Nina RW
Clinical Nutrition Research Unit, Copenhagen University Hospital Gentofte, Denmark

Guelfi, Kim
School of Sport Science, Exercise and health, The University of Western Australia, Australia

Haakstad, Lene AH
Norwegian School of Sports Sciences, Department of Sports Medicine, Norway

Harrison, Cheryce
Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Australia

Hauner, Hans
Else Kröner-Fresenius-Zentrum für Ernährungsmedizin, Klinikum rechts der Isar, Technical University of Munich, Germany

Jensen, Dorte M
Department of Endocrinology, Gynaecology and Obstetrics, Odense University Hospital, University of Southern Denmark, Denmark
Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark

Kinnunen, Tarja I
Faculty of Social Sciences, University of Tampere, Tampere, Finland
Khoury, Janette
Department of Obstetrics and Gynaecology, Oslo University Hospital, Norway

Luoto, Riitta
Department of Health Sciences, University of Tampere, Tampere, Finland
UKK Institute for Health Promotion, Tampere, Finland

McAuliffe, Fionnuala
UCD Perinatal Research Centre, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland

Motahari, Narges

Department of Midwifery, Mazandaran University of Medical Sciences, School of Nursing and Midwifery, Iran

Mørkved, Siv
Department of Public Health and Nursing, Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Norway
Department of Clinical Service, St. Olavs Hospital, Trondheim University Hospital, Norway

Owens, Julie
The Robinson Research Institute, School of Medicine, Department of Obstetrics and Gynaecology, University of Adelaide, Australia

Perales, María
Facultad de Ciencias de la Actividad Fısica y del Deporte-INEF, Universidad Politecnica de Madrid, Spain

Petrella, Elisabetta
Obstetrics and Gynecology Unit, Mother Infant Department, University of Modena and Reggio Emilia, Italy

Phelan, Suzanne
Kinesiology Department, California Polytechnic State University, San Luis Obispo, USA

Poston, Lucilla
Division of Women's Health, Women's Health Academic Centre, King's College London, St. Thomas' Hospital, London, United Kingdom

Rauh, Kathrin
Else Kröner-Fresenius-Centre for Nutritional Medicine, Chair of Nutritional Medicine, Technische Universität München, Germany
Competence Centre for Nutrition (KErn), Germany

Renault, Kristina M
Department of Obstetrics and Gynaecology, Copenhagen University Hospital Hvidovre, Denmark
Obstetric Clinic, JMC, Copenhagen University Hospital Rigshospitalet, Denmark

Sagedal, Linda R
Department of Obstetrics and Gynecology, Sorlandet Hospital, Kristiansand, Norway

Salvesen, Kjell Å
Department of Obstetrics and Gynaecology, St. Olavs Hospital, Trondheim University Hospital, Norway
Department of Laboratory Medicine Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, Norway

Shen, Garry X
Department of Internal Medicine, University of Manitoba, Canada

Shub, Alexis
Department of Obstetrics and Gynaecology, University of Melbourne, Australia, Department of Perinatal Medicine, Mercy Hospital for Women, Australia

Scudeller, Tânia
Department of Management and Health Care, São Paulo Federal University (UNIFESP), Brazil

Surita, Fernanda G
Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas, Brazil

Stafne, Signe N
Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Norway
Department of Clinical Service, St. Olavs Hospital, Trondheim University Hospital, Norway

Teede, Helena
Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Australia

Tonstad, Serena
Department of Obstetrics and Gynaecology, Oslo University Hospital, Norway

van Poppel, Mireille NM
Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Center, Netherlands
Institute of Sport Science, University of Graz, Austria

Vinter, Christina A
Department of Gynaecology and Obstetrics, Odense University Hospital, University of Southern Denmark, Denmark

Vistad, Ingvild
Department of Obstetrics and Gynecology, Sorlandet Hospital, Kristiansand, Norway

Yeo, SeonAe
School of Nursing, University of North Carolina at Chapel Hill, North Carolina, USA

Dodds, Julie
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Kerry, Sally
Pragmatic Clinical Trials Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Jackson, Louise
Health Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Barton, Pelham
Health Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Molyneaux, Emma
Section of Women's Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

Martin, Alba A
Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS), Madrid, Spain

Rayanagoudar, Girish
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Ruifrok, Anneloes E
Department of Obstetrics and Gynecology, Academic Medical Centre, The Netherlands
Department of Obstetrics and Gynaecology, Faculty of Medicine, VU University Medical Center, The Netherlands

Roberts, Tracy
Health Economics Unit, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Christine JM de Groot
Department of Obstetrics and Gynaecology, Faculty of Medicine, VU University Medical Center, The Netherlands

Coomarasamy, Arri
Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom

Mol, Ben W
Robinson Research Institute, School of Medicine, University of Adelaide
The South Australian Health and Medical Research Institute, Adelaide, Australia

Zamora, Javier
Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS) and CIBER Epidemiology and Public Health, Spain

Khan, Khalid S
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

Riley, Richard D
Research Institute for Primary Care and Health Sciences, Keele University, United Kingdom

Thangaratinam, Shakila
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom
Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

for i-WIP (International Weight Management in Pregnancy) Collaborative Network

Corresponding author
Khalid S Khan
Women's Health Research Unit, Centre for Primary Care and Public Health,
Barts and The London School of Medicine and Dentistry,
Queen Mary University of London

Abstract

Objective

Policies and guidelines to tackle obesity and excess weight gain in pregnancy need to be underpinned by robust evidence. We synthesised the evidence on the overall, and differential effects of interventions based on diet and physical activity, primarily on gestational weight gain and composite maternal and offspring outcomes, according to women's body mass index, age, parity, ethnicity and pre-existing medical condition; and secondarily on individual complications.

Design

Systematic review and Individual Participant Data (IPD) meta-analysis

Data sources

Major electronic databases from inception to February 2017 without language restrictions.

Eligibility criteria for selecting studies

Randomised trials on diet and physical activity based interventions in pregnancy.

Data synthesis

Statistical models accounted for clustering of participants within trials and heterogeneity across trials, leading to summary mean difference or odds ratios with 95% confidence intervals for the effects overall, and in subgroups (interactions).

Results

We obtained IPD from 36 randomised trials (12,526 women). There was less weight gain in the intervention group than control (mean difference -0.70 kg; 95% CI -0.92 to -0.48, I^2=14.1%; 33 studies, 9,320 women). Though summary effect estimates favoured the intervention, the reductions in maternal (OR 0.90, 95% CI 0.79 to 1.03, I^2 = 26.7%; 24 studies, 8,852 women) and offspring (OR 0.94, 95% CI 0.83 to 1.08, I^2 = 0%; 18 studies, 7,981 women) composite outcomes were not significant. There was no evidence of differential intervention effects across subgroups, for either gestational weight gain or composite outcomes.

There was strong evidence that interventions reduced the odds of caesarean section (OR 0.91, 0.83 to 0.99, I^2= 0%; 32 studies, 11,410 women), but not for other individual complications in IPD meta-analysis. When IPD was supplemented with study-level data from studies that did not provide IPD, the overall effect was similar, with stronger evidence of benefit for gestational diabetes (OR 0.76, 95% CI 0.65 to 0.89, I^2= 36.8%; 59 studies, 16,885 women).

Conclusion

Diet and physical activity based interventions reduce gestational weight gain and lower the odds of caesarean section. There is no evidence that effects differ across subgroups of women.

Systematic review registration CRD42013003804

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Word count: 340

Introduction

Half of all women of childbearing age worldwide are overweight or obese.[1-3] Obesity and excessive gestational weight gain put mother and offspring at risk, both in pregnancy and in later life.[4-6] The resultant costs to the health service and society are considerable.[7,8] Increasingly, healthcare organisations and research funding bodies prioritise research on interventions and strategies to reduce maternal weight related adverse outcomes in pregnancy.[9-12]

Syntheses of study-level data on effects of diet and physical activity based interventions in pregnancy[13] have shown an overall benefit on limiting gestational weight gain, but the findings varied for their protective effect on maternal and offspring outcomes.[13,14] Importantly, the subgroups of women who may benefit the most from such interventions are not known.[15] For this, primary studies do not have sufficient power,[16,17] and study-level data meta-analyses are limited by the absence of published details of subgroup effects,[18] and by potential ecological bias.[19] These problems can be addressed by evidence synthesis using raw individual-level data from relevant studies.[20,21]

We undertook an Individual Participant Data (IPD) meta-analysis to assess the effects of diet and physical activity based interventions, primarily on gestational weight gain and on composite maternal and offspring outcomes, in subgroups defined by body mass index (BMI), age, parity, ethnicity and pre-existing medical condition. Furthermore, we assessed the overall effects, and those of individual interventions (diet, physical activity, mixed), on critically important maternal and offspring complications. In addition to using IPD, we also assessed the impact of incorporating study-level data from other studies not providing IPD.

Methods

The IPD meta-analysis was performed using a pre-specified protocol (PROSPERO CRD42013003804),[22] and was reported in line with The PRISMA-IPD (Preferred Reporting Items for Systematic reviews and Meta-Analysis of Individual Participant Data) recommendations.[23]

Literature search and study identification

We searched the major electronic databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and Health Technology Assessment Database (HTA) from October 2013 to March 2015 to update our previous search in this field for randomised trials on diet and physical activity based interventions in pregnancy.[13] The search was further updated twice; in January 2016, and in February 2017 to identify additional new studies. We searched the Internet by using general search engines including Google, and contacted researchers in the field to identify relevant trials. There were no language restrictions. The details of the search strategy are provided in Appendix 1.

Studies were selected in a two-stage process by two independent researchers (ER and NM/AM/EM). In the first step, potential citations were identified. Next, we did a detailed evaluation of the full manuscripts of potential papers and selected articles that fulfilled the eligibility criteria. We included randomised trials that assessed the effects of diet based, physical activity based, and mixed interventions in pregnancy, on maternal and offspring outcomes. As the mixed intervention we classified any complex, multi-component interventions targeting women’s nutrition, level of physical activity, and associated with them habits and behaviour. We excluded studies that only included women with gestational diabetes at baseline, those that involved animals, trials reporting only non-clinical outcomes, and studies that were published before 1990.The primary outcomes were gestational weight gain, a composite of maternal, and a composite of offspring outcomes. The secondary outcomes were individual maternal and offspring complications. The components of the composite outcomes were determined by a two round Delphi survey of researchers in this field, and were considered to be critically important to clinical practice.[24] The maternal composite outcome included gestational diabetes mellitus, hypertensive diseases in pregnancy, preterm delivery and caesarean section. The offspring composite outcome included stillbirth, small-for-gestational age (SGA) fetus, large-for-gestational age (LGA) fetus, and admission of the newborn to the neonatal intensive care unit (NICU).

We defined gestational weight gain as the difference between maternal weight at booking and the last weight measured before delivery. We accepted the primary authors' definition and reporting of gestational diabetes mellitus, pregnancy induced hypertension, pre-eclampsia, caesarean section, stillbirth and admission to NICU. We defined preterm delivery as birth before 37 weeks of gestation, and SGA and LGA as babies with birth weight below the 10th and at or over 90th centile respectively, adjusted for mother's BMI, parity and gestational age at delivery.[25]

Establishment of IPD Collaborative Network and database

We established the International Weight Management in Pregnancy (i-WIP) IPD Collaborative Network by contacting researchers of eligible studies.[26] A bespoke database was developed, and we requested collaborators for relevant data in any format. We sent three reminders when there was no response.

Quality assessment of the included studies

The quality of the randomised trials was assessed by two independent reviewers using a risk of bias tool for sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias.[27] We considered a study to have a high risk of bias if it scored so in at least one of following domains: randomisation, allocation concealment, blinding of outcome assessment, or incomplete outcome data; all items should be scored as low risk for a study to be classified as low risk of bias.

Data extraction and assessment of IPD integrity

Two independent reviewers (ER, NM) undertook data extraction at study-level for inclusion and exclusion criteria, the characteristics of the intervention, and the reported outcomes. We sought to obtain IPD from relevant studies published until July 2015, which was the endpoint for IPD acquisition, to allow sufficient time for data cleaning, standardisation and amalgamation of datasets. We also extracted the published study-level data for all relevant studies published until February 2017, including those published beyond the individual data acquisition timeline, and those for which IPD were not provided by study authors.

We obtained IPD for individual maternal characteristics that were determined *a priori* such as BMI, age, parity, ethnicity, socioeconomic status, and pre-existing medical condition. Continuous variables were kept continuous, but some were also categorised when considered to be clinically useful. These included categorisations based on BMI (normal 18.5 - 24.9 kg/m², overweight 25 – 29.9 kg/m², obese ≥30 kg/m²), and age (cut off of 20 years). Mother's ethnicity was classified as Caucasian or non-Caucasian. The mother's educational status was used to indicate socioeconomic status. We defined the status to be "low" if the mother did not complete secondary education to A-level, "medium" if she completed secondary education (A-level equivalent) and "high" if she completed any further higher education. We defined the pre-existent medical condition as diabetes mellitus, early onset of gestational diabetes, or hypertension.

We considered participants to be adherent to the intervention based on the following criteria: completion of at least 70% of the intervention protocol, dataset provided information on adherence in a 'yes/no' format or was deemed to be adherent as per the study criteria. We performed range and consistency checks on all IPD and produced summary tables. The randomisation ratio, baseline characteristics and the method of analysis in the IPD dataset were compared with the published information. Any discrepancies, missing data, obvious errors, and inconsistencies between variables or outlying values were queried and rectified as necessary with input from the original authors.

Data synthesis

We undertook a two-stage IPD meta-analysis[21] for each primary outcome to obtain summary estimates (mean difference for gestational weight gain and odds ratios for binary outcomes) and 95% confidence intervals (CI) for the intervention effects. We assessed the effects across all interventions overall, and for individual interventions. A two-stage IPD meta-analysis was used to obtain summary estimates of the subgroup effects (interactions) of interest, which compared differential effects of interventions across the primary outcomes. We additionally evaluated whether there are any differential effects of interventions for individual complications, according to the BMI (normal, overweight, obese). All analyses were designed to preserve the intention-to-treat principle.

The two-stage meta-analysis was undertaken as follows. The first stage involved analysing the IPD in each trial separately, to account for the clustering of participants within trials, and to obtain the estimates of interest and their variances. For the cluster-randomised trials, we included a random intercept for a unit of randomisation to account for this further clustering. For the outcome of gestational weight gain, we used analysis of covariance in each trial to regress the final weight value against the intervention while adjusting for baseline weight and centres in cluster-randomised trials. For maternal and offspring outcomes, we used a logistic regression model for each trial separately, with the intervention as a covariate. We excluded women with confirmed glucose intolerance or hypertensive disorder at baseline, as defined by the primary authors, in the analysis of composite adverse pregnancy outcomes. To assess potential intervention effect modifiers, we extended the aforementioned models to include interaction terms between participant-level covariates and the intervention (i.e. treatment-covariate interaction terms).

In the second stage, we pooled the derived effect estimates (i.e. treatment effects or treatment-covariate interactions) across trials using a random effects model fitted using restricted maximum likelihood (REML). The random effects approach allowed us to account for unexplained between-study heterogeneity in effects across studies. This produced summary estimates and 95% confidence intervals for the intervention effects and the interactions (subgroup effects). The Hartung-Knapp correction was applied when subsequently deriving 95% confidence intervals (CI) for the true mean effect, to help account for the uncertainty of the estimate of between-study heterogeneity.[28,29]

We included studies that did not contribute IPD, by incorporating their extracted study-level data within the second stage of the IPD meta-analysis framework, to obtain summary estimates of intervention effects that combined IPD and non-IPD studies. Sensitivity analyses were also performed by excluding studies with high risk of bias, by analysing the primary outcomes separately for each intervention type (diet, physical activity and mixed), by excluding participants not adherent to the intervention, by analysing change in BMI instead of weight gain, and by excluding maternal weight gain estimates from pregnancies that ended before 37 completed weeks of gestation to avoid systematic differences.

Heterogeneity was summarised using the I-squared statistic, the estimated between-study variance ('tau-squared'),[30] and approximate 95% prediction intervals (PIs), which indicate the potential intervention (or interaction) effect in a new population similar to those included in the meta-analysis.[31]

Small-study-effects (potential publication bias) were investigated by using contour enhanced funnel plots alongside visual examination and statistical tests for asymmetry (Egger's test for continuous outcomes or Peter's test for binary outcomes).[32] We assessed for IPD availability bias by comparing the summary results when including non-IPD studies with those from IPD studies.[33] Further, we compared the symmetry of funnel plots before and after inclusion of non-IPD studies. All meta-analyses were undertaken using Stata software version 12.1 (StataCorp LP, College Station, TX, USA), and statistical significance was considered at the 5% level.

Results

Study selection

We identified 58 trials published up to June 2015, of which 36 studies (62%, 36/58) provided IPD, [16,17,34-67] that accounted for data from 80% of the participants

(12,526/15,541); 22 studies (3,015 women) did not provide IPD (Fig 1).[68-88] A further 45 (9,945 women) trials[89-133] were identified after the IPD acquisition timeline until February 2017.

Characteristics of included studies and participants

IPD were available from 36 trials in 16 countries: 22 studies[17,34,36-39,41,42,47,48,51-54,56-58,60,62-64,134] were from Europe, four each from North America (the US and Canada),[44,55,66,67] Australia,[16,43,45,50] and South America (Brazil)[35,49,61,65], one study each from Egypt[40] and Iran.[46] Twenty-three IPD studies included women of any BMI,[34-38,42,44-48,52,53,55,56,58,60-62,65-67,134] seven included only obese women,[17,39-41,50,63,64] and six included obese and overweight women.[16,43,49,51,54,57] The interventions included those mainly based on diet (4 IPD studies),[47,62,63,65] mainly based on physical activity (16 IPD studies),[35-37,42,46,49-53,58,60,61,66,67,69] and those based on a mixed approach of diet, physical activity and/or behaviour modifying techniques (15 IPD studies).[17,34,39-41,43-45,48,54-56,64,134] One study had a three-arm design with intervention arms being: physical activity only and a mixed approach.[57] The characteristics of all IPD studies, and also those that did not contribute IPD are provided in Appendix 2.

Over 80% of women in the IPD meta-analyses were of Caucasian origin, and at least half were classified as high socioeconomic status. Around 45% of women were nulliparous, 40% were obese, and a similar proportion was classified as having sedentary status with no exercise at baseline (Table 1). IPD were available to assess effects of interventions on gestational weight gain (33 studies, 9,320 women), composite maternal outcomes (24 studies, 8,852 women) and composite offspring outcomes (18 studies, 7,981 women). The largest IPD was available for the outcome of LGA fetus (34 studies, 12,047 women), followed by preterm delivery (32 studies, 11,676 women), SGA fetus (33 studies, 11,666 women), any caesarean section (32 studies, 11,410 women), hypertensive diseases in pregnancy (22 studies, 9,618 women), and gestational diabetes (27 studies, 9,427 women). We did not have access to IPD of 51% of all eligible women (13,023/25,549) from 67 studies (Fig. 1).

Quality of included studies

Overall, trials had a low risk of bias in random sequence generation (75%, 62/83). Over 90% (34/36) studies that contributed to the IPD were assessed as low risk of bias in this domain compared with to 58% of the non-IPD studies (28/67). Two IPD studies (2/36) and one non-IPD (3/67) were considered high risk for allocation concealment. Blinding of outcome assessment was appropriate in 44% (16/36) and 33% (22/67) of IPD and non-IPD studies respectively (Fig. 2). Fewer IPD studies (5/36) were assessed as high risk of bias for incomplete outcome data than non-IPD studies (15/67). The summary of the risk of bias estimates for all eligible studies and those that did, and did not contribute to IPD are provided in Fig 2. We did not encounter any issues that we were not able to clarify with the IPD contributor during the IPD integrity check.

Effects of interventions on pregnancy outcomes

Gestational weight gain

Based on IPD meta-analysis (33 studies, 9,320 women), diet and physical activity based interventions resulted in significantly less gestational weight gain compared to control (summary mean difference -0.70 kg; 95% CI -0.92 to -0.48 kg, I^2=14.1%), after adjusting for baseline weight and clustering. The approximate 95% prediction interval for the intervention effect in a new setting was -1.24 to -0.16 Kg. (Table 2a)

Differential effects in subgroups

There was no strong evidence of a treatment-covariate interaction for baseline BMI when treated as a continuous covariate (-0.02 kg change in intervention effect per 1-unit increase in BMI, 95% CI -0.08 to 0.04), or when compared as overweight vs. normal (-0.11 kg, 95% CI -0.77 to 0.55), obese vs. normal (0.06 kg, 95% CI -0.90 to 1.01), and obese vs. overweight (-0.09 kg, 95% CI -1.05 to 0.86). We also did not observe evidence of a subgroup effect for age (-0.03 kg per 1-year increase in age, 95% CI -0.08 to 0.02), parity (0.10 kg change in effect for multiparity vs. nulliparity, 95% CI -0.39 to 0.60), ethnicity (0.05 kg change in effect for non-Caucasian vs. Caucasian, 95% CI -1.27 to 1.37), and underlying medical condition (1.51 kg change in effect for women with at least one condition vs. none, 95% CI -2.01 to 5.02). The findings were consistent when continuous covariates were analysed as categorical measures based on clinically relevant cut-points (Table 3a).

Sensitivity analyses

The reduction in gestational weight gain due to the intervention was consistently observed when analysis was restricted to studies with low risk of bias (-0.67 kg, 95% CI -0.95 to -0.38; 15 studies, 5,585 women), women adherent to the intervention (-0.76 kg, 95% CI -1.00 to -0.52; 33 studies, 8,565 women), women followed up until over 37 weeks gestation (-0.91 kg, 95% CI -1.17 to -0.66; 28 studies, 5,324 women), and for BMI instead of maternal weight as an outcome (-0.30 kg/m^2, 95% CI -0.39 to -0.21; 31 studies, 9,238 women).

Addition of studies that did not contribute IPD

Meta-analysis undertaken by supplementing the IPD with study-level data from studies (48 studies, 8,210 women) that did not contribute IPD, we observed a larger beneficial intervention effect for weight gain (summary mean difference -1.1 kg; 95% CI -1.46 to -

0.74; 81 studies, 17,530 women). The benefit was also consistently observed for individual interventions based on diet, physical activity or mixed approach (Table 2a).

Composite maternal and offspring outcomes

In the IPD meta-analyses, the summary estimates favoured the intervention group for reduction in odds of composite maternal (OR 0.90, 95% CI 0.79 to 1.03, I^2 = 26.7%; 24 studies, 8,851 women) and offspring outcomes (OR 0.94, 95% CI 0.83 to 1.08, I^2 = 0%; 18 studies, 7,981 women), but were not statistically significant (Table 2).

Differential effects across subgroups

We observed no strong evidence of differential subgroup effects for either maternal composite outcome according to baseline BMI (treatment-covariate interaction 1.00, 95% CI 0.98 to 1.02), age (interaction 1.01, 95% CI 0.99 to 1.03), parity (interaction 1.03, 95% CI 0.75 to 1.39), ethnicity (interaction 0.93, 95% CI 0.63 to 1.37), and underlying medical condition (interaction 1.44, 95% CI 0.15 to 13.74) (Table 3b).

A similar lack of differential effect was observed for composite offspring outcome in mothers grouped according to baseline BMI (interaction 0.98, 95% CI 0.95 to 1.00), age (interaction 1.01, 95% CI 0.98 to 1.04), parity (interaction 0.94, 95% CI 0.64 to 1.37), ethnicity (interaction 1.12, 95% CI 0.75 to 1.68), and underlying medical condition (interaction 0.58, 95% CI 0.03 to 9.81) (Table 2c). The findings did not change for maternal and offspring outcomes when BMI and age were analysed as continuous instead of categorical variables.

Individual maternal outcomes

Overall, we observed a significant reduction in caesarean section (OR 0.91, 95% CI 0.83 to 0.99, I^2 = 0%; 32 studies, 11,410 women) with interventions compared to routine care, in the IPD meta-analysis. The reduction in other individual outcomes such as gestational diabetes (OR 0.89, 95% CI 0.72 to 1.10, I^2 = 23.8%; 27 studies, 9,427 women), hypertensive diseases in pregnancy (OR 0.95, 95% CI 0.78 to 1.16, I^2 = 24.2%; 22 studies, 9,618 women), and preterm delivery (OR 0.94, 95% CI 0.78 to 1.13, I^2 = 17.3%; 32 studies, 11,676 women) were not statistically significant in IPD meta-analyses (Table 2a). We did not observe any differential effect according to baseline BMI category (normal, overweight, obese) for any of the individual maternal outcomes (Appendix 3a). The findings were consistent when study-level data from non-IPD studies were meta-analysed with IPD, but with a stronger evidence of benefit for gestational diabetes. The reduction in gestational diabetes (OR 0.76, 95% CI 0.65 to 0.89, I^2 = 36.8%; 59 studies, 16,885 women) became significant (Table 2a).

Amongst individual interventions, those based mainly on physical activity showed a reduction in gestational diabetes in both IPD (OR 0.67, 95% CI 0.46 to 0.99, I^2= 0%; 10 studies, 2,700 women) and in combined (IPD and non-IPD) meta-analyses (OR 0.66, 95% CI 0.53 to 0.83, I^2= 0%; 27 studies, 6,755 women). While the summary estimates for physical activity based interventions favoured caesarean section (OR 0.82, 95% CI 0.67 to 1.01, I^2= 0%; 13 studies, 3,046 women) and hypertensive diseases in pregnancy (OR 0.74, 95% CI 0.42 to 1.33, I^2= 6.0%; 7 studies, 2,565 women) in IPD meta-analyses, the addition of non-IPD studies resulted stronger evidence of benefit for these complications, with reduction in the respective odds by 17% (OR 0.83, 95% CI 0.73 to 0.95, I^2= 0%; 32 studies, 6,587 women) and 32% (OR 0.68, 95% CI 0.49 to 0.93, I^2= 0%; 20 studies, 5,125 women).

A strong effect was observed for preterm birth with diet based interventions in both IPD (OR 0.28, 95% CI 0.08 to 0.96, I^2= 0%; 4 studies, 1,344 women) and combined analyses (OR 0.32, 95% CI 0.14 to 0.70, I^2= 0%; 7 studies, 1,696 women), but the overall sample sizes were relatively small (Table 2a). There was no evidence of benefit with mixed interventions for any maternal outcomes.

Individual offspring outcomes

There was no strong evidence that interventions had an effect on individual offspring outcomes such as stillbirth (OR 0.81, 95% CI <0.001 to 256.69, I^2 = 0%; 2 studies, 3,719 women), SGA fetus (OR 1.06, 95% CI 0.94 to 1.20, I^2 = 0%; 33 studies, 11,666 women), LGA fetus (OR 0.90, 95% CI 0.76 to 1.07, I^2 = 38.0%; 34 studies, 12,047 women) and admission to NICU (OR 1.01, 95% CI 0.84 to 1.23, I^2 = 0%; 16 studies, 8,140 women) based on the IPD meta-analyses. The significance of the findings did not change when non-IPD studies were added to the IPD meta-analyses (Table 2b). The numbers of eligible participants for whom data were obtained, effect estimates and confidence intervals for all above analyses are available from the study authors on request. There was no differential effect for any individual offspring outcome according to the BMI category (Appendix 3b).

Small-study effects

We found visual and statistical evidence (Egger's test p=0.04) of small study effects in the contour enhanced funnel plots for the IPD meta-analysis of the overall effect on gestational weight gain. The asymmetry of the plot was not improved by the addition of study-level data from non-IPD studies to the meta-analysis. When studies with high risk of bias were excluded from the analysis, the symmetry of the funnel plot improved (Egger's test p=0.61). We found significant evidence of small-study effects for the composite maternal (Peter's test p=0.04), but not for the offspring composite outcome (p=0.85) (Appendix 4).

Discussion

Statement of principal findings

Our large, collaborative IPD meta-analysis confirms that diet and physical activity based interventions in pregnancy reduce gestational weight gain. This beneficial effect was consistently observed irrespective of maternal BMI, age, parity, ethnicity or pre-existing medical condition; and held when studies at high risk of bias were excluded. The findings are generalisable, with the 95% prediction interval suggesting a beneficial effect on gestational weight gain when the intervention is applied in a new population or setting. There is no strong evidence that interventions reduce the risk of composite maternal and offspring outcomes, with no variation in effect observed across the subgroups.

For individual outcomes, interventions reduce caesarean section without a significant reduction in other maternal and offspring complications. The effects of interventions for individual maternal and offspring complications are consistent irrespective of the BMI of the mother. Addition of study-level data from non-IPD studies to the IPD meta-analysis increased the precision of estimates, without a change in the direction of effect, and showed additional benefit for gestational diabetes. Amongst individual interventions, those mainly based on physical activity lowered the odds of gestational diabetes.

Strengths and weaknesses of the study

This is the first IPD meta-analysis, to our knowledge, to assess the differential effects of diet and physical activity based interventions for important, clinically relevant outcomes, in subgroups of women who were identified *a priori.* Establishment of the i-WIP group facilitated the collaboration of key researchers in this area and provided access to the largest IPD in this field. This allowed us to extract data that were not published, with larger sample sizes for outcomes such as preterm birth, small and large for gestational age fetuses, and admission to the neonatal intensive care unit for IPD than study-level meta-analysis. Furthermore, we were able to minimise the heterogeneity in the population, by excluding individual women who did not fulfil the inclusion criteria. We compared the quality of studies that contributed to the IPD, which were generally of higher quality than those that did not contribute IPD.

Access to IPD provided us with substantially increased power (compared to individual trials) to robustly estimate treatment-covariate interactions, and to avoid the ecological bias observed in aggregate meta-regression of study-level covariates.[19,21] It also allowed us to adjust for baseline weight using analysis of covariance in each trial,[135] which is the best approach to analysing continuous outcomes,[136] though rarely used in individual trials. Our reporting of 95% prediction intervals for the overall, and differential effects of interventions, across subgroups, allowed us to quantify the range of effects across populations of interest.

The subgroups were chosen in response to the National Institute for Health and Care Excellence's (NICE) call for assessment of the effectiveness of lifestyle interventions in pregnancy, for specific groups of women considered to be at high risk of complications, such as teenagers, ethnic minorities, and women who enter pregnancy obese.[15] We assessed treatment covariate interactions for subgroups as both continuous and categorical variables. We chose 20 years to be the cut-off for age, as it allowed us to assess the effect of intervention in teenagers, where pregnancy may alter normal growth processes and increase their risk of becoming overweight or obese.[137] Adolescent mothers also retain more weight postpartum than mature control subjects.[137]
Due to the variation in reporting, we were only able to broadly classify the ethnicity of women as Caucasian or non-Caucasian. We combined diet based, physical activity based and mixed approach interventions to provide an overall estimate, and also reported their individual effects.[13,138] Since more than one clinical outcome is considered to be important to clinical care, we assessed the effects of interventions on maternal and offspring composite outcomes, whose individual components were identified through a robust Delphi process.[24] The varying definitions may have an impact on findings for gestational diabetes and pre-eclampsia, where the cut offs and the criteria for diagnosis differed. Another limitation is that the vast majority of our population has a medium-to-high education, a factor favouring compliance with interventions.

IPD repository

By establishing the i-WIP IPD live repository through the support of the individual research teams, we ensured that in addition to the standardisation, there was robust safeguarding of data. The continuing growth of the repository is crucial for future research in this area [139], and will accelerate update of the meta-analysis for the various relevant outcomes as new studies are published. We were successful in obtaining individual data from 80% of all participants within the IPD acquisition timeline. While every effort was made to include IPD from the latest studies identified in the updated search, we were limited by the considerable time needed to prepare the IPD datasets, which involved data access, setting up of institutional contracts, cleaning and formatting of accessed data, resolution of queries with individual researchers, and standardisation and merging of the data. This restricted our ability to include studies published after the agreed data acquisition time line in the IPD meta-analysis. In a high priority area such as obesity and weight gain in pregnancy, there has been a rapid increase in the number of published studies, with at least 10 trials published per year since 2011, and 16 published in 2016. We sought to maximise the information needed to inform the findings by combining study-level data from non-IPD studies to the IPD meta-analyses. The conclusions appeared to be robust for nearly all outcomes. Furthermore, the non-availability of IPD from these studies did not appear to contribute to the observed small study effects, since the asymmetry of the funnel plot was not altered when the non-IPD studies were added. Non-IPD studies were also generally at a higher risk of bias.

Gestational weight gain

Diet and physical activity based interventions reduce gestational weight gain. We have shown that this beneficial effect is observed in all women irrespective of maternal characteristics. The findings are consistent for any type of intervention, even when restricted to only high quality studies and to women adherent to the intervention, and when non-IPD are added to IPD. Mothers with excess weight gain in pregnancy are at increased risk of postpartum weight retention.[140] This increase in interpregnancy BMI may contribute to risks of entering subsequent pregnancies as overweight or obese, with adverse outcomes in subsequent pregnancy. [141] Furthermore, this may increase their risk of cardiovascular morbidity and mortality in later life.[142] Compared to published evidence to-date,[13] we identified a smaller reduction in gestational weight gain of 0.7 kg with interventions. The effect of such a reduction in gestational weight gain (compared to routine care) on post-partum weight retention and long-term outcomes is not known.

Maternal and offspring outcomes

Despite the summary effect estimates favouring the interventions for composite maternal and offspring outcomes, these were not significant. Interventions significantly reduced the odds of caesarean section. Previous systematic reviews showed a trend towards reduction in this risk overall, and for individual interventions (diet, physical activity, mixed), [13] but were limited by the small sample sizes and paucity of reporting, compared to the 11,000 women included in our IPD meta-analysis. Of the individual interventions, physical activity in pregnancy showed a trend towards reduction in caesarean section in IPD meta-analysis, which became significant, with minimal heterogeneity when non-IPD were added. The physical activity component in most studies involved a structured exercise of moderate intensity (aerobic classes, stationary cycling) with resistance training that varied in frequency (Appendix 5).

Although the direction of effect appeared to favour the intervention for other maternal outcomes, they were not significant. Addition of non-IPD to the IPD meta-analysis resulted in significant reduction in gestational diabetes. However, unlike our IPD analysis, we were not able to implement the strict inclusion and exclusion criteria, standardise the analysis strategy (e.g. adjust for baseline), and ascertain occurrence of outcome in the combined analysis with study-level data. Physical activity based interventions significantly reduced the odds of gestational diabetes in IPD meta-analysis, and also when combined with non-IPD. This benefit could be mediated through mechanisms that resulted in improved glycaemic parameters and outcomes in gestational diabetes and type 2 diabetes, through increased insulin sensitivity, and reduced oxidative stress. Exercise in pregnancy may also have a potential role in preventing hypertensive diseases in pregnancy. The effects of diet and physical activity on maternal and offspring outcomes did not vary according to the body mass index of the woman, highlighting the potential benefits for all and not selected groups of mothers.

Interventions based on diet showed a reduction in preterm birth, although the analysis included relatively small numbers of women. We did not identify any benefits with interventions in preventing any adverse offspring outcome, despite a sample size that was two to three folds more than published data for some outcomes, consistent with previous findings.[14] The lack of adverse effects such as small for gestational age and preterm birth with diet and physical activity in pregnancy, should reassure mothers who have traditionally been advised not to undertake structured exercise or manage their diet in pregnancy.

Implications for clinical practice

Currently in the UK, only obese women are offered access to dietician and specific antenatal classes for advice on diet and lifestyle, to minimise gestational weight gain. Based on our work, it is likely that women of all BMI groups could benefit with specific advice on diet and physical activity for weight gain, and some maternal outcomes. Healthcare professionals should avoid variations in care and lifestyle advice provided to mothers based on ethnicity, age and underlying medical conditions, since no differential effects were found.

Discussions about diet and physical activity in pregnancy, which are delivered as part of antenatal care, should incorporate specific estimates of benefit for caesarean section and gestational weight gain, and the likelihood of preventing gestational diabetes. Mothers should be reassured regarding the safety of the interventions, particularly on physical activity and structured exercise in pregnancy, by highlighting the benefits and lack of harm. This may improve engagement and compliance with the intervention. Importantly, such interventions in pregnancy could be considered in global efforts to reduce caesarean section in relevant populations.

Implications for further research

Whether the observed benefit in gestational weight gain with diet and physical activity translates to long-term benefits to the mother and child needs to be assessed. Evaluation of any differential effects according to the individual components of the intervention such as duration, frequency, provider, and setting, on individual outcomes is required to provide detailed recommendations. The effects of these interventions on mothers in low- and middle-income countries, particularly in those countries with high rates of caesarean section and gestational diabetes, need to be ascertained with large randomised trials. There is a need to develop a harmonised core outcome set for future reporting of clinical trials in this area, to maximise the meaningful interpretation of published data. This is particularly relevant for rare but important outcomes such as shoulder dystocia, birth trauma and venous thromboembolic events.

Conclusion

Diet and physical activity based interventions in pregnancy limit gestational weight gain, with no evidence that this effect differs across subgroups defined by maternal characteristics. Caesarean section odds are also reduced.

Word count: 5325

What is already known

1. Increased weight gain in pregnancy is associated with maternal and fetal complications.
2. Interventions based on diet and/or physical activityin pregnancy minimise gestational weight gain.
3. Interventions based on diet and physical activity may have a potential role in preventing adverse pregnancy outcomes.

What this study adds

1. Diet and physical activity based interventions consistently reduce gestational weight gain across various subgroups of women categorised by age, parity, Body Mass Index (BMI), ethnicity and pre-existing medical condition.
2. The reduction in odds of composite adverse maternal and composite adverse offspring outcomes with diet and physical activity is not significant, and does not vary across various subgroups of women.
3. Interventions significantly lower the odds of caesarean section, and have no effect on offspring outcomes.

Contributors

ST, RR, CdG, AER and SK developed the protocol. JD overlooked the project and drafted the manuscript. ST, ER, NM conducted the review, drafted the manuscript and led the project. KSK, BWM provided input into the protocol development and the drafting of the initial manuscript. ER, EM, AM undertook the literature searches, study selection. AER, ER, ST, EM, GR acquired IPD. MvP, LP, CAV, FM, JMD, JO, RB, MP, JGC, FS, SY, AB, RD, HT, CH, LH, GXS, AS, NEB, NMo, JK, STo, RL, TIK, KG, FF, EP, SP, TTS, KR, HH, KMR, LRS, IV, SNS, SM, KAS, DMJ, MV, AA, NRWG contributed data to the project and provided input at all stages of the project. ER, GR and NM mapped the variables in the available datasets. ER and NM cleaned and quality checked data. NM harmonised the data. NM, SK, RR conducted the data analysis. TR, LJ, PB provided input into the protocol. APB provided input into the conduct of study. JZ provided methodological support. KSK, AC and BWM were involved in project development and provided input at all stages. All authors critical appraised the final draft of the report.

Declaration of interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Patient and Public Involvement

Patient and Public Involvement was obtained in interpretation of findings only.

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