Effects of lifestyle interventions in pregnancy on maternal and offspring outcomes: Individual participant data (IPD) meta-analysis of randomised trials

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17 Oct 2016

Dr Fiona Godlee
Editor-in-Chief
The BMJ

Re: Effects of diet and physical activity-based interventions in pregnancy on maternal and offspring outcomes: Individual patient data (IPD) meta-analysis of randomised trials

Dear Dr Godlee

A substantial proportion of the global efforts on preventing obesity and its complications, involve pregnant women. We previously published a systematic review in BMJ that identified the overall beneficial effect of lifestyle interventions on gestational weight gain (Thangaratinam et al BMJ 2012). The paper was widely cited (total citations 369; first 2 years of publication 189 citations) with an Altmetric score of 82. The work also identified significant gaps in evidence, particularly on whether there are particular groups of mothers who may benefit the most from interventions. This was also highlighted as a research priority by the National Institute of Healthcare and Excellence (NICE).

We were funded by the NIHR HTA to undertake Individual Participant (IPD) Data Meta-analyses, to assess if the beneficial effect on gestational weight gain persisted across all groups of mothers irrespective of age, parity, ethnicity, socioeconomic status and pre-existing medical condition, and improved pregnancy outcomes. This work was done in partnership with World Health Organisation (WHO) under the umbrella of the i-WIP (International Weight Management in Pregnancy) Collaborative network with individual data from 36 trials (over 12,000 women, 22 countries) on lifestyle interventions in pregnancy.

The interventions were consistently beneficial across all groups of women in reducing gestational weight gain, and they significantly reduced the rates of caesarean section. When non-IPD was combined with IPD, there was a significant reduction in gestational diabetes. We did not observe a significant reduction in other maternal and offspring outcomes.

By involving leading researchers and policy makers in this field globally, we expect our findings to influence national and international guidelines, including the WHO. We strongly feel that the work is relevant to the scope of the BMJ, and we will be grateful if you could consider our manuscript for publication in your journal.

Yours sincerely

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Abstract

Objective

Numerous lifestyle studies have addressed obesity and excess weight gain in pregnancy. Initiatives to tackle this problem need to be underpinned by evidence synthesis. We assessed the overall effects of lifestyle interventions on gestational weight gain and pregnancy outcomes, and the effects according to women's age, parity, ethnicity, socioeconomic status and pre-existing medical condition.

Design

Systematic review and Individual Participant Data Meta-Analysis

Data sources

Major electronic databases from inception to January 2016 without language restrictions.

Eligibility criteria for selecting studies

Randomised trials on diet and lifestyle 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 individual participant data 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, 9320 women). Though summary estimates favoured the intervention, the reduction in maternal (OR 0.90, 0.79 to 1.03, I^2 = 26.7%; 24 studies, 8852 women) and offspring (OR 0.94, 0.83 to 1.08, I^2 = 0%; 18 studies, 7981 women) composite outcomes was not significant. Amongst individual outcomes, there was a significant reduction in caesarean sections (OR 0.91, 0.83 to 0.99, I^2= 0%; 32 studies, 11410 women), but not in other complications. Across subgroups, there was no differential intervention effect on gestational weight gain and composite outcomes.

Conclusions

Lifestyle interventions in pregnant women are effective in reducing gestational weight gain, and in lowering the odds of caesarean section. There is no evidence that effects differ across subgroups of women.

Systematic review registration CRD42013003804

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Introduction

Half of all women of childbearing age worldwide are overweight or obese.[1-4] Obesity and excessive gestational weight gain put mother and offspring at risk, both in pregnancy and in later life.[5-7] The resultant costs to the health service and society are considerable.[8,9] Increasingly, healthcare organisations and research funding bodies prioritise research on interventions and strategies to reduce maternal weight related adverse outcomes in pregnancy.[10-13]

Syntheses of study-level data on effects of diet and physical activity based interventions in pregnancy[14] have shown an overall benefit on gestational weight gain, but the findings varied for their protective effect on maternal and offspring outcomes.[14,15] Importantly, the subgroups of women who may benefit the most from such interventions are not known.[16] For this, primary studies do not have sufficient power,[17,18] and aggregate data meta-analyses are limited by the absence of published details of subgroup effects[19] and potential ecological bias.[20] These problems can be addressed by evidence synthesis using raw individual-level data from relevant studies.[21,22]

We undertook Individual Participant Data (IPD) meta-analyses to assess the effects of lifestyle interventions on gestational weight gain, and on composite and individual maternal and offspring outcomes in all women, and in subgroups defined by age, parity, ethnicity, socioeconomic status and pre-existing medical condition.

Methods

The Individual Participant Data meta-analysis was performed using a pre-specified protocol (PROSPERO CRD42013003804)[23] and reported in line with The PRISMA-IPD

(Preferred Reporting Items for Systematic reviews and Meta-Analysis of Individual Participant Data) recommendations.[24]

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 lifestyle interventions in pregnancy.[14] The search was further updated in January 2016 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). 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 lifestyle interventions based on diet and/or physical activity in pregnancy on maternal and offspring outcomes. We excluded studies on women with gestational diabetes at baseline, those that involved animals or reported only non-clinical outcomes, and studies that were published before 1990.

The primary outcomes were gestational weight gain, composite maternal and composite 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.[25] The maternal composite outcome included gestational diabetes mellitus (GDM), hypertensive diseases in pregnancy, preterm delivery and caesarean section. The offspring composite outcome included stillbirth, small-for-gestational age (SGA), large-for-gestational age (LGA) fetus, and admission of the offspring to the neonatal intensive care unit (NICU).

We defined gestational weight gain as the difference between maternal booking weight and the last weight measured before delivery. We accepted the primary authors' definition and reporting of gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), pre-eclampsia (PE), caesarean section, stillbirth and admission to Neonatal Intensive Care Unit (NICU). We defined small-for-gestational age and large-for-gestational age 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.[26]

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.[27] 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.[28] 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 outcomes reported. We sought to obtain Individual Participant Data from relevant studies published until July 2015, which was the endpoint for individual participant data acquisition, to allow sufficient time for data cleaning, standardisation and amalgamation of datasets. We also extracted the published aggregate data for all relevant studies published until January 2016, including those published beyond the individual data acquisition timeline, and those for which Individual Participant Data were not provided by study authors.

We obtained IPD for individual maternal characteristics such as Body Mass Index (BMI), age, parity, ethnicity, socioeconomic status, pre-existing medical condition, type of intervention, and individual outcomes. 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). The mother's educational status was considered to be representative of the socioeconomic status. We defined the status to be "low" if 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 pre-existent medical condition as diabetes mellitus, gestational diabetes, or hypertension.

We considered the following participants to be adherent to the intervention: 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 Individual Participant Data meta-analysis[22] for each outcome separately 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, and the subgroup effects (interactions) of interest. All analyses were designed to preserve the intention-to-treat principle.

The first stage of meta-analysis involved analysing the IPD in each trial separately, accounting for the clustering of participants within trials, to obtain the estimates (and their variances) of interest. For the cluster-randomised trials, we included a random intercept for 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, whilst adjusting for baseline weight and for 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, and produced summary estimates for the mean (average) effects across studies. 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.[29,30] Heterogeneity was summarised using the I-squared statistic, the estimated between-study variance ('tau-squared'),[31] 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.[32] All meta-analyses were undertaken using the STATA software, and statistical significance was considered at the 5% level.

Sensitivity analysis

Sensitivity analyses were 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 estimates analysed before 37 completed weeks of gestation to avoid systematic differences. We analysed separately each component of the intervention to ensure validity of the findings for the composite outcome. We included studies that did not

contribute IPD, by incorporating their extracted aggregate 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.

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).[33] We assessed for IPD availability bias by comparing the summary results when including non-IPD studies with those from IPD studies.[34] Further, we compared the symmetry of funnel plots before and after inclusion of non-IPD studies.

Results

Study selection

We identified 58 trials published up to June 2015, of which 36 (12,526 women) provided IPD, [17,18,35-68] and 22 (3015 women) did not provide IPD (Fig. 1).[69-89] A further 25 (4950 women) trials[90-114] were identified after the IPD data acquisition timeline, including those published until Jan 2016.

Characteristics of included studies and participants

IPD were available from 36 trials of women from 16 countries: 22 studies[18,35,37-40,42,43,48,49,52-55,57-59,61,63-65,115] were from Europe, four each from North America (the US and Canada),[45,56,67,68] Australia,[17,44,46,51] and South America (Brazil)[36,50,62,66], one study each from Egypt[41] and Iran.[47] Twenty-three IPD studies included women of any BMI,[35-39,43,45-49,53,54,56,57,59,61-63,66-68,115] seven included only obese women,[18,40-42,51,64,65] and six included obese and overweight women.[17,44,50,52,55,58] The lifestyle interventions included diet-based (4 IPD studies),[48,63,64,66] physical activity-based (16 IPD studies),[36-38,43,47,50-

[54,59,61,62,67,68,70] and a mixed approach of diet, physical activity and/or behaviour modifying techniques (15 IPD studies).[18,35,40-42,44-46,49,55-57,65,115] One study had a three-arm design with intervention arms being: physical activity only and a mixed approach.[58] 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 to have sedentary status with no exercise at baseline (Appendix 3). IPD were available to assess effects of interventions on gestational weight gain (33 studies, 9320 women), composite maternal (24 studies, 8852 women) and offspring outcomes (18 studies, 7981 women). The largest IPD was available for the outcome of large-for-gestational age fetus (34 studies, 12,047 women), followed by preterm delivery (32 studies, 11,676 women), small-for-gestational age fetus (33 studies, 11666 women), caesarean section (32 studies, 11,410 women), hypertensive diseases in pregnancy (22 studies, 9618 women), and gestational diabetes (27 studies, 9427 studies). We did not have access to IPD of 39% of all eligible women (7965/20,491) from 47 studies (Fig. 1).

Quality of included studies

Overall, trials had a low risk of bias in random sequence generation (75%, 62/83). The studies that contributed to IPD were assessed as low risk of bias in over 90% (34/36) in comparison to 60% of the non-IPD studies (28/47). Two IPD studies (2/36) and one non-IPD (1/47) were considered high risk for allocation concealment. Blinding of outcome assessment was appropriate in 44% (16/36) and 28% (13/47) 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 (10/47). The summary of 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 encountered any issues that we weren't 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, 9320 women), lifestyle 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 (PI) for the intervention effect in a new setting was -1.24 to -0.16 Kg.

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 categorised measures based on clinically relevant cut-points (Table 1a).

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, 5585 women), women adherent to the intervention (-0.76 kg, 95% CI -1.00 to -0.52; 33 studies, 8565 women), women followed up until 37 weeks gestation (-0.91 kg, 95% CI -1.17 to -0.66; 28 studies, 5324 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, 9238 women). Meta-analysis combining the 33 IPD studies with aggregate data from 34 eligible studies (13,606 women) that did not contribute IPD showed an even larger beneficial intervention effect for weight gain (summary mean difference -1.2 kg; 95% CI -1.59 to -0.77; 67 studies, 22926 women). The benefit was also 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 of reduction in odds of composite maternal (OR 0.90, 95% CI 0.79 to 1.03, I^2 = 26.7%; 24 studies, 8851 women) and offspring outcomes (OR 0.94, 95% CI 0.83 to 1.08, I^2 = 0%; 18 studies, 7981 women) slightly favoured the intervention group, but were not statistically significant. We observed no strong evidence of differential subgroup effects for either maternal or offspring composite outcomes according to baseline BMI, age, parity, ethnicity and underlying medical condition (Table 1).

Individual maternal outcomes

We observed a significant reduction in caesarean section (OR 0.91, 95% CI 0.83 to 0.99, I^2 = 0%; 32 studies, 9250 women) with lifestyle 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, 9427 women),

hypertensive diseases in pregnancy (OR 0.95, 95% CI 0.78 to 1.16, I^2 = 24.2%; 22 studies, 9618 women), and preterm delivery (OR 0.94, 95% CI 0.78 to 1.13, I^2 = 17.3%; 32 studies, 11676 women) were not statistically significant in IPD meta-analyses, despite the summary estimates favouring the intervention group (Fig. 3). The findings were consistent when aggregate data from non-IPD studies were meta-analysed with IPD, with a stronger evidence of benefit for gestational diabetes. The reduction in gestational diabetes (OR 0.78, 95% CI 0.66 to 0.93, I^2 = 29.5%; 47 studies, 13441 women) became significant (Table 2a).

Of the individual interventions, studies on physical activity showed a significant reduction in gestational diabetes in both IPD (OR 0.67, 95% CI 0.46 to 0.99, I^2= 0%; 10 studies, 2700 women) and combined (IPD and non-IPD) meta-analyses (OR 0.66, 95% CI 0.52 to 0.84, I^2= 0%; 20 studies, 4680 women). A similar 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, 1344 women) and combined analyses (OR 0.32, 95% CI 0.14 to 0.70, I^2= 0%; 7 studies, 1696 women), but the overall sample sizes were small (Table 2a).

Individual offspring outcomes

There was no strong evidence that lifestyle interventions had an effect on individual offspring outcomes such as stillbirth (OR 0.81, 95% CI 0.00 to 256.69, I^2 = 0%; 2 studies, 3719 women), small-for-gestational age fetus (OR 1.06, 95% CI 0.94 to 1.20, I^2 = 0%; 33 studies, 11666 women), large-for-gestational age fetus (OR 0.90, 95% CI 0.76 to 1.07, I^2 = 38.0%; 34 studies, 12047 women) and admission to the neonatal intensive care unit (OR 1.01, 95% CI 0.84 to 1.23, I^2 = 0%; 16 studies, 8140 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 number of eligible

participants for which data were obtained, effect estimates and confidence intervals for all above analyses are available from the study authors on request.

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 overall effect on gestational weight gain. The asymmetry of the plot was not improved by addition of aggregate 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 lifestyle 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 were generalisable across heterogeneous populations and settings, 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 was no strong evidence that interventions reduced the risk of composite maternal and offspring outcomes, even though the summary odds ratio estimates were less than one.[116] For individual outcomes, there was evidence that the odds of caesarean section were significantly lowered with interventions. Although the summary estimates favoured a reduction in all individual

maternal outcomes, the findings were not significant. There was no effect on most individual offspring complications. When aggregate data from non-IPD studies were included with the IPD meta-analysis, the direction of effect of intervention on outcomes was consistent, with a much stronger evidence for reduction in gestational diabetes.

Strengths and weaknesses of the study

Ours is the first IPD meta-analysis, to our knowledge, to assess the differential effects of lifestyle interventions for important, clinically relevant subgroups of women who were identified *a priori.* Establishment of the i-WIP group facilitated 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 aggregate meta-analysis. We compared the quality of studies that contributed to the IPD, with 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.[20,22] IPD also allowed us to adjust for baseline weight using analysis of covariance in each trial,[117] which is the best approach to analysing continuous outcomes,[118] 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 variation in reporting required us to broadly classified women into Caucasian or non-Caucasian for ethnicity, and to use mother's education as a surrogate for socio

economic status. We combined diet based, physical activity based and mixed approach interventions under the umbrella of lifestyle interventions, since they are not exclusive of each other, and it is difficult to disentangle the effects individual components.[14,119] 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.[25] We accepted the authors' definition of outcomes. This may have an impact on findings for gestational diabetes and pre-eclampsia, where the cut offs and the criteria for diagnosis differed.

While every effort was made to include the latest studies identified in the updated search, we were limited by the considerable time needed to set-up the IPD meta-analysis, for cleaning, formatting, standardising and merging of the accessed data. This restricted our ability to include studies published after the agreed data acquisition time line in the IPD meta-analysis. However, when aggregate data from non-IPD studies were added to the IPD meta-analyses, the conclusions appeared to be robust for nearly all outcomes. Further, 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.

Strengths and weaknesses in relation to other studies

Previous systematic reviews have shown an overall reduction in gestational weight gain with lifestyle interventions. We have shown that this beneficial effect is observed in all women irrespective of maternal characteristics, and even when restricted to only high quality studies and to women adherent to the intervention.[14] Mothers with excess weight

gain in pregnancy are more likely to retain weight postpartum, which pre-disposes to them to cardiovascular morbidity and mortality in later life,[121] thereby increasing their risks of entering subsequent pregnancies as overweight or obese. The impact of a 0.7 kg reduction in weight gain (compared to routine care) from lifestyle interventions on post-partum weight retention, and long-term outcomes are not known.

The effects on individual components of the intervention showed a significant reduction only for caesarean section, and not other maternal outcomes, although the direction of effect appeared to favour the intervention. Compared to our previous aggregate meta-analysis[14] that showed a non-significant reduction in caesarean section, the IPD meta-analysis included twice the number of participants, accounting for the improved precision and significance of estimates.

When the data from non-IPD studies were added to the IPD meta-analysis, the reduction in gestational diabetes became significant. It is possible to attribute this effect to the increase in sample size. However, unlike IPD meta-analysis, we were unable to ascertain the occurrence of outcomes, to adjust for baseline maternal weight, or ensure their quality. We did not identify any benefits with interventions in preventing any adverse offspring outcome, despite a sample size that was two to three fold more than published data for some outcomes, consistent with previous findings.[14]

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. Provision of estimates of benefit for important

outcomes such as caesarean section and gestational weight gain is likely to improve engagement and compliance with the intervention. Additional efforts should be made to tackle variations in care and lifestyle advice provided to mothers based on ethnicity, age and underlying medical conditions.

National and international guidelines should take into account the absence of differential effects in benefits observed based on maternal characteristics in making their recommendations on diet and physical activity in pregnancy. The lower weight gain in pregnancy observed with lifestyle interventions may reduce subsequent postpartum weight gain. Importantly, diet and lifestyle activity based interventions in pregnancy should have an important role in global efforts to reduce caesarean section. They have the potential to reduce gestational, thereby preventing pregnancy complications, and progression to type-2 diabetes after delivery.

Implications for further research

Whether the magnitude of benefit observed for individual outcomes vary with maternal characteristics need further evaluation. The effects of these interventions on mothers in low- and middle-income countries, particularly 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. The effect of lifestyle interventions on long-term maternal and childhood outcomes needs assessment through IPD meta-analysis.

Conclusion

Lifestyle interventions in pregnancy reduce excess gestational weight gain, and there is no evidence that this effect differs across subgroups defined by maternal characteristics. Caesarean section odds are also reduced.

Word count: 4297

What is already known

1. Increased weight gain in pregnancy is associated with maternal and fetal complications.
2. Diet and lifestyle based interventions in pregnancy minimise gestational weight gain.
3. Interventions based on diet and lifestyle may have a potential role in preventing adverse pregnancy outcomes.

What this study adds

1. Lifestyle interventions consistently reduce gestational weight gain across various subgroups of women categorised by age, parity, Body Mass Index (BMI), socio economic status and pre-existing medical condition.
2. The reduction in risk of composite adverse maternal and composite adverse offspring outcomes with lifestyle interventions in pregnancy is not significant overall, and across various subgroups of women.
3. Interventions significantly lower the risk of caesarean section.

Contributors

AER, ST, RR, CdG 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 undertook the literature searches, study selection. AER, ER, ST, EM, GR acquired Individual Participant Data. 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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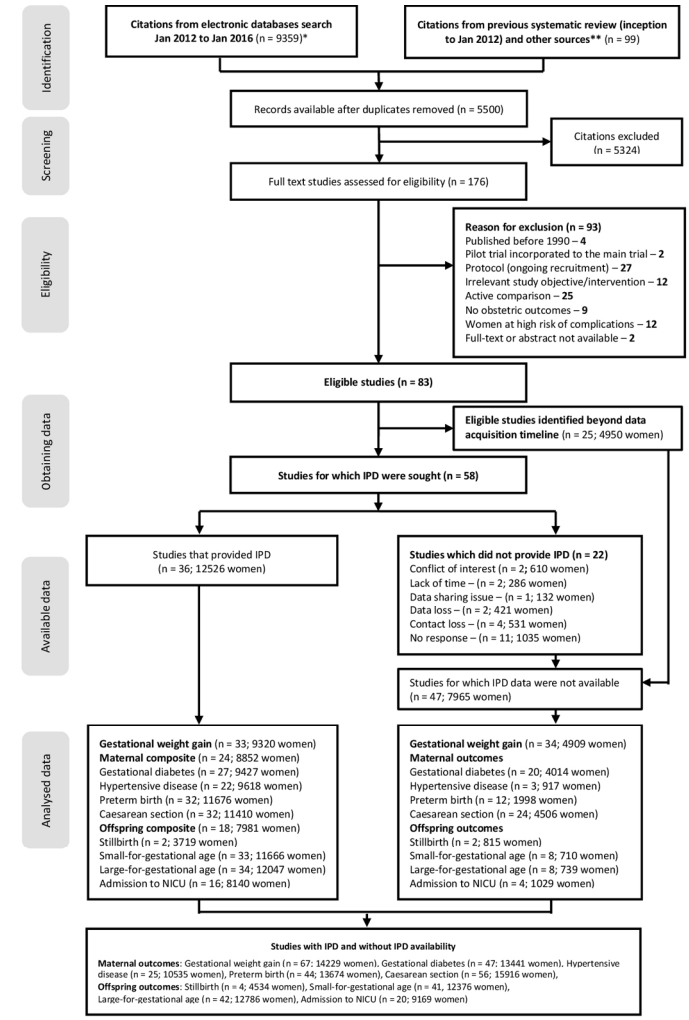
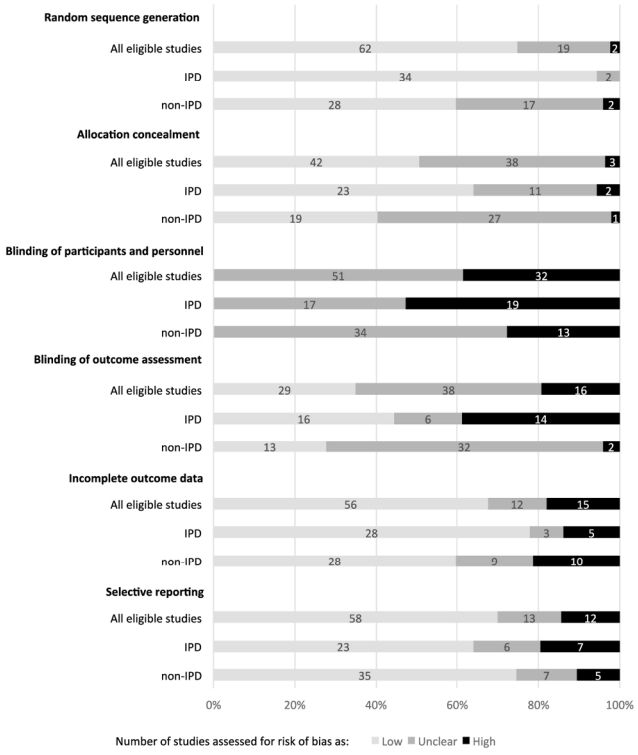
Fig 1 Identification and selection of studies in Individual Participant Data (IPD) meta-analysis of lifestyle interventions on pregnancy outcomes



** Database search was updated three times: in October 2013 (9359 records), March 2015 (3551 records) and Jan 2016 (1379 records);*
*** Other sources: reference search, personal communication, and Google search;*
IPD: individual participant data, NICU: Neonatal Intensive Care Unit

209x297mm (200 x 200 DPI)

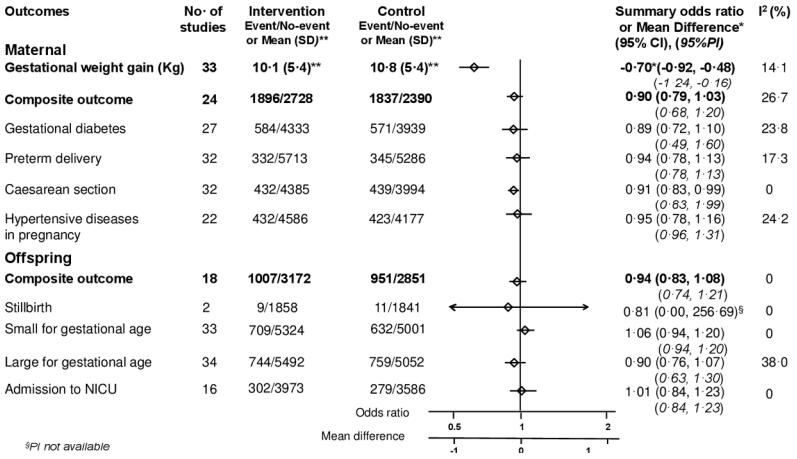
Fig 2. Assessment of risk of bias in all eligible studies (N = 83), studies with IPD (N = 36), and studies without access to IPD (N = 48)



IPD – Individual Participant Data

209x297mm (200 x 200 DPI)

Fig 3. Effects of lifestyle interventions in pregnancy on maternal and offspring outcomes evaluated in IPD (Individual Participant Data) meta-analysis



CI Confidence Interval; PI Prediction Interval

209x297mm (200 x 200 DPI)

Table 1. Differential effects of lifestyle 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	3376	-0·77 (-1·15, -0·39)		
Overweight	28	2574	-0·75 (-1·22, -0·27)	-0·02; -0·08, 0·04 *(-0·21, 0·17)*[§1]	39·8
Obese	31	3335	-0·85 (-1·41, -0·29)		
Parity					
Nulliparous	27	4513	-0·80 (-1·17, -0·43)	0·10; -0·39, 0·60 *(-0·83, 1·04)*[§2]	4·8
Multiparous	27	4548	-0·62 (-0·88, -0·37)		
Ethnicity					
Caucasian	21	6814	-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	9045	-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	4335	-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 (9285 women); [§2]Multipara vs. nullipara, 24 studies (7247 women); [§3]Non-Caucasian vs. Caucasian, 12 studies (4439); [§4]Per yr of age 32 studies, (9277 women); [§5]At least one medical condition vs. none, 5 studies (1196 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	2445	0·91 (0·65, 1·28)		
Overweight	19	2222	1·04 (0·86, 1·26)	1·00; 0·98, 1·02 *(0·98, 1·02)*[§1]	0
Obese	20	4181	0·92 (0·80, 1·05)		
Parity					
Nulliparous	21	4613	0·87 (0·71, 1·07)	1·03; 0·75, 1·39 *(0·53, 2·00)*[§2]	34·0
Multiparous	22	4186	0·92 (0·78, 1·07)		
Ethnicity					
Caucasian	15	6510	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	8656	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	3135	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 (8848 women); [§2]Multipara vs. nullipara, 20 studies (8053 women); [§3]Non-Caucasian vs. Caucasian, 9 studies (4851); [§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)*	I² (%)
Baseline Body mass index (BMI)					
Normal	7	1843	0·93 (0·60, 1·43)		
Overweight	12	2065	0·83 (0·61, 1·13)	0·98; 0·95, 1·00 *(0·94, 1·02)* [§1]	18·5
Obese	13	4327	0·92 (0·72, 1·19)		
Parity					
Nulliparous	16	4152	0·97 (0·80, 1·17)	0·94; 0·64, 1·37 *(0·39, 2·28)* [§2]	35·5
Multiparous	15	4048	0·91 (0·72, 1·15)		
Ethnicity					
Caucasian	11	6018	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	8061	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	3407	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 (7978 women); [§2]Multipara vs. nullipara, 15 studies (7295 women); [§3]Non-Caucasian vs. Caucasian, 9 studies (5146); [§4]Per yr of age, 18 studies (7965 women); [§5]At least one medical condition vs· none, 3 studies (925 women); CI: confidence interval; MD – mean difference; PI: prediction interval

Table 2. Effect of interventions on maternal and offspring outcomes by intervention type based on Individual Participant Data (IPD) meta-analysis, and by incorporating non-IPD to IPD meta-analysis

a) Maternal outcomes

	Overall number of studies (women)	Intervention Mean, SD	Control Mean, SD	MD (95% CI)	I^2 (%)
Gestational weight gain					
Overall (IPD)	**33 (9320)**	**10·1, 5·4**	**10·8, 5·4**	**-0·70 (-0·92, -0·48)**	**14·1**
(Combined IPD and non-IPD)	*67 (22926)*	*10·6**	*11·8**	*-1·18 (-1·59, -0·77)*	*74·8*
Diet	4 (1168)	10·2, 4·4	11·0, 4·8	-0·72 (-1·48, 0·04)	0·0
	11 (1864)	*9·6**	*12·1**	*-3·04 (-5·14, -0·95)*	*92·9*
Physical activity	15 (2915)	9·8, 4·4	10·8, 4·8	-0·73 (-1·11, -0·34)	0·0
	31 (5540)	*10·9**	*11·7**	*-0·80 (-1·09, -0·51)*	*25·8*
Mixed approach	15 (5369)	10·2, 6·0	10·6, 5·9	-0·71 (-1·10, -0·31)	34·9
	26 (6957)	*10·9**	*11·8**	*-0·92 (-1·33, -0·50)*	*51·5*
	Overall number of studies (women)	**Intervention Event/ No-event**	**Control Event/ No-event**	**OR (95% CI)**	**I^2 (%)**
Maternal composite outcome					
Overall	**24 (8851)**	**1896/2728**	**1837/2390**	**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 (2311)	346/850	367/748	0·81 (0·61, 1·09)	10·8
Mixed approach	13 (6259)	1508/1742	1438/3009	0·97 (0·84, 1·12)	34.9
Gestational diabetes					
Overall	**27 (9427)**	**584/4333**	**571/3939**	**0·89 (0·72, 1·10)**	**23·8**
	47 (13441)	*756/6161*	*828/5696*	*0·78 (0·66, 0·93)*	*29·5*
Diet	4 (490)	13/208	19/250	1·03 (0·30, 3·61)	0·0
	7 (900)	*31/396*	*56/417*	*0·68 (0·28, 1·62)*	*38·0*
Physical activity	10 (2700)	90/1351	121/1247	0·67 (0·46, 0·99)	0·0
	20 (4680)	*167/2192*	*242/2079*	*0·66 (0·52, 0·84)*	*0·0*
Mixed approach	14 (6355)	481/2992	441/2787	1·02 (0·79, 1·32)	35·2
	21 (7979)	*558/3573*	*540/3308*	*0·90 (0·72, 1·13)*	*30·8*
Hypertensive diseases in pregnancy					
Overall	**22 (9618)**	**432/4586**	**423/4177**	**0·95 (0·78, 1·16)**	**24·2**
	25 (10535)	*455/5019*	*448/4613*	*0·97 (0·82, 1·15)*	*19·1*
Diet[§]	3 (397)	18/161	39/179	0·59 (0·07, 4·65)	35·8
Physical activity	7 (2565)	55/1387	73/1347	0·74 (0·42, 1·33)	6·0
	8 (2627)	*55/1273*	*76/1223*	*0·72 (0·41, 1·25)*	*8·5*
Mixed approach	13 (6797)	359/3183	322/2933	1·05 (0·86, 1·28)	19·4
	15 (7652)	*382/3585*	*344/3341*	*1·05 (0·88, 1·25)*	*7·0*
Preterm birth					
Overall	**32 (11676)**	**332/5713**	**345/5286**	**0·94 (0·78, 1·13)**	**17·3**
	44 (13674)	*382/6660*	*412/6210*	*0·93 (0·80, 1·08)*	*2·0*
Diet	4 (1344)	9/647	35/653	0·28 (0·08, 0·96)	0·0
	7 (1696)	*13/819*	*45/819*	*0·32 (0·14, 0·70)*	*0·0*
Physical activity	13 (3249)	96/1566	73/1569	1·29 (0·90, 1·85)	0·0
	19 (4615)	*138/2189*	*122/2166*	*1·11 (0·85, 1·47)*	*0·0*
Mixed approach	16 (7219)	228/3525	243/3223	0·91 (0·73, 1·12)	0·0
	19 (7499)	*241/3652*	*251/3355*	*0·93 (0·76, 1·14)*	*0·0*

	Overall number of studies (women)	Intervention Event/ No-event	Control Event/ No-event	OR (95% CI)	I^2 (%)
Caesarean section					
Overall	**32 (11410)**	**432/4385**	**439/3994**	**0·91 (0·83, 0·99)**	**0·0**
	56 (15916)	*983/6079*	*1050/5644*	*0·90 (0·83, 0·97)*	*9·4*
Diet	4 (1340)	117/535	149/539	0·78 (0·50, 1·22)	0·0
	7 (1732)	*238/610*	*264/620*	*0·88 (0·65, 1·17)*	*0·0*
Physical activity	13 (3046)	96/1566	73/1569	0·82 (0·67, 1·01)	0·0
	27 (5657)	*565/2253*	*638/2201*	*0·86 (0·74, 1·00)*	*11·5*
Mixed approach	16 (7160)	228/3525	243/3223	0·95 (0·84, 1·08)	17·6
	23 (8663)	*1273/3216*	*1266/2908*	*0·91 (0·82, 1·03)*	*21·8*

b) Offspring outcomes

	Overall number of studies (women)	Intervention Event/ No-event	Control Event/ No-event	OR (95% CI)	I^2 (%)
Offspring composite outcome					
Overall	**18 (7981)**	**1007/3172**	**951/2851**	**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 (1274)	138/495	143/498	0·99 (0·67, 1·46)	0·0
Mixed approach	12 (6494)	835/2545	797/2317	0·95 (0·81, 1·11)	4·7
Stillbirth[†]					
Overall	**2 (3719)**	**9/1858**	**11/1841**	**0·81 (0·00, 256·69)**	**0·0**
	4 (4534)	*12/2261*	*14/2247*	*0·85 (0·24, 3·02)*	*0·0*
Small for gestational age					
Overall	**33 (11666)**	**709/5324**	**632/5001**	**1·06 (0·94, 1·20)**	**0·0**
	41 (12376)	*739/5680*	*658/5299*	*1·06 (0·95, 1·19)*	*0·0*
Diet	4 (1337)	41/610	47/639	0·92 (0·45, 1·88)	0·0
	5 (1437)	*46/655*	*50/686*	*0·96 (0·53, 1·76)*	*0·0*
Physical activity	14 (3272)	244/1409	233/1402	1·05 (0·84, 1·34)	12·3
	19 (3712)	*263/1635*	*249/1565*	*1·05 (0·85, 1·29)*	*0·0*
Mixed approach	16 (7193)	425/3312	370/3086	1·08 (0·92, 1·28)	0·0
	18 (7363)	*430/3390*	*376/3167*	*1·08 (0·92, 1·27)*	*0·0*
Large for gestational age					
Overall	**34 (12047)**	**744/5492**	**759/5052**	**0·90 (0·76, 1·07)**	**38·0**
	42 (12786)	*784/5848*	*807/5347*	*0·88 (0·73, 1·07)*	*40·7*
Diet	4 (1408)	155/529	176/548	0·91 (0·60, 1·37)	0·0
	5 (1508)	*157/577*	*187/587*	*0·77 (0·43, 1·39)*	*37·2*
Physical activity	15 (3330)	141/1557	135/1528	0·96 (0·59, 1·54)	34·3
	19 (3686)	*147/1737*	*142/1660*	*1·01 (0·68, 1·50)*	*31·1*
Mixed approach	16 (7450)	468/3406	481/3095	0·89 (0·67, 1·17)	51·0
	19 (7733)	*480/3534*	*500/3219*	*0·87 (0·66, 1·14)*	*50·2*
Admission to Neonatal Intensive Care Unit					
Overall	**16 (8140)**	**302/3973**	**279/3586**	**1·01 (0·84, 1·23)**	**0·0**
	20 (9169)	*358/4429*	*356/4026*	*0·95 (0·80, 1·13)*	*0·0*
Diet	1 (289)	3/164	17/422	*na*[#]	*na*
	2 (389)	*11/179*	*29/170*	*0·33 (0·00, 47·97)*	*0·0*
Physical activity	3 (1166)	31/603	40/601	0·77 (0·21, 2·81)	20·8
	4 (1240)	*34/586*	*43/577*	*0·79 (0·35, 1·78)*	*0·0*
Mixed approach	13 (6818)	268/3381	230/3122	1·10 (0·89, 1·35)	0·0
	15 (7673)	*313/3664*	*288/3408*	*1·03 (0·85, 1·24)*	*0·0*

Combined IPD and non-IPD analysis are provided in Italics.
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

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

Appendix 2 Characteristics of eligible randomised trials on lifestyle 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	2199	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	1554	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 ≥ 25
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 cluster

b. Studies that did not contribute IPD

Study ID	Country	Sample size*	Intervention	BMI group
Asbee 2009	US	100	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	US	46	Diet	All BMI groups
Briley 2002	US	20	Diet	All BMI groups
Brownfoot 2016	Australia	741	Mixed approach	All BMI groups
Clapp 2000	US	46	Physical Activity	All BMI groups
Cordero 2014	Spain	247	Physical Activity	All BMI groups
Daley 2015	UK	68	Mixed approach	All BMI groups
Das 2015	US	36	Diet	All BMI groups
de Oliveria Melo 2012	Brazil	171	Physical Activity	All BMI groups
Dekker 2015	US	35	Physical Activity	BMI ≥ 30
Deveer 2013	Turkey	100	Diet	All BMI groups
Di Carlo 2014	Italy	120	Diet	All BMI groups
Garshasbi 2005	Iran	212	Physical Activity	All BMI groups
Gesell 2015	US	87	Mixed approach	All BMI groups
Gomez Tabarez 1994	Colombia	60	Diet	BMI ≥ 30
Hawkins 2015	US	68	Mixed approach	BMI ≥ 25
Herring 2016	US	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	US	287	Mixed approach	All BMI groups
Jing 2015	China	221	Mixed approach	All BMI groups
Koivusalo 2015	Finland	269	Mixed approach	BMI ≥ 25
Kong 2014	US	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	US	15	Mixed approach	All BMI groups
Mujsindi 2014	US	79	Diet	BMI ≥ 25
Murtezani 2014	Republic of Kosovo	63	Physical Activity	All BMI groups
Polley 2002	US	110	Mixed approach	BMI ≤ 30
Price 2012	US	62	Physical Activity	All BMI groups
Qiuling Li 2014	China	118	Mixed approach	All BMI groups
Quinlivan 2011	Australia	124	Diet	BMI ≥ 25
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
Thornton 2009	US	232	Diet	BMI ≥ 30
Vesco 2014	US	114	Mixed approach	BMI ≥ 30

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

Appendix 3 Baseline characteristics of women included in studies that contributed to the IPD meta-analysis on lifestyle interventions in pregnancy

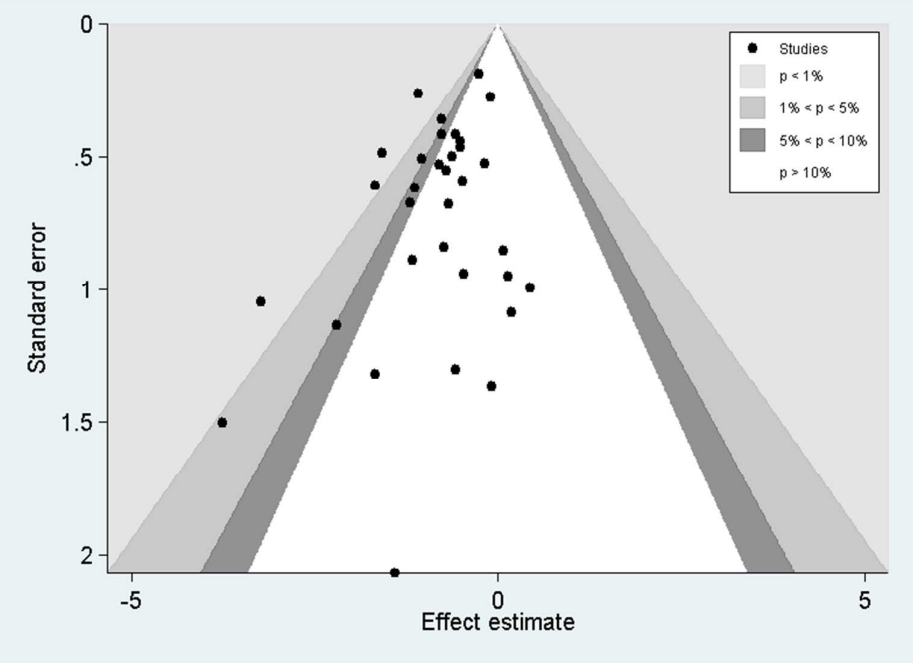
Baseline characteristics	No. of studies	No. of women	Intervention Mean (SD) or N (%) †	Control Mean (SD) or N (%) †
Age (yrs)	35	12006	30.0 (5.1)	30.1 (5.2)
Normal weight (BMI 18.5 – 24.9)	34	12031	1974 (31.7%)	1842 (31.8%)
Overweight (BMI 25 – 29.9)	34	12031	1578 (25.3%)	1523 (26.3%)
Obesity (BMI ≥ 30)	34	12031	2680 (43.0%)	2434 (42.0%)
Race/Ethnicity:	27	10020		
Caucasian (incl Russia & Australia)			4562 (88%)	4217 (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	8914		
Low			722 (15.6%)	724 (16.9%)
Medium			1372 (29.6%)	1292 (30.2%)
High			2536 (54.8%)	2268 (52.9%)
Smoker	29	10958	875 (15.4%)	865 (16.4%)
Parity:	33	11805		
0			3027 (49.5%)	2692 (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	1761 (44.6%)	1731 (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*

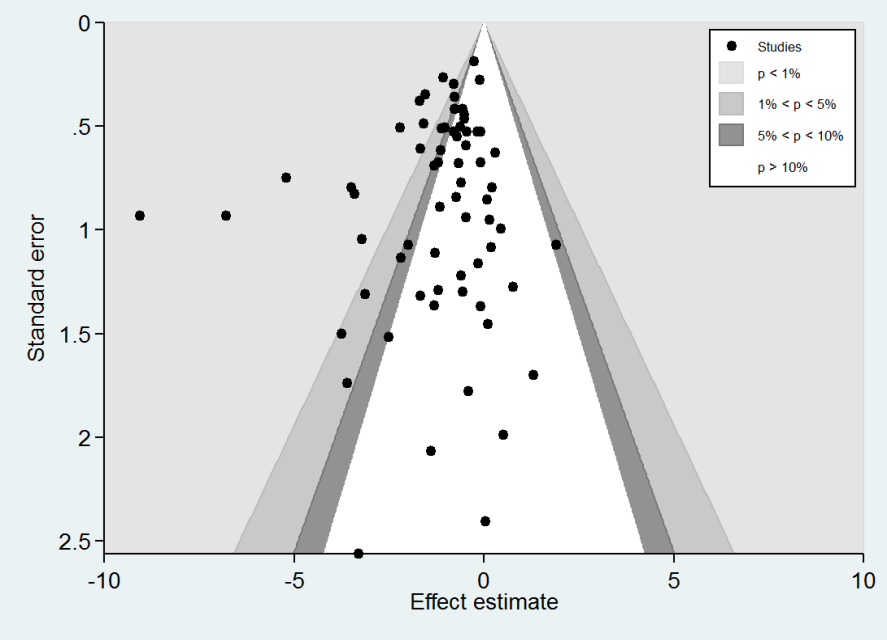
Appendix 4 Assessment of small study effects on of trials in IPD meta-analysis of lifestyle interventions in pregnancy

a. Gestational weight gain

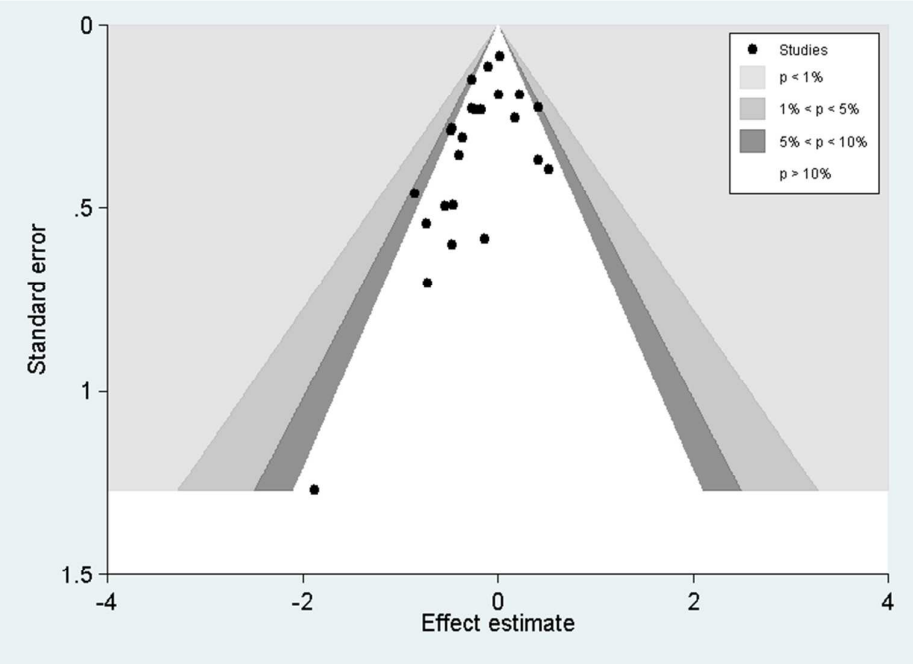
IPD studies



IPD and non-IPD studies



b. Maternal composite outcome



c. Offspring composite outcome