Diet and physical activity based interventions in pregnancy: Study-level and Individual Participant Data (IPD) meta-analyses

By

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Statement of originality

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Dedication

To my friends and family

Abstract

Evidence synthesis is considered a corner stone of modern health care and clinical practice. Systematic reviews of randomised trials, when undertaken with meta-analysis provide summary estimates on the effectiveness of interventions. However, the findings of meta-analysis are often limited by the selective reporting of primary studies, and the variations in population, intervention and outcomes. Furthermore, difficulties in disentangling the study and individual level associations in meta-analysis make them susceptible to ecological fallacy, and may lead to incorrect conclusions.

Meta-analysis using Individual Participant Data (IPD) has the potential to overcome many of the above limitations, by using raw trial data. Access to IPD minimises problems from incomplete or incorrect reporting of trial outcomes, by verifying reported results, and by standardising the definition of outcomes where possible. Importantly, this allows detecting any variation in the effects of interventions according to characteristics of the participants. Amalgamated individual datasets assembled to address the effectiveness question, can be further used to explore secondary objectives such as the relationship between surrogate and clinical outcomes. This maximises the use of available clinical data, and addresses the problem of research waste.

In this thesis, I evaluated the effects of diet and physical activity based interventions in pregnancy on maternal and offspring outcomes using both study-level and IPD meta-analyses, and assessed the differential effects of interventions on outcomes according to mother's BMI pre or in early pregnancy. I reviewed the variation in outcomes reported in this field, and developed composite outcomes for IPD meta-analysis. I also evaluated the relationship between weight gain in pregnancy and clinical outcomes in pregnancy using the IPD meta-analysis methodology.

Executive Summary

Aims

The aim of this thesis was to evaluate the effects of diet and physical activity based interventions in pregnancy on clinical outcomes using standard and advance methods of evidence synthesis; assess the variation in outcomes and their clinical importance in a trial with those interventions and examine the relationship between gestational weight gain and important clinical outcomes.

Methods

Delphi methodology, systematic reviews of literature, and meta-analyses using study-level and individual participant data of randomised controlled trials (RCTs).

Results

Composite outcomes

Developed composite outcomes comprise of four maternal (gestational diabetes, hypertensive disorders in pregnancy, preterm birth, caesarean section) and four offspring outcomes (stillbirth, small for gestational age, large for gestational age, and admission to neonatal intensive care unit). The components to assess maternal composite outcome were available in two-thirds (66.7%, 24/36) and for offspring composite in half (50%, 18/36) of the studies in the IPD meta-analysis. The effect of interventions was not statistically significant neither on the maternal nor on the offspring composite – Odds Ratio (OR) 0.90 (95% CI 0.79, 1.03) and OR 0.94 (95% CI 0.83, 1.08), respectively. The direction of the pooled effect was consistent between the composite and its components for the maternal composite and variable for the offspring outcomes.

Effects of diet and physical activity based interventions

The IPD meta-analysis of 36 RCTs (>12 500 women) showed a significant effect of diet and physical activity based interventions in pregnancy in reducing gestational weight gain (Mean Difference -0.70 kg, 95% CI -0.92, -0.48) and chance of caesarean section delivery (OR 0.91, 95% CI 0.83, 0.99) in comparison to routine antenatal care. There was no effect of the interventions on any of the offspring complications. Incorporation of outcome data unavailable on study-level returned more modest magnitude of the summary estimates in comparison to effects obtained using study-level data of trials that shared IPD. The addition of study-level data from non-IPD trials changed the magnitude and the statistical significance of the summary effects on GDM – from OR 0.89 with only IPD (95% CI 0.72, 1.10; 27 studies, 9 427 women) to OR 0.76 (95% CI 0.65, 0.89; 59 studies, 16 885 women). It has also changed the funnel plot structure in the meta-analysis for gestational weight gain (Egger's test p = 0.04 with only IPD to p= 0.61).

The IPD meta-analysis shows that the effects of diet and physical activity based interventions on the maternal and the offspring outcomes did not differ by women's BMI status. While the study-level meta-regression indicated that the interventions might reduce gestational weight gain stronger for the obese women – coefficient -0.22 (95% CI -0.33, -0.11) for each 10% change in the proportion of women in the obese class.

Outcomes in trials with diet and physical activity based interventions

66 primary publications from trials with diet and physical activity based interventions in pregnancy reported 142 outcomes. Half of those outcomes appeared in the publications once (72/142). 'Critically important' outcomes are reported less often in comparison to 'non-critical' ones (15.5%, 22/142 vs 68.3%, 97/142). The overall quality of outcome reporting varied between trials with the least frequently provided information on the methods to improve the quality of outcome measures (33.3%, 22/66 publications).

Gestational weight gain and pregnancy outcomes

IPD from 4 429 pregnant women randomised to the control arms of RCTs with diet and physical activity based interventions were available for the analysis. Women who most often exceeded the IOM recommendation belonged to the overweight (51.5%, 641/ 1 245 women) and the obese groups (44.5%, 695/ 1 562 women) while women with normal BMI most often gained below the recommended amounts (40%, 649/1 622 women). Each kilogram of gestational weight gain within the IOM ranges was not link with a change in the chances of preterm birth, caesarean section, or birth of LGA and SGA infant. Not achieving of the recommended weight was associated with the decreasing chance of giving birth to LGA infant with each kilogram below the lower limit among the obese women (OR 0.80, 95% CI 0.65, 0.99). Each kilogram of weight gain above the upper limit was associated with an increase in the chance of caesarean section (adjusted 1.04, 95% CI 1.01, 1.08) and delivering LGA infant (adjusted 1.08, 95% CI 1.05, 1.12) regardless on women's BMI status.

Conclusions

Diet and physical activity based interventions in pregnancy moderately reduced gestational weight gain and decrease the odds of caesarean delivery. Overall, IPD meta-analysis improved the robustness of the evidence synthesis of RCTs with diet and physical activity based interventions. However, more attention is needed for the data-related issues in IPD meta-analysis as the purported benefits of the method are not always practically realised. The use of the composite outcomes was hampered by the variable availability of important clinical outcomes. The introduction of minimal core outcome set would facilitate the comparison of the wide range of the evaluated interventions and improve implementation of the composite outcomes. Gestational weight gain was found to be associated with the odds of delivering LGA infant and caesarean section. Future research should aim to collect and report a minimal set of outcomes, and ensure better reporting of study conduct and its findings.

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Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
ANCOVA	Analysis of covariance	i-WIP	International Weight management In Pregnancy
BMI	Body Mass Index	LGA	Large-for-Gestational Age
CI	Confidence Interval	MD	Mean Difference
COMET	Core Outcome Measures in Effectiveness Trials	NICU	Neonatal Intensive Care Unit
CONSORT	Consolidated Standards of Reporting of Randomised Controlled Trials	NIHR	National Institute for Health Research
COS	Core Outcome Set	OR	Odds Ratio
CROWN	CoRe Outcomes in Women's and Newborn health	PE	Pre-eclampsia
EBM	Evidence Based Medicine	PIH	Pregnancy Induced Hypertension
GDM	Gestational Diabetes Mellitus	QR	Quartile
IOM	Institute of Medicine	REML	Restricted maximum likelihood
IPD	Individual Participant Data	RCT	Randomised Controlled Trial
I^2	I-squared statistic	SD	Standard Deviation
IQR	Inter Quartile Range	SGA	Small-for-Gestational Age

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Peer-reviewed publications arising from this thesis

No	Publications	Title	Chapter
1	Rogozińska E, D'Amico MI, Khan KS, et al. BJOG 2016; 123(2):190-8	Development of composite outcomes for Individual Patient Data (IPD) meta-analysis on effects of diet and lifestyle in pregnancy: A Delphi survey	3
2	Rogozińska E, Marlin N, Betran AP et al. BMJ 2017; 358:j3119	Effects of diet and physical activity-based interventions on maternal and fetal outcomes in pregnancy: Individual participant data (IPD) meta-analysis of randomised trials	4,5
3	Health Technol Assess 2017; 21(41)		
4	Rogozińska E, Marlin N, Feng Y, et al. JOGR 2017; doi:10.1111/jog.13338	Variations in reporting of outcomes in randomised trials on diet and physical activity in pregnancy: a systematic review	6
5	Rogozińska E, Marlin N, Khan KS et al. EBM 2017; doi: 10.1136/ebmed-2017-110775	Meta-analysis using individual participant data from randomised trials: opportunities and limitations created by access to raw data	8

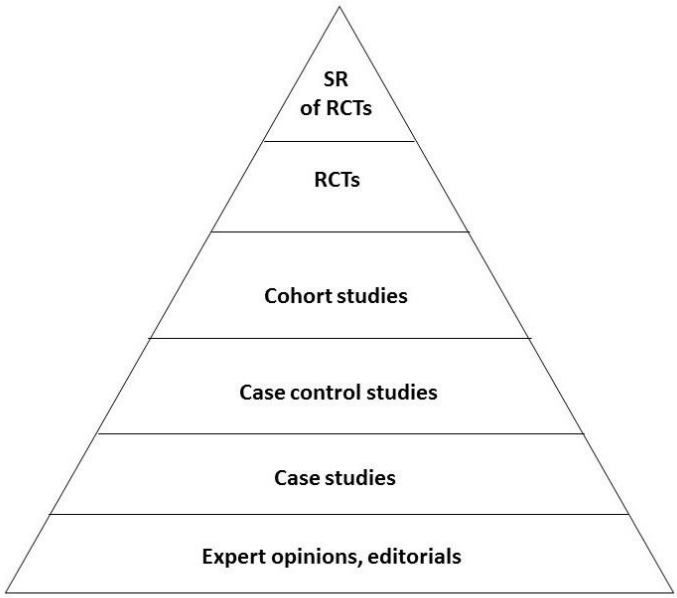
Chapter 1 Introduction

1.1. Evidence synthesis of randomised trials and its role in the modern health care

Decisions in health care and medicine to effectively inform clinical practice should be based on all available body of evidence.[1] 'Evidence synthesis' is a term used to describe a formal way of systematic and critical appraisal of information. For over three decades it has played a pivotal role in medical decision making and has constituted the basis of Evidence-Based Medicine (EBM).[2] The overarching aim of the evidence synthesis is to inform clinical practice, identify new research questions, and improve the design of future studies.[3,4]

While evidence synthesis refers to a broader concept of data synthesis, a systematic review is a process of identification, evaluation, and provision of a summary of the findings from all studies relevant to the prespecified question.[5] The key strengths of this approach, in contrast to the traditional review, are transparency and reproducibility. This systematic and transparent approach to bringing together all of the available evidence on a given subject, and minimises bias arising from an unwarranted emphasis on 'exciting' studies.[5-7] Additionally, it incorporates formal quality appraisal of trial design and conduct.[5,7,8] In the hierarchy of evidence, a systematic review with meta-analysis of randomised controlled trials (RCTs) is being considered the highest level of evidence synthesis when assessing the effectiveness of interventions[9] (Figure 1.1).

Figure 1.1 Hierarchy of evidence in medical research



RCT, randomised controlled trial; SR, systematic review

Systematic reviews identify research gaps and are a key part of research grant applications. Moreover, they are used to inform policy making and health care guideline.[3,10] Leading health organisations such as the World Health Organisation (WHO) worldwide [11], National Institute for Health and Clinical Excellence (NICE)[12,13], Scottish Intercollegiate Guidelines Network (SIGN)[14] in the UK in their guidelines development process rely on the best available evidence synthesised and reported following rigorous methods.

1.2. Challenges in evidence synthesis

The exponential increase in the volume of currently available evidence with varied reporting[15], results in systematic reviews being redundant or irrelevant[16]. Around 65% of systematic reviews on the same topic failed to include any additional outcomes[16]. Meta-analysis was introduced to quantify the summary estimates, and to interpret the overall body of evidence.[8,17] Furthermore, meta-analysis can improve the precision of effect estimates in comparison to individual studies, quantify true differences in the estimated effect between the

studies, detect problems with existing evidence and generate new hypotheses.[17] The greatest advantages of this method its inexpensiveness and accessibility to researchers without advanced statistical skills. The majority of meta-analyses uses data extracted from trials publications or obtained directly from study authors in a summary form.[5,7] However, study level summaries have reduced power to identify patients who benefit the most from interventions.[18]

Subgroup analyses within systematic reviews could assess the effects in particular groups of patients, nonetheless, they are subject to availability of data in trials' publications.[19] Such findings are usually considered to be a hypothesis-generating exercise [20]. Another approach is to identify factors (e.g. participant characteristics) that modify the response to the intervention, through meta-regression. Due to difficulty in disentangling the study-level and individual-level associations,[20-22] both methods are susceptible to ecological fallacy, [23] and can lead to incorrect conclusions.

The study-level meta-analysis depend on the quality of trial reporting therefore being vulnerable to biases arising from inaccurate or incomplete reporting. Reporting bias arises when the research findings are revealed selectively due to their nature.[5] Trials with undesirable or unimpressive findings tend to be published with happens with a significant delay or not published at all. It has been recognized that 'positive' trials (with a significant findings) have a greater chance of being published sooner, in English and in a high impact journal rather than the 'negative'.[24] This extreme case of reporting bias, referred to as 'publication bias', over the years has been extenivelly discussed in the methodological literature[25-30], however, it is not as prevalent as other reporting-related issues hampering evidence synthesis.

Selective or incomplete reporting of outcome data can potentially have a substantial impact on the validity of a systematic review.[31,32] An evaluation of Cochrane reviews showed that 37%

of pre-specified outcomes were later not reported in trials publications.[33] Furthermore, two-third of Cochrane reviews was missing some percentage of participants' data on a single primary outcome.[34] Other research has shown an association between positive result for the outcome and the completeness of its reporting.[35] Outcomes are not being reported (or are reported only partially), defined and measured in various ways making evidence synthesis, and drawing meaningful conclusions difficult.[36]

Outcomes in clinical trials and evidence synthesis should be selected based on their importance and relevance to patient care. However, the challenge with collections of important health outcomes in the trials is that might rarely occur or be expensive to measure.[37] Surrogates of important health outcomes are frequently used in clinical trials to overcome those constraints.[38] They are based on an assumption of a direct link between the surrogate and the important health outcomes.[37] However, they are frequently reported inadequately[39] and for many surrogates this link might be questionable as the response to the intervention on the surrogate might be different in comparison to the main outcome of interest e.g. cholesterol level and stroke rates[40,41].

1.3. Methods to improve evidence synthesis

The recently published EBM manifesto call for the tools to eradicate the systematic bias and error in the research underpinning health care.[42] Meta-analysis using individual participant data (IPD) is one of the tools that have the potential to fulfil the EBM manifesto's goals. By overcoming the limitations of the study-level synthesis, IPD meta-analysis earned a status of a 'gold standard' in evidence synthesis of effectiveness trials.[43-45] The advantages of this advanced approach to meta-analysis are numerous,[43,45,46] such as the ability to account for the correlation between multiple endpoints, deal with missing data, or verify results presented in the original study reports. Access to IPD allows addressing outcome-related problems in evidence synthesis such as outcome reporting bias.[45,46] When more than one clinical outcome

is considered to be relevant or events are infrequent use of composite outcome seems to be a reasonable option.[47-49] However, this type of meta-analyses are prone to challenges due to data acquisition (availability bias) and the statistical analysis requires more advanced methods and skills than meta-analysis using data extracted from the articles.[45] A recent study showed that only 25% of evaluated IPD meta-analyses obtained 100% of eligible trial data with the most frequently lack of specific reason for IPD unavailability.[50] The meta-analysis using IPD is a costly and time-consuming approach to evidence synthesis what potentially contributes to their low uptake in clinical decision making.[51]

Variation in choice of trial outcomes and the quality of their reporting recently gained more attention on the medial research agenda.[52-54] In response to the problems associated with use and reporting of outcomes in primary and also secondary studies a concept of a core outcome set (COS) has been established.[52] COS is a minimal list of critical outcomes identified through a robust and transparent way. The outcomes from such a list should be routinely collected and reported in all trials in a specific clinical area.[52] It has been indicated [34,55] and subsequently demonstrated[56] that introduction of COS has the potential to address the problems with selection and reporting of trial outcomes therefore improving the evidence synthesis and the health care.[57]

1.4. Obesity and high weight gain in pregnancy

Maternal obesity and Body Mass Index (BMI) above 25 kg/m^2 in pregnancy have been linked with an increased risk of poor health outcomes for the women and her child.[58-60] Obese women are a higher risk of a miscarriage, problematic labour or metabolic and cardiovascular disorders.[61] Whereas, their children are deemed to be at risk of prematurity[62] and major congenital malformation[63], and in the long-term childhood obesity and associated with it illnesses.[60] Advice on the optimal gestational weight gain and ways to achieve it are among the main controversies around the management of obesity in pregnancy.[64] The evidence also

suggests that high weight gain in pregnancy is associated with an increased chance of maternal and fetal complications[65-67] even for women entering pregnancy with BMI within the normal range.[68,69] Furthermore, women with a high gestational weight gain in their first pregnancy are more likely to enter subsequent pregnancies heavier putting themselves and their future offspring at a higher risk of health problems.[70]

The most frequently referenced guidelines on the amount of weight gain in pregnancy to avoid poor pregnancy outcomes are issued by the Institute of Medicine (IOM). The IOM recommendations initially released in 1990, then updated in 2009, advise women entering pregnancy to gain 11 16 kg, 7 – 11 kg or 5 – 9 kg if they entered pregnancy with normal BMI, overweight or obese, respectively.[71] However, the health policy makers worldwide do not always recommend these ranges due to the low certainty of the evidence used to inform the IOM guidelines.[72-74] The studies evaluating the relationship between gestational weight gain and the adverse pregnancy outcomes are limited by similar factors.

1.5. Effect of diet and physical activity based interventions in pregnancy

Acceptable and safe interventions to manage women's weight in pregnancy have been sought with diet, physical activity, weight gain monitoring and behavioural change techniques being at the forefront. Over 40 systematic reviews of RCTs (eight Cochrane reviews including their updates) evaluating the effects of diet and physical activity based interventions in pregnancy have been published between 2003 and 2017. The reviews included from none up to 61 trials evaluated the effects of the interventions overall or individually grouping them as 'diet only', 'physical activity only', or a combination of both diet and physical activity. The main outcomes of interest were gestational weight in pregnancy and gestational diabetes (GDM) with a wide range of secondary maternal and offspring outcomes. The interventions were evaluated in various population – women across entire spectrum of BMI values or in its particular spectrum (overweight, obese), women at risk of pregnancy complications, etc. The

majority of them concluded that the findings are either inconclusive or uncertain. The main limitations were poor quality of identified trials, clinical and statistical heterogeneity of the pooled effects that could not be address by subgroup analysis or in meta-regression, variation in the type of evaluated outcomes and interventions (components, duration, and frequency). A tabulated summary of the aims, populations and results of the individual systematic reviews with their references is available in Appendix 1.1.

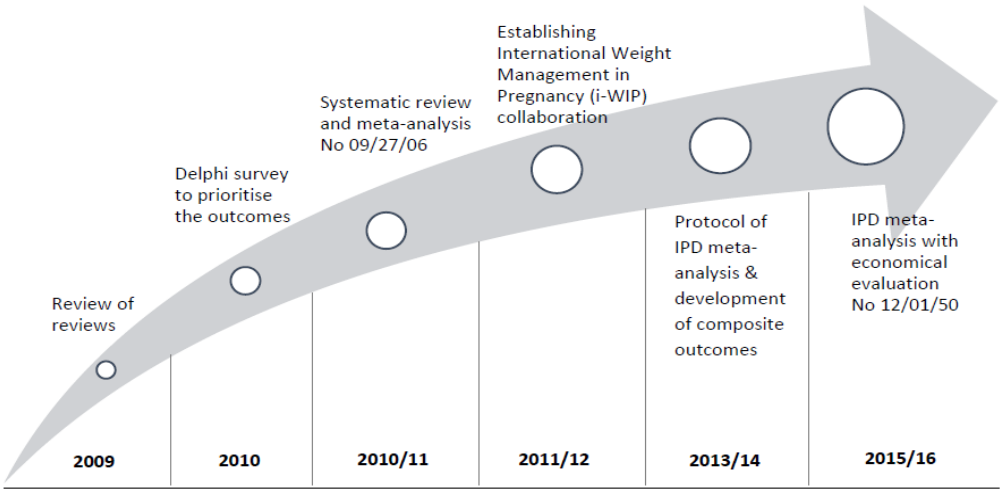
1.6. IPD meta-analysis and establishment of collaborative group

A systematic review commissioned by the National Institute for Health Research (NIHR) of 44 RCTs on diet and physical activity based interventions showed a significant reduction in gestational weight gain (review's primary outcome) with the diet and physical activity-based interventions when compared to a routine antenatal care.[75,76] The evidence synthesis also showed some evidence of the positive effect of the interventions in the reduction of pre-eclampsia and shoulder dystocia.[76] The subgroup analysis of diet-only studies showed a greater reduction in gestational weight gain that all interventions combined. The limitations of the systematic review were similar to others limited namely the substantial statistical heterogeneity in the pooled effects, uneven reporting of important clinical outcomes across the studies, and lack of information on the effects of interventions by potential intervention effect modifiers like booking BMI, women's age or ethnic origin.

A collaborative group of investigators involved in the primary trials with diet and physical activity based interventions in pregnancy was established in 2011 with a successful grant application for an IPD meta-analysis of RCTs with diet and physical activity that followed soon after[77](Figure 1.2). Within the next years, the international Weight management In Pregnancy (i-WIP) collaboration brought together over 50 researchers from 16 countries across five continents.[78] The primary objective of the i-WIP IPD meta-analysis was to determine the differential effects of weight management interventions in pregnancy on

maternal weight gain and composite maternal and composite fetal outcomes in subgroups women based on BMI at booking, age, parity, ethnicity and underlying medical conditions. The study's secondary aim was to address an issue of the relationship between the amount of weight gained during pregnancy and the risk of adverse pregnancy accounting for women's BMI at the beginning of pregnancy.[79]

Figure 1.2 Work leading to Individual Participant Data meta-analysis on effects of diet and physical activity based intervention in pregnancy



IPD, Individual Participant Data

1.7. Aims and objectives of the thesis

The overarching aim of this thesis was to evaluate the use and impact of advanced methods of research synthesis when applied to RCTs of the effects of diet and physical activity based interventions in pregnancy. The specific objectives of this thesis were as follows:

1) Develop composite outcomes for assessing effects of diet and physical activity based interventions in pregnancy in order to perform the i-WIP IPD meta-analysis
2) Assess overall summary effects of the interventions on pregnancy outcomes using IPD and study-level meta-analysis

3) Assess the modifying effect of maternal booking BMI on the treatment effect using meta-analysis based on IPD and study-level meta-analysis
4) Assess the variation in reporting of trial outcomes in RCTs with diet and physical activity in pregnancy
5) Evaluate the gestational weight gain and corresponding adherence to the IOM 2009 recommendations[80] as a surrogate of clinically important outcomes

The following techniques were applied to address the above questions concerning effects of diet and physical activity based interventions in pregnancy: Delphic surveys, IPD collation, IPD meta-analysis variants, meta-regression to explore study heterogeneity, and multivariable models for evaluating associations.

In my thesis, I will not attempt to quantify the potential gains from accessing IPD in comparison to aggregate-data for meta-analysis of effectiveness trials. Furthermore, as the impact of potential sources of heterogeneity such as non-compliance or risk of bias in individual studies has been covered in detail in the HTA NIHR report, it will not be discussed within the scope of this thesis.

Chapter 2 Overview of methods used in the thesis

2.1. Introduction

The aim of this chapter is to describe and explain methods used to address the overall aims of this thesis. The individual objectives of the chapters and the methods are outlined in Table 2.1. I first describe the process of developing a composite outcome to be used in i-WIP IPD meta-analysis (section 2.1). Next, I describe the systematic review methodology used to address objectives 1 to 4 of this thesis on effectiveness of intervention (section 2.2). The section explains the general principles guiding systematic review process and explains how it is applied in individual chapters. Further details on the methods are provided in Chapters 4, 5 and 6. Thirdly, I provide description of the statistical methods used to pool together by using a) study-level data extracted from the studies' publications, and b) participant-level data obtained from original trials where possible. The fourth section discusses sources of bias in evidence synthesis in particular the outcome reporting and availability bias, and impact of effect estimates from small trials ('small-study effects'). In the final section of this chapter, I described development of regression models presented in this thesis.

Table 2.1 Questions in the structured format for individual chapters

Chapter Number	Population	Intervention or Exposure	Outcome(s)	Method(s)
Objective I: Development and use of composite outcome in IPD meta-analysis				
3	Researchers from i-WIP Collaborative Group	Outcomes relevant to women's weight management antenatally	Maternal and offspring outcomes	Delphi survey criteria for composite outcome development
Objective II: Overall effect of interventions: IPD and study-level meta-analysis				
4	Pregnant women from RCTs with interventions based on diet and physical activity in pregnancy	IPD meta-analysis vs meta-analysis using study-level data	Gestational weight gain, maternal and offspring outcomes	Systematic review Study-level and two-stage IPD meta-analysis
Objective III: Modifying effect of booking BMI: IPD and study-level meta-analysis				
5	Pregnant women from RCTs with interventions based on diet and physical activity in pregnancy	IPD meta-analysis vs meta-regression using study-level data	Gestational weight gain, maternal and offspring outcomes	Meta-regression and two-stage IPD meta-analysis
Objective IV: Variation in outcome reporting				
6	Trials with interventions based on diet and physical activity in pregnancy	Reporting of clinical outcomes	Type and range of outcomes in RCTs Quality of outcome reporting	Systematic review and regression analysis
Objective V: Relationship between gestational weight gain and adverse pregnancy outcomes				
7	Participants from control arms of RCTs with interventions based on diet and physical activity in pregnancy	Gestational weight gain within respective IOM ranges	Maternal and offspring outcomes	One-stage IPD meta-analysis

RCT, randomised controlled trial; IPD, individual participant data; IOM, Institute of Medicine

2.2. Development of composite outcome using Delphi methodology

2.2.1.Rationale for composite outcome

One of the main reasons for using composite outcomes in medical research is the problem of selecting just one outcome important to patient care.[47] More commonly the choice in not obvious and varies from researcher to researcher. Secondly, outcomes perceived as critically important e.g. maternal mortality or eclampsia are rarely encountered what makes it difficult to power any study to detect an effect of the intervention on these without recruiting thousands of women and making study logistically challenging. The introduction of composite outcomes allows addressing above pitfalls; however, it comes with certain challenges. Composite outcomes, frequently used in cardiovascular research, have been accused of leading to exaggerated estimates of observed treatment effects and difficulty with their interpretations.[41,81]

In order to ensure that the composite outcome will be a valid one, it needs to include outcomes that are relevant and critically important to a given research question. Historically, the importance of the outcomes was defined by a panel of experts led by the ones with the greatest seniority. The introduction of Delphi methodology to harvest opinions and prioritise them introduced an egalitarian spirit and allowed the less senior specialist to have their saying. Delphi methodology has been used to prioritise outcomes by their relevance to patient care when evaluating diet and physical activity based interventions in pregnancy and subsequently develop composite outcomes, separately for the women and the offspring, for use in i-WIP IPD meta-analysis (chapter 3).

2.2.2.Delphi methodology

The Delphi survey consists of a predefined number of iterations. The survey usually begins with an open-ended question that is circulated to a group of experts and opinion leaders on the topic. After obtaining the responses from the pannelists, they are analysed in a qualitative way aiming to tease out common themes. The finding of the initial survey is used to inform the subsequent, more structured questionnaire. The second questionnaire tends to ask to rate or rank presented items and facilitates a quantitative analysis of the responses. Convergence in the consecutive rounds of the survey indicates a consensus among the panellists' responses.[82,83] The primary list of outcomes (equivalent to an open-ended questionnaire) was derived from a systematic review and a previous Delphi survey[75]. The panel of experts was established by inviting to the surveys the researchers involved in development and conduct of RCTs evaluating the effects of diet and physical activity based interventions on pregnancy outcomes. The invitation was also extended on to researchers involved in the conduct of the i-WIP IPD meta-analysis.[79] The majority of the panellists belongs to the i-WIP Collaborative Group (section 1.6).

2.2.3. Application of Delphi method in the thesis

The survey was run in two stages between June and September 2013. On the first stage, the researchers were invited to score the previously established list of maternal and offspring outcomes. Each outcome, on the list was provided with the median and Inter Quartile Range (IQR) for its importance as derived from the previous work.[75] The panellists could score the outcomes between one and nine; a score of 9 is considered to be critical, and 1 is of limited importance to patient care (Likert scale). During this round the responders were presented with an opportunity to add outcomes they considered to be important, yet not appearing on the list. In the case of lack of response, the panellist received two reminders after two, and four weeks from the date when the survey was sent initially. Those who did not respond in the first

round were not invited to a subsequent one. All available responses were assessed, and the medians and IQR of received scores were calculated for individual outcomes.

In the second round, the panellists received the average scores from round one collated with their individual scoring. They were asked to reflect on the scoring and again assign ranks to the outcomes. An IQR of two or less was assumed to indicate a consensus among the responses. The panellists were unaware of other responders' scores throughout the entire process. I was responsible for sending the surveys, collating the data and was the only person who knew the responses of the individual panellists. After both rounds the scores for individual outcomes were collated and summarised.

2.2.4. Criteria of composite outcome's components

The outcomes with a median response score of seven or more accompanied by IQR of 2 or less indicating consensus among the responders in the Delphi survey were considered candidates for the development of the composite outcomes. The outcomes in order to be considered a component for inclusion in the composite outcome had to meet the following criteria:

a) Considered to be critically important by the Delphi panel
b) Outcomes of equal importance
c) With similar rates of occurrence
d) Independent of each other, and
e) Based on prior evidence of the same direction of the intervention effect.[47,49]

The composite outcome of adverse events was developed separately for the women, and the offspring and the outcomes considered surrogate of women's or offspring's morbidity and mortality were eliminated from the process.

2.3. Systematic review of the effectiveness trials

A systematic review is a process of identification, evaluation and summary of the findings from all studies relevant to the prespecified question.[84] There are five main steps of a systematic review: framing a clearly defined and focused question, systematic and comprehensive literature search, assessment of study quality, a summary of evidence and their interpretation. The review earns term "systematic" whenever it followed above process[85] and the key strengths of this approach, in contrast to traditional review, are transparency and reproducibility.[11,84] The systematic review is guided by a structured question describing population, intervention of interest, comparator and outcome(s) (PICO acronym). It is important to evaluate how the each of them can differ between existing trials as this will substantially impact subsequent steps of the review process e.g. study selection and evidence synthesis.[85] The review question should be defined before embarking on the systematic review and not substantially changed during the entire process.[7,86] The authors are also encouraged to register their work prospectively to avoid duplication of efforts, reduce bias and to promote transparency.[87]

Identification of relevant evidence in the systematic review should be extensive and performed in relevant electronic databases of medical literature supplemented by a manual search of the grey literature. This approach prevents cherry-picking of the studies and allows to generate a comprehensive list of citations to address the question. There should be no language and time restriction unless there is a clear rationale for implementing them e.g. intervention changed substantially over the years. The assessment of citations and full text of potentially eligible publications should be done by independent individuals, exclusion and inclusion reasons documented and the entire selection process described.[88]

2.4.1.Methods applied in this thesis

Both systematic reviews conducted in this thesis followed PICO question (Table 2.2). The aim of the review in chapter 4 was to evaluate the effect of diet and physical activity based interventions in pregnancy of gestational weight gain and adverse pregnancy outcomes. It was guided by a prospectively developed and registered protocol (PROSPERO registration number: CRD42013003804). The aim of the systematic review in chapter 6 was to evaluate the range and frequency of outcomes reported in trials on diet and physical activity based interventions in pregnancy. When reporting results in chapters 4 and 6, I complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards[89,90].

The systematic reviews conducted in this thesis were based on a comprehensive literature search without language restrictions. The search strategy was based on the structure developed in the previous work[76] and combined search terms (and their variants) such as 'pregnancy', 'body mass index' and 'randomised controlled trials' (Appendix 2.1). The searches were performed in databases such as Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials and Health Technology Assessment Database between October 2013 and March 2015, and updated in January 2016 and February 2017. Search updates extended onto three additional databases i.e. PsycINFO, Scopus, and Web of Science. Additionally, non-systematic methods were used to identify any potentially relevant non-indexed reports and supplement the databases searches. These comprised of hand search, an Internet search using general engines, and inquiry among the members of the i-WIP Collaborative Group about any potentially relevant trials.

Table 2.2 Components of structured question for systematic reviews in the thesis

Question Components	Chapter 4	Chapter 6
Population	Pregnant women with BMI ≥ 18.5 kg/m^2 without diabetes or early onset GDM	
Interventions	Diet, physical activity or mixed approach (diet, physical activity, weight gain monitoring or behaviour modifying technique)	
Comparison	Routine antenatal care	
Main outcomes	Gestational weight gain, maternal composite outcome, offspring composite outcome	Type of clinical outcomes
Secondary outcomes	Individual components of maternal composite outcome Individual components of offspring composite outcome	
Study design	Randomised controlled trial (full-scale, pilot and feasibility studies with clustering on individual or centre level)	
Publication type	Conference abstracts and posters, full-scale trial publications	Only publications from full-scale trials

BMI, Body Mass Index; GDM, gestational diabetes;

2.4. Meta-analysis of effectiveness trials

Meta-analysis is a quantitative method allowing for pooling of the numeric data across all relevant studies.[91,92] The aim of the meta-analyses performed in chapters 4 and 5 was to synthesis the evidence on the overall effects of diet and physical activity in pregnancy on gestational weight gain and maternal and offspring outcomes, and in subgroups of women based on the pre- or early pregnancy BMI. Meta-analysis methods was also used in chapter 7 to evaluate the relationship between gestational weight gain and the adverse pregnancy outcomes.

2.4.1.Study and participant level meta-analysis

Most frequently, meta-analyses are based on study-level data extracted from trials' publications or obtained directly from study authors. Alternatively, it can be performed using participant-level data.[18,45] In study-level data meta-analysis, data for binary outcomes is extracted to two-by-two tables and for continuous outcomes mean and standard deviations (SD) are sought. IPD meta-analysis uses data on particpant rather than study or group level can be code in binary or categorical ways or as a discreat values. For example in IPD meta-analysisparticpant age would be analyesd as a individual values for each particpant in a study rather than as an average age of all the particpants in that study. There are two equivalent approaches to IPD meta-analysis– one and two-stage.[93,94] In a two-stage approach the estimates (and their variances) of interest the IPD from individual trials are analysed separately accounting for the clustering of participants within trials. This step produces summary estimates for each study that are subsequently pooled together using appropiate models as in a typical meta-analysis of study-level data.

It is paramount importance to preserve clustering of participants with the original studies as neglecting this may lead to incorrect estimation of the effect estimates and flawed conclusions[95]. In the one stage approach, IPD from individual datasets is used in the same model while accounting for the within-study clustering. The two-stage is a more laborious approach to IPD meta-analysis, however easier to implement than the one-stage[94]. The later one is quicker but more prone to technical problems due to the complexity of models. In both types (IPD and study-level data meta-analysis) the data is being pooled using random or fixed effects model to obtain summary estimates – risk ratio (RR) or odds ratio (OR) for dichotomous outcomes, and mean difference (MD) or standardised mean difference (SMD) for the continuous outcome with their 95% Confidence Intervals (CIs).

2.4.2.Exploration of between study heterogeneity

Studies included in systematic reviews inevitably differ from each other. Their recruited participants across different health care settings were guided by different protocol etc. Examining those differences and defining the generalizability of findings is one of the most important tasks when conducting meta-analysis.[96] Commonly the variability in studies characteristics is described using term 'heterogeneity' – clinical (variability in participants' characteristics, interventions, etc.) or statistical. The statistical heterogeneity is encountered when the difference between the effects pooled across the studies are greater than one would expect due to pure chance.[97] However, the observed variation in the estimated effect sizes can be misleading, as it comprises of a true variation in effect sizes and the random error.

The inconsistencies between the effects across the studies can be formally quantified using measures such as Q statistic (a measure of weighted squared deviations), τ^2 (the between-study variance) or I^2 (the proportion of true heterogeneity to total observed variation).[98] The measure frequently used to assess inconsistency across the studies in systematic reviews is I^2. With its scale ranging from 0 and 100%, it is not sensitive to the metric of the effect size and the number of pooled studies. Alternativelly, τ^2 as the measure of between-studies variance or τ (standard deviation of the true effects) can be used. In contrast to I^2 metric, those measures reflect the scale of the effect size (e.g. log odds) and are not sensitive to the number of pooled studies.

When interpreting the heterogeneity the choice of the effect measure should be considered, as in some instances observed heterogeneity may be an artificial consequence of an inappropriate choice of the effect measure. For example, in case of binary outcomes when the baseline risks in the control groups vary across the studies, the homogeneous relative effect estimates (odds

ratios or risk ratios) are accompanied by a heterogeneous absolute estimates (risk differences), and vice versa.[5]

In study-level data meta-analysis, exploration of between-study heterogeneity is frequently done through a subgroup analysis or a meta-regression.[99,100] The subgroup analysis involves grouping extracted data according to characteristic of interest e.g. participant's age or intervention does, in order to make comparisons between them.[19] Meta-regression is an extension to the subgroup analysis used to explore the impact of continuous and categorical characteristics even in the same statistical model.[99] In principle, the method is analogous to a simple regression; hence, it is generally advice to use this approach only if there are ten or more studies in meta-analysis.[101] The coefficient obtained from meta-regression describes how the intervention effect changes with an each a unit increase in the explored characteristic. Subgroup analyses as well as meta-regression should be predefined and carefully planned as if not performed correctly they can lead to incorrect conclusions.[102]

There are various methods available to address the issue of heterogeneity in the intervention effects in IPD meta-analysis. The modifying effect of participants' or intervention's characteristics can be explore by pooling of within-trial covariate interactions, in a one-stage model including the interaction term between the characteristic and the intervention effect, through testing for difference between covariate subgroups in their pooled treatment effects or by combining the pooling of within-trial covariate interactions with meta-regression.[103] The choice of correct methods is crucial as they may lead to substantially different findings.

2.4.3.Methods applied in this thesis

The meta-analyses conducted to address objectives specified in chapters 4 and 5 were performed in accordance with current recommendations for performing study-level data and IPD meta-analysis for effectiveness research questions.[93,94] For each outcome, a two-stage

IPD meta-analysis was performed to obtain summary estimates and 95% confidence intervals for the intervention effects and the interactions (subgroup effects). The two-stage approach was used rather than a one-stage approach due to the large numbers of studies, the need to deal with both parallel group and cluster randomised trials, and the need to adjust for baseline factors. In all analyses (unless otherwise stated) the IPD and study-level data were pooled using random-effects model (REML), to obtain summary estimates (MD for a continuous outcome, and OR for dichotomous outcomes) with their 95% CIs.

The random-effects model was applied to all analyses allowing to account for unexplained between-study heterogeneity in effects between studies, therefore derived summary estimates are average effects across studies. Following Cochrane Handbook, I formally quantified the between-study heterogeneity using the I^2 metric with the cut-offs of 25%, 50%, and 75% as indicators of 'low', 'moderate', and 'high' degrees of heterogeneity, respectively.[5] I chose the I^2 measure over other indicators e.g. τ^2 as it is easy interpretation and comparability between analyses.

The IPD meta-analysis framework can be also used to explore secondary questions in comparison to the main assessment of intervention effectiveness.[46] In this thesis the IPD meta-analysis methodology was used to evaluate the association between gestational weight gain (surrogate of maternal morbidity) and important clinical outcomes (chapter 7). The analyses follow the same framework as for the effectiveness questions maintaining clustering of participants within the original study. Analyses in all chapters were performed using Stata statistical software (version 12.1, StataCorp, College Station, TX, USA) with statistical significance of effects considered at the 5% level. More details on the specifics of the analyses and the models are available in methods' sections of the relevant chapters.

2.5. Investigating bias in evidence synthesis

Before drawing a conclusion from findings of any systematic review it is paramount to evaluate any factors that potentially could have distorted them.[104] The validity of the systematic review can be assessed in two ways: whether the study asks a suitable research question, and if it answers the question correctly and in an unbiased way. The later one in often describes as study's 'internal validity' and refers to the methodological quality of individual studies as well as the methodology of the systematic review and meta-analysis.

2.5.1. Quality assessment of randomised trial

The synthesis of evidence is as good and informative as the quality of included individual studies. The 'quality' of the study can be understood as the level to which appropriate measures were employed to reduce bias and error in study design, conduct, and analysis.[7] Any systematic error, or deviation from the truth, in results or inferences is a label with a term 'bias'[5]. The term 'risk of bias' is more commonly used than the bias itself as the study findings may be unbiased despite methodological defects.

In RCTs, the key aspects determining the quality of the trials are a method of participants' allocation to study arms, study conduct, detection of the events of interest, attrition from the study and its reporting.[105] Allocation to the study groups is usually assessed by looking at randomisation procedures and the methods implemented to ensure concealment of the participants' allocation. Studies with incorrectly conducted randomisation and those where the personnel knew the allocation sequence tends to show greater and more positive results rather then those where the randomisation and allocation concealment were implemented correctly. Sequence generation in order to correctly balance the characteristics of participants between the study groups should be truly random namely there is no way of predicting based on the clinical characteristics or other factors to which arm the participant will be allocated to.

Biases that might arise during the trial (performance and detection biases) are down to the difference in the care provided to the participants depending on the study arm they were allocated to. A way to address this issue is by ensuring that all involved in the studies are not aware of the intervention allocation status during the course of the trial. This procedure is commonly known as blinding or masking. Depending on the nature of the intervention, blinding of participants and personnel during the course of the trial is not always possible. However, it is possible to ensure that the researchers assessing the final health outcomes and the statistical team are unware of the original allocation. Bias due to attrition is assessed by looking at the numbers of participants that left the study and the reasons for dropping out. Bias in trial design and conduct can also arise due to other inaccuracies such as failure to deliver allocated intervention due to poor compliance, poor quality assurance or misconduct at the stage of data analysis (lack of statistical plan or its change post data collection).

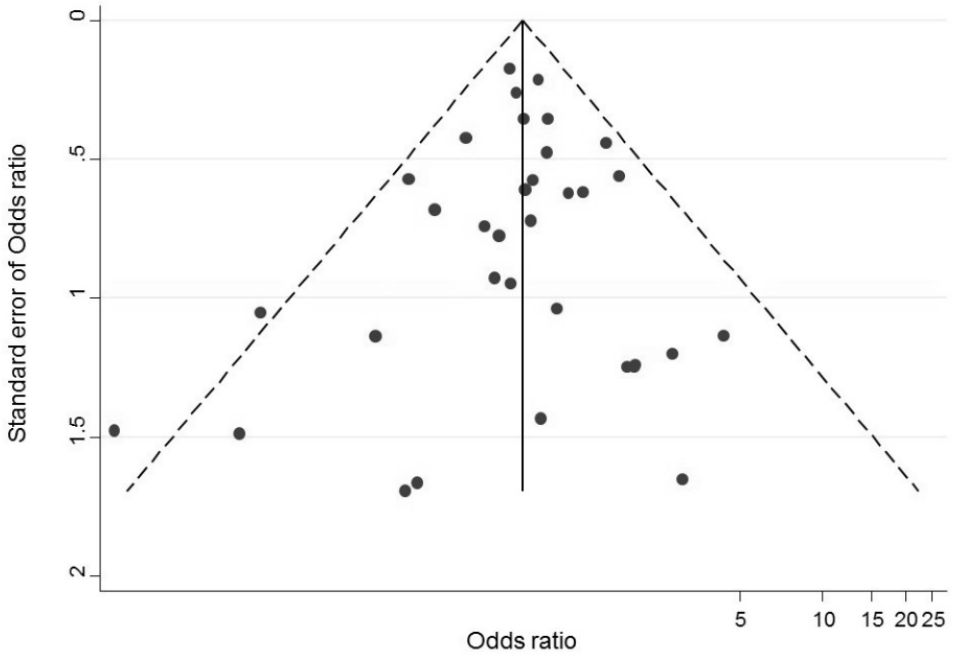
Typically, systematic review with meta-analysis relay on the data extracted from trial report, therefore an important source of bias to consider is one arsing due to poor or inaccurate reporting. Flawed, partial or even lack of reporting of any of the study elements and especially the health outcomes can have a major impact on the findings of any evidence synthesis. The risk of bias due to the selective outcome reporting arises whenever there is a suspicion that the decision about which and how to report the trial outcomes was made post-hoc and basing on the statistical significance of the findings. These mechanisms leads to over reporting of positive results that distort the magnitude of the pooled effect estimate in meta-analysis.[36,106]

Reporting biases arise when the nature and direction of results influences their dissemination. This might occur on the within-study level or on the study-level. The former one, commonly known as outcome reporting bias, frequently affects trial outcomes that are analysed differently than initially specified in the trial protocol, or not reported at all. The later one, an extreme case of reporting bias, is referred to as ‘publication bias’.[5]

2.5.2.Small study effects

Publication bias as important concern in meta-analysis as the over-representation of 'positive' findings can distort the summary effect estimate and lead to over optimistic conclusions. Universally presented graphic of contribution of individual studies to the summary effect is funnel plot; a scatter graph of the effect estimates derived from individual studies against a measure of each study's size or precision (standard error).[24] The term 'funnel plot' has been coined to describe the graphic presentation of the relationship between the effect estimates and their precision with the precision of the effect estimates improving with the growing sample size of the study (Figure 2.1).

Figure 2.1 Symmetrical structure of funnel plot



The loss of lot's symmetrical shape indicates probability of bias in the pooled effects due to over representation of positive or negative effects from studies with small sample size[28]. However, the observed asymmetry is not synonymous with 'publication bias', as it can arise due to other factors such as between-study heterogeneity or poor compliance with an intervention in smaller trials in comparison to larger ones.[24] Discussed asymmetry can be

examined in a formal statistical way; however, it is generally recommended for those test to be applied if ten or more studies is available for meta-analysis.[24]

2.5.3.Availability bias in IPD meta-analysis

A source of bias affecting meta-analysis using IPD is the number and the nature of studies from which participant-level data is not available.[107,108] Availability bias is discussed only in the case of IPD meta-analysis as it addressed the issues of variable access to the IPD. The current guidance on the appraisal of IPD meta-analyses of randomised trials advocates checking for the proportion of trials from which IPD was obtained.[46] The rationale behind this recommendation is that the studies for which IPD is not available might be substantially different making the group of IPD studies not representative of the entire evidence base e.g. studies with not available IPD might be small and of a lower quality. Furthermore, the guidelines recommend assessing the impact of unavailable data on the pooled effect through a sensitivity analysis combining the effect estimates derived from IPD studies with those from study-level data extracted from publications for studies where IPD was not available.[46]

2.5.4.Investigation of bias in this thesis

Out of a wide range of sources of bias that can affect the summary effects, in my thesis I will focus on the ones most relevant to IPD meta-analysis i.e. outcome reporting bias (addressable thanks to access to IPD) and availability bias (unique to IPD meta-analysis). The quality of RCTs was assessed using Cochrane risk of bias tool where one of three grades (low, high or unclear risk of bias) was assigned to each of the domains.[98] As the impact of the trials' quality on the pooled effect estimates is not the subject of my work, it will not be presented and discussed in this thesis. The assessment of small studies effects was performed by generating funnel plots and where the number of available records allowed using suitable statistical tests – Peter's test for the binary and Egger's test for the continuous outcome.[24] The availability bias was assessed by comparing the summary estimates from IPD studies alone with those

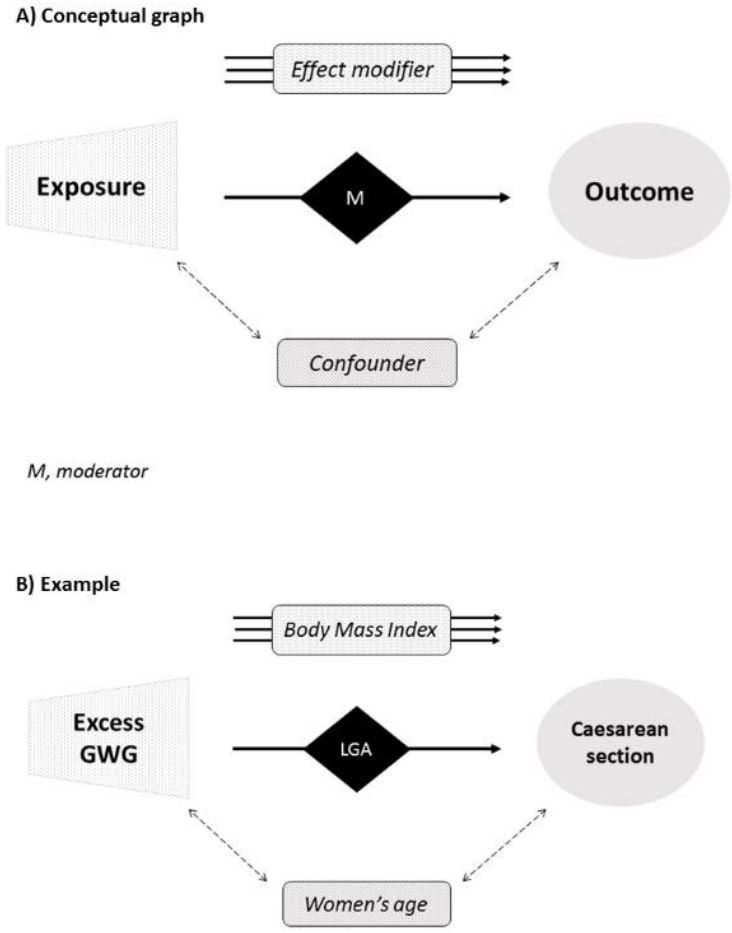
with the addition of non-IPD studies. Further details on the investigation of biases are available in section 4.2.

2.6. Examining associations

The objective of many studies in health care research is to analyse the association between an exposure and an outcome of interest. The goal of any work of this kind is to obtain an unbiased estimator for this association. The statistical method used to address this type of research question is regression modelling.[109,110] Depending on the type of the outcome variable, the regression can be logistic (binary outcomes), linear (continuous outcomes), Poisson (counts) or Cox (time-to-event outcomes). Nevertheless, regardless of the regression type, the modelling strategy aims to obtaining the best fitting model to represent the examined association.

Before embarking on the modelling, it is paramount to examine the relationship between our exposure and the chosen outcome, as it can be affected by the external factors. The relationship can be obscured by a factor not lying directly on the exposure-outcome pathway, however, independently linked with both the exposure and the outcome – a confounder. (Figure 2.2). If the factor transmits the effect of the exposure onto the outcome, we classify it as a mediator. The observed relationship can also vary by different levels of the examined factor. In this case, we observe a modifying effect and the factor of inquest an effect modifier. In principle, when modelling, we aim to control for all relevant confounders and examine effect modifiers (exposure – covariate interactions) to identify relevant risk groups while mediators are not included in the modelling strategies.

Figure 2.2. Developing regression model - choosing confounders and effect modifiers



There are various conceptual strategies of building regression models to examine associations.[110] The model examining the association can be adjusted for relevant confounders including them as independent terms in the in the multiple regression equation; however, doing so we risk the overfitting of the model. Alternatively, we can begin with a crude model (the exposure and the outcome) and gradually develop it by adding identified confounders, examining their significance level and the change in the coefficient (stepwise forward selection). In the reverse process (backward elimination), we begin with a full model from which we drop the covariates depending on how their removal change the coefficient and the significance level of other covariates. If the model includes interaction term (exposure and potential effect modifier) the decision about is retention or removal from the model depends only on the interactions significance level. Generally, the significance level for the interactions is higher than one for the confounders.[110]

2.6.1. Examining associations in this thesis

In this thesis, exploration of the relationship between an exposure or a factor, and an outcome has been performed in two chapters. In chapter 6, using linear regression models, I explored the relationship between publication features and quality of outcome reporting score. The applied modelling strategy was a backward elimination of the candidate factors until a final model that included only relevant exposures and identified confounders with or without interaction terms. In chapter 7, I explored the relationship between the gestational weight gain outside the IOM recommendations and adverse pregnancy outcomes. I used multilevel logistic regression with an interaction term between the degree of departure from the recommended range (each kilogram of deviation) and its direction (above or below the recommendation limits). The associations estimated were reported as crude odds ratios and adjusted for as many confounders as possible taking into account their availability and outcome event rate. More details description of models and modelling strategies are provided in the methods sections of the relevant chapters.

Chapter 3 Development and use of the composite outcomes in Individual Participant Data meta-analysis

3.1. Introduction

Meta-analysis using IPD in comparison to study-level data has greater power to detect any differential treatment effect across groups. This avoids issue of ecological fallacy, and has the ability to model the individual risk status across participants within trials, to explain variability in outcomes at the participant-level.[45,46,93] The i-WIP Collaborative Group was established to assess the effects of diet and physical activity based interventions in pregnant women on maternal, offspring outcomes using IPD meta-analysis.[79]

Identification of the appropriate outcome (s) for evaluation of the interventions effect in pregnancy is challenging, as frequently more than one outcome is considered to be clinically important. Furthermore, the analysis is often limited by the low incidence of individual outcomes, and it is difficult to predict the number of trials for which IPD will be obtained. A recent study showed that only a small proportion (25%) of IPD meta-analyses obtains 100% of eligible IPD.[50]

Composite outcome measures are used in primary trials to overcome the problem of low frequencies and clinical importance.[47,49] The development of such outcomes should be based on clear pre-specified criteria with transparency in reporting. Currently, a robustly developed composite outcome measure does not exist for diet and physical activity based interventions in pregnancy.

3.1.1.Aims

The aim of the work presented in this chapter is to develop composite maternal and composite offspring outcomes for evaluation in i-WIP IPD meta-analysis.

3.2. Methods

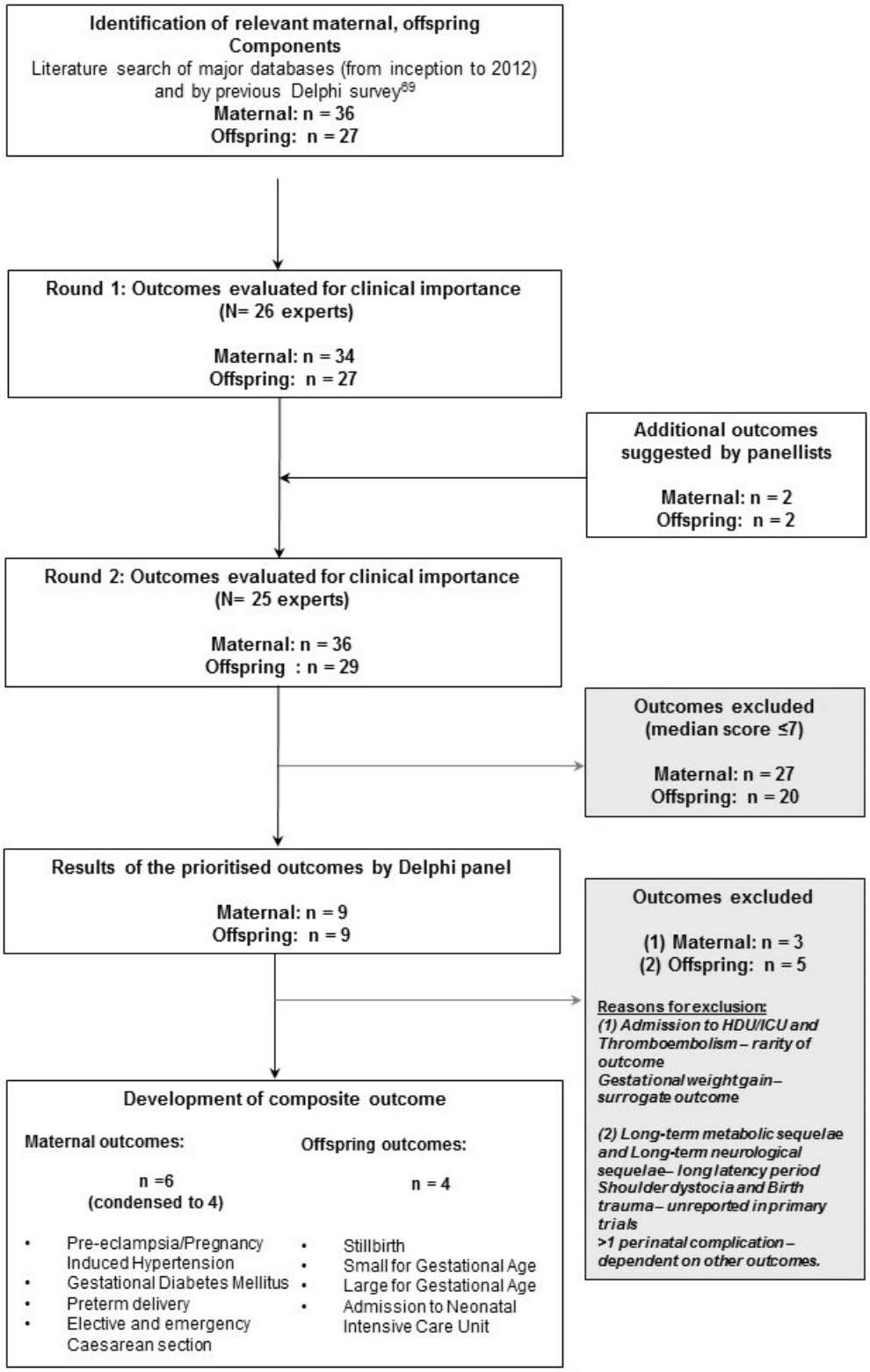
The details of the methods used to develop the composite outcomes are available in section 2.2. The effect of interventions on the composite outcome was assessed using IPD meta-analysis methodology (sections 2.4 and 4.2). The composite outcome was available for the analysis if all its components were recorded for the given participant. For example, the maternal composite was available if data on GDM, preterm birth, caesarean section and hypertensive disorder were collected in a given study. Following current guidelines on the use and analysis of composite outcomes in medical studies, the effects of diet and physical activity based interventions were presented for the composites (maternal and offspring) and their components.[111] The analyses with the maternal composite outcome excluded participants with baseline diabetes mellitus, GDM or pregnancy induced hypertension, as these baseline medical conditions are components of the outcome.

3.3. Results

3.3.1. Characteristics of the Delphi panel

The Delphi panel comprised of 26 clinicians and clinical academics from 11 countries with expertise in diet and lifestyle interventions in pregnancy. This included 16 obstetricians, four physiotherapists, two nutritionists, two midwives, one epidemiologist, and an endocrinology specialist. Majority of the panellists are involved in research in high-income countries Australia (3), Europe (18), North America (3), and two from an upper-middle income country (Brazil). Over 90% (24/26) of the panellists have experience of conducting randomised trials on diet and lifestyle interventions. Overall, the panel members have been responsible for five diet based, seven physical activity based, and 12 mixed intervention studies. Twenty-six panellists ranked the maternal outcomes and 25 ranked the offspring outcomes for their importance to patient care. Details on the rounds of the Delphi survey and development of composite outcomes are presented on the flow chart (Figure 3.1).

Figure 3.1 Rounds of Delphi survey and selection of outcomes for composite outcomes



3.3.2. First round

All panellists, (100% 26/26) completed the questionnaire consisting of 34 maternal outcomes and 27 offspring outcomes in the initial list. Fifteen (15/34, 44%) maternal outcomes were scored as critical to patient care and 19 (19/34, 56%) outcomes were scored as important but not critical (Figure 3.2). The outcome threatened miscarriage was not considered to be critical to patient care (median <6). Eleven (41% 11/27) offspring outcomes were scored as critical to patient care and 16 (59%, 16/27) outcomes were scored as important (Figure 3.3). The panellists suggested consideration of pre-eclampsia and pregnancy induced hypertension to be two distinct outcomes and this was added to the list of rating in the second round. Similarly, the panel advised that elective and emergency caesarean section to be considered separately, and these were added to the list for scoring in the second round. Neurodevelopment at two years of age and fetal cord blood (insulin or c-peptide) were added to the second round based on the recommendations of the panellists.

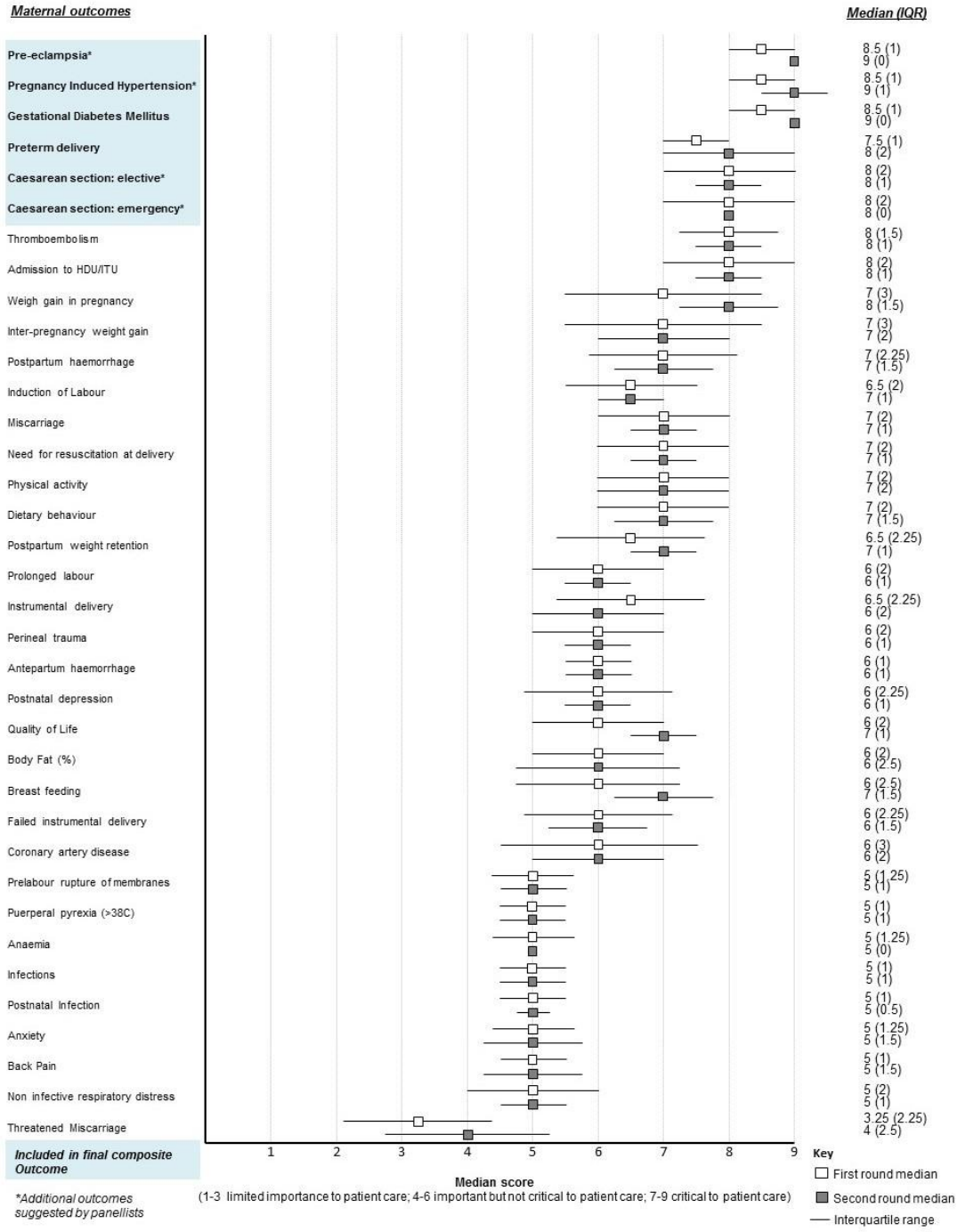
The individual scores showed some minimal variation (IQR ≤ 2) for twelve of the critical maternal outcomes, namely pre-eclampsia, pregnancy induced hypertension, gestational diabetes mellitus, preterm birth, elective caesarean, emergency caesarean section, thromboembolism, admission to High Dependency Unit (HDU)/ Intensive Therapy Unit (ITU), miscarriage, need for resuscitation at delivery, physical activity, and dietary behaviour. For the eleven critical offspring outcomes there was minimal variation (IQR≤2) shown in: stillbirth, SGA, LGA, admission to NICU, shoulder dystocia, occurrence of less than one perinatal complication, birth trauma, long term neurological sequelae, long term metabolic sequelae, hypoglycaemia, and respiratory distress syndrome.

3.3.3. Second round

Twenty-five (96%, 25/26) panellists took part in the second iteration. Eighteen (18/36, 50%) maternal outcomes had a median score of ≥7 and were considered to be critical to patient care, while 18 outcomes had a median score of ≥4 and were considered to be important. There was a narrowing of IQR for the seventeen of the outcomes showing consensus between panellists (Figure 3.2). Eleven (38%, 11/29) offspring outcomes scored between 7 and 9, and were considered to be critical to patient care. The offspring outcomes that progressed to the second round are shown in Figure 3.3.

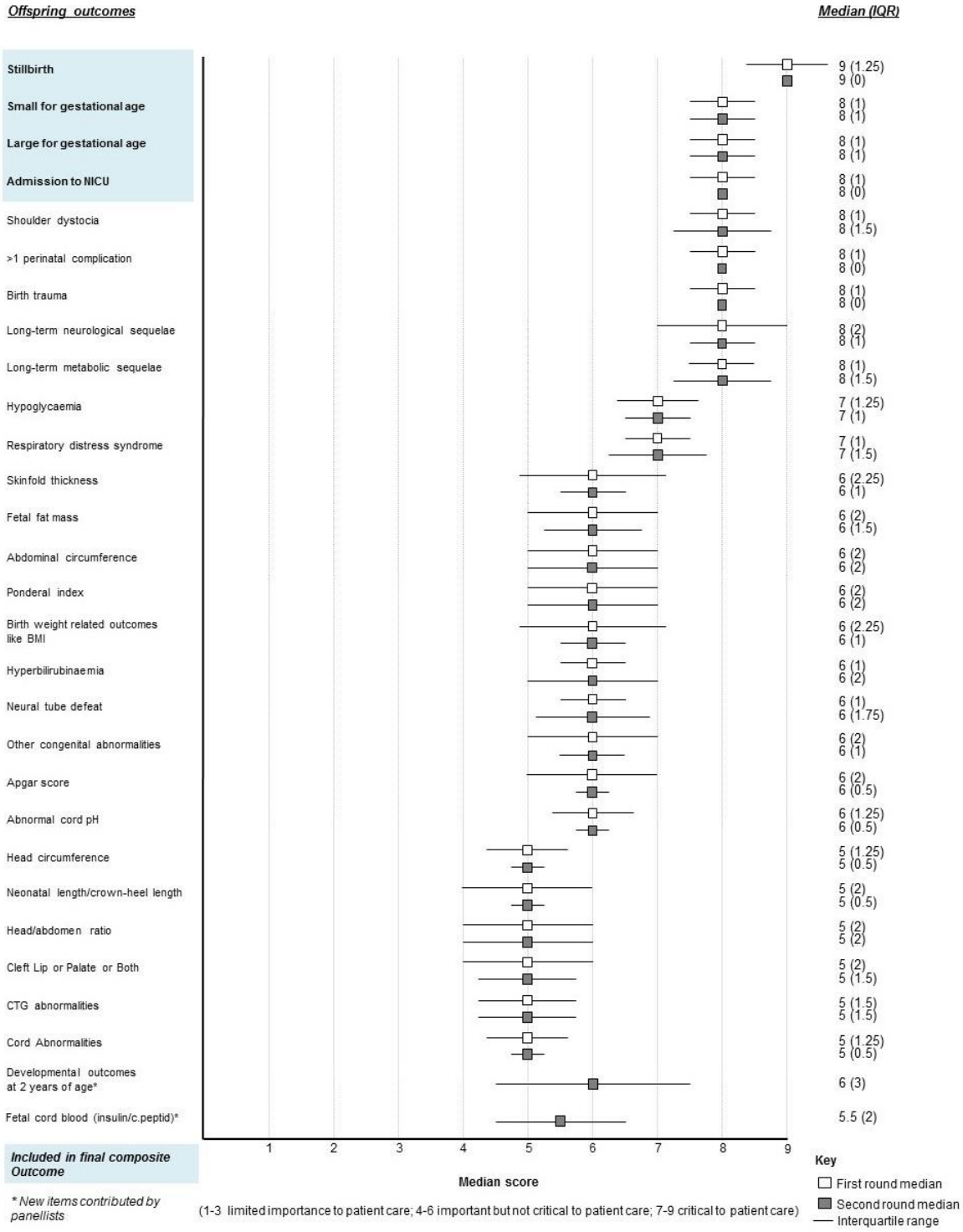
The scoring of maternal and offspring outcomes between the previous and the current panel was overall congruent (Appendix 3.1). Miscarriage, physical activity, postpartum weight retention, quality of life, and breast-feeding were considered to be critically important in the current Delphi panel but only important in the previous panel. Instrumental delivery and failed instrumental delivery were critically important in previous Delphi panel but only important in this panel. Threatened miscarriage was of limited importance to patient care in the previous Delphi but considered as important by the current Delphi panel. Abnormal cord pH was critically important in the previous panel but only important in the current panel.

Figure 3.2 Maternal outcomes



HDU, High Dependency Unit; ITU, Intensive Therapy Unit

Figure 3.3 Offspring outcomes



3.3.4. Selection of the components

Nine maternal and nine offspring outcomes with a score ≥8 were evaluated for their inclusion as components of the composite outcomes (Figure 3.2 and Figure 3.3). The following maternal components were included: PE or PIH, GDM, elective or emergency caesarean section, and preterm birth. Outcomes that occurred rarely such as thromboembolism, not well reported such as admission to HDU or ICU, or surrogate for maternal morbidity such as gestational weight gain were not included in the final list.

The following offspring components fulfilled the selection criteria for inclusion in the composite: stillbirth, SGA infant, LGA infant, and admission to NICU. Given the long time frame required to assess the risk of long-term metabolic sequelae and neurodevelopment of the baby, they were excluded from the offspring composite. Rare outcomes such as shoulder dystocia and birth trauma significant overlap with LGA, and were poorly reported, leading to their exclusion. Finally, the outcome of more than one perinatal complications was excluded as it was considered to be significantly dependent on the other offspring outcomes.

3.3.5. Use of the composite outcomes in IPD meta-analysis

The composite outcomes were used in IPD meta-analysis of 36 RCTs with diet and physical activity based interventions described in details in chapter 4. The maternal composite outcome was available in two-third (24/36) and offspring composite outcome in half (18/36) of studies with IPD (Table 3.1). Components of the maternal composite were available in more than half studies with the least frequently available outcome being the occurrence of hypertensive disorders (22/36 studies). The availability of the components of the offspring composite was less balanced with a high availability of two outcomes (SGA and LGA) for the majority of the studies. The other two components – stillbirth and admission to NICU – were available in less than half of the studies with only two studies out of 22 (Table 4.3) with the data on stillbirth rates included in the IPD meta-analysis of individual components of the composite outcomes.

The directions of the interventions' effect on the individual components of the maternal composite was consistent with the effect on the composite. The effect on the offspring composite and its components was less consistent, however the point estimates of the effects on the individual outcomes were within the 95% CI for the effect on the offspring composited.

Table 3.1 Effects of diet and physical activity based interventions on pregnancy outcomes summarised using Individual Participant Data

Outcome	Number of studies (Number of events/ participants)	OR (95% CI)	I^2 (%)
Maternal composite outcome	**24 (3 733/ 8 851)**	**0.90 (0.79, 1.03)**	**26.7**
Gestational diabetes	27 (855/ 9 427)	0.89 (0.72, 1.10)	23.8
Hypertensive diseases in pregnancy	22 (1 155/ 9 618)	0.95 (0.78, 1.16)	24.2
Preterm birth	32 (677/11 676)	0.94 (0.78, 1.13)	17.3
Any caesarean section	32 (3 033/ 11 410)	0.91 (0.83, 0.99)	0.0
Offspring composite outcome	**18 (2 034/ 7 981)**	**0.94 (0.83, 1.08)**	**0.0**
Stillbirth	2 (20/ 3 719)	0.81 (<0.01, 256.69)	0.0
Small for gestational age	33 (1 341/ 11 666)	1.06 (0.94, 1.20)	0.0
Large for gestational age	34 (1 503/ 12 047)	0.90 (0.76, 1.07)	38.0
Admission to NICU	16 (581/ 8 140)	1.01 (0.84, 1.23)	0.0

OR, odds ratio, CI, confidence intervals; NICU, Neonatal Intensive Care Unit

3.4. Discussion

3.4.1.Main findings

The composite outcomes comprise of four maternal (gestational diabetes, hypertensive disorders in pregnancy, preterm birth, caesarean section) and four offspring outcomes (stillbirth, SGA, LGA, and admission to NICU). The maternal composite outcome was

available in two-third and offspring composite in half of the studies available for the IPD meta-analysis with RCTs on diet and physical activity in pregnancy. The point estimates of the pooled effect were consistent for the maternal composites and its components and variable for the offspring composite and its components.

3.4.2.Strengths and limitations

In the presented work to develop composite outcomes, I implemented robust and validated methods. The outcomes were prioritised through a consensus involving leading multidisciplinary clinicians and researchers in the field and subsequently assessed for their eligibility to become components of the composite according to recommended criteria.[49] This is the first formally developed composite measure for evaluation of antenatal diet and physical activity based interventions in IPD meta-analysis. One of the major strengths of this project was the use of Delphi methodology. The two-stage survey described in this chapter validated the work of the prior panel[75], thus increasing the reliability and reproducibility of the developed composites outcomes. The panels were independent and comprised of experts with relevant expertise in the area of the weight management in pregnancy. The second Delphi panel widened the area of expertise by involving researchers from wider disciplines and had a global reach. Furthermore, the majority of the panellists have experience in clinical trials with diet and physical activity in pregnancy. The response rate to the surveys was of over 90% in both rounds.

The list of maternal and offspring outcomes used in the survey was firstly identified through a systematic review and evaluated by the first panel[75]. The Delphi panel methodology improved the panel's work and avoided counterproductive group dynamics such as domination of discussion by senior members. Finally, all the critically important outcomes were evaluated in a systematic manner against pre-specified rigorous criteria (section 2.2) prior to their inclusion in the final composite outcomes.

The findings are based on individual and group opinions and are strongly dependant on the composition of the panel. Any potential bias was minimised through validating the findings of one panel against another that comprised of the international experts in the field. However, it needs to be noted that a different consensus group may have chosen other components for inclusion in the composite. The optimal size of a Delphi panel to generate consensus is not defined.[83,112] Decision regarding the size of the panel was based on the pragmatic balance between good representativeness of the clinical opinions and the minimisation of the dropout rate[113]. A small panel might not represent a good range of opinions on the topic, and a larger panel may lead to low response and high drop-out rates[83].

The number of studies with available IPD is difficult to predict before embarking on IPD meta-analysis. Therefore, the use of a composite outcome seems a sensible solution to overcome the issue of low event rates. Even though frequently used in primary studies, composite outcomes receive their share of criticism.[41,81] An alternative method allowing evaluating the effects of the interventions on multiple outcomes in IPD meta-analysis exist[114,115]; however, the complexity of the models and the methods used in their development might make them difficult to apply in all IPD meta-analyses.

Not all collected outcomes data could be used in IPD meta-analyses. In some analysis, with stillbirth being the extreme example, the statistical models excluded studies with zero events and imbalances between the compared arms. There are statistical methods allowing forcing studies with zero events into the models[116]; however, decision on their application needs to be balance against the validity of obtained summary effect estimates.

3.4.3.Interpretation

Composite outcomes developed to use in IPD meta-analysis on the effects of diet and physical activity based interventions in pregnancy comprise of major maternal and offspring complications. The components of both composite outcomes were identified using Delphi methodology and with the involvement of the international group of experts in the field increasing composites credibility. The maternal composite comprises of systemic diseases developing during pregnancy (GDM and hypertensive diseases) and delivery-related complications (preterm birth and caesarean section). All outcomes included in the composites received a score of eight or more with the majority having an IQR of one or less indicating consensus among the panellists' responses. The prevalence of the majority of the complications is currently on the rise[117-119], and their occurrence poses a major challenge for the health care due to their short and long-term consequences.[120] The frequency varies between individual outcomes with the caesarean section being the most frequent and hypertensive diseases the rarest event.

The offspring composite outcome encompasses stillbirth, infant's growth and the need for infant's admission to NICU. All offspring outcomes were ranked by the panellist as critically important to the management of women's weight in pregnancy. However, their frequency and subjectivity differ. Stillbirth is the rarest of the all offspring outcomes with the global average of 18 occurrences per 1000 births in 2015.[121] Admission to NICU is commonly used as an indicator of neonatal morbidity, but in the light of recent research, its validity is questionable.[122] SGA and LGA are clinically used indicators of a small or an excessive infant size capturing cases from the opposite extremes of the growth spectrum.

The decision on the inclusion of described components in the composite was a balance between rigorous and pragmatic criteria. It was intended to adhere to the pre-specified criteria

as closely as possible, but also abstain from including components that were not commonly available. This resulted in the inclusion of outcomes perceived as subjective, e.g. admission to NICU or caesarean section. It could be argued that when participants and personnel cannot be blinded to the type of intervention they receive, one should refrain from using clinician driven outcomes. As above mentioned outcomes are highly relevant to women's antenatal management (both classified as critically important) and uniformly reported across trials, I decided to include them in the composites. Nevertheless, the nature of those outcomes needs to be acknowledged when interpreting the results of the analysis

The main challenges in using composite outcomes in IPD meta-analysis on diet and physical activity based interventions in pregnancy were the variation and availability of the outcomes in the individual trials. Access to IPD facilitated computation of unavailable outcome data for SGA, LGA and preterm birth thanks to the availability of variables with gestational age and birth weight; however, this was not possible for all outcomes. Critically important events such as thromboembolism or admission to HDU or ICU for the maternal composite outcome, and shoulder dystocia and birth trauma for the offspring composite could not be included in the composites due to their rare collection in the primary trials.

The acceptability of the composite outcome rests on the assumption that the effect (its direction and magnitude) observed on the composite applies to all of its components.[49] The effect of the diet and physical activity based interventions on the maternal composite had the same direction and similar magnitude as on the individual components, however, lacked statistical significance. The effect of the interventions on the offspring composite and its components was more variable with no statistically significant findings. The rationale for development and use of the composite outcome in the i-WIP study was to address the issue of multiple outcomes and a low number of events for the individual outcomes. When the IPD meta-analysis was planned, the anticipated number of participant records available for the

analysis was lower than the one eventually assembled. The patchwork nature of the amalgamated IPD set led to a general smaller amount of data the composite outcomes than for the individual components. This trend is especially visible for the offspring outcomes with the weakest component of the composite being stillbirth. The extremely wide confidence intervals around the interventions' effect on this outcome are caused by low event rate and lack of any events in over 90% of the trials that recorded this outcome.

3.4.4.Conclusions

The i-WIP IPD meta-analyses evaluated the effect of diet and physical activity based interventions in pregnancy on the composite maternal and offspring outcomes. In order to maintain methodological rigour, the effect of the interventions on the components of the composites was investigated in a sensitivity analysis. The composition and implementation of the composite in the IPD meta-analysis were strongly determined by the availability of the individual components and their frequency in the individual trials that contributed the IPD.

The restrictions in the implementation of the composites in IPD meta-analyses resulting from lack consensus on which outcomes should be collected in trials with diet and physical activity in pregnancy could be reduced by two strategies. Firstly, by developing minimum core outcome sets for reporting in primary clinical trials. This concept is strongly promoted by The Core Outcome Measures in Effectiveness Trials (COMET) and the Core Outcomes in Women's Health (CROWN) initiatives.[52,53] Secondly, by designing prospective IPD meta-analyses with pre-specified relevant outcomes as in the case of early-onset intrauterine growth restriction.[123]

Chapter 4 Understanding the differences in the results from study-level and individual participant data meta-analysis: an empirical example of diet and physical activity based interventions in pregnancy

4.1. Introduction

Decisions in health care to effectively inform clinical practice and health care should ideally be based on all available body of evidence.[1] Systematic reviews with meta-analysis are considered the highest quality of the evidence for questions on the effectiveness of interventions.[4,9] A systematic review identifies all available evidence on a given topic and meta-analysis formally combines the data increasing the power and precision of the intervention effect.[92,124] Most frequently the method relies on study-level data extracted from trial publications making them prone to limitations due to poor reporting of primary trials.[18] An alternative approach to meta-analysis uses participant rather than study-level data.[18,125] This approach facilitates more powerful statistical analyses, gives the ability to detect any potential interactions between intervention effects and participants' characteristics, and allows to overcome the limitations associated with trial reporting.[43,45] Furthermore, access to trial data and direct contact with the researchers who conducted it facilitate an extensive data integrity checks that enhance the robustness of obtained estimates.

Despite being a powerful tool and labelled a 'gold standard' for the synthesis of effectiveness research, IPD meta-analysis is not free from constraints. By relying only on the raw trial data, the approach is at risk of not incorporating all available evidence on the subject (totality of evidence) and so called 'availability bias'.[108] In light of recent findings showing that only 25% of published IPD meta-analyses gained access to IPD from all eligible trials[50] the potential bias due to availability of IPD cannot be ignored. Yet, the evaluation of 199 IPD meta-analyses showed that only around 17% of studies combined IPD with study-level data from

studies where IPD was not available.[107] Moreover, findings from meta-analyses based on study-level data and IPD may differ, leading to different conclusions regarding the effect of interventions[45] even when based on identical trials[126]. A recent Cochrane review formally compared effect estimates and their precision for 190 comparisons of study-level and IPD meta-analyses. The review found that 20% of comparisons disagreed on the statistical significance. Those with concordant results with respect to significance level, 15% disagreed in direction of effect.[126]

Obesity and high weight gain in pregnancy put women and their offspring at an increased risk of short and long-term poor health outcomes[60,127]. The number of women who enter pregnancy with BMI above 25 kg/m^2 or exceed the amounts of gestational weight gain recommended by Institute of Medicine (IOM) is on a rise.[128] Acceptable and safe interventions to manage women's weight in pregnancy are needed, with interventions targeting women's diet and physical activity currently being extensively explored. Within the last ten years over 40 systematic reviews have looked at the effects of diet and physical activity based interventions. The reviews varied in their scope by the population of interest (different BMI groups), type of primary outcome, and derived conclusions; however, their limitations tend to be similar, namely a substantial heterogeneity in the pooled effects, variation in the type of evaluated outcomes, and variability in the type of evaluated interventions (Appendix 1.1).

4.1.1.Aims

The i-WIP IPD meta-analysis was conducted to address an unexplained heterogeneity in the pooled effects obtained from a study-level meta-analysis, and to explore the modifying effect of women's characteristics such as BMI, age or parity.[76,79] The work presented in this chapter reports the findings of the i-WIP IPD meta-analysis and contrasts them with results obtained from study-level meta-analysis. The emphasis was especially placed on the following questions: (a) What are the effects of diet and physical activity based interventions using IPD

meta-analysis? (b) How does inclusion of previously unreported outcomes alter the findings of meta-analysis in the group of trials where IPD was available? (c) What is the impact of the availability bias when evidence is synthesised using only IPD meta-analyses? (d) Compared to meta-analysis using only study-level data, what is the added value of IPD meta-analysis combined with study-level data from studies without access to IPD?

4.2. Methods

The systematic review and meta-analyses described in this chapter were conducted as outlined in the methods section 2.3. The studies were selected in a two-stage process. The citations identified through a systematic search of electronic databases were first assessed at the title and abstract level for their eligibility. The full texts of identified candidate citations were obtained and once more assessed for their eligibility as outlined in section 2.3. Trials which recruited women with gestational diabetes at baseline, studies that involved animals or reported only non-clinical outcomes, and studies that were published before 1990 were excluded. Where possible, both steps were repeated independently by a second reviewer (see the acknowledgements). The datasets with IPD from eligible trials were further refined by excluding pregnant women with multiple gestations, and women with BMI below 18.5 kg/m^2 (counter indication for limiting gestational weight gain).

The effects of the interventions in the IPD meta-analysis were evaluated on gestational weight gain, maternal and offspring composite outcomes.[79] The composite outcomes could not be used to investigate the differences in meta-analyses based on study-level and raw trial data. Therefore, I investigated the effects of interventions on the individual components of the composite outcomes, except for stillbirth and hypertensive diseases. The effect of the interventions on stillbirth rates could not be assessed due to a small number of studies available for meta-analysis. The effect on the hypertensive diseases was not explored as the

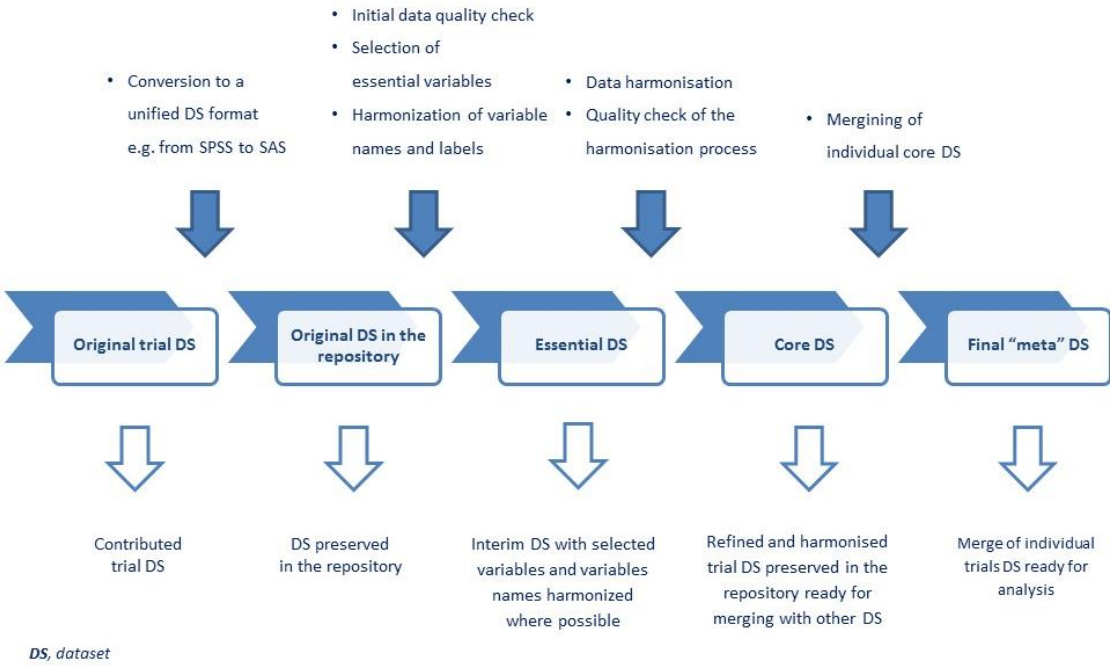
outcome in the primary trials was reported as an occurrence of pre-eclampsia or PIH or a combination of both.

4.2.1. IPD meta-analysis

Acquisition of participant-level data was guided by a pre-defined list of data items (Appendix 4.1). The initial assessment of data availability lead to refinement of the data list and retrieval of most frequently collected participants' characteristics and outcomes. All originally obtained datasets were uploaded and stored on a secured server hosted by Centro Rosarino de Estudios Perinatales (CREP) (Rosario, Argentina), and can be accessed via a web-based gateway.[78] CREP is a WHO Collaborative Centre in Child and Maternal Health with extensive expertise in data collection and maintenance. All data manipulations followed a standard operating procedure (Figure 4.1), and were performed and documented within the environment provided by CREP.

The final format of data in the dataset used in the IPD meta-analysis was selected based on the most frequent denominator and accounting for the number of studies with a given format and sample size. Loss of information through dichotomizing was balanced with the number of studies that could be included using a certain format. Details of the key variables grouping can be found in Appendix 4.2. Range and consistency checks were performed on all datasets. Where possible, the randomisation ratio, baseline characteristics and outcomes were compared with the values reported in trials publications. Any inconsistencies or coding ambiguities were checked with the dataset contributor, recorded on the data query sheet and amended where necessary.

Figure 4.1 Flow chart of data harmonisation in the i-WIP IPD meta-analysis



In all analyses any multiple treatment arms were combined into one intervention arm. The booking BMI values were grouped according to the WHO classification into normal (18.50 – 24.99 kg/m²), overweight (25 – 29.99 kg/m²), and obese (≥ 30 kg/m²) categories.[129] The women's educational status was used as an indicator of her socioeconomic status and women were categorised as "low" (did not complete secondary education to A-level), "medium" (completed secondary education to A-level or equivalent), and "high" (women completed any education higher than secondary). Parity, smoking in pregnancy, and any diabetes-related events were all coded in a binary way (1 "yes", 0 "no").

Gestational weight gain was defined as the difference between the final available weight and early or pre-pregnancy weight (if the early one was not available) and reported in kilogrammes. Definitions of GDM, caesarean section, and admission to NICU were adopted as per definitions in the original studies. Definitions of preterm birth, SGA and LGA were unified across all trials for which the outcome data were available. Preterm birth was defined as delivery before 37 weeks of gestational age. SGA and LGA with birth weight below the

120 10th and over the 90th centile respectively were adjusted for the mother's BMI, parity and
121 gestational age at delivery.[130]
122
123 A two-stage IPD meta-analysis was carried out in accordance with current standards and
124 following the framework described in section 2.4. A two-stage rather than a one-stage
125 approach was implemented due to the large number of studies, and the need to deal with both
126 parallel group and cluster randomised trials. A random intercept for a unit of randomisation
127 was used when analysing cluster-randomised trials. Gestational weight gain was analysed
128 using analysis of covariance (ANCOVA) in each trial to regress the final weight value against
129 the intervention while adjusting for baseline weight and centres in cluster-randomised trials.
130 For dichotomous outcomes for each trial a logistic regression model was used individually,
131 where intervention allocation was considered a covariate.
132
133 The IPD was combined with study-level data from trials where IPD was not available (later
134 referred to as non-IPD trials) following a three-step approach. Firstly, the effect estimates and
135 their variances were obtained from individual trials where IPD was available. Subsequently,
136 the effect estimates and their variances were derived from study-level data extracted from trial
137 publication (non-IPD trials). Finally, the effect estimates and their variances from both steps
138 were pooled using the random-effects model, as described in section 2.4.
139

140 *4.2.2.Study-level meta-analysis*

141 Data for dichotomous and continuous outcomes were extracted as described in section 2.4.
142 Numeric data presented in a different format then desired were transformed accordingly and a
143 record of those transformations was made. All information reported in the studies'
144 publications was extracted into designated data collection forms. Where possible, the
145 extraction was performed by a second independent reviewer. Any disagreements were
146 resolved by consensus or by a third reviewer (see the acknowledgements).

When referring to 'study-level meta-analysis' throughout the thesis, this signifies a meta-analysis using study-level data extracted from trials' publications, unless otherwise stated. All the study-level meta-analyses followed the framework described in section 2.4 and 2.5. The group sizes used for binary outcomes were used as reported for the main analysis in the publications from the individual trials. In order to assess the robustness of the summary effects for the binary outcomes, I also performed a sensitivity analysis using the numbers of randomised participants as the group sizes. The incorporation of cluster-RCTs was planned according to currently recommended methods.[5]

4.2.3.Comparisons

The effects of diet and physical activity based interventions in pregnancy obtained from IPD meta-analyses were used in three comparisons. Firstly, to examine the impact of including previously unreported outcomes from trials that shared IPD, by comparing the results of study-level (A) vs. IPD (B). Secondly, to examine the impact of availability bias in the findings of IPD meta-analysis, by comparing the only IPD (B) vs. IPD supplemented with study-level data, where IPD is not available (C). Finally, I compared the results of a study-level meta-analysis of all published trials (D) vs. the results obtained from meta-analysis combing IPD supplemented with study-level data (C). The number of trials contributing to the analyses A to D varied and they are given in Table 4.1.

In all comparisons the findings of meta-analyses were assessed for the following: the direction and the magnitude of summary effect estimates; width of 95% CI and its position with respect to the value of no-difference (zero for MD, one for OR); statistical heterogeneity (I^2); and funnel plot structure with a formal statistical assessment of its asymmetry, where possible.

Table 4.1 Meta-analyses of trials on diet and physical activity based interventions using IPD and study-level data

Group	Description of data	Meta-analysis	Number of trials
A	Study-level data from trials that shared IPD	Study-level	35
B	Participant level data from trials that shared IPD	IPD	36
C	Participant level data from trials that shared IPD and study-level data extracted from publications, if IPD was not available	Combined IPD & study-level	103
D	Study-level data extracted from publications of all eligible trials regardless of whether they shared IPD or not	Study-level	102

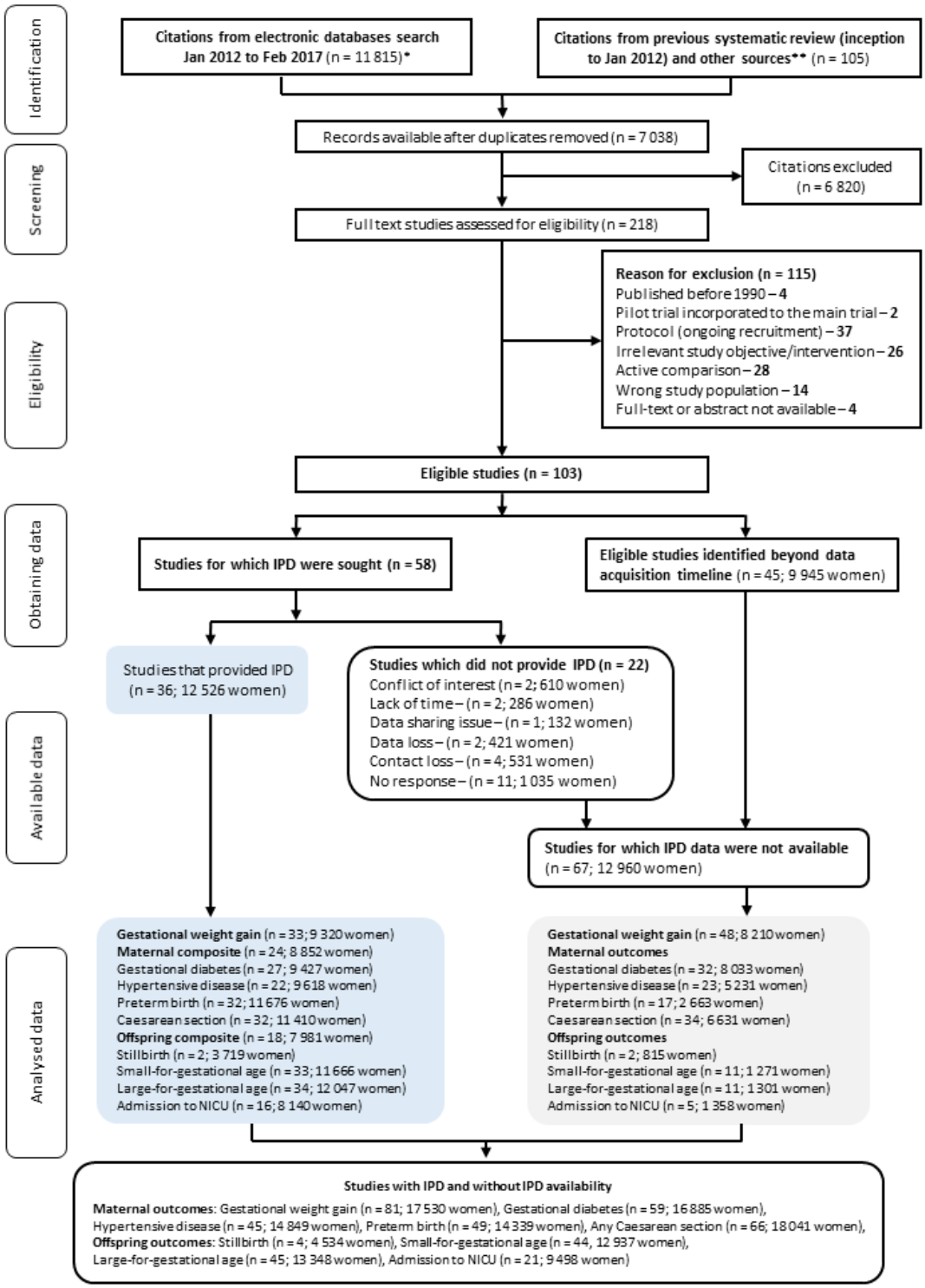
IPD, Individual Participant Data

4.3. Results

There were 103 eligible trials on diet and physical activity based interventions delivered antenatally (Figure 4.1). One trial was identified through direct communication with the collaborating research team[131], and its results were never published. The authors of 58 trials[131-188] were invited to join the i-WIP Collaborative Group and contribute their trial data with 36 teams responding positively to the invitation and collectively contributing data from 12 526 pregnant women randomised to their trials[131,132,134,138-140,142,146,147,150-152,155,157-159,162,164-170,172,173,175-178,181,184-188]. The most frequent reason for not obtaining the IPD in 22 of 58 approached trials was a lack of any response to the invitation and a lack of an alternative way to contact research team (11/22 studies). The remaining 45 trials (9 945 women) [189-233] were identified past the data acquisition deadline through two subsequent literature updates in January 2016 and February 2017 (Figure 4.1). Overall, the IPD was available from 35% of

190 eligible trials (36/103); however, the number of randomised women in and outside the IPD
191 was balanced (12 526 vs. 12 960 women).

192
193 Figure 4.1 Selection of trials with antenatal diet and physical activity based interventions



** 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 (1547 records);*
*** Other sources: reference search, personal communication, and Google search;*
IPD: individual participant data, NICU: Neonatal Intensive Care Unit

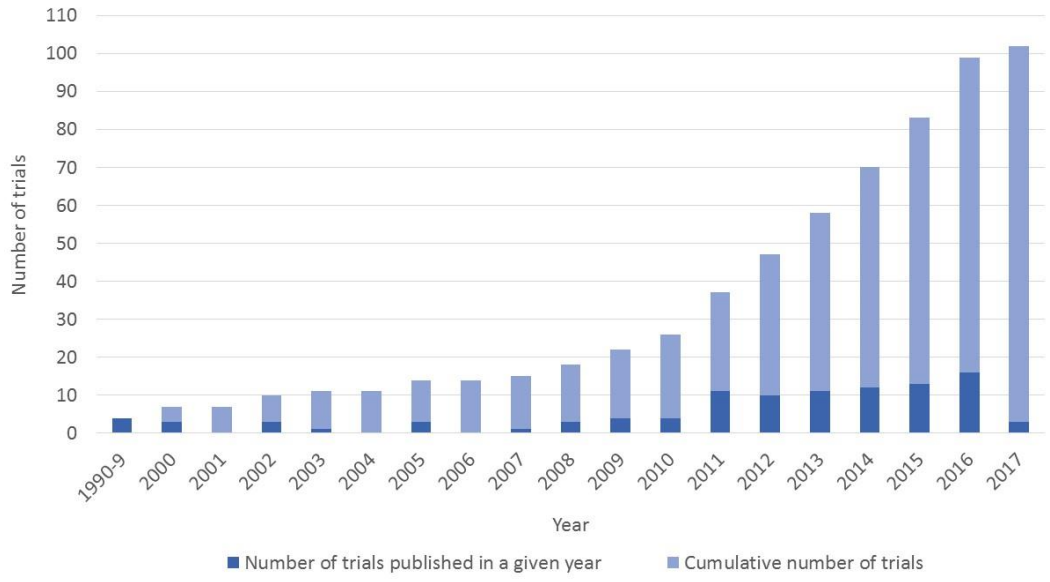
194
195

4.3.1. Characteristics of the included trials

The majority of the eligible trials were published within the last ten years (Figure 4.2). The median of publication year was 2011 for IPD trials, 2008 for the trials that authors were invited to share that data without success, and 2015 for newly identified studies. The IPD and non-IPD trials were comparable with regards to the type of recruited women, evaluated interventions and countries of trial conduct. (Table 4.2)

Among the IPD trials, 11.1% (4/36) had more than one treatment arm.[142,150,176,188] The one unpublished IPD trial was a small physical activity feasibility study conducted in the United States. Out of all IPD trials, 38.9% (14/36) of the trials shared the IPD from a less women than the declared number of the randomised in the trial. The median discrepancy between the randomised and contributed number of participant records is 9% (range 1% – 44%). The characteristics of all IPD trials, and also those that did not contribute IPD are provided in Appendix 4.3.

Figure 4.2 Trials with diet and physical activity based interventions published between 1990 and 2017 (up to February)



Out of seven evaluated outcomes, the most frequently reported outcomes in the included trials were gestational weight gain 75% (77/103), followed by caesarean section 56% (58/103), and GDM 49% (50/103). The frequency of reported outcomes in the group of IPD and non-IPD studies (publication-level) was comparable (Table 4.3).

Table 4.2 Characteristic of eligible trials with diet and physical activity in pregnancy (publication-level)

Characteristics	All eligible published trials	IPD available	IPD not available		
			Overall	Acquisition deadline	
				Published before	Published after
Number of studies *(Number of women)*	102 (25 942)	35 (12 508)	67 (12 960)	22 (3 015)	45 (9 945)
Publication year *median (IQR)*	2013 (5)	2011 (2)	2014 (7)	2008 (9)	2015 (2)
Population					
All BMI values,[†] (n, %)	67, *65.0%*	22, *63.9%*	44, *65.7%*	16, *72.7%*	28, *62.2%*
Overweight and obese, (n, %)	19, *18.4%*	5, *13.9%*	14, *20.9%*	2, *9.1%*	12, *26.7%*
Obese only, (n, %)	17, *16.5%*	8, *22.2%*	9, *13.4%*	4, *18.2%*	5, *11.1%*
Intervention type					
Diet-based, (n, %)	15, *14.6%*	4, *11.1%*	11, *16.4%*	7, *31.8%*	4, *8.9%*
Physical activity-based, (n, %)	47, *45.6%*	15, *44.4%*	31, *46.3%*	8, *36.4%*	23, *51.1%*
Mixed approach[§], (n, %)	41, *39.8%*	16, *44.4%*	25, *37.3%*	7, *31.8%*	18, *40.0%*
Country of conduct					
Lower-middle income, (n, %)	4, *3.9%*	1, *2.9%*	3, *4.5%*	1, *4.5%*	2, *4.4%*
Upper-middle income, (n, %)	19, *18.4%*	5, *14.3%*	14, *20.9%*	5, *22.7%*	9, *20.0%*
High income, (n, %)	80, *77.7%*	30, *85.7%*	50, *74.6%*	16, *72.7%*	34, *75.6%*

IQR, Inter Quartile Range; BMI, Body Mass Index; [†]Li 2014 trial recruited women with BMI only within normal range; [§]Renault 2013, Simmons 2016 classified as mixed approach trials

Outcome availability in the group of the studies with IPD differed between the publication and dataset level. The number of trials where the outcome data were available on the dataset-level improved for all of the evaluated outcomes. The greatest gain in outcome data availability was observed for two offspring outcomes (SGA and LGA). Out of 35 studies that share IPD, SGA was reported in 14.3% (5/35) in comparison to 94% (34/36) of the dataset with available event rate of this outcome. Ten studies (28.6%) reported occurrence of LGA while the event rate of this outcome was available in all 35 datasets. Despite the increase in the number of studies where data on the admission to NICU on the dataset-level (IPD) in comparison to publication-level, the outcome had the lowest availability (58%) among all seven assessed outcomes.

Table 4.3 Availability of outcome data in the trials with diet and physical activity based interventions in pregnancy

Characteristics	All eligible published studies (N = 102)	IPD available		Non-IPD*		
		Study-level* (N = 35)	IPD (N = 36)	Overall (N = 67)	Acquisition deadline	
					Published before (N = 22)	Published after (N = 45)
Gestational weight gain (kg)	77, *74.8%*	27, *77.1%*	33, *92%*	48, *71.6%*	19, *86.4%*	29, *64.4%*
GDM	50, *48.5%*	18, *51.4%*	30, *83%*	32, *47.8%*	7, *31.8%*	25, *55.6%*
Preterm birth	34, *33.0%*	17, *48.6%*	34, *94%*	17, *25.4%*	6, *27.3%*	11, *24.4%*
Caesarean section	58, *56.3%*	23, *65.7%*	34, *94%*	35, *52.2%*	10, *45.5%*	25, *55.6%*
SGA	16, *15.5%*	5, *14.3%*	34, *94%*	11, *16.4%*	3, *13.6%*	8, *17.8%*
LGA	21, *20.4%*	10, *28.6%*	36, *100%*	11, *16.4%*	2, *9.1%*	9, *20.0%*
Admission to NICU	10, *9.7%*	5, *14.3%*	21, *58%*	5, *7.5%*	2, *9.1%*	3, *6.7%*

IPD, Individual Participant Data; GDM, Gestational diabetes mellitus; SGA, Small for gestational age infant; LGA, Large for gestational age infant NICU, Neonatal Intensive Care Unit;
**trial publication*

4.3.2. Characteristics of participants in IPD trials

Over 80% of participants in the IPD trials were classified as Caucasian and around half of them had obtained a higher degree. The average age comparable between intervention and control arms being around 30 years. Women were mostly in their first pregnancy and not physically active prior their pregnancy. A detailed comparison of participant characteristics in both arms of IPD trials is available in Appendix 4.4.

4.3.3. Quality assessment

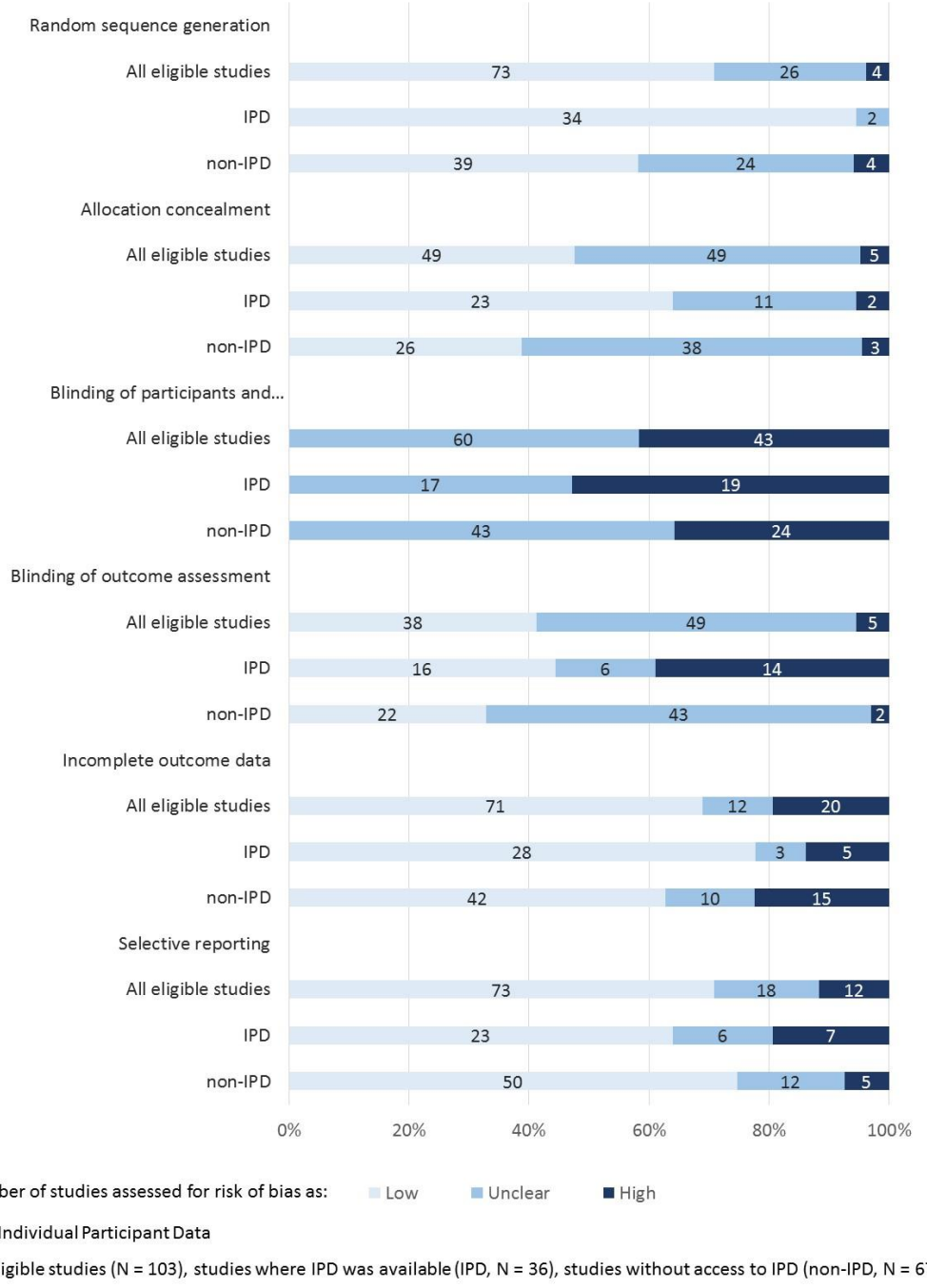
Overall, included trials were assessed as being of a low risk of bias in random sequence generation (75%, 73/103). Over 90% (34/36) of the trials that contributed to the IPD meta-analysis were assessed as being of a low risk of bias in this domain in comparison to 58% of those that did not (28/67). Two IPD (2/36) and one non-IPD (3/67) trials 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 trials, respectively. Fewer IPD trials (5/36) were assessed as high risk of bias for incomplete outcome data compared to the non-IPD trials (15/67). A detailed assessment of the study quality for individual trials is provided in Appendix 4.5. There were no major issues during the IPD quality check that could not be resolved with the IPD contributor assistance. All discrepancies between the data reported in the trials' publications and contributed IPD were documented.

4.3.4. Findings of IPD meta-analysis

Based on IPD meta-analysis, diet and physical activity based interventions resulted in significantly less gestational weight gain compared to routine antenatal care (MD -0.70 kg, 95% CI -0.92, -0.48 kg, I^2 = 14.1%, 33 studies, 9 320 women), after adjusting for baseline weight and clustering. There was a significant reduction in number of caesarean sections (OR

0.91, 95% CI 0.83, 0.99, I^2 = 0%; 32 studies, 9 250 women), with the interventions compared to routine care. (Table 4.4)

Figure 4.3 Risk of bias assessment for all eligible trials, trials where IPD was available, and those without access to IPD



IPD, Individual Participant Data

All eligible studies (N = 103), studies where IPD was available (IPD, N = 36), studies without access to IPD (non-IPD, N = 67)

Table 4.4 Meta-analyses of trials with diet and physical activity based interventions provided in pregnancy

Outcome	Meta-analysis	Number of trials (Number of participants)	Effect estimate* (95% CI)	I^2 (%)	Funnel plot[#]
Gestational weight gain (kg)	*(A) Study-level of only IPD trials*	27 (8 697)	-1.01 (-1.41, -0.61)	61.0	0.14
	(B) IPD	32 (9 320)	-0.70 (-0.92, -0.48)	14.1	0.04
	(C) IPD and study-level	81 (17 530)	-1.10 (-1.46, -0.74)	73.8	0.61
	(D) Study –level of all published trials	74 (16 599)	-1.29 (-1.70, -0.88)	77.2	0.15
GDM	*(A) Study-level of only IPD trials*	18 (8 898)	0.84 (0.63, 1.12)	52.8	0.04
	(B) IPD	27 (9 427)	0.89 (0.72, 1.10)	23.8	0.03
	(C) IPD and study-level	59 (16 885)	0.76 (0.65, 0.89)	36.8	0.03
	(D) Study –level of all published trials	50 (16 356)	0.75 (0.64, 0.88)	44.0	0.03
Preterm birth	*(A) Study-level of only IPD trials*	17 (9 003)	0.79 (0.63, 0.99)	7.9	0.64
	(B) IPD	32 (11 676)	0.94 (0.78, 1.13)	17.3	0.32
	(C) IPD and study-level	49 (14 339)	0.92 (0.79, 1.08)	8.7	0.63
	(D) Study –level of all published trials	34 (11 666)	0.80 (0.67, 0.95)	1.2	0.86
Caesarean section	*(A) Study-level of only IPD trials*	23 (9 178)	0.91 (0.82, 1.01)	0	0.13
	(B) IPD	32 (11 410)	0.91 (0.83, 0.99)	0	0.88
	(C) IPD and study-level	66 (18 041)	0.89 (0.83, 0.96)	16.2	0.98
	(D) Study –level of all published trials	58 (15 858)	0.90 (0.83, 0.97)	6.5	0.90
SGA	*(A) Study-level of only IPD trials*	5 (2 807)	1.19 (0.83, 1.71)	0	NA
	(B) IPD	33 (11 666)	1.06 (0.94, 1.20)	0	0.74
	(C) IPD and study-level	44 (12 937)	1.05 (0.94, 1.18)	0	0.33
	(D) Study –level of all published trials	16 (4 078)	1.10 (0.87, 1.40)	0	0.03
LGA	*(A) Study-level of only IPD trials*	10 (5 583)	0.90 (0.69, 1.19)	27.8	0.72
	(B) IPD	34 (12 047)	0.90 (0.76, 1.07)	38.0	0.86
	(C) IPD and study-level	45 (13 348)	0.86 (0.71, 1.04)	41.0	0.71
	(D) Study –level of all published trials	21 (6 884)	0.82 (0.62, 1.10)	39.6	0.93
Admission to NICU	*(A) Study-level of only IPD trials*	5 (5 387)	1.02 (0.84, 1.13)	0	NA
	(B) IPD	16 (8 140)	1.01 (0.84, 1.23)	0	0.44
	(C) IPD and study-level	21 (9 498)	0.97 (0.82, 1.14)	0	0.16
	(D) Study –level of all published trials	10 (6 745)	0.99 (0.85, 1.15)	0	0.06

**Mean Difference for gestational weight gain and Odds Ratio for binary outcomes; CI, Confidence Interval*
[#]Statistical test for the funnel plot asymmetry (Egger's for gestational weight gain, Peter's for binary outcomes); funnel plots available in Appendix 4.6
GDM, gestational diabetes; SGA, small for gestational age infant; LGA, large for gestational age infant; NICU, Neonatal Intensive Care Unit; NA, not applicable due to less than 10 observation

The reduction in other maternal outcomes such as gestational diabetes (OR 0.89, 95% CI 0.72, 1.10, I^2 = 23.8%; 27 studies, 9 427 women), and preterm birth (OR 0.94, 95% CI 0.78, 1.13, I^2 = 17.3%; 32 studies, 11 676 women) were not statistically significant. There was no strong evidence that diet and physical activity based interventions had an effect on offspring outcomes such as SGA infant (OR 1.06, 95% CI 0.94, 1.20, I^2 = 0%; 33 studies, 11 666 women), LGA infant (OR 0.90, 95% CI 0.76, 1.07, I^2 = 38.0%; 34 studies, 12 047 women), and admission to NICU (OR 1.01, 95% CI 0.84, 1.23, I^2 = 0%; 16 studies, 8 140 women). The effect estimates and their standard errors by individual studies are available in Appendix 4.7.

4.3.5.Impact of unreported outcomes

The direction of the summary effects, in the subgroup of studies that shared IPD, was consistent between study-level (A) and IPD meta-analyses (B) across all evaluated outcomes. The summary effects derived from study-level data were greater in magnitude in comparison to IPD in four out of seven evaluated outcomes (Table 4.4). The difference in the effects on the gestational weight gain was 0.31 kg (MD -1.01 kg, 95% CI -1.41, -0.61 study-level IPD trials versus MD -0.70 kg, 95% CI -0.92, -0.48 directly from IPD). Among the binary outcomes, the greatest discrepancy in the pooled effect was observed for preterm birth (OR 0.79, 95% CI 0.63, 0.99 study-level versus OR 0.94, 95% CI 0.78, 1.13 IPD) and SGA (OR 1.19, 95% CI 0.83, 1.71 study-level versus OR 1.06, 95% CI 0.94, 1.20 IPD). However, in all comparisons, the point estimates lied within each other CIs.

The precision of the summary effects was greater in the IPD meta-analysis. For two outcomes of the seven evaluated, the statistical significance of the derived effects differed between the meta-analysis using study-level and that using IPD. For preterm birth, the CIs around the pooled effect derived from study-level data did not cross the line of no-difference for OR (95% CI 0.63, 0.99). In the IPD meta-analysis, the CIs spanned from 0.78 to 1.13. The opposite was seen in case of the caesarean section where 95% CIs around the pooled

effect estimates (OR 0.91 in both cases) were from 0.82 to 1.01 in the study-level data meta-analysis, and from 0.83 to 0.99 when IPD was used. All the IPD meta-analyses showed low to moderate between-study heterogeneity. The same heterogeneity was seen in the study-level data meta-analysis, except for gestational weight gain and GDM where the I^2 was greater than 50%.

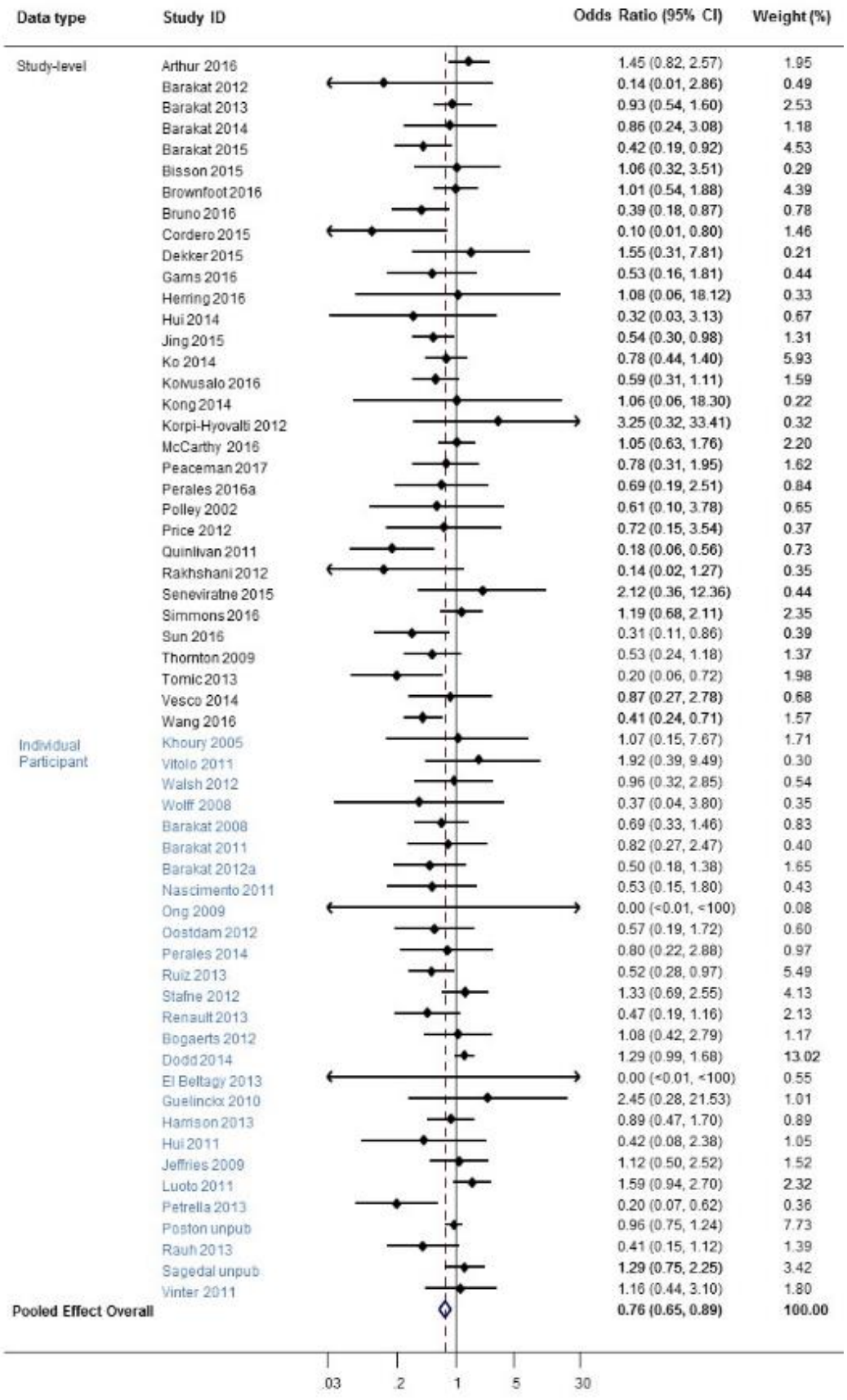
The comparison of the funnel plots between two approaches was not possible for SGA and admission to NICU as the study-level meta-analysis included insufficient number of trials for a meaningful assessment of the plots asymmetry. However, in the cases of both outcomes, the formal test for the funnel plot asymmetry using IPD did not show any significant asymmetry in the scatter of the effect sizes and their standard errors. For the remaining outcomes, only in the case of gestational weight gain did the funnel plot asymmetry tests differ between the two approaches – Egger's test for meta-analysis using study-level IPD trials and IPD trials was 0.14 and 0.04, respectively.

4.3.6.Impact of data availability

Overall, the meta-analyses with combined IPD and non-IPD trials (C) contained more studies and returned the summary effect estimates of a greater magnitude than meta-analysis with IPD alone (B). The direction of the summary effect estimates was consistent between IPD meta-analyses with and without non-IPD trials. The effect on gestational weight gain was greater by 0.31 kg in the meta-analysis with IPD and non-IPD trials (MD -1.10 kg, 95% CI -1.46, -0.74), compared to IPD alone (MD -0.70 kg, 95% CI -0.92, -0.48) (Table 4.4)

Among the binary outcomes, the greatest discrepancy in the value of the summary effect estimates was noted for GDM with OR 0.89 (95% CI 0.72, 1.10) from the IPD meta-analysis and OR 0.76 (95% CI 0.65, 0.89) in the IPD meta-analysis with non-IPD trials. (Figure 4.4)

Figure 4.4 Forest plot with the pooled effect of the interventions on gestational diabetes from combined meta-analysis with IPD and study-level data from trials with unavailable IPD



The meta-analyses for this outcome also differed regarding the statistical significance moving from not statistically significant effect in IPD meta-analysis to statistically significant effect in IPD meta-analysis with non-IPD trials. The between-study heterogeneity increased with the addition of non-IPD trials in four outcomes did not change in two outcomes and decreased in one outcome. Formal assessment of the funnel plot asymmetry was possible for all outcomes. The addition of non-IPD trials in IPD meta-analyses changed the funnel plot asymmetry from skewed to symmetrical in the meta-analyses of the gestational weight gain (Egger's test p = 0.61).

4.3.7.Totality of evidence on the effects of the interventions

Overall, the meta-analyses that combined IPD and non-IPD trials (C) contained more trials than meta-analyses with the study-level data (D). The direction of effects was consistent across the comparisons for all outcomes. The summary effects derived from the combined meta-analyses (IPD and non-IPD) tended to be more modest than the effects obtained from the study-level meta-analysis. The pooled effects for gestational weight gain differed between the meta-analyses by 0.14 kg with a greater reduction observed on the study-level (MD -1.24 kg, 95% CI -1.64, -0.84) (Table 4.4). Among the binary outcomes, the greatest discrepancy in the summary estimates was noted for preterm birth, with OR 0.92 (95% CI 0.79, 1.08) in the combined meta-analysis and OR 0.80 (95% CI 0.67, 0.95) in the study-level meta-analysis. The CIs around the summary effects were narrower in the combined meta-analyses for two outcomes (SGA and LGA). The statistical significance differed between the two approaches for preterm birth. The study-level meta-analysis suggested 20% statistically significant reduction in the odds of premature birth (OR 0.80, 95% CI 0.67, 0.95), in comparison to 8% non-statistically significant reduction (OR 0.92, 95% CI 0.79, 1.08) with combined IPD and non-IPD meta-analysis.

The level of the between-study heterogeneity was comparable between the two approaches, with low to moderate heterogeneity for the majority of the outcomes. Only for gestational weight gain, the heterogeneity estimate was above 50%. The comparison of the funnel plot asymmetry was possible for all the outcomes with an observed change in the statistical significance of the scatter distribution in one case. The funnel plot asymmetry for SGA was p = 0.03 and p = 0.33 (Peter's test) for the meta-analysis using study-level published trials and IPD with non-IPD trials, respectively. For the study-level meta-analyses, the pooled estimates obtained using number of randomised participants did not differ from the estimates obtained using sample sizes as reported in the publications (Appendix 4.8). Forest plots with the effect estimates derived from the study-level data are available in Appendix 4.9.

4.4. Discussion

4.4.1.Main findings

The findings for the IPD meta-analysis of 36 RCTs with over 12 500 women that showed diet and physical activity based interventions in pregnancy having a statistically significant effect in moderately reducing gestational weight gain. There was evidence that the odds of having a caesarean section were significantly lowered with the interventions, in comparison to routine antenatal care. Although the summary estimates favoured a reduction in all individual maternal outcomes, the findings were not statistically significant. There was no effect of the intervention on the evaluated offspring complications.

In contrast to data reported in the published reports, access to IPD from 36 RCTs allowed to incorporate more trials into the meta-analysis for all evaluated outcomes. Incorporation of previously unavailable data returned modest summary effects compared to the effects obtained using study-level data from publication of trials that contributed IPD to the i-WIP study. The statistical significance of the pooled effect changed in two cases and had no clear

impact on the heterogeneity level. The addition of study-level data from non-IPD trials changed the magnitude and the statistical significance of the summary effects in the meta-analysis for GDM, and changed the funnel plot structure in the meta-analysis for gestational weight gain. In most cases, incorporation of study-level data from trials where IPD was not available increased the between-study heterogeneity. The study-level meta-analyses and IPD meta-analysis with the addition of non-IPD trials (study-level data) provided comparable results with similar levels of between-study heterogeneity. The statistical tests for the funnel plot asymmetry were mostly coherent between the two approaches except for one outcome (SGA).

4.4.2.Strengths and limitations

The work presented here addresses important issues on the impact of unreported data, availability bias, and merits of performing IPD meta-analyses of RCTs on the effect of diet and physical activity in pregnancy. The meta-analyses complied with the current standards for their conduct and provided a comprehensive range of sensitivity analyses, allowing investigating the robustness of the summary effect estimates. The evidence synthesis included 103 RCTs, of which IPD was available from 36 RCTs with data from half of all women randomised to those trials. Out of 67 studies where IPD was not available, 45 were identified past the data acquisition time meaning that around two-thirds of those studies were not available due to logistics rather than the nature of their findings. Despite comprehensiveness of the searches, two studies were not picked up in the searches.[234,235] However, their impact on the analyses was insignificant.

Evaluated interventions comprised of a wide range of components such as different types of physical activity, diets, weight monitoring, and behaviour modifying techniques (Appendix 4.10). The complexity of the evaluated interventions was one of the major limitations for interpretation of the findings due to difficulty in disentangling the impact of trial type (diet,

physical activity, or mixed approach) from a true impact of unreported outcome data or study availability bias. Furthermore, the access to IPD allowed adjusting for baseline weight using analysis of covariance in each trial, which was not possible for the trials without access to IPD. Nevertheless, despite the heterogeneous environment, the tendency towards a greater magnitude of the summary effects with study-level published trials was visible for all evaluated outcomes. The between-study heterogeneity was formally quantified using I^2 measure. Despite potential concerns over dependency of this measure on the sample size, I did not observe an impact of the number of participants in the analyses and the I^2 value. For example, in the meta-analyses with preterm birth or gestational weight gain the increase in the sample sizes across the comparisons was not followed by substantial change in the value of I^2 measure.

A small proportion of all eligible trials (around 7%) did not contribute data to the quantitative synthesis of evidence. No attempt was made to contact authors of trials published in a format of conference abstracts. Also, no contact was made with the authors of non-IPD trials for more accurate trial design assessment, in case of lack of sufficient details in the publications or trial protocols. The risk of bias assessment of IPD trials was additionally supported by information obtained directly from the trials' authors.

It was not always possible to match the trials' populations where the IPD was available between the publications and records contributed to IPD meta-analysis. The discrepancies between the numbers of randomised and contributed participants records were queried with the trials' authors, and in most cases explained by loss to follow-up. Trial level discrepancies in the effect estimates reported in the publications and derived from IPD were rare and occurred mostly in small trials (Appendix 4.11). The comparison between the effect estimates was not done using formal methods and did not account for clustering of intra-study outcomes (more than 75% of trials studies contributed to more than one meta-analysis). Trials overlap also exists between the meta-analyses in all described comparisons, which might have led to a

dilution of the true effects. All the aspects discussed above should be taken into account when interpreting the findings of this work. However, observed trends are consistent with those reported in the literature for the comparisons between IPD and study-level meta-analyses.[126]

4.4.3. Interpretation

Within-study selective reporting of differences between evaluated interventions depending on statistical significance is one of the most important sources of bias affecting clinical trials.[26] Access to IPD in a meta-analysis of trials on diet and physical activity in pregnancy showed that around 30% of collected outcome data are not reported in the trial reports, such as admission to NICU not being reported in over two-thirds of studies. Preterm birth, SGA, and LGA were generated using gestational age and birthweight at delivery, if not captured in the originally contributed dataset. The ability to compute the outcome data facilitate incorporation to the meta-analyses number of trials that could not be analyses on the study-level. Yet, availability of the outcome data did not always lead to their inclusion in the meta-analysis. For example, a low number of stillbirths or lack of weight gain measures (baseline and final) hampered inclusion of all trial data for these outcome in the IPD meta-analysis. Gestational weight gain is perceived as a surrogate of maternal morbidity.[236] However, around 40% of included trials were powered to detect the effect of the intervention on this outcome. The variability in the magnitude of the effect, heterogeneity and small study effects across the meta-analyses might be more of an indicator of the quality of the data analysis in the primary trials rather than the impact of unreported outcome data.

Although the analyses found little or no evidence of the effect for diet and physical activity based interventions on the composite outcomes (maternal and offspring) this cannot be interpreted as ‘evidence of no effect’. Despite wide confidence intervals crossing the null, there was a consistent summary effect estimates favouring the intervention on some of the

assessed outcomes. A more in-depth exploration of the effect estimates in individual trials and their direction could help to gain a better idea of the certainty of the intervention effect.

The consistent skewness in the funnel plot asymmetry in the meta-analyses for GDM could be due to failure to collect or report this outcome in the smaller studies. The reasons for not reporting GDM might be numerous e.g. obtaining an undesirable effect on the outcome (reporting bias). The other explanation could be that the trialist did not consider the outcome important enough in the context of the research question e.g. trials with physical activity based interventions among the obstetric outcomes reported GDM less frequently than labour or delivery related events (disucssed in detail in chapter 6, Table 6.1). The variability in outcome definition could partially explain the moderate heterogeneity in the GDM meta-analysis. Diagnosis of GDM in the group of IPD trials was based on a broad range of guidelines that algorithms and reference standards did not always overlap with each other.[237,238] This problem could not be addressed even in IPD meta-analysis during data harmonisation due to the limited time and complexity of the task.

The authors of guidance on the appraisal of IPD meta-analyses of randomised trials advocate checking for the proportion of trials from which IPD was obtained.[46] Yet, only 25% of IPD meta-analyses manages to obtain IPD from all identified trials.[50] Since the publication of the systematic review that laid the grounds for the i-WIP IPD meta-analysis[76], there has been a significant increase in the number of trials evaluating the effects of diet and physical activity based interventions in pregnancy. With 45 new trials published within the last 3 years achieving the goal of being current and obtaining the majority of, if not all, IPD is virtually impossible. This emphasizes, the importance of sensitivity analysis in studies using an IPD approach to meta-analysis where IPD is combined with study-level data from trials, where IPD was not available due to refusal or study's time frames.

4.4.4.Conclusion

Interventions with diet and physical activity in pregnancy have the potential to reduce the gestational weight gain and the reduction of the risk of cesarean section. The effect of the interventions in reducing the odds of cesarean section was consistent regardless of the range and type of meta-analysis. My work showed that the effect of interventions without access to IPD and incorporation of unreported outcomes would be inflated. Furthermore, not incorporating trials with unavailable IPD would probably lead the researchers to abandon further exploration of the effect of the interventions on GDM.

The synthesis of only study-level and a combination of study-level and IPD for the totality of evidence mostly led to similar conclusions on the effects of diet and physical activity based interventions on the pregnancy outcomes. As an IPD meta-analysis is time and resource consuming approach to evidence synthesis, therefore the rationale for embarking on it needs to return tangible benefits. Evaluation of the summary effect might not be a sufficient justification for implementing IPD meta-analysis approach to evidence synthesis however it improves its robustness.

Chapter 5 Meta-regression and individual participant data meta-analysis to assess treatment-covariate interactions: empirical example of BMI influence on the effect of diet and physical activity

5.1. Introduction

Studies included in a systematic review inevitably differ from each other. All those differences contribute to heterogeneity in the pooled effect estimates and might prevented the formal pooling of the effects across the studies in extreme cases.[97] Exploration of the heterogeneity in the pooled effect is an essential aspect of evidence synthesis.[96] One of the main reasons, for high heterogeneity, is the characteristic of populations in the individual studies. The concept that subgroups of patients might benefit more from the interventions than the general because of their particular characteristics lies at the basis of stratified medicine.[100] Identification of such groups should be clinically based and defined *a priory* to prevent data dredging.[19]

Meta-regression and subgroup analysis are commonly used in study-level meta-analysis to explore the heterogeneity or identify subgroups of clinical relevance.[97,99] In meta-regression the influence of specific factors (e.g. participant characteristics) is examined in regression analysis against the effect estimates. Subgroup analyses are used when data for subgroups of patients of interest are available for each study. However, the findings of both methods might be misleading for two main reasons. Firstly, results extracted from trial publications are average estimates of the population in the study, and subgroup effects ('treatment-covariate interactions') are rarely reported in sufficient detail. Secondly, meta-regression that examines the across-trial association between overall treatment effect and average patient characteristics (e.g. mean age) has low power to detect genuine subgroup effects and is also prone to study-level confounding.[20,101,239] Meta-analysis using IPD has the potential to overcome the

limitations of the methods relying on study-level data.[43-45] Access to participant-level data in IPD meta-analysis allows deriving the effects of interventions for a particular subgroup directly from participant records. This substantially increases power to detect the effect of participants' characteristics truly modifying the effect of the interventions.[240,241]

Diet and physical activity based interventions have been extensively studied for their potential to achieve better pregnancy outcomes. These studies involve women with varied BMI values (see Appendix 1.1). A comprehensive systematic review of the RCTs on diet and physical activity showed that the interventions were effective in reducing gestational weight gain, with potential to improve pregnancy outcomes.[76] However, the findings were limited by the inability to explain heterogeneity of effects for important outcomes, and the paucity of published detail on the effects of interventions in various BMI groups, and other clinically important characteristics. One of the main recommendations that arose from the project was the need to synthesise participant-level data to assess any differential effect of the benefits observed with interventions in various groups of women including BMI category.[76]

The i-WIP IPD meta-analysis summarised the effects of diet and physical activity based interventions on gestational weight gain, adverse composite maternal and composite offspring outcome, and determined whether the effects deferred according to women's characteristics.[79] The i-WIP study collected data from 36 RCTs with over 12,500 participant records.

5.1.1. Aims

The aim of work presented in this chapter was to investigate potential differences between the study-level and IPD meta-analysis approach to detect the modifying effect of woman's BMI on the effects of diet and physical activity based interventions in pregnancy on maternal and offspring outcomes.

5.2. Methods

Trials and IPD used to address chapter's objective have been identified and obtained through a process described in detail in sections 2. In the IPD meta-analysis, continuous characteristics were summarised as means (with SD), and dichotomous and categorical as frequencies. Gestational weight gain, the only continuous outcome, was kept as pre- or early pregnancy weight and the last available weight before the delivery. The maternal and offspring complications were coded in a binary way (Yes/No). For details of IPD acquisition and handling see section 4.2. On the study-level, women's characteristics were used as reported in the publications of the eligible trials. Where possible, women's BMI was captured as an average value of all the women included in the individual trial, and as a proportion of women with normal BMI, overweight and obese. Gestational weight gain was extracted as mean with accompanying SD, remaining maternal and offspring outcome were recorded as event rates and extracted to two-by-two tables (see section 2.4).

5.2.1.IPD meta-analysis

As specified in section 2.4, a two-stage approach to IPD meta-analysis was applied accounting for cluster design, if necessary. For the continuous outcome of weight gain, the analysis of covariance was performed in each trial to regress the final weight value against the intervention while adjusting for baseline weight value. For the binary outcomes, a logistic regression was applied in each trial separately with intervention as a covariate. All models were extended to include interaction terms between participant-level covariates and the intervention. The characteristic of interest (women's BMI) was used as a continuous and a categorical covariate (normal, overweight, and obese). The coefficients for binary outcomes were log transformed to OR with their respective 95% CI.

5.2.2.Study-level meta-analysis

For the study-level analysis, a meta-analysis without pooling of the effect estimates (OR for binary outcomes and MD for gestational weight gain) was first performed to obtain the effect estimates and their respective standard errors (SE) on the individual trial level.[242] For the binary outcomes, the OR were log-transformed and their SE calculated. Secondly, I fitted weighted least-squares linear regression models with the respective effect estimates as the outcome variable, the covariates as predictors, and the weights equal to the inverse of the variance of the effect estimates.[243] The models for dichotomous outcomes were not corrected for lack or imbalance in the event rates. The study-level BMI data were used as an average BMI of women in the study (continuous) or as a proportion of normal, overweight, and obese women. For easier interpretation of the coefficients, the originally extracted proportions of women in the respective BMI groups were multiplied by 10 (10% change in the proportion of women). The coefficients for binary outcomes were again transformed to OR with their respective 95% CI. Where possible, a sensitivity analysis was performed using study-level data from the group of studies that contributed to IPD-meta analysis.

5.2.3.Comparisons

The comparison between study-level and IPD exploration of modifying the effect of women's BMI on the effects of interventions in was performed for gestational weight gain and individual maternal and offspring outcomes. Similarly to work presented in chapter 4, the composite outcomes could not be used to investigate the differences between the meta-analyses based on study-level and IPD. Therefore the comparisons were made for the gestational weight gain, GDM, caesarean section, preterm birth, SGA, LGA and admission to NICU. Stillbirth and hypertensive diseases were not used for the reasons given in section 4.2.

Firstly, I obtained the interactions between women's BMI and the effects of interventions using IPD from the trials that contributed to the i-WIP study. Secondly, I performed a meta-regression using the study-level data extracted from all eligible trials where the outcome and the covariate of interest were available. The results of both approaches were compared for the significance of the modifying effect of the covariates on the effects of the diet and physical activity in pregnancy on the maternal and offspring outcomes.

5.3. Results

5.3.1. Studies characteristics

Out of 103 RCTs with diet and physical activity based interventions in pregnancy (Figure 4.1 in section 4.3) data from 89 was available for study-level meta-regression. The remaining 14 studies could not be used due to lack of outcome data or incomplete reporting of BMI value at baseline. The majority of 89 trials recruited women regardless of their BMI value, 20% included only obese and overweighed, and 14.6% only obese women (Table 5.1). The average BMI was 27.8 kg/m^2 and was provided in 73 out of 89 trials. The proportion of women in respective BMI categories were was reported in more than half of the trials (50/89) with 38% (19/50) reporting inclusion of some proportion of women with normal BMI, 74% (37/50) of overweight and 90% (45/50) of obese women.

Table 5.1 Characteristics of studies used in meta-regression

Baseline characteristics		**Number of studies** (Number of women)	**Proportion of studies or Average value**
BMI inclusion criteria[†]			
	Any BMI	55 (15 180)	61.8%
	Only normal BMI	1 (160)	1.1%
	Normal and overweight	2 (211)	2.2%
	Obese	13 (3 517)	14.6%
	Overweight and obese	18 (4 804)	20.2%
Weight recorded			
	Pre-pregnancy	36 (7 443)	40.4%
	Early pregnancy	27 (8 346)	30.3%
	Pre or early pregnancy	1 (382)	1.1%
	Unclear or not given	25 (7 701)	28.1%
Weight, kg		46 (12 500)	75.1
BMI, kg/m^2		73 (20 347)	27.8
Proportion of women in a given BMI category[†]			
	Normal BMI	19 (2 941[§])	22.8
	Overweight	37 (3 423[§])	26.5
	Obese	45 (6 431[§])	48.9

BMI, Body Mass Index; [†] as reported in the study; [§]numbers estimated basing on the reported proportion of women

In the group of trials where IPD was available, 23 included women regardless of their early or pre-pregnancy BMI, five included only obese and overweight women, and eight included only obese women. The data on women's BMI was available for the majority of the studies (34/36) with the average value of 29.2 kg/m^2 (SD 6.6). Over two-third of women included in those trials were obese, 31.7% had normal BMI, and 25.8% were overweight (Table 5.2)

Table 5.2 Characteristics of studies with available Individual Participant Data

Baseline characteristics	**Number of studies (Number of women)**	**Frequencies or Mean (SD)**
BMI inclusion criteria[†]		
Any BMI	23 (6 742)	63.9%
Obese	8 (2 897)	22.2%
Overweight and obese	5 (2 704)	13.9%
Weight, kg	33 (11 748)	80.0 (19.0)
BMI, kg/m^2	34 (12 031)	29.2 (6.6)
Proportion of women in a given BMI category:		
Normal weight	24 (12 031)	3816, 31.7%
Overweight	32 (12 031)	3101, 25.8%
Obesity	34 (12 031)	5114, 42.5%
Gestational weight gain (kg) by BMI category		
Normal weight	21 (3376)	11.9 (4.6)
Overweight	29 (2574)	11.1 (5.2)
Obesity	31 (3335)	8.4 (5.7)
Weight, kg		
Pre-pregnancy	23 (2 406)	73.1 (17.9)
Early pregnancy	26 (3 482)	79.1 (18.5)

BMI, Body Mass Index (kg/m²)

5.3.2.IPD meta-analysis

The IPD meta-analysis showed no evidence of an interaction between women's BMI and the effects of diet and physical activity based interventions in case of gestational weight gain. The interaction was not significant whether the BMI was used as a continuous covariate (-0.02 kg change in intervention effect per 1-unit increase in BMI, 95% CI -0.08, 0.04). The results were similar when in the comparison between the categories: overweight vs. normal (-0.11 kg, 95% CI -0.77, 0.55), obese vs. normal (0.06 kg, 95% CI -0.90, 1.01), and obese vs. overweight (-0.09 kg, 95% CI -1.05, 0.86) (Table 5.3).

Table 5.3 Interactions between the effects of diet and physical activity based interventions and early or pre-pregnancy Body Mass Index for gestational weight gain using IPD meta-analysis

Covariate	**Number of studies (Number of women)**	**Pooled interaction term, 95% CI**	**I^2 (%)**
BMI continuous*	31 (9 285)	-0.02 (-0.08, 0.04)	39.8
Overweight vs normal	21 (5 178)	-0.11 (-0.77, 0.55)	32.0
Obese vs normal	21 (4 221)	0.06 (-0.90, 1.01)	32.7
Obese vs overweight	28 (5 426)	-0.09 (-1.05, 0.86)	46.9

BMI, Body Mass Index (kg/m^2); CI, Confidence Interval
**change in the effect per unit increase in covariate (BMI)*

The analyses did not show any evidence of an interaction between the women's BMI and the effects of the interventions for any of the maternal and offspring outcomes (Table 5.4). The analyses with categorised BMI differ in the number of studies and participants as not all trials recruited women across all three groups. The between-study heterogeneity for interaction terms was low to moderate with the I^2 above 25% present for all the models with the gestational weight gain.

Table 5.4 Interactions between the effects of diet and physical activity based interventions and early or pre-pregnancy Body Mass Index for predefined outcomes using IPD meta-analysis

Outcome	Covariate	Number of studies (Number of women)	Pooled interaction term OR, 95% CI	I^2 (%)
GDM	BMI continuous*	25 (9 316)	1.00 (0.97, 1.02)	0.0
	Overweight vs normal	12 (3 503)	0.92 (0.40, 2.10)	16.4
	Obese vs normal	12 (2 849)	1.05 (0.44, 2.51)	1.6
	Obese vs overweight	13 (3 978)	0.99 (0.60, 1.65)	0.0
Preterm birth	BMI continuous*	31 (11 603)	0.98 (0.94, 1.02)	0.1
	Overweight vs normal	7 (2 660)	1.11 (0.42, 2.93)	0.0
	Obese vs normal	7 (2 143)	0.80 (0.24, 2.63)	0.0
	Obese vs overweight	11 (4 376)	0.56 (0.30, 1.06)	0.0
Caesarean section	BMI continuous*	32 (11 398)	1.00 (0.98, 1.02)	0.1
	Overweight vs normal	19 (5 217)	1.07 (0.76, 1.51)	0.0
	Obese vs normal	19 (4 248)	0.88 (0.55, 1.41)	0.0
	Obese vs overweight	28 (6 131)	0.91 (0.69, 1.2)	0.0
SGA infant	BMI continuous*	31 (11 556)	0.98 (0.95, 1.00)	0.0
	Overweight vs normal	16 (5 271)	1.01 (0.57, 1.81)	7.5
	Obese vs normal	16 (4 265)	0.68 (0.35, 1.31)	0.0
	Obese vs overweight	20 (5 467)	0.65 (0.42, 1.03)	0.0
LGA infant	BMI continuous*	32 (11 979)	1.00 (0.97, 1.02)	0.0
	Overweight vs normal	12 (3 881)	1.19 (0.7, 2.04)	29.0
	Obese vs normal	12 (3 067)	1.38 (0.79, 2.41)	0.0
	Obese vs overweight	21 (5 956)	1.04 (0.72, 1.50)	0.0
Admission to NICU	BMI continuous*	14 (7 725)	0.97 (0.92, 1.02)	0.2
	Overweight vs normal	7 (2 501)	0.83 (0.36, 1.92)	0.0
	Obese vs normal	7 (1 982)	1.45 (0.52, 4.08)	0.0
	Obese vs overweight	11 (4 383)	0.99 (0.35, 2.77)	23.7

CI, Confidence Interval; OR, odds ratio; BMI, Body Mass Index (kg/m^2); GDM, gestational diabetes; SGA, Small for gestational age; LGA, Large for gestational age; NICU, Neonatal Intensive Care Unit;
**change in the effect per unit increase in covariate (BMI)*

5.3.1.Study-level meta-analysis

The effect of diet and physical activity based interventions on gestational weight gain was significantly modified by women's BMI in the model where the BMI was coded as the proportion of women in the individual classes. The effects of the interventions was significantly modified by an increase in the proportion of obese women by each 10% (coeff. -0.22, 95% CI -0.33, -0.11) (Table 5.5)

Table 5.5 Interactions between the effects of diet and physical activity based interventions and early or pre-pregnancy Body Mass Index for gestational weight gain using meta-regression

Covariate	**Number of studies**	**Pooled interaction Coeff. (95% CI)**	**I^2 (%)**
1-unit of change in the value of:			
Average BMI	63	-0.08 (-0.17, 0.21)	77.7
10% change in the proportion of women in BMI strata of:			
Normal BMI	47	-0.11 (-0.27, 0.04)	
Overweight	47	-0.09 (-0.29, 0.11)	79.4
Obese	47	-0.22 (-0.33, -0.11)	

CI, Confidence Interval; BMI, Body Mass Index (kg/m^2);

The modifying effect was not statistically significant for the other BMI groups or when the covariate was used as an study-level avaerage. The meta-regressions for the remaining maternal outcomes did not provide any evidence for a modifying effect of women's BMI on the effect of diet and physical activity based interventions in pregnancy regardless whether an average BMI or a proportion of women in the particular BMI groups was used (Table 5.6).

The exploration using study-level data was not possible for all three offspring outcomes. For admission to NICU, meta-regression was not possible as there were less than ten studies with the outcome and the covariate data. The analyses for SGA and LGA were limited meta-regression only with BMI as an average from the individual trials. The interaction between the

study-level covariate and the interventions effects were OR 1.02 (95% CI 0.97, 1.08, I^2 = 0%, 15 studies) for SGA, and OR 1.03 (95% CI 0.97, 1.09, I^2 = 33.4%, 19 studies) for LGA per 1-unit of increase in the value of the average BMI. The study-level analysis limited to the studies that contributed to IPD meta-analysis was possible for only four maternal outcomes and only with BMI as a study-level average. None of the results was statistically significant. (Appendix 5.1)

Table 5.6 Interactions between the effects of diet and physical activity based interventions and early or pre-pregnancy Body Mass Index for maternal outcomes using meta-regression

Outcome	Covariate	Number of studies	OR (95% CI)	I^2 (%)
	1-unit of change in the value of:			
GDM	*Average BMI*	45	1.02 (0.98, 1.05)	24.5
Preterm birth		30	0.98 (0.93, 1.02)	0.0
Caesarean section		49	1.01 (0.99, 1.02)	0.0
	10% change in the proportion of women in BMI strata of:			
GDM	*Normal BMI*	35	1.01 (0.95, 1.07)	
	Overweight	35	0.96 (0.90, 1.02)	33.9
	Obese	35	0.98 (0.95, 1.01)	
Preterm birth	*Normal BMI*	21	0.98 (0.92, 1.05)	
	Overweight	21	1.03 (0.89, 1.19)	3.5
	Obese	21	0.96 (0.91, 1.01)	
Caesarean section	*Normal BMI*	33	0.98 (0.96, 1.01)	
	Overweight	33	0.99 (0.96, 1.03)	0.0
	Obese	33	1.00 (0.98,1.01)	

OR, odds ratio; CI, Confidence Interval; BMI, Body Mass Index (kg/m^2); GDM, gestational diabetes

The between-study heterogeneity for the interaction terms was low to high across the models. The most heterogeneous (I^2 > 75%) results were among the models evaluating effect of the covariates on the interventions' effect on the gestational weight gain.

5.3.2.Study-level versus IPD meta-analysis

The study-level meta-analysis showed a statistically significant relationship between the proportion of obese women and the effects of the evaluated interventions on gestational weight gain. The relationship was not present in the IPD meta-analysis. The results of the study-level and IPD meta-analyses were concordant for the remaining outcomes regardless whether the women's BMI was used as continuous or categorical value. In comparison to study-level meta-analysis, access to IPD allowed me to explore the modifying effect of women's BMI, as a continuous and categorical covariate, on the interventions' effect on all the offspring outcomes. The study-level meta-analysis for SGA and LGA could be performed only using BMI as an average value for the population recruited in the individual studies. The between-study heterogeneity for the interaction terms was more variable on the study-level and in the models with gestational weight gain much higher than on the IPD-level.

5.4. Discussion

5.4.1.Main findings

Access to participant-level data allowed me to conduct a more profound and comprehensive exploration of the modifying effects of women's BMI on the effects of diet and physical activity based interventions on maternal and offspring outcomes. The IPD meta-analysis shows that the effects of diet and physical activity based interventions on the maternal and the offspring outcomes did not differ by women's BMI status. The results of the study-level meta-regression indicate that the effect of interventions on minimising gestational weight gain may be stronger for the obese women than for overweight or women with normal BMI. The heterogeneity in the treatment-covariate interactions was lower when the IPD rather than study-level data were analysed.

5.4.2. Strengths and limitations

The meta-analyses conducted in this chapter complied with the current standards and provided an empirical comparison between study-level and IPD meta-analytical approaches to effect modification by participant characteristics. The trials used in the comparisons were identified through a robust and systematic process. The IPD meta-analysis was guided by prospectively developed protocol and according to current standards of conducting this type of evidence synthesis.[79] Access to IPD from 36 RCTs with diet and physical activity based interventions in pregnancy (> 12 500 participants) provided sufficient power (compared to individual trials) to estimate treatment-covariate interactions. It has allowed incorporation of unreported outcome data, and adjustment for baseline weight using analysis of covariance in each trial which is most suitable for the analysis of continuous outcomes.[244] In comparison to other empirical explorations, I ensured that the study-level meta-analyses had a sufficient number of studies as per current recommendations for running meta-regression.[240]

Diet and physical activity based interventions comprise of a wide range of complex components with various types of physical activity, modification of diet, etc. In contrast to work by Berlin et al.[240] that explored the magnitude of the ecological bias on a drug example, the complexity of the interventions increased noise in the comparisons consequently limiting its power to quantify the ecological bias. The initial work plan envisaged to identify a group of studies with similar interventions regarding the components, type of delivery, frequency and duration that could be used for the study-level versus IPD comparison. The subgroup of trials on physical activity met those criteria; however, the variable reporting of the study-level data prevented me from pursuing this part of the exploration.

Finally, it was not always possible to match the trials' populations where the IPD was available between the publications and records contributed to IPD meta-analysis. However, almost two-thirds of the IPD trials shared the data from all randomised participants. The

comparison did not account for clustering of outcomes within-studies and the trial overlap between study-level and IPD meta-analyses. As I did not correct for multiple testing when considering BMI subgroups, observed statistically significant findings should be treated with caution due to increased risk of the type 1 error.

5.4.3.Interpretation

Investigating sources of heterogeneity in the summary effects or identification of subgroups of participants that benefit more from the evaluated interventions are important elements of evidence synthesis.[96] Commonly used approaches such as subgroup analysis and estimation of treatment-covariate interaction in meta-regression lack the statistical power and are limited by the reporting of primary studies. Although meta-analyses using IPD is widely regarded as 'gold standard' for evidence synthesis of effectiveness research[43,45,46] it is logistically more challenging and resource intensive than study-level meta-analyses. It is important to ensure that the benefits are emerging from deploying this method outweighs its costs.[239,245]

The study-level meta-analysis indicated that the effect of the interventions in the reduction of gestational weight gain might be stronger among obese pregnant women. Whereas, the meta-analyses using IPD showed no evidence to support the belief that the women from any specific BMI class would benefit from the interventions more than the others. If the results of the IPD meta-analysis were not available, the findings of meta-regression could have been used to support the provision of a specific antenatal advice on diet and physical activity in pregnancy to minimise gestational weight gain only to this group of women. However, basing on presented findings from IPD meta-analysis, on average, these interventions reduce gestational weight gain with the comparable magnitude across BMI groups. Therefore, their provision only to obese women would have to be justified by other health benefits e.g. development of healthier eating habits.[246]

The significant interaction between the interventions' effect and the categorical covariate in this work could have emerged due to poor reporting of primary studies, high between study variance in the characteristic of the categorical covariate, and study-level confounding. Only half of studies with reported average BMI also provided the number of women within the individual BMI classes. Nevertheless, the model with BMI as a proportion of women in individual BMI classes identified a statistically significant interaction. The trials that reported only the average BMI recruited women regardless of their BMI status across four continents while the studies in where the proportions were reported were conducted in predominantly in high income countries (US, Europe and Australia).

Meta-regression is known for its low statistical power to detect interactions and depends on the variation in the covariates values within and between the studies.[247] However, if the ranges of the covariate within studies are narrow, and the means are broadly spaced across the studies (between-study ranges) the power to detect potential modifying effect of this covariate in meta-regression is high.[247] The variation in the within and the between study-level average BMI was much lower than for the covariate capturing the proportion of obese. Furthermore, almost one-third of the studies reporting the proportion of obese women recruited only from this BMI class with another one-third having more than 50% of women with BMI above 30. The trials with the obese participants were mostly conducted in the high income countries such as UK, Denmark, Belgium, Canada or US (Appendix 4.3) making it difficult to disentangle the effect of the high BMI from the 'country' effect.

5.4.4.Conclusion

The effect of diet and physical activity in pregnancy on maternal and offspring outcomes did not differ depending on women's BMI pre or early in pregnancy. Meta-regression is well known for its limitations and this work provides another empirical example that the findings obtained with this methods should be interpreted with great caution. The IPD meta-analysis

provided a robust and less biased evidence for the treatment-covariate interaction then the study-level meta-regression.

Chapter 6 Outcome reporting in trials with diet and physical activity based interventions in pregnancy

6.1. Introduction

Numerous RCTs have evaluated the effects of diet and physical activity based interventions in pregnancy on maternal and offspring outcomes with their main objective being to minimise morbidity and mortality. Given the relatively small number of severe complications, systematic reviews and meta-analysis are crucial to synthesise evidence from individual studies to provide robust estimates with precision. Selective reporting of trial results can seriously impair evidence synthesis, and its usefulness to inform clinical practice.[31,36] Trials on diet and physical activity in pregnancy usually involve a multidisciplinary team of researchers from varied backgrounds e.g. obstetrics, dietetics, sport medicine, midwifery, etc. that may have an important impact on the choice of primary and secondary outcomes in the trials. A Delphi ranking of maternal and offspring outcomes according to their importance in the management of maternal weight in pregnancy has been previously used to inform a systematic review of medical literature for the main research institute in the UK.[75] However, the proportion of published studies that have reported the prioritised outcomes has not been evaluated.

The Consolidated Standards of Reporting Trials (CONSORT) statement was introduced to standardise and improve reporting of RCTs.[248] The statement clearly specified how the design, conduct and analysis of RCTs should be described in a transparent and robust manner. Since its introduction in 1996[248], the statement has been updated twice[249,250] and became a mandatory requirement of article submission process for a number of medical journals.[251,252]

The findings of a systematic review of RCTs included in Cochrane reviews suggest that journal endorsement of CONSORT may benefit the completeness of reporting of RCTs.[253] However, the impact of (CONSORT) statement on the quality of outcome reporting has not been evaluated so far.

6.1.1.Aims

The aim of the work in this chapter was to address the knowledge gap and assess the variations in outcomes reported. The quality of the reported outcomes can be affected by miscellaneous factors related to study or journal where the trial findings were published.[254,255] Therefore, the second aim of the presented work was to assess the quality of outcome reporting in RCTs with diet and physical activity based interventions in pregnancy and explore the impact of those factors on that quality.

6.2. Methods

The systematic review used to inform this chapter followed the PICO question described in chapter 2.3. The search strategy used in the previous work was adopted to identify new studies.[76] The search was performed from October 2013 to March 2015 in previously defined databases additionally including the Cumulative Index to Nursing & Allied Health Literature (CINAHL) database. The inclusion criteria for the review were RCTs with diet, and physical activity based interventions in pregnancy that enrolled women without diabetes at entry into the trial were modified for this systematic review. Previously identified studies and the new citations were assessed for their eligibility and excluded if reporting an only change in the consumption of particular food groups or metabolic indices of physical activity, trial protocols, and conference abstracts.

All reported outcomes were extracted into a data collection form and subsequently classified as 'critically important', 'important' or 'not important' in the management of maternal weight in pregnancy using the findings of two-stage Delphi survey as a reference.[75] Trial and publication details such as country of trial conduct, year of publication, characteristics of the intervention(s) were collected and tabulated. The journals that published finding of the eligible trials were classified in two ways: a) as general (e.g. BMJ or JAMA) vs. specialist journals (obstetrics, diabetes, etc.), and b) as obstetrics focused vs. other specialities (dietetics, sports medicine, etc.). Where possible a journal impact factor as per The Thomson Reuters metrics[256] was obtained for the given publication year e.g. an article published in BMJ in 2014 would be assigned an impact factor of 16.3, and the one published in 2012 impact factor of 17.22. The year of publication was additionally dichotomized into before and after the update of CONSORT statement in 2010[249] (the cut-off year 2011).

The quality of outcome reporting was evaluated following the approach adopted by Harman et al.[257]. The approach uses a 6-item questionnaire with the following questions:

1. Was the primary outcome clearly stated?
2. If the outcome was clearly stated as primary, was its definition provided?
3. Was the secondary outcome(s) listed?
4. If the secondary outcome(s) was clearly named as secondary, was it accompanied by a definition(s)?
5. Was the explanation of the outcomes use in statistical analysis given?
6. Was the description of methods used to enhance quality of the outcome measure, if available?

Questions 1, 3, 5 and 6 ask for a yes/no response with 1-point assigned in case of positive response. When the outcome was not clearly defined as 'primary' or 'secondary' (questions 1 and 3) the precision of its definition was not assessed (questions 2 and 4) and assigned 'not applicable' status. The final score indicating quality of the outcome reporting was defined as

the proportion of points out of a maximum of 6 points. The quality of outcome reporting score per published article was the proportion of the assigned points out of 6. The non-applicable items were treated as missing values.

Extracted outcomes were evaluated, and a proportion of papers reporting individual outcomes was estimated. The results were stratified by predefined groups of outcomes 'critically important' and 'important' to women's care. Furthermore, the proportions of outcomes were stratified by the intervention type evaluated by a given trial (diet only, physical activity only or mixed approach). Reporting of 'critically important' and 'important' outcomes by intervention type was formally compared using Pearson Chi^2. All continuous data were examined for non-linearity and log transformed where necessary.

The association of quality of outcome reporting score with study quality and journal characteristics (journal impact factor, year of publication) was initially assessed using Spearman's rank correlation. Furthermore, the impact of the CONSORT statement on was assessed through a comparison of studies published before and after the statement update in 2010. The multiple linear regression models with a bootstrapping sampling method (1000 iterations, with a set seed) were used to explore the relationship between the pre-specified items and the quality of outcome reporting score.[258] The bootstrapping method was used to address the non-normal distribution of the quality of outcome reporting score that could not be addressed using typically used methods (e.g. log transformation). The factors for the final multivariable analysis were selected following a step-down approach setting the p-value for the exit at $p = 0.2$. When eliminating categorical variables, the p-value for exit was the one with the lowest values for all the categories. The overall significance of the categorical variables was checked using global post-estimation tests (Wald tests).

The sensitivity analysis examined the impact of adopting alternative approaches to calculating the quality of outcome reporting score and variable selection for the final multivariate model.

The final sensitivity analysis explored the impact of feasibility and pilot trials that were not powered to detect the intervention effect for the clinical outcomes. All analysis methods were defined a priori except the grouping of the publication according to their pre or post CONSORT 2010 status.

6.3. Results

6.3.1. Characteristics of included studies

The systematic search of medical databases returned 3,551 potential citations. After the abstract and full text screening, 66 trials published in 78 papers met the inclusion criteria; 12 publications reported results of secondary analyses of ten trials ().
).

The results of secondary analyses, on average, were published one year later than the primary findings. The main trial publications were often published in obstetrics journals (29/66). The majority of findings was published after the introduction of the CONSORT statement in 1996, and more than half of the trials (40/66, 60.6%) after its update in 2010 (Figure 6.2). The median impact factor in this group of publications was 3.04 (IQR 1.50, 4.39) with the impact factor ranging between 0 and 17 (Appendix 6.1). Eligible trials assessed the effect of diet based interventions in 12 instances, mixed (diet and physical activity) approach in 23, and physical activity only in 31 (Appendix 6.1). In comparison to the primary publications, the secondary analyses were published in journals with a lower impact factor.

Figure 6.1 Selection of studies and outcomes in trials with diet and physical activity based interventions in pregnancy

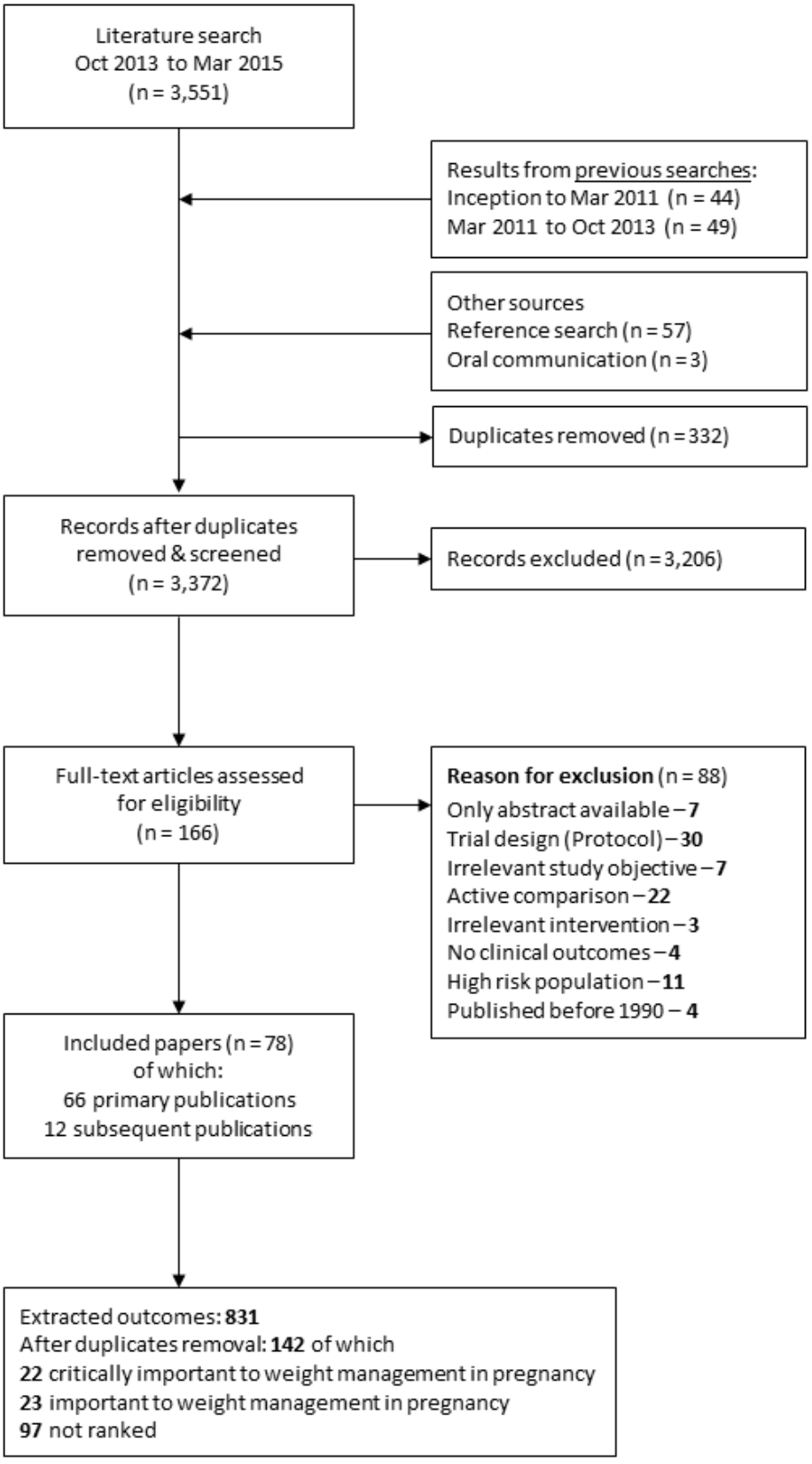
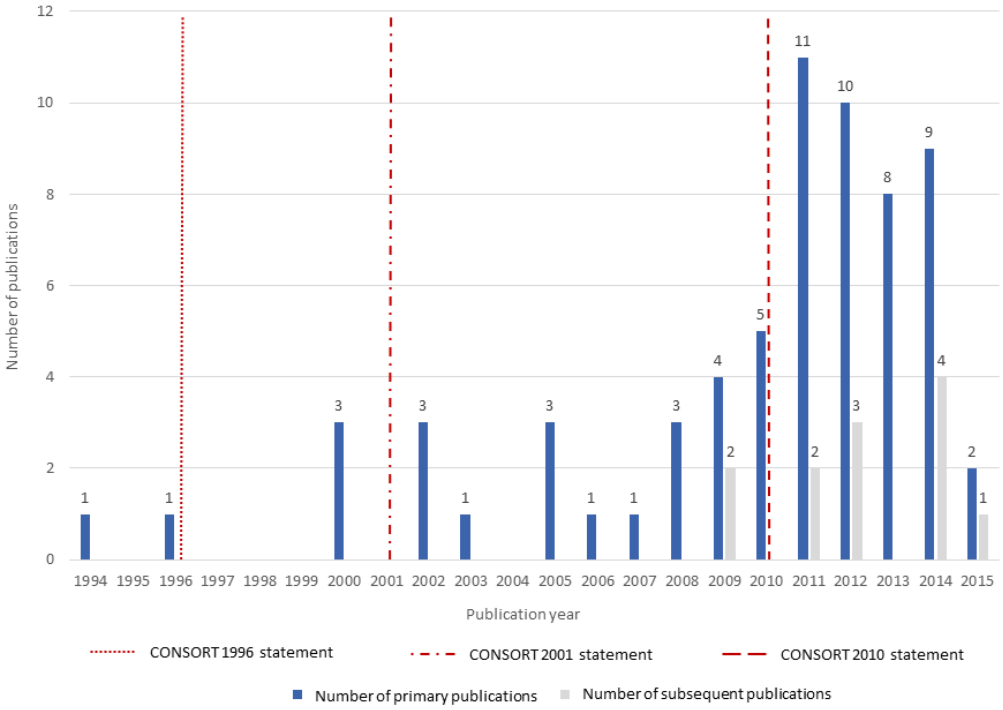


Figure 6.2 Number of primary and secondary publications from RCTs with diet and physical activity based interventions in pregnancy



6.3.2. Variation in reported outcomes

The trials on diet and lifestyle interventions in pregnancy reported 142 outcomes, half of them (72/142, 50.7%) appeared in the evaluated publications only once e.g. women's anxiety was reported as an outcome in only one trial. The median number of outcomes reported per trial was 12 (IQR 8, 15). When stratified by intervention type, the median of outcomes per trial was 13 (IQR 10, 18) in group of trials with mixed approach interventions, 11 (IQR 8, 15) in group of physical activity only trials, and the lowest in diet only group (median 10, IQR 6, 14).

Using a ranking of outcomes derived from a previously conducted Delphi survey[75], 142 identified in this evaluation outcomes were classified as follows: 22 as 'critically important', 23 as 'important' to women's care, and remaining 97 were not listed (for details see Appendix 6.2). Among the outcomes classified as 'critically important', the most frequently reported were caesarean section (40/66, 60.6%), GDM (38/66, 57.6%) and preterm birth (32/66, 48.5%) (

Table 6.1).

Table 6.1 Critically important outcomes reported in trials of diet and physical activity based interventions in pregnancy

Outcome group	Measured outcome	Delphi rank*	*Diet (N = 12)*	*Physical activity (N = 31)*	*Mixed (N = 23)*	*Total (N = 66)*
Maternal	Gestational Diabetes Mellitus	8	*6(50%)*	*11(35%)*	*21(91%)*	*38(58%)*
	Pregnancy-induced hypertension	8	*3(25%)*	*12(39%)*	*8(35%)*	*23(35%)*
	Preeclampsia	8	*3(25%)*	*5(16%)*	*10(44%)*	*18(27%)*
	Induction of labour	8	*1(8%)*	*1(3%)*	*7(30%)*	*9(14%)*
	PIH or pre-eclampsia	8	*1(8%)*	-	*3(13%)*	*4(6%)*
	Thromboembolism	8	-	-	*1(4%)*	*1(2%)*
	Caesarean section	7	*6(50%)*	*19(61%)*	*15(65%)*	*40(61%)*
	Preterm birth	7	*7(58%)*	*11(35%)*	*14(61%)*	*32(48%)*
	Instrumental delivery	7	*1(8%)*	*10(32%)*	*4(17%)*	*15(23%)*
	Post-partum haemorrhage	7	*1(8%)*	*1(3%)*	*1(4%)*	*3(5%)*
	Dietary habits (Mother)	7	-	-	*2(9%)*	*2(3%)*
	Threatened abortion	7	-	*1(3%)*	-	*1(2%)*
Infant	Small for gestational age	8	*1(8%)*	*6(19%)*	*5(22%)*	*12(18%)*
	Stillbirth and neonatal death	8	*3(25%)*	*2(6%)*	*3(13%)*	*8(12%)*
	Admission to NICU	8	*1(8%)*	*1(3%)*	*5(22%)*	*7(11%)*
	Shoulder dystocia	8	-	-	*3(13%)*	*3(5%)*
	Birth trauma (Infant)	8	-	-	*2(9%)*	*2(3%)*
	Composite: newborn complications	8	-	*1(3%)*	-	*1(2%)*
	Large-for-gestational age	7	*1(8%)*	*5(16%)*	*12(52%)*	*18(27%)*
	Blood pH (Infant)	7	-	*2(6%)*	*1(4%)*	*3(5%)*
	Hypoglycaemia (Infant)	7	-	-	*3(13%)*	*3(5%)*
	Resuscitation at birth	7	-	-	*1(4%)*	*1(2%)*

**according to published Delphi ranking[75], N, number of publications; NICU, Neonatal Intensive Care Unit; PIH, Pregnancy-induced hypertension*

Table 6.2 Important outcomes reported in trials of diet and physical activity based interventions in pregnancy

Outcome group	Measured outcome	Delphi rank*	*Diet (N = 12)*	*Physical activity (N = 31)*	*Mixed (N = 23)*	*Total (N = 66)*
Maternal	Gestational weight gain	6	*10(83%)*	*23(74%)*	*23(100%)*	*56(85%)*
	Miscarriage	6	*3(25%)*	*3(10%)*	*16(70%)*	*22(33%)*
	Antepartum level of physical activity	6	-	*6(19%)*	*12(52%)*	*18(27%)*
	Post-partum weight retention	6	*3(25%)*	*2(6%)*	*7(30%)*	*12(18%)*
	Body leanness (Mother)	6	-	*8(26%)*	*2(9%)*	*10(15%)*
	Low back pain	6	-	*4(13%)*	-	*4(6%)*
	Length of labour	6	*1(8%)*	*3(10%)*	-	*4(6%)*
	Postnatal depression	6	-	*1(3%)*	*3(13%)*	*4(6%)*
	Perineal trauma	6	*1(8%)*	*1(3%)*	*1(4%)*	*3(5%)*
	Quality of life	6	-	*1(3%)*	*1(4%)*	*2(3%)*
	Preterm rupture of membranes	6	-	*1(3%)*	*1(4%)*	*2(3%)*
	Post-partum infection (Mother)	6	*1(8%)*	-	*1(4%)*	*2(3%)*
	Haemorrhage antepartum	6	-	-	*1(4%)*	*1(2%)*
	Antepartum infection (Mother)	6	-	-	*1(4%)*	*1(2%)*
	Breastfeeding	5	-	-	*3(13%)*	*3(5%)*
	Anxiety level	5	-	-	*1(4%)*	*1(2%)*
Infant	Birthweight	6	*11(92%)*	*27(87%)*	*20(87%)*	*58(88%)*
	Apgar score	6	*5(42%)*	*21(68%)*	*6(26%)*	*32(48%)*
	Body leanness (Infant)	6	*1(8%)*	*5(16%)*	*2(9%)*	*8(12%)*
	Fetal biometry	6	*2(17%)*	*3(10%)*	-	*5(8%)*
	Hyperbilirubinemia (Infant)	6	-	-	*2(9%)*	*2(3%)*
	Encephalopathy (Infant)	6	-	-	*1(4%)*	*1(2%)*
	Infant's size	5	*3(25%)*	*10(32%)*	*5(22%)*	*18(27%)*

**according to published Delphi ranking[75], N, number of publications;*

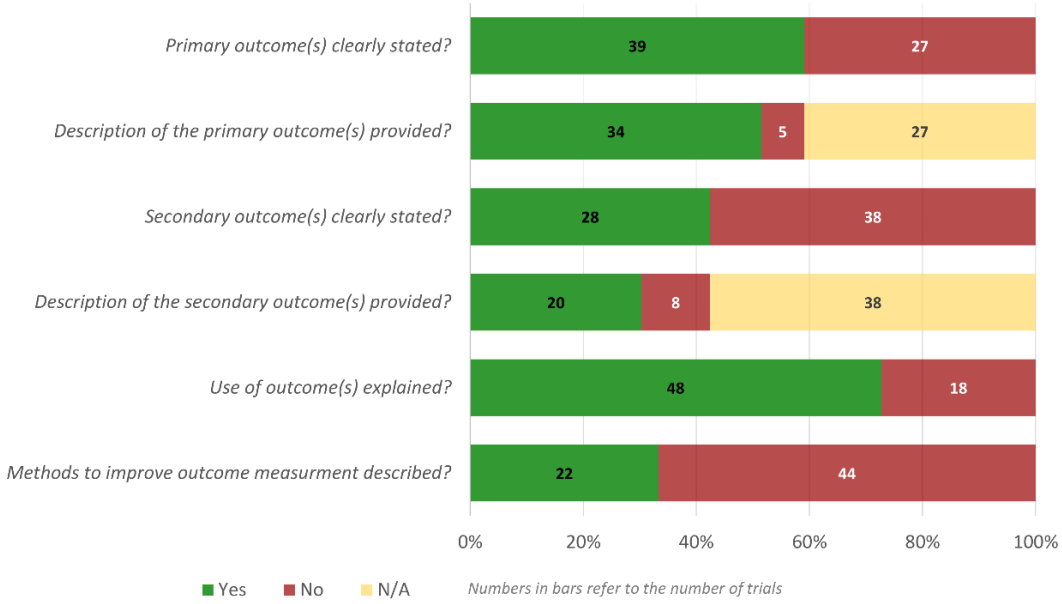
In the ‘important’ group those were gestational weight gain (56/66, 84.5%), infant weight at birth (58/66, 87.9%) and Apgar score (32/66, 48.5%) (

Table 6.1). No significant difference has been noted in the proportion of 'critically important' or 'important' outcomes reported by studies grouped by their intervention type (diet only, physical activity only or mixed approach) (Pearson Chi2, p = 0.11).

6.3.3. Quality of outcome reporting

The primary outcome was clearly specified in more than a half of assessed primary publications (39/66). When reported, outcome description allowed its reproducibility in most of the cases (34/39, 87.2%). The outcomes described as 'secondary' were mentioned in 42% of assessed primary publications (28/66), with 20 of 28 (71.4%) providing outcome definitions that would allow for their reproducibility. The authors of the included publications explained the statistical methods used to analyse outcomes in 48 primary publications (72.7%). Methods of quality improvement of outcome measure in the trial (e.g. staff training) was reported in one-third (22/66, 33.3%) of the evaluated primary publications (**Error! Not a valid bookmark self-reference.**). Overall, the median score of quality of outcome reporting in evaluated group of primary publications was 0.60 (IQR 0.25, 0.83) (maximum score of one).

Figure 6.3 Quality of outcome reporting in trials with diet and physical activity based interventions in pregnancy



6.3.1.Factors influencing outcomes' quality

The results of a univariate analysis indicate a significant positive correlation between the outcome quality score and publication features such as year of publication, and journal's impact factor (Table 6.2). The outcome quality score was negatively correlated with two of the trial's design features: allocation concealment and incomplete outcome data. None of the factors when evaluated in the multivariate regression model preserved the statistically significant association with quality of outcome reporting (Table 6.2).

The comparison of the trials published before and after update of the CONSORT guideline in 2010 showed a statistically significant difference in the quality of outcome reporting between studies published before and after update release (Wilcoxon rank sum test, $p<0.01$) (Appendix 6.3).

Table 6.3 Association between study and publication factors with quality of outcome reporting

Factor		Coeff. Univariate	95% CI	p-value	Coeff. Multivariate	95% CI	p-value
Journal characteristics							
Year of publication		0.02	(0.01,0.04)	<0.01	-	-	-
Impact Factor^		0.02	(-0.00,0.05)	0.05	-	-	-
Journal Type							
	specialized vs general	-0.06	(-0.29,0.17)	0.59	-	-	-
	obstetric vs non-obstetric	-1.1e-4	(-0.16,0.16)	0.99	-	-	-
Trial quality assessment (Risk of bias)							
Random sequence generation	*Unclear vs Low*	-0.05	(-0.24,0.15)	0.64*	-	-	-
	High vs Low	-0.44	(-0.64,-0.23)	<0.01*	-	-	-
Allocation concealment	*Unclear vs Low*	-0.22	(-0.37,-0.07)	<0.01**	-0.18	(-0.34,-0.01)	0.03
	High vs Low	-0.29	(-0.75,0.17)	0.22**	-0.26	(-0.66,0.15)	0.21
Blinding of participants and staff	*Unclear vs Low*	0.03	(-0.08, 0.14)	0.63	-	-	-
	High vs Low	0.06	(-0.53, 0.17)	0.31	-	-	-
Blinding of outcomes assessment	*Unclear vs Low*	-0.12	(-0.29,0.04)	0.14	-	-	-
	High vs Low	0.02	(-0.18,0.21)	0.86	-	-	-
Incomplete outcome data	*Unclear vs Low*	-0.09	(-0.37,0.19)	0.55*	-0.06	(-0.33,0.22)	0.68
	High vs Low	-0.27	(-0.43,-0.11)	<0.01*	-0.21	(-0.39,-0.03)	0.03
Selective reporting	*Unclear vs Low*	0.14	(-0.15,0.45)	0.34	-	-	-
	High vs Low	-0.009	(-0.22,0.27)	0.94	-	-	-
Type of intervention							
Exercise vs Diet		0.13	(-0.08,0.34)	0.26	0.12	(-0.08,0.32)	0.24
Mixed approach vs Diet		0.26	(0.21,0.58)	0.02	0.19	(-4e-3,0.39)	0.05

^*For 6 studies we were unable to extract impact factor; therefore for analysis of impact factor N = 60*
**p-value for a Global test <0.01, ***p-value for a Global test <0.05*

6.4. Discussion

6.4.1.Main findings

Trials examining the effects of diet and physical activity based interventions in pregnancy reported various maternal and offspring outcomes. 'Critically important' outcomes e.g. GDM or caesarean section are reported less often in comparison to 'non-critical' ones like gestational weight gain or birth weight. The overall quality of outcome reporting varied between trials. The least frequently provided aspect of outcome description was the methods implemented to improve the quality of outcome measures. This work was not able to detect an impact of study or journal-specific characteristics on the overall quality of outcome reporting in the primary publications from trials with diet and physical activity based interventions in pregnancy.

6.4.2.Strengths and limitations

The work in this chapter carefully evaluated the diversity and the quality of outcome reporting in RCTs on diet and physical activity based interventions in pregnancy following recognized standards for evidence synthesis. An existing ranking of pregnancy outcomes importance was applied to assess the relevance of identified outcomes. The identification of relevant publications was made through a systematic database search without language restrictions. The quality of study design was assessed using the Cochrane risk of bias.[105] All steps of the quality assessment were completed by two independent reviewers. In the areas where there are no formal guidelines (quality of outcome reporting), we adhered to principles of conduct of rigorous scientific research and the impact of all the assumptions was explored through a set of a priori defined sensitive analyses.

Although, the studies were limited to those published after 1990, the majority of the trial publications on diet and physical activity based intervention in pregnancy were published within the last twenty years. Nevertheless, the number of studies available for the investigation of the link between publication features and the quality of outcome reporting score was insufficient to detect statistically significant associations in the multivariate analysis.

The outcomes were ranked for their importance to weight management during pregnancy through the Delphi survey conducted among clinicians with the expertese in the topic. It is possible that a different panel would identified a different set of prioritised outcomes. Yet, the majority of the most frequently reported outcomes were captured by the survey and ranked as 'critically important' or 'important' in the context of the antenatal care.

The quality of outcome reporting was assessed using the questionnaire presented in Harman et al. paper.[257] This has been successfully applied in other systematic reviews evaluating the variation and quality of outcome reporting.[254,255,259] Nevertheless, the questionnaire has certain limitations such as not accounting for results published as a secondary analyses from the original trials or that the description of the primary or the secondary outcomes cannot be assessed, if outcomes in the publications are not clearly indicated. A more objective and less ambiguous tools should be developed to assess the quality of outcome reporting from clinical trials.

6.4.3. Interpretation

Medical research to guide and influence clinical practice and policy development needs to provide evidence on the effects of interventions on the outcomes relevant to all relevant stakeholders.[41] In the work presented in this chapter showes a range of trial outcomes that

reflects the variety of specialities investigating the effect of diet and physical activity based interventions on pregnancy outcomes.

The most commonly reported outcomes are surrogates for maternal and neonatal morbidity such as gestational weight gain and birthweight. None of the outcomes classified as 'critically important' to maternal or infant health had comparable reporting coverage as earlier mentioned surrogates. Even though data allowing to compute outcomes such preterm birth or birth of LGA or SGA infant (infant's weight and gestational age at birth), appeared in the majority of evaluated publications.

Reproducibility is a fundamental principle of scientific research.[260] The aim of the CONSORT statement is to ensure reporting of randomised trials in a sufficient detail allowing their reproducibility.[248] A clear description of primary and secondary outcomes in the trial allows other researchers to reevaluate the effect of the intervention in different settings on similar outcomes.[36] The evaluation of the primary publications included in this work revealed that it would not be possible to reproduce the main outcome for more than one-third of the trials; the secondary outcomes were insufficiently reported in over half of publications. The weakest aspect of outcome reporting was a lack of sufficient detail in the description of methods used to enhance the quality of outcome measurements. This might not affect outcomes such as the type of delivery or occurrence of stillbirth, but may weaken the reliability of the outcomes where a thorough training and repeated measurements play a significant role, for example, high blood pressure or pre-eclampsia.

In comparison to other studies in the area of women's health[254,255,259], I did not find any link between the quality of outcome reporting and the publication or journal features. The *posthoc* exploration of the articles published before and after the update of the CONSORT statement in 2010 seems to indicate an improvement in outcomes reporting. Though, this finding should be interpreted with cauction due to a post-hoc nature of this exploration.

6.4.4.Conclusion

The range and variable frequency of outcomes reported in RCTs with diet and physical activity based interventions in pregnancy suggest a need for a consensus on the choice of the key trial outcomes. More effort needs to be invested in improving the communication between the various health care professions researching the effect of diet and physial activity on pregnancy outcomes. This could be achieved through the development and introduction of a COS, a minimum set of outcomes that should be collected and reported alongside other outcomes of research interest.[52] This concept first introduced in the context of rheumatoid arthritis trials [261] developed by the COMET Initiative has strongly resonated with the researchers and journal editors in the women's and newborn health area.[53,262]

Despite clear guidance in CONSORT statement on how to report primary and secondary outcomes from RCTs a fair proportion of the trials failed to provide a satisfactory description of their outcomes. Researchers need to pay more attentions to the quality of trial reporting in order to improve the uptake of their trials in systematic reviews. Consequently, contributing to the improvement of the antenatal weight management through better quality evidence and reduction of research waste.

Chapter 7 Gestational weight gain as an indicator of important pregnancy outcomes

7.1. Introduction

Gestational weight gain is a frequently evaluated outcome in randomised trials of diet and physical activity based interventions. Even though weight gain in pregnancy is considered to be a surrogate of maternal morbidity[80], around 40% of RCTs with diet and physical activity based interventions in pregnancy use it as their primary outcome.[263] This rate is two-fold higher than the use of surrogates in other areas of medical research.[39]

Weight gain in pregnancy is a natural response of women's body to accommodate the growing fetus.[71] However, the relationship between the gestational weight gain and the important health outcomes e.g. preterm birth or caesarean section, is ambiguous. Some evidence indicates that insufficient or excessive weight might lead to undesired or even serious health complications.[236] Women's pre-pregnancy BMI is a well-known risk factor for numerous pregnancy complications.[72,80] Obese pregnant women are at higher risk of developing GDM, preeclampsia or postpartum weight retention, while their children of congenital malformation[63], being born with a low Apgar score[59] and childhood obesity.[60]

As the combination of both those factors might led to an increase chance of pregnancy complications, the USA Institute of Medicine (IOM) issued in guidelines on the optimal weight gain in pregnancy.[71] It aims to minimise the negative health outcomes due to inadequate gestational weight gain. The subsequent updated guideline in 2009 advice normal BMI, overweight or obese women entering pregnancy to gain 11.5 – 16 kg, 7 – 11.5 kg or 5 – 9 kg, respectively.[71] These cut-offs were identified through synthesis of evidence from large observational studies, some of them over 10 years old, and from experts' input. The clinical outcomes taken into consideration were birth of LGA infant, birth of SGA infant, emergency

caesarean section and postpartum weight retention of more than 5kg.[80] Nevertheless, not all policy makers worldwide follow the IOM recommendations owing to the low certainty of the evidence used to inform the IOM guidelines.[73,74]

One of advocated advantages of accessing individual participant data from primary trails is the ability to use it to explore so call 'secondary clinical questions' for example a relationship between a surrogate and hard clinical outcomes. (ref)

7.1.1. Aims

The main aim of the work in this chapter was to examine the relationship between gestational weight gain and adverse pregnancy using i-WIP IPD of randomised trials on diet and physical activity based interventions in pregnancy.[79] Specifically, we examined this association in the group of women gaining within the IOM recommendations, and quantified the impact of each kilogram of weight gain beyond the IOM recommended ranges on adverse outcomes.

7.2. Methods

For the purpose of the analyses in this chapter, I limited the IPD assembled to address the effectiveness question in chapters 4 and 5 to records from women randomised to standard antenatal care (non-treated arm), with singleton pregnancies and with early or pre-pregnancy BMI $\geq$ 18.5 kg/m^2.

Exposure

Gestational weight gain (see section 2.4.2 for details) was grouped according to the IOM 2009 criteria as below, within or above the recommendations by women's booking BMI.[80] For gestational weight gain outside the criteria (below or above), I calculated an absolute difference between the recorded and recommended value (degree of GWG outside the IOM

ranges) and coded the direction of the difference (above or below the recommended range). For example, for women with BMI between 18.5 – 24.9 kg/m^2 (normal group) the recommended weight gain is 11.5 to 16 kg. Hence, weight gain of 18 kg was coded as 2 kg excess while weight gain of 10 kg as 1.5 kg deficit. Gestational weight coded as degree of gestational weight gain (excess or deficit) and its direction (above or below the IOM criteria) was the main exposure in the statistical models presented in this chapter.

Outcomes

Pregnancy complications (dependant variables) were derived from the maternal and offspring outcomes prioritized for their important to weight management in pregnancy (chapter 3). The analyses were performed for caesarean section, birth of LGA or SGA infant (dependant variables), and preterm birth. All outcomes except caesarean section could be standardised across all available datasets. LGA and SGA were defined using as growth above 90th centile and below the 10th centile.[130] Preterm birth was defined as delivery before 37 weeks' of gestational age.

Models development

For each outcome, we assessed the causal pathways to identify all relevant confounder candidates (section 2.6). The confounders were evaluated for their availability in the dataset and importance from the clinical perspective (Appendix 7.1). Owing to low numbers and an uneven distribution of identified confounders across the individual dataset it was possible to adjust the models only for the factors that were considered most important from the clinical perspective. Preterm birth was controlled for current smoking status (yes/no). Models with SGA were adjusted for current smoking status, women's age (continuous), and parity (nullipara/multipara). Covariates in the analyses with caesarean section were any diabetes-related event (yes/no), women's age, gestational age at infant's delivery (continuous), parity and curring smoking status; and LGA was adjusted for any diabetes-related events and women's age (Appendix 7.2).

Statistical analysis

For women gaining weight within IOM recommendation, I calculated the frequency of adverse outcome occurrence and then examined the impact of gaining weight within these ranges on the odds of predefined outcomes. For women gaining above or below the IOM recommended ranges, the difference between the observed weight gain and the limits of the reference ranges was computed. I used a one-stage IPD meta-analytical framework to quantify the relationship of each kilogram of GWG outside the IOM recommendations with pregnancy complications. Adopted model was the statistical model between the exposure and the outcome was assessed using a mixed-effects logistic regression model accounting for clustering of participants within studies and allowing random effects for study. The distribution of the random effects is assumed to be Gaussian. The models included an interaction term between the magnitude of the difference and its direction i.e. below or above the IOM recommendation (Appendix 7.2). All analyses were additionally stratified by women's booking BMI and adjusted for relevant confounders. Only data from control arms of randomised trials included in the i-WIP database was used to inform the main analyses. No imputation of missing data was attempted.

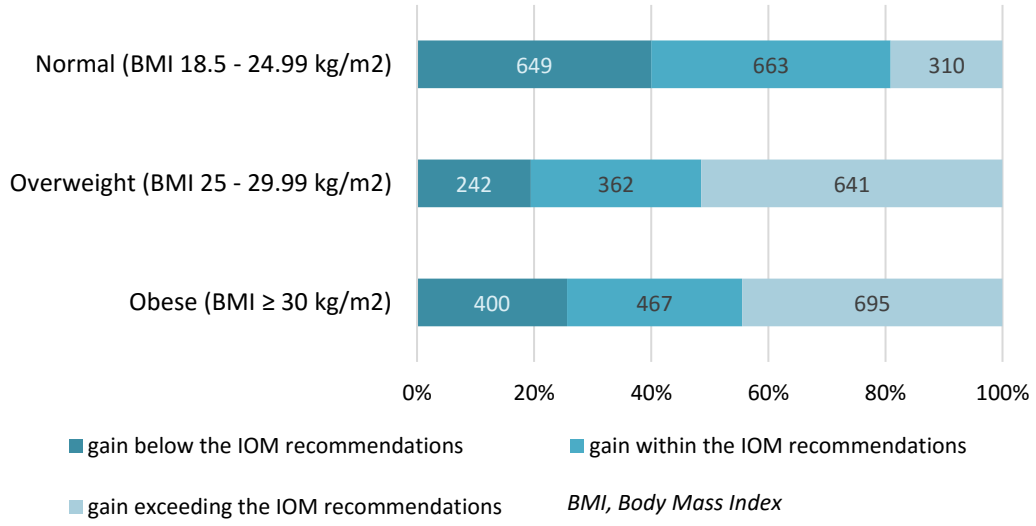
7.3. Results

7.3.1. Characteristics of women

Information on booking BMI was available in 35 trials (5 799 women randomised to control arms) collected in the i-WIP IPD meta-analysis. Data on adherence to IOM recommendations was available for 76.4% of women (4 429/ 5 799). The majority of women were of Caucasian origin (91.3%); over half were highly educated (55.8%) and were in their first pregnancy (51.3%). A detailed summary of characteristics of women for which data on gestational weight gain was available is summarised in Table 7.1

Overall 29.1% (1 291/4 429) of women allocated to the control arms of the trials gained less than recommended, and 37.1% (1 646/ 4 429) exceeded the IOM targets. The adherence varied across the BMI groups with 51.5% (641/ 1 245) of overweight and 44.5% (695/ 1 562) of obese women exceeding the recommended by IOM gestational weight gain in the comparison to 19.1% (310/ 1 622) in the group of women with normal BMI. A reverse trend was present for the gain below the IOM targets (Table 7.1).

Figure 7.1 Proportion of women by BMI strata with respect to their adherence to the recommendations of Institute of Medicine (IOM)



7.3.2.Gestational weight gain within the IOM recommendations

One-third (33.7%, 1 492/4 429) of pregnant women randomised to control arms in trials on diet and physical activity gained in pregnancy according to the IOM recommended ranges. The most frequent adverse outcome was caesarean section 23.4% (340/1 456), followed by birth of SGA infant 10.6% (157/1 482), birth of LGA infant 9.1% (135/1 492), and preterm birth 3.8% (57/1 483). The order of outcome incidence was comparable across all three BMI classes. The frequency of caesarean section was the highest among the obese women (33.3%, 152/456) in comparison to 21.7% among the overweight women (76/351) and 17.3% (112/649) in the group with normal BMI (Appendix 7.3).

Table 7.1 Characteristics of participants and pregnancy outcomes with known gestational weight gain

Characteristics and pregnancy outcomes	Number of studies	Number of women	Mean (SD) or Frequency (%)
Baseline characteristics			
Age (years)	35	4424	30.1 (5.14)
Height (cm)	31	4422	165.0 (7.0)
Weight* (kg)	33	4445	77.13 (18.4)
BMI (kg/m^2)	34	4429	28.32 (6.37)
BMI categories	33	4445	
Normal (BMI 18.5-24.99 kg/m^2)			*1 622 (36.6)*
Overweight (BMI 25-29.99 kg/m^2)			*1 245 (28.1)*
Obese (BMI ≥ 30 kg/m^2)			*1 562 (35.3)*
Ethnic origin	24	3536	
Caucasian			*3 232 (91.3)*
Asian			*87 (2.5)*
Black			*70 (2.0)*
Central/South American			*63 (1.8)*
Middle East			*32 (0.9)*
Other			*52 (1.5)*
Education level	28	3332	
Basic			*453 (13.6)*
Intermediate			*1 019 (30.6)*
Higher			*1 860 (55.8)*
Parity	30	4317	
0			*2 113 (51.3)*
1+			*2 204 (48.7)*
Current smoker	27	3964	693 (16.5)
Sedentary before pregnancy	25	2760	1 383 (50.1)
Family history of diabetes	10	1784	708 (26.2)
Hypertension at baseline	20	2154	53 (2.3)
Any hypertensive event in pregnancy	25	3502	318 (9.1)
Any case of diabetes*	31	4422	594 (10.4)
Gestational age at delivery (weeks)	32	4419	39.6 (1.6)
Normal vaginal delivery	31	4348	2 788 (64.1)
Instrumental delivery	31	4348	439 (10.1)
Delivery before 37 weeks	32	4423	187 (4.2)
Any caesarean section	31	4353	1 121 (25.8)
Elective			363 (8.3)
Emergency			385 (8.8)
Unspecified			373 (8.6)
Small-for-gestational age infant	31	4414	462 (10.5)
Large-for-gestational age infant	33	4445	500 (3.2)

**Early or pre pregnancy; BMI, Body Mass Index*

Crude and adjusted analyses did not provide any evidence that the weight gain (by a kilogram) within the IOM recommended ranges was associated with a change in the odds of evaluated adverse pregnancy outcomes (Table 7.3).

7.3.1. Gestational weight gain outside the IOM recommendations

Overall, about two-thirds (66.3%, 2937/4429) of women in the dataset did not meet the IOM recommended ranges for weight gain in pregnancy. Among the women who were not achieving their targets the highest deviation from the lower range value was noted for women with normal BMI (Table 7.2)

Table 7.2 Difference between recorded and target gestational weight gain (kg) among women gaining below and above the recommendations of Institute of Medicine

Weight gain by BMI group	**Number of women**	**Kilograms of weight outside the IOM targets**		
		Median	**(25Q, 75Q)**	**Range**
Below the IOM recommendations (lower limit)				
Normal BMI (11 kg)	649	3.4	(1.9, 5.0)	16.6
Overweight (7 kg)	242	2.0	(0.9, 3.5)	12.3
Obese (5 kg)	400	2.4	(1.1, 4.1)	14.6
Above the IOM recommendations (upper limit)				
Normal BMI (16 kg)	310	2.0	(1.0, 4.6)	13.9
Overweight (11 kg)	641	2.9	(1.1, 5.6)	29.5
Obese (9 kg)	695	3.6	(1.8, 6.5)	21.0

BMI, Body Mass Index; IOM, Institute of Medicine; Q, quartile

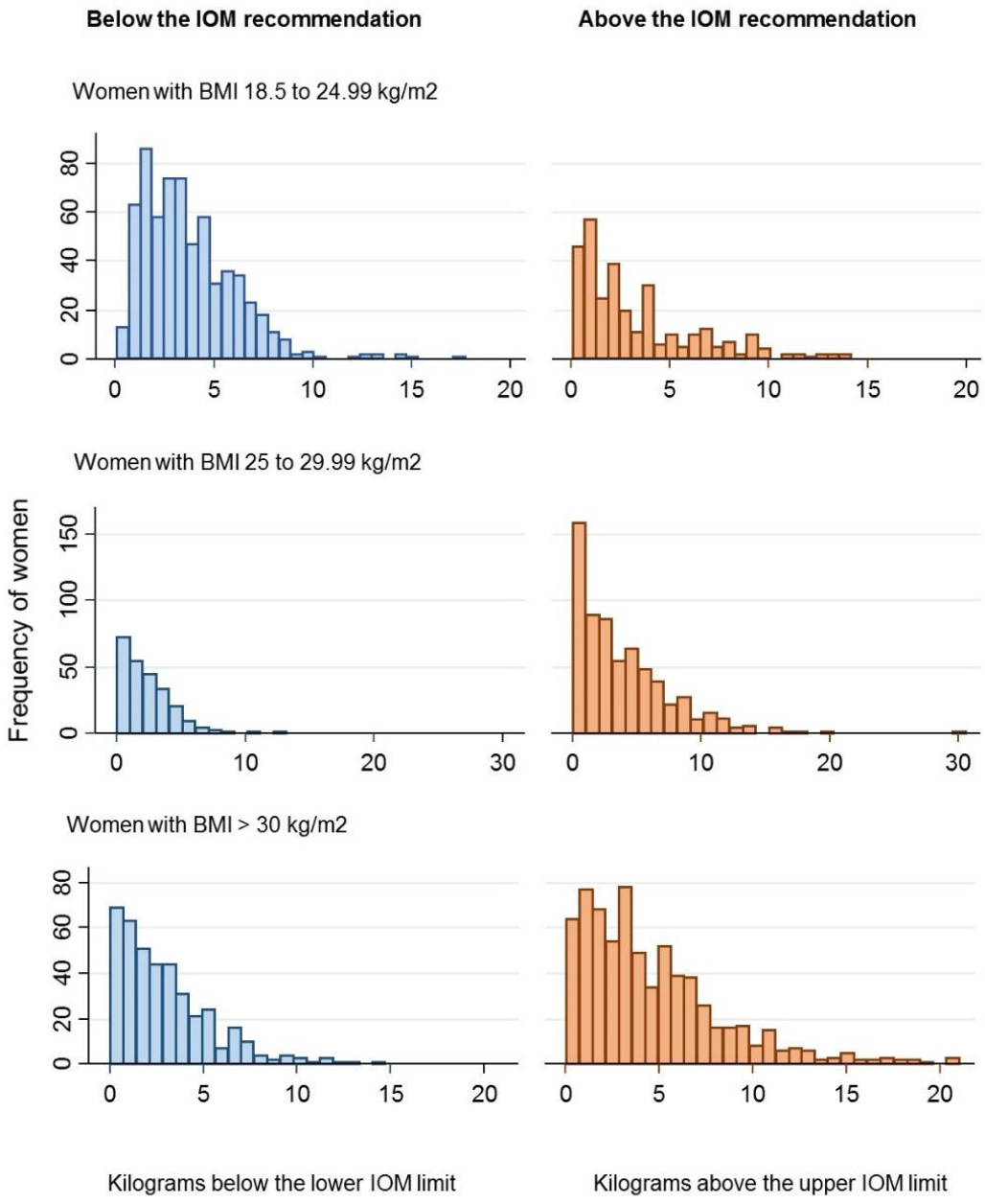
Table 7.3 Relationship between gestational weight gain within the IOM recommendation and the odds of adverse pregnancy outcomes

Outcome	**Baseline BMI**	***Number of studies***	***Number of events/ Number of women***	***Crude OR (95% CI)***	***Number of studies***	***Number of events/ Number of women***	***Adjusted OR (95% CI)***
Preterm birth[1]	*Overall*	30	57/1 483	0.97 (0.88, 1.07)	26	46/1 310	1.07 (0.86, 1.34)
	Normal	20	22/662	1.02 (0.78, 1.35)	18	17/553	1.04 (0.76, 1.43)
	Overweight	26	19/360	1.23 (0.81, 1.87)	23	15/333	1.33 (0.83, 2.13)
	Obese	30	16/461	1.01 (0.66, 1.55)	26	14/424	0.90 (0.57, 1.42)
Small for gestational age infant[2]	*Overall*	30	157/1 482	0.94 (0.88, 1.00)	25	142/1 300	0.94 (0.83, 1.08)
	Normal	20	64/662	1.00 (0.85, 1.18)	18	58/549	1.00 (0.84, 1.19)
	Overweight	26	39/360	0.77 (0.57, 1.05)	23	36/333	0.77 (0.57, 1,06)
	Obese	30	54/460	0.98 (0.77, 1.25)	25	48/418	0.94 (0.73, 1.22)
Any caesarean section[3]	*Overall*	30	340/1 456	0.93 (0.88, 0.98)	24	295/1 268	0.95 (0.86, 1.05)
	Normal	20	112/649	0.98 (0.85, 1.12)	17	97/533	0.98 (0.85, 1.12)
	Overweight	26	76/351	0.99 (0.80, 1.24)	22	70/323	0.95 (0.74, 1.20)
	Obese	30	152/456	0.93 (0.78, 1.10)	24	128/412	0.90 (0.75, 1.08)
Large for gestational age infant[4]	*Overall*	31	135/1 492	1.06 (0.99, 1.14)	30	133/1 483	1.07 (0.93, 1.23)
	Normal	20	62/663	1.02 (0.85, 1.23)	19	62/658	1.02 (0.85, 1.23)
	Overweight	26	37/362	1.11 (0.83, 1.49)	25	36/360	1.16 (0.86, 1.56)
	Obese	31	36/467	1.16 (0.85, 1.59)	30	35/465	1.15 (0.84, 1.58)

BMI, Body Mass Index; OR, odds ratio; CI, confidence intervals; 1. Adjusted for smoking; 2. Adjusted for smoking, age, and parity; 3. Adjusted for any event of diabetes, age, gestational age at delivery, smoking; 4. Adjusted for adjusted for any event of diabetes, age

Women who exceeded the most from the upper IOM limits had BMI above 30. The differences between the mean and the median in the difference between recorded and recommended weight gain were the most pronounced among women who exceeded the recommendations. The histograms on Figure 7.2 show that women most frequently exceed the limits by 2, 3 and over 3.5kg in normal BMI, overweight and obese groups, respectively.

Figure 7.2 Histograms of gestational weight outside the IOM recommended targets by Body Mass Index group



The most frequent adverse outcome among women gaining below the IOM recommendations was caesarean section 21.8% (277/1 271), followed by SGA 14.5% (186/1 280), LGA 7.1% (92/1 291), and preterm birth 6.3% (81/1 286) (Appendix 7.3). The frequency of caesarean section among the overweight and the obese women (around 20%) was higher than for the women with normal BMI (13.1%, 83/636). The frequency of SGA was of 19.4% (77/397) among obese women, 13.7% (33/241) in the overweight and 11.8% (76/642) normal BMI groups. Caesarean section was also the most frequent outcome among women whose weight exceeded the IOM recommendations (31.1%, 503/1 618) followed by LGA (16.2%, 267/1 646), and SGA (7.1%, 117/1 641). The overall frequency of preterm birth in this group was low with 49 events in the group of 1 643 women.

None of the overall models, listed in Table 7.4, showed a statistically significant association between a kilogram of gestational weight gain below the IOM recommendation and the odds of examined maternal and offspring outcomes. The analysis within the BMI strata found 20% reduction in the odds of LGA (adjusted OR 0.80, 95% CI 0.65, 0.99) among the obese women with 1-unit of weight gain below lower IOM limit (5 kg) recommended for this BMI group.

Overall, the odds of caesarean section and LGA increased by 4% (adjusted OR 1.04, 95% CI 1.01, 1.08) and 8% (adjusted OR 1.08, 95% CI 1.05, 1.12), respectively, for each kilogram of weight gain above the upper IOM limits (Table 7.5). In the analyses within BMI strata the association between weight gain and caesarean section was statistically significant only in the overweight group with an 11% increased chance of outcome occurrence (adjusted OR 1.11, 95% CI 1.05, 1.18) with one kilogram of increase in weight gain above the upper limit recommended for this BMI strata (11 kg).

Table 7.4 Relationship between a kilogram of gestational weight gain below the IOM recommendations the odds of adverse pregnancy outcomes

Outcome	**Baseline BMI**	***Number of studies***	***Number of events/ Number of women***	***Crude OR (95%CI)***	***Number of studies***	***Number of events/ Number of women***	***Adjusted OR (95%CI)***
Preterm birth [1]	*Overall*	30	81/1 286	1.02 (0.93, 1.12)	26	72/1 176	0.99 (0.90, 1.09)
	Normal	20	34/647	1.11 (0.98, 1.26)	18	28/578	1.09 (0.94, 1.25)
	Overweight	29	15/241	0.73 (0.50, 1.07)	25	15/229	0.74 (0.51, 1.08)
	Obese	30	32/398	1.01 (0.87, 1.16)	26	29/369	1.00 (0.86, 1.16)
Small for gestational age infant[2]	*Overall*	30	186/1 280	1.06 (1.00, 1.13)	25	167/1 146	1.07 (1.00, 1.14)
	Normal	20	76/642	1.10 (0.99, 1.22)	17	68/564	1.11 (0.99, 1.25)
	Overweight	29	33/241	1.16 (0.97, 1.40)	24	29/216	1.21 (0.99, 1.48)
	Obese	30	77/320	1.04 (0.95, 1.15)	25	70/366	1.02 (0.93, 1.13)
Any caesarean section[3]	*Overall*	30	277/1 271	0.94 (0.88, 1.00)	24	243/1 127	0.94 (0.88, 1.01)
	Normal	20	83/636	0.87 (0.77, 0.99)	16	74/549	0.85 (0.75, 0.98)
	Overweight	29	54/239	0.93 (0.78, 1.11)	23	42/213	0.91 (0.73, 1.12)
	Obese	30	140/396	0.99 (0.92, 1.09)	24	127/365	1.00 (0.92, 1.09)
Large for gestational age infant[4]	*Overall*	31	92/1 291	0.91 (0.81, 1.01)	30	92/1 274	0.90 (0.81, 1.01)
	Normal	20	48/649	0.94 (0.80, 1.09)	19	48/636	0.95 (0.82, 1.11)
	Overweight	29	14/242	1.09 (0.83, 1.43)	28	14/239	1.11 (0.84, 1.47)
	Obese	31	30/400	0.80 (0.64, 0.98)	30	30/399	0.80 (0.65, 0.99)

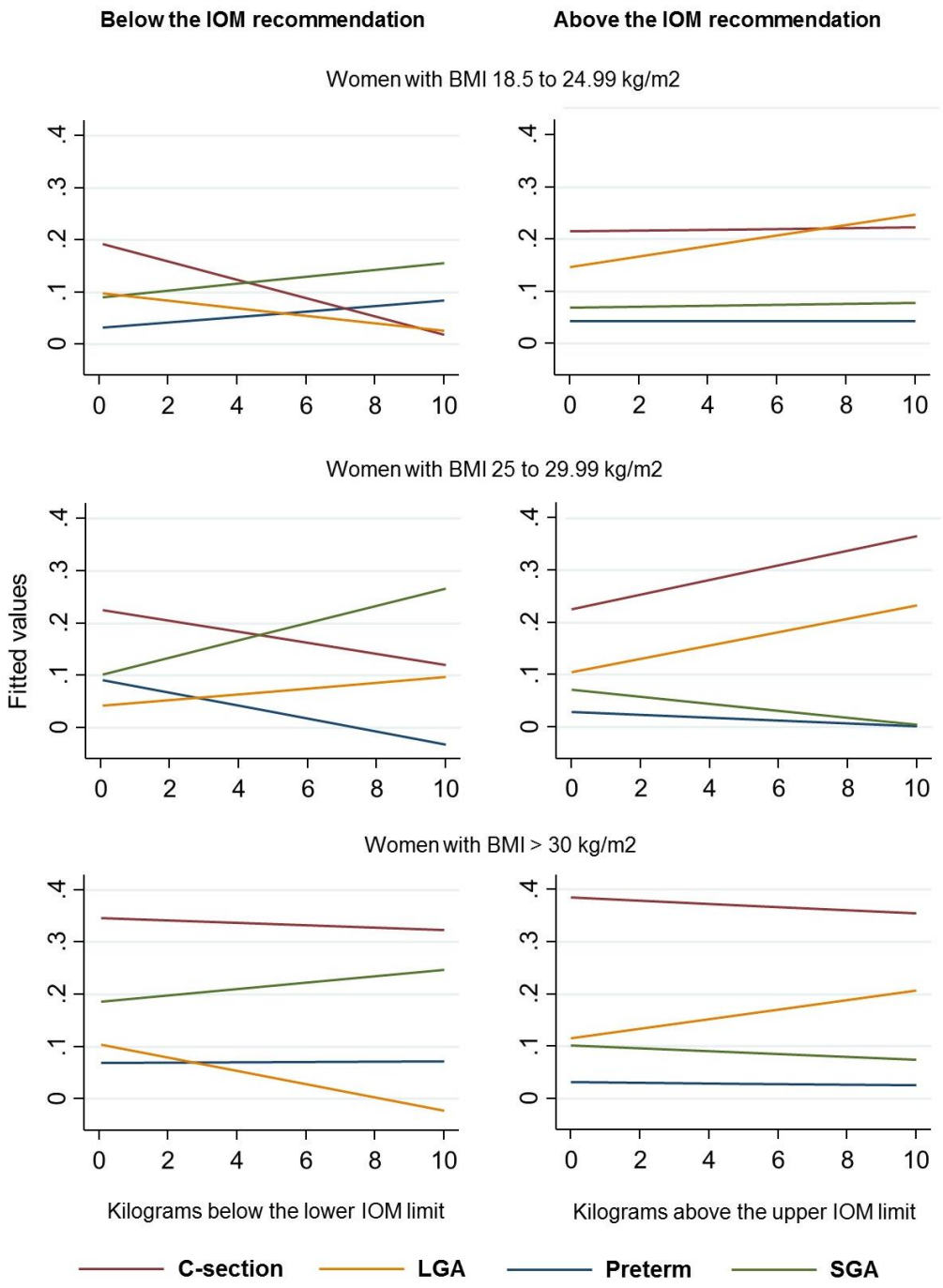
BMI, Body Mass Index; OR, odds ratio; CI, confidence intervals; 1. Adjusted for smoking; 2. Adjusted for smoking, age, and parity; 3. Adjusted for any event of diabetes, age, gestational age at delivery, smoking; 4. Adjusted for adjusted for any event of diabetes, age

Table 7.5 Relationship between a kilogram of gestational weight gain above the IOM recommendations and the odds of adverse pregnancy outcomes

Outcome	**Baseline BMI**	***Number of studies***	***Number of events/ Number of women***	***Crude OR (95%CI)***	***Number of studies***	***Number of events/ Number of women***	***Adjusted OR (95%CI)***
Preterm birth[1]	*Overall*	30	49/1 643	0.95 (0.87, 1.04)	26	46/1 459	0.96 (0.88, 1.06)
	Normal	20	14/309	1.00 (0.84, 1.20)	18	13/256	1.05 (0.88, 1.26)
	Overweight	29	13/640	0.85 (0.67, 1.07)	25	12/564	0.87 (0.68, 1.10)
	Obese	30	22/694	0.97 (0.86, 1.10)	26	21/639	0.98 (0.86, 1.10)
Small for gestational age infant[2]	*Overall*	30	117/1 641	0.96 (0.91, 1.02)	25	104/1 454	0.95 (0.89, 1.01)
	Normal	20	26/308	1.02 (0.90, 1.17)	17	24/254	1.02 (0.89, 1.18)
	Overweight	29	31/609	0.86 (0.74, 0.99)	24	30/564	0.86 (0.74, 1.00)
	Obese	30	60/693	0.97 (0.90, 1.04)	25	50/636	0.94 (0.86, 1.03)
Any caesarean section[3]	*Overall*	30	503/1 618	1.05 (1.02, 1.08)	24	475/1 432	1.04 (1.01, 1.08)
	Normal	20	68/300	1.02 (0.93, 1.12)	16	66/248	1.06 (0.96, 1.17)
	Overweight	29	174/631	1.10 (1.04, 1.16)	23	166/554	1.11 (1.05, 1.18)
	Obese	30	261/687	1.00 (0.96, 1.04)	24	243/630	1.00 (0.96, 1.05)
Large for gestational age infant[4]	*Overall*	31	267/1 646	1.08 (1.04, 1.12)	30	265/1 640	1.08 (1.05, 1.12)
	Normal	20	49/310	1.06 (0.96, 1.17)	19	48/309	1.05 (0.96, 1.17)
	Overweight	29	104/641	1.10 (1.04, 1.16)	28	103/638	1.11 (1.05, 1.17)
	Obese	31	114/695	1.07 (1.02, 1.13)	30	114/693	1.07 (1.02, 1.13)

BMI, Body Mass Index; OR, odds ratio; CI, confidence intervals; 1. Adjusted for smoking; 2. Adjusted for smoking, age, and parity; 3. Adjusted for any event of diabetes, age, gestational age at delivery, smoking; 4. Adjusted for adjusted for any event of diabetes, age

Figure 7.3 The relationship between the weight gain outside the IOM recommendation and the odds of adverse pregnancy outcomes by Body Mass Index group



In the stratified analysis for LGA the association was statistically significant in the group of women with BMI above 25 (Figure 7.3). The chance of giving a birth to LGA infant was increasing by 11% in overweight group (adjusted OR 1.11, 95% CI 1.05, 1.17) and 7% in the

obese group (adjusted OR 1.07, 95% CI 1.02, 1.13) with each 1-unit in weight gain beyond the upper IOM limits for these groups – 11kg and 9kg, respectively. The interaction between the amount of weight gain outside the IOM ranges and its direction (above or below the IOM ranges) was statistically significant ($p < 0.05$) in the models for SGA, LGA and caesarean section.

7.4. Discussion

7.4.1.Main findings

Women who most frequently exceeded the IOM recommendation belonged to the overweight and the obese classes. Women whose BMI was within the normal range tended to gain less rather than exceed the recommended amounts. There was no evidence for an association between each kilogram of weight gained within the IOM range and the pregnancy complications. Each kilogram below the lower limit of the recommended amount was associated with the decreasing chance of giving birth to LGA infant among the obese women. Conversely, each kilogram of weight gain above the upper limits was associated with increased chance of caesarean delivery and birth of LGA infant regardless of women's BMI status.

7.4.2.Strengths and limitations

The association between gestational weight gain and pregnancy complications was examined using IPD derived from and RCTs with diet and physical activity based interventions conducted in 16 different countries across three continents and guided by prospectively developed protocols. This way the work presented in this chapter avoids limitations of previous primary research usually constrained to a specific cohort of women (geographical or BMI limitations), and the previous secondary studies.[66,128,264-267] Use of IPD allows

overcoming limitations of study-level meta-analyses such as ecological fallacy and detect true participant-level association rather than the study-level ones.[241,268] Moreover, direct contact with the trials' authors facilitated thorough check or data integrity and allowed to standardise definitions of three out of four evaluated outcomes (preterm birth, SGA and LGA). A one-stage IPD meta-analysis approach was used to quantify the association between weight gain and the pregnancy complications within the IOM categories per current standards i.e. accounting for within-study clustering of the participant.[95]

The confounders were identified through a non-systematic literature search and prospectively priorities from the clinical perspective. The infant's birthweight was not considered as a confounder in any of the models. The reason for not accounting for birth weight was its entangling with the gestational and the individual outcomes. Namely, baby's weight constitutes part of gestational weight gain, as well as a component used to identify SGA or LGA infants. The outcomes were selected from a group of maternal and offspring outcomes prioritised for their importance to women's care in the context of gestational weight gain management (see chapter 3). The four critically important outcomes mostly overlap with those considered by the IOM committee when developing the recommendations on the optimal gestational weight gain (LGA, SGA, and caesarean section).[80] Most of the research looking the validity of the IOM recommendations tends to lump together all the women not meeting or exceeding the target weight gain indicating that the risk of adverse outcomes are comparable for women who deviate from the target levels by one and by more than five or ten kilograms. The approach adopted in this work provided quantifying the relationship by a 1-unit of change in weight gain providing a more accurate description of the relationships between the gestational weight gain and the pregnancy complications.

Use of data from women allocated to control arms improved the interpretability of the findings. The drawback of this decision was a smaller number of participants and events than collected that led to an inability to detect potentially meaningful associations i.e. the

relationship between gestational weight gain and preterm birth in the group of overweight women. The exploration of the association within the BMI strata was chosen over the inclusion of interaction term with women's BMI due to the complexity of the statistical models with a three-way interaction resulting in potentially difficult to clinically interpret findings. The additional challenge posed a multifaceted nature of the dataset with a clustering of data within the original trials that recruited women across different spectrums of BMI values (Appendix 7.4). The statistical models could not be adjusted for all potentially relevant confounders due to low event rate, and inconsistent availability of important covariates in the individual trial datasets.

The problem of uneven availability of the data also affected the examined exposure. It was not always possible to use the measurement at the same time point for the initial weight value (use of pre or early pregnancy weight) and ensure its unbiased recording (not self-reported). Moreover, gestational weight gain was not always available in the original datasets leading to a loss of 23.6% of available data from women allocated to the control arms. Furthermore, lack of multiple measurements of women's weight in the original trials prevented me from exploring the relationship between the gestational weight gain and PIH, PE and GDM. In all three cases, the interventions provided after the diagnosis could meaningfully alter the weight gain and alter the potential association. This limitation also affects the evidence synthesis of observational studies[62,66,128,265,269,270], and could have not been overcome despite access to IPD. The final limitation of this work is a lack of correction for multiple testing that should be taken into account when interpreting the analyses findings.

This work is an extension of secondary analyses planned in the main i-WIP study.[79] It was initially intended to incorporate fractional polynomial terms[271] as the relationship between the weight gain in pregnancy, and the adverse pregnancy outcomes were expected to be non-linear.[79] Examination of data structure and its distribution lead me to assume a linear trend instead. The assumption of a linear relationship between gestational weight gain and the

pregnancy complications might not be describing the nature of the association in the most accurate way; however, it was a pragmatic decision compromising between the complexity of statistical analysis, and its feasibility and interpretability.

7.4.3.Interpretation

Weight gain within the IOM ranges is frequently used in the literature as the reference standard when examining the link between the weight gain in pregnancy with the pregnancy complications.[65,66,128,265] The underlying assumption is that weight gain within the ranges will help women to achieve positive pregnancy outcomes taking into account their background risk.[71] The IOM recommendation for each BMI group gives the flexibility of weight gain within the 5 kg range. Part of my work was to evaluate the frequency of individual outcomes in those ranges and examine if the odds of outcomes change with each kilogram within the 5kg range. The frequency of deliveries through a caesarean section was consistent with the numbers reported in the observational studies. With the average of 26%, it is almost twice-fold of the rate considered acceptable by the healthcare community.[272] However, the value is consistent with the global caesarean rates trends that are on the rise since 1990.[117] Conversely, the occurrence of preterm birth among the women adherent to the IOM recommendations was much lower than the global estimates.[118] The fact that the majority of the trials recruited in high-income countries where the prevalence is lower than the world average could contribute to the low frequency of this outcome.[273] The incidence of SGA and LGA were comparable to those reported in the literature.[128] The analyses did not provide any evidence to support a belief that the odds of those outcomes altered with each kilogram within the recommended ranges.

Weight gain below the IOM ranges was linked with increased odds of SGA infant and preterm birth, and decreased odds of giving birth to LGA infant[128,264,265]; however, the findings are inconsistent across the literature.[62,274] In this research, the only statistically significant

relationship found was in the group of obese women between the low weight gain and decreasing chance of LGA infant. Obese pregnant women are a group of particular interest due to the high risk of short- and long-term complication.[60] A systematic review of 18 cohort studies with obese women by Kapadia et al.[265] evaluating the safety of weight gain below the IOM recommendation reported the decrease odds of LGA by 23% as well as caesarean section. As the authors relied on the study-level data, it is not known how many kilograms away from the lower limit were women in the individual studies, therefore who mainly drives the observed 23% decrease. The majority of obese pregnant women in the control arms of available RCTs were between 2 – 3 kg below the IOM lower limit for this BMI group (5 kg). The findings of the analysis suggest comparable to reported by Kapadia et al.[265] reduction in the odds of LGA with kilogram below the lower limit; however, it needs to be treated with caution due to lack of adjustment for multiple testing and other than the linear relationship between the weight gain and the outcome odds.

In line with the previous research, the analysis presented in this chapter supports the link between excessive weight gain and the increased odds of LGA and caesarean section. The odds of LGA reported in the literature range anything between 70% to over a four-fold increase, and between 30% and 80% increase for caesarean section.[128,264,274] None of the previous studies describes the distribution of women exceeding the recommendations by each kilogram above the upper range. The odds of caesarean section and LGA in the analyses decreased with each kilogram above the upper limit regardless of the BMI group by 4% and 8%, respectively. The strength and significance of the association varied between the BMI groups, however the subgroup differences were not formally compared.

The majority of women in the control arms exceeded the upper IOM limits between 2 to 3.5 kg depending on the BMI category. In combination with the potential nonlinear relationship between the weight gain and the complications, the association could be driven and most accurate for those exceeding the recommendation only by a few kilograms. The exploration

did not find evidence to support the link between the excessive weight gain and decreased odds of preterm birth or birth of SGA infants. There are no clear biologic mechanisms for the link between excessive weight gain during pregnancy and preterm birth[69] with inconclusive findings from the prior studies.[62,128,274] Unexpected is a lack of statistically significant association for SGA which decreased odds was consistently linked with the high weight gain in pregnancy.[128,264,274]

Despite the clinical importance of GDM and hypertensive disease and their link with maternal BMI status, I was not able to examine the associations due to lack of weight measures at the point of diagnosis. This problem has been encountered previously by the IOM committee when assessing evidence for the recommendation on the optimal gestational weight gain.[80] A study that addressed this problem, published year after the guideline update, suggest that high rates of gestational weight gain may indeed increase a woman's risk of developing GDM.[67] The authors noticed that the association between the gestational weight gain and odds of GDM was primarily attributed to weight increase in the first trimester, and stronger in the obese and overweight groups, and among women of a non-Caucasian origin.[67]

On average, the women in the control arms of RCTs with diet and physical activity more frequently did not achieve (29.1%) and less frequently exceeded (37.1%) with the IOM 2009 targets in comparison to rates reported in the literature.[128,264,274,275] Yet, this varied across the BMI groups with over two-third of women with normal BMI not achieving the recommended minimum of 11 kg, over half of overweight and 45% of obese women exceeding the maximum weight gain specified for their categories. A small proportion of women with normal BMI with high gestational weight gain (19.1%) lowered the overall percentage of women exceeding the recommendation. The overall proportion of the overweight and the obese women in this category is closer to the rates reported in the review by Goldstein et al.[128] The high non-achievers rate among women with normal BMI could be explained by women having healthier lifestyle habits than those of overweight and obese women who probably eat

less healthy and led more sedentary lifestyle prior their pregnancy.[246,276] Secondly, the participation in the trials could be a factor on its own. A recent systematic review looking at the health outcome of women who participated in the RCTs in comparison to non-participants showed that on average participating women experience better outcomes than non-participants.[277]

7.4.4.Conclusion

Women receiving usual care, i.e. in control arms of 36 trials on the effect of diet and physical activity in pregnancy, who started overweight or obese exceeded the IOM targets most frequently. A detailed exploration of the amounts of weight gained above the limits showed that the women mostly exceeded them by only a few kilograms. Nevertheless, each kilogram of weight gain above the recommended amount increased the odds of LGA and caesarean delivery regardless of the women's BMI value at the beginning of the pregnancy.

Chapter 8 Conclusions and recommendations

8.1. Summary of key findings

The work presented in this thesis expands the research objectives defined in the HTA NIHR funded IPD meta-analysis utilising its materials (data and the collaborative group). In this thesis, I evaluated and synthesised data from 103 RCTs on diet and physical activity based interventions in pregnancy. Of these individual participant data were available from 36 RCTs with over 12 500 records. The work was supported by the members of the international i-WIP Collaborative Group that involved researchers from 16 countries and over 40 academic or research institutions. The summary of the key findings from this thesis in a structured format has been presented in Table 8.1.

8.1.1. Composite outcome

The aim of the work presented in chapter 3 was to develop composite outcomes for use in IPD meta-analysis of RCTs with diet and physical activity based interventions provided antenatally. The composite outcomes comprised of four individual maternal and four offspring outcomes. The components comprising maternal composite outcome was available in two-thirds, and for the offspring composite in the half of the studies in the i-WIP IPD meta-analysis. The pooled point estimate of effect of interventions on the composites and their components was consistent for the maternal composite, and variable in case of the offspring composite. The main limitation is using a composites in the i-WIP study was the inconsistent availability of outcome data across the datasets in the individual trials.

209 Table 8.1 Summary of the key findings from the thesis

Chapter	Objectives	Method(s)	Main findings
3	Develop composite outcome to use in IPD MA	Delphi methodology	• The components of the composite outcomes are as follows: o Maternal composite: GDM, preterm birth, caesarean section, hypertensive disorders in pregnancy; o Offspring composite: stillbirth, SGA, LGA, admission to NICU. • The composite outcomes in IPD meta-analysis of RCTs of diet and physical activity were available for a lower number of participates than their individual components. • The point estimates of effect of the maternal composite and its components were in the same direction, but for the offspring composite and its components they were variable.
4	Compare the effects of the interventions on pregnancy outcomes using IPD and study-level MA	Systematic review Two-stage IPD MA Study-level meta-analysis	• IPD MA analysis has shown a significant reduction in gestational weight gain and the odds of caesarean section with diet and physical activity based interventions in pregnancy in comparison to routine care • Incorporation of unreported outcome data in IPD MA lowered the magnitude of the summary effects in comparison to those observed on the study-level in the group of studies where IPD was available • The addition of study-level data from studies where IPD was not available changed the statistical significance of the interventions' effect on GDM in most cases increasing the between-study heterogeneity.

210 *GDM, gestational diabetes; SGA, small for gestational age; LGA, large for gestational age; NICU, neonatal intensive care unit; RCT, randomised controlled trial; IPD, individual participant*
211 *data; MA, meta-analysis;*

Chapter	Objectives	Method(s)	Main findings
5	Compare modifying effect of women's BMI on the effect of interventions using IPD and study-level MA	Systematic review Two-stage IPD MA Study-level meta-analysis (meta-regression)	• There is no evidence that the effect of diet and physical activity based interventions on pregnancy outcomes alter depending on the women's BMI • The results of study-level meta-regression could lead to incorrect conclusions that the effect of interventions on gestational weight gain is stronger in the class of obese women.
6	Assess the variation in outcome reporting and the quality of outcome reporting in trials with diet and physical activity in pregnancy	Systematic review Regression analysis	• 'Critically important' outcomes like GDM or caesarean section are reported less often in comparison to 'non-critical' ones e.g. gestational weight gain or birth weight. • The overall quality of outcome reporting varied between trials with the least frequently provided information on the methods to improve the quality of outcome measures. • The study and journal features were not associated with the quality of outcome reporting in the primary publication from trials on diet and physical activity in pregnancy.
7	Examine the relationship between gestational weight gain and adverse pregnancy outcomes accounting for adherence to the IOM recommendations	One-stage IPD MA	• Women who most frequently exceeded the IOM recommendation belonged to the overweight and the obese groups. • Weight gain within the IOM ranges was not significantly associated with the evaluated pregnancy outcomes. • Not achieving the IOM range by seems to be associated with a decreasing odds of LGA among obese women. • Weight gain above the IOM limit seems to be associated with an increased odds of caesarean section and LGA regardless of BMI.

212 *BMI, body mass index; IPD, individual participant data; MA, meta-analysis; GDM, gestational diabetes; IOM, Institute of Medicine; LGA, large for gestational age;*

8.1.2.IPD meta-analysis

Chapters 4 and 5 evaluated the summary effect of the interventions and the modifying effect of women's pre or early pregnancy BMI of the summary effects, respectively; using meta-analysis with IPD and study-level data. The findings of the IPD meta-analysis showed that diet and physical activity based interventions in pregnancy significantly reduced gestational weight gain and the odds of caesarean section in comparison to routine antenatal care. Although the summary estimates favoured a reduction in all individual maternal outcomes, the findings were not statistically meaningful. There was no effect of the intervention on the evaluated offspring complications.

In comparison to data reported in the published reports, access to IPD from 36 RCTs allowed me to incorporate more trials into the meta-analysis for all evaluated outcomes. Incorporation of previously unavailable data returned a more modest magnitude of the summary estimates in comparison to effects obtained the study-level data of trials that shared IPD. The statistical significance of the pooled effect changed in two cases and no clear impact on the heterogeneity level. The addition of study-level data from non-IPD trials changed the magnitude and the statistical significance of the summary effects in the meta-analysis for GDM and changed the funnel plot structure in the meta-analysis for gestational weight gain. In most cases, incorporation of study-level data from trials where IPD was not available increased the between-study heterogeneity. The study-level meta-analyses and IPD meta-analysis with the addition of non-IPD trials (study-level data) provided comparable results with similar levels of between-study heterogeneity.

Furthermore, my work provides another empirical example supporting the notion that results of meta-regression need to be interpreted with great caution. Meta-analysis using IPD provided more robust and less biased evidence then the study-level meta-regression. There is

no evidence that the effect of diet and physical activity based interventions on pregnancy outcomes alter depending on the women's BMI.

Overall, the access to IPD improved the robustness of the evidence synthesis of trials with diet and physical activity in pregnancy. The main limitation of the meta-analysis using IPD was a low event rate and lack of baseline and final measures for continuous outcomes that prevent inclusion of individual trials in the meta-analysis.

8.1.3. Variation in outcome reporting

Chapter 6 contains the assessment of outcome reporting in trials examining the effects of diet and physical activity based interventions in pregnancy. The work has revealed a wide range of maternal and offspring outcomes evaluated in those trials that varies in frequecy and importance to women's care. 'Critically important' outcomes e.g. GDM or caesarean section are reported less often in comparison to 'non-critical' ones like gestational weight gain or birth weight. The overall quality of outcome reporting varied between trials with the least frequently provided information on the methods to improve the quality of outcome measures. This work was not able to detect any impact of study or journal-specific characteristics on the overall quality of outcome reporting in the group of primary publications from trials with diet and physical activity based interventions in pregnancy.

8.1.4. Gestational weight gain and pregnancy complications

The aim of the final chapter was to examine the relationship between gestational weight gain and adverse pregnancy outcomes accounting for adherence to the IOM recommendations. The overweight and the obese women frequently exceeded the IOM recommendation while women with BMI within the normal range tended to gain less rather than exceed the recommended amounts. The exploration did not find any evidence for an association between each kilogram of weight gained within the IOM range and the pregnancy complications. The

weight gain (by one kilogram of change) below the lower limit of the IOM recommended amount was associated with the decreasing chance of delivering LGA infant in the obese class. Conversely, each kilogram of weight gain above the upper limits was associated with increased chance of caesarean delivery and birth of LGA infant regardless of women's BMI status.

8.2. Recommendations for research practice

8.2.1.Composite outcomes in IPD meta-analysis

Delphi methodology is a valuable method when prioritising of outcomes to develop composite outcomes. It is recommended to use outcomes as measured in the original trials rather than the composite endpoints as the availability of the individual components may vary between the original trials included in IPD meta-analysis, and access to IPD still not address the issue of the rarity of events. In the situation when the composite outcome is deployed, limitations of its use should be explained and the effect on the components presented and discussed.

8.2.2.Assessing variation in outcome reporting

The quality of outcome reporting in this thesis was assessed using the questionnaire presented by Harman et al.[257] More objective and less ambiguous tools should be developed for the future evaluations of the quality of outcome reporting in clinical trials. Secondly, authors of the primary studies should provide more detail when describing the outcomes and participants' characteristics.

8.2.3.IPD meta-analysis

Access to individual records increases the number of trials available for meta-analysis. Use of the elementary data for outcomes with relatively simple definitions should be planned for in order to generate data not collected in original trials. Mapping of definitions and additional

data that could help to standardise the outcome across the trials may not tackle the issues, but it can save time and make the IPD meta-analysis findings more current. The sensitivity analysis with the inclusion of non-IPD studies (availability bias) is an important element of IPD meta-analysis that should be mandatory if the proportion of studies where the IPD was not available is high.

8.2.4.Gestational weight gain as a primary outcome

There is evidence for the link between the gestational weight gain (low and high as per IOM standards) and the chance of delivering LGA infant. However, neither meta-analyses using IPD or the study-level data showed a meaningful effect of diet and physical activity based interventions on the LGA infant. Excessive weight gain was linked with the increased odds of the caesarean section which can be significantly reduced with the interventions. Taking into account the variation in the weight measurements and that the caesarean section is already frequently reported in the trials, there is no reason to justify powering of the future research to detect the effect of the interventions on the change in gestational weight gain.

8.3. Recommendation for future research questions

8.3.1.IPD meta-analyses

The meta-analysis of IPD being a resource-demanding approach to evidence synthesis of RCTs requires a thorough and honest evaluation of what is achievable and what is not. We might need to accept that due to no uniform data coding some research is not usable for synthesis thus has been permanently lost. The efforts associated with obtaining IPD and its harmonisation need to be balanced by the potential gains achievable through a complex and profound statistical analysis. More guidance is needed on the impact of unavailable data and how to interpret it. Current guidelines recommend adding non-IPD studies to IPD meta-

analysis when a substantial proportion of trials IPD was not obtained at the beginning of the project. In the areas of medical research where the new evidence emerges annually, staying up-to-date while conducting IPD meta-analysis is exceptionally challenging. Therefore, adding newly published trials is as important as incorporating the not shared ones.

8.3.2.Effects of diet and physical activity in pregnancy

The unwarranted variation of trials' outcomes could be achieved through the development and introduction of a COS – a minimum set of outcomes that should be collected and reported alongside other outcomes of research interest.[52] This concept strongly promoted by the COMET initiative has also been embraced by the researchers and editors of obstetrics and gynaecology journals.[53,262] The CROWN initiative recognizes the limitations imposed by the variation in outcome reporting and promotes COS as a way to improve the evidence synthesis and to draw more meaningful conclusions. Furthermore, the introduction of COS in other medical areas has been shown to lead to improvement in the consistency of outcome reporting.[56] The i-WIP Collaborative Group gathering researchers from various research specialities have a fantastic potential to pursue an effort towards the identification of COS for use and reporting from trials with diet and physical activity based interventions in pregnancy. Secondly, the group has the potential to lobby for standardisation of definitions for outcomes such as gestational diabetes and improvement in documentation of caesarean section as elective or emergency.

The i-WIP IPD meta-analysis has shown that the interventions have the potential to moderately reduce gestation weight gain and decrease the chance of caesarean section. Further research, should focus on whether the effect differs for any subgroup of women and types of cesarean section. In my work, I did not explore the complexity of the evaluated interventions. Evaluation of any differential effects according to the individual components of the intervention (duration, frequency, provider, and setting) on the important health outcomes

is required to provide more detailed recommendations. The analyses of interventions components done so far were limited by the number of available studies and use of only study-level data.[234,278] Access to IPD and direct contact with the research teams allows to overcome previous limitations, and apply advanced meta-analytical methods as it was done for the behavioural programs for type 2 diabetes mellitus.[279]

Further to WHO priority research questions[120], more evidence needs to be ascertained with large randomised trials on the effect of interventions in developing countries like China or Brazil which face similar obstetric complications as those encountered in high-income countries e.g. high rate of cesarean sections or gestational diabetes.[117,119] The research conducted in the high-income settings should shift towards studies exploring the effective implementation of the interventions. Finally, it needs to be assessed whether the benefit of diet and physical activity observed on the short term outcomes translates to long-term benefits to the mother and the baby.

8.4. Implication for clinical practice

The findings of this work have the potential to influence national and international guidelines on healthy eating and physical activity during pregnancy to achieve better health outcomes. To-date, the findings of the i-WIP meta-analysis were used to inform the recommendations on the physical activity for pregnant women issued by the UK Chief Medical officer.[280]

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Appendices

Appendix 1.1 Overview of systematic reviews with meta-analysis evaluating effects of diet and physical activity based interventions in pregnancy in comparison to routine care

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
1	**Kramer 2002[1] (Cochrane)**	To assess the effects of advising healthy pregnant women to engage in regular aerobic exercise on physical fitness, labour and delivery, and the outcome of pregnancy	Healthy pregnant women	Physical activity	Change in level of maternal physical fitness, anthropometric measures; pre-eclampsia, duration of labour, and type of delivery; fetal and infant outcomes	10	**Limitations** Not described **Conclusions** Effect on the main outcome ⇧ Mother or infant outcomes (?)
2	**Leet 2003[2]**	To examine if differences in birthweight are dependent upon the physical conditioning of the mother previous to pregnancy, how long she continued to exercise during her pregnancy, and the type of controls used for comparison	Healthy pregnant women	Physical activity	Birth weight	8	**Limitations** Only studies in English **Conclusions** Effect on the main outcome ⇔

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
3	**Liu 2005**[3]	To evaluate the effectiveness of interventions to prevent excessive weight gain in pregnancy	Healthy pregnant women	Mixed approach	Proportion of women exceeding the upper limit of the IOM recommended gestational weight gain range	3	**Limitations** Only studies in English Published 1980 – 2005 Poor quality of included studies **Conclusions** Effect on the main outcome ⇧
4	**Kramer 2006**[4] **(Cochrane)**	To assess the effects of advising healthy pregnant women to engage in regular aerobic exercise, or to increase or reduce the intensity, duration, or frequency of such exercise, on physical fitness, the course of labour and delivery, and the outcome of pregnancy	Healthy pregnant women	Physical activity	Change in level of maternal physical fitness, anthropometric measures; pre-eclampsia, duration of labour, and type of delivery; fetal and infant outcomes	14	**Limitations** Not described **Conclusions** Effect on the main outcome ⇧ Mother or infant outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
5	**Dodd 2008**[5]	To assess the benefits and harm of dietary and lifestyle interventions during pregnancy to improve maternal and infant outcomes for pregnant women who are overweight or obese	Overweight and obese pregnant women	Mixed approach	Weight gain, maternal, fetal, and infant health outcomes	2	**Limitations** No search limits Low number of eligible studies and lack of power to detect clinically important effects **Conclusions** Effect on the main outcomes (?)
6	**Kuhlmann 2008**[6]	To assess whether effective weight-management interventions exist for this population	Pregnant or postpartum women	Physical activity	Pregnancy weight gain in excess of the IOM recommendations or postpartum weight retention	1	**Limitations** Only studies in English Published 1985 – 2007 Differences in measures, number of participants, follow-up periods, design and reported information made comparisons and overall conclusions difficult **Conclusions** Effect on the main outcome ⇧

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
7	**Schlüssel 2008**[7]	To investigate the effects of physical activity during pregnancy on selected maternal-child health outcomes.	Healthy pregnant women	Physical activity	Primary: pre-eclampsia, gestational hypertension, GDM, gestational weight gain, miscarriage, mode of delivery, fetal growth or development, birth weight, length at birth, preterm birth	0	**Limitations** Only studies in Portuguese, English, or Spanish Published 1980 – 2005 Most included studies lacked any kind of standardization as to the type of activities what made it difficult to compare the studies' results. **Conclusions** Effect on the main outcomes (?)
8	**Tieu 2008**[8] **(Cochrane)**	To assess the effects of dietary advice in preventing GDM	Healthy pregnant women	Diet	Primary: LGA, macrosomia, perinatal mortality, GDM, mode of birth (normal vaginal birth, operative vaginal birth, caesarean section) Secondary: various maternal and infant outcomes	3	**Limitations** No search limits A small number of trials with a relatively small group of women, variation in reported outcomes, heterogeneity (mainly in gestational weight gain) and quality and reporting of included studies. **Conclusions** Effect on the main outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
9	**Dodd 2010[9]**	To assess the benefits and harms of antenatal dietary or lifestyle interventions for pregnant women who are overweight or obese	Overweight and obese pregnant women	Mixed approach	Primary: LGA infant Secondary: various maternal and infant outcomes	9	**Limitations** Heterogeneity (interventions' intensity), inconsistency in outcome reporting, not reporting of subgroups, poor quality of included studies **Conclusions** Effect on all evaluated outcomes (?)
10	**Skouteris 2010[10]**	identify, and evaluate the effect of key variables designed to modify risk factors for excessive weight gain in pregnant women that have been targeted in interventions over the last decade	Healthy pregnant women	Mixed approach	Primary outcome: Excessive gestational weight gain	6	**Limitations** Only studies in English Published 2000 – 2010 Use of self-reported pre-pregnancy weight and weight at 37 weeks of gestation. **Conclusions** Effect on the main outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
11	**Ronnberg 2010**[11]	To determine if published trials of interventions to reduce excessive gestational weight gain are of sufficient quality to inform clinical recommendations	Healthy pregnant women	Mixed approach	Primary outcome: Total gestational weight gain, rate of gestational weight gain per week, proportion of women exceeding IOM weight gain recommendations	3	**Limitations** Only studies in English or any Scandinavian language Not reporting of the effect by BMI group, small sample size, heterogeneity in the mode, intensity, frequency and duration of the interventions, use of surrogate endpoints in all included trials **Conclusions** Effect on the main outcomes (?)
12	**Streuling 2011**[12]	To find out whether physical activity during pregnancy might help avoid high GWG	Healthy pregnant women	Physical activity	Total gestational weight gain	12	**Limitations** No search limits Heterogeneity and losses to follow up **Conclusions** Effect on the main outcome ⇧

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
13	**Tanentsapf 2011**[13]	Primary: evaluate the effect of dietary interventions for reducing GWG, Secondary: to examine the impact of these interventions on child and maternal health outcomes	Healthy pregnant women with singleton pregnancy	Diet	Primary: % of women who gained above the IOM recommendations, % of women with excess GWG, total GWG or weekly GWG Secondary: various maternal and infant outcomes	13	**Limitations** No search limits Inability to quantify the intensity of different interventions due to lack of details in the included papers; methodological quality of the studies (7/13 with high risk of bias); variation is measuring gestational weight gain; lack of power to capture intervention effects on some clinical outcomes; **Conclusions** Effect on the main outcome ⇧ Effect on the secondary outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
14	**Gardner 2011[14]**	To assess the effect of interventions aimed to reduce gestational weight gain through changes in diet or physical activity	Healthy pregnant women	Mixed approach	Primary: gestational weight gain	10	**Limitations** Only in English Published 1990 – 2010 Women without any chronic health conditions Variation in characteristics of participants, the methodological quality of included studies and reporting of interventions components. **Conclusions** Effect on the main outcome ⇧
15	**Quinlivan 2011[15]**	To estimate whether antenatal dietary interventions restrict maternal weight gain in obese pregnant women without compromising newborn birth weight	Overweight and obese pregnant women	Diet	Primary outcome: Gestational weight gain Secondary outcome: birth weight	4	**Limitations** Not reported **Conclusions** Effect on the main outcome ⇧ Effect on the secondary outcome ⇔

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
16	**Campbell 2010[16] (ScHARR)**	To investigate the health impact of improved management of weight gain in pregnancy	Pregnant women with singleton pregnancy	Mixed approach	Primary outcome: Weight-related outcomes, dietary and physical activity outcomes Other mother and offspring related outcomes	5	**Limitations** Human studies Published 1990 – 2008 Small number of studies **Conclusions** Effect on the main outcome ⇔
17	**Nascimento 2011[17]**	To evaluate the effects of exercise on weight gain and perinatal outcomes among overweight and obese pregnant women	Overweight and obese pregnant women	Mixed approach	Gestational weight gain, pregnancy hypertension, pre-eclampsia, GDM, preterm birth, birth weight, quality of life, cardiovascular capacity	3	**Limitations** Published 1980 – 2010 **Conclusions** Few studies confirmed the positive effect of exercise in controlling weight gain during pregnancy

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
18	**Sui 2012[18]**	Assess the benefits and harms of an exercise intervention for pregnant women who are overweight or obese	Overweight and obese pregnant women	Physical activity	Primary: maternal gestational weight gain Secondary: various maternal and infant outcomes	7	**Limitations** No search limits Variation in the nature of provided interventions, their timing, duration and compliance; studies with small sample sizes and methodological flaws. **Conclusions** Effect on the main outcome ⇧ Effect on the secondary outcomes (?)
19	**Thangaratinam 2012[19]**	To evaluate the effects of dietary and lifestyle interventions in pregnancy on maternal and fetal weight and to quantify the effects of these interventions on obstetric outcomes.	Pregnant women	Mixed approach	Primary outcomes: Gestational weight gain Secondary outcomes: various maternal and infant outcomes	44	**Limitations** No search limits Heterogeneity in the effects of the interventions, rarely reported subgroup effects, low quality of evidence for important obstetric outcomes. **Conclusions** Effect on the main outcome ⇧ Effect on the secondary outcomes ⇧

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
20	**Muktabhant 2012[20] (Cochrane)**	To evaluate the effectiveness of interventions for preventing excessive weight gain during pregnancy and associated pregnancy complications	Pregnant women	Mixed approach	Primary: excessive weight gain Secondary: various maternal and infant outcomes	27	**Limitations** No search limits Significant methodological limitations and small effect sizes. **Conclusions** Effect on the main outcome (?)
21	**Oteng-Ntim 2012[21]**	To determine the efficacy of antenatal dietary, activity, behaviour or lifestyle interventions in overweight and obese pregnant women to improve maternal and perinatal outcomes	Overweight and obese pregnant women	Mixed approach	Gestational weight gain, GDM, Caesarean section, LGA, birth weight	13	**Limitations** Clinical trials Low quality studies, small sample size, and lack of effect for BMI subgroups when a mixed group of obese and overweight women was included. **Conclusions** Effect on gestational weight gain ⇧ Effect on GDM ⇔

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
22	**Choi 2013**[22]	To review the effectiveness of interventions with physical activity only and with diet in managing weight among overweight or obese pregnant or postpartum women	Overweight and obese pregnant or postpartum women	Mixed approach	Not pre-specified	7	**Limitations** Only studies in English or Korean Published 2000 – 2011 Heterogeneity, variation in studies' quality and reporting. **Conclusions** Effect on the gestational weight gain ⇧
23	**Lamina 2013**[23]	To assess the effect of aerobic training on maternal weight in pregnancy	Pregnant women	Physical activity	Gestational weight gain	11	**Limitations** Only studies in English Clinical heterogeneity, variation in recruitment period and not reporting effects by BMI subgroups in BMI mixed studies. **Conclusions** Effect on the main outcome ⇧

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
24	**Fuber 2013[24]** **(Cochrane)**	To evaluate the effectiveness of interventions that reduce weight in obese pregnant women	Obese pregnant women	Mixed approach	Primary: Serious maternal morbidity, neonatal admission to NICU, Perinatal death Secondary: various maternal and infant outcomes	0	No search limits No relevant RCTs
25	**Gresham 2014[25]**	To synthesized effects of dietary interventions before or during pregnancy on neonatal and infant outcomes	Pregnant or postpartum women	Diet[1]	Primary outcomes: Neonatal and infant outcomes	15	**Limitations** Small number of included trials, variation in reported outcomes, moderate to high heterogeneity for neonatal outcomes not explained by a subgroup analysis. **Conclusions** Effect on the main outcomes (?)

[1] And nutritional factors

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
26	**O'Brien 2014[26]**	To systematically review the literature on the use of technology supported lifestyle interventions for healthy pregnant women and their impact on maternal outcomes	Overweight and obese pregnant women	Mixed approach	Primary: fasting maternal glucose, GDM, gestational weight gain Secondary: intervention uptake, acceptance, dietary or physical activity modification	5	**Limitations** Only studies in English The design of included studies (feasibility or acceptance studies), intensity and duration of interventions, and trials geographical location (mainly the Unated States). **Conclusions** Effect on the gestational weight gain ⇧ The absence of data for important pregnancy outcomes (?)
27	**Elliott-Sale 2015[27]**	To review the evidence from studies employing exercise-only interventions for weight management among pregnant and postpartum women	Pregnant or postpartum women	Physical activity	Primary: change in body weight	5	**Limitations** Published 1990 – 2013 Focus on physical activity only **Conclusions** Effect on the main outcome (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
28	**Bain 2015[28] (Cochrane)**	To assess the effects of combined diet and exercise interventions for preventing GDM and associated adverse health consequences for women and their babies	Healthy pregnant women	Mixed approach	Primary: GDM, mode of birth (normal vaginal, operative vaginal birth, caesarean section), LGA, perinatal mortality Secondary: various maternal and infant outcomes	13	**Limitations** No search limits Variations in the trials' quality, type of the interventions, assessed populations, and definitions of outcomes across the included trials. **Conclusions** Effect on GDM ⇔ Effect on the other outcomes (?)
29	**Muktabhant 2015[29]** **(Cochrane)**	To evaluate the effectiveness of interventions for preventing excessive weight gain during pregnancy and associated pregnancy complications	Pregnant women	Mixed approach	Primary: excessive weight gain Secondary: various maternal and infant outcomes	49	**Limitations** No search limits Included studies were mainly conducted in developed countries; moderate to high statistical heterogeneity. **Conclusions** Effect on the main outcome ⇔ derived from a High-quality evidence Effect on the other outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
30	**Sanabria-Martınez 2015[30]**	To assessing the effectiveness of physical exercise interventions during pregnancy to prevent GDM and excessive maternal weight gain.	Healthy pregnant women	Physical activity	Pirmary outcome: GDM, excessive mean gestational weight gain	13	**Limitations** Only studies in English or Spanish Non-blinded data extraction, medium to the low quality of included studies, and variation in reporting of studies' findings and diagnostic criteria of the primary outcome (GDM). **Conclusions** Effect on the main outcomes ⇧
31	**O'Brien 2016[31]**	To systematically review effect of dietary and lifestyle interventions in pregnant women with a normal BMI on maternal and infant outcomes	Pregnant women with normal BMI	Mixed approach	Primary: total gestational weight gain, the proportion of women exceeding the IOM guidelines, weight retention defined more than 5 kg weight gain at 12 months postpartum Secondary: various maternal and infant outcomes	12	**Limitations** No search limits Small sample size, use of self-reported pre-pregnancy BMI in included studies, poor description of the evaluated interventions and adherence to them, and variation in the interventions' components. **Conclusions** Effect on the main outcome ⇧ derived from evidence limited by relatively small sample size

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
32	**Song 2016**[32]	To examine the effect of lifestyle intervention on the risk of GDM	Healthy pregnant women	Mixed approach	Primary outcome: GDM	29	**Limitations** Only studies in English or Chinese Included studies were mainly conducted in developed countries; lack of power to investigate the effects of individual components of the interventions and dose-response relationship. **Conclusions** Effect on the main outcome ⇔

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
33	**Perales 2016**[33]	To understand what evidence exists with regard to maternal and offspring benefits of aerobic and resistance training during pregnancy	Healthy pregnant women	Physical activity	Not pre-specified	61	**Limitations** Only studies in English Small sample size, high loss to follow-up, differences among studies in frequency, intensity, duration or timing of exercise, low adherence to the training schedule, and weak overall quality of included studies. **Conclusions** Effect on the maternal cardiorespiratory fitness and prevention of urinary incontinence ⇧ Effect on the other outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
34	**Gresham 2016**[34]	To determine the effect of dietary intervention before or during pregnancy on pregnancy outcomes	Pregnant women	Diet[1]	Not pre-specified	14	**Limitations** Only studies in English Human studies Small number of included studies, variation in outcome reporting, statistical heterogeneity in outcomes such as blood pressure, GDM and length of gestation that could not be explained by subgroup analyses. **Conclusions** Effect on the evaluated outcomes ⇧ but small
35	**McDonald 2016**[35]	To examine the relationship between exercise dose and reductions in weight gain during pregnancy in exercise interventions.	Pregnant women	Physical activity	Gestational weight gain	21	**Limitations** No search limits Probability of missing out trials Heterogeneity of the exercise doses prescribed and insufficient reporting of the received dose. **Conclusions** Effect on the evaluated outcomes (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
36	**Zhang 2016**[36]	To examine the effects of low-GI diets on maternal and newborn outcomes	Pregnant women with single fetus	Diet	Gestational weight gain, fasting blood glucose, insulin use, 2-h postprandial glucose, glycated HbA1c, cesarean delivery, gestational age at delivery, birth weight, Ponderal index, LGA, SGA, macrosomia, head circumference, body length, birth centile, and birthweight centile prematurity, abdominal circumference	11	**Limitations** Human studies Heterogeneity and small number of studies **Conclusions** Effect on the evaluated outcomes (?)
37	**Magro-Malosso 2017**[37]	To evaluate the effect of exercise on the risk of preterm birth in overweight and obese pregnant women	Overweight or obese pregnant woman	Physical activity	Primary: preterm birth (<37 wks) Secondary: Gestational age at delivery, cesarean delivery, GDM, birth weight, low birth weight, macrosomia, stillbirth	9	**Limitations** No search limits Additional intervention (dietary) provided in some of the included studies, variation in type, duration amd intensity of main intervention, variation in the main outcome definition (spontaneous and indicated preterm birth) **Conclusions** Effect on the main outcome ⇧ Effect on GDM ⇧

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
38	**da Silva 2017[38]**	To compare the associations between leisure-time physical activity in pregnancy and maternal and child health outcomes between RCTs and cohort studies	Healthy pregnant women	Physical activity	Primary outcomes: gestational weight gain, GDM, pre-eclampsia, birthweight, preterm birth and fetal growth	30	**Limitations** Only studies in English, Portuguese or Spanish **Conclusions** Effect on the gestational weight gain, GDM, preterm birth and LGA⇧ Effect on pre-eclampsia ⇔
39	**Donazar-Ezcurra 2017[39]**	To review literature on the effectiveness of nutritional factors before or during pregnancy to prevent GDM	Women before pregnancy and pregnant	Diet[1]	Primary outcome: GDM	8	**Limitations** Only studies in English, French or Spanish Probable publication bias **Conclusions** Effect on the main outcome (?)

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
40	**Fealy 2017[40]**	To test if routine weighing as a stand-alone intervention can reduce gestational weight gain	Pregnant women	Mixed approach	Gestational weight gain, excessive gestational weight gain according to IOM guidelines pregnancy, infant and birth outcomes	2	**Limitations** Only studies in English Human studies Small number of studies with lack of blinding of participants and personnel. **Conclusions** Effect on the main outcome ⇔
41	**Tieu 2017[41]** **(Cochrane)**	To assess the effects of dietary advice in preventing GDM	Healthy pregnant women	Diet	Primary: LGA, macrosomia, perinatal mortality, GDM, mode of birth (normal vaginal birth, operative vaginal birth, caesarean section) Secondary: various maternal and infant outcomes	11	**Limitations** Heterogeneity, and moderate to low quality of included studies. **Conclusions** Effect on the GDM ⇧ derived from very low-quality evidence Effect on the PIH ⇧ Effect on the other outcomes ⇔

No.	Review ID	Review aim	Population	Intervention	Outcome(s)	Number of included RCTs	Limitations and conclusions
42	**Yeo 2017**[42]	To review studies targeting gestational weight gain in obese and overweight women by implementing prenatal lifestyle interventions	Overweight or obese pregnant woman	Mixed approach	Primary outcome: gestational weight gain	32	**Limitations** Published 2005 – 2016 High heterogeneity in the effects, probable bias due to lack of blinding in the included studies. **Conclusions** Effect on the main outcome ⇧ was more efficacious when delivered by primary care providers during routine prenatal care

RCT, Randomised Controlled Trial; IOM, Institute of Medicine; GDM, gestational diabetes; NICU, neonatal intensive care unit; SGA, small for gestationa age infant; LGA, large for gestational age infant;

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Appendix 2.1 Search strategy for identification of randomised trials on diet and physical activity in pregnancy – 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

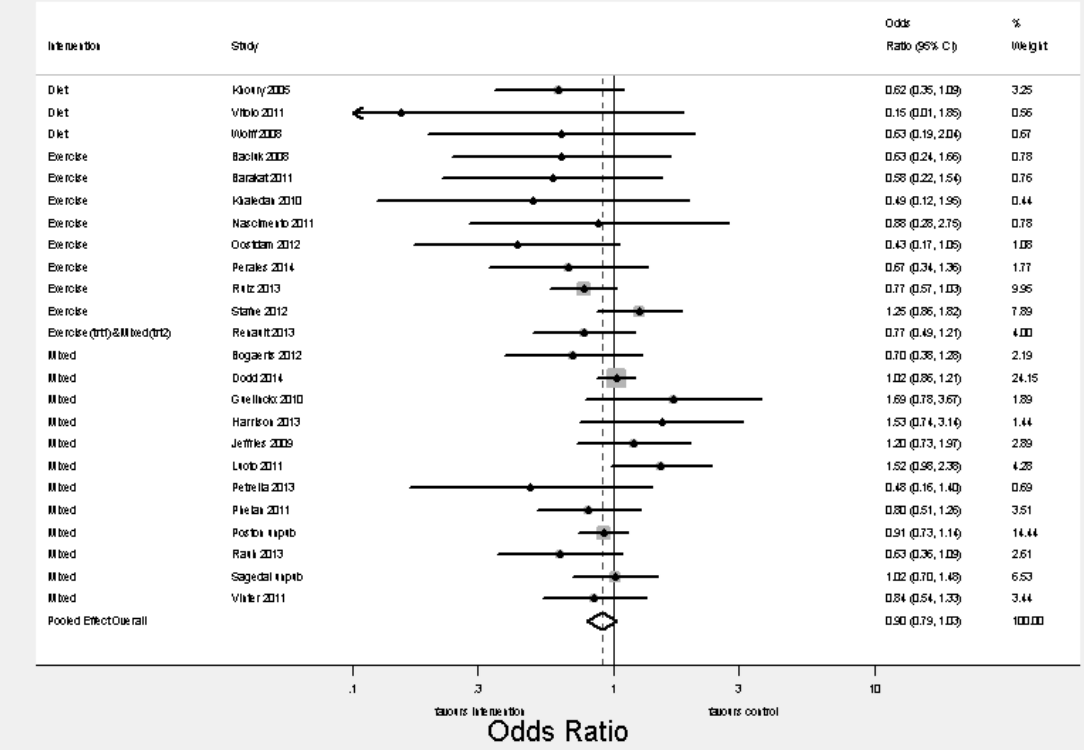
Appendix 3.1 Maternal and offspring outcomes ranked by the previous Delphi survey of 19 panellists

Maternal outcomes	Previous panel		Offspring outcome	Previous panel	
	Median	IQR		Median	IQR
Pre-eclampsia	8	2	Intrauterine death	8.5	1
Pregnancy Induced Hypertension	8	2	Small for Gestational Age	8	1.25
Gestational Diabetes Mellitus	8	0.25	Large for Gestational Age	7	1.25
Preterm birth	7	2	Admission to NICU	8	1
Caesarean section: elective	7	1	Shoulder dystocia	8	1
Caesarean section: emergency	7	1	> 1 perinatal complication	8	1
Thromboembolism	8	1.25	Birth trauma	8	0.5
Admission to High Dependency Unit/Intensive Treatment Unit	8	1	Longterm neurological sequelae	8	2.25
Weight gain in pregnancy	6	1.25	Longterm metabolic sequelae	7.5	1.25
Interpregnancy weight gain	7	1.25	Hypoglycemia	7	1
Postpartum haemorrhage	7	0.25	Respiratory Distress Syndrome	7	1
Induction of Labour	8	1.25	Skinfold thickness	6	1
Miscarriage	6	1.5	Fetal fat mass	6	1.25
Need for resuscitation at delivery	7	0.25	Abdominal circumference	6	1.25
Physical activity	6	0.25	Ponderal index	6	2
Dietary behaviour	7	0.25	Birthweight related outcomes like BMI	6	2
Postpartum weight retention	6	1.25	Hyperbilirubinemia	6	2
Prolonged Labour	6	1	Neural Tube Defect	6	2

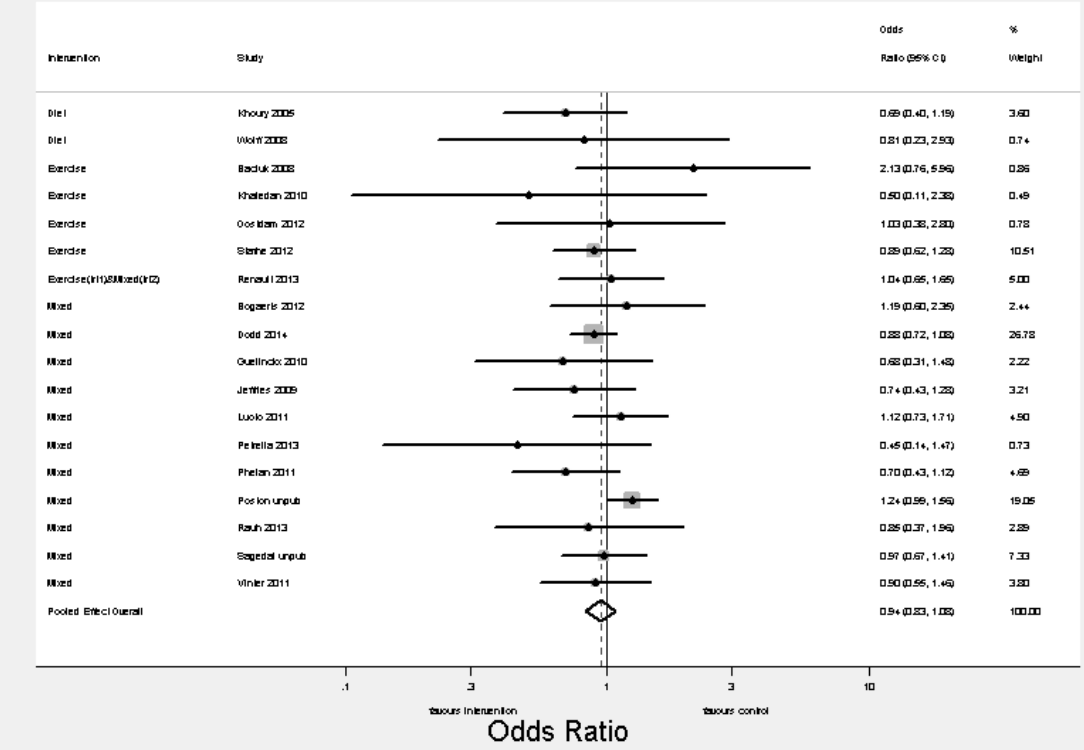
Maternal outcomes	Previous panel		Offspring outcome	Previous panel	
	Median	IQR		Median	IQR
Instrumental delivery	7	1.25	Other congenital abnormalities	6.5	1.25
Perineal Trauma	6.5	1	Apgar score	6	1
Antepartum Haemorrhage	6	1	Abnormal cord pH	7	2
Postnatal depression	6	2.25	Head circumference	5	0.25
Quality of Life	6	1.25	Neonate length/crown-heel length	5	0.25
Body fat (%)	6	2.25	Head/abdomen ratio	5	1
Breast feeding	5	2.25	Cleft Lip or Palate or Both	6	1.25
Failed instrumental delivery	7	2	CTG abnormalities	5.5	1.25
Coronary artery disease	6	3.25	Cord Abnormalities	5	2.25
Prelbour rupture of membranes	6	1.25	Developmental outcome at 2 year of age*	-	-
Anaemia	5	3			
Infections	6	2			
Postnatal Infection	6	2.25			
Anxiety	5	0.5			
Back pain	6	2			
Non infective respository distress	5.5	2.25			
Threatened Abortion	3.5	2			

Appendix 3.2 Forest plots with maternal and offspring composite outcomes

Maternal composite outcome in the individual studies



Offspring composite outcome in the individual studies



1213 Appendix 4.1 List of sought data items for i-WIP IPD meta-analysis

iWIP IPD meta-analysis project: "Effects of weight management interventions on maternal and fetal outcomes in pregnancy"	
Variable name *Variables marked with (*) are the mandatory ones*	**Collected/Reported** *Please specify: Yes/No*
Baseline characteristics Please state way of information obtained: *self-reported / measured by health worker / medical chart*	
Age*	
Height*	
Weight at baseline*	
BMI at baseline*	
Pre-pregnancy weight *	
Pre-pregnancy BMI*	
Race*	
Ethnicity*	
Gestational age at baseline*	
Known medical condition (please specify)	
Mental health and medication (depression, anxiety, QoL, etc.)	
History of pregnancy abnormalities (e.g. GDM)	
Number of fetuses*	
Gravidity*	
Parity*	
Smoking*	
Educational status*	
Socioeconomic status (income, work)*	
Substance misuse – alcohol	
Substance misuse – drugs	
Baseline diet*	
Baseline physical activity*	
Lifestyle*	
Intervention	
Type: Diet, Physical Activity, Behavioural	
Intervention components	
Intervention provider	
Setting	
Gestational age of commencement	
Frequency	
Format (individual, groups)	

Outcomes	
Maternal	
GA at delivery *	
Last Weight*	
Last BMI*	
GA at which last wt or BMI was calculated*	
Gestational weight gain (GWG)* *and how it was calculated*	
Weight at 3, 6 and 12 months after delivery (post-partum)	
Institute of Medicine (IOM) guidelines adherence	
Mental health	
Obstetric *(if definition is not specified in the protocol please provide used definition of the outcome)*	
Pre-eclampsia (PE)* with GA of onset	
Gestational diabetes mellitus (GDM)* with GA of onset	
GDM Biochemistry, GTT values	
Pregnancy induced hypertension (PIH)* with GA of onset	
Induction of labour (IOL)* with GA of onset and Indication	
Mode of delivery*	
Preterm birth*	
Shoulder dystocia*	
Postpartum haemorrhage (Atonic, Traumatic; 3rd degree tear 4th degree tear; Antepartum haemorrhage)	
HELLP (Hemolysis Elevated Liver enzymes and Low Platelets)	
Admission to HDU/ITU*	
Meconium stained liquor	
Dietary behaviour	
Physical activity	
Breast feeding	
Severe infection needing admission	
Venous thromboembolism*	
Pulmonary embolism	
Adverse events (neurological, haematological, gastrointestinal, pain, etc.)	

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Fetal *(if definition is not specified in the protocol please provide used definition of the outcome) Please state way of information obtained: self-reported / measured by health worker / medical chart*	
Birth weight*	
1' Apgar Score	
5' Apgar Score	
Admission to NICU*	
Respiratory distress syndrome (RDS)	
Intra-uterine death*	
Birth trauma*	
Hypoglycaemia	
Hyperbilirubinaemia	
Large for gestational age	
Small for gestational age*	
Birth length	
Head circumference	
Abdominal circumference	
Crown-heel length (CRL)	
Hypoxic ischaemic encephalopathy	
Cord pH (Arterial; Venous)	
Infant death	
Long term neurological sequel*	
Other	
Any long-term neonatal or childhood outcome	
Losses to follow-up - mother	
Losses to follow-up - baby	
Compliance*	

1217
1218

Appendix 4.2 Grouping of variables ethnic origin, education and physical activity before pregnancy

Ethnic origin

Caucasian including Russia& Australia	Asian	Black	Central/South American	Middle East including Iran & Turkey	Other
Australia	Malaysia	AfroCaribbean	Argentina	Iran	Aboriginal/TSI
Austria	Nepal	Tunisia	Brazil	Iraq	Australia / Aboriginal
Belgian/Dutch	Pakistan	Uganda	Brazil Black	Israel	Fiji
Belgium	Pakistani	Zimbabwe	Brazil Pardo	Lebanon	NZ
Bosnia	Philippines	Maghreb	Brazil White	Middle Eastern	Non-Caucasian
Bosnia-Herzegovina	South East Asian		Chile	Turkey	Other
Bulgaria	Sri-Lanka		Colombia		
Croatia	Taiwan		Columbia		
Czech	Thailand		El Salvador		
Denmark	Uzbekistan		Mexico		
East-European	Vietnam				
England	Japan				
European					
Finn/engl/swed/russ					
France					
Germany					
Greece					
Hungary					
Iceland					
Italian					
Italy					
Kosovo					
Latvia					
Lebanon					
North American White					
Norway					
Other White					
Pakistani					
Poland					
Romania					
Russia					
Serbia					
Slovakia					
Spain					
Sweden					
The Faroes					
Turkey					
Ukraine					
White Irish					
Yugoslavia					

Education level

Low	Medium	High
< 12 yrs (preparatory school or occupational school)	12 yrs (high school)	Vocational training school <4years addl edu
<4 years of study	4-8 years of study	> 12 yrs (university or equivalent to it)
First degree	A level (or equivalent)	>8 years of study
Grammar school <=10 years	GCE (or equivalent)	>=4years addl edu
LBO	General secondary school	College/University<4yrs
Less than high school	General upper secondary education	Further education 1-2 years
Low	HAVO_VWO	Graduate degree
Low(basic or secondary education)	High school	Graduated, 14yrs
None	High school / Grammar school	Graduated, 16yrs
Preliminary, 5yrs	High school diploma	HBO
Preliminary, 9yrs	High school, 12yrs	High(university degree)
Primary	Intermediate secondary school	Higher degree
Primary and secondary school	MBO	Post graduate education
Primary education	Medium(polytechnic education)	Post-graduate
Primary or less	Secondary	Tertiary
Primary school	Secondary school 12 years	Tertiary education 3-4 years (Bachelor level)
VMBO	Upper secondary school	Undergraduate
Year 10 or below	Vocational upper secondary education	University
Year 11 or equivalent	Year 12 or equivalent	University degree
Elementary school	complete secondary	University/university College <4yrs
Grade school(<6yrs)	high school	University/university College >4yrs
junior high school(7-9yrs)	high school (13 years)	Vocational qualification
Less than Primary school	high school(10-12yrs)	WO
middle	medium length education	Year 12 or equivalent
middle school (8 years)	school max 10yrs, additional education	bachelors level
primary school	technical, additional education	college(university)
school max 10yrs, education unfinished	until 18 year, possible a speciality of 1/2 year	college/university degree
some secondary	vocational training	college/university4yrs+
technical/high school, education unfinished		complete 3rd level
		graduate or professional education
		graduated
		high school, additional education
		masters level or higher
		post-graduation level
		same college(<4yrs)
		some 3rd level
		university

Physical activity prior pregnancy

No exercise / sedentary	At least some activity
<600 MET-min/week	10000+ steps/dy
<600 met/hr/week	600+ MET-min/week
Accelerometer <2.5 hrs/wk	600+ met/hr/week
Does not attend gym	Accelerometer 2.5+ hrs/wk
Does not exercise regularly at inclusion	Does attend gym
Less than 10000 steps/dy	Exercise regularly at inclusion
Low	Handiwork
Paffenbarger PA questionnaire <1000cals	Hard
Sedentary	High
Sedentary Work	Light-moderate
Work mainly sedentary	Moderate
Completely inactive	Moderate-hard
Completely sedentary	Paffenbarger PA questionnaire 1000+cals
Lying	Physically active
Sitting	Work in movement
Some activity occasionally	Work standing
	Work standing and in movement
	active
	active (PPAQ)
	active (exercise two to three times a week)
	active work
	high performance athlete
	housewife
	professional athlete
	something active
	standing
	very active
	very active (regular exercise four to five times a week)
	walking

1230 Appendix 4.3 Characteristics of eligible randomised trials on diet and physical activity
1231 based interventions in pregnancy

Study ID	Country	Sample size*	Intervention	BMI group
Studies contributing IPD				
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

**Refers to sample size in IPD meta-analyses*
[§]Trials with randomisation by cluster

Study ID	Country	Sample size*	Intervention	BMI group
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
Studies that did not contribute IPD				
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

**Refers to sample size in IPD meta-analyses*
[§]Trials with randomisation by cluster

Study ID	Country	Sample size*	Intervention	BMI group
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
Studies that did not contribute IPD (cont.)				
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	293	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

**Refers to sample size in IPD meta-analyses*

Study ID	Country	Sample size*	Intervention	BMI group
Studies that did not contribute IPD (cont.)				
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 sample size in IPD meta-analyses*

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Appendix 4.4 Characteristics of women randomised to trials included in the i-WIP IPD meta-analysis

Baseline characteristics	N studies	N obs*	Control Mean (SD) or N (%)#	Intervention Mean (SD) or N (%)#
Age (years)	35	12006	30.1 (5.2)	30.0 (5.1)
Age category	35	12006		
- 20+ years			5634 (97.4%)	6080 (97.7%)
- Less than 20 years of age			151 (2.6%)	141 (2.3%)
Height (cm)	31	11689	165.0 (7.0)	165.4 (6.7)
Race/Ethnicity:	27	10020		
- Caucasian incl. Russia&Austr			4217 (87.2%)	4562 (88%)
- Asian			156 (3.2%)	157 (3.0%)
- Black			292 (6.0%)	292 (5.6%)
- Central/South American			64 (1.3%)	67 (1.3%)
- Middle East incl. Iran&Turkey			37 (0.8%)	37 (0.7%)
- Other			68 (1.4%)	71 (1.4%)
Education Mum l/m/h	29	8914		
- Low			724 (16.9%)	722 (15.6%)
- Medium			1292 (30.2%)	1372 (29.6%)
- High			2268 (52.9%)	2536 (54.8%)
Current smoker	29	10958	865 (16.4%)	875 (15.4%)
Ex-smoker (pre pregnancy)	13	4099	456 (23.8%)	523 (24.0%)
Adherent (intervention group only)	18	3321	n/a	2022 (60.9%)
Parity	33	11805		
- 0			2692 (47.3%)	3027 (49.5%)
- 1			2083 (36.6%)	2136 (34.9%)
- 2			634 (11.1%)	647 (10.6%)
- 3			165 (2.9%)	179 (2.9%)
- 4+			113 (2.0%)	129 (2.1%)
No exercise / Sedentary	27	7583	1731 (47.6%)	1761 (44.6%)
Baseline BMI category	34	12031		
- Normal (BMI 18.5-24.9)			1842 (31.8%)	1974 (31.7%)
- Overweight (BMI 25-29.9)			1523 (26.3%)	1578 (25.3%)
- Obese (BMI 30+)			2434 (42.0%)	2680 (43.0%)
Previous macrosomia	8	2906	400 (29.1%)	390 (25.5%)
Previous GDM	11	4297	49 (2.4%)	60 (2.9%)
GDM	20	8256	14 (0.4%)	23 (0.6%)
Diabetes Mellitus	25	9589	9 (0.2%)	6 (0.1%)
PIH	20	5695	37 (1.3%)	47 (1.6%)
Hypertension	23	5494	54 (2.1%)	73 (2.5%)
Diabetes Mellitus or Hypertension	20	5124	57 (2.4%)	75 (2.8%)

* Refers to total number of observations across all studies and treatment arms

Percentage refers to proportion out of observations in control or intervention arms respectively

1238 Appendix 4.5 Risk of bias assessment for individual trials on diet and physical activity based interventions

Study	Randomisation sequence	Allocation concealment	Blinding participants and personnel	Blinding of outcomes assessors	Incomplete outcome data	Selective reporting
Arthur 2016	U	U	U	U	U	U
Asci 2016	L	L	U	U	L	L
Althuizen 2012	L	L	U	L	L	U
Asbee 2009	L	L	U	U	U	H
Baciuk 2008	L	L	H	L	L	L
Badrawi 1993	U	U	U	U	U	U
Barakat 2008	U	U	U	L	L	L
Barakat 2011	L	U	U	U	L	L
Barakat 2012	U	U	U	U	L	L
Barakat 2012a	L	U	U	U	H	L
Barakat 2013	U	U	U	L	L	L
Barakat 2014	L	U	U	U	L	L
Barakat 2015	L	L	U	L	L	L
Bisson 2015	L	L	H	L	L	L
Blackwell 2002	H	U	U	U	H	L
Bogaerts 2012	L	U	H	H	L	L
Bruno 2016	L	U	H	L	H	L
Briley 2002	U	U	U	U	H	L
Brownfoot 2016	L	L	H	U	L	L
Clapp 2000	L	U	U	U	L	L
Cordero 2014	U	U	H	U	H	L
Daly 2017	U	U	H	U	H	U
Daley 2015	L	L	H	H	L	L
Das 2015	U	U	U	U	U	U
Dekker 2015	L	L	U	U	L	L
de Oliveria Melo 2012	L	L	H	L	L	L
Deveer 2013	H	H	U	U	L	L
Di Carlo 2014	U	L	H	L	U	L

Risk of bias: L – low U – unclear H – high

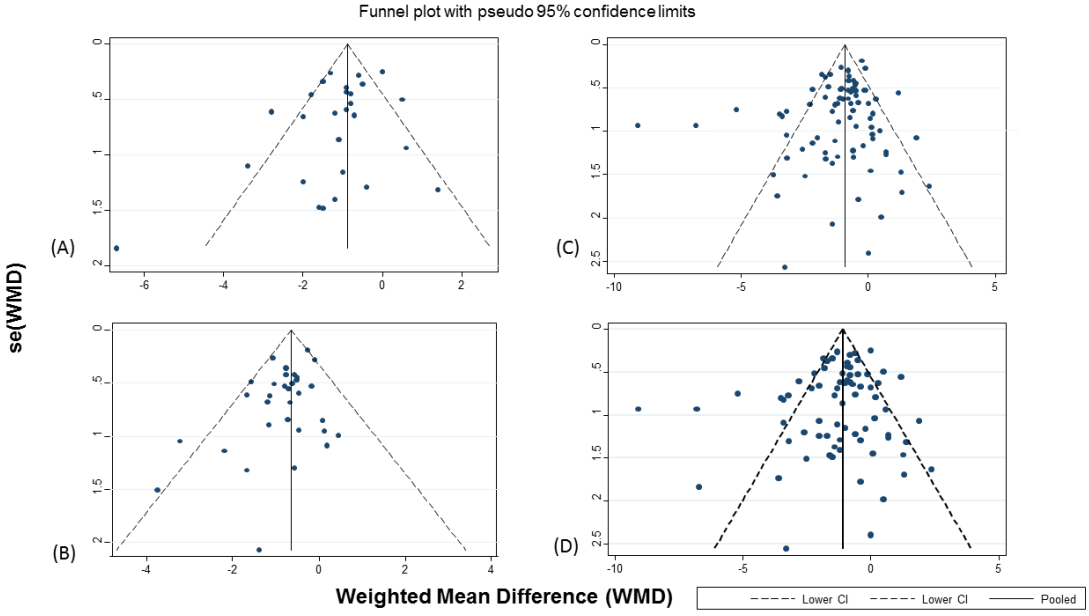
Study	Randomisation sequence	Allocation concealment	Blinding participants and personnel	Blinding of outcomes assessors	Incomplete outcome data	Selective reporting
Dodd 2014	L	L	U	L	L	L
El Beltagy 2013	L	L	U	L	L	U
Garshasbi 2005	U	U	U	U	L	L
Garnaes 2016	L	L	H	L	L	L
Gesell 2015	L	L	U	U	H	L
Gomez Tabarez 1994	U	U	U	U	L	U
Guelinckx 2010	L	U	U	H	H	H
Haakstad 2011	L	L	U	L	L	H
Harrison 2013	L	L	U	L	L	L
Hawkins 2015	U	U	U	L	L	L
Herring 2016	L	L	U	U	L	L
Hopkins 2010	U	U	U	U	H	L
Huang 2011	L	U	U	L	H	L
Hui 2011	L	U	H	U	L	L
Hui 2014	L	U	H	L	L	H
Jackson 2010	L	L	H	U	L	L
Jeffries 2009	L	L	U	L	L	L
Jing 2015	L	U	U	L	L	L
Kihlstrand 1999	U	U	H	U	L	U
Khaledan 2010	L	U	H	H	L	L
Khoury 2005	L	L	U	L	L	L
Ko 2014	L	U	U	L	L	L
Koivusalo 2016	L	L	U	L	U	U
Kong 2014	L	L	H	U	L	L
Korpi-Hyovalti 2012	L	L	H	H	L	H
Lee 1996	L	U	U	U	U	H
Luoto 2011	L	L	H	H	L	L
Marquez 2000	U	U	U	U	H	H
McCarthy 2016	L	L	H	L	L	L
Mujsindi 2014	U	U	U	U	U	U
Risk of bias:	L – low	U – unclear	H – high			

Study	Randomisation sequence	Allocation concealment	Blinding participants and personnel	Blinding of outcomes assessors	Incomplete outcome data	Selective reporting
Murtezani 2014	L	U	U	U	L	L
Nascimento 2011	L	L	H	H	L	L
Ong 2009	L	U	H	H	L	L
Oostdam 2012	L	L	H	L	H	L
Peaceman 2017	U	U	U	L	L	U
Parat 2015	U	U	U	U	L	U
Perales 2014	L	L	H	L	L	L
Perales 2016	L	U	U	L	H	L
Perales 2016a	L	U	H	L	H	L
Petrella 2013	L	H	H	H	L	H
Phelan 2011	L	L	U	L	L	L
PetrovFieril 2015	L	L	H	L	H	L
Polley 2002	U	U	U	U	L	L
Poston 2015	L	L	H	H	L	L
Prevedel 2003	L	L	H	H	U	L
Price 2012	L	L	H	U	H	U
Li 2014	U	U	U	U	L	L
Quinlivan 2011	L	L	U	L	L	L
Rakhshani 2012	L	L	H	L	H	L
Ramirez Valez 2011	L	L	H	L	H	L
Ramirez Valez 2013	U	U	U	U	U	U
Rauh 2013	L	L	H	H	L	U
Renault 2013	L	L	H	H	L	H
Ronnberg 2014	L	L	H	L	L	L
Ruiz 2013	L	U	U	U	L	U
Sagedal 2016	L	L	U	L	L	H
Santos 2005	L	U	U	U	U	L
Sedaghati 2007	U	U	U	U	H	L
Seneviratne 2015	L	L	U	U	L	L
Simmons 2016	L	L	U	L	L	L
Risk of bias:	L – low	U – unclear	H – high			

Study	Randomisation sequence	Allocation concealment	Blinding participants and personnel	Blinding of outcomes assessors	Incomplete outcome data	Selective reporting
Smith 2016	U	U	U	U	L	L
Sun 2016	H	H	U	U	L	L
Stafne 2012	L	L	H	H	L	L
Tomic 2013	H	H	U	U	L	L
Toosi 2016	L	U	H	U	L	L
Wang 2017	U	U	H	U	L	L
Thornton 2009	L	U	U	U	L	L
Vesco 2014	L	U	U	U	L	L
Vinter 2011	L	L	H	H	L	H
Vitolo 2011	L	H	H	L	L	H
Walsh 2013	L	L	H	U	L	H
Wolff 2008	L	L	U	H	H	L
Willcox 2017	L	L	H	U	L	L
Yeo unpub	U	U	U	U	U	U
Yeo 2000	L	L	H	L	L	L
Risk of bias:	L – low	U – unclear	H – high			

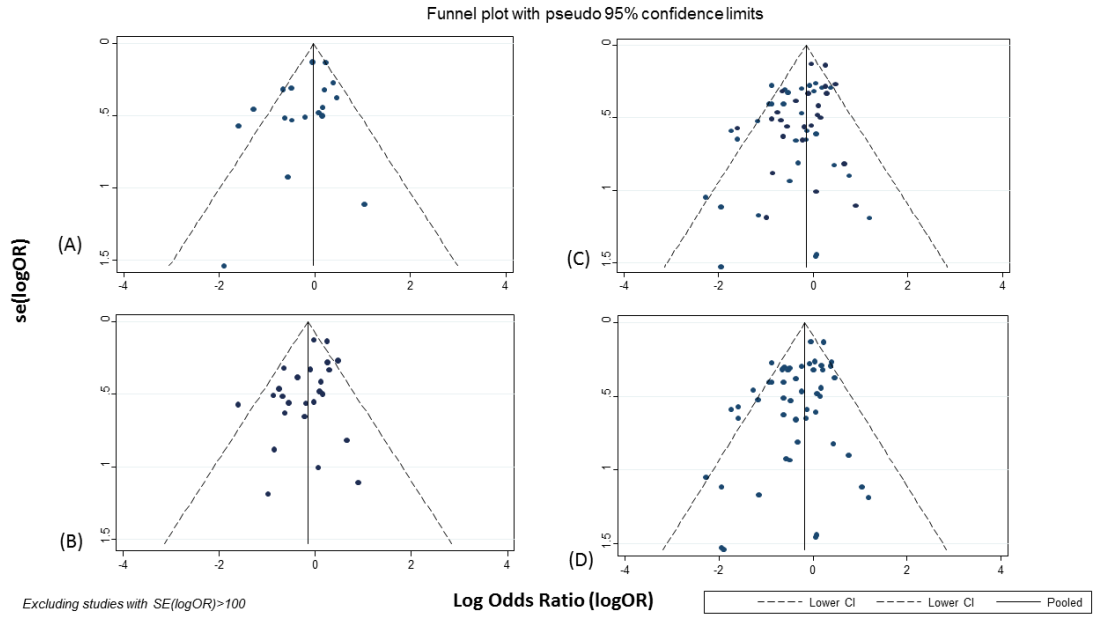
Appendix 4.6 Funnel plots for meta-analyses of trials on diet and physical activity based interventions

Gestational weight gain



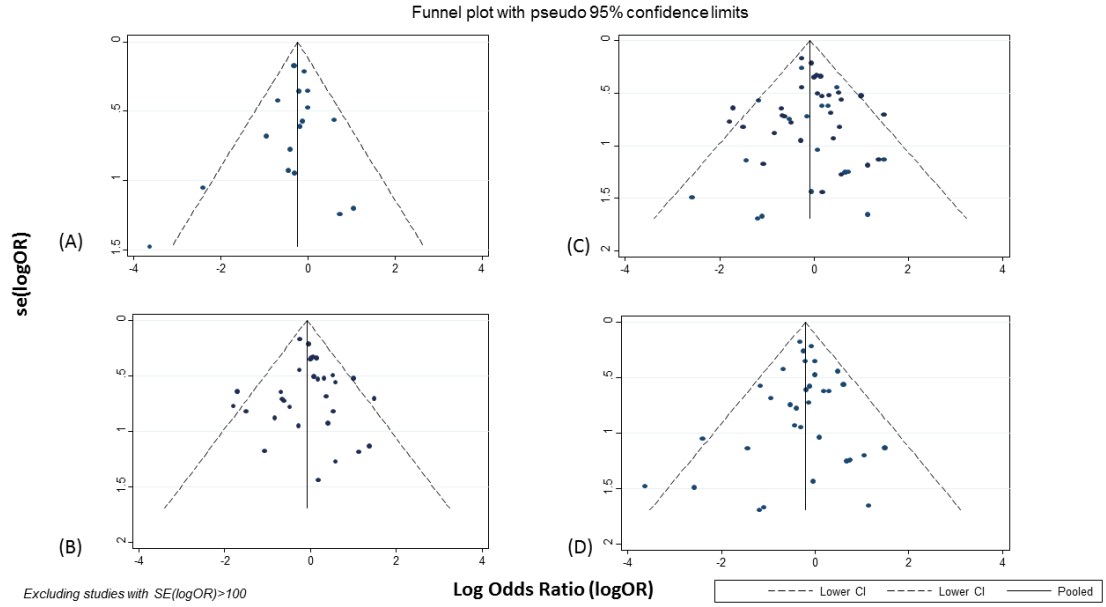
(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Gestational diabetes



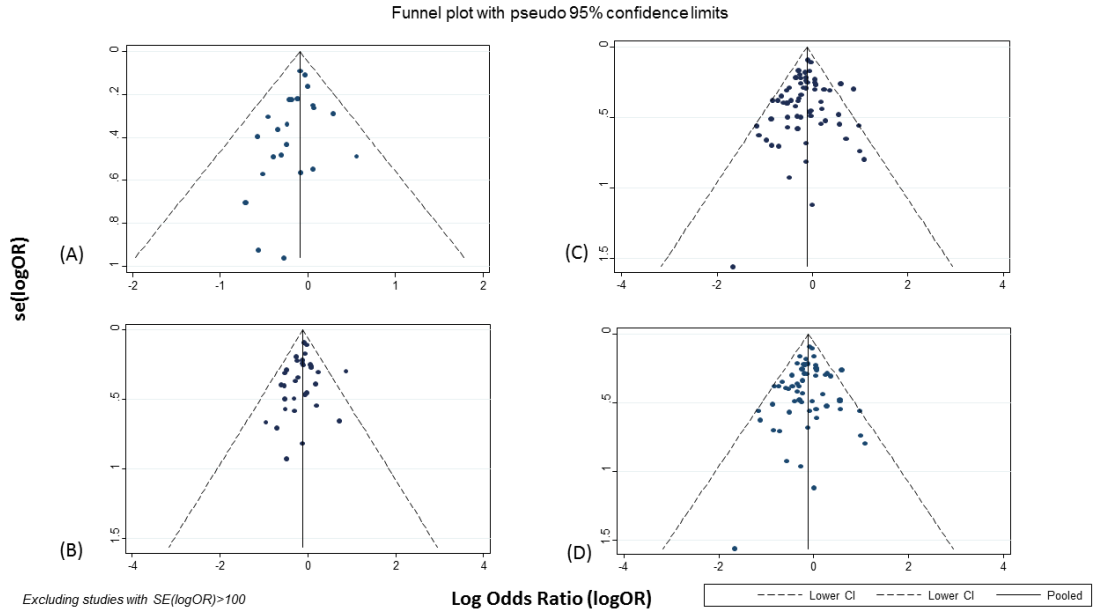
(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Preterm birth



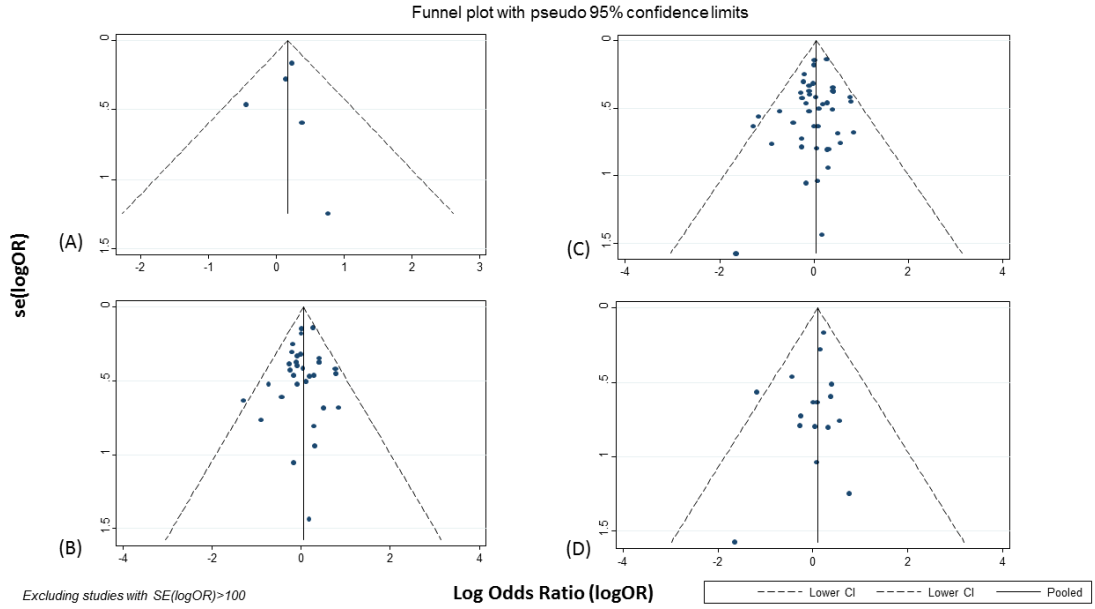
(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Caesarean section



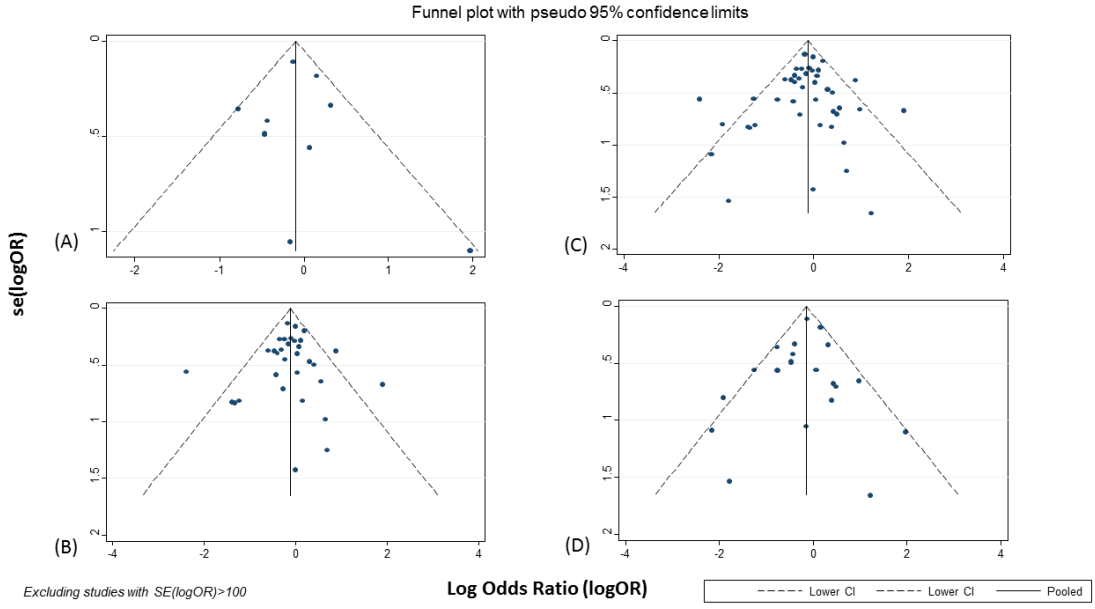
(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Small for Gestational Age (SGA)



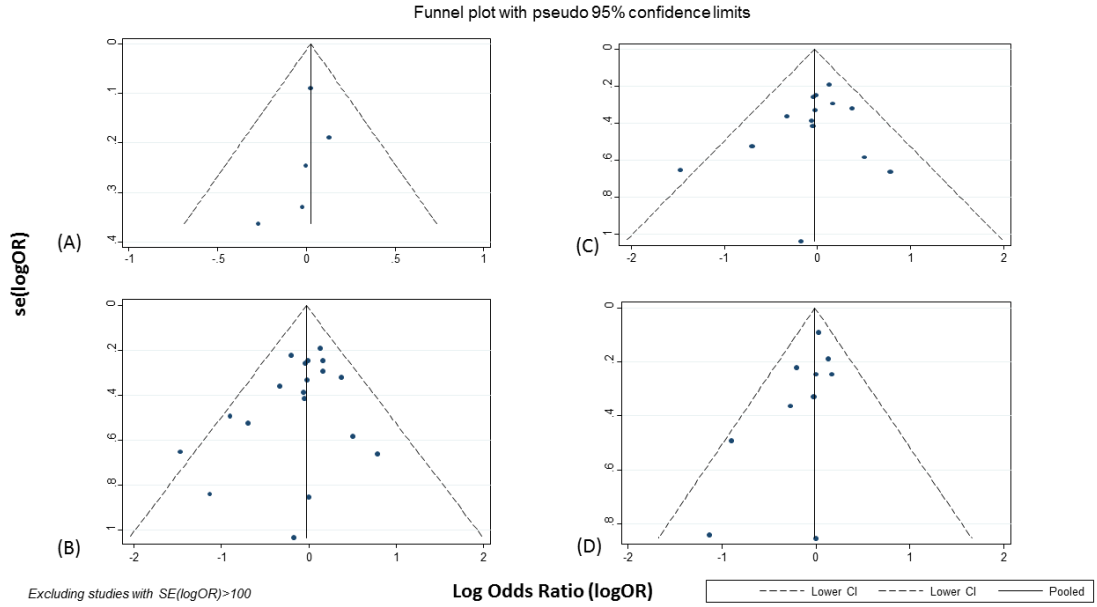
(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Large for Gestational Age (LGA)



(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Admission to Neonatal Intensive Care Unit (NICU)



(A) Study-level of only IPD trials; (B) Individual Participant Data; (C) IPD and study-level; (D) Study –level of all published trials

Appendix 4.7 Effect estimates derived from Individual Participant Data

Gestational weight gain

Study ID	ES	seES	Sample size
Althuizen 2012	0.450257	0.99408	191
Baciuk 2008	-1.66513	1.319366	69
Barakat 2008	-0.47299	0.592639	140
Barakat 2012a	-1.579053	0.487956	279
Bogaerts 2012	-3.220636	1.046076	197
Dodd 2014	-0.102647	0.276536	1586
Guelinckx 2010	0.184219	1.085839	168
Haakstad 2011	-0.72458	0.842061	82
Harrison 2013	-0.568627	0.418545	213
Hui 2011	-1.158225	0.891469	183
Jeffries 2009	-0.788455	0.528606	232
Khaledan 2010	-0.674955	0.680337	39
Khoury 2005	-0.620036	0.502042	198
Luoto 2011	-0.702901	0.550609	382
Nascimento 2011	-0.46649	0.942019	80
Ong 2009	-0.567741	1.299728	12
Oostdam 2012	0.134949	0.950506	80
Perales 2014	-1.197192	0.675496	164
Petrella 2013	-3.749265	1.502137	61
Phelan 2011	-0.515103	0.466411	389
Poston 2015	-0.172835	0.528419	415
Prevedel 2003	0.076834	0.853281	39
Rauh 2013	-1.675133	0.607498	226
Renault 2013	-1.041364	0.508377	376
Ruiz 2013	-1.074056	0.264285	927
Sagedal 2016	-0.768288	0.416029	575
Stafne 2012	-0.258392	0.186998	725
Vinter 2011	-1.132644	0.617247	292
Vitolo 2011	-0.508094	0.444175	292
Walsh 2012	-0.765013	0.358049	622
Wolff 2008	-2.198558	1.13611	56
Yeo 2000	-1.393053	2.068035	14

ES, effect estimate (here: Mean Difference), seES, standard error of effect estimate,

Gestational diabetes

Study ID	ES	seES	Sample size
Barakat 2008	-0.36849469	0.3819699	140
Barakat 2011	-0.19782574	0.5623516	67
Barakat 2012a	-0.68548432	0.515098	279
Bogaerts 2012	0.08134555	0.4813407	197
Dodd 2014	0.25264678	0.1349276	2199
El Beltagy 2013	-17.577264	2864.9277	93
Guelinckx 2010	0.89794013	1.1079748	170
Harrison 2013	-0.11370972	0.3286657	150
Hui 2011	-0.85629897	0.879438	178
Jeffries 2009	0.1108539	0.4148326	257
Khoury 2005	0.06317839	1.0070003	289
Luoto 2011	0.46609731	0.2690104	391
Nascimento 2011	-0.63990287	0.6271261	72
Ong 2009	-18.461306	7279.2081	13
Oostdam 2012	-0.55734566	0.5596459	102
Perales 2014	-0.22314345	0.6530473	163
Petrella 2013	-1.5998685	0.571972	61
Poston 2015	-0.03682727	0.1267981	1305
Rauh 2013	-0.88088878	0.5073073	234
Renault 2013	-0.7602864	0.4621562	359
Ruiz 2013	-0.6536812	0.318625	927
Sagedal 2016	0.25837647	0.2809408	578
Stafne 2012	0.28373445	0.3320668	698
Vinter 2011	0.15262963	0.5000527	304
Vitolo 2011	0.65232516	0.8152198	50
Walsh 2012	-0.04000533	0.5542469	92
Wolff 2008	-0.98941308	1.1858658	59

ES, effect estimate (here: log odds ratio), seES, standard error of effect estimate

Preterm birth

Study ID	ES	seES	Sample size
Althuizen 2012	-0.629296	0.72201	197
Baciuk 2008	-0.280302	0.946614	69
Barakat 2008	1.371479	1.131208	140
Barakat 2011	1.130361	1.181881	67
Barakat 2012a	0.319782	0.51884	279
Bogaerts 2012	0.364643	0.684917	197
Dodd 2014	-0.254295	0.169831	2139
El Beltagy 2013	-1.506923	0.82059	93
Guelinckx 2010	0.532708	0.818466	177
Haakstad 2011	0.581443	0.560164	101
Harrison 2013	0.518587	0.496589	215
Hui 2011	-0.840305	0.879046	183
Jeffries 2009	-0.258955	0.447638	257
Khoury 2005	-1.799033	0.773226	289
Luoto 2011	0.996546	0.52278	394
Nascimento 2011	1.482686	0.704326	78
Oostdam 2012	-1.077106	1.173179	97
Perales 2014	-0.49091	0.780328	165
Perales 2016	0.405464	0.926634	163
Petrella 2013	-19.44475	2259.364	61
Phelan 2011	0.005698	0.341554	389
Poston 2015	-0.05378	0.21302	1520
Prevedel 2003	0.581922	1.269431	39
Rauh 2013	-0.693148	0.648282	232
Renault 2013	0.07238	0.505073	411
Ruiz 2013	0.140046	0.336628	927
Sagedal 2016	-0.007247	0.353403	586
Stafne 2012	0.048833	0.327951	852
Vinter 2011	0.168137	0.530756	304
Vitolo 2011	-1.71778	0.640655	293
Walsh 2012	-0.670092	0.711171	703
Wolff 2008	0.17589	1.439	59

ES, effect estimate (here: log odds ratio), seES, standard error of effect estimate

Caesarean section

Study ID	ES	seES	Sample size
Althuizen 2012	-0.281182	0.364428	199
Baciuk 2008	-0.530628	0.495164	70
Barakat 2008	-0.067823	0.464495	140
Barakat 2011	-0.517018	0.568658	67
Barakat 2012a	-0.535422	0.30806	279
Bogaerts 2012	-0.239059	0.338778	197
Dodd 2014	-0.089633	0.090508	2137
El Beltagy 2013	-0.030772	0.452117	93
Guelinckx 2010	0.178192	0.388622	177
Haakstad 2011	-0.960743	0.66252	59
Harrison 2013	0.863298	0.296343	215
Hui 2011	-0.491408	0.926239	168
Jeffries 2009	0.066182	0.269686	257
Khaledan 2010	-0.711166	0.704462	39
Khoury 2005	-0.538822	0.398729	289
Luoto 2011	0.227199	0.303525	394
Nascimento 2011	-0.315474	0.492255	78
Oostdam 2012	-0.309661	0.579334	105
Perales 2014	-0.610763	0.393796	165
Petrella 2013	0.187599	0.542858	61
Phelan 2011	-0.125789	0.238685	342
Poston 2015	-0.035199	0.107015	1520
Prevedel 2003	0.708651	0.653393	39
Rauh 2013	-0.481158	0.287668	232
Renault 2013	-0.242285	0.21886	414
Ruiz 2013	-0.059256	0.170007	881
Sagedal 2016	0.050169	0.248779	587
Stafne 2012	-0.126525	0.217977	851
Vinter 2011	0.069769	0.261587	304
Vitolo 2011	-0.107631	0.250861	292
Walsh 2012	-0.263815	0.192839	700
Wolff 2008	-0.133531	0.812843	59

ES, effect estimate (here: log odds ratio), seES, standard error of effect estimate

Large for gestational age

Study ID	ES	seES	Sample size
Althuizen 2012	0.064351	0.332771	229
Baciuk 2008	0.544112	0.642315	70
Barakat 2008	-1.390385	0.820693	140
Barakat 2011	0.693147	1.25	67
Barakat 2012a	-1.237948	0.81097	279
Bogaerts 2012	0.036716	0.562388	197
Dodd 2014	-0.186563	0.127125	2199
El Beltagy 2013	-2.404239	0.558057	93
Guelinckx 2010	-0.471857	0.370974	195
Haakstad 2011	0.293806	0.463687	101
Harrison 2013	0.887707	0.373173	238
Hui 2011	-0.237294	0.446524	183
Jeffries 2009	-0.166303	0.312092	282
Khaledan 2010	0.641854	0.976029	39
Khoury 2005	-0.312756	0.360691	289
Luoto 2011	-0.359532	0.268775	395
Nascimento 2011	-0.435318	0.580941	82
Oostdam 2012	1.910543	0.668601	105
Perales 2014	-1.341843	0.83218	165
Perales 2016	-0.012423	1.422971	163
Petrella 2013	0.139262	0.811059	61
Phelan 2011	-0.094738	0.259592	393
Poston 2015	0.187199	0.193071	1554
Prevedel 2003	-17.80793	3367.344	39
Rauh 2013	0.395453	0.495525	244
Renault 2013	-0.035516	0.285067	425
Ruiz 2013	-0.608843	0.368008	927
Sagedal 2016	-0.249216	0.267835	600
Stafne 2012	0.106696	0.279196	854
Vinter 2011	0.028987	0.396677	304
Vitolo 2011	-0.398085	0.391981	301
Walsh 2012	-0.007288	0.15375	759
Wolff 2008	-0.282863	0.706121	59
Yeo 2000	20.27408	4137.378	16

ES, effect estimate (here: log odds ratio), seES, standard error of effect estimate

Small for gestational age

Study ID	ES	seES	Sample size
Althuizen 2012	-0.251659	0.425426	197
Baciuk 2008	0.837247	0.680559	69
Barakat 2008	0.7817	0.449593	140
Barakat 2011	0.287682	0.806226	67
Barakat 2012a	-0.214255	0.304595	279
Bogaerts 2012	0.04025	0.416234	197
Dodd 2014	0.011783	0.145345	2137
El Beltagy 2013	0.307827	0.939271	87
Guelinckx 2010	-0.439672	0.609046	177
Haakstad 2011	0.508119	0.684167	88
Harrison 2013	0.405465	0.375859	215
Hui 2011	0.188836	0.468184	183
Jeffries 2009	-0.274199	0.384784	256
Khaledan 2010	-21.63677	7868.748	39
Khoury 2005	-0.089034	0.398805	287
Luoto 2011	0.286462	0.461252	394
Nascimento 2011	-1.292768	0.631236	78
Oostdam 2012	0.105361	0.50277	96
Perales 2014	0.771351	0.417465	163
Perales 2016	0.398496	0.374174	163
Petrella 2013	-0.897942	0.763211	58
Phelan 2011	-0.172658	0.461765	377
Poston 2015	0.266571	0.138488	1520
Prevedel 2003	-0.17185	1.055998	39
Rauh 2013	-0.728239	0.520752	231
Renault 2013	-0.012526	0.317471	411
Ruiz 2013	-0.001215	0.179354	927
Sagedal 2016	0.401208	0.345554	586
Stafne 2012	-0.192311	0.250363	852
Vinter 2011	-0.103022	0.374503	303
Vitolo 2011	-0.099271	0.331179	290
Walsh 2012	-0.098542	0.523154	701
Wolff 2008	0.17589	1.439	59

ES, effect estimate (here: log odds ratio), seES, standard error of effect estimate

Admission to Neonatal Intensive Care Unit

Study ID	ES	seES	Sample size
Bogaerts 2012	0.7815578	0.65979291	195
Dodd 2014	-0.041112	0.25569686	2199
Guelinckx 2010	13.797323	1834.2978	182
Harrison 2013	0.3676373	0.32001206	215
Jeffries 2009	-0.0521861	0.4138228	256
Khoury 2005	-1.4736638	0.65185031	289
Luoto 2011	0.1633553	0.29298172	391
Oostdam 2012	-0.7024785	0.52340718	62
Petrella 2013	-0.1758908	1.0347559	61
Phelan 2011	-0.0632624	0.38672555	378
Poston 2015	0.1279526	0.19045119	1554
Rauh 2013	11.624728	486.09195	231
Renault 2013	0.5050779	0.581917	399
Sagedal 2016	-0.011788	0.24594802	585
Stafne 2012	-0.3301969	0.35919882	839
Vinter 2011	-0.0235308	0.32924349	304

ES, effect estimate (here: log odds ratio), seES, standard error of effect estimate

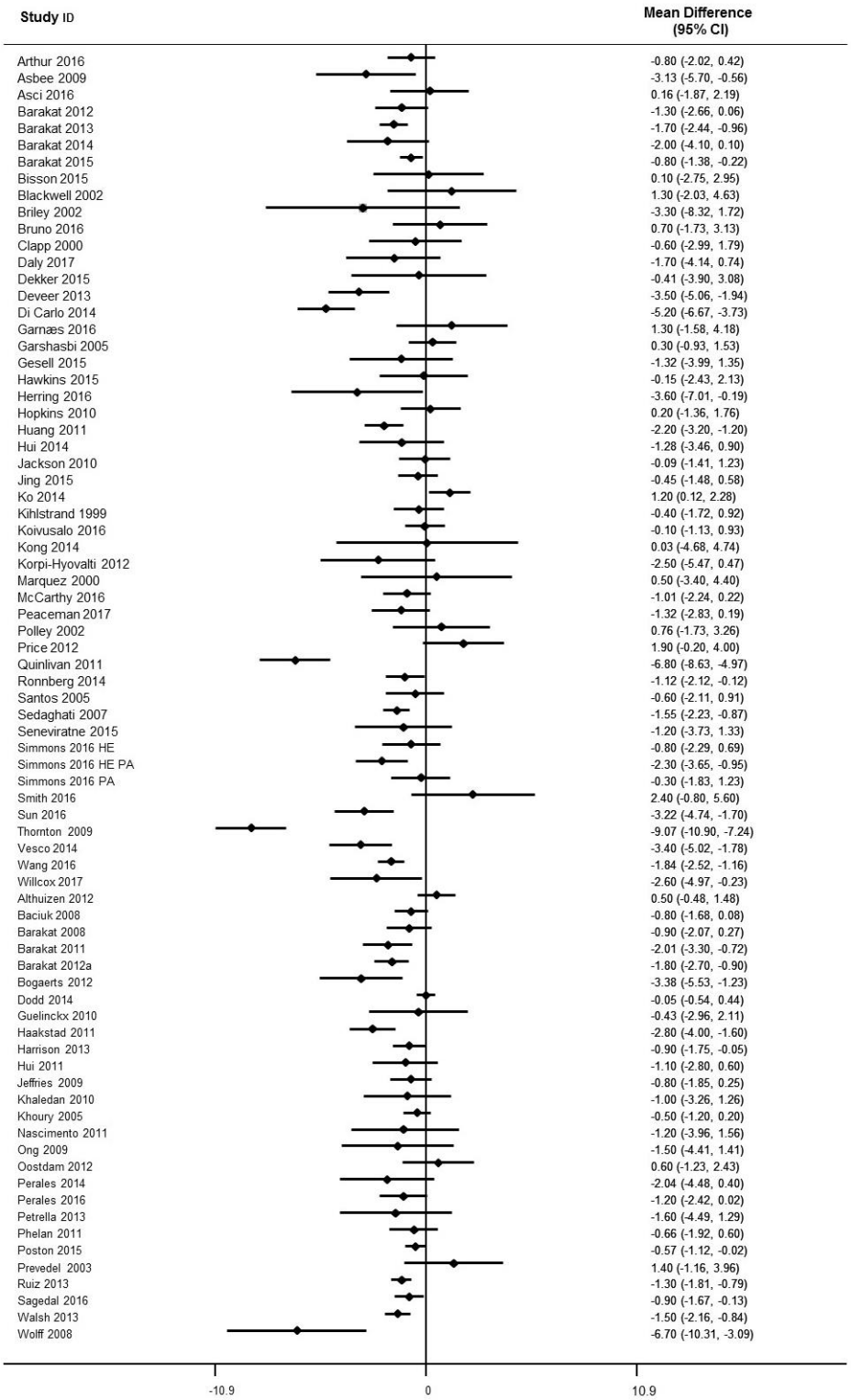
Appendix 4.8 Effect estimates and their precision for binary outcomes derived from the study-level meta-analysis with numbers of randomised as a reference sample size

Outcome	Number of studies (Number of participants)	Odds ratio (95% CI)
Gestational diabetes	50 (18 457)	0.75 (0.64, 0.89)
Caesarean section	58 (17 406)	0.90 (0.84, 0.97)*
Preterm birth	34 (12 444)	0.80 (0.67, 0.95)
Large for gestational age	21 (7 451)	0.82 (0.62, 1.10)
Small for gestational age	16 (4 459)	1.10 (0.87, 1.40)
Admission to NICU	10 (7 063)	0.99 (0.85, 1.15)

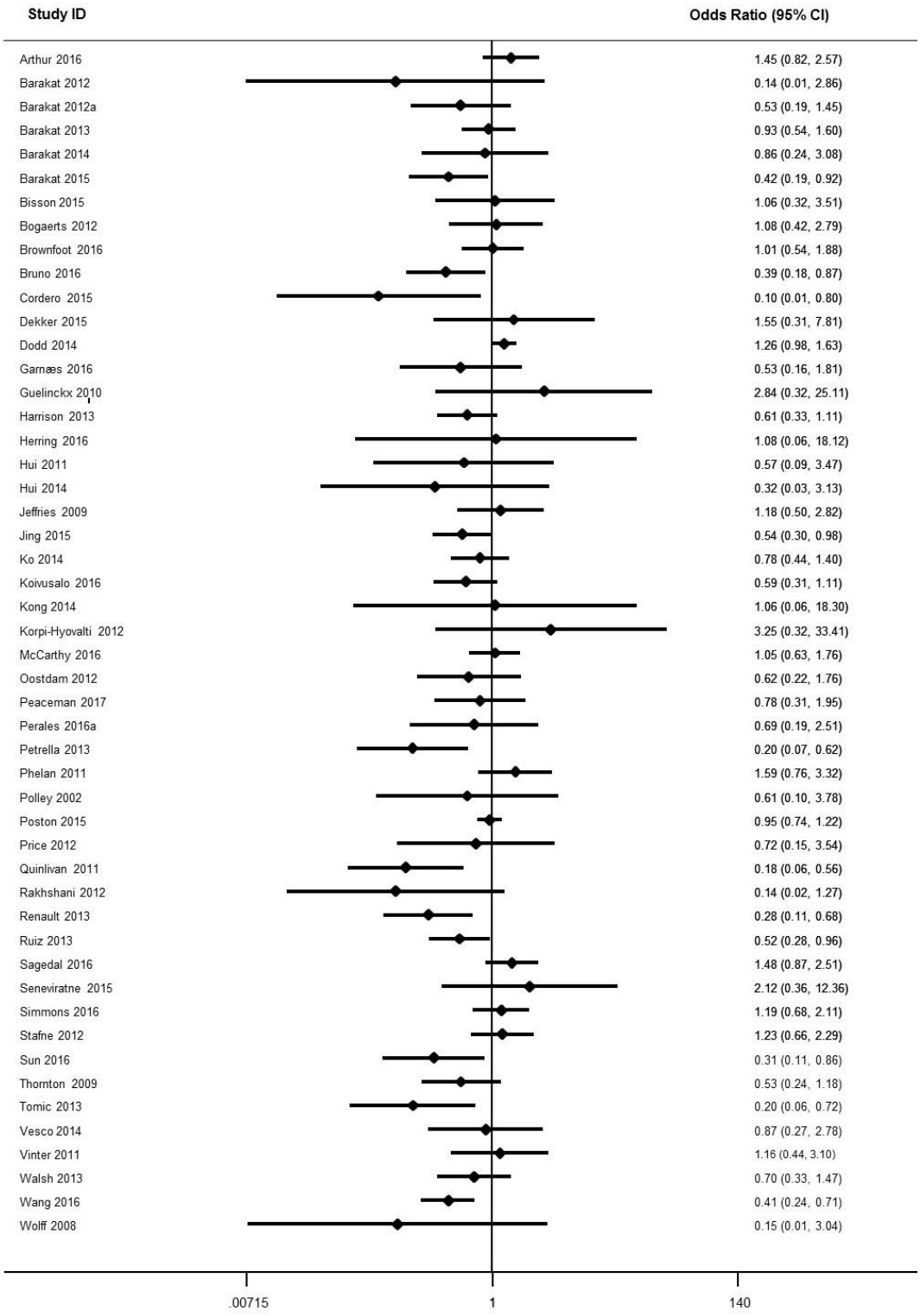
**DerSimonian and Laird method; REML did not converge;*

Appendix 4.9 Forest plots with the individual effect estimates derived from study-level data

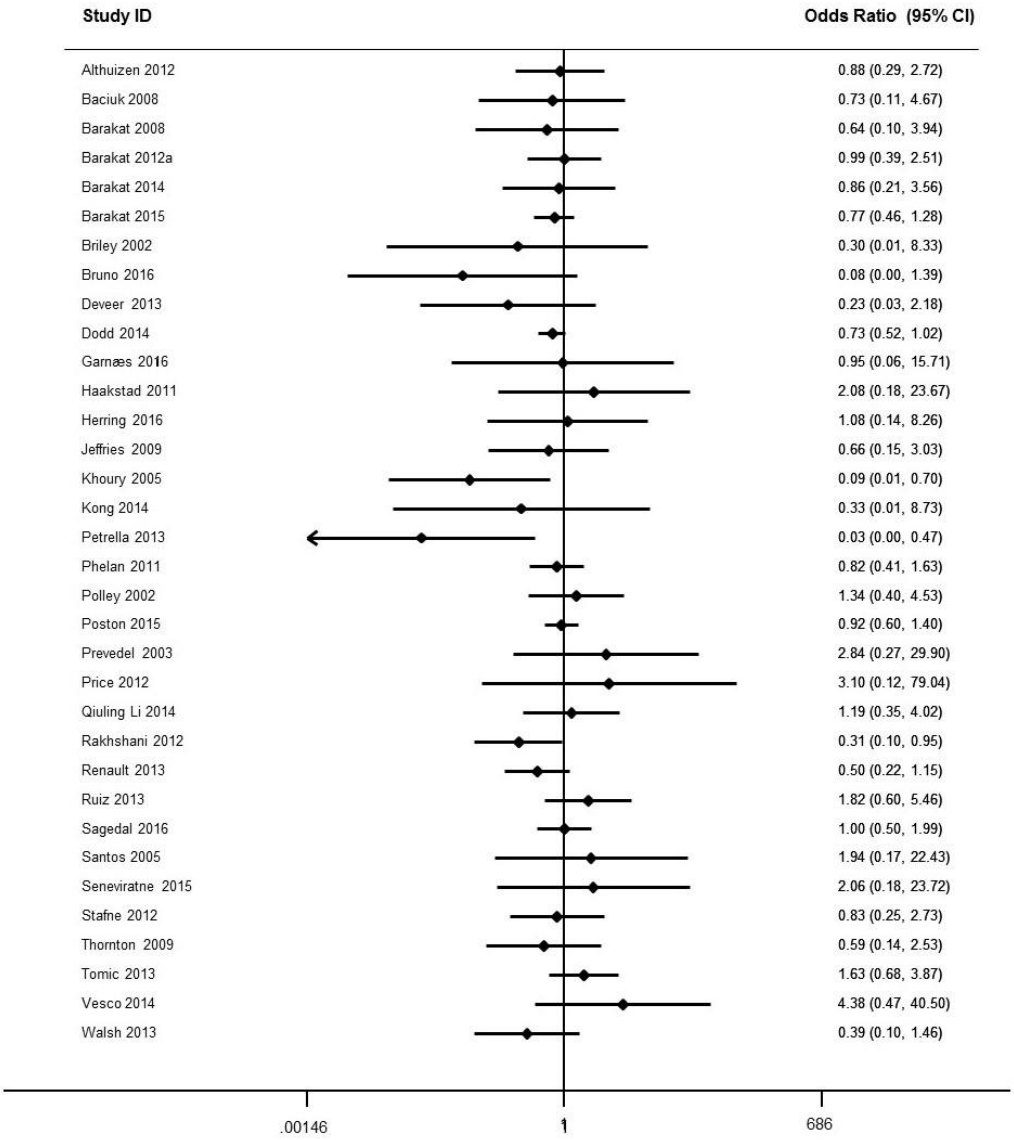
Gestational weight gain



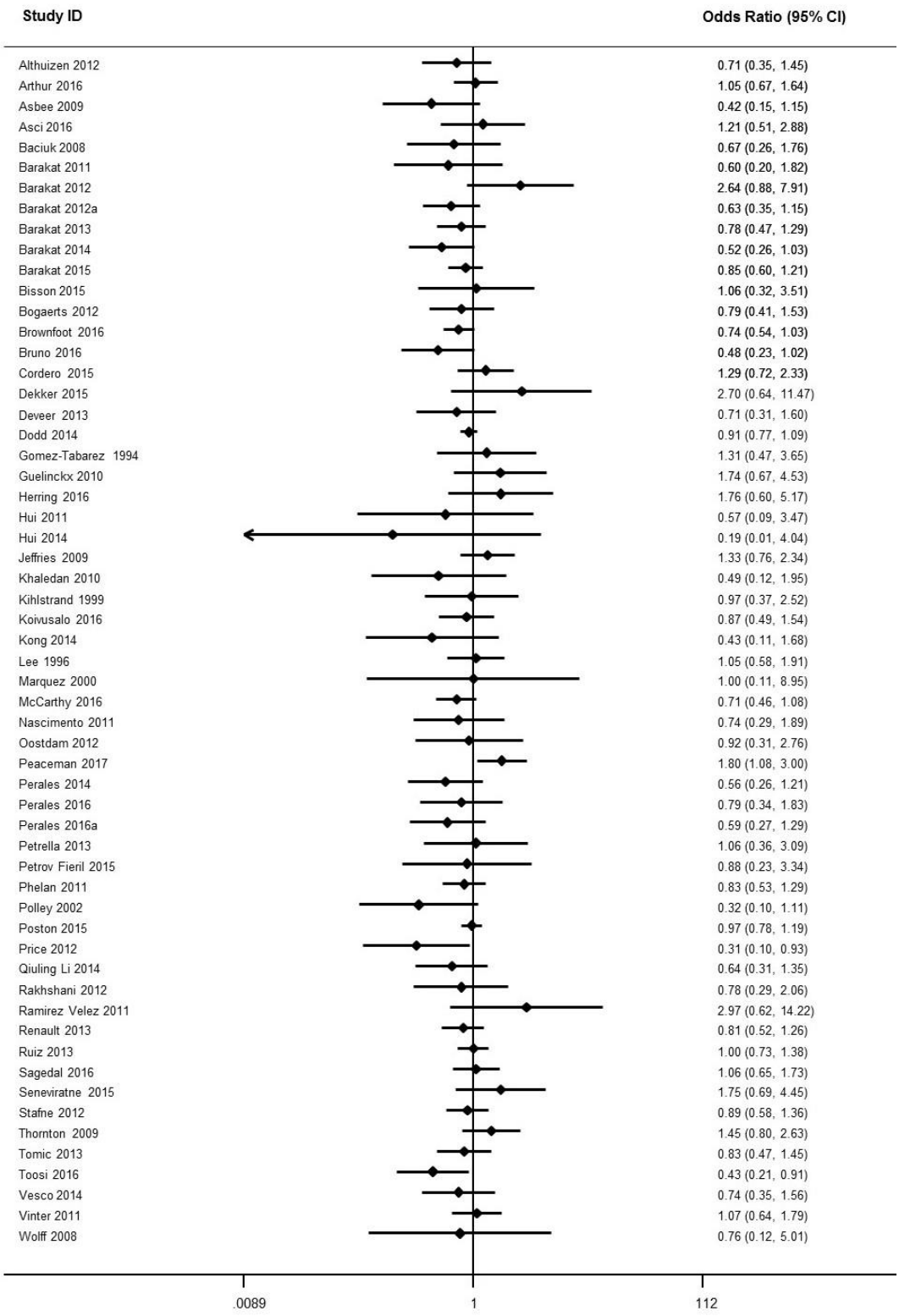
Gestational diabetes



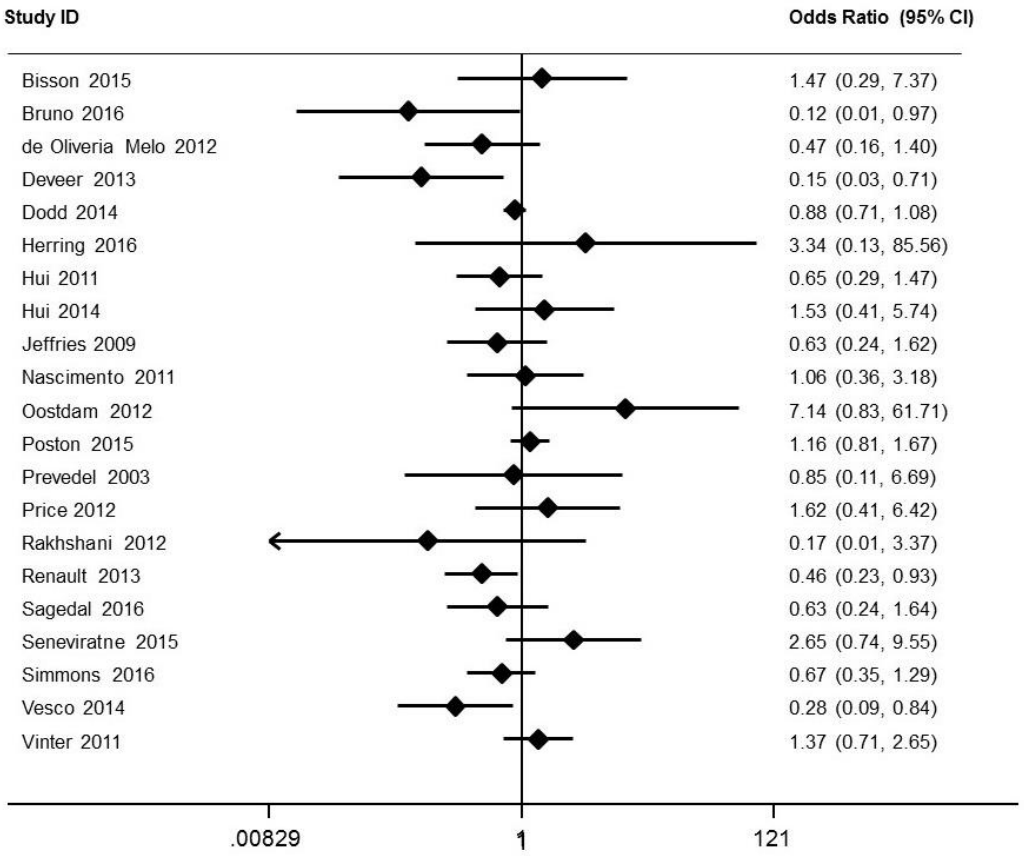
Preterm birth



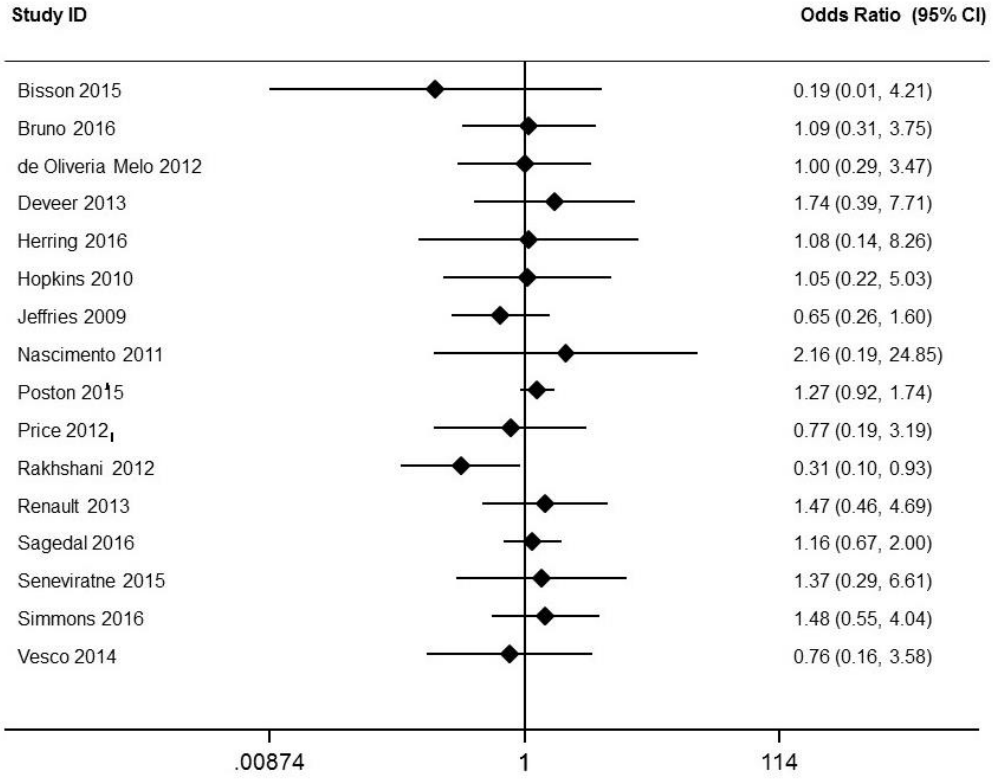
Caesarean section



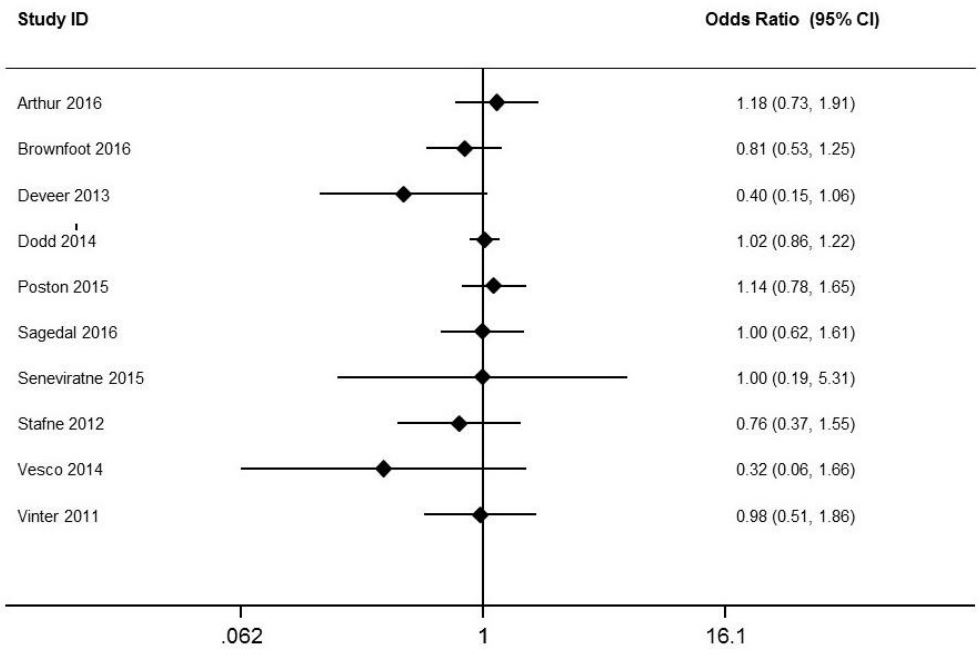
Large for gestational age



Small for gestational age



Admission to Neonatal Intensive Care Unit



1350 Appendix 4.10 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 Number of participants Intervention 80 Control 80	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. 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	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,

Study Year Language	Participants	Interventions	Control	Outcomes
Barakat 2012a 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 Intervention 160 Control 160	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 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	Usual care	• Type of delivery (Normal, instrumental, Caesarean) • 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

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Study Year Language	Participants	Interventions	Control	Outcomes
Dodd 2011 (LIMIT)	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 behavioral 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 fiber, 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 behavioral 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 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).	Usual hospital guidelines, with no routine provision of dietary, lifestyle and behavioral 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 • 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 ≥ 600 mL); • Perineal trauma • Wound infection; • Endometritis • Use of postnatal antibiotics • Length of postnatal hospital stay; • Thromboembolic disease • Maternal death

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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) 65 Intervention (Passive) 65 Control 65	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 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.	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

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

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. Particpant 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

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Study Year Language	Participants	Interventions	Control	Outcomes
Khoury 2005 English	Inclusion criteria: • 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 • Not vegetarian or following a Mediterranean-type diet Exclusion criteria: • High-risk pregnancies caused by: diabetes, endocrine disease, hypertension, drug abuse, 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) • Number of participants Intervention 141 Control 149	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 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.	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

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)

Study Year Language	Participants	Interventions	Control	Outcomes
Ong 2009 English	Inclusion criteria: • Singleton pregnancy • Normal 18 week anatomy scan • No evidence of cardiovascular disease • No preexisting diabetes Number of participants Intervention 6 Control 6	Physical activity: home-based 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.	No intervention	• Weight gain from 18 to 28 weeks • Post-intervention glucose and insulin levels on oral glucose tolerance test

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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). Number of participants Intervention 101 Control 83	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 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.	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

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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 • Women who just started regular physical activity, or used herbal products or dietary supplements known to affect body weight, Number of participants Intervention 33 Control 30	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 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’)	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.

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 Intervention 783 Control 772	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 not fruit and reduce saturated fatty acid intake.	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 • Insulin or metformin treatment in pregnancy • Quality of life • Anthropometry including mid-arm, hip, thigh circumference and skin-fold thickness • Diet and physical activity • Depression • Smoking • Birthweight of baby • Gestational age at delivery • Neonatal death • Neonatal complications • Baby's anthropometry including head/abdominal circumference and skin-fold thickness

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 (83)	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 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	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

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 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.	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

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 recommendations 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

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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

Study Year Language	Participants	Interventions	Control	Outcomes
Walsh 2012 English Number of participants Intervention 394 Control 406	Inclusion criteria: • Secundigravid women with previous macrosomic infant (birthweight > 4 kg) 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	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 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").	Routine antenatal care with no specific dietary recommendation or advice about gestational weight gain.	Primary: • Mean birth weight centiles and ponderal indices at 14, 28 and 34 weeks gestation, at birth and 3 months post-partum 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

1361

Study Year Language	Participants	Interventions	Control	Outcomes
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

1362

Study Year Language	Participants	Interventions	Control	Outcomes
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

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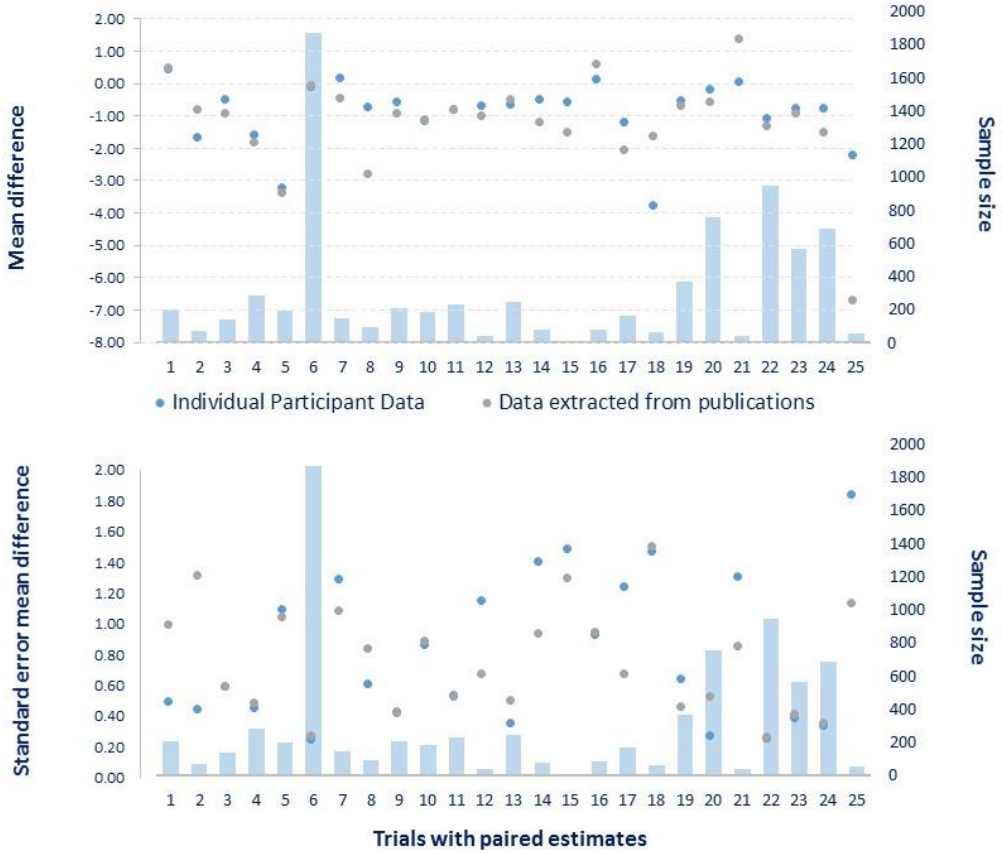
Study Year Language	Participants	Interventions	Control	Outcomes
Yeo Unpublished (Protocol) English	Inclusion criteria Gestational age less than 12 weeks gestation plus one or more of the following: • History of preeclampsia • Type 2 diabetes • Chronic hypertension • BMI ≥ 30 kg/m2 either pre-pregnancy or at first visit in the first trimester for primiparous women • Diastolic blood pressure ≥ 90 mmHg before 12 weeks gestation Exclusion criteria: • Multiple pregnancy • Vaginal bleeding • Diagnosed placenta previa • Any condition prohibiting regular exercise (walking exercise and stretching) between 12 to 22 weeks gestation • 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	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 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	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

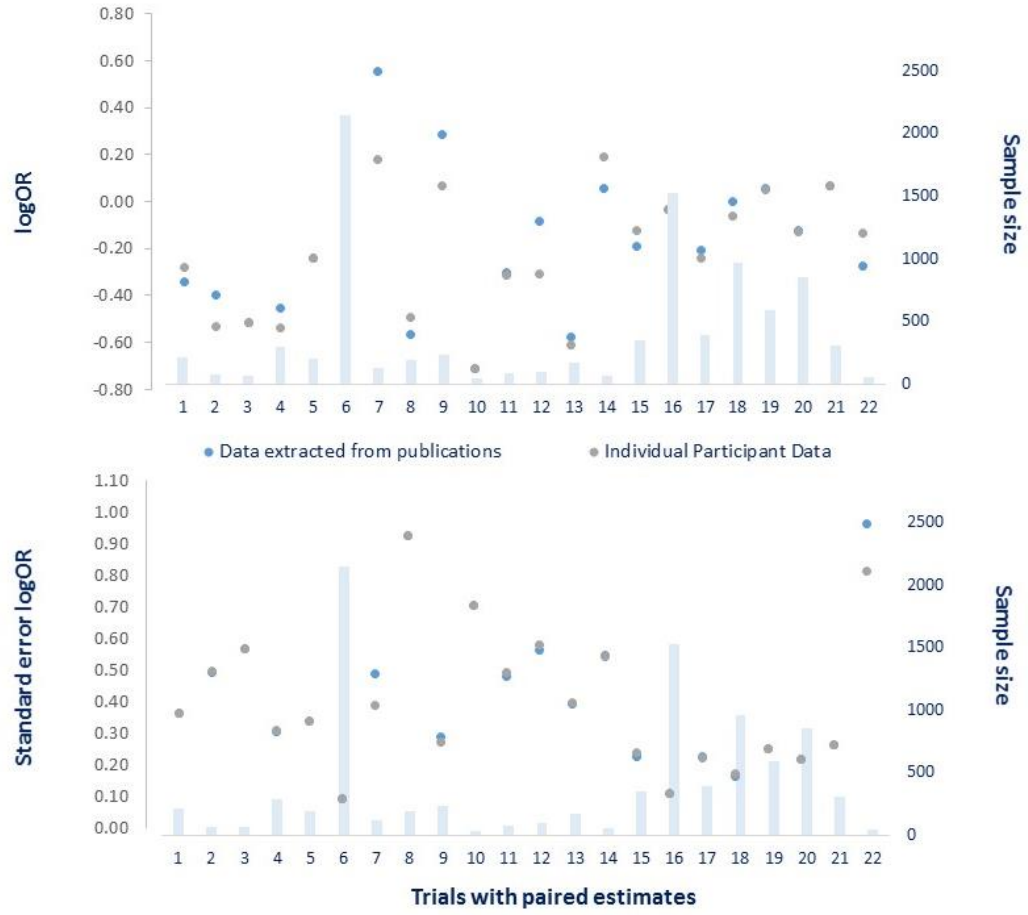
Appendix 4.11 Comparison of the effect estimates derived from study-level and Individual Participant Data in the group of trials contributing to the i-WIP IPD meta-analysis

		Difference between MD (kg)			Difference between se MD (kg)		
Continuous measure	*n of pairs*	median	min	max	median	min	max
Gestational weight gain	*25*	0.40	0.01	4.50	0.14	0.00	0.87
		Difference between logOR			Difference between se logOR		
Binary measures	*n of pairs*	median	min	max	median	min	max
Caesarean section	*22*	0.05	0.00	0.38	0.00	0.00	0.15
Preterm	*17*	0.28	0.00	15.81	0.08	0.00	2257.89
GDM	*17*	0.08	0.00	0.91	0.01	0.00	0.35
LGA	*10*	0.25	0.04	17.65	0.07	0.01	3366.3
SGA	*5*	0.25	0.03	2.06	0.08	0.02	0.61
Admission to NICU	*5*	0.01	0.00	0.07	0.00	0.00	0.17

Gestational weight gain



Caesarean section



Appendix 5.1 Interactions between the effects of the interventions and women's BMI – meta-regression using study-level data extracted from publications (i-WIP studies)

Outcome	Number of studies	Interaction term for one unit of change in average BMI	I^2 (%)
		Coef. (95% CI)	
Gestational weight gain	25	0.01 (-0.08, 0.11)	60.5%
		OR (95% CI)	
Gestational diabetes	17	0.98 (0.93, 1.05)	44.2
Preterm birth	16	0.98 (0.91, 1.04)	4.0
Caesarean section	22	1.01 (0.99, 1.03)	0.0

OR, odds ratio; CI, Confidence Interval; BMI, Body Mass Index;

1382 Appendix 6.1 Characteristics of included papers from RCTs on diet and physical activity in pregnancy

Paper ID	Publication Type	Journal language	Trial Type	Country	Obstetrics & Gynecology Journal	Specialist/ General Journal	Intervention Type	Impact Factor[#]
Althuizen 2012	primary	English	main	The Netherlands	Yes	specialist	Mixed	3.407
Asbee 2009	primary	English	main	US	Yes	specialist	Mixed	4.357
Baciuk 2008 RepH08	primary	English	main	Brazil	Yes	specialist	Exercise	1.084
Baciuk 2008 RepH09	subsequent	English	main	Brazil	Yes	specialist	Exercise	1.167
Barakat 2008 BrJSpM	primary	English	main	Spain	No	specialist	Exercise	2.126
Barakat 2008 IntJOb	subsequent	English	main	Spain	No	specialist	Exercise	4.343
Barakat 2011	primary	English	main	Spain	Yes	specialist	Exercise	3.468
Barakat 2012	primary	English	main	Spain	No	specialist	Exercise	3.668
Barakat 2012a	primary	English	main	Spain	Yes	specialist	Exercise	1.495
Barakat 2013	primary	English	main	Spain	No	specialist	Exercise	3.668
Blackwell 2002	primary	English	main	US	No	specialist	Diet	0.457
Bogaerts 2012	primary	English	main	Belgium	No	specialist	Mixed	4.691
Briley 2002	primary	English	main	US	No	specialist	Diet	2.868
Callaway 2010 ANZJObsGyn	subsequent	English	pilot	Australia	Yes	specialist	Exercise	1.620
Callaway 2010 BMCPregC	subsequent	English	pilot	Australia	Yes	specialist	Exercise	2.834
Callaway 2010 DiabCare	primary	English	pilot	Australia	No	specialist	Exercise	7.141
Clapp 2000	primary	English	main	US	Yes	specialist	Exercise	2.600

Paper ID	Publication Type	Journal language	Trial Type	Country	Obstetrics & Gynecology Journal	Specialist/ General Journal	Intervention Type	Impact Factor[#]
de Oliveria Melo 2012	primary	English	main	Brazil	Yes	specialist	Exercise	4.730
Deveer 2013	primary	English	main	Turkey	No	specialist	Diet	1.093
Di Carlo 2014	primary	English	main	Italy	Yes	specialist	Diet	1.279
Dodd 2014 BMCMed	subsequent	English	main	Australia	No	general	Mixed	7.280
Dodd 2014 BMJ	primary	English	main	Australia	No	general	Mixed	16.3
Garshasbi 2005	primary	English	main	Iran	Yes	specialist	Exercise	0.952
Gomez Tabares 1994	primary	Non-English	main	Colombia	Yes	specialist	Diet	N/A
Guelinckx 2010	primary	English	main	Belgium	No	specialist	Mixed	6.606
Haakstad 2011 BMCPregC	subsequent	English	main	Norway	Yes	specialist	Exercise	2.834
Haakstad 2011 EurJCRepH	primary	English	main	Norway	Yes	specialist	Exercise	1.456
Harrison 2013 IntJBehNPA	subsequent	English	main	Australia	No	specialist	Mixed	3.680
Harrison 2013 Obes	primary	English	main	Australia	No	specialist	Mixed	4.389
Hawkins 2015	primary	English	pilot	US	No	specialist	Mixed	3.064
Hopkins 2010	primary	English	main	New Zealand	No	specialist	Exercise	6.495
Huang 2011	primary	English	main	Taiwan	No	specialist	Mix	1.777
Hui 2006	primary	English	pilot	Canada	No	specialist	Mix	0.411
Hui 2011	primary	English	main	Canada	Yes	specialist	Mix	3.407
Hui 2014	primary	English	main	Canada	Yes	specialist	Mix	2.150

Paper ID	Publication Type	Journal language	Trial Type	Country	Obstetrics & Gynecology Journal	Specialist/ General Journal	Intervention Type	Impact Factor[#]
Jackson 2010	primary	English	main	US	No	specialist	Mix	2.237
Jeffries 2009	primary	English	main	Australia	No	specialist	Mix	2.894
Jing 2015	primary	English	main	China	Yes	specialist	Mixed	1.563
Khaledan 2010	primary	Non-English	main	Iran	No	specialist	Exercise	N/A
Khoury 2005	primary	English	main	Norway	Yes	specialist	Diet	3.100
Kong 2014	primary	English	pilot	US	No	specialist	Exercise	4.459
Korpi-Hyovalti 2012	primary	English	main	Finland	No	specialist	Diet	3.013
Lee 1996	primary	English	main	UK	No	specialist	Exercise	N/A
Luoto 2011 EurJClinNut	subsequent	English	main	Finland	No	specialist	Mixed	2.462
Luoto 2011 PlosMed	primary	English	main	Finland	No	general	Mix	14.659
Marquez 2000	primary	English	main	US	No	specialist	Exercise	2.363
Nascimento 2011	primary	English	main	Brazil	Yes	specialist	Exercise	3.407
Ong 2009	primary	English	main	Australia	No	specialist	Exercise	2.426
Oostdam 2012	primary	English	main	The Netherlands	Yes	specialist	Exercise	3.407
Perales 2014	primary	English	main	Spain	No	specialist	Exercise	1.482
Perales 2014a	primary	English	main	Spain	No	specialist	Exercise	1.415
Petrella 2013	primary	English	main	Italy	Yes	specialist	Mixed	1.495
Phelan 2011	primary	English	main	US	No	specialist	Mixed	6.669

Paper ID	Publication Type	Journal language	Trial Type	Country	Obstetrics & Gynecology Journal	Specialist/ General Journal	Intervention Type	Impact Factor[#]
Polley 2002	primary	English	main	US	No	specialist	Mixed	2.706
Poston 2013	primary	English	pilot	UK	Yes	specialist	Mixed	2.834
Prevedel 2003	primary	Non-English	main	Brazil	Yes	specialist	Exercise	N/A
Price 2012	primary	English	pilot	US	No	specialist	Exercise	4.431
Qiuling Li 2014	primary	Non-English	main	China	No	general	Exercise	N/A
Quinlivan 2011	primary	English	main	Australia	Yes	specialist	Diet	1.237
Ramirez Velez 2011 JObsGyn	primary	English	main	Colombia	Yes	specialist	Exercise	0.942
Ramirez Velez 2011 RevSPub	subsequent	English	main	Colombia	No	specialist	Exercise	1.328
Rauh 2013	primary	English	main	Germany	Yes	specialist	Mixed	2.150
Renault 2013	primary	English	main	Denmark	Yes	specialist	Mixed	3.468
Ronnberg 2014	primary	English	main	Sweden	Yes	specialist	Exercise	3.862
Ruiz 2013	primary	English	main	Spain	No	general	Exercise	5.698
Santos 2005	primary	English	main	Brazil	Yes	specialist	Exercise	3.700
Sedaghati 2007	primary	English	main	Iran	No	general	Exercise	N/A
Stafne 2012 BJOG	subsequent	English	main	Norway	Yes	specialist	Exercise	3.407
Stafne 2012 ObsGyn	primary	English	main	Norway	Yes	specialist	Exercise	4.730
Thornton 2009	primary	English	main	US	No	general	Diet	1.275
Vesco 2014	primary	English	main	US	No	specialist	Mixed	4.389

Paper ID	Publication Type	Journal language	Trial Type	Country	Obstetrics & Gynecology Journal	Specialist/ General Journal	Intervention Type	Impact Factor[#]
Vinter 2011 AOGS	subsequent	English	main	Denmark	Yes	specialist	Mixed	2.005
Vinter 2011 DiabCare	primary	English	main	Denmark	No	specialist	Mixed	8.087
Vinter 2011 DiabMed	subsequent	English	main	Denmark	No	specialist	Mixed	3.064
Vitolo 2011	primary	Non-English	main	Brazil	Yes	specialist	Diet	0.608
Walsh 2012	primary	English	main	Ireland	No	general	Diet	17.215
Wolff 2008	primary	English	main	Denmark	No	specialist	Diet	3.640
Yeo 2000	primary	English	main	US	Yes	specialist	Exercise	0.878

N/A – not available
[#]*the Thomson Reuters*

1387 Appendix 6.2 List of measured outcomes reported in articles from trials with diet and physical
1388 activity interventions in pregnancy not covered by the Delphi ranking

Measured outcomes	Number of studies
Adequate for gestational age	3
Adherence to intervention	7
Admission to SCBU	1
Anal incontinence	1
Antepartum hospital admissions	2
Biomarkers: insulin resistance	12
Birth injury (Neonate)	1
Bleeding	1
Blood pressure (Mother)	14
Blood pressure Postpartum (Mother)	1
Body image (Mother)	2
Bone density (Neonate)	1
Breathlessness	1
Calf pain	1
Cardiovascular capacity (Mother)	1
Chest pain	1
Child weight development	1
Chronic hypertension	1
Composite: maternal morbidity	1
Composite: Vascular complications	1
Delivery: Mode of delivery	2
Delivery: post term	3
Delivery: term	1
Delivery: vaginal	14
Discharged home on oxygen	1
Dizziness	1
Endometritis (Mother)	1
Energy expenditure (Mother)	2
Energy intake	4
Excessive weight gain IOM	23
Fatigue	3
Fecal incontinence	1
Fetal blood circulation	1
Fetal distress	1
Fetal Harte Rate (FHR)	1
Fitness level	6
Flexibility of spine	1
Food intake	13
Food knowledge	1
Gender (Neonate)	6
Gestational age at delivery	47
Headache	1

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Measured outcomes	Number of studies
Health promoting behavior	1
Health Questionnaire (Mother)	1
Hospitalization Postpartum	1
Intrauterine growth restriction	2
Ketonuria (Mother)	1
Knowledge of weight gain guidelines	1
Labor: Blood loss (Mother)	1
Labor: Chorioamnionitis (Mother)	1
Labor: Lacerations (Mother)	2
Labor: pain score	1
Level of physical activity Postpartum	1
Lipids level (Neonate)	1
Lipids levels (Mother)	4
Low Birthweight	10
Macrosomia	26
Maternal Harte Rate	2
Meconium	1
Metabolic parameters (Neonate)	1
Mother's death	3
Musculoskeletal problems	1
Nausea	3
Necrotizing enterocolitis (Neonate)	1
Need for GDM treatment	1
Neonatal asphyxia	1
Pain overall	2
Painful contractions	1
Patent ductus arteriosus	1
Pelvic girdle	1
Physical Discomfort	1
Placenta size	4
Polyhydramnios (Neonate)	1
Postpartum hospital stay	1
Postpartum recovery	1
Proven systemic infection (Neonate)	1
Respiratory disease (Neonate)	1
Respiratory Distress Syndrome (RDS)	1
Respiratory exchange (Mother)	2
Respiratory morbidity (Neonate)	1
Respiratory support	1
Retinopathy (Neonate)	1
Risk perception (Mother)	1
Seizures (Neonate)	1
Self-efficacy	1
Skin temperature (Mother)	1

1390

Appendix 6.3 Quality of outcome reporting in primary publications issued before and after update of CONSORT statement in 2001 and 2010

N	Median (IQR)	N	Median (IQR)	Wilcoxon rank-sum
Published ≤2001		**Published>2001**		**p-value**
5	0.25 (0.0, 0.5)	61	0.6 (0.25, 0.83)	0.19
Published ≤2010		**Published>2010**		
26	0.42 (0.25, 0.60)	40	0.67 (0.45, 0.83)	<0.01

Appendix 7.1 List of considered confounders for the relationship between gestational weight gain outside the Institute of Medicine ranges and adverse pregnancy outcomes

a) Outcome: any type of caesarean section

Considered confounders	Remarks
• Booking BMI (kg/m2)	Stratification factor
• Diabetes prior to pregnancy or in pregnancy	Mandatory confounder
• Age	Potential confounder (1)
• Gestational age at delivery	Potential confounder (2)
• Parity	Potential confounder (3)
• Smoking	Potential confounder (4)
• Education level	Potential confounder (5)
• Ethnic origin	Potential confounder (6)
• Exercise prior to pregnancy	Potential confounder (7)
• Pre-existing vascular disease such as hypertension	Potential confounder (8) Available as 'Baseline hypertension'
• Induction of labour	Potential confounder (9)
• Multiple pregnancy	Only singletons in the dataset
• Pregnancy interval of more than 10 years	*Information not available in the dataset*
• Family history of pre-eclampsia	*Information not available in the dataset*
• Previous history of pre-eclampsia	*Information not available in the dataset*
• Pre-existing renal disease	*Information not available in the dataset*
• Previous macrosomia	*Information not available in the dataset*

b) Outcome: baby born large for gestational age

Considered confounders	Remarks
• Booking BMI (kg/m2)	Stratification factor
• Diabetes prior to pregnancy or in pregnancy	Mandatory confounder, available as any diabetes related event
• Age	Potential confounder (1)
• Parity	Potential confounder (2)
• Smoking	Potential confounder (3)
• Education level	Potential confounder (4)
• Ethnic origin	Potential confounder (5)
• Exercise prior to pregnancy	Potential confounder (6)

Considered confounders	Remarks
• Pre-existing vascular disease such as hypertension	Potential confounder (7), baseline hypertension
• Multiple pregnancy	Dataset with singleton pregnancy only
• Previous macrosomia	*Low availability in the dataset*
• Pregnancy interval of more than 10 years	*Information not available in the dataset*
• Family history of pre-eclampsia	*Information not available in the dataset*
• Previous history of pre-eclampsia	*Information not available in the dataset*
• Pre-existing renal disease	*Information not available in the dataset*

c) Outcome: baby born small for gestational age

Considered confounders	Remarks
• Booking BMI (kg/m^2)	Stratification factor
• Smoking	Mandatory confounder
• Age	Potential confounder (1)
• Parity	Potential confounder (2)
• Education level	Potential confounder (3)
• Ethnic origin	Potential confounder (4)
• Exercise prior to pregnancy	Potential confounder (5)
• Pre-existing vascular disease such as hypertension	Potential confounder (6)

d) Outcome: delivery before 37 weeks' gestation

Considered confounders	Remarks
• Booking BMI (kg/m^2)	Stratification factor
• Smoking	Mandatory confounder
• Age	Potential confounder (1)
• Diabetes prior to pregnancy or in pregnancy	Potential confounder (2)
• Parity	Potential confounder (3)
• High blood pressure	Potential confounder (4) Available as any hypertensive disease in pregnancy
• Education level	Potential confounder (5) Used as a proxy of socioeconomic status
• Ethnic origin	Potential confounder (6)
• Exercise prior to pregnancy	Potential confounder (6)
• Multiple pregnancy	Only singletons in the dataset

```
Appendix 7.2 Specification of regression models
** Outcome: Caesarean section
* Analysis within the IOM recommendation by BMI cat
* crude models
* All women
xtmelogit outcm_csbin gwg if adh_iom==1 || study_name:, or nolog
tab outcm_csbin if e(sample)
* Normal BMI
xtmelogit outcm_csbin gwg if adh_iom==1 & b_bmi_cat==0 || study_name:, or nolog
tab outcm_csbin if e(sample)
* Overweight
xtmelogit outcm_csbin gwg if adh_iom==1 & b_bmi_cat==1 || study_name:, or nolog
tab outcm_csbin if e(sample)
* Obese
xtmelogit outcm_csbin gwg if adh_iom==1 & b_bmi_cat==2 || study_name:, or nolog
tab outcm_csbin if e(sample)

* adjusted models
* All women
xtmelogit outcm_csbin gwg i.b_bmi_cat anydiabetes age ga_delivery parity smoker_curr if
adh_iom==1 || study_name:, or nolog
tab outcm_csbin if e(sample)
* Normal BMI
xtmelogit outcm_csbin gwg anydiabetes age ga_delivery parity smoker_curr if adh_iom==1
& b_bmi_cat==0 || study_name:, or nolog
tab outcm_csbin if e(sample)
* Overweight
xtmelogit outcm_csbin gwg anydiabetes age ga_delivery parity smoker_curr if adh_iom==1
& b_bmi_cat==1 || study_name:, or nolog
tab outcm_csbin if e(sample)
* Obese
xtmelogit outcm_csbin gwg anydiabetes age ga_delivery parity smoker_curr if adh_iom==1
& b_bmi_cat==2 || study_name:, or nolog
tab outcm_csbin if e(sample)

** Departure from the IOM recommendations
** Below the IOM recommendations
* crude models

```

```
* All women
xtmelogit outcm_csbin c.DR##i.direction if adh_iom!=1 || study_name:, or nolog
tab outcm_csbin direction if e(sample)
* Normal BMI
xtmelogit outcm_csbin c.DR##i.direction if adh_iom!=1 & b_bmi_cat==0 || study_name:, or
nolog
tab outcm_csbin direction if e(sample)
* Overweight
xtmelogit outcm_csbin c.DR##i.direction if adh_iom!=1 & b_bmi_cat==1 || study_name:, or
nolog
tab outcm_csbin direction if e(sample)
* Obese
xtmelogit outcm_csbin c.DR##i.direction if adh_iom!=1 & b_bmi_cat==2 || study_name:, or
nolog
tab outcm_csbin direction if e(sample)

** Above the IOM recommendations
* All women
xtmelogit outcm_csbin c.DR##b(1).direction if adh_iom!=1 || study_name:, or nolog
* Normal BMI
xtmelogit outcm_csbin c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==0 || study_name:,
or nolog
* Overweight
xtmelogit outcm_csbin c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==1 || study_name:,
or nolog
* Obese
xtmelogit outcm_csbin c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==2 || study_name:,
or nolog

* adjusted models
** Below the IOM recommendations
* All women
xtmelogit outcm_csbin c.DR##i.direction i.b_bmi_cat anydiabetes age ga_delivery parity
smoker_curr if adh_iom!=1 || study_name:, or nolog
tab outcm_csbin direction if e(sample)
* Normal BMI
xtmelogit outcm_csbin c.DR##i.direction anydiabetes age ga_delivery parity smoker_curr if
adh_iom!=1 & b_bmi_cat==0 || study_name:, or nolog
tab outcm_csbin direction if e(sample)
* Overweight
```

```
xtmelogit outcm_csbin c.DR##i.direction anydiabetes age ga_delivery parity smoker_curr if adh_iom!=1 & b_bmi_cat==1 || study_name:, or nolog
tab outcm_csbin direction if e(sample)
* Obese
xtmelogit outcm_csbin c.DR##i.direction anydiabetes age ga_delivery parity smoker_curr if adh_iom!=1 & b_bmi_cat==2 || study_name:, or nolog
tab outcm_csbin direction if e(sample)

** Above the IOM recommendations
* All women
xtmelogit outcm_csbin c.DR##b(1).direction i.b_bmi_cat anydiabetes age ga_delivery parity smoker_curr if adh_iom!=1 || study_name:, or nolog
* Normal BMI
xtmelogit outcm_csbin c.DR##b(1).direction anydiabetes age ga_delivery parity smoker_curr if adh_iom!=1 & b_bmi_cat==0 || study_name:, or nolog
* Overweight
xtmelogit outcm_csbin c.DR##b(1).direction anydiabetes age ga_delivery parity smoker_curr if adh_iom!=1 & b_bmi_cat==1 || study_name:, or nolog
* Obese
xtmelogit outcm_csbin c.DR##b(1).direction anydiabetes age ga_delivery parity smoker_curr if adh_iom!=1 & b_bmi_cat==2 || study_name:, or nolog

** Outcome: Large for gestational age
* Within the IOM recommendations
* crude models
* All women
xtmelogit outcb_lga gwg if adh_iom==1 || study_name:, or nolog
tab outcb_lga if e(sample)
* Normal BMI
xtmelogit outcb_lga gwg if adh_iom==1 & b_bmi_cat==0 || study_name:, or nolog
tab outcb_lga if e(sample)
* Overweight
xtmelogit outcb_lga gwg if adh_iom==1 & b_bmi_cat==1 || study_name:, or nolog
tab outcb_lga if e(sample)
* Obese
xtmelogit outcb_lga gwg if adh_iom==1 & b_bmi_cat==2 || study_name:, or nolog
tab outcb_lga if e(sample)

* adjusted models
```

```
* All women
xtmelogit outcb_lga gwg i.b_bmi_cat anydiabetes age if adh_iom==1 || study_name:, or nolog
tab outcb_lga if e(sample)
* Normal BMI
xtmelogit outcb_lga gwg anydiabetes age if adh_iom==1 & b_bmi_cat==0 || study_name:, or
nolog
tab outcb_lga if e(sample)
* Overweight
xtmelogit outcb_lga gwg anydiabetes age if adh_iom==1 & b_bmi_cat==1 || study_name:, or
nolog
tab outcb_lga if e(sample)
* Obese
xtmelogit outcb_lga gwg anydiabetes age if adh_iom==1 & b_bmi_cat==2 || study_name:, or
nolog
tab outcb_lga if e(sample)

* Departure from IOM recommendations
* Below IOM recommendations
* crude models
* All women
xtmelogit outcb_lga c.DR##i.direction if adh_iom!=1 || study_name:, or nolog
tab outcb_lga direction if e(sample)
* Normal BMI
xtmelogit outcb_lga c.DR##i.direction if adh_iom!=1 & b_bmi_cat==0 || study_name:, or
nolog
tab outcb_lga direction if e(sample)
* Overweight
xtmelogit outcb_lga c.DR##i.direction if adh_iom!=1 & b_bmi_cat==1 || study_name:, or
nolog
tab outcb_lga direction if e(sample)
* Obese
xtmelogit outcb_lga c.DR##i.direction if adh_iom!=1 & b_bmi_cat==2 || study_name:, or
nolog
tab outcb_lga direction if e(sample)

* Above the IOM recommendations
* All women
xtmelogit outcb_lga c.DR##b(1).direction if adh_iom!=1 || study_name:, or nolog
* Normal BMI
```

```
xtmelogit outcb_lga c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==0 || study_name:, or nolog

* Overweight

xtmelogit outcb_lga c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==1 || study_name:, or nolog

* Obese

xtmelogit outcb_lga c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==2 || study_name:, or nolog


* adjusted models

* Below the IOM recommendations

* All women

xtmelogit outcb_lga c.DR##i.direction i.b_bmi_cat anydiabetes age if adh_iom!=1 || study_name:, or nolog

tab outcb_lga direction if e(sample)

* Normal BMI

xtmelogit outcb_lga c.DR##i.direction anydiabetes age if adh_iom!=1 & b_bmi_cat==0 || study_name:, or nolog

tab outcb_lga direction if e(sample)

* Overweight

xtmelogit outcb_lga c.DR##i.direction anydiabetes age if adh_iom!=1 & b_bmi_cat==1 || study_name:, or nolog

tab outcb_lga direction if e(sample)

* Obese

xtmelogit outcb_lga c.DR##i.direction anydiabetes age if adh_iom!=1 & b_bmi_cat==2 || study_name:, or nolog

tab outcb_lga direction if e(sample)


* Above IOM recommendations

* All women

xtmelogit outcb_lga c.DR##b(1).direction i.b_bmi_cat anydiabetes age if adh_iom!=1 || study_name:, or nolog

* Normal BMI

xtmelogit outcb_lga c.DR##b(1).direction anydiabetes age if adh_iom!=1 & b_bmi_cat==0 || study_name:, or nolog

* Overweight

xtmelogit outcb_lga c.DR##b(1).direction anydiabetes age if adh_iom!=1 & b_bmi_cat==1 || study_name:, or nolog

* Obese

xtmelogit outcb_lga c.DR##b(1).direction anydiabetes age if adh_iom!=1 & b_bmi_cat==2 || study_name:, or nolog
```

```
** Outcome: Small for gestational age

* Within the IOM recommendations
* crude models
* All women
xtmelogit outcb_sga gwg if adh_iom==1 || study_name:, or nolog
tab outcb_sga if e(sample)
* Normal BMI
xtmelogit outcb_sga gwg if adh_iom==1 & b_bmi_cat==0 || study_name:, or nolog
tab outcb_sga if e(sample)
* Overweight
xtmelogit outcb_sga gwg if adh_iom==1 & b_bmi_cat==1 || study_name:, or nolog
tab outcb_sga if e(sample)
* Obese
xtmelogit outcb_sga gwg if adh_iom==1 & b_bmi_cat==2 || study_name:, or nolog
tab outcb_sga if e(sample)

* adjusted models
* All women
xtmelogit outcb_sga gwg i.b_bmi_cat smoker_curr age parity if adh_iom==1 || study_name:,
or nolog
tab outcb_sga if e(sample)
* Normal BMI
xtmelogit outcb_sga gwg smoker_curr age parity if adh_iom==1 & b_bmi_cat==0 ||
study_name:, or nolog
tab outcb_sga if e(sample)
* Overweight
xtmelogit outcb_sga gwg smoker_curr age parity if adh_iom==1 & b_bmi_cat==1 ||
study_name:, or nolog
tab outcb_sga if e(sample)
* Obese
xtmelogit outcb_sga gwg smoker_curr age parity if adh_iom==1 & b_bmi_cat==2 ||
study_name:, or nolog
tab outcb_sga if e(sample)

* Departure from IOM recommendations
* crude models

* Below the IOM recommendations
```

```
* All women
xtmelogit outcb_sga c.DR##i.direction if adh_iom!=1 || study_name:, or nolog
tab outcb_sga direction if e(sample)
* Normal
xtmelogit outcb_sga c.DR##i.direction if adh_iom!=1 & b_bmi_cat==0 || study_name:, or
nolog
tab outcb_sga direction if e(sample)
* Overweight
xtmelogit outcb_sga c.DR##i.direction if adh_iom!=1 & b_bmi_cat==1 || study_name:, or
nolog
tab outcb_sga direction if e(sample)
* Obese
xtmelogit outcb_sga c.DR##i.direction if adh_iom!=1 & b_bmi_cat==2 || study_name:, or
nolog
tab outcb_sga direction if e(sample)

* Above the IOM recommendations
* All women
xtmelogit outcb_sga c.DR##b(1).direction if adh_iom!=1 || study_name:, or nolog
* Normal
xtmelogit outcb_sga c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==0 || study_name:, or
nolog
* Overweight
xtmelogit outcb_sga c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==1 || study_name:, or
nolog
* Obese
xtmelogit outcb_sga c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==2 || study_name:, or
nolog

* adjusted models
* Below the IOM recommendations
* All women
xtmelogit outcb_sga c.DR##i.direction i.b_bmi_cat smoker_curr age parity if adh_iom!=1 ||
study_name:, or nolog
tab outcb_sga direction if e(sample)
* Normal
xtmelogit outcb_sga c.DR##i.direction smoker_curr age parity if adh_iom!=1 &
b_bmi_cat==0 || study_name:, or nolog
tab outcb_sga direction if e(sample)
* Overweight
```

```
xtmelogit outcb_sga c.DR##i.direction smoker_curr age parity if adh_iom!=1 &
b_bmi_cat==1 || study_name:, or nolog
tab outcb_sga direction if e(sample)
* Obese
xtmelogit outcb_sga c.DR##i.direction smoker_curr age parity if adh_iom!=1 &
b_bmi_cat==2 || study_name:, or nolog
tab outcb_sga direction if e(sample)

* Above the IOM recommendations
* All women
xtmelogit outcb_sga c.DR##b(1).direction i.b_bmi_cat smoker_curr age parity if adh_iom!=1
|| study_name:, or nolog
* Normal
xtmelogit outcb_sga c.DR##b(1).direction smoker_curr age parity if adh_iom!=1 &
b_bmi_cat==0 || study_name:, or nolog
* Overweight
xtmelogit outcb_sga c.DR##b(1).direction smoker_curr age parity if adh_iom!=1 &
b_bmi_cat==1 || study_name:, or nolog
* Obese
xtmelogit outcb_sga c.DR##b(1).direction smoker_curr age parity if adh_iom!=1 &
b_bmi_cat==2 || study_name:, or nolog

** Outcome: Preterm birth
* Within the IOM recommendations
* crude models
* All women
xtmelogit outcm_preterm gwg if adh_iom==1 || study_name:, or nolog
tab outcm_preterm if e(sample)
* Normal
xtmelogit outcm_preterm gwg if adh_iom==1 & b_bmi_cat==0 || study_name:, or nolog
tab outcm_preterm if e(sample)
* Overweight
xtmelogit outcm_preterm gwg if adh_iom==1 & b_bmi_cat==1 || study_name:, or nolog
tab outcm_preterm if e(sample)
* Obese
xtmelogit outcm_preterm gwg if adh_iom==1 & b_bmi_cat==2 || study_name:, or nolog
tab outcm_preterm if e(sample)

* adjusted models
* All women
```

```
xtmelogit outcm_preterm gwg i.b_bmi_cat smoker_curr if adh_iom==1 || study_name:, or nolog
tab outcm_preterm if e(sample)
* Normal
xtmelogit outcm_preterm gwg smoker_curr if adh_iom==1 & b_bmi_cat==0 || study_name:, or nolog
tab outcm_preterm if e(sample)
* Overweight
xtmelogit outcm_preterm gwg smoker_curr if adh_iom==1 & b_bmi_cat==1 || study_name:, or nolog
tab outcm_preterm if e(sample)
* Obese
xtmelogit outcm_preterm gwg smoker_curr if adh_iom==1 & b_bmi_cat==2 || study_name:, or nolog
tab outcm_preterm if e(sample)

* Departure from the IOM recommendations

* Below the IOM recommendations
* Overall
xtmelogit outcm_preterm c.DR##i.direction if adh_iom!=1 || study_name:, or nolog
tab outcm_preterm direction if e(sample)
* By BMI category
* Normal BMI
xtmelogit outcm_preterm c.DR##i.direction if adh_iom!=1 & b_bmi_cat==0 || study_name:, or nolog
tab outcm_preterm direction if e(sample)
* Overweight
xtmelogit outcm_preterm c.DR##i.direction if adh_iom!=1 & b_bmi_cat==1 || study_name:, or nolog
tab outcm_preterm direction if e(sample)
* Obese
xtmelogit outcm_preterm c.DR##i.direction if adh_iom!=1 & b_bmi_cat==2 || study_name:, or nolog
tab outcm_preterm direction if e(sample)

*Above the IOM recommendations
* Overall
xtmelogit outcm_preterm c.DR##b(1).direction if adh_iom!=1 || study_name:, or nolog
* Normal BMI
```

```
xtmelogit outcm_preterm c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==0 ||
study_name:, or nolog

* Overweight

xtmelogit outcm_preterm c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==1 ||
study_name:, or nolog

* Obese

xtmelogit outcm_preterm c.DR##b(1).direction if adh_iom!=1 & b_bmi_cat==2 ||
study_name:, or nolog


* adjusted models

* Below the IOM recommendations

* Overall

xtmelogit outcm_preterm c.DR##i.direction i.b_bmi_cat smoker_curr if adh_iom!=1 ||
study_name:, or nolog

tab outcm_preterm direction if e(sample)

* Normal BMI

xtmelogit outcm_preterm c.DR##i.direction smoker_curr if adh_iom!=1 & b_bmi_cat==0 ||
study_name:, or nolog

tab outcm_preterm direction if e(sample)

* Overweight

xtmelogit outcm_preterm c.DR##i.direction smoker_curr if adh_iom!=1 & b_bmi_cat==1 ||
study_name:, or nolog

tab outcm_preterm direction if e(sample)

* Obese

xtmelogit outcm_preterm c.DR##i.direction smoker_curr if adh_iom!=1 & b_bmi_cat==2 ||
study_name:, or nolog

tab outcm_preterm direction if e(sample)


*Above the IOM recommendations

* Overall

xtmelogit outcm_preterm c.DR##b(1).direction i.b_bmi_cat smoker_curr if adh_iom!=1 ||
study_name:, or nolog

* Normal BMI

xtmelogit outcm_preterm c.DR##b(1).direction smoker_curr if adh_iom!=1 & b_bmi_cat==0
|| study_name:, or nolog

* Overweight

xtmelogit outcm_preterm c.DR##b(1).direction smoker_curr if adh_iom!=1 & b_bmi_cat==1
|| study_name:, or nolog

* Obese

xtmelogit outcm_preterm c.DR##b(1).direction smoker_curr if adh_iom!=1 & b_bmi_cat==2
|| study_name:, or nolog
```

1803 Appendix 7.3 Outcomes by adherence category overall and stratified by BMI group

Outcome	below IOM recommendation, n/N, %	within IOM recommendation n/N, %	exceeding IOM recommendation n/N, %
All women			
Preterm birth	81/1286, 6.30	57/1483, 3.84	49/1643, 2.98
Any Caesarean section	277/1271, 21.79	340/1456, 23.35	503/1618, 31.09
Large for gestational age	92/1291, 7.13	135/1492, 9.05	267/1646, 16.22
Small for gestational age	186/1280, 14.53	157/1482, 10.59	117/1641, 7.13
Normal BMI			
Preterm birth	34/647, 5.26	22/662, 3.32	14/309, 4.53
Any Caesarean section	83/636, 13.05	112/649, 17.26	68/300, 22.67
Large for gestational age	48/649, 7.40	62/663, 9.35	49/310, 15.81
Small for gestational age	76/642, 11.84	64/662, 9.67	26/308, 8.44
Overweight			
Preterm birth	15/241, 6.22	19/360, 5.28	13/640, 2.03
Any Caesarean section	54/239, 22.59	76/351, 21.65	174/631, 27.58
Large for gestational age	14/242, 5.79	37/362, 10.22	104/641, 16.22
Small for gestational age	33/241, 13.69	39/360, 10.83	31/640, 4.84
Obese			
Preterm birth	32/398, 8.04	16/461, 3.47	22/694, 3.17
Any Caesarean section	140/396, 21.79	152/456, 33.33	261/687, 37.99
Large for gestational age	30/400, 7.50	36/467, 7.71	114/695, 16.40
Small for gestational age	77/397, 19.40	54/460, 11.74	60/693, 8.66

1804 *n, number of events; N, number of participants; BMI, Body Mass Index; IOM, Institute of Medicine*
1805
1806

Appendix 7.4 Summary of women's BMI values in the individual studies (control arms)

Study ID	N	mean	p50	p25	p75	IQR
Althuizen 2012	98	24.63467	23.82395	22.07191	25.84027	3.768362
Baciuk 2008	37	23.44865	22.6	20.8	24.7	3.900002
Barakat 2008	68	23.52538	23.18855	21.2562	25.32342	4.067217
Barakat 2012a	143	24.04824	23.4375	21.63115	25.39063	3.759476
Bogaerts 2012	63	34.42619	33.62	30.76	37.47	6.710001
Dodd 2014	779	32.33017	31	27.6	35.4	7.800001
Guelinckx 2010	55	33.84554	32.41922	30.17882	36.93213	6.753304
Haakstad 2011	40	25.40345	24.81339	22.6717	27.01273	4.341032
Harrison 2013	103	30.9632	28.61703	25.83978	35.2784	9.438614
Hui 2011	86	25.84535	25.1	22	28	6
Jeffries 2009	110	25.34926	24.63958	22.04779	27.18163	5.133839
Khaledan 2010	21	28.86803	29.02494	26.37024	31.24499	4.874756
Khoury 2005	103	24.15098	23.98752	22.57563	25.63201	3.056385
Luoto 2011	166	26.58152	26.22571	23.52941	29.05475	5.525341
Nascimento 2011	41	38.01005	37.63132	32.47498	41.83867	9.363686
Ong 2009	5	34.09023	32.31834	31.66208	36.07157	4.409492
Oostdam 2012	39	34.58955	34.15533	31.4133	36.04343	4.630131
Perales 2014	74	24.36338	23.265	21.35	25.71	4.359999
Petrella 2013	28	33.09059	31.6	27.75	37.93438	10.18438
Phelan 2011	195	27.72668	26.42051	23.49711	31.1191	7.62199
Poston unpub	221	37.06561	36.1	33.1	39.4	6.300003
Prevedel 2003	18	25.47645	23.89095	21.6409	25.84648	4.20558
Rauh 2013	77	24.77493	23.31	21.18	26.75	5.57
Renault 2013	132	34.32167	33.18733	31.65409	36.26231	4.608221
Ruiz 2013	457	23.86211	23.03	21.26	25.4	4.139999
Sagedal unpub	286	24.55519	23.61073	21.79931	26.06168	4.262371
Stafne 2012	340	24.86972	24.39019	22.53685	26.37694	3.840092
Vinter 2011	148	34.32917	33.47135	31.80073	36.94463	5.143908
Vitolo 2011	149	25.71625	24.91588	22.40588	27.88762	5.481741
Walsh 2012	317	26.9183	25.7	23.7	29.2	5.5
Wolff 2008	30	34.75333	34	32.1	36.6	4.5
Yeo 2000	0	.	.	.	.	.
Yeo unpub	0	.	.	.	.	.
Total	4429	28.32074	26.79244	23.38714	32.2	8.812857