Diet and physical activity in pregnancy to prevent gestational diabetes

Individual Participant Data (IPD) meta-analysis on differential effects of interventions with economic evaluation

1. Summary of Research

Background

Women with gestational diabetes, a condition with high blood sugars diagnosed for the first time in pregnancy, are at increased risk of complications in pregnancy and type 2 diabetes after delivery. Diet and physical activity interventions have the potential to prevent gestational diabetes. However, variations in the population, intervention, and outcome definitions in primary trials has limited the translation of evidence on lifestyle interventions into practice. Individual participant data (IPD) meta-analysis can address these limitations.

Aims

To determine using IPD meta-analysis, whether diet and physical activity based interventions prevent gestational diabetes, and its complications, if the benefits vary according to the maternal characteristics and the type of intervention, and whether they are cost-effective, by updating and expanding the NIHR funded i-WIP (International Weight Management in Pregnancy) database.

Objectives

Primary objectives
To assess the

1. overall effects across all interventions, and according to each type of intervention (diet, physical activity, mixed), on gestational diabetes as defined by NICE (National Institute of Health and Care Excellence), and by any criteria
2. differential effects of interventions across subgroups based on maternal body mass index (BMI), age, parity, ethnicity, and socioeconomic status

Secondary objectives
To evaluate

3. the effects of interventions in women with gestational diabetes on critically important outcomes in the offspring and mother
4. whether the effect varies according to the intervention's characteristics
5. the effects on gestational diabetes diagnosed using other specific criteria
6. the cost-effectiveness of interventions using decision analytic modelling

Methods

Identification of new trials and data acquisition

Our i-WIP living database currently includes IPD from 37 trials (17,106 women, 16 countries) reporting the effects of lifestyle interventions on gestational diabetes (until June 2018). A further 21 trials (7,660 women) have agreed to share IPD and are in the process of transferring the data.

Quality assessment and data harmonisation

We will add new studies and variables to the existing i-WIP database, assess study quality, harmonise new data, and extract data on the individual's blood glucose values used to diagnose gestational diabetes, intervention components, and offspring and maternal complications.

Data synthesis

We will perform one-stage and two-stage random effects meta-analyses to obtain the pooled intervention effect for primary and secondary outcomes. We will examine whether the maternal characteristics modify intervention effect by extending the meta-analysis framework to summarise treatment-covariate interaction terms, whilst avoiding ecological bias and study-level confounding.[1]

Our cost effectiveness analysis will be based on outcomes for a hypothetical cohort of 10,000 pregnant women derived from the results of the IPD meta-analysis. A secondary analysis will compare costs and outcomes for subgroups of women. We will undertake additional analysis to compare the cost effectiveness by type of intervention if sufficient data are available on which to draw sensible assumptions.

Sample size

Of the 27,538 women (71 studies) with eligible data, we have a sample size of 24,766 women from 58 studies that have shared/agreed IPD. This provides us with over 90% power to detect any interactions between overall effects (across all intervention types combined) and most subgroups for a 30% reduction in gestational diabetes; for a 25% reduction in gestational diabetes our IPD sample size accrued so far has over 80%, and around 75-80% for most other subgroups.

2. Background and rationale

2.1. The problem

In the UK, at least 40,000 mothers are diagnosed every year with gestational diabetes, a condition with glucose intolerance identified for the first time in pregnancy.[2] Obesity, poor dietary habits, sedentary lifestyle, advancing maternal age, and lowered thresholds for the diagnosis contribute to the rising rates of gestational diabetes, affecting between 8-24% of all pregnancies.[3]

Mothers with gestational diabetes and their offspring are prone for complications both in the short and long term. During pregnancy, mothers are at risk of pre-eclampsia, caesarean section, traumatic vaginal delivery, preterm delivery and major haemorrhage. The overall cost of care for a woman with gestational diabetes is 34% greater than for someone without the condition.[4] After delivery, about 50% of women with gestational diabetes progress to type-2 diabetes in the first 5-10 years. This is a major contributory factor to the National Health Service's (NHS) spend on type 2 diabetes, which is projected to increase from £8.8 to £13 billion per year in the next 25 years.[5] The baby is at risk of stillbirth, large for gestational age, birth injury, hypoglycaemia and hyperbilirubinaemia during pregnancy and birth, and has a high likelihood of obesity and diabetes in later life.[6]

There is a clear need for effective and safe interventions to prevent gestational diabetes and its complications.

2.2. Priority area for the NHS

Each year, £97 billion of public money is spent on treating disease and only £8 billion preventing it across the UK – an imbalance in urgent need of correction. The Secretary of State for Health and Social Care has prioritised prevention as one of his early priorities for the NHS and social care.[7] The recently unveiled 'Prevention is better than cure' document is in line with the NHS Long Term Plan, particularly in the context of additional funding of £20.5 billion/year promised for the next 5 years to the NHS.[8] The Government's Prevention vision highlights the need for 'systems capable of sifting anonymised patient data to target early intervention and bespoke treatment plans'. The

Prevention document identifies the problem of diabetes and obesity and the potential role of lifestyle interventions. Our proposal fits with the above priorities.

With half of the 40,000 women with gestational diabetes progressing to type 2 diabetes every year besides suffering complications in pregnancy, gestational diabetes prevention is important to the NHS. Despite the research investment made by NIHR (National Institute for Health Research) on preventing gestational diabetes,[9-12] very little has translated into practice recommendations. There are no systems-level practice and policy-level evidence-based strategies targeting pregnancy. The Diabetes Prevention Programme (DPP) in the UK does not include prevention of gestational diabetes in its Programme.

Our proposal is directly aligned with the Prevention agenda for the NHS. Our focus is on identifying effective lifestyle interventions to prevent gestational diabetes using anonymised existing data thereby minimising research waste. Another key aim is to find specific subgroups who may benefit from the targeted intervention. In the context of emerging additional large randomised trial data on lifestyle interventions, in addition to IPD meta-analysis, cost-effectiveness modelling is a key requirement and priority area for any implementation and scaling-up plans, which we address in our proposal.

2.3. Current evidence

In the UK, the NIHR Health Technology Assessment (HTA) has funded primary trials and meta-analyses on the effects of diet and physical activity interventions in pregnancy. Our aggregate meta-analysis (HTA commissioned call 2010) demonstrated the beneficial effects of lifestyle interventions on gestational weight gain, but highlighted the limitations of using study-level data. There were very few studies and the quality of evidence was low with high heterogeneity for clinical outcomes such as gestational diabetes.

Our International Weight management in Pregnancy (i-WIP) Collaborative Network's (40 researchers, 16 countries) IPD meta-analysis (HTA No. 12/01/50) showed that lifestyle interventions reduced weight gain in ***all*** women and that the with benefit was not limited to specific groups of women. There was a fall in the rate of gestational diabetes with lifestyle interventions in IPD meta-analysis, but this was estimated with large uncertainty (OR 0.89, 95% CI 0.72, 1.10). When we added aggregate data from studies that did not contribute individual data to the IPD meta-analysis, we found stronger evidence of a reduction in gestational diabetes, but questions on effectiveness remained due to the inherent bias with this approach.[13, 14] The recent Cochrane review's aggregate meta-analysis in this area also showed similar findings.[15] The Cochrane review found the quality of evidence to be low due to variations in the definitions, small sample sizes with imprecise estimates, and statistical heterogeneity. A further review attempted to identify subgroups that may benefit the most from intervention, but was limited by access to only aggregate and not IPD to make robust recommendations.[16]

The above reviews did not include the recently published large trials indicating potential beneficial effects of lifestyle intervention on gestational diabetes: the ESTEEM trial (1230 women, 2019) on Mediterranean diet reduced gestational diabetes, a component of the composite primary outcome, by 35%;[17] the St Carlos trial (800 women) showed similar reduction in gestational diabetes, but had lower power.[18]

2.4. Where are the gaps in evidence?

Despite the publication of over 70 trials to-date on the effects of lifestyle interventions on gestational diabetes (>£10 million funding), the following key gaps have prevented translation of findings into clinical practice, guidelines, and policy frameworks. **Firstly,** the beneficial effect for gestational diabetes with lifestyle interventions was only observed when aggregate data on lifestyle interventions (with its inherent bias and limitations) were combined with IPD, and not in IPD meta-

analysis alone. **Secondly,** we do not know if the beneficial effects of diet and physical activity apply to all pregnant women, or only to subgroups of women with risk factors such as high body mass index, high maternal age, ethnic minority origin and low socioeconomic status. In trial publications, participant-level information is not available and subgroup effects ('treatment-covariate interactions') are rarely reported in sufficient detail. **Thirdly,** implementation of lifestyle interventions in a scalable way is hindered by the lack of details about the type, intensity and setting of the effective interventions, and the cost effectiveness of the intervention. **Fourthly,** the effect of interventions on gestational diabetes as applied to UK practice and defined by NICE (National Institute for Health and Care Excellence), and the expected effect on clinically important outcomes, such as the complications in women with gestational diabetes is not known.

2.5. Why is an IPD meta-analysis on prevention of gestational diabetes needed now?

Meta-analysis of IPD, where the raw participant-level data are obtained and synthesised across trials, is a recommended approach to overcome the above limitations.[19] Our proposed IPD meta-analysis will leverage our unique access to the NIHR funded i-WIP dataset on antenatal lifestyle interventions to prevent gestational diabetes (see section 3.1). This dataset has been updated regularly to ensure that additional IPD are seamlessly and rapidly integrated as new studies get published.

IPD meta-analysis will have greater power than aggregate meta-analysis to detect any differential treatment effect across groups as it can model individual risk status (prognostic factor values) across participants within trials, and thus explain variability in patient outcome. [19] In contrast, aggregate data meta-analysis can only model average risk status values across studies, and thus only explain between-study variation. [20, 21] Availability of IPD alleviates the need to use published results and is thus less likely to be affected by selective and biased reporting than an aggregate data meta-analysis. IPD meta-analysis will also allow us to identify and subsequently target the interventions to those groups that show clear benefit with lifestyle interventions in pregnancy.

By accessing the raw values in IPD meta-analysis, we can assess the effects of interventions on gestational diabetes defined as per different criteria, and on offspring and maternal complications. From experience, retrieval of raw data in IPD may permit the inclusion of a greater number of participants and events not reported in the original publication. [13, 14] For example, even if data on preterm birth were not published, we can report the outcome if raw data on gestational age at delivery were available.[9, 11] Table 1 summarises these and other potential benefits of the IPD approach for our research.

Table 1. Added value of proposed IPD meta-analysis over aggregate data meta-analysis

Aggregate data meta-analysis limitations	Added value of proposed IPD meta-analysis
Clinical heterogeneity due to varied definitions of gestational diabetes	Can provide intervention effects for various definitions of gestational diabetes by accessing the individual blood glucose values
Varied characteristics of the participants; only average data available	Can determine differential effects of intervention according to maternal characteristics by accessing the individual participant's body mass index, age, parity, ethnicity and socio-economic status
Variations in the types, intensity, frequency, provider, setting and delivery of the intervention making it difficult to make recommendations	Can substantially improve power to identify differential effects according to the type, and characteristics of the intervention, to inform policy makers
Unable to determine the effects of interventions on gestational diabetes with complications, which is a reflection of the severity of the condition	Can evaluate if lifestyle interventions prevent complications in women with gestational diabetes by accessing the individual data of women with gestational diabetes, and whether they had complications

Relies on definitions of outcomes provided by study authors. For e.g., preterm birth <37 weeks	Can standardise definition of outcomes. For example can report effect on both early (<34 weeks) and late preterm birth (34-37 weeks) by accessing the gestational age at delivery

3. Work leading to the proposal

3.1. Establishment and consolidation of i-WIP network and database

Our proposal builds on an already established suite of work programmes funded by the NIHR and supported by WHO (World Health Organization). Our i-WIP Collaborative group (established in 2013) is the **largest living global database on diet and physical activity interventions in pregnancy**, and we continue to accrue new datasets. To-date, we have access to cleaned, formatted and standardised data of 27 studies (9,427 women) on the effects of diet and physical activity on gestational diabetes.[9, 11] Our updated search (until June 2018) has identified 41 new studies (15,810 women) reporting on gestational diabetes, and a further 3 trials have been identified through the links established with our collaborators. We already have data from 10 of the new trials (5,597 women) completed after our IPD meta-analysis in 2017, and a further 21 new trials (7,660 women) are in the process of transferring data. Overall, our current IPD sample size is at least 24,766 women.

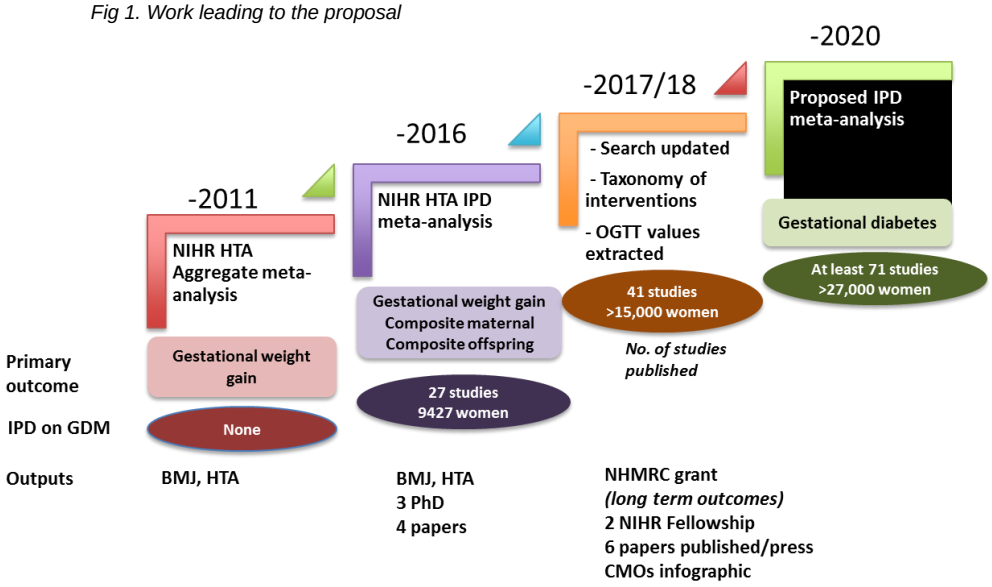
Table 2. List of studies currently in the i-WIP database studies that have agreed to share data

	Study year	Country	Sample size	Intervention Type	BMI	Socio economic status*	Age	Ethnic origin	Parity
IPD CURRENTLY IN i-WIP 17,106 (37 trials)									
1	Al Wattar 2019 (ESTEEM)*	UK	**1230**	Diet	Yes	Yes	Yes	Yes	Yes
2	Assaf-Balut 2017*	Spain	**800**	Diet	Yes	Yes	Yes	Yes	Yes
3	Barakat 2008	Spain	**160**	Physical Activity	Yes	Yes	Yes	Yes	Yes
4	Barakat 2011	Spain	**80**	Physical Activity	Yes	Yes	Yes	Yes	Yes
5	Barakat 2012a	Spain	**320**	Physical Activity	Yes	Yes	Yes	Yes	Yes
6	Bisson 2015*	Canada	**50**	Physical Activity	Yes	Yes	Yes	Yes	Yes
7	Bogaerts 2012	Belgium	**205**	Mixed approach	Yes	Yes	Yes	Yes	Yes
8	Bruno 2016*	Italy	**191**	Mixed approach	Yes	NK	Yes	Yes	Yes
9	Dodd 2014	Australia	**2212**	Mixed approach	Yes	Yes	Yes	Yes	Yes
10	El Beltagy 2013	Egypt	**100**	Mixed approach	Yes	No	Yes	Yes	Yes
11	Garnæs 2016*	Norway	**91**	Physical Activity	Yes	Yes	Yes	Yes	Yes
12	Guelinckx 2010	Belgium	**195**	Mixed approach	Yes	No	Yes	No	Yes
13	Haakstad 2011*	Norway	**105**	Physical Activity	Yes	Yes	Yes	NK	NK
14	Harrison 2013	Australia	**228**	Mixed approach	Yes	Yes	Yes	No	Yes
15	Hui 2011	Canada	**224**	Mixed approach	Yes	No	Yes	No	No
16	Jeffries 2009	Australia	**286**	Mixed approach	Yes	Yes	Yes	Yes	Yes
17	Kunath 2019	Germany	**2286**	Mixed approach	Yes	Yes	Yes	Yes	NK
18	Luoto 2011	Finland	**442**	Mixed approach	Yes	Yes	Yes	Yes	Yes
19	Nascimento 2011	Brazil	**82**	Physical Activity	Yes	Yes	Yes	Yes	Yes
20	Ong 2009	Australia	**12**	Physical Activity	Yes	No	Yes	Yes	Yes
21	Oostdam 2012	Netherlands	**124**	Physical Activity	Yes	Yes	Yes	Yes	Yes
22	Perales 2014	Spain	**184**	Physical Activity	Yes	No	Yes	Yes	Yes
23	Perales 2016*	Spain	**299**	Physical Activity	Yes	Yes	Yes	NK	Yes
24	Petrella 2013	Italy	**63**	Mixed approach	Yes	Yes	Yes	Yes	Yes
25	Phelan 2011	US	**401**	Mixed approach	Yes	Yes	Yes	Yes	Yes
26	Poston 2015	UK	**1555**	Mixed approach	Yes	Yes	Yes	Yes	Yes
27	Rauh 2013	Germany	**250**	Mixed approach	Yes	Yes	Yes	Yes	Yes
28	Renault 2013	Denmark	**425**	Mixed approach	Yes	Yes	Yes	Yes	Yes
29	Ronnberg 2014*	Sweden	**445**	Physical Activity	Yes	NK	Yes	NK	Yes
30	Ruiz 2013	Spain	**962**	Physical Activity	Yes	Yes	Yes	Yes	Yes
31	Sagedal 2016	Norway	**606**	Mixed approach	Yes	Yes	Yes	No	Yes
32	Stafne 2012	Norway	**855**	Physical Activity	Yes	Yes	Yes	Yes	Yes
33	Vinter 2011	Denmark	**360**	Mixed approach	Yes	Yes	Yes	No	Yes
34	Vitolo 2011	Brazil	**315**	Diet	Yes	Yes	Yes	No	Yes
35	Walsh 2013	Ireland	**797**	Diet	Yes	Yes	Yes	Yes	Yes
36	Willcox 2017*	Australia	**100**	Mixed approach	Yes	Yes	Yes	NK	Yes
37	Wolff 2008	Denmark	**66**	Diet	Yes	Yes	Yes	No	Yes
IPD OF NEW STUDIES AGREED TO SHARE IPD 7,660 (20 trials)									
1	Arthur 2016	Australia	**400**	Mixed approach	Yes	NK	Yes	NK	NK
2	Barakat 2014	Spain	**251**	Physical Activity	Yes	NK	Yes	Yes	Yes
3	Barakat 2016	Spain	**850**	Physical Activity	Yes	NK	Yes	Yes	Yes
4	Brownfoot 2016	Australia	**782**	Mixed approach	Yes	NK	Yes	Yes	Yes
5	Cordero 2015	Spain	**342**	Physical Activity	Yes	Yes	Yes	Yes	Yes
6	da Silva 2017	Brazil	**639**	Physical Activity	Yes	Yes	Yes	Yes	Yes
7	Daly 2017	Ireland	**88**	Physical Activity	Yes	NK	Yes	NK	NK
8	Dodds 2017	Australia	**641**	Mixed approach	Yes	Yes	Yes	NK	NK
9	Herring 2016	US	**66**	Mixed approach	Yes	Yes	Yes	Yes	Yes
10	Hui 2014	Canada	**113**	Mixed approach	Yes	Yes	Yes	Yes	NK
11	Kennelly 2018	Ireland	**565**	Mixed approach	Yes	Yes	Yes	Yes	Yes
12	Koivusalo 2015	Finland	**293**	Mixed approach	Yes	Yes	Yes	NK	Yes
13	McCarthy 2016	Australia	**382**	Mixed approach	Yes	NK	Yes	Yes	Yes
14	Perales 2016a	Spain	**241**	Physical Activity	Yes	Yes	Yes	Yes	Yes
15	Phelan 2018	US	**264**	Mixed approach	Yes	Yes	Yes	Yes	Yes
16	Sewell 2017	UK	**30**	Diet	NK	Yes	NK	NK	Yes
17	Simmons 2017	Europe	**436**	Mixed approach	Yes	Yes	Yes	Yes	Yes
18	Simpson (HELP)	UK	**598**	Mixed approach	Yes	NK	Yes	NK	NK
19	Smith 2016	US	**45**	Mixed approach	Yes	NK	Yes	NK	Yes
20	Tomic 2013	Croatia	**334**	Physical Activity	Yes	Yes	Yes	NK	Yes
21	Wang 2016	China	**300**	Physical Activity	Yes	NK	NK	Yes	NK
IPD OF NEW STUDIES IN CONTACT 2,772 (14 trials)									
1	Abdel-Aziz 2018	Egypt	**200**	Diet	Yes	Yes	Yes	Yes	NK
2	Cahill 2018	US	**267**	Mixed approach	Yes	Yes	Yes	Yes	Yes
3	Dekker 2015	Australia	**50**	Physical Activity	Yes	NK	Yes	NK	Yes
4	Jing 2015	China	**262**	Mixed approach	Yes	NK	Yes	NK	NK
5	Ko 2014	US	**1124**	Physical Activity	Yes	NK	Yes	Yes	Yes
6	Kong 2014	US	**42**	Physical Activity	Yes	NK	Yes	NK	Yes
7	Polley 2002	US	**120**	Mixed approach	Yes	Yes	Yes	Yes	Yes
8	Price 2012	US	**91**	Physical Activity	Yes	NK	Yes	Yes	Yes
9	Rakhshani 2012	India	**68**	Physical Activity	Yes	Yes	Yes	NK	NK
10	Seneviratne 2015	New Zealand	**75**	Physical Activity	Yes	Yes	Yes	Yes	Yes
11	Sun 2016	China	**74**	Mixed approach	Yes	Yes	Yes	Yes	Yes
12	Van Horn 2018	US	**281**	Mixed approach	Yes	Yes	Yes	Yes	Yes
13	Vesco 2014	US	**118**	Mixed approach	Yes	Yes	Yes	Yes	Yes
IPD OF NEW STUDIES = 10,432 (34 trials)									
TOTAL IPD FOR PROPOSAL = 27,752 (71 trials) *provided since the completion of the i-WIP project									

Following extensive collaboration with members of the i-WIP consortium, we have obtained additional data on all available oral glucose tolerance test (OGTT) values, which will be used in the proposed i-WIP GDM project.

Mutual trust and common research goal are the cornerstones of our i-WIP collaborative group. We have robust operating procedures in place for data access, publication and data sharing. The i-WIP network has a strong track record in maximising the resources available in its database. The global database access and the robust partnership has led to over 10 publications,[9, 11, 22-30] PhD studentships (E Rogozinska, A Flynn, A Boath), NIHR Fellowships (N Marlin, N Heslehurst), and 2 NHMRC grants. Our work was central to the development of the recent UK Chief Medical Officers' (CMO) infographic recommendations on the benefits of physical activity in pregnancy and has informed international guidelines on antenatal care.[31, 32] Fig 1 illustrates the outputs and work leading to the proposal.

Fig 1. Work leading to the proposal



3.2. Evidence syntheses: Aggregate and IPD meta-analyses

Our NIHR commissioned aggregate meta-analysis (HTA No. 12/01/50) on lifestyle interventions in pregnancy was the first to definitively show that diet and physical activity interventions in pregnancy reduced gestational weight gain. The quality of evidence was low for other outcomes, and highlighted the limitations in using study-level data to determine the effects on gestational diabetes.[33, 34]

Our subsequent IPD meta-analysis (see section 2.3) showed that all women irrespective of body mass index (BMI), age, parity, and socio-economic status benefitted from diet and physical activity interventions in reducing gestational weight gain.[9] We do not know if the same is true for gestational diabetes, for which we found a potential for prevention with lifestyle interventions. Furthermore, studies used various definitions of gestational diabetes according to NICE (National Institute for Health and Care Excellence), WHO (World Health Organization) and IADPSG (International Association of Diabetes and Pregnancy Study Groups) necessitating the need to access individual data to draw robust conclusions. The above gaps in evidence led to this proposal.

3.3. Taxonomy of complex lifestyle interventions in i-WIP trials

One of the main challenges to implementing lifestyle interventions in pregnancy is the vast number and complexity of interventions with varied components, making it difficult to identify the role of various components to the observed effect.

To address this issue, over the past 3-years, our team of researchers in London and Melbourne have categorised the interventions in all i-WIP trials according to their core components and delivery methods. We mapped the components of the interventions using the TIDieR (Intervention Description and Replication) framework,[35] and categorised by type (diet, physical activity, mixed), frequency, intensity (high, medium, low), duration (pre-pregnancy, first, second trimester), delivery (face-to-face, e-health; individual, group sessions), setting (primary, secondary care), theoretical underpinning (e.g., problem solving, action planning) and resources utilised. We also used a 96-item framework[36] to identify the behavioural change components applied within interventions. This work is crucial to our proposed plan to identify those components of the intervention that are most effective in preventing gestational diabetes.

3.4. Prioritisation of outcomes for evaluation

In our mapping of reported outcomes in studies on lifestyle interventions, gestational diabetes was one of the commonest outcome reported in 58% of the trials (38/66).[22] The Delphi survey of our international group (26 experts, 11 countries) ranked gestational diabetes to be critically important to the care of women, alongside hypertensive disorders in pregnancy, preterm birth and caesarean section. We will evaluate these as secondary outcomes in our proposal.[22] For offspring outcomes, stillbirth, large for gestational age babies and admission to the neonatal unit were considered to be critically important and are included as secondary outcomes in this proposal. Many of the safety outcomes are the same as the pregnancy complications evaluated in our proposal. For e.g., preterm birth, small for gestational age, stillbirth, perinatal death are all currently being evaluated. As part of the core outcome set development group for gestational diabetes, we have identified the minimal outcomes for reporting, which are incorporated in our proposal along with safety outcomes.

3.5. Economic evaluation

Our previous cost-effectiveness analysis (HTA report 2017) based on IPD meta-analysis indicated the likelihood of cost per case of gestational diabetes avoided to be around £3,000.[11] But the relatively small numbers of studies reporting non-significant reductions in gestational diabetes limited the findings. Since then, the number of studies have doubled.

In collaboration with Monash University, we recently updated (2019) the cost-effectiveness of lifestyle interventions using aggregate data on reducing a composite outcome of gestational diabetes or pre-eclampsia. The base-case model for overall interventions was close to cost-neutral. There were 2.25% fewer cases of gestational diabetes and/or preeclampsia (control: 11.8% vs intervention 9.5%), at an overall cost of AUD 34 per person. The incremental cost-effectiveness ratio was AUD 1,507 per case prevented. Models were cost-saving for the obese women (BMI ≥ 30kg/m^2) and was essentially cost-neutral for overweight women (BMI ≥25 kg/m^2). [37]There is need for an updated UK economic model that is underpinned by the IPD meta-analysis findings of lifestyle interventions'' effect on gestational diabetes in light of the above progress.

4. Why is HTA Evidence synthesis stream appropriate for this proposal?

The HTA Programme 'funds research about the clinical and cost-effectiveness and broader impact of healthcare treatments for those who plan, provide or receive care from the NHS and social care services.' Our proposal assesses the clinical and cost effectiveness of the lifestyle interventions with direct benefit to women and their babies by reducing gestational diabetes. Given the limited NHS resources, our proposal will meet NHS priorities by determining if the interventions should target specific groups of women and provide the necessary cost-effectiveness information. By determining the optimal intensity and type of lifestyle intervention, our work will directly lead to clear recommendations by guideline bodies, policy makers and Commissioning Groups, with a 'clear trajectory to patient

benefit', with translation into clinical practice in the NHS within the next 5 years. Finally, by building on previous research investment our work will minimise research waste, key goal for NIHR.

5. Aims and objectives

Aims

To determine whether diet and physical activity-based interventions in pregnancy reduce the risk of gestational diabetes and its complications to the mother and baby, and if the effects vary according to maternal characteristics and the intervention components, and if they are cost-effective.

Objectives

Primary

1. To evaluate the effects of diet and physical activity-based lifestyle interventions in pregnancy, across all interventions, and for each type of intervention (diet-based, physical activity-based, mixed) on gestational diabetes as defined by NICE (The National Institute for Health and Care Excellence) and any criteria
2. To assess the differential effects of interventions according to the maternal characteristics (BMI, age, parity, ethnicity and socioeconomic status) on gestational diabetes

Secondary

3. To evaluate in women with gestational diabetes, the effects of the interventions on critically important outcomes in a) maternal complications (hypertensive diseases, caesarean section or preterm birth) and b) offspring complications (stillbirth, large for gestational age or admission to the neonatal unit)
4. To categorise the interventions by core components and undertake network meta-analysis to rank them by effectiveness (see section 3.3)
5. To assess the effects of interventions for specific other definitions of gestational diabetes (WHO, IADPSG, modified IADPSG), and on fasting and 2-hour post-prandial glucose levels
6. To determine the cost-effectiveness of interventions using decision analytic modelling

6. Research Plan

6.1. Health technologies assessed

We will evaluate three main interventions for gestational diabetes prevention in pregnancy: diet-based, physical activity-based, and mixed approach interventions incorporating diet and physical activity components underpinned by behavioural approach. Diet-based interventions include various dietary patterns such as Mediterranean-style diet, low calorie diet, low glycaemic index diet, which are offered by clinicians, dieticians, physiotherapists or commercial companies in both primary and secondary care settings. The interventions are delivered using vehicles such as print or digital media, face-to-face meetings in either 1-1 or group sessions, and are commenced at various time points in pregnancy and delivered in an intense regimented or pragmatic manner. The physical activity-based interventions involved moderate exercise such as aerobic dance program, hydrotherapy, stationery cycling or light intensity resistance training. The mixed approach includes both diet and physical activity with behavioural component.

6.2. Design

IPD meta-analysis of randomised trials

6.3. Methods

Our IPD meta-analytical approach will follow existing methodological guidelines and adhere to the PRISMA-IPD reporting statement[38] developed by members of our team. We will address the following structured question in our project (Table 3).

Table 3: Research question in a structured format

Question Components	
Population	Pregnant women with a BMI ≥ 18.5 kg/m^2 in early pregnancy
Interventions	Diet based Physical activity based Mixed approach - Diet and/or physical activity with behavioural component
Outcomes	**Primary outcomes** Gestational diabetes defined as per 2015 NICE criteria (fasting glucose 5.6 mmol/l or above, and 2 hour glucose 7.8 mmol/l or above after a 75 g oral glucose tolerance test),[2] and any criteria **Secondary outcomes** Gestational diabetes with maternal and /or offspring complications *Maternal*: hypertensive diseases including pre-eclampsia, caesarean section, preterm birth, need for pharmacological therapy for hyperglycemia *Offspring*: shoulder dystocia, respiratory distress syndrome, neonatal hypoglycemia, stillbirth, neonatal death, perinatal death, Apgar score at 1 and 5 minutes, birthweight, gestational age at birth, small/large for gestational age and admission to the neonatal unit Gestational diabetes as defined specifically using IADPSG,[39] modified IADPSG [10, 40] and WHO criteria[41]
Study design	Randomised trials

6.3.1. Identification of relevant trials and data acquisition

The i-WIP database is a 'living' repository. We continuously update our search annually; the last update was in June 2018. Our final search update for the proposed i-WIP GDM meta-analysis will be in March 2020, and we will continue our efforts to contact researchers of new studies to join the Collaboration.

We will update the search using our existing search strategy[9] to identify all relevant trials that have been published and unpublished (completed). This step is particularly necessary because new research evidence have appeared since completion of our systematic review (HTA 09/27/06). The following databases will be searched: MEDLINE, EMBASE, BIOSIS, LILACS, Pascal, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). Our detailed search strategy is available as an HTA monograph.[11] Language restrictions will not be applied.

The i-WIP IPD collaborators will examine the included study list to identify any studies or data that might have been missed. We will include full reports or conference abstracts of trials with random allocation (individual or cluster) on diet and physical activity-based interventions in pregnancy compared to standard antenatal care. Any trials that included women at baseline with gestational diabetes will be excluded.

In the first two months into the project, we will ensure that the data from all new studies (identified up to Aug 2020) have been deposited and will verify their quality. Our existing memorandum of understanding will cover the provision of data by the principal investigators of the individual trials, and any publication of the IPD meta-analysis project will be in the name of the collaborative group, with all contributors listed. The i-WIP group's long-standing working partnership will examine the protocol for refinements; discuss the variables on which the data are to be collected, the data checking procedures and the main analyses to be performed; and agree on a timetable and a publication policy.

6.3.2. Data collection, quality check and harmonisation

Our existing i-WIP dataset will be enlarged by adding new studies. We will use our previously peer-reviewed robust methods to assess the quality of the new studies, and extract and format the relevant data.[11] We will use the Risk of Bias tool developed by the Cochrane Collaboration to score the quality of each study.[42] Sensitivity analyses will examine the robustness of statistical and clinical conclusions to inform the inclusion or exclusion of trials deemed to be at high risk of bias.

We will extract additional data from existing and new studies where possible on the diagnostic criteria and oral glucose tolerance test values used to diagnose gestational diabetes. We will also extract relevant information on the intervention components, and offspring and maternal complications. We will follow the established, tested and trialled procedures used for data harmonisation in the i-WIP database.[43] This will facilitate smooth and timely execution of the most time-consuming stage of the study, i.e. data cleaning and its harmonisation.

6.3.3. Data synthesis

- Overall effect and sub types of intervention

The effectiveness of the diet and physical activity-based interventions will be assessed using IPD meta-analytical framework.[24] The main outcomes will be gestational diabetes as defined by NICE,[2] and by any criteria. For each intervention type (all interventions, diet-based, physical activity-based, and mixed approach), we will perform one-stage and two-stage IPD random-effect meta-analyses to obtain the pooled intervention effect on gestational diabetes via REML estimation or for non-continuous outcomes, ML estimation. Confidence intervals will be inflated to account for uncertainty in variance estimates (e.g. using Hartung-Knapp and Kenward-Roger corrections).[44] One-stage and two-stage analyses usually give similar results, and so any discrepancies will be resolved.[45] We will use a random effects meta-analysis approach, which allows for between-study heterogeneity in intervention effect. If no between-study heterogeneity is found to exist, this model suitably reverts to a fixed effect model.

Heterogeneity will be summarised using the I^2 statistic (which provides the proportion of total variability that is due to between-study heterogeneity) and the estimated between-study variance ('tau-squared'). To reveal the impact of heterogeneity more clearly, we will also calculate a 95% prediction interval for the intervention effect when applied in an individual clinical setting. The above analyses will also be undertaken for secondary outcomes, and gestational diabetes defined using other specific criteria such as IADPSG,[39] modified IADPSG,[10, 40] and WHO.[41]

- Differential effect by subgroups (treatment-covariate interactions)

We will examine whether a woman's BMI, age, parity, ethnicity, and socioeconomic status modify intervention effect. This will be undertaken by extending the two-stage and one-stage meta-analysis framework to include and then summarise treatment-covariate interaction terms, which provides the change in intervention effect for a 1-unit change in the covariate. Ecological bias due to study-level confounding will be avoided using the deft approach of Fisher et al.[1] Continuous variables will be kept as continuous to avoid arbitrary dichotomisation, and non-linear relationships and interactions modelled using restricted cubic splines and fractional polynomials. Subgroup analyses, if not carefully planned, can lead to misleading results e.g. due to the play of chance with multiple testing.[42] Thus caution will be used in interpretation of the collective set of subgroup results, and adjustment for multiple testing considered as necessary. However, we reiterate here that our IPD meta-analysis will increase the power (often > 80%) to detect genuine subgroup effects (treatment-covariate interactions) and will also allow us to examine if there is consistency in the subgroup effect from study to study, rather than being a chance finding in a single study for example.

- Examining potential sources of bias

Small study effects (potential publication bias) will be investigated through the construction of contour-enhanced funnel plots and appropriate statistical tests. To examine the impact of studies with unavailable IPD, we will extract (where available) appropriate aggregate study-level data (e.g., interaction estimates) and incorporate them alongside the IPD using two-stage IPD random-effect meta-analysis.[46]

- Dealing with missing variables

Multiple imputations will be used to impute partially missing variables within each study separately, under a missing at random assumption. If there are systematically missing variables then, where considered plausible, these will also be imputed by borrowing information across studies, while allowing for heterogeneity and clustering in a multi-level imputation model.[47]

6.4. Sample size consideration

Brookes et al[48] note that about 4 times the size of a single trial is required to detect an interaction with the same size as the overall treatment effect. We currently have access to the data shared/agreed for at least 24,766 women (58 studies). The sample size has the potential to be increased further to 27,538 women (71 studies) and beyond, depending on decisions to share data by other identified studies, and by the number of new studies published after June 2018.
We have undertaken a simulation-based approach to calculate the power of estimating genuine treatment-covariate interactions in our planned IPD meta-analysis, conditional on the number of trials, number of participants available in each trial, and the covariate characteristics (e.g. proportion Caucasian, mean and SD of BMI), whilst allowing for between-study heterogeneity in the treatment effect and the control group risk. [49, 50] We calculated the power to detect a particular treatment-covariate interaction effect size in the subset of trials that report each covariate of interest (BMI, age, ethnicity, parity, and socioeconomic status). The results are shown in Table 4 below for an assumed interaction between covariate and treatment effect for a 30% (OR 0.70) and 25% reduction in gestational diabetes (OR 0.75) using the sample size of available/agreed IPD (58 trials), and if all 71 trials shared their IPD. We expect to have sufficient events for the overall effect, and for most of the secondary outcomes with 5291 caesarean sections, 1154 preterm births; 1769 hypertensive diseases; 2483 large-for-gestational age babies; and 1420 babies admitted to the neonatal unit.

*Table 4. Estimated power by simulation based on the IPD currently available in i-WIP database**

Covariate (subgroup) of interest		Assuming all 71 trials identified so far provide their IPD		For the 58 trials with IPD available/agreed	
		No. of trials (total participants) available for the covariate	Estimated power by simulation	No. of trials (total participants) available for the covariate	Estimated power by simulation
Assuming an interaction between covariate and treatment effect that corresponds to an OR of 0.70					
BMI**	Obese vs. non-obese	70 (27,722)	99.0%	56 (24,443)	97.6%
Age	Continuous assuming linear trend	69 (27,422)	79.1%	55 (24,143)	78.4%
Ethnicity	Caucasian vs. non-Caucasian	48 (21,958)	93.4%	39 (19,394)	90.4%
Parity	Nulliparous vs. multiparous	59 (22,253)	95.4%	48 (19,718)	93.4%
Socioeconomic status	High vs. low	50 (21,136)	95.0%	41 (19,426)	90.0%
Assuming an interaction between covariate and treatment effect that corresponds to an OR of 0.75					
BMI**	Obese vs. non-obese	70 (27,722)	92.8%	56 (24,443)	89.2%
Age	Continuous assuming linear trend	69 (27,422)	72.4%	55 (24,143)	65.2%
Ethnicity	Caucasian vs. non-Caucasian	48 (21,958)	79.8%	39 (19,394)	74.4%
Parity	Nulliparous vs. multiparous	59 (22,253)	85.8%	48 (19,718)	77.2%
Socioeconomic status	High vs. low	50 (21,136)	85.4%	41 (19,426)	83.2%

* assuming baseline risk of gestational diabetes is 11% on average, varying from 2% to 43% according to trial characteristics; ** BMI Body Mass Index

6.5. Decision analytic modelling

The success of any intervention in preventing gestational diabetes must consider the resources required to achieve this outcome. Additional costs must be justified in terms of any additional benefits attributed to them. The main objective is to determine the relative cost-effectiveness of interventions involving diet and physical activity to prevent gestational diabetes and complications compared to usual care.

6.5.1. Our Clinical Data

The primary maternal outcome in this study relates to the impact of gestational diabetes on the mother as well as maternal complications (pre-eclampsia, preterm birth, caesarean section). Offspring outcomes include stillbirth, small for gestational age, large for gestational age babies and admission to the neonatal care unit.

For the intervention effect, data from the IPD meta-analysis will estimate pooled effect odds ratios for the development of gestational diabetes. The baseline risk for the usual care group will be calculated on the pooled data for the control groups included in the trials. Maternal outcomes will not be considered where they are already observed at baseline, i.e. we will not count the presence of gestational diabetes in women who had diabetes at baseline. The estimated risk of maternal death will be from appropriate recent sources.[51, 52]

6.5.2. Cost Data

NHS reference costs will provide much of the required cost data and additional secondary sources will be interrogated. Costs from all secondary sources will be inflated as appropriate using the hospital and community health services pay and prices index.[53] Costs presented in foreign currency will be converted to UK pounds using historical annual average rates[54] and then inflated to current prices. The estimation of the cost of the weight management interventions will be based on the results of a systematic review (to be updated) of economic evaluations of weight management interventions in pregnancy which has already been conducted in our previous study on this topic[11] which was conducted for our previous study. The earlier review identified four studies that were concerned with the cost-effectiveness of lifestyle interventions for women with gestational diabetes. Estimates of antenatal and postnatal care costs are available in our previous systematic reviews of the literature as previously reported in our earlier study.[11]

6.5.3. Methods

In the model based economic analysis, diet and physical activity-based interventions in pregnancy will be compared with care as usual (control). The appropriate model is a decision tree due to the short-term nature of the decision problem. The model will developed using TreeAge Pro 2017 software (TreeAge Software, Inc., Williamstown, MA, USA). The structure and pathways will be informed by the data and trials included in the IPD meta-analysis, clinical input, NICE guidelines on the management of women in pregnancy and the approaches adopted in our previous model-based economic evaluations.[11] For completeness, the model will include all the potential pathways that could be followed by the women. Women will enter the model at the point of randomisation, to receive the intervention or care as usual (control). It is likely that a number of assumptions will be required to complete the model-based analysis.

6.5.4. Analysis

Several separate analysis are likely to be required. The main analysis will compare costs and outcomes for a hypothetical cohort of 10,000 pregnant women, based on the results of the IPD meta-analysis for all women. A secondary analysis is likely to compare costs and outcomes for sub-groups of women based on their characteristics such as BMI, age, ethnicity, parity and socio-economic status to

allow exploration of whether a lifestyle intervention in selective subgroups of women a more cost-effective strategy compared with care as usual.

For all analyses, the relative cost-effectiveness of the intervention will be evaluated using effect size estimates from the IPD meta-analysis. An incremental approach will be adopted with a focus on the additional costs and benefits associated with a move from care as usual to diet and lifestyle interventions to manage weight gain in pregnancy. The results will be reported in terms of an incremental cost-effectiveness ration (ICER) of cost per unit of benefit gained, measured in natural clinical outcomes. The analysis will be conducted from the perspective of the health service (NHS) and only direct health service will be included. The time-horizon adopted for both the primary and secondary analyses will be the start of pregnancy until the mother and infant are discharged from hospital following the birth. Missing data will be addressed in the IPD meta-analysis.

6.5.5. Sensitivity analysis

Deterministic and probabilistic sensitivity analyses (PSA) will explore the effects of the inherent uncertainty in the parameter estimates on the results produced by the model. For PSA, Monte Carlo simulation will be used to sample from the distributions to allow the effect of parameter uncertainty to be evaluated. 1000 repeated random draws from the distributions to indicate how variation in the model parameters would affect the results and hence illustrate the decision uncertainty. Beta distributions will be used for binomial data, lognormal distributions for odds ratios and Gamma distributions for costs. When there are more than two possibilities at a chance node, a Dirichlet distribution would be applied but to populate a Dirichlet distribution all included studies must have reported data for all the branches from the appropriate chance node – this was not our previous experience. Using the Net Monetary Benefit (NMB) for each of the 1000 simulations, the proportion of times the intervention has the highest NMB will be calculated for a range of threshold values for the maximum willingness to pay for a major outcome averted. These will be summarised graphically using a cost-effectiveness acceptability curve (CEAC) to show the uncertainty surrounding the cost-effectiveness of the intervention, for a range of thresholds for cost-effectiveness. A value of information analysis will be conducted to estimate the expected costs of uncertainty. The expected cost of uncertainty is calculated by estimating the probability of making a wrong decision based on existing evidence, and the consequences of this wrong decision. The expected value of perfect information (EVPI) estimates the difference between the expected value of the decision made with perfect information and the decision made based on existing evidence. EVPI was calculated based on the methods described in Claxton and Posnett. Among the many deterministic analysis to be explored the effect of considering a longer time horizon will also be included.

7. Dissemination

Dissemination of research findings is a key responsibility of the researcher. Apart from it being an ethical obligation, dissemination of the results to the following groups is necessary to facilitate rapid translation of relevant findings into clinical care.

Professional groups and organisations: The findings will be shared through email, meetings and presentations by building on the existing links developed by co-applicants as members of Academic Committees, working groups and executive committees with Royal Colleges of Obstetricians and Gynaecologists (RCOG), Physicians (RCGP), General Practitioners (RCGP), Midwives (RCM), Diabetes Clinical Study Groups of Diabetes UK and Association for the Study of Obesity (ASO). The maternal medicine CSG (Clinical Study Group) at RCOG will facilitate dissemination to clinicians and midwives across UK (see letter of support).

Policy makers and guideline developers: Prof Thangaratinam and Dr Heslehurst are part of the working group on lifestyle interventions to tackle maternal obesity chaired by the Directors for

Prevention, and Clinical Director for Obesity and Diabetes at NHS England. Both Directors are interested in our i-WIP Programme of work. We will invite them to the 1-day workshop where our findings will be presented, and implications on translation into clinical practice will be discussed in detail. Outputs will be presented to the UK CMOs (physical activity is a standing item on their meeting agenda) mimicking the dissemination and implementation of the new CMO Infographic for physical activity and pregnancy/postpartum. We have a track record of working with National Guideline Alliance (NGA) for NICE guidelines in our current HTA-funded work on fetal growth restriction, to ensure that the findings are shared with NICE guideline committees on antenatal care and diabetes in pregnancy.

NHS Providers and healthcare professionals: We will work with Pan London Diabetes in Pregnancy Community of Practice group, leads of Maternity Transformation Programme (London, Black Country Local Maternity Services Healthy Pregnancy Work-stream), Clinical Directors, and CCG leads in the interpretation and dissemination of findings. Key members from these groups will be invited to join our independent project steering group to generate ideas for how we can adapt interventions to ensure generalisability. We will link engage with primary care and public health professionals through Applied Research Collaborations (ARC) in West Midlands, North Thames and South London who will co-adopt the proposal (see letters of support), and aid in the active dissemination of the findings and widen our engagement with Academic Health Science Networks (AHSN).

Patient and Public: A regular newsletter will be sent to the collaborators updating and highlighting the work. We will also liaise closely with Katie's Team, Diabetes UK, British Nutrition Foundation (BNF), British Dietetics Association (BDA), local community groups (Women's Health and Family services, East London), Obesity UK and other interested groups to share our findings. Mrs Moss, our PPI member is part of the Women's Voices group in RCOG and will promote our findings within RCOG curriculum. We will take advantage of North Thames ARC's successful PPI infrastructure, their lay Research Advisory Panel (RAP) and virtual Document Review Panel, and engage with the CRN North Thames and Barts Health's pilot 'Patient Ambassador' schemes to disseminate findings to the community

Global Networks: ST, HT, CH are part of HiPPP (Health in Preconception, Pregnancy and Post Birth) Collaborative group, an international network to improve lifestyle and prevent maternal obesity and complications such as gestational diabetes. The findings will be disseminated through HiPPP's extensive contacts including stakeholders across community, government, private and public health services, workplaces, primary care, women, and international collaborators. NH is a member of the European Association for the Study of Obesity and the World Obesity Federation, and we will leverage her links with these groups to further disseminate the findings.

Digital and media coverage: In addition to publications and presentations, the details of the project and findings can be accessed at the institutional websites of the collaborators, i-WIP website, and GONET (Global Obstetrics Network – letter of support provided). We will share the research findings by staging press releases and through with relevant, factual and informative reporting. We will replicate our dissemination strategy that was covered by over 100 media outlets (i-WIP, ESTEEM publications).

Stakeholder workshop: After completion of the project, we will convene a workshop of above stakeholders to obtain their views on the integration of effective interventions into routine care, the barriers and facilitators, the resource requirements, and how the interventions could be adapted to local needs. We have experience in doing so, for example, we are working with Black Country LMS on implementing local needs specific interventions to improve detection of diabetes in women with a history of gestational diabetes.

8. Barriers for further research, development, adoption and implementation

Currently, the key barriers to implementation of effective interventions to prevent gestational diabetes include: lack of robust evidence on the effectiveness; lack of clarity about key components of complex diet and physical activity interventions; and lack of information on costs associated with interventions; lack of information on who should be targeted. Our IPD meta-analysis will answer these questions.

Another important challenge is to ensure that interventions and economic models are fit-for-purpose for policy making, by basing them on objective, rigorous evidence, and by having them flexible enough to allow policymakers to make different assumptions to assess the impact on mother and child at various time points. This requires frequent and in-depth interactions between multi-disciplinary researchers and policymakers, which is currently lacking. This is a key area where we plan to focus our efforts through a comprehensive dissemination strategy (see section 7).

The collaborative efforts need to take into account the equity challenges within systems such as low socioeconomic status, deprivation, and ethnicity, which are linked to variations in gestational diabetes rates, and affect access to interventions. Organisational or delivery system-wide challenges depend on the setting, type of intervention, mode of delivery (digital, groups, individual-based), and workforce skills. An additional challenge is to rebalance the ongoing local, regional and national efforts and initiatives to tackle diabetes and obesity, with maternity transformation strategies focusing on improved maternal and child health, alongside efficient workforce skills development.

We will robustly address these by first identifying if the interventions need to be targeted to these groups, and then by working with policy makers and PPI groups to identify ways to implement and reach communities that have the most need. Economic evaluation within a complex system of pregnancy is difficult, with their emergent properties and the interactions between various confounding variables within the system. We will address these by providing the evidence on cost-effectiveness of lifestyle interventions, that can be adapted to various settings.

By working with key organisations, groups including influential knowledge brokers such as Diabetes UK, and the public, we will work towards incorporating prevention of gestational diabetes through lifestyle interventions into any priorities set to reduce maternal and new-born mortality and morbidity.

9. Expected impact of prevention of gestational diabetes

- *Anticipated direct impact*

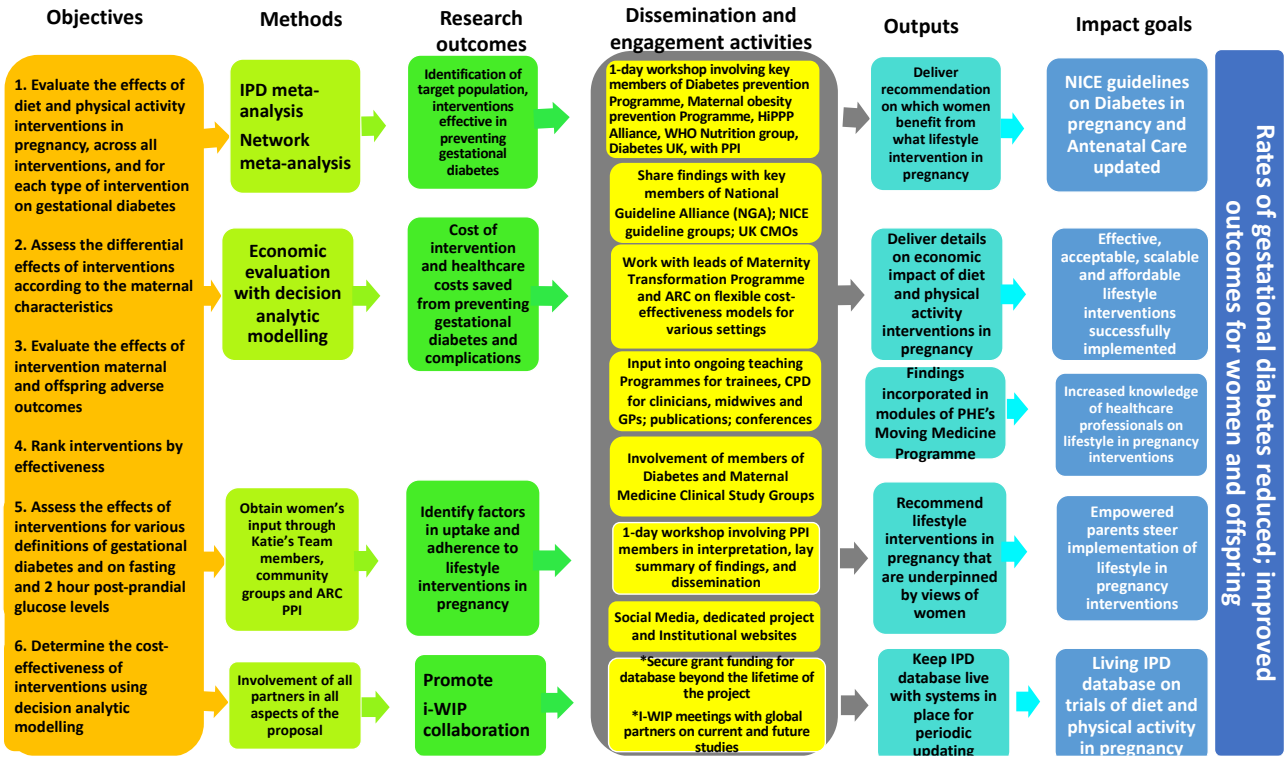
Guidelines: We expect our findings to be incorporated into NICE antenatal care guidelines on recommended diet and physical activity interventions in pregnancy, NICE diabetes in pregnancy guidelines, and RCOG Green Top guidelines on obesity in pregnancy. The UK CMO's recommendations on physical activity in pregnancy will be updated based on our findings. We will share our findings with the WHO guideline development group, which will include details on which interventions are effective, acceptable and scalable.

Policies: Our work will directly feed into the ongoing efforts of NHS England to identify effective lifestyle interventions to prevent maternal obesity and complications like gestational diabetes. We expect our findings to lead to recommendations for implementation, which may necessitate pilot projects in real-life scenario. Current dietary recommendations including 5-a-day may need to be expanded if additional beneficial components such as nuts and olive oil used in Mediterranean-style diet have been found to be effective.

NHS, primary care and public health strategies: If specific subgroups of women were found to benefit the most, this can lead to re-organisation or commencement of new services in primary and

secondary care. For e.g., if women with obesity were found to benefit the most, current weight management services will need to incorporate the specific components of the intervention found to be most effective in preventing gestational diabetes. Furthermore, with increasing access to digital interventions, these findings could lead to the delivery of the intervention to virtual target groups. The cost-effectiveness findings and details on the type of effective intervention are key factors in implementing this plan.

Fig 2. Pathway to impact



Improved knowledge of healthcare professionals: The outputs will be included in Public Health England's Moving Medicine Programme modules (Foster is Chair of their Academic Advisory Committee) will help doctors, midwives, and physiotherapists advise patients on how physical activity can help to prevent gestational diabetes. Our comprehensive dissemination strategy will reach a wide range of healthcare professionals. Healthcare professionals will be better informed on what type of lifestyle intervention to recommend to pregnant women, which would be underpinned by the views of women.

Expanded living i-WIP database: By incorporating new studies and data, the existing i-WIP database will be more than doubled in size, with the ability to update itself as new studies emerge. Our arrangement with global collaborators ensures that any of the collaborators can apply to their funders to both access and maintain the database in the future.

- *Anticipated long-term impact*

Improved outcomes for women and children: In the long-term, implementation of lifestyle interventions has the potential if found to be effective by up to 35%, resulting in up to 14,000 fewer women with gestational diabetes each year. This could translate to a reduction in maternal and offspring morbidity associated with the condition during pregnancy. This has a further potential to have an impact on Type 2 diabetes prevalence, and positive impact on an individual's health, reduced economic burden to the society and lowered NHS costs. At the population level, reduction in type 2

diabetes will lead to a total potential saving of £299 million within 5 years and £4.5 billion within 25 years.[55]

10. Contribution to Collective Research Effort

Prevention of gestational diabetes and diabetes overall continues to be a priority area nationally and for research. The NIHR has funded many primary studies evaluating the effects of pharmacological and non-pharmacological interventions to prevent gestational diabetes and its complications.[9-12] Despite this, the effectiveness of lifestyle intervention for preventing gestational diabetes is still uncertain, and there are currently no national or international guidelines on recommended interventions to prevent gestational diabetes. Our proposal will provide definitive answers to this.

We have previously shown in our IPD meta-analysis that women of all body mass index (BMI) groups could benefit from specific advice on diet and physical activity for weight gain in pregnancy. Findings from this proposal will show whether this benefit extends to gestational diabetes and other maternal or neonatal outcomes. Identification of the subset of women who would benefit from lifestyle interventions in pregnancy to prevent gestational diabetes will allow us to evaluate whether targeted management of these group of women will improve their pregnancy outcomes. We will also be able to evaluate whether there is any differential effect according to the individual components of the intervention on pregnancy outcomes, which is required to provide detailed recommendation.

For the first time, the UK Chief Medical Officers (CMOs) have included advice on exercise in pregnancy in their physical activity guidelines,[58] informed by our work on physical activity for weight gain in pregnancy (both aggregate and IPD meta-analysis),[11, 33] which highlighted the potential of lifestyle interventions in reducing gestational diabetes. Our collaborative partnership with the CMOs mean that findings from this proposal will be swiftly implemented in updating the CMOs recommendation to include the effects of these interventions in reducing gestational diabetes and other pregnancy outcomes.

The World Health Organization (WHO) have refrained from recommending lifestyle interventions for the prevention of gestational diabetes in their guideline recommendation on antenatal care in pregnancy due to low certainty in the available evidence.[56] Views of healthcare providers and women have suggested that in the presence of good quality evidence, they would be keen to offer and accept lifestyle advice that may lead to a healthy baby and better pregnancy outcomes including prevention of gestational diabetes.[57] The WHO have made assessing the effects of lifestyle interventions in pregnancy on maternal outcomes including gestational diabetes, as well as assessing whether these are generalizable to all women a priority in their research recommendations.[56]

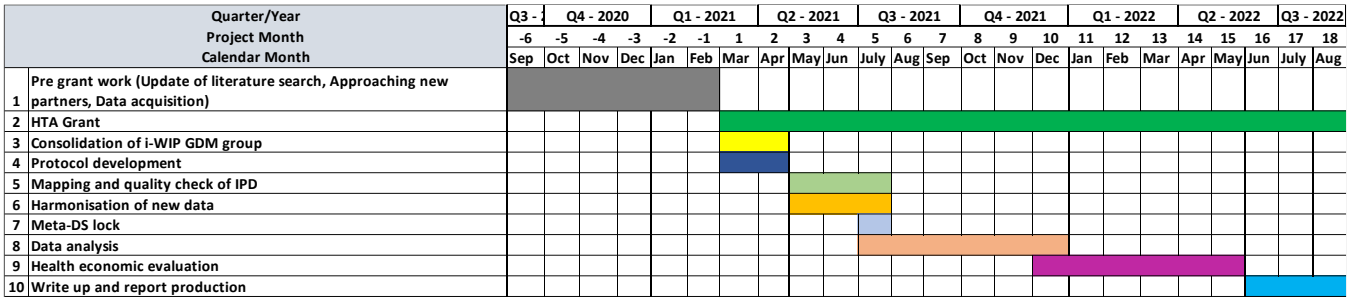
Our work with Prof Teede at Monash University on the taxonomy of complex lifestyle interventions in pregnancy will provide detailed description of physical activity patterns and categorise these based on the frequency, intensity and duration. This is necessary to inform specific guideline recommendation, and our cost effectiveness evaluation will build on our previous work.

Funding from the NIHR and WHO in establishing the i-WIP collaborative group as the largest global database on diet and physical activity interventions in pregnancy, provides an opportunity to answer numerous research questions in relation to lifestyle intervention in pregnancy.

11. Project timetable

The project will span over 18 months (Mar 2021 – August 2022) with a six-month pre-grant phase (Sep 2020 - Feb 2021). When the funding is confirmed, we will commence the work in the pre-grant phase that will allow us to start the project in March 2021. This will consist of an update of the literature search, contacting new potential partners (authors of recently published trials) and data

acquisition. The new i-WIP GDM group will be consolidated at the project's start and within two months from the start of the project, we will finalise the study protocol with the collaborative group input (Mar 2021 – Apr 2021). Data-related work such as quality check, harmonization and merging will last three months with meta-dataset lock planned in July 2021 and data analysis from July to Dec 2021. The economic evaluation will be carried out following the analysis from Dec 2021-May 2022, with 3 months for write-up of the HTA report.



Key project deliverables

Update meta-dataset with GDM-related data
Final study report for the funder
Scientific publication in a high-impact journal
Infographic for lay audience summarising study findings.

Fig 3. Gantt chart

12. Project management

Queen Mary University of London (QMUL) will be the Sponsor and host organisation, with ST as the Chief Investigator. Subcontracts will be put in place between QMUL and Institutions of the co-applicants on data sharing, responsibilities and the expected contributions of each party. We already have agreements in place to access the datasets, and we will get the collaborators to reconfirm the use of their data for this particular project. The i-WIP Data Access Committee (DAC) has reviewed the proposal for this project and has given its support and approval to access the I-WIP data (letter of support attached). The i-WIP Publication Committee will oversee the publications arising from the project.

The CI is responsible for the conduct of the project and decision-making. All staff will share the same duty of care to prevent unauthorised disclosure of personal information and act according to the Data Protection Act 1998 & Good clinical governance. A project management group (PMG) will manage the work with monthly meetings. An Independent Project Steering Committee will provide overall supervision and ensure adherence to Research Governance framework and GCP Guidelines. The Project Steering Committee will meet three times and will include one PPI member, public health specialist, statistician, clinician, midwife, dietician, and physical activity expert.

13. Ethics / Regulatory approvals

The current proposal is an evidence synthesis project involving meta-analysis of anonymised datasets. No further ethical considerations or approvals are needed for this project, in line with our other IPD meta-analyses.

14. Patient and Public Involvement

The Katherine Twining Network's Katie's Team has been actively involved in the preparation of this application and is part of the research team (co-applicant) undertaking the project. The group includes mothers, pregnant women, carers and family members with an interest in improving the quality of research within women's health. Katie's Team members contributed to the fine-tuning of the primary

outcomes of this proposal by providing feedback on what they consider to be an important outcome. A PPI member will provide input though participation in Steering Committee meetings. Katie's team will contribute to study reports and help in the dissemination of the findings. We will also liaise closely with Diabetes UK, Obesity UK, British Nutrition Foundation (BNF) and other interested groups regarding the dissemination of the findings of the analysis. We have provided further detail in the section dedicated to PPI in the application and will follow the PPI framework that we have developed for engagement in the proposed project.

15. Project expertise

The proposed project continues the collaborative work of the i-WIP network. We carefully planned the inclusion of co-applicants from the UK and abroad with a wide, complementary, diverse and expertise in clinical, methodological, and implementation work involving IPD and aggregate meta-analyses, and primary trials on diet and physical activity-based interventions in pregnancy. Support from the Global Obstetrics Research Network (GONet www.globalobstetricsnetwork.org) and World Health Organization (WHO) has strengthened the i-WIP Collaborative Group. We have credibility and links to influence strategy within our profession both at the national and international levels.

Prof Thangaratinam: successfully led the HTA funded the IPD and aggregate meta-analyses on diet and physical activity in pregnancy;[33] leads the global i-WIP collaborative group, and the NIHR funded IPPIC (International Prediction of Pregnancy Complications) IPD Network; manages women with gestational diabetes in her role as Consultant Obstetrician.
Prof Riley: leading expert in methods for IPD meta-analysis; many IPD methodology papers published; leads a dedicated statistical training course on IPD meta-analytical methods and on prognosis research methods to identify treatment-covariate interactions.
Dr Foster: expertise in physical activity research; led the UK Chief Medical Officers' infographic on physical activity in pregnancy, and harmonisation of the physical activity exposure measures as well as PI of the UK Physical activity guidelines for pregnancy and post-partum evidence reviews. He is Chair of UK CMOs Expert Committee for Physical Activity, providing advice on physical activity promotion to the governments of the four nations in the UK.
Dr Heslehurst: Nutritionist and translational research expert in maternal obesity. Dr Heslehurst is funded through an NIHR career development Fellowship, and is working on the NIHR-funded i-WIP database by applying adiposity prognostic measures/models to stratify estimates of the effectiveness of interventions at preventing adverse outcomes. She is also a trustee for the Association for the Study of Obesity, a UK charitable organisation dedicated to the understanding, prevention and treatment of obesity.
Dr Nirantharakumar: Public Health Consultant and Senior Lecturer; focuses on preventing gestational diabetes and subsequent Type 2 diabetes, funded by MRC Fellowship.
Prof Roberts: Health economics lead for i-WIP studies
Ngawai Moss: Mother and member of Katie's Team since 2015 with previous experience of providing input into trials on lifestyle and other interventions in women's health; she is also a member of the INVOLVE Advisory Group and a lay member on the NIHR Programme Grants for Applied Research Sub Panel.
Prof Teede: Leads the work on taxonomy of lifestyle interventions in pregnancy; implementation research on prevention of gestational diabetes; clinical diabetologist and Chief Investigator (CI) of two NHMRC Centres for research excellent in Women's health, with Prof Thangaratinam as international CI collaborator.
Dr Betran: researcher in maternal and perinatal health at Department of Reproductive Health and Research at WHO; i-WIP data access executive committee member.

Prof Simpson: behavioural scientist with extensive experience of evidence synthesis of complex interventions. She has developed and led three NIHR and MRC funded trials of lifestyle interventions (HTA 08/04/44; MRC G0802038 and PHR 12/180/20).
Prof Hitman: Diabetologist, CI on FP7 project on effects of lifestyle in pregnancy on obesity and diabetes in South Asian women.
Prof Poston: Led the NIHR primary trial on effects of diet and physical activity in pregnancy on gestational diabetes.
Dr Allotey: experience in IPD and aggregate meta-analyses, and research fellow co-ordinator of the IPPIC projects (pre-eclampsia, fetal growth restriction and stillbirth)
Dr Iliodromiti: Expertise in reproductive and perinatal epidemiology, data linkage and big data analysis
Frances Austin: Registered dietitian specialising in antenatal diabetes, obesity, under-weight, education & training
Dr Dodds: Senior manager of Barts Research Centre for Women's Health and responsible for overall governance.

16. Success criteria and barriers to proposed work

- **Identifying new studies**

We expect to have identified all relevant studies that have been published since the completion of our last IPD meta-analysis in 2017. The risk of us unable to complete this by the start of the project is minimal, as our last search update will be performed in September 2020, allowing us sufficient pre-grant time to identify new trials. We have in-house resources to do the preliminary work.

- **Addition of new data and variables to the i-WIP database**

The proposed project includes two components that require completion prior to analysis: deposit, coding and standardisation of data from new studies; and inclusion of new variables to the existing database such as individual blood sugar levels used to diagnose gestational diabetes in the oral glucose tolerance test. We have already started contacting authors, and have started depositing new data to the database. Over the next 10 months, we expect to have the data of most of the collaborators in the database. Our partnership with Australian team has already resulted in the extraction, cleaning, coding and standardisation of blood sugar levels in the existing studies. Hence, we will only need to obtain the information from the newer studies.

- **Cleaning and formatting of the data and analysis**

Based on our experience of conducting IPD meta-analyses, delays in formatting are usually the result of delays in access to the data. Since we will ensure that we have access to all relevant data by the first month of the project, we expect the 6 months allocated for cleaning and formatting the data to be sufficient. Our statistical team is familiar with the i-WIP data and the database, with expertise in this area. Hence, we do not expect major difficulties with the analysis.

- **Staff**

If there are any staff dropouts, we have sufficient flexibility in ensuring that the work will not be halted, by involving our core funded BARC (Barts Research Centre for Women's Health) staff in the project, until replacement is made.

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