Improving health outcomes for pregnant women with metabolic risk factors

Randomised and observational studies and evidence synthesis

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Women's health research unit

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Barts and The London School of Medicine and Dentistry

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1. Al Wattar BH, Dodds J, Placzek A, Spyreli E, Moore A, Hooper R, Beresford L, Roseboom TJ, Bes-Rastrollo M, Hitman G, Khan KS, Thangaratinam S. Effect of simple, targeted diet in pregnant women with metabolic risk factors on maternal and fetal outcomes (ESTEEM): study protocol for a pragmatic multicentre randomised trial. BMJ open. 2016 Oct 1;6(10):e013495.

2. Al Wattar BH, Pidgeon C, Learner H, Zamora J, Thangaratinam S. Online health information on obesity in pregnancy: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016 Nov 30;206:147-52.

3. Al Wattar BH, Mylrea-Lowndes B, Morgan C, Moore AP, Thangaratinam S. Use of dietary assessment tools in randomized trials evaluating diet-based interventions in pregnancy: a systematic review of literature. Current Opinion in Obstetrics and Gynecology. 2016 Dec 1;28(6):455-63.

4. Al Wattar, B.H., Dodds, J., Placzek, A., Spyreli, E., Moore, A., Hooper, R., Beresford, L., Roseboom, T.J., Bes-Rastrollo, M., Hitman, G. and Khan, K.S. Shakila Thangaratinam. Mediterranean diet based intervention in pregnancy to improve maternal and fetal outcomes: Methodological challenges and lessons learned from the multicentre ESTEEM study. Contemporary Clinical Trials Communications. In press

Contributions to each paper are stated in appendix 1. All appropriate licensing copyrights have been obtained and copies of all original manuscripts are enclosed at the end of the appendix section.

Abstract summary

The epidemic of maternal obesity is increasing worldwide. Simple, effective and acceptable interventions are needed to combat obesity and improve pregnancy outcomes in women with metabolic risk factors such as dyslipidaemia and obesity. Dietary and lifestyle interventions reduce gestational weight gain, however, their effect on maternal and fetal outcomes is not clearly known. I conducted a large pragmatic randomised trial to evaluate the effectiveness of a Mediterranean-based dietary intervention to reduce the risk of adverse maternal and fetal outcomes in pregnant women with metabolic risk factors (The ESTEEM trial). The intervention significantly reduced gestational diabetes and gestational weight gain by an average of 1.2 Kg with some protective effect on fetal outcomes. I analysed the methodological challenges encountered in the trial and discussed applied solutions.

I conducted a systematic review on the commonly used dietary assessment tools in trials involving pregnant women to assess their characteristics, validity, and applicability. Self-reporting dietary tools were the most commonly used to assess dietary intake in pregnancy such as food frequency questionnaires. Only 8% of studies validated the chosen tools and applied a defined adherence criterion. I applied the findings of this review to develop and validate a custom designed food frequency questionnaire, and a short 12 items questionnaire, to assess the participants' adherence in the ESTEEM study. I assessed the dietary intake in a randomised cohort from the ESTEEM study and compared the questionnaires' accuracy to 24 hour dietary recalls as the reference method. Both the FFQ and the short questionnaire performed well for assessing the adherence to and the intake of key foods in the Mediterranean diet.

I systematically reviewed available online information sources on the risks and management of obesity in pregnancy in the English language. I assessed 53 websites for their information credibility, accuracy, readability, content and technological quality. Overall I found that non-governmental funded websites that are obesity-specific and targeting healthcare users presented better overall information quality.

Objectives

1. To evaluate the effect of a Mediterranean-based dietary intervention on maternal and fetal outcomes in pregnant women with metabolic risk factors (ESTEEM trial).
2. To explore potential methodological challenges and solutions for randomised trials evaluating dietary interventions in pregnancy.
3. To assess the quality of available tools to evaluate dietary intake in pregnancy.
4. To evaluate the quality of available online information on the management and risks of obesity in pregnancy.
5. To develop and validate accurate dietary assessment tools to measure participants' adherence to a Mediterranean-based dietary intervention in pregnancy.

Methods

The methods used by me in my thesis to address the above objectives are as follows:

- Multicentre randomised trial (objective 1, 2)
- Systematic review of observational studies (3,4)
- Primary study on quality of website (4)
- Primary validation study (5)

Results

The ESTEEM study involved 1252 randomised women with metabolic risk factors. There was some protective effect of the dietary intervention on reducing the primary maternal outcome (OR 0.76, 95% CI 0.56-1.03, p=0.07) with more visible effect against GDM (OR 0.65, 95% CI 0.47-0.91, p=0.01) than pre-eclampsia (OR 1.43, 95% CI 0.84-2.43, p=0.19). The protective effect of the intervention on the primary composite fetal outcome was more evident (OR 0.59, 95% CI 0.32-1.07, p=0.07) when accommodating for adherence with the intervention. The dietary intervention significantly reduced gestational weight gain (OR -1.24, 95% CI -2.27-0.21, p=0.018). Delivering the intervention resulted in a significant change of dietary intake towards a Mediterranean-based diet with participants in the intervention group consuming more key foods items including extra virgin olive oil (p=<0.001), nuts (p=<0.001), pulses (p=0.047), fish (p=<0.001), and white meat (p=<0.001). They also consumed less red meat (p=<0.001), and butter margarine (p=<0.001).

There were five key challenges encountered in ESTEEM, recruiting participants, delivering the intervention, engaging the clinical staff at recruiting centers, assessing the participants' adherence and finally deciding on the relevant outcome measures. We increased the number of recruiting centres and the recruitment period. We engaged clinical staff through a number of tailored training and education sessions. We designed the intervention sessions to involve partners and the whole family where possible to improve adherence. We developed and validated a short user-friendly dietary questionnaire to assess the adherence in the ESTEEM population. We sought consensus from a panel of experts to define the composite primary outcomes.

Out of 58 dietary trials in pregnancy, only 39 used dietary assessment tools in their design. The most commonly used assessment tool was a multiple-days food diary (23/39, 59%) and a food frequency questionnaire (FFQ) (12/39, 31%). Only three studies validated their assessment tools and three used pre-defined criteria to assess participants' adherence to the intervention. The rationale for using a particular tool was poorly reported with no apparent association with study characteristics.

We assessed 53 websites for their information and technological quality. Obesity-specific websites provided lower credibility compared to general health websites (p=0.008). Websites targeting health users were easier to read (p=0.001). Non-governmental funded websites demonstrated higher content quality (p=0.005). Websites that are obesity focused, targeting health users and funded by non-governmental bodies demonstrated higher composite quality scores (p=0.048).

The agreement between the FFQ and the 24h recalls was good for key foods in the Mediterranean diet such as meat (ICC 0.56), and fish (ICC 0.52). The agreement for olive oil and nuts intake was poor with moderate quintile cross-classification agreement. There was a good agreement in 8 out of 12 questions in the ESTEEM Q with their matched values from the FFQ. The total index score did not correlate well between the ESTEEM Q and the FFQ (Pearson 0.24, ICC 0.24 (95% CI 0.00 - 0.55), p=0.07).

Conclusion

A Mediterranean-based dietary intervention is helpful to reduce gestational diabetes and gestational weight gain in a high risk pregnant population. The solutions to methodological challenges encountered in ESTEEM can help future trials on diet in pregnancy to boost adherence, engage clinical staff and define outcomes. The use of self-reporting dietary assessment tools is popular in dietary trials but limited in validity and applicability. The food frequency and short questionnaires developed for the ESTEEM study are useful tools to assess participants' dietary intake and adherence to the Mediterranean-based dietary intervention.

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Preface

The work presented in this thesis was carried out during my placement at the Women's health research unit, at Queen Mary, University of London as a clinical research fellow from 2014 to 2016 in collaboration with Bart's health NHS Trust.

The primary supervisor of my PhD studies was:
Professor Shakila Thangaratinam: Professor of Maternal and Perinatal Health - Women's Health Research Unit - The Blizard Institute - Barts and the London School of Medicine and Dentistry - Queen Mary University of London

My secondary supervisors were:

- Professor Javier Zamora: Professor of Biostatistics - Women's Health Research Unit - The Blizard Institute - Barts and the London School of Medicine and Dentistry - Queen Mary University of London
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- Professor Khalid Khan: Professor of women's health and clinical epidemiology - Women's Health Research Unit - The Blizard Institute - Barts and the London School of Medicine and Dentistry - Queen Mary University of London

Synopsis

The work presented in this thesis evaluated the effectiveness of lifestyle and dietary interventions to improve the health outcomes for pregnant mothers with metabolic risk factors and their offspring. The thesis includes the primary findings of the ESTEEM trial, a large multicenter randomised study aiming to evaluate the effect of Mediterranean diet on pregnancy outcomes in high-risk population. It also includes systematic reviews on online health information sources and the tools used to assess dietary intake, and primary validation work for dietary assessment tools used in the ESTEEM study.

Dedication

To my family – Hala, Baha, Chirin, Baihas, Elena, Ibaa, Amr and Julie. Thank you for your unconditional support in good and bad times.

Acknowledgments

I am hugely in debt to my supervisors Shakila, Javier and Khalid. You have been the perfect mentors, role models, friends, and colleagues. You generously taught me all I needed to complete this work and more. I hope I will be able to guide other researchers in the future like you taught me and always perform up to your like.

I would like to thank the ESTEEM study research team for their support and work on this project. In particular, I would like to thank Anna Placzek the ESTEEM trial co-ordinator who always been a pleasant companion and a dear friend throughout this long journey.

My position as the ESTEEM research fellow has been funded through the generous grant of Bart's charity for the ESTEEM study (grant number 732/2029). I would like to thank Bart's charity for supporting our project and women's health research in general.

Many thanks to the staff at the women's health research unit at QMUL. It was a great pleasure to work in this unit and to share the experience with you all.

To my peers, the postgraduates research students, Ewelenia, John, Soha, and Martin. Thank you for being great friends and colleagues, and for tolerating my crazy twists over the last two years.

To the clinical consultants at the Royal London hospital, thank you for your great support and welcoming gestures. In particular great thanks to Mr.Ramesn Navaratnarajah who helped me to settle in the unit and always offered great support.

Lastly, special thanks to Elena, who tolerated the ups and downs of this long journey and was there to listen when needed.

Abbreviations

CACE	Complier-Averaged Causal Effect
CRF	Case Report Forms
DMC	Data Monitoring Committee
EDTA	Ethylenediaminetetraacetic acid
ESTEEEM Q	ESTEEEM Questionnaire
FFQ	Food Frequency Questionnaire
GDM	Gestational Diabetes Mellitus
HDL	High-density lipoprotein
ITT	Intention To Treat analysis
LDL	Low-density lipoprotein
NICE	The National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
REC	Research Ethics Committee
SGA	Small For Gestational Age
TSC	Trial Steering Committee

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CHAPTER 1

INTRODUCTION

1.1 Maternal obesity and pregnancy

The epidemic of obesity is rising to an alarming level internationally (1), affecting up to two-thirds of the population in some developed countries.(2) Industrialised food production, international trade, and sedentary lifestyle are some of the factors contributing to this epidemic. The impact of obesity on public health is substantial. With an increased risk of cardiovascular disease, cancer, diabetes and metabolic disorders, the burden of obesity on healthcare in the UK is expected to rise to 2 billion pounds per year.(3)

The prevalence of maternal obesity, in particular, is rising at a substantial rate. In the UK almost every other woman entering pregnancy is obese or overweight.(4) Pregnant women with metabolic risk factors such as obesity, dyslipidaemia and chronic hypertension are at higher risk of adverse pregnancy outcomes.(5) Obese mothers entering pregnancy experience an exaggerated physiological response characteristic of high insulin resistance, hyperlipidaemia, coagulation disturbance and hyper-inflammatory state.(6) This contributes to higher oxidative stress leading to endothelial dysfunction and abnormal trophoblastic functionality.(7)

Mothers with metabolic risk factors are at higher risk of pre-eclampsia, gestational diabetes, pre-term birth and birth by caesarean section.(8) Dyslipidaemia increases the risk of cardiovascular disease in pregnancy and contributes to higher gestational weight gain irrespective of associated factors and significantly.(9) Chronic hypertension contributes to higher risk of pre-eclampsia, fetal growth restriction, placental abruption and preterm birth.(10) Developing metabolic disease in pregnancy is associated with worse long-term health outcomes including cardiac disease, strokes and maternal mortality.(11)

The offspring of obese mothers is also affected by the suboptimal in-utero environment leading to permanent changes in the offspring's metabolism and epigenetics. The in-utero over-nutrition status predisposes children to neonatal complications, childhood obesity, diabetes, and asthma.(6) This adverse impact is spreading over many generations contributing to a progressive surge in maternal and childhood adiposity worldwide.(12)

1.2 Lifestyle modification interventions

The huge impact of maternal obesity on public health emphasises the demand for cheap, effective and scalable interventions internationally. Current guidelines by the IOM and NICE offer general recommendation on the optimal gestational weight gain, physical activity and dietary habits in pregnancy.(13,14) Only 40% of women are adherent to these guidelines and effective implementation is lacking.(15)

To date, most available pharmacological interventions such as aspirin, calcium, folic acid and vitamin-D had limited effect on improving pregnancy outcomes.(16) Evidence on the benefits of bariatric surgery for excessive obesity before pregnancy, while seems to be positive, remains limited.(17) Recent population studies confirms the beneficial effect of pre-pregnancy surgery in morbidly obese women on reducing short term outcomes such as gestational diabetes and large for gestational age.(18,19) However, long term outcomes continue to be scares and the intervention could increase morbidity and antenatal surveillance. (19)

Lifestyle and dietary interventions have potentials to reduce metabolic risk factors and improve pregnancy outcomes.(8) Compared to other lifestyle interventions, diet-based ones were associated with reduced gestational weight gain and improved pregnancy outcomes.(8)

In a non-pregnant population, healthy lifestyle interventions were associated with significant reduction in the risk of cardiovascular disease, metabolic disorders, and cancer.(20) Pregnancy offers an ideal window of opportunity to invoke a change in mothers' lifestyle driven by the wellbeing of the baby (21) and the planned regular antenatal encounters.(22) Lifestyle interventions including dietary, physical and mixed interventions; can significantly reduce gestational weight gain in a high-risk population (8,23). However, the large variation in the evaluated interventions and the choice of clinical outcomes restricts meaningful evidence synthesis.(8)

1.3 Dietary assessment tools

Assessing dietary intake following lifestyle modification intervention is complicated in pregnancy due to the high inter-rater variability and the regular changes in dietary requirement per trimester. Many factors can affect the accuracy of dietary assessment such as the study design, the planned intervention, and the population characteristics. Self-reporting dietary assessment tools are commonly used in nutritional studies for their ease of use and low cost.(24) These, however, have a number of limitations that could affect their validity and reliability when used in a pregnant population. Choosing the right dietary assessment tools is essential to ensure the validity of nutritional studies. Evidence on the best suitable tools for use in pregnancy is inconsistent.(25) There is a need to screen current practice and generate guidance on the most applicable dietary assessment tools for nutritional trials in a pregnant population.

1.4 Online health information on obesity in pregnancy

Patients and health professionals commonly consult the Internet for relevant health information in developed countries, the quality of available online sources is however, inconsistent (26). Poor quality information can adversely influence mothers' behaviour in pregnancy leading to worse health outcomes.(27) Engaging mothers' in the decision making for their health care can help to boost adherence and improve outcomes.(28) Introducing lifestyle interventions on a large scale is complex and requires easy, cheap and accessible dissemination medium. The retention of healthy lifestyle habits is quite poor beyond the life of a clinical trial.(21) The use of the internet and online health information dissemination is emerging as a potential solution.(28) The quality of online health information on obesity in pregnancy is unknown and a systematic assessment is warranted.

1.5 Mediterranean diet

Countries surrounding the Mediterranean sea share a common dietary regime characteristic of high consumption of vegetables, fruits, fish, olive oil as the main source of cooking fat and mixed nuts such as walnuts, almonds and hazelnuts; medium consumption of poultry, white meat, dairy products, and wine with meals; and low consumption of red meat, processed and fast food rich in animal fat. The population of south Greece and Italy has the lowest levels of obesity, cardiovascular disease and certain types of cancer.(29) Recent randomised trials confirmed the effectiveness of Mediterranean diet in reducing metabolic risk factors and improving health outcomes in the non-pregnant population.(30) Many studies evaluated the role of Mediterranean diet in improving pregnancy outcomes, however, the majority are small, observational studies with high risk of bias.(8) Evidence of the effect of Mediterranean diet on pregnancy outcomes consists mainly of observational longitudinal studies (31–34),

majority of which focus on gestational weight gain as a surrogate outcome (35) or on long-term neonatal outcomes.(36,37)

There is a need to evaluate the role of Mediterranean diet in improving pregnancy outcomes in high-risk population, its feasibility, and its effect on long-term maternal and fetal outcomes. Evaluating dietary based interventions in randomised trials has various methodological challenges.(38) Unlike drugs and medications, assessing the effect of diet on health outcomes is complex. Dietary trials are prone to various confounders such as the participants' adherence to the dietary intervention, the assessment of dietary intake, the lack of blinding and the willingness to alter habitual diet.(38,39) This is further complicated in pregnancy due to the high intra-rater variability and the rapid change in dietary requirements.(40)

1.6 Aim and objectives

The objectives of this thesis are as follow:

- To evaluate the effect of a Mediterranean-based dietary intervention on the maternal and fetal outcomes in a pregnant population with metabolic risk factors.
- To explore potential methodological challenges and solution for randomised trials evaluating dietary interventions in pregnancy.
- To review current practice in assessing dietary intake in pregnancy.
- To review and evaluate available online information on the management and risks of obesity in pregnancy,
- To develop and validate accurate dietary assessment tools to measure participants' compliance with a Mediterranean-based dietary intervention.

1.7 Framing the research questions

In table (1.1) I have highlighted the structured research questions I attempted to answer in this thesis.

Table (1.1): Structured research questions for each chapter of this thesis

Chapter number	Population	Intervention / test	Outcome	Study design
	How to evaluate the effect of Mediterranean-based dietary intervention on maternal and fetal outcomes in a high-risk pregnant population with metabolic risk factors?			
2	Pregnant women with metabolic risk factors	Mediterranean diet based	Maternal and fetal outcomes	Protocol of pragmatic randomised trial embedded in a cohort study
	What are the methodological challenges of randomised trials evaluating dietary interventions in pregnancy and potential solutions?			
3	Randomised trials	Dietary interventions in pregnancy	Methodological challenges and solutions	Discussion and analysis of the ESTEEM trial experience
	What is the quality of online information on the risks and management of obesity in pregnancy?			
7	Websites with information about obesity in pregnancy	Credibility, accuracy, readability, content quality and technology	Quality assessment of information and technology	Systematic review
	What dietary assessment tools are currently used in randomised trials evaluating dietary interventions in pregnancy?			
4	Dietary assessment tools in nutritional studies in pregnancy	Characteristics of used tools	Methodological choices, validity, reliability	Systematic review
	What is the validity of a food frequency questionnaire and a short questionnaire to assess the dietary intake of pregnant women following Mediterranean diet compared to 24 hour dietary recalls?			
5	A semi-quantified food frequency questionnaire and short dietary questionnaire	Assessment of dietary intake in a randomised trial in pregnancy	Validity compared to 24 hour dietary recalls	Primary validation study
	What is the effect of a Mediterranean-based dietary intervention on maternal and fetal outcomes in a pregnant population with metabolic risk factors			
6	Pregnant women with metabolic risk factors	Mediterranean based diet	Composite maternal and fetal outcome	Primary pragmatic randomised trial

CHAPTER 2

EFFECT OF SIMPLE, TARGETED DIET IN PREGNANT WOMEN WITH METABOLIC RISK FACTORS ON MATERNAL AND FETAL OUTCOMES (ESTEEM): STUDY PROTOCOL FOR A PRAGMATIC MULTICENTRE RANDOMISED TRIAL EMBEDDED IN A COHORT STUDY

In this chapter, I describe the protocol of the ESTEEM study which formed the basis of my research.

2.1 Abstract

Introduction Pregnant women entering pregnancy with existing metabolic risk factors are at higher risk of adverse maternal and fetal outcomes. Introducing a Mediterranean-based dietary intervention early on in pregnancy can help to modify these risks and improve pregnancy outcomes. There is a need to evaluate the effectiveness of a simple, targeted Mediterranean-based dietary intervention on improving maternal and fetal outcomes in a high-risk pregnant population.

Methods and analysis The ESTEEM was designed as a pragmatic multi-centre randomised trial embedded in a cohort study. We recruited pregnant women who met a pre-defined inclusion criteria and randomised those with metabolic risk factors (BMI ≥30 Kg/m^2, serum triglycerides ≥1.7 mmol/L, or chronic hypertension of ≥140 mm Hg systolic or ≥90 mm Hg diastolic blood pressure) to either receive a Mediterranean based dietary intervention or to routine antenatal care. Participants in the intervention group received tailored dietary advice and were encourage to make SMART objectives to change their diet towards a Mediterranean lifestyle. The primary outcome was a composite maternal outcome of pre-eclampsia or gestational diabetes and a composite fetal outcome of stillbirth, small for gestational age fetus or admission to the neonatal intensive care unit. The secondary outcomes included maternal, fetal, dietary, and laboratory outcomes.

Conclusion The ESTEEM study was designed to evaluate the effectiveness of Mediterranean based dietary intervention on maternal and fetal outcomes in a high-risk pregnant population. The findings of ESTEEM will impact current practice and will be readily transferable to clinical settings.

2.2 Introduction

The epidemic of obesity is rapidly increasing affecting public health worldwide.(41) About 30% of women of reproductive age are obese in the USA and the UK.(42,43) Entering pregnancy with metabolic risk factors significantly increase the risk of adverse maternal and fetal outcomes such as gestational diabetes, pre-eclampsia, stillbirth and neonatal death.(44) High levels of triglycerides and cholesterol, increased adiposity and dyslipidaemia are independent risk factors for pre-eclampsia and gestational diabetes.(45,46) This phenomenon is aggravated by many factors such as the poor dietary habits, sedentary lifestyle, and underlying genetic predisposition.(47)

Dietary and physical activity interventions have shown a beneficial effect on reducing gestational weight gain, with varied effect on pregnancy outcomes.(8) Recent studies confirm the beneficial effect of Mediterranean-based dietary pattern in reducing metabolic risk factors.(48) The consumption of a Mediterranean diet rich in extra-virgin olive oil and nuts contributed to reducing cardiovascular and metabolic disease and improving health outcomes in a non-pregnant population.(49) Mediterranean diet in pregnancy seems to reduce the incidence of pre-eclampsia, gestational diabetes and fetal growth restriction.(50–52) However, the majority of available studies in a pregnant population are non-randomised, of poor quality, and focus on specific components of the diet, rather than modifying the overall dietary pattern.(8)

There is a need for an adequately powered pragmatic randomised trial to evaluate the beneficial effect of a Mediterranean diet in pregnancy that is simple, feasible and targeting women at most risk of complications.

2.3 Aim and objectives

The aim of the ESTEEM study was to assess the effectiveness of a Mediterranean diet based intervention in pregnant women with metabolic risk factors to improve maternal and fetal outcomes.

The primary objective of the study was to compare, in a high risk pregnant population, the effect of a simple, targeted Mediterranean-based diet, supplemented with extra-virgin olive oil and nuts, composed within culturally appropriate recipes and food options, on a composite maternal (pre-eclampsia or gestational diabetes) and fetal outcome (stillbirth, small for gestational age fetus or admission to neonatal intensive care unit), to routine antenatal care.

The secondary objectives were: to assess the effect of the dietary intervention on different individual maternal and fetal complications; to assess the effect of the dietary intervention on the participants' lipid profile in the two randomised groups; to evaluate the risk of complications in women with and without metabolic risk factors in the cohort group; to study the effect of the dietary intervention on the risk of composite maternal and fetal outcomes in the following subgroups: obese women, women with raised triglycerides and women with chronic hypertension; and to establish a cohort for medium and long term follow-up of mothers and babies after birth.

2.4 Methods

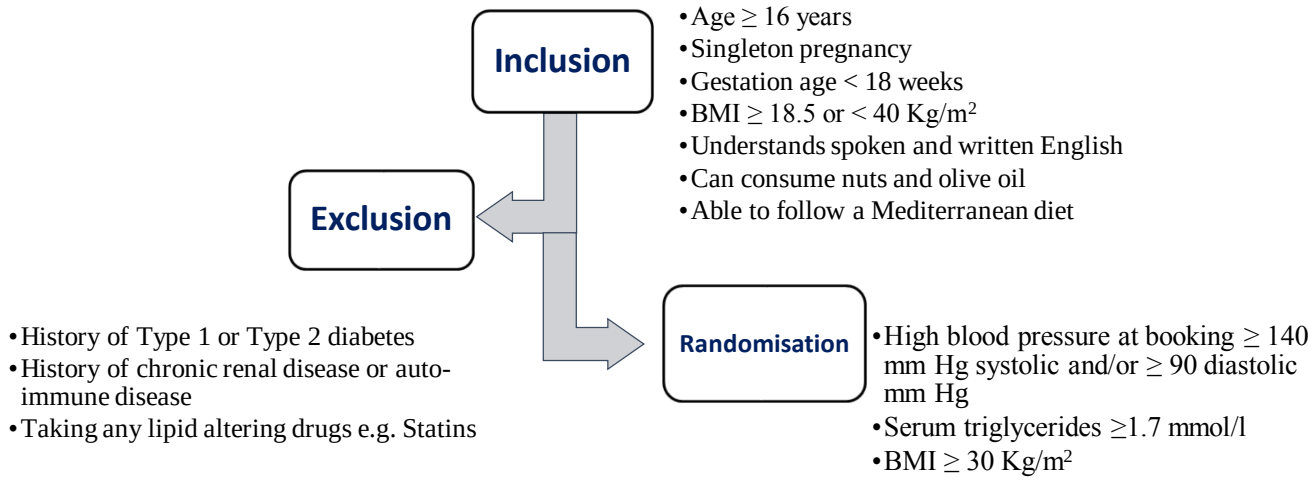
2.4.1 Study design

ESTEEM was a randomised trial embedded in a cohort study. The study recruited in five large maternity units in England (Royal London hospital, Whipps Cross university hospital, Newham university hospital, St George's university hospital, and the Birmingham women's hospital) from September 2014 to September 2016.

NHS Research Ethics Committee approval was obtained in all centres (UK IRAS integrated research application system; reference 14/EE/1048). ESTEEM is registered online with clinicaltrials.gov (NCT02218931).

The inclusion and exclusion criteria for the recruitment and randomisation process in ESTEEM is highlighted in figure (2.4.1)

Figure (2.4.1): The criteria for recruitment and randomisation to the ESTEEM study



2.4.2 Study conduct

Pregnant women due for their first booking antenatal visit were provided with the ESTEEM Patient Information Sheet (Appendix 2) at least twenty-four hours prior to the hospital booking visit to ensure that they have adequate time to consider the trial. In case it did not reach a participant in advance, the ESTEEM research team introduced the trial verbally to the participants before completing the consent form in the antenatal clinic. Participants were asked to complete an additional written consent form prospectively to collect and store umbilical cord blood samples after delivery for use in future studies. This was not mandatory to join the study. Examples of both consent forms are submitted as supporting information (Appendix 3).

Following consent, the research team collected the participant's baseline information (age, ethnicity, socioeconomic status, access to healthy food and physical activity, smoking, substance misuse, pre-existing medical conditions, mental health history, obstetric history, family history) (Appendix 4, A), measured their blood pressure, weight, height, BMI, and took a venous blood sample to measure their lipid profile (triglycerides, cholesterol, HDL, LDL, VLDL) and assess their suitability for randomisation. Women were eligible for randomisation to the trial if they have any of the following risk factors: obesity (BMI ≥30 Kg/m^2), raised serum triglycerides (≥1.7 mmol/L) (53), or chronic hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic blood pressure) (Figure 2.4.1).

Randomisation was performed via a password protected internet-based data management system in a ratio of (1:1). Minimisation (with a random element to ensure allocation concealment) was used to ensure balanced groups for maternal weight, gravidity, and ethnicity. Women who fulfil the above criteria were randomly allocated to the intervention

group or the control group. Women with no metabolic risk factors were allocated to the cohort arm to collect their maternal and fetal outcomes at the end of the pregnancy.

2.4.3 Intervention

The ESTEEM dietary intervention is based on Mediterranean diet, with education to modify lifestyle choices. The key components of the diet include high intake of fruit and vegetables, non-refined grains, legumes, moderate to high consumption of fish, small to moderate intake of poultry and dairy products such as yoghurt and cheese, low consumption of red meat and processed meat and avoidance of sugary drinks, fast food, and food rich in animal fat. In particular, ESTEEM advocates high intake of nuts (including walnuts, hazelnuts, and almonds) and high intake of extra virgin olive oil as the main source of fat (Appendix 6, A).

Following randomisation, women in the intervention arm were invited to attend the ESTEEM antenatal clinic to start the intervention by 18 weeks gestation. All participants were interviewed by the ESTEEM study dietician or a trained allied health professional to assess their baseline diet and deliver the dietary intervention on a 1-1 basis. The dietician used a 24 hours food recall followed by focused questions to estimate the participant's basal dietary intake and identify elements for change towards a Mediterranean diet (Appendix 5, E). Once identified, the participants were encouraged to set and record personalised goals following the SMART model (specific, measurable, achievable, relevant and time-specific) to implement the highlighted dietary changes.(54) These goals were recorded in the participant's case record and were used to track progress in subsequent visits.

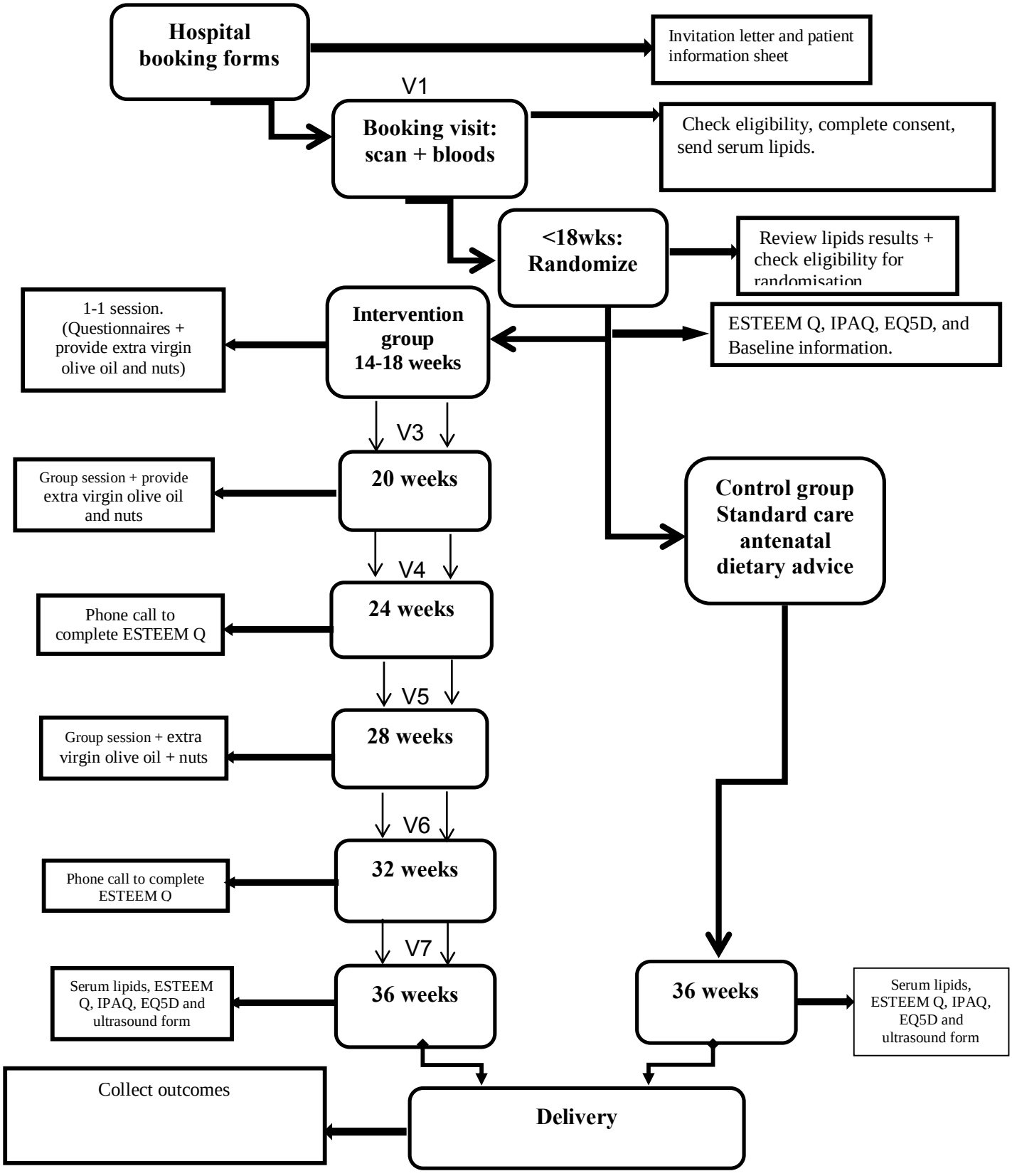
The dietician provided basic education on the benefits of Mediterranean diet on the pregnancy and the drawbacks of poor adherence to the intervention. Starting at this session and throughout the pregnancy, women were provided with extra virgin olive oil and sachets of nuts (such as walnuts, hazelnuts, and almonds) and were instructed to consume 0.5 litre/week of extra virgin olive oil for the whole family and 30 g/d of mixed nuts individually. The dietician also provided culturally modified cooking recipes to help the women include the components of Mediterranean lifestyle into their diet such as nuts and fish plus factsheets on the benefits of consuming these nutrients in pregnancy.

Both groups of participants were asked to complete the following questionnaires by 18 weeks gestation: the ESTEEM questionnaire (a 12 items short dietary questionnaire specifically designed to assess the intake of Mediterranean food groups), the IPAQ questionnaire to assess participant's physical activity (55) and the EQ-5D questionnaire to assess their quality of life.(56) (Appendix 5)

Participants were then invited to two further intervention sessions at 20 and 28 weeks gestation. These sessions were delivered in a group setting including mothers and where possible their partners. The trial dietician delivered bespoke presentations providing basic dietary education, good food habits, healthy shopping advice, reading food labels, beneficial dietary elements in the Mediterranean diet and general pregnancy health advice. Women were encouraged to share their experience with the dietary changes, explore obstacles to adopting the intervention and potential solutions. Two follow-up phone calls were made to participants in the intervention group at 24 and 32 weeks gestation to check on their wellbeing, and assess their adherence.

Between 36 weeks gestation and delivery participants from both groups were invited to a final 1-1 follow-up session to assess dietary intake, physical activity, quality of life, repeat the serum lipids profile blood test, and measure their weight and blood pressure (Figure 2.4.2).

Figure (2.4.2): Flow chart of the ESTEEM study conduct.



Participants in the intervention group who missed the first appointment at 18 weeks, were given another appointment at 20 weeks of gestation. Those who attended the initial intervention sessions but failed to turn up to subsequent ones were kept in the intervention group as long as they adhered to the intervention and collected the nuts and olive oil.

Participants who missed a group session were rescheduled within a two-week window. Subsequent failures to attend were recorded as a deviation of the protocol.

2.4.4 Control group

The control group were provided with the usual antenatal dietary advice as per NICE guidelines on antenatal care, weight management in pregnancy and hypertension in pregnancy.(57–59) Folic acid and vitamin D supplementation were provided as per national recommendations for all participants.

2.4.5 Umbilical cord blood samples collection and storage

Umbilical cord blood samples were collected from all consented participants upon delivery of the baby for use in future studies. Blood was collected from the umbilical cord and the placenta (using a syringe and a needle) and saved in a 10 mls EDTA dry tubes. All samples were initially stored for a maximum of 72 hours at the site of collection and were coded anonymously by the supervising midwife with no information identifying the study participants. The research team then moved the stored samples to an accredited tissue bank facility (The Blizard Institute – Queen Mary University of London) to be stored in -80 °C

freezer. Samples will be stored in accordance with the institutional Data Protection Policy for the lifetime of the study and 10 years after its completion.

2.4.6 Outcome measures

The primary outcome was a composite maternal outcome defined as pre-eclampsia (new onset or superimposed) or gestational diabetes; and a composite fetal outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th centile) or admission to the neonatal intensive care unit. (Appendix 7) The choice of composites was decided in consensus among the trial steering committee, the data monitoring committee, and the trial management team based on a Delphi survey of key stakeholders prioritising outcomes' reporting for obesity in pregnancy research. (60)

The secondary outcomes were

maternal: pre-eclampsia, gestational diabetes, gestational weight gain, admission to high dependency unit or intensive care unit, antepartum haemorrhage, mode of delivery, preterm delivery (<37 weeks, and < 34 weeks), anaemia, and physical activity.

fetal and neonatal: small for gestational age (<10th centile), very small for gestational age (< 3rd centile), large for gestational age (> 90th centile), stillbirths, birth weight (in Kg using both customised and population centiles), admission to neonatal intensive care units, neonatal deaths, and hypoxic ischaemic encephalopathy.

dietary: food intake for olive oil, nuts, vegetables, fish, fruits, pulses, red meat, white meat, butter/margarine, sugary drinks, commercial sweets, and micronutrients.

laboratory: maternal serum lipids including levels of triglycerides, high-density lipoproteins (HDL), the ratio of triglycerides (ratio of triglycerides to HDL) and non-high-density lipoprotein cholesterol (Non-HDL, cholesterol minus HDL).

2.4.7 Sample size

We estimated the prevalence of the composite maternal and fetal outcome in our population at 24%. We expected the ESTEEM dietary intervention to reduce it by 30%. (8,107) To ensure an 80% power at the 5% significance level we needed to randomise 982 women. We increased the target sample size to 1230 women to allow for a 20% dropout rate.

2.4.8 Statistical analysis

2.4.8.1 Primary analysis

Participants who were enrolled in error or failed to consent were excluded post randomisation. We included those who withdrew their consent unless they specified otherwise. The primary analysis was conducted on intention-to-treat (ITT) for all reported outcomes. Non-adherent participants were included in the ITT.

Baseline demographics and clinical characteristics were summarised as percentages for categorical variables, mean (standard deviation) for parametric continuous variables, and median (interquartile range) for non-parametric ones.

We reported the intervention effect on the risk of composite maternal and fetal outcomes as an odds ratio with 95% confidence interval, using a multivariable logistic regression. We

adjusted for the minimisation factors, as well as age, history of previous gestational diabetes, family history of hypertensive disorders (hypertension and/or pre-eclampsia), family history of diabetes, history of stillbirth and the recruitment centre. These covariates were selected based on prior evidence. We reported crude and adjusted odds ratios with 95% confidence intervals. Post randomisation miscarriage or medical termination of pregnancy were excluded from all analyses of the primary composite fetal outcome.

A secondary analysis for the primary outcome was performed accounting for the participants' adherence to the intervention using a complier-averaged causal effect (CACE) analysis.(16) We used generalised latent variable modelling via the 'gllamm' command in Stata to estimate the CACE adjusting for covariates.(17) Adherence to the intervention was assessed primarily against the number of sessions attended (at 14-18, 20 and 28 weeks gestation), and if needed supplemented with dietary information collected using the ESTEEM Questionnaire.

2.4.8.2 Subgroups and secondary outcomes analysis

We repeated the primary ITT analysis for the primary composite outcome in each of the following subgroups: women with obesity (BMI $\geq$ 30 Kg/m^2), with raised triglycerides ($\geq$1.7 mmol/l), and with raised blood pressure (systole $\geq$140mm Hg or diastole $\geq$ 90 mm Hg). We reported specific subgroup odds ratios with 95% confidence intervals and tested for an interaction term.

Secondary outcomes were analysed using a multivariable logistic regression for binary outcomes and a linear regression for continuous outcomes, with a normalising transformation

where necessary. Where a continuous outcome was also assessed at baseline, this was adjusted for as an additional covariate. Preterm delivery was analysed as a binary indicator for preterm delivery (<37 weeks) and early preterm delivery (<34 weeks). Mode of delivery was dichotomised into vaginal delivery vs. caesarean section and analysed as a binary variable. We used separate logistic regression models within vaginal deliveries and caesarean section to compare normal vaginal delivery to instrumental vaginal delivery and elective caesarean section to emergency caesarean section, respectively.

We used the GROW centile charts to calculate birth centiles and determine the incidence of small, very small and large for gestational age.(61) Population centile charts were used in an additional sensitivity analysis adjusting for gestational age only. We used the Metabolic Equivalent of Task method to estimates the minutes/week physical activity from the IPAQ questionnaire as a continuous outcome.(18)

The study statistician and the chief investigator remained blinded to not bias the analysis and interpretation of results. Unblinded summaries and reports using computer code were provided to the Data Monitoring Committee (DMC) by an independent statistician from the PCTU. All analyses were conducted using STATA version 12 or higher (StataCorp, College Station, TX, 2012).

2.4.8.3 Missing data

We did not anticipate any missing primary outcome data, as the selected outcomes should be recorded for all women and newborn infants. Minimisation factors were essential to randomise participants and no missingness was expected. We used mean imputation or a

missing indicator for continuous and categorical variables to compensate for any missed baseline covariates.

Only participants with complete outcome measures at baseline were included in the analysis. This approach is unbiased if the data were 'Missing at Random' i.e. missingness for the outcome is related to the observed covariates. We planned to conduct a sensitivity analysis if >5% of data for the primary outcome is missing to explore the missing at random assumption. The analysis for secondary outcomes included participants with complete outcome data only.

2.4.9 Food frequency and ESTEEM questionnaires

To assess the dietary intake of participants in the randomised trial we used a specially developed food frequency questionnaire (FFQ) and a short 12 items questionnaire (the ESTEEM Q) relevant to Mediterranean diet (Appendix 5). Details on the development and the validation of these questionnaires are discussed in chapter (6).

2.4.10 Internal pilot

We performed an internal pilot in the first 3 months of the study to evaluate the rates of recruitment to the trial and test its procedures. We sought feedback from service users on the design of the patient information materials during the first three months of the study setup phase. We also assessed the number of pregnant women screened for recruitment and the ratio of those who were eligible for randomisation. We examined the participants' reasons for declining recruitment, withdrawing from the trial and deviating from the protocol.

We planned to survey the clinical staff at the end of the pilot phase if we failed to recruit >50% of forecasted eligible women to identify any issues affecting recruitment. Similarly, we planned to review the feasibility of the trial if we failed to recruit >50% of the target population within the first 6 months of the trial.

2.4.11 Trial committees

ESTEEM has a Trial Steering Committee (TSC) formed of four independent members, including a representative from Action on Pre-eclampsia, a charity dedicated to the wellbeing of women diagnosed to have pre-eclampsia, and a service user with a history of pre-eclampsia. The TSC provided independent supervision for the trial conduct in the form of advice to the Co-Investigators and the sponsor on all aspects of the trial. The TSC ensured that the trial is conducted according to the principles of Good Clinical Practice in Clinical Trials and that all participants were recruited to the trial safely. All planned protocol amendments were discussed and approved by the TSC, Main REC and the sponsor before implementing them.

An independent Data Monitoring Committee (DMC) was formed to review updates on the results and the study progress. Interim analyses of safety and study outcomes were provided to the DMC in strict confidence by an independent statistician from the PCTU. The DMC advised the chair of the TSC if, in their view, the trial should stop on safety grounds, or if any protocol modifications were needed.

2.4.12 Data handling and confidentiality

The Chief Investigator had the overall responsibility to ensure that the participants' anonymity is protected and maintained at all times in the study. All information collected on the study participants were kept confidential and managed in accordance with the Research Governance Framework for Health and Social Care, the Data Protection Act (1998-UK), the NHS Caldicott Guardian (Health Service Circular: HSC 1999/012), and the Research Ethics Committee (REC) Approval.

All data collected in the study were entered by the research team onto a dedicated password protected electronic database hosted on the PCTU server using a secure computer and internet connection. The staff stored all collected paper case report forms (CRF) as a backup at each site. We performed regular monitoring on collected data checking for consistency, viability, quality and out-of-range errors. Any missed or incomplete records were sent back to the relevant study site to cross check against paper-based forms.

All collected data were anonymised prospectively to ensure the participants' confidentiality. Disclosure of personal information was not permitted to any third party without appropriate approval by the sponsor. All records will be kept securely by the sponsor for a further 20 years upon completing the study.

2.4.13 Auditing and quality assurance

The Chief Investigator had the overall duty to ensure that the trial is conducted in compliance with all applicable regulatory requirements including but not limited to the principles of the Declaration of Helsinki (1996), the Research Governance Framework, Good Clinical

Practice, local research office policies and procedures, and any subsequent protocol amendments.

We employed a number of interventions to capture non-compliance including monitoring visits, regular auditing, site communications, and updates. All recruiting sites performed remote data monitoring including random cases checking to ensure data validity. Any major discrepancies found during the site visits were recorded and escalated to the sponsor.

The sponsor kept a log of any non-compliance to capture any trends developing or escalating. Any issues were resolved by the trial team within a time frame fixed by the sponsor.

2.4.14 Adverse Events

Adverse events were defined as any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporarily associated with study activities. Serious adverse events were defined as any unexpected incidence of death, life-threatening condition, hospitalisation (including prolongation of existing hospitalisation), disability or incapacity (persistent or significant), congenital anomaly or birth defect, or any condition judged as medically significant by the investigator

The incidence of any adverse event was recorded in the participant's individual study file, the medical notes, and the CRF and was followed up by the research team appropriately. Serious adverse events were reported within 24 hours of noticing the event to the sponsor and within 15 days to the main research ethics committee.

2.4.15 Dissemination of study findings

Delivering the ESTEEM study successfully was possible thanks to the hard efforts of a large team of stakeholders including doctors, nurses, midwives, nutritionists and others. The success of publishing the study's results will be dedicated to and shared among all collaborators equally.

The trial management committee is responsible for publishing the ESTEEM findings in high impact open access peer-reviewed journals where possible. Recruiting centres were not permitted to publish partial data obtained from participants in the ESTEEM study without discussion with the Chief Investigator and/or the TSC.

2.5 Conclusion

The ESTEEM study is designed to evaluate the effectiveness of Mediterranean based dietary intervention in a high-risk pregnant population on maternal and fetal outcomes. The findings of ESTEEM will impact current practice and will be readily transferable to clinical settings.

This chapter led to the following publication:

Al Wattar BH, Dodds J, Placzek A, Spyreli E, Moore A, Hooper R, Beresford L, Roseboom TJ, Bes-Rastrollo M, Hitman G, Khan KS, Thangaratinam S. Effect of simple, targeted diet in pregnant women with metabolic risk factors on maternal and fetal outcomes (ESTEEM): study protocol for a pragmatic multicentre randomised trial. BMJ open. 2016 Oct 1;6(10):e013495.

CHAPTER 3

EVALUATING THE EFFECT OF MEDITERRANEAN-BASED DIETARY INTERVENTION IN PREGNANCY ON MATERNAL AND FETAL OUTCOMES: METHODOLOGICAL CHALLENGES AND LESSONS LEARNED FROM THE ESTEEM STUDY

In this chapter, I discuss the various methodological challenges and the lessons learned from the ESTEEM study.

3.1 Abstract

Introduction Evaluating complex dietary interventions in randomised trials involves unique methodological challenges relevant to the nature of the intervention, the target population and assessing participants' adherence. ESTEEM was a randomised trial evaluating the effectiveness of a Mediterranean-based dietary intervention on maternal and fetal outcomes in a high-risk pregnant population. Here we discuss the various methodological challenges and the solution applied during the ESTEEM study.

Methods We screened and recruited pregnant women at their first booking appointment against our predefined inclusion criteria. Participants with metabolic risk factors were randomised to either a Mediterranean-based dietary intervention or routine antenatal care. The intervention was delivered by the trial dietician over three sessions at 18, 20 and 28 weeks gestation. The primary outcomes was a composite maternal outcome of pre-eclampsia and/or gestational diabetes and a fetal composite outcome of stillbirth, small for gestational age fetus and/or admission to the neonatal intensive care unit.

Challenges and solutions There were five key challenges encountered in ESTEEM, recruiting participants, delivering the intervention, engaging the clinical staff at recruiting centres, assessing the participants' adherence and finally deciding on the primary outcome measures. We improved the recruitment rate to ESTEM by increasing the number of participating centres and prolonging the recruitment period. We introduced a number of educational interventions to engage clinical midwives and other healthcare providers at each site. We delivered the intervention early on in the pregnancy to promote the dietary effect on

healthy placentation and reduce metabolic risk factors. We encouraged our participants to attend the intervention group sessions with their partners and involve the whole family with the dietary intervention to improve adherence. We developed and validated a short user-friendly dietary questionnaire to assess the intake of key foods in the Mediterranean diet. We defined the study composite primary outcome in consensus based on input from a panel of experts on dietary research in pregnancy.

Conclusion The ESTEEM experience offers an insight into future pragmatic nutritional studies in pregnancy.

3.2 Introduction

Dietary and lifestyle interventions have been the focus of much research recently to improve health outcome and combat the obesity epidemic.(8,62) The effect of Mediterranean diet, in particular, is shown to reduce metabolic risk factors and cardiovascular disease.(63–65) However, the evidence on its effectiveness to improve pregnancy outcomes remains limited.(23,62)

Evaluating complex dietary interventions in a pregnant population poses unique methodological and conceptual challenges.(38,40) The validity of nutritional studies can be undermined by many variants such as the participants' adherence to the intervention, the variation in the dietary requirement in pregnancy and the choice of outcome measures.(66)

We undertook a multicentre randomised trial (ESTEEM) to assess the effectiveness of a Mediterranean-based diet intervention to improve health outcomes in pregnant women with metabolic risk factors. In this chapter, I highlight the methodological challenges and the lessons learned from the ESTEEM study.

3.3 Methods

ESTEEM was designed as a randomised trial embedded in a cohort study. The study ran from September 2014 till September 2016 in five tertiary maternity units in the UK. The inclusion and exclusion criteria are highlighted in figure (2.4.1). The primary outcome was a composite maternal outcome defined as pre-eclampsia (new onset or superimposed) or gestational diabetes; and a fetal composite outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th centile) or admission to the neonatal intensive care unit.

The ESTEEM dietary intervention is based on the Mediterranean diet lifestyle (Appendix 6, A). The intervention was introduced by a series of dietary education sessions providing individual dietary advice towards a Mediterranean diet, grocery shopping advice, cooking recipes for a healthy diet and advice for appropriate meal choices at restaurants.

Participants were also consented to collect umbilical cord samples after delivery to be used for future research on the effect of the dietary intervention on fetal biochemical outcomes.

We aimed to randomise 1230 women with metabolic risk factors to detect a 30% reduction in the primary maternal and fetal outcomes and maintain an 80% power at the 5% significance while allowing for a 20% dropout rate.

3.4 Challenges and solutions

3.4.1 Recruitment

We initially estimated a 14-months period to achieve the recruitment target. However, based on the pilot analysis we detected a slower than expected recruitment rate. We resolved to increase the number of recruitment centres from three to five major tertiary maternity units and extend the recruitment period by four months. Establishing and managing multiple recruitment centres requires significant investment in resources. In view of the limited funding, we planned a stepwise opening and closer of the ESTEEM recruiting centres to troubleshoot local challenges and allocate resources accordingly. This helped to ease off the pressure on the research team in view of the relatively long intervention and follow-up periods.(67)

To help deliver the intervention and the follow ups, we rolled out a series of evidence-based measures aimed to embed the trial conduct into clinical practice at the every recruiting centre.(68) We delivered a series of research training sessions targeting clinical midwives to enable them to recruit and consent participants during their booking sessions in the antenatal clinic. We supplemented these with a series of talks and interactive sessions for all the clinical staff and healthcare providers to emphasise the benefits of involving patients in clinical research. We complemented the top recruiting midwives at each of the sites offering acknowledgment certificates, institutional staff newsletters promotions in addition to small financial incentives and vouchers. Overall clinical midwives consented a third of participants recruited into ESTEEM.

We deployed posters, stands, and leaflets at every antenatal booking reminding clinical staff to approach women to join ESTEEM. We also attached an additional ESTEEM eligibility sheet to all booking clinical notes. The ESTEEM research team maintained daily presence at recruiting antenatal clinics to support clinical staff and boost recruitment. Participants who required additional time to consider the trial before consenting were followed up with telephone calls by the research team.

3.4.2 Intervention delivery and Engagement

Maximising the exposure to the dietary intervention is likely to improve its effectiveness inducing healthier in utero conditions and reducing existing metabolic risk factors.(69) This promoted us to deliver the intervention early on in pregnancy by 18 weeks gestation. Unfortunately, this was not always feasible, as many participants were not able to attend their initial appointment. To improve our retention rate we decided to reschedule non-attenders

extending the intervention window till 20 weeks gestation. Typically all booking women attend a 20 weeks ultrasound scan as per the NICE antenatal care guideline (59) which helped us to maximise the number of participants in the intervention arm. Data from our pilot phase suggested that participants are more likely to continue in the trial if they attended the first planned session.

Participants' culture and dietary habits are major confounders in nutritional trials, particularly in pregnant women.(70) Engaging participants in the planning of the intervention is advised to promote belief and adherence to the intervention.(71) Certain food groups are culturally more emphasised in pregnancy (72) and mothers are also more likely to follow advice from friends and family members, compared to health care professionals.(73) Interactive interventions based on the social cognitive theory are effective to improve adherence to lifestyle intervention on the longer term.(74) We encouraged our participants to set up their own SMART objectives (specific, measurable, achievable, relevant and time-specific) and dietary goals towards a Mediterranean lifestyle. This was aimed to engage participants in the intervention and improve adherence. We involved partners and the whole family where possible particularly in larger families where pregnant women may not do the cooking and the shopping for the entire household. We delivered a number of educational sessions to boost the participants' basic nutritional knowledge and emphasise the benefits of Mediterranean diet to both mother and baby.

Some of the key elements in the Mediterranean diet, namely extra virgin olive oil and mixed nuts, were relatively expensive to purchase locally by our participants. The high-cost element could reduce consumption and affect adherence.(75) This prompted us to provide supplies of these two food items to our participants throughout the pregnancy.

We planned the following two intervention sessions (at 20 and 28 weeks) in a group setting of the participants and their partners. The aim of these sessions was to provide further knowledge on the benefits of Mediterranean diet, share experiences, success stories and explore obstacles to adhering to the intervention. The sessions also included bespoke educational presentations on reading food labels plus advice on healthy shopping habits and shared grocery lists.

Poor attendance often reduced the group size to one or two participants only. For those participants who missed a session or two, we attempted to reschedule or arranged to send them the nuts and extra virgin olive oil by post to ensure they maintained their intake and compliance with the intervention.

3.4.3 Assessment of dietary intake

Estimating the participants' dietary intake at baseline and after delivering the intervention is an integral requirement in nutritional studies.(38) In pregnancy, dietary assessment is complicated by the increased inter-rater variability and the constant change in dietary requirements.(40) The population characteristics can also influence the dietary assessment process; our population consisted mainly of multiparous women, often from a transiently immigrant background. Many of them had low literacy of English language, were in full-time employment or looked after larger families. Considering these factors we needed a short, sensitive and user-friendly assessment tool.

Our dietician used a 24-hour dietary recall coupled with the multi-pass technique (76) and a series of focused open-ended questions to assess the participant's baseline dietary habits. This enabled our dieticians to identify areas for improvement and the necessary changes towards adopting a Mediterranean based diet.

Following on discussions among the ESTEEM management committee, we decided to use a modified food frequency questionnaire (FFQ) and a short 12-items questionnaire (ESTEEM Q) (Appendix 5) to assess adherence throughout the trial. Details on the development and validation of these tools are discussed in chapter (6).

Using the FFQ proved less popular than expected. Only 30% of our participants in the control group completed and returned their FFQ's after randomisation. Adopting a pragmatic approach, we decided to use the FFQ for validation purposes only and aborted its use later on in the trial.

We used the ESTEEM Q as a measure of adherence secondary to the number of attended sessions. We identified 12 semi-quantified questions relevant to the Mediterranean diet coupled with 7 dichotomous questions on conditions specific to pregnancy that could affect the participants' dietary intake. We modified a similar questionnaire that was validated for use in a non-pregnant population following a Mediterranean based dietary intervention.(77)

We asked our participants to retain and return empty packets of consumed nuts and extra virgin olive oil as another marker of adherence. However, due to the poor return rate, we aborted the use of this method later on in the trial.

Initially, we planned to use specific biomarkers to objectively assess the intake of key food items in addition to completing the self-reporting dietary questionnaires. Alpha-linolenic acids and hydroxytyrosol are two commonly used serum biomarkers to assess the intake of nuts and olive oil in nutritional studies.(78) Our hypothesis was to increase the intake of unsaturated fatty acids by increasing the consumption of these two food items particularly as well as other elements of the Mediterranean diet. Thus, objectively assessing the intake of nuts and olive oil would support the validity of our findings. However, measuring these biomarkers involves high cost and significant staff involvement. Furthermore, collecting numerous serum samples for trial use only is invasive and could put off participants from continuing the trial.(78)

Considering all these factors our main measure of adherence was the number of attended intervention sessions supplemented with scores derived from the ESTEEM Q.

3.4.4 Control group selection

Setting up an appropriate control medium is often complicated in nutritional studies due to the large variation among participants.(79) Establishing the efficacy of specific food items requires the introduction of an appropriate control diet or the withdrawal of evaluated food items from the comparison group.(80)

The objective of ESTEEM was to evaluate the effectiveness of the dietary intervention as a whole in routine clinical settings. Adhering to this pragmatic approach, we did not employ any dietary restrictions on the participants in the control arm. This will emphasise the external validity of ESTEEM findings making it directly transferable to clinical settings.

This, however, comes with certain limitations. The ESTEEM population was ethnically diverse encompassing multiple food cultures and dietary habits; some of the participants in

the control arm might already follow a Mediterranean lifestyle. ESTEEM was a non-blinded trial; while no interaction was planned between the two groups, it is plausible that some control subjects might have adopted certain food items in the Mediterranean diet such as extra virgin oil. Variations in food intake among participants were inevitable, particularly as many of them were from transiently immigrant families adopting new food habits.

3.4.5 Assessment of outcomes

Our focus in ESTEEM was to assess the effectiveness of the dietary intervention on the maternal and fetal outcomes relevant to clinical practice. To date, a large number of nutritional trials in pregnancy focused on evaluating gestational weight gain with fewer trials focusing on particular maternal or fetal outcomes.(8) Detecting a significant difference in clinical outcomes often requires a large sample size which was not always feasible.(81) In ESTEEM, we sought advice from a large panel of experts on obesity in pregnancy research and used a multi-stage modified Delphi survey to generate consensus on the most relevant outcomes.(60) Both gestational diabetes and pre-eclampsia were prioritised for maternal outcomes in addition to stillbirth, small for gestational age and admission to NICU for fetal outcomes. Our trial steering committee advised to include these important measures in one composite maternal/fetal outcome in addition to reporting on each of theme independently as secondary outcomes. The large sample size recruited to ESTEEM will ensure enough confidence to detect a significant difference in the intervention group and reduce type 1 error.

Reporting on changes in dietary outcomes from baseline to delivery is an important element in ESTEEM. As our primary assessment tool for the dietary intake was the ESTEEM Q, we were only able to report on the changes of major food groups' intake with no information on other important elements such as energy estimates and micronutrients.

Collecting outcomes at delivery was logistically challenging within the allocated time window. We nominated a dedicated team member for every recruiting site to screen the labour and postnatal wards daily and crosscheck new deliveries against our electronic records. This helped to reduce the loss to follow-up rate and ensure complete recording of outcomes.

Our objective to collecting cord blood samples for future research also proved more complicated than planned. A significant proportion of our participants declined to take part in this aspect of ESTEEM. Collecting and freezing the samples appropriately was logistically challenging due to staff and resources limitations. We sought help from clinical midwives on the delivery suite to assist in collecting cord blood samples upon delivery and save them on labour ward. We identified consenting mothers by adding a special ESTEEM stickers to their maternity notes to remind the supervising clinical midwife (Table 3.4.5.1).

Table (3.4.5.1): Summary of encountered challenges and applied solutions in ESTEEM.

Domain	Challenge	Solution
Recruitment	Large sample size and slow recruitment rate	Extended recruitment by 4 months and opened more recruitment centres.
		Engaged clinical staff in the recruitment and follow-up process
		Assigned dedicated research staff to screen antenatal clinics daily
Delivery of the intervention	Poor attendance to initial intervention sessions	Extended the intervention window up to 20 weeks gestation

Participants engagement with the study	Various food cultures and dietary habits among participants	Tailored intervention based on individual food habits assessment
	Improve adherence to the intervention	Actively engaged participants and their families in planning the required dietary changes to comply with the intervention
		Provided group dietary educational sessions
		Provided nuts and extra virgin olive oil throughout the pregnancy
Adherence to the intervention	Assessing basal dietary intake	Used of a multi-pass 24-hour dietary recall with focused questions
	Choice of dietary assessment tool	Developed and validated a user-friendly short dietary questionnaire specific to Mediterranean diet
Control group	Choice of control participants	Adopted a pragmatic approach with no specific dietary requirement in the control group
Outcomes	Choice of primary outcome	Developed a composite outcome of maternal and fetal outcomes prioritised by a panel of experts.
	Complete outcome collection	Assigned dedicated research staff to screen postnatal and labour ward and crosscheck participants against electronic records

3.5 Discussion

The dietary intervention in ESTEEM was focused on improving maternal intake of key food items rich in unsaturated fatty acids such as nuts, fish, and extra virgin olive oil.

Our hypothesis was that a high intake of unsaturated fatty acids can reduce oxidative stress and insulin resistance in pregnancy which can improve the endothelial function lowering the incidence of metabolic disease namely gestational diabetes and pre-eclampsia.(82) Improving the metabolic status can also ameliorate the in-utero conditions leading to better placentation and normal birth weight.(50)

Our knowledge on the distribution of fatty acid in pregnancy and the associated metabolic changes remains limited.(83) Unlike lean pregnant women, obese mothers tend to develop higher levels of plasma lipids such as triglycerides and very low-density lipoprotein compared to static levels of unsaturated fatty acids.(84) The effect of this unbalanced ratio on the in-utero environment and fetal outcomes also remains unclear. Comparing biochemical outcomes between the high risk and low-risk groups in ESTEEM will clarify the role of diet to improve the metabolic profile in pregnancy.

Adding a qualitative aspect to nutritional studies is also important to explore mothers' beliefs and attitude towards changing their lifestyle before, during and after pregnancy.(85) In ESTEEM we conducted a number of semi-structured interviews with mothers and their partners in the randomised groups to assess satisfaction and potential obstacles to adopting the Mediterranean diet.

The adverse effect of maternal obesity on long-term maternal and fetal outcomes is well established; entering pregnancy as obese is associated with increased risk of developing type 2 diabetes, cardiovascular disease and childhood asthma. (86,87) Our randomised cohort will offer a follow-up medium to study the effect of the dietary intervention on long-term health outcomes. Dietary studies are often restricted to the pregnancy period offering little insight on the maintenance of the intervention in the postpartum period and beyond.(62) Advances in dietetics' technology can simplify data collection in future studies. The use of mobile apps and internet-based interventions has been reported to be helpful in maintaining diabetic control and studying the effect of diet on other chronic diseases.(88,89) Such methods could

be particularly helpful for better dietary assessment in the postpartum and long-term follow-up.(90)

3.6 Conclusion

Evaluating dietary and lifestyle interventions in pregnancy involves a number of methodological challenges. The ESTEEM experience offers an insight into future pragmatic nutritional studies in pregnancy.

This chapter led to the following publication:

Al Wattar, B.H., Dodds, J., Placzek, A., Spyreli, E., Moore, A., Hooper, R., Beresford, L., Roseboom, T.J., Bes-Rastrollo, M., Hitman, G. and Khan, K.S. Thangaratinam S. Mediterranean diet based intervention in pregnancy to improve maternal and fetal outcomes: Methodological challenges and lessons learned from the multicentre ESTEEM study. Contemporary Clinical Trials Communications. In press

CHAPTER 4

ONLINE HEALTH INFORMATION ON OBESITY IN PREGNANCY: A SYSTEMATIC REVIEW

In this chapter, I have conducted a systematic review of available online information on prevention, risks, and management of obesity in pregnancy in English. I have assessed the quality of available information looking into the credibility, the accuracy, the readability, the content quality and the technological quality of included websites to assess the role of the internet as an effective medium to disseminate reliable health information on obesity in pregnancy.

4.1 Abstract

Objective To assess the quality of health information available online for healthcare users on obesity in pregnancy and evaluate the role of the internet as an effective medium to advocate a healthy lifestyle in pregnancy.

Study design We used the poly-search engine Polymeta and complimented the results with Google searches (from inception till July 2015) to identify relevant websites. All open access websites in English providing advice on the risks and management of obesity in pregnancy were included. Two independent reviewers assessed the quality of information provided in each of the included websites for credibility, accuracy, readability, content quality and technology. We compared websites' quality according to their target population, health topic, and source of funding.

Results Fifty-three websites were included. A third of websites were focused on obesity in pregnancy and two-thirds targeted healthcare users. The median value for the overall credibility was 5/9, 7/12 for accuracy, 57.6/100 for readability, 45/80 for content quality and 75/100 for technology. Obesity-specific websites provided lower credibility compared to general health websites (p=0.008). Websites targeting health users were easier to read (p=0.001). Non-governmental funded websites demonstrated higher content quality

(p=0.005). Websites that are obesity focused, targeting health users and funded by non-governmental bodies demonstrated higher composite quality scores (p=0.048).

Conclusion Online information on obesity in pregnancy is varied, more work is needed to standardise and improve the quality of reporting of online health information on this topic. Governmental bodies in particular need to invest more efforts to improve the quality of online health information on obesity in pregnancy.

4.2 Introduction

The fast spread of obesity continues to be a major health challenge internationally.(91) The incidence of obesity is rising in all age groups particularly in women of childbearing age.(5) This is affecting up to a third of pregnant women in western countries such as the USA (34%) and the UK (25%).(92) Entering pregnancy with a high BMI increases the risk of maternal and fetal complications such as gestational diabetes, pre-eclampsia, stillbirth and cesarean section.(5) The chief Medical Officer of England has emphasised the importance of encouraging women of reproductive age to adopt a healthier lifestyle before pregnancy.(93)

The widespread of the Internet has facilitated the sharing and dissemination of health information in developed countries.(94) Internet-based platforms can host effective, cheap, innovative and widely accessible interventions to improve health outcomes.(93) These are especially applicable to chronic and long-term disease such as obesity and diabetes.(95) The quality of health information provided online for healthcare users, in general, is inconsistent.(26) Disseminating poor quality health information over the internet can be confusing and counterproductive leading to worse health outcomes.(96,97)

The quality of health information available online on the risks and management options for obesity in pregnancy is not known. We systematically evaluated the quality of online information on the topic of obesity in pregnancy.

4.3 Methods

This study was conducted following a prospective protocol (CRD42015020192) and reported the findings in accordance with the PRISMA statement.(98) (Appendix 12)

4.3.1 Identification of websites

We performed Google searches to produce a comprehensive list of search terms and identify internet websites providing information on obesity in pregnancy (Appendix 11). We used the poly-search engine Polymeta (https://polymeta.com/) to search the following search engines simultaneously: Google, Ask, Yahoo, Bing, and Blekko from inception till July 2015. We complimented the findings with searches in Google using the different portals of English speaking countries such as google.com; google.co.uk; google.com.au; google.ca; and google.co.nz. We screened the first 10 pages arbitrarily of every search, compiled the results in one electronic database and removed duplicates. We included all websites in English reporting information relevant to obesity in pregnancy. We excluded websites with no open access and those with password protected content. We also excluded websites solely replicating scientific articles or clinical guidelines.

4.3.2 Quality assessment

We assessed the included websites for their quality of information and technology in duplicate. We divided the websites into categories depending on their target population (healthcare users vs general population), health topic (obesity-specific vs general health) and source of funding (governmental, commercial and non-governmental (NGO)). Websites or blogs started or maintained by patients and health charities were classed as NGOs. Websites hosted by public health organisations such as the National Health Service were classed as governmental.

4.3.3 Information quality

We assessed the information provided on the website for its credibility, accuracy, readability and content quality. We scored the inspired credibility based on the content relevance, information source, utility, currency, hierarchy of evidence, editorial review process, statement of the original source, availability of a disclaimer (including details on ownership, sponsorship, funding and advertising), omissions and a mechanism for feedback. A score of 0 or 1 was given for each item if absent or present respectively.(99)

We evaluated the accuracy of provided information against peer reviewed published guidelines (100) (101) on pre-conception counselling, prenatal diagnosis, antenatal maternal risks, fetal risks, intrapartum complications and the role of diet and physical activity in pregnancy. Each of these items was assessed if not reported, briefly reported or reported in sufficient detail given a score of 0, 1 or 2 respectively.

We assessed the readability of websites using an online readability calculator (readability-score.com), using the Flesch Reading Ease test. Easy to read texts had higher readability scores from 0 to 100.(102) We used the DISCREN tool to evaluate the websites' content quality.(103) This validated tool was composed of 16 items including the assessment of sources of bias, an adequate description of the benefits and risks of reported treatments, and the advocacy of shared decision making with patients. We gave a score to each of these items ranging between 1 if completely not mentioned and 5 if mentioned in sufficient detail.

4.3.4 Technological quality

We used the Nibbler software to evaluate the overall technological quality of the included websites (nibbler.silktide.com). Each website was assessed for its accessibility (such as ease

of locating information on the website, page titles, and URL format), the rated user experience (such as the content value, mobile availability, the content format, quality of internal links etc.), the marketing (links to social media, meta tags, popularity, freshness etc.) and the quality of informatics used (such as quality of headings, titles, images, printability etc.). Scores ranged between 0 and 100 for each criterion with an overall score out of 100.

4.3.5 Data analysis

We used intra-class correlation coefficients (ICC) to assess the agreement between the two assessors' quality scores. We judged the agreement to be poor for a score less than 0.2, good for a score between 0.6 and 0.8, and very good for a score greater than 0.8.(104) We used the mean of the two assessors' scores for the quality analysis. We reported parametric data using means and standard deviations, and for non-parametric data we reported medians and ranges. We standardised the scores for each domain to a mean of 0 and a standard deviation of 1 in order to generate a composite quality score for each website. We used the following formula to generate Z score ($z = (x - \mu) / \sigma$) where μ is the mean of each sample and σ is the standard deviation. We generated composite quality score for each website by calculating the mean of the calculated Z scores for each quality domain (composite score = Z scores (credibility+ accuracy+readability+content quality+ technological quality)/5).

We used the Kolmogorov–Smirnov and the kruskal-wallis one way ANOVA tests to compare the different quality scores among websites according to their target users, health topic, and source of funding. We used the Student-T and the oneway ANOVA tests to compare the composite quality mean scores among these groups. We performed a post-hoc multiple comparison test for statistically significant between-group results using the Least Significant

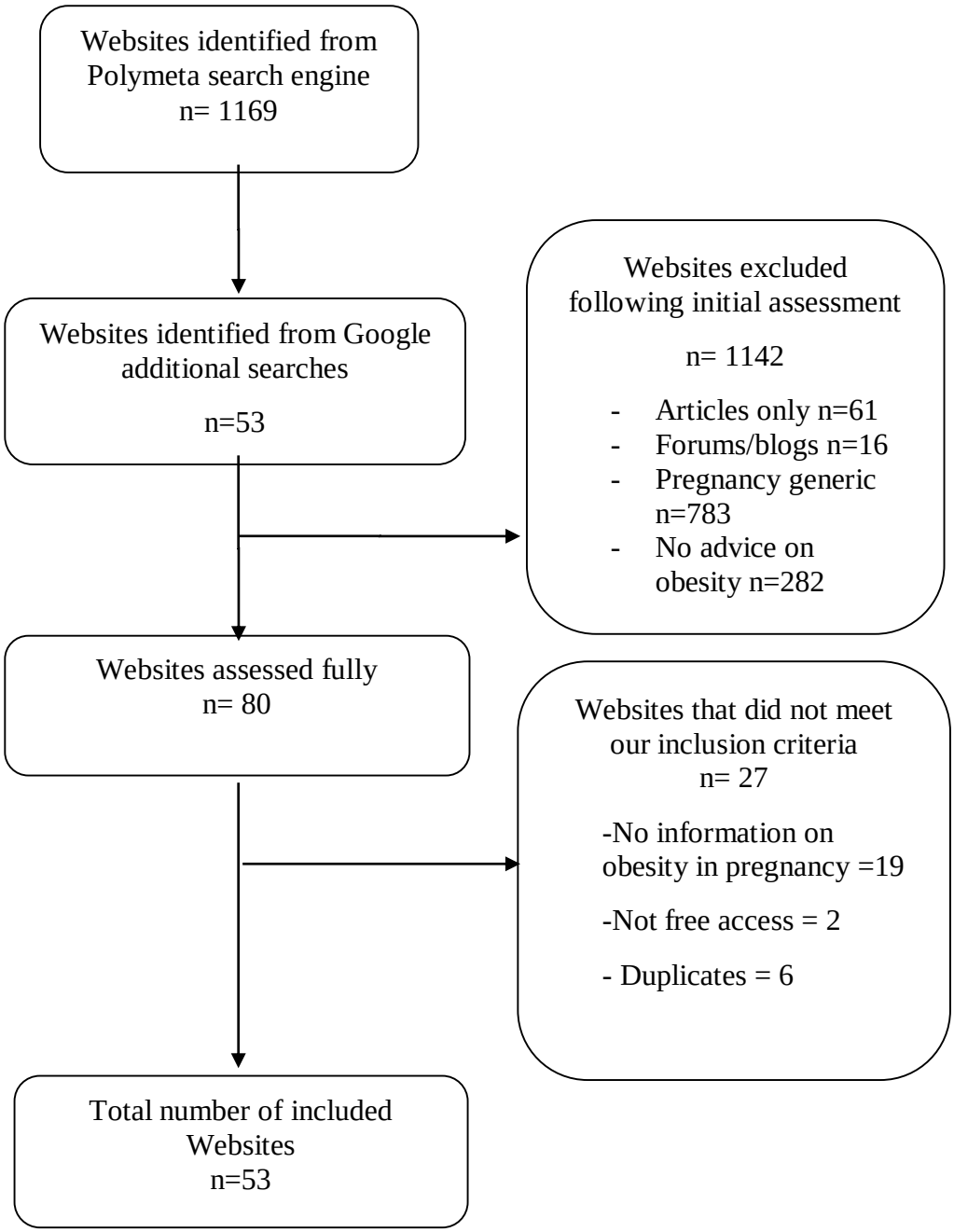
Difference tests (LSD). We tested the association between the composite quality score and the funding source using a linear regression model and accommodated for the websites target users and the topic of focus.

4.4 Results

4.4.1 Characteristics of websites

We identified 1169 potentially relevant websites. We excluded 652 websites on initial assessment and assessed 517 websites in full. Only 53 of these met our inclusion criteria and were assessed for information and technology quality (Figure 4.4.1).

Figure (4.4.1): Flow chart of the selection and inclusion process for websites providing health information on obesity in pregnancy**.**



About 30% of included websites were dedicated to obesity in pregnancy (17/53, 32%) and two-thirds targeted women and healthcare users (37/53, 70%). About half of these websites were American (27/53, 51%) and a third were British (17/53, 32%). Only seven websites provided an open access forum for users to discuss health-related information (7/53, 13%).

Fifty seven percent of included websites displayed a privacy statement (30/53, 57%) and more than a third had nominated authors and an editorial panel (21/53, 40%). We identified 12 commercial, 18 governmental and 23 NGO funded websites. Table (4.4.1) summarises the characteristics of included websites. There was a very high agreement between the quality scores of the two assessors (ICC= 0.92).

Table (4.4.1): Characteristics of included websites.

Website URL	Country	Obesity specific	Healthcare user focused	Listed Authors	Patient forum	Privacy statement	Source of funding	Composite quality score
aafp.org	USA	No	No	Yes	No	Yes	NGO	0.16
acog.org	USA	No	Yes	No	No	Yes	NGO	0.53
babycenter.com	USA	No	Yes	Yes	No	Yes	NGO	0.96
babycentre.co.uk	UK	No	Yes	No	Yes	Yes	NGO	1.09
beststart.org	CAN	Yes	No	No	No	No	NGO	-0.32
cdc.gov	USA	No	Yes	No	No	Yes	GOV	-0.01
commonhealth.wbur.org	USA	No	Yes	Yes	Yes	Yes	NGO	0.07
contemporaryobgyn.modernmedicine.com	USA	No	No	Yes	No	Yes	NGO	0.12
cuh.org.uk	UK	Yes	No	No	No	No	GOV	0.01
esht.nhs.uk	UK	Yes	Yes	Yes	No	No	GOV	-0.04
fitpregnancy.com	USA	No	No	Yes	No	Yes	NGO	-0.08
gloshospitals.nhs.uk	UK	Yes	Yes	No	No	No	GOV	-0.19
gponline.com	UK	No	No	Yes	No	Yes	NGO	0.26
health.ny.gov	USA	No	No	No	No	Yes	GOV	-0.42
health.qld.gov.au	AUS	Yes	Yes	No	No	No	GOV	0.74
health.ucsd.edu	USA	No	Yes	No	No	Yes	COM	-0.42

hqip.org.uk	UK	No	No	Yes	No	No	NGO	0.34
hse.ie	IRE	No	No	No	No	No	GOV	0.35
instituteofmidwifery.org	USA	No	No	Yes	No	No	NGO	-0.43
ivfplus.com.au	AUS	No	Yes	No	No	No	COM	-0.67
keepingyouwell.com	USA	No	Yes	No	No	Yes	COM	-0.79
mainlinegi.com	USA	No	Yes	Yes	No	Yes	COM	0.38
marchofdimes.org	USA	No	Yes	No	Yes	Yes	NGO	0.62
markscrogginsmd.com	USA	No	Yes	No	No	No	COM	-0.67
mayoclinic.org	USA	No	Yes	No	No	Yes	COM	0.43
netmums.com	UK	No	Yes	No	Yes	Yes	NGO	-0.20
newkidscenter.com	USA	No	Yes	No	No	No	NGO	-0.39
nhs.uk	UK	No	Yes	No	Yes	No	GOV	0.70
nichd.nih.gov	USA	No	No	No	No	Yes	GOV	-0.30
noo.org.uk	UK	No	No	Yes	No	Yes	GOV	-0.10
obesityaustralia.org	AUS	Yes	Yes	Yes	No	Yes	NGO	-0.08
obfocus.com	USA	No	Yes	No	No	Yes	COM	-0.26
parents.com	USA	No	Yes	Yes	No	Yes	COM	0.33
patient.info	UK	No	Yes	Yes	Yes	No	NGO	0.04
plus-size-pregnancy.org	USA	Yes	Yes	No	No	Yes	NGO	-1.68
plymouthhospitals.nhs.uk	UK	Yes	Yes	No	No	No	GOV	-0.51
pwhce.ca	CAN	No	No	Yes	No	No	NGO	-0.33
qegateshead.nhs.uk	UK	Yes	Yes	Yes	No	No	GOV	-0.25
raisingchildren.net.au	AUS	No	Yes	Yes	Yes	Yes	NGO	0.80
rcog.org.uk	UK	Yes	Yes	No	No	No	NGO	0.96
rdehospital.nhs.uk	UK	Yes	Yes	No	No	No	GOV	0.03

royalberkshire.nhs.uk	UK	Yes	Yes	Yes	No	No	GOV	-0.19
sahealth.sa.gov.au	AUS	Yes	Yes	No	No	No	GOV	-0.93
seslhd.health.nsw.gov.au	AUS	No	Yes	No	No	No	GOV	0.14
stockport.nhs.uk	UK	Yes	Yes	No	No	No	GOV	0.62
tommys.org	UK	Yes	No	Yes	No	Yes	NGO	0.37
uhs.nhs.uk	USA	Yes	Yes	No	No	No	GOV	0.24
urmc.rochester.edu	USA	No	Yes	No	No	Yes	NGO	-0.69
webmd.boots.com	USA	No	No	Yes	No	Yes	COM	0.54
webmd.com	USA	No	No	Yes	No	Yes	COM	-0.23
whattoexpect.com	USA	No	Yes	Yes	No	Yes	NGO	0.74
womenandinfants.org	USA	No	Yes	No	No	Yes	COM	-1.02
yourplussizepregnancy.com	USA	Yes	Yes	No	No	Yes	COM	-0.36

AUS: Australia

IRE: Ireland

USA: United States of America

UK: United Kingdom

NGO: Non-governmental organisation

GOV: Governmental

COM: Commercial

4.4.2 Quality of websites

The median value for the overall credibility of websites was 5/9 (range 1-8), 7/12 for accuracy (range 2.5-11), 57.6/100 for readability (range 25-89.4) and 45/80 for content quality (range 20-62). The overall median technology quality value was 75/100 (range 40-99). The value of the different technology assessment criteria included the following: 72/100 for accessibility (range 41-97), 72/100 for user experience (range 33-92), 73/100 for marketing score (range 11-98) and 62/100 for informatics (range 42-91).

There was higher credibility for the information on obesity-specific websites compared to general health ones (p=0.008) with no difference in other quality measures between the two groups. Websites targeting the general population had similar quality measures compared to those targeting healthcare users, except for lower readability score (p=0.001). The content quality was associated with the source of funding; NGO funded websites demonstrated better content quality compared to commercial and governmental websites (p=0.005). None of the remaining quality measures was affected by the source of funding (Table 4.4.2).

Table (4.4.2): Summary of information and technology scores per websites group. Quality is summarised per median and range for each domain.

	Credibility			**Accuracy**			**Readability**			**Content quality**			**Technology**		
	Median	Range	P value	Median	Range	P value	Median	Range	P value	Median	Range	P value	Median	Range	P value
Obesity specific	4	1-7	0.008	7	3–11	0.6	50	25-89	0.49	47	20-60	0.14	77	40-99	0.09
General health	5.5	2-8		7.5	3-11		58	40-70		44	20-62		72	47-83	
Healthcare user focused	5	1-8	0.97	7	3-11	0.32	60	31-89	0.001	44	20-62	0.56	75	50-89	0.69
General focus	5.2	4-7		8	5-11		45	25-67		49	35-62		77	40-99	
Commercial	5	2-7	0.12	6	4-11	0.43	54	31-89	0.61	37	20-45	0.005 *	74	50-99	0.87
Governmental	4.5	3-7		7	3-11		55	36-70		47	30-62		75	60-89	
NGO	5.5	1-8		8	3-11		59	25-72		49	20-62		76	40-85	

*Post-hoc analysis:

Com vs Gov p= 0.003

Gov vs NGO p=0.47

Com vs NGO p=0.004

The mean composite quality scores were not different among any of the websites groups.

NGO funded websites that are obesity-specific and targeting healthcare users demonstrated higher composite quality scores (β=0.410, p=0.048). Table (4.4.3) summarises the composite quality scores of compared groups.

Table (4.4.3): Mean standardised composite quality scores and standard deviation per websites group.

	Composite score		P value
	Mean	SD	
Obesity specific	-0.09	0.62	0.30
General health	0.74	0.49	
Healthcare user focused	0.0019	0.63	0.97
General focus	-0.003	0.31	
Commercial	-0.22	0.53	0.206
Governmental	-0.0061	0.43	
NGO	0.12	0.63	

4.5 Discussion

4.5.1 Summary of findings

The quality of information available online on obesity in pregnancy was quite varied. Countries with higher internet use in the healthcare sector, such as the UK and the USA, had a higher number of dedicated health websites. Interestingly there were more pregnancy dedicated websites funded by non-governmental sources compared to the other two groups. This, however, did not significantly affect the overall quality of health information provided. The distribution of the composite quality scores was relatively wide suggesting poor

adherence to available evidence-based guidelines on best practice to disseminate health information online.(26)

Websites with limited funding (from individuals or small charities) demonstrated good information quality scores overall compared to the governmental ones that usually enjoy much larger funding and institutional support. The quality of used informatics technology was overall good in most included websites, probably due to an overall improvement in the available websites building tools.(105)

Websites targeting pregnant women and other healthcare users employed much simpler and readable language compared to specialist websites. This could be attributed to the use of lay terms, avoiding jargon and complex medical language commonly used in websites dedicated to healthcare professionals. The content quality was significantly higher in the NGO funded websites. Overall, governmental health bodies did not invest enough efforts to develop reliable online health information that are amenable and relevant to the wider public.

4.5.2 Limitations

The results of this study are limited by the number of search engines used and the inclusion of websites in English language only. Our criteria to assess the information accuracy was driven by clinical importance with no input from lay users. Other health issues affecting pregnant women with obesity such as infertility and postpartum care might carry similar importance to lay health users. Quality assessment was conducted using non-validated criteria

with subjective assessment. While there was high correlation between the two assessors' scores, there is a need to develop and validate assessment tools for health information quality.

4.5.3 Implications for practice

Modern healthcare systems need to adopt innovative, cheap and effective interventions to combat obesity on a wider scale. Sharing health information over the internet has a number of advantages including easy accessibility, low setup cost, unrestricted access and easy data storage with safe and interactive databases.(106) Online based systems can provide reliable and standardised health information to help improve the overall quality of shared care. This is particularly applicable to the postpartum period where the continuity of medical care is often lost and the chance for retaining added weight is higher.(107)

Online healthcare information, in general, is still of mixed quality (26) and limited measurable applicability.(108) The guidelines published by the American Medical association are set to improve the quality of health information websites and standardise practice.(109) Their applicability, however, remains limited in current practice.(110)

The quality of NGO funded websites specifically addressing obesity in pregnancy provided higher information quality; women should be encouraged to use them. Official healthcare bodies should invest more to improve the quality of governmental websites in order to stop the epidemic of obesity and improve public health in general. Involving multiple stakeholders including lay health users in the design and delivery of health information online can help to improve the overall quality. Our review has identified the top quality websites to help pregnant women with obesity, health providers are encouraged to disseminate our findings.

4.6 Conclusion

Online information on obesity in pregnancy is varied, more work is needed to standardise and improve the quality of reporting of online health information on this topic. Governmental bodies in particular need to invest more efforts to improve the quality of online health information on obesity in pregnancy.

This chapter is based on the following publication:

Al Wattar BH, Pidgeon C, Learner H, Zamora J, Thangaratinam S. Online health information on obesity in pregnancy: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016 Nov 30;206:147-52

CHAPTER 5

USE OF DIETARY ASSESSMENT TOOLS IN RANDOMISED TRIALS EVALUATING DIET-BASED INTERVENTIONS IN PREGNANCY: A SYSTEMATIC REVIEW

In this chapter, I have conducted a systematic review of the literature looking into the methods used to assess dietary intake in randomised trials on dietary intervention in pregnancy.

5.1 Abstract

Background Accurate assessment of participants' dietary intake is a key element in interventional studies on lifestyle and dietary interventions. Dietary assessment in pregnancy is often complicated by the high inter-rater variability and the rapid change in dietary requirement. We performed a systematic review of the literature on commonly used dietary assessment tools in nutritional studies in a pregnant population.

Methods We updated our previous search (until January 2012) using Medline and EMBASE up to December 2015 including all randomised trials on diet and lifestyle interventions in pregnancy. We screened and assessed relevant studies in duplicate by two independent reviewers. We assessed the characteristics of the dietary assessment tools, the timing, and frequency of use, and they were validated within the study population. We used the Chi-squared test to check for any methodological factors associated with the relevant dietary assessment tools.

Results In total 58 randomised trials met our inclusion criteria. Of these, only 67% (39/58, 67%) employed some form of dietary assessment. The most commonly used assessment tool was a multiple days' food diary (23/39, 59%), followed by a food frequency questionnaire (FFQ) (12/39, 31%) and a 24-hour recall (8/39, 20%). The majority of studies did not validate their assessment tools in their pregnant population (36/39, 92%) and none assessed their tools' reliability. The use of dietary biomarkers was uncommon in pregnancy, reported only in one study. Only three studies (3/39, 8%) used pre-defined criteria to assess participants'

adherence to the intervention. The rationale for using a particular tool was poorly reported. There was no association between the choice of dietary assessment tools and study quality (p= 0.10), study sample size (p= 0.19), year of publication (before or after 2005) (p=0.88), type of journal (general vs. specialist) (p = 0.33) or the journal impact factor (p=0.48).

Conclusion Self-reporting dietary assessment tools are the most commonly used in nutritional studies in pregnancy. Evidence to support their applicability and validity in pregnancy is poor. More research is needed to develop and validate pregnancy specific dietary assessment tools.

5.2 Introduction

Implementing diet and lifestyle interventions in pregnancy has the potential to improve maternal and fetal outcome such as gestational diabetes, pre-eclampsia and preterm birth in a high-risk population.(8,111)

Assessing the participants' habitual intake and their adherence to the dietary intervention is essential in interventional nutritional studies. Longitudinal dietary histories recording the subjects' dietary intake prospectively, commonly used as the gold standard in a non-pregnant population, are expensive and labour intense tools.(112) Other forms of self-reporting tools such as food diaries and food frequency questionnaires can offer a suitable and user-friendly substitute.(113–115)

Dietary assessment tools need be accurate, reliable, and valid for use within the study population to preserve internal validity.(112) Maintaining these characteristics in a pregnant population is often challenging due to the high inter-rater variability, (25) the common eating disorders, the rapid physiological changes, and the variation in energy requirements per trimester.(40)

We undertook a systematic review to assess the characteristics and quality of the dietary assessment tools used in randomised trials on pregnant women, and the factors associated with their use.

5.3 Methods

5.3.1 Search strategy

We updated our previously published search for randomised studies on diet and lifestyle interventions in pregnancy (January 2012) using Medline and EMBASE until December 2015 to identify any new studies. The search strategy was designed in a multistep process by combining search terms related to pregnancy and diet.(8) There were no language restrictions. The detailed search strategy is outlined in Appendix (9).

5.3.2 Study selection

We performed the study selection process in two stages. First, we screened the full titles and abstracts of all citations to identify potentially relevant studies. Then we assessed the full articles of shortlisted studies against our inclusion criteria. We included all randomised trials evaluating dietary interventions in pregnancy. We excluded non-randomised studies, those in animals and studies in a non-pregnant population. Any discrepancies were resolved by consensus among the reviewers.

5.3.3 Quality assessment of included studies

We assessed the quality of included randomised studies using the Jadad score.(116) One point was awarded for each of the following: study described as randomised, the randomisation method was appropriate; the study was described as double blinded, the allocation method was appropriate; the withdrawals and dropouts were described. Studies with a score above three were considered to be of high quality. A score of three was considered to be of moderate quality and studies with a score of two or less were considered to be of low quality.

5.3.4 Data extraction and analysis

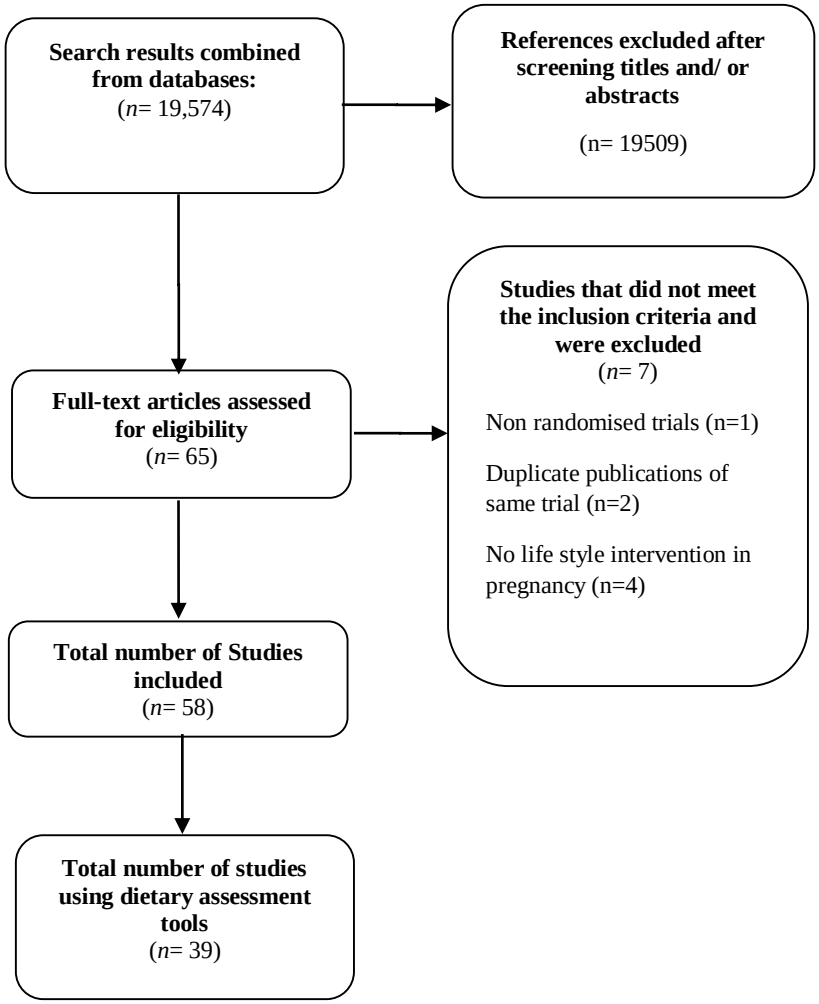
We extracted the data in duplicate using an electronic data extraction tool. We collected data on the study design, the country of the study, the characteristics of the randomised population, the study sample size, the type of the evaluated dietary interventions, the primary and secondary outcomes, and the journal's impact factor. Journals with an impact factor of more than 10 were considered to be of high impact. We also reported on the type of the used dietary assessment tool, the time and the frequency of use within the trial, and if any evaluation of its validity and/or reliability was conducted.

We reported frequencies and percentages for binary data using Microsoft Excel (2007) (Microsoft Corp., Redmond, WA, USA). We used logistic regression modelling to assess the effect of the reported study characteristics on the probability of using the relevant dietary assessment tool in the study population. Statistical analysis was conducted using SPSS (V20) (IBM Inc., New York, NY, USA).

5.4 Results

Electronic database search revealed 19,563 potentially relevant citations. Of these 58 randomised trials met our inclusion criteria and were assessed in full. In total, we included 39 studies (39/58, 67%) that employed a dietary assessment tool in our review reporting on 9728 pregnant women. Figure (5.4.1) details the study identification and inclusion process.

Figure (5.4.1): Identification and selection of studies that used dietary assessment tools to evaluate the effects of diet-based interventions in pregnancy on maternal and fetal outcomes.



5.4.1 Characteristics of included studies

The largest number of studies was conducted in the USA (10/39, 27%), followed by Australia (6/39, 15%). The majority of included studies recruited women with any BMI (21/39, 54%) and only 5 targeted obese pregnant women with a BMI ≥30 (5/39, 13%). Thirteen studies focused on dietary interventions to reduce gestational diabetes with 10 studies recruiting women with positive diagnosis (10/39, 26%) and 3 recruiting women at high risk for gestational diabetes (3/39, 8%). Almost all of the included studies delivered the intervention

by the end of the second trimester (35/39, 90%). The majority of evaluated dietary intervention were in the form of counselling and advice to pregnant women (30/39, 77%) and 9 studies evaluated a combination of dietary and physical activity advice (9/39, 23%).

Most studies were published in specialist medical journals and only 13% were published in general medical ones (5/39, 13%). Of these, only two were published in a journal with an impact factor> 10 (2/39, 5%). Table (5.4.1) provides a brief summary of the characteristics of the included studies.

Table (5.4.1): Characteristics of randomised controlled trials on pregnant women using dietary assessment tools.

Author and year	Country of study	Journal	Characteristics of intervention population	BMI	GA at intervention	Dietary intervention	Diet assessment tool
Asemi et al 2014	Iran	European Journal of Clinical Nutrition	Primigravida, age 18–40, diagnosed with GDM at 24–28 week gestation.	Any	24-28 weeks	DASH diet was rich in fruits, vegetables, whole grains, low-fat dairy products, low in saturated fats and cholesterol, refined grains and sweets	Weekly 3-day dietary records (2 weekdays and one weekend day)
Bechtel-Blackwell et al 2002	USA	Clinical Nursing Research	African American primagravidas, age 13-18	Any	First trimester to early second trimester	Nutritional education	CASI (24-hour dietary recall + general nutrition questions)
Bo et al 2014	Italy	Diabetes, Obesity, and Metabolism	Age 18–50; GDM diagnosis, singleton pregnancy.	<40	24-26 weeks	Individually prescribed diet + physical activity	FFQ
Bosaeus et al 2015	Sweden	Nutrional Journal	Age 20–45, European decent, non-diabetic, no neuroleptic drugs, and vegetarianism or veganism	18.5 -24.9	12-18 weeks	Individualised dietary counselling	FFQ
Briley et al 2002	USA	Journal of The American Dietetic Association	African American with no pre-existing health conditions or diet	Any	<24 weeks	In home, prenatal nutritional advice	24 hour recalls

Ferrara et al 2011	USA	Diabetes Care	Singleton pregnancy with gestational diabetes, age ≥18, English speaking	Any	After diagnosis of GDM	Diet, Exercise and Breastfeeding Intervention (DEBI) for women with gestational diabetes	7 days dietary fat intake diary
Grant et al 2011	Canada	Diabetes Research and Clinical Practice	Age 18–45, diagnosed with GDM or IGT, no chronic illness affecting carbohydrate metabolism; No type 1 or type 2 diabetes; not using insulin prior to providing consent	Any	<34 weeks	dietary counselling on non-starchy food	3 days food diary
Grant et al. 2011	Canada	Diabetes Research and Clinical Practice	Singleton pregnancy, age 18-45, diagnosed with GDM.	Any	28 weeks	Patients introduced to diabetes food guide and current Canadian dietary recommendations.	3 days diary + FFQ
Guelinckx et al 2010	Belgium	The American Journal of Clinical Nutrition	Obese white pregnant women < 15 weeks gestation	>29	15 weeks	Nutritional advice from a brochure +/- lifestyle education by a nutritionist	7 days food diary
Hauner et al 2012 (Infant)	Germany	The American Journal of Clinical Nutrition	Singleton pregnancy. Age 18-43. <15 weeks gestation, willing to implement the dietary recommendations, sufficient German language skills.	18-30	15 weeks	Fish oil supplement + vitamin E daily during pregnancy and lactation. + detailed nutritional counselling from trained research assistants.	7 days food diary
Hawkins et al 2015	USA	Diabetic Medicine	Hispanic women age18–40, no history of Type 2 diabetes, hypertension, heart disease or chronic renal disease; no current medications adversely influence glucose tolerance; planning to continue the pregnancy to term.	≥ 25	< 18 weeks	In-person behavioural counselling sessions and 30 minutes of moderate-intensity activity per week	24 hour recalls
Hui et al 2011	Canada	British Journal of Obstetrics and Gynaecology	Nondiabetic urban-living pregnant women (<26 weeks gestation)	Any	26 weeks	Community-based group exercise sessions + home exercise and dietary counselling	3 days food diary
Ilmonen et al 2011	Finland	Clinical Nutrition	Pregnant women less than 17 weeks gestation and no metabolic diseases	Any	<17 weeks	Dietary counselling with probiotics or placebo	3 days food diary
Jackson et al 2010	USA	Patient Education and Counselling	English speaking, ≥18 years, <26 weeks gestation	Any	26 weeks	Teaching and counselling session about nutrition, exercise and weight gain using the (Video Doctor)	FFQ (18 items)
Jeffries et al 2009	Australia	Medical Journal of Australia	English speaking, ≤14 weeks gestation, age 18-45 years	Any	14 weeks	Nutritional advice	Eating habit questionnaire (used to distract from aim of project)
Jelsma et al 2013	Netherlands	BMC Pregnancy & Childbirth	Pregnant women at risk of GDM < 19+6 weeks. Singleton pregnancy, age < 18 years.	>29	<19 weeks + 6 days	Five Individual sessions and 4 optional telephone calls with a lifestyle coach. Daily intake of Vitamin D.	3 days food diary + FFQ (12 items)

Khoury et al 2005	Norway	American Journal of Obstetrics and Gynecology	Singleton pregnancy, non-smoking, white ethnicity, age 21-38	19-32	17-18 weeks	Nutritional advice, low Cholesterol diet and supplement intake in pregnancy	7 days weighed dietary diary
Kiefferv et al 2014	USA	American Journal of Public Health	Hispanic pregnant women, age < 18 years, resident in southwest Detroit residents, <20 weeks gestation.	Any	<20 weeks	Healthy Mothers on the Move dietary programme implemented in 2 home visits and 9 group meetings over 11 weeks.	FFQ
Korpi-Hyovalti et al 2012	Finland	The British Journal of Nutrition	Pregnant women at high risk of gestational diabetes	Any	12 weeks	Dietary and lifestyle advice	4 days food diary
Luoto et al 2011	Finland	PLOS Medicine	Pregnant euglycaemic women, 8-12 weeks gestation, at least one risk factor for GDM	Any	8-12 weeks	Individual intensified counselling on physical activity, diet, and weight gain	FFQ (181 items)
Man Shek et al 2014	China	Arch Gynecol Obstet	Chinese, residents in Hong Kong, age≥18, diagnosed with IGT but otherwise in general good health, understand Chinese language.	Any	28-30 weeks	Dietary advice, individual optimal caloric intake measured, individual counselling by a registered dietician	5 days food diary
Moreno-Castilla et al 2013	Spain	Diabetes Care	Age 18-45, singleton pregnancy, diagnosis of GDM <35 weeks.	Any	<35 weeks	Individualised dietary advice	3 days food diary
Moses et al 2009	Australia	Diabetes Care	Age 18-45, singleton pregnancy, no previous GDM, non-smoker, diagnosis of GDM	Any	28-32 weeks	Individualised dietary advice	3 days food diary
Moses et al 2009	Australia	American journal of Nuitrition	<20 weeks gestation, singleton pregnancy, age >18, ability to read and understand English	Any	20 weeks	Detailed dietary education tailored for the assigned diet	3 days food diary
Moses et al 2014	Australia	The American Journal of Clinical Nutrition	<20 weeks gestation, singleton pregnancy, 18 years or older, read and understand English	Any	<20 weeks	Detailed dietary education tailored for assigned diet and individual requirements for pregnancy	3 days food diary
Petrella et al 2013	Italy	Journal of Maternal-Fetal & Neonatal Medicine	Age >18 years, singleton pregnancy	≥25	12 weeks	Therapeutic Lifestyle Changes (TLC) Program	FFQ (158 Items)
Polley et al 2002	USA	International Journal of Obesity	Age >18 years, singleton pregnancy, gestation <20 weeks	≥19.8	20 weeks	Education about weight gain, healthy eating, and exercise.	Short FFQ (13 items)
Poston et al 2013	UK	BMC Pregnancy & Childbirth	Obese, singleton pregnancy, gestation 15-18 weeks	≥30	15-18 weeks	One-to-one and group sessions with health trainer providing dietary and physical activity advice	24 hour recalls + short FFQ
Quinlivan et al 2011	Australia	Australian and New Zealand Journal of	Singleton pregnancies, obese or overweight, English speaking	≥25	Not reported	Dietary advice and clinical psychology	24-hour itemised food consumption recalls

		Obstetrics and Gynaecology					
Rae et al 2000	Australia	Australian and New Zealand Journal of Obstetrics and Gynaecology	Pregnant women with GDM.	>110% of ideal body weight	<28+1 weeks	Nutritional advice on a moderately energy restricted diabetic diet.	3 days food diary
Rauh et al 2013	Germany	BMC Pregnancy & Childbirth	Age >18 years, singleton pregnancy, <18 weeks gestation with sufficient German language skills	≥18.5	18 weeks	Advice on healthy lifestyle, diet and physical activity with individualised goals	7 days dietary diary
Rhodes et al 2010	USA	American journal of Nuitrition	BMI 25-45, age ≥25, singleton pregnancy.	25-45	13-28 weeks	Nutritional education, dietary counselling and food provision	24-hour recalls
Rönö et al 2014	Finland	BMC Pregnancy & Childbirth	History of GDM/ BMI ≥ 30, < 20 weeks	≥30	20 weeks	lifestyle counselling encouraging healthy diet and physical activity	3 day food diary
Sagedal et al 2013	Norway	BMC Public Health	Singleton pregnancy, >18 years old, <20 weeks gestation, fluent in Norwegian or English	>19	<20 weeks	Dietary counselling + pamphlets containing 10 dietary recommendations + hands-on cooking class + access to interactive website with information on nutrition during pregnancy	82 items FFQ + 24 hour recalls
Thornton et al 2009	USA	Journal of the National Medical Association	Obese pregnant women with singleton pregnancy.	≥30	12-18 weeks	Advised on a balanced nutritional regimen.	Daily food diary throughout pregnancy
Vesco et al 2013	USA	Obesity	Age >18, > 8 weeks gestation (at first antenatal booking).	≥30	7-21 weeks	Combination of diet and exercise recommendation + behavioural self - management.	7 days food diary
Walsh et al 2012	Ireland	British Medical Journal	Secundigravid, singleton pregnancies, previous macrosomia of >4kg, aged ≤18	Any	<18 weeks	Nutritional advice following a low glycaemic index diet	3 days food diary
Wang et al 2015	China	Asia Pac J Clin Nutr	Diagnosed with GDM, age 22-38, no pregnancy-related complications, no history of diabetes, hypertension or GDM.	Any	24-28 weeks	Individualised dietary guidance	24 hour recalls
Wolff et al 2008	Denmark	International Journal of Obesity	Non-diabetic, non-smoking, Caucasian, aged 18-45	≥30	15 weeks	Nutritional advice and provision of supplements	7 days weighed food diary

GDM: Gestational diabetes mellitus

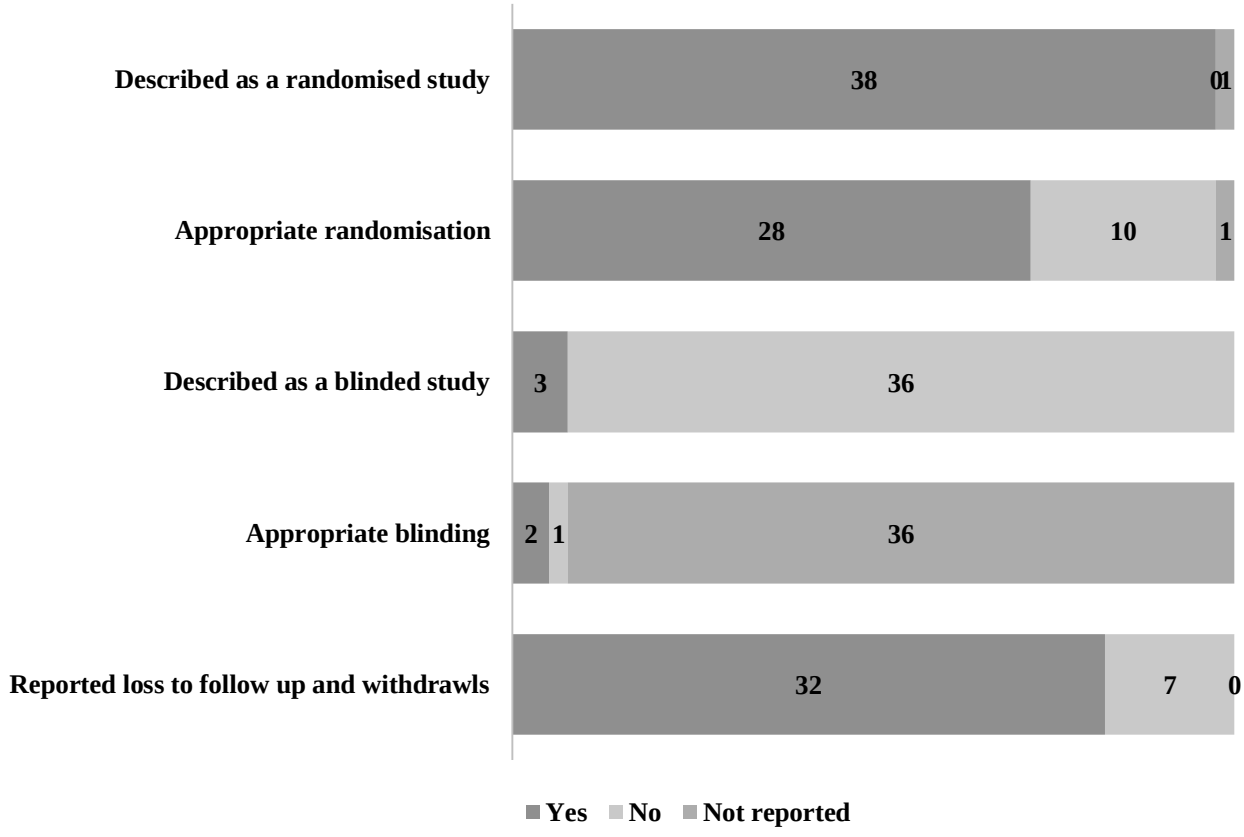
IGT: intolerance glucose test

FFQ: Food frequency questionnaire

5.4.2 Quality assessment of studies using dietary assessment tools

The randomisation method was appropriate in two-thirds of the studies (28/39, 72%) and only three were blinded (3/39, 8%). Allocation concealment was adequate in only two studies (2/39, 5%). More than 80% of the included studies described the withdrawals and loss to follow-up appropriately (32/39, 82%) (Figure 5.4.2).

Figure (5.4.2): Summary of study quality assessment using the Jadad criteria.



5.4.3 Characteristics of dietary assessment tools

The most commonly used tool to assess dietary intake in pregnancy was short-term food diaries (23/39, 59%), followed by food frequency questionnaires (FFQ) (12/39, 31%) and 24-hour recalls (8/39, 20%). Four studies used two assessment tools jointly.(117–120) There was a large variation in the use of short-term food diaries. Three days diaries were the most commonly used (13/23, 57%), followed by 7 days diaries (8/23, 35%). The use of weighted food diaries was only reported in two studies.(117,121)

Most studies that used a FFQ adopted or modified a previously validated version in a similar or different study population (6/39, 15%). Assessed FFQs ranged in the number of included items between 13 and 181.(122–128)

Two studies developed and validated the FFQ in the study population using non-weighted 5 days food diaries (2/39, 5%) (129) and 24 hour recalls.(120) Only one study validated the content of the 24-hour recall via a panel of experts.(130) A predefined adherence criteria to the dietary intervention was only provided in four trials (4/39, 10%).(129,131–133) Dietary biomarkers were used to assess the effectiveness of the intervention in three studies only (3/39, 8%) (117,121,125) and to assess participants' adherence to the intervention and change in dietary intake in one trial only.(128) (Table 4.4.1)

5.4.4 Factors associated with use of dietary assessment tools

Logistic regression modelling revealed no relationship between the decision to use dietary assessment tools and the study quality (β= 1.183, p= 0.10), year of publication (before or after 2005) (β= -0.997, p=0.36), journal impact factor (β= -0.063, p=0.195), type of journal (general vs. specialist) (β=0.684, p= 0.529) or the study sample size (β= -0.001, p= 0.199).

5.5 Discussion

Our review summarises the use and quality of dietary assessment tools in randomised trials on dietary interventions in a pregnant population. Less than two-thirds of interventional studies included a dietary measurement process. This practice did not seem to correlate with methodological choices such as the study quality or the sample size. Self-reporting tools were the most commonly used, which is consistent with common practice outside pregnancy.(134)

5.5.1 Limitations

The majority of included studies did not provide detailed information on the rationale for choosing their preferred dietary tools which limited evidence synthesis on best practice. Only a handful of studies validated their assessment tools in the study population. This limited our ability to describe the best validation methods for dietary tools in pregnancy.

5.5.2 Dietary tools in pregnancy

The use of self-reporting dietary tools is common in pregnancy. These, however, commonly result in over or under-estimation of intake data. Food diaries are more likely to under-estimate certain nutrients in female and obese participants.(135) The lack of standardised portion sizes and measurement tools also increases variability.(136) Using multiple days diaries over a long period of time can increase dropouts (137) and bias habitual intake.(138)

The use of FFQs in pregnancy was also popular. FFQs' sensitivity to capture dietary changes in trial settings is generally trivial (139), and can be affected by a number of factors such as the number of items in the FFQ, the population literacy, the study sample size, and the type of the dietary intervention introduced.(40) FFQs' reliability in pregnancy is further undermined due to the instability of dietary intake between trimesters and common eating disorders such

as hyperemesis. Adopting a previously validated FFQ in a similar population is a common practice in nutritional trials.(140) However, the high inter-rater variability in pregnancy can increase the random error in FFQs and undermine their accuracy.(135)

24-hour recalls can capture day to day variability in dietary intake with reasonable sensitivity in trial settings.(136) The quality of the recalls can be improved by testing their content and face validity(23), using the multi-pass method (120) and by combining them with other assessment methods such as a FFQ.(118) A number of factors can affect their validity in pregnancy such as poor participant's attention, memory gaps, and variation in estimating portion sizes.(135)

5.5.3 Implication for future research

Pregnancy increases the systematic and random reporting errors in the dietary assessment process. A number of methods can be employed to improve the quality of dietary assessment in pregnancy. Validating and combining dietary assessment tools can help to reduce the reporting bias.(141) Accommodating for basic metabolic rate and expected energy intake in the study population is also helpful to reduce bias.(142) The use of biomarkers to assess specific nutrients' intake can offer a more accurate assessment.(78) With many biomarkers now available, it is possible to objectively assess the intake of many nutrients of interest using urine or blood samples.(66) Added cost, workload and invasive testing are potential drawbacks.(66) Furthermore, the changing physiology in pregnancy might affect the accuracy of some biomarkers. The applicability of biomarkers in pregnancy is still limited by the gap of knowledge on their validity, reliability, and reproducibility.(143) Employing new

technological methods such as mobile and internet-based assessment tools can also help to reduce measurement error.(144)

5.6 Conclusion

Self-reporting dietary assessment tools are commonly used in interventional dietary trials in pregnancy. The quality and applicability of existing tools are low with poor consideration for the characteristics of a pregnant population.

This chapter led to the following publication:

Al Wattar BH, Mylrea-Lowndes B, Morgan C, Moore AP, Thangaratinam S. Use of dietary assessment tools in randomized trials evaluating diet-based interventions in pregnancy: a systematic review of literature. Current Opinion in Obstetrics and Gynecology. 2016 Dec 1;28(6):455-63.

CHAPTER 6

VALIDATION OF SEMI QUANTITATIVE FOOD QUESTIONNAIRES IN A BRITISH PREGNANT POPULATION

In this chapter, I conducted a primary validation study of a custom designed food frequency questionnaire and a short dietary questionnaire within the ESTEEM trial pregnant population.

6.1 Abstract

Background Pregnancy poses many limitations on the assessment of dietary intake in nutritional studies. We validated a food frequency questionnaire (FFQ) and a short 12 items questionnaire (ESTEEMQ) against 24 hours dietary recalls to assess the dietary intake in a randomised, high-risk, multi-ethnic British pregnant population.

Methods We assessed the dietary intake of pregnant women who met the inclusion criteria for the ESTEEM trial before delivering the intervention in the second pregnancy trimester. We used three 24 hour dietary recalls as the reference method. We adapted our FFQ and ESTEEMQ from previously validated versions in dietary studies on the Mediterranean diet. We tested the agreement between the FFQ and the 24 hour recalls for mean values of food groups, energy, and micronutrients using intraclass correlation coefficients, Kappa statistics, and the Bland & Altman method. We identified the intake quintiles and reported the degree of gross misclassification and complete or adjacent agreement. Similarly, we assessed the agreement between the ESTEEMQ and the FFQ to assess participants' adherence to the intervention.

Results Sixty-five participants were included. Half were Asians (33/65, 50.7%) and 66% had a BMI ≥30 Kg/m^2 (43/65, 66.4%). The agreement between the FFQ and the 24-hour recalls was good for key foods in the Mediterranean diet such as meat (ICC 0.56) and fish (ICC 0.52). Other important food groups such as bread (ICC 0.46), legumes (ICC 0.25), and pastries, cakes & sweets (ICC 0.21) demonstrated moderate agreement. The ICC agreement for olive oil and nuts intake was poor with moderate quintile cross-classification. The

agreement between the ESTEEM Q and the FFQ was moderate to good for 8 out of 12 questions with moderate index score correlation. The majority of participants suffered from pregnancy-related gastro-intestinal disorders such as nausea and vomiting (82%).

Conclusion Our modified FFQ and ESTEEM Q are useful tools to assess adherence to a Mediterranean-based dietary intervention in a multi-ethnic British pregnant population.

6.2 Introduction

Nutritional studies aim to evaluate the effect of dietary and lifestyle interventions on health outcomes and associated disease such as diabetes and cardiovascular events.(145) Accurate assessment of baseline nutrients intake, adherence to the intervention and changes in habitual dietary intake are integral components in randomised nutritional studies.(38)

In pregnancy, randomised studies often use self-reporting dietary assessment tools to record food intake and dietary habits.(81) However, the high inter-rater variability and rapid changes in dietary requirements specific to pregnancy pose many limitations on the validity of these tools.(40) Their validity can be further undermined by contributing factors such as the low population literacy, the iteration associated with frequent use, and the reduced sensitivity when assessing complex dietary interventions. Assessing the validity, reliability, and accuracy of the chosen dietary assessment tool within the study population is therefore warranted.(40)

We undertook a randomised trial (ESTEEM) to evaluate the effect of a Mediterranean-based dietary intervention on pregnancy outcomes in a multi-ethnic British population.(146) Our objective was to validate a purposely developed food frequency questionnaire (FFQ) to assess the dietary intake of the ESTEEM population. We also evaluated the performance of a modified short 12 items questionnaire to assess the participants' adherence to the dietary intervention.

6.3 Methods

6.3.1 Study design

We conducted a prospective validation study within a randomised trial on the effect of Mediterranean diet on maternal and fetal outcomes (ESTEEM). The recruitment and randomisation criteria for ESTEEM is highlighted in figure (2.4.1).

Participants of the validation study were recruited consecutively by the ESTEEM trial dietician from both arms of the study at their first appointment (<18 weeks gestation). Following consent, participants were asked to complete all dietary assessment questionnaires before delivering the dietary intervention.

6.3.2 Dietary assessment

We used a series of three consecutive 24-hour dietary recalls as the reference method to test the validity of the FFQ. Participants were also asked to complete the ESTEEM Questionnaire to assess its validity against the FFQ.

6.3.2.1 24-hour dietary recalls

During the first face to face meeting, each participant completed two 24 hour recalls covering the intake of the last 48 hours. The following day the ESTEEM dietician collected a third recall over the phone before starting the intervention. We used a generic 24-hour recall proforma to collect data coupled with the multi-pass method to improve recall.(76) We aimed to capture two weekdays and one weekend day recalls where possible. Household measurements were used to estimate portion sizes. We estimated the daily intake for each participant from the mean of the three 24 hour recalls.

6.3.2.2 Semi-quantified FFQ

We adapted the ESTEEM FFQ from a previously validated version used for dietary assessment in a Mediterranean pregnant population in Spain (INfancia y Medio Ambiente (INMA)).(147) We added specific items to capture locally consumed food items specific to our population such as Asian and Afro-Caribbean food.(148–150) The FFQ included 111 questions, each with nine possible responses for consumption frequency ranging from 'never or less than once per month' to 'six or more per day'. We added 11 multiple choices questions to assess eating habits specific to a Mediterranean diet and common pregnancy eating disorders that could affect dietary intake such as nausea and vomiting. Portion sizes were standardised using The Food Standards Agency UK portion sizes.(151) We piloted the FFQ amongst the ESTEEM trial service user team to test its face and content validity which were judged to be high. We asked the ESTEEM team to evaluate the developed FFQ at different stages against established and validated questionnaires during dedicated consultation meetings.

6.3.2.3 ESTEEM Questionnaire (ESTEEM Q)

The ESTEEM Q was based on a previously validated version in a Mediterranean non-pregnant population.(77) We modified it to include 10 questions on the consumption of key food items in the Mediterranean diet and 2 questions on dietary preference for white meat and extra virgin olive oil. Two questions were omitted compared to the original version, one concerning alcohol intake (not applicable in pregnancy); and one concerning the intake of a Spanish sauce (Sofrito) which is not commonly consumed in a British population. A score of 0 or 1 was given for each question against a pre-specified cut-off value. The reference values were adopted from a previously validated adherence criteria for the Mediterranean diet.(152)

The sum of these scores generated an index score of each participant's adherence to the intervention (range 0-12). We added 7 dichotomous questions to screen for common pregnancy eating disorders that could affect dietary intake e.g. nausea and vomiting.

6.3.3 Data collection

We recorded the data in each participant's trial written case record files and later entered them into the ESTEEM secure internet database anonymously. We generated mean nutrients and food intake values from the FFQ using the method described in the development of the EPIC FFQ.(153) We calculated the daily average nutrient intake for each participant by multiplying the frequency of consuming each nutrient by its composition within the specified portion size.(153) We obtained nutrient values from The McCance & Widdowson's Composition of foods Integrated dataset.(154)

We used the same method to calculate the nutrient values from the ESTEEM Q scores using matching questions in the FFQ for each food item. We used Dietplan v06 (Forestfield Software Ltd, Horsham, United Kingdom) to calculate mean nutrients and food intake values from the completed 24-hour dietary recalls.

6.3.4 Statistical analysis

We estimated a sample size of 65 to be sufficient to validate the tools within the study population based on previous literature.(140) We assessed nutrients data for completeness and excluded cases with >20% of missing data entries in the FFQ and the ESTEEM Q. We excluded cases reporting unrealistic high total energy intake on the FFQ for women in the second trimester of pregnancy (>95th centile). We performed normality testing and assessed the type of data distribution (Type A or B) when non-normal distribution was detected. We

applied the relevant log transformation method to the type of data using established models such as the Box-Cox (53) and added a small constant to avoid taking the log of zero. We calculated the "density" of intake (intake divided by the total energy intake) as a way of adjusting for total energy intake as well as analysing absolute food and nutrients intake values.

We tested the agreement between the mean intake values of food groups, energy, and micronutrients from the FFQ and the 24-hour recalls using intraclass correlation coefficients. We used the Bland & Altman (155) method to graphically check the agreement between the two tools by plotting of the differences of the measurements against their means. We used paired t-tests to investigate evidence of consistent disagreement. We identified the intake quintiles for each variable from the 24-hour food recall data and reported the degree of gross misclassification (the proportion classified into opposite quintiles) and complete or adjacent agreement (the proportion classified into the same or an adjacent quintile) compared to the FFQ as additional indices of validity.

We used Kappa statistics to determine the agreement between the ESTEEM Q questions and their matched values derived from the FFQ. We used paired t-tests to investigate evidence of consistent disagreement in the dataset. We calculated the Pearson product moment correlations to test the association between the mean ESTEEM Q index score and that derived from the FFQ.

We considered the agreement between nutrient values using ICC to be good for a score above 0.5, acceptable for 0.49-0.2 and poor if <0.2.(156)

For Kappa statistics, good agreement was judged as values above 0.6, acceptable agreement for values between 0.6 and 0.2, and poor agreement for values below 0.2.(156)

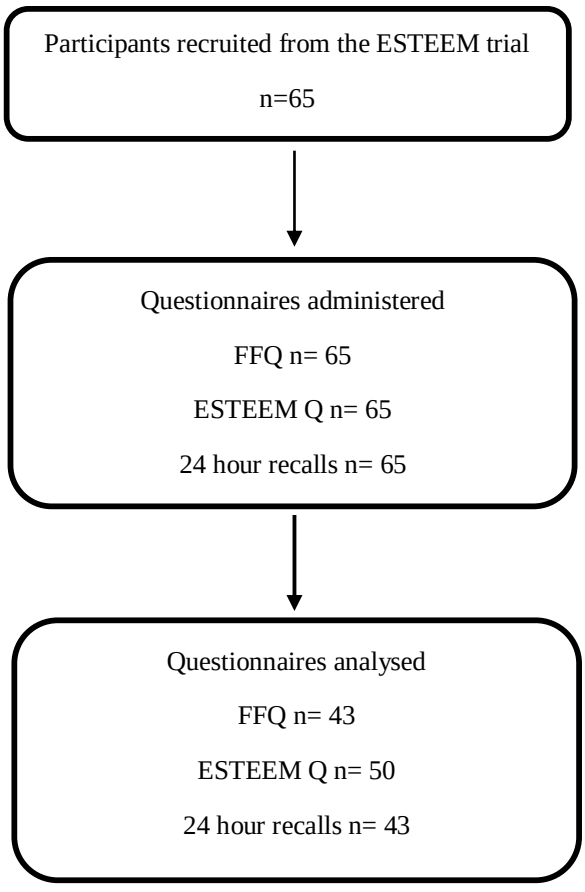
We judged the Quintile cross-classification of the agreement between the two tools as good if ≥ 50% were in the same quartile and ≤ 10% were in opposite quintiles. The agreement was judged as poor if <50% were in the same quartile and >10% in in opposite quintiles. Values in between these ranges were judged as moderate agreement.(156)

6.4 Results

6.4.1 Characteristics of participants

In total, 65 participants completed the dietary assessment tools. We excluded 15 women from the FFQ validation against the 24h recalls (4 cases due to incomplete FFQ data, and 11 for over reporting of the total energy intake) (Figure 6.4.1).

Figure (6.4.1): Flow chart of the ESTEEM validation study



The mean participants' age was 31.57 (SD 5.14). The median gravidity was 2 (range 1-9) and median parity was 1 (range 0-5). Half the participants were Asian (33/65, 50.7%), a third were White (17/65, 26.1%) and 18% were Black (12/65, 18.4%). More than half had a BMI ≥30 Kg/m^2 (43/65, 66.4%). Table (6.4.1) provides a summary of the participants' baseline characteristics.

Table (6.4.1): Baseline characteristics for pregnant women in the ESTEEM validation study

Mean age	31.57 (SD 5.14)
Median parity	1 (range 0-5)
Median gravidity	2 (range 1-9)
Ethnicity	
White	17/65 (26%)
Asian	33/65 (51%)
Black	12/65 (18%)
Other	3/65 (5%)
Body mass index (Kg/m^2)	
Normal (≤24.9)	11/65 (17%)
Overweight (25-29.9)	11/65 (17%)
Obese (≥30)	43/65 (66%)

6.4.2 FFQ vs 24 hour recalls

Overall, food groups mean values demonstrated moderate agreement with those of the 24 hour recalls (Table 6.4.2).

The agreement was good for key foods in the Mediterranean diet such as meat (ICC 0.56) and fish (ICC 0.52). Other important food groups such as bread (ICC 0.46), vegetables (ICC 0.20), legumes (ICC 0.25), eggs (ICC 0.23) and pastries, cakes & sweets (ICC 0.21) demonstrated acceptable agreement. The agreement for olive oil and nuts intake was poor with moderate quintile cross-classification agreement. Majority of food groups demonstrated good quintile cross-classification agreement except eggs, legumes, olive oil and nuts.

Table (6.4.2): Summary of mean values of food groups between FFQ and 24 hour recalls.

Food group	FFQ (Mean (SD))	24-hour recall (Mean (SD))	ICC	P value	Quintile gross misclassification (%)	Quintile complete or adjacent agreement (%)
Dairy products	194.7 (144.7)	94.0 (66.2)	0.31	0.008	0	66
Eggs	25.1 (26.4)	18.3 (26.9)	0.23	0.064	0	37.5
Meat	95.0 (73.9)	95.7 (68.7)	0.56	0.026	0	64
Fish	85.0 (90.0)	40.9 (58.1)	0.52	<0.001	2	44
Fruits	345.5 (233.0)	152.5 (125.3)	0.11	<0.001	8	64
Fruit juice	71.6 (96.8)	37.0 (73.0)	0.23	<0.001	12	28
Vegetables	323.1 (192.0)	118.8 (85.9)	0.20	<0.001	8	60
Potatoes	97.5 (62.3)	47.0 (50.9)	0.05	<0.001	12	60
Bread	70.3 (63.7)	83.4 (76.0)	0.46	0.008	2	54
Legumes	30.7 (34.1)	19.8 (27.0)	0.25	0.22	8	32
Nuts	4.7 (9.2)	2.6 (7.6)	0.14	0.007	84	16
Oils	15.5 (11.3)	5.3 (7.5)	0.00	<0.001	16	44
Pastries, cakes & sweets	34.4 (38.2)	33.9 (36.8)	0.21	0.16	2	70

The agreement for most macronutrients was moderate (protein ICC 0.46, carbohydrate ICC 0.45, Non-starch polysaccharides ICC 0.40, fat ICC 0.36, fatty acids ICC 0.25). Unsaturated fatty acids (PUFA, MUFA, Linoleic acid, and Marine n3 Fatty Acid) showed poor agreement with moderate quintile cross-classification agreement (Table 6.4.3). Cross-classification agreement for most remaining micronutrients was good to moderate. Appendix (9) illustrates the Bland-Altman graphs for both food groups and nutrients between the FFQ and the 24-hour recalls.

Table (6.4.3): Summary of mean values of energy and nutrients between FFQ and 24 hour recalls.

Energy and nutrients	FFQ	24-hour recall	ICC	P value	Quintile gross misclassification (%)	Quintile complete or adjacent agreement (%)
Protein (g)	88.4 (35.7)	61.3 (18)	0.46	0.30	6	66
Carbohydrate (g)	261.8 (96.5)	191 (72)	0.45	0.01	2	66
Sugars (g)	111.3 (45.7)	61.6 (28.5)	0.09	0.00	4	60
NSP (g)	201 (7.3)	14.6 (7.3)	0.40	0.80	4	64
Fat	96.0 (34.4)	60.1 (18.1)	0.36	0.001	2	66
Fatty Acids	31.5 (11.7)	20.0 (8.0)	0.25	0.022	2	56
MUFA	38.7 (13.6)	18.9 (6.7)	0.00	<0.001	16	42
PUFA	23.8 (10.0)	11.2 (5.6)	0.00	<0.001	8	48

Linoleic acid (g)	12.1 (5.7)	4.9 (3.9)	0.00	<0.001	16	48
Marine n3 Fatty Acid (g)	4.1 (3.0)	0.02 (0.03)	0.00	<0.001	32	40
Cholesterol (mg)	319.9 (184.9)	181.7 (112.2)	0.60	0.014	2	72
Sodium (mg)	3163.9 (1225.5)	2068.9 (1069.0)	0.18	0.064	2	60
Potassium (mg)	3707.4 (1143.3)	2265.2 (784.5)	0.18	<0.001	6	54
Calcium (mg)	971.4 (364.8)	567.9 (215.0)	0.41	<0.001	6	70
Magnesium (mg)	345.4 (111.7)	213.7 (90.3)	0.26	<0.001	6	58
Phosphorous (mg)	1476.6 (540.3)	1012.3 (306.3)	0.40	0.91	0	62
Iron (mg)	15.6 (5.3)	9.10 (4.4)	0.14	<0.001	8	52
Copper (mg)	1.6 (0.6)	1.1 (0.7)	0.05	0.31	4	62
Zinc (mg)	24.7 (20.5)	6.6 (2.8)	0.00	<0.001	10	42
Chloride (mg)	5066.3 (1936.4)	2995.9 (1573.4)	0.07	0.001	4	54
Manganese (mg)	4.6 (1.8)	2.8 (2.0)	0.20	<0.001	2	66
Iodine (µg)	265.3 (169.2)	80.1 (37.3)	0.00	<0.001	12	42
Selenium (µg)	77.2 (44.8)	36.2 (14.8)	0.13	<0.001	6	56
Retinol (µg)	479.9 (983.5)	180.8 (120.4)	0.14	0.001	2	64
Carotene (µg)	625.7 (251.3)	2179.3 (2256.5)	0.00	<0.001	20	40
Vitamin D (µg)	7.1 (6.9)	1.8 (1.9)	0.20	<0.001	6	58
Vitamin E (mg)	17.6 (7.8)	6.7 (3.5)	0.00	<0.001	16	42

Thiamine (mg)	1.6 (0.5)	1.2 (0.6)	0.29	0.51	0	68
Riboflavin (mg)	1.8 (1.1)	1.0 (0.4)	0.03	0.001	8	60
Niacin (mg)	25.1 (15.2)	16.8 (6.7)	0.11	0.88	2	56
Vitamin B6 (mg)	2.6 (1.3)	1.6 (0.6)	0.00	0.10	4	58
Vitamin B12 (µg)	9.9 (9.3)	3.0 (2.3)	0.31	<0.001	8	64
Folate (µg)	316.8 (113.0)	190.7 (94.4)	0.29	0.002	4	68
Pantothenate (mg)	7.1 (2.9)	3.5 (1.2)	0.00	<0.001	10	50
Biotin (µg)	38.1 (14.9)	21.5 (13.9)	0.25	<0.001	2	56
Vitamin C (mg)	163.8 (74.5)	95.6 (77.8)	0.21	<0.001	0	56

6.4.3 ESTEEM Q vs FFQ

Eight out of the 12 questions in the ESTEEM Q demonstrated moderate to good agreement with the FFQ (Olive oil use κ 0.52, fruits κ 0.36, butter/margarine κ 0.33, sugary drinks κ 0.50, fish κ 0.30, commercial sweets κ 0.35 and nuts κ 0.36) (Table 6.4.4). Agreement for estimating the quantity of olive oil consumed (κ 0.00) and pulses intake (κ 0.15) was poor between the two tools. There was poor correlation and agreement between the ESTEEM Q total index score and that derived from the FFQ (Pearson 0.24, ICC 0.24 (95% CI 0.00 - 0.55), p=0.07) (Table 6.4.4).

Table (6.4.4): Summary of mean values of food groups and index score between Esteem Q and the FFQ.

A: Food groups

ESTEEM question	Cut off value	Agreement (%)	Expected Agreement (%)	Kappa	Standard Error	P
Do you use olive oil as the main fat to cook with? (Y/N)	Yes	77.6	53.6	0.52	0.14	0.00
How many tablespoons do you consume of olive oil in a given day (including oil used for frying, salads, meals eaten away from home, etc.)?	≥4 Tbsp5	91.5	91.5	0.00	-	-
How many servings of vegetable do you consume per day? (1 serving = 200 g or palm size [consider side dishes as half a serving])	≥2	48	57.3	0.22	0.13	0.95
How many fruit units (including natural fruit juices) do you consume per day (1 unit = 1 piece of fruit, or equivalent (10 grapes, slice of melon) or small glass of juice)?	≥3	68	50	0.36	0.14	0.00
How many servings of red meat (lamb, beef, goat, pork), processed meat (sausages, hamburgers) or red meat products (bacon, ham) do you consume per day? (1 serving: 100–150 g or small palm-sized portion)	<1	85.7	82.3	0.20	0.13	0.07
How many servings of butter, margarine, or cream do you consume per day? (1 serving: One teaspoon)	<1	77.6	66.3	0.30	0.14	0.01
How many drinks containing sugar do you consume per day? (e.g. tea or coffee, canned fizzy drinks or sweetened fruit squash)	<1	76	51.7	0.50	0.14	0.00
How many servings of pulses (e.g. lentils, beans, dahl) do you consume per week? (1 serving : 150 g, fist size)	≥3	69.4	63.8	0.15	0.11	0.08
How many servings of fish or shellfish (white fish, oily fish e.g. salmon, or shellfish like mussels) do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish, a palm-sized portion)	≥3	66	51.1	0.30	0.12	0.00
How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<2	69.4	52.8	0.35	0.14	0.00
	≥3	79.1	67.4	0.36	0.11	0.00

How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g, small handful)						
Do you preferentially consume chicken or turkey instead of veal, pork, hamburger, or sausage?	Yes	65	50	0.30	0.15	0.03

B: Mean total index score

Variable	Mean	95% Confidence intervals	Pearson product moment correlation	ICC	P value
EQ Total Score	5.4	4.8 - 5.9			
			0.24	0.24 (95% CI 0.00 - 0.55)	0.07
FFQ-gen EQ Total Score	5.1	4.6 - 5.6			

6.4.4 Dietary habits

The majority of participants included in the study suffered from nausea and vomiting in the first part of their pregnancy (41/50, 82%). About half of them reported that this has affected their usual dietary intake (27/50, 54%). Half the participants reported other eating disorders common in pregnancy such as fullness of stomach (32/50, 64%), indigestion (27/50, 54%) and constipation (25/50, 50%). (Table 6.4.5).

Table (6.4.5): Summary of reported eating disorders reported by pregnant women in the second trimester.

Question	Yes n (%)	No n (%)	Missing n (%)
FFQ (N=50)			
Nausea or vomiting during your pregnancy	41 (82%)	8 (16%)	1 (2%)
Symptoms affecting food intake in the last 4 months	27 (54%)	20 (40%)	3 (6%)
ESTEEM Q (N=50)			
Fullness of Stomach	32 (64%)	17 (34%)	1 (2%)
Bloatedness	22 (44%)	27 (54%)	1 (2%)
Vomiting	14 (28%)	35 (70%)	1 (2%)
Nausea	19 (38%)	30 (60%)	1 (2%)
Indigestion	27 (54%)	22 (44%)	1 (2%)
Constipation	25 (50%)	23 (46%)	2 (4%)
Diarrhoea	5 (10%)	44 (88%)	1 (2%)

6.5 Discussion

6.5.1 Summary of main findings

Overall, our FFQ demonstrated a moderate performance for a number of key food items relevant to Mediterranean diet such as fish intake. There was good to moderate quintile cross-classification agreement allocation for key micronutrients such as PUFA and MUFA. However, the FFQ had low accuracy for capturing the intake of less commonly consumed food items such as nuts and olive oil, as well as most micronutrients. This could be attributed to the large variation in food intake at the beginning of the pregnancy leading to reduced FFQ accuracy

Compared to the FFQ, the ESTEEM Q performed well for most key food groups in a Mediterranean diet with a reasonable overall index score agreement. Some of the key items such as red meat and vegetables were poorly captured by the ESTEEM Q compared to the FFQ. This could be attributed to the multiple questions allocated for each food group in the

FFQ potentially serving as a memory aid. A large number of our participants suffered from pregnancy-related eating disorders when completing the questionnaire which contributes to higher inter-rater variability and lower dietary assessment accuracy.(40)

6.5.2 Strength and limitations

To our knowledge, this study is the first to design and test the validity of a food frequency questionnaire in a British multi-ethnic population with a focus on Mediterranean diet. We assessed the dietary intake at a neutral phase before introducing the ESTEEM intervention to reduce bias. We used a sound methodology for validating dietary assessment tools and adjusted it for pregnancy settings.

We amended our questionnaires to accommodate for local food culture and increase sensitivity. We designed our FFQ to be user-friendly by reducing the number of questions compared to previous versions and standardising the portion sizes. We aimed to reduce systematic bias in the 24 hour recalls by including multiple measurements of weekdays and weekends, using the multi-pass method, and by using a food picture atlas to help standardise portion sizes.(157,158) We reported on common pregnancy eating disorders in our population as potential confounders which are rarely assessed in similar studies.(159)

Our findings are limited by the over-reporting of energy and certain food items in the FFQs. This may be due to misunderstanding the FFQ questions and memory gaps.(160) We addressed this by excluding overtly skewed cases from the analysis. The study's time frame was relatively short which may have reduced the accuracy for assessing the intake of less commonly consumed food items. Our sample size was relatively small and restricted to pregnant women with metabolic risk factors which might affect the study generalisability.

6.5.2 Implication for research

To date, there is a limited number of food frequency questionnaires that are validated for use in a multi-ethnic pregnant population.(161) Choosing the appropriate assessment tool for the study population and its design is essential to maximise accuracy.(40) We modified the ESTEEM FFQ to use it as a user-friendly tool that would appeal to pregnant women who often had limited free time and low literacy. Overall the performance of our FFQ was similar to other validated FFQs for use in pregnant population on Mediterranean diet.(147,159,162) The low sensitivity and overestimation of certain food items suggest a limitation consistent with the use of self-reporting dietary assessment tools in general. Novel technological methods could improve the accuracy of self-reporting tools (163) such as mobile apps (164) and portable cameras (165), however, their applicability to pregnancy is still limited.

Substituting the FFQ with a shorter and more focused questionnaire in dietary trials is common.(166) The performance of the ESTEEM Q supports its validity to assess the participants' adherence to the Mediterranean-based dietary intervention. Linking the scores derived from The ESTEEM Q to pregnancy outcomes will help evaluate the effect of adherence on health outcomes.(152)

6.6 Conclusion

Our modified FFQ and ESTEEM Q are useful tools to assess adherence to a Mediterranean-based dietary intervention in a multi-ethnic British pregnant population.

CHAPTER 7

PRAGMATIC MULTICENTRE RANDOMISED TRIAL ON THE EFFECT OF SIMPLE, TARGETED DIET IN PREGNANT WOMEN WITH METABOLIC RISK FACTORS ON MATERNAL AND FETAL OUTCOMES (ESTEEM)

7.1 Abstract

Introduction Mediterranean diet can help to reduce metabolic risk factors and improve pregnancy outcomes. We conducted a randomised trial (ESTEEM) to evaluate the effectiveness of a Mediterranean-based dietary intervention on maternal and fetal outcomes.

Methods ESTEEM was an open-label randomised trial recruiting in five large maternity units for 24 months. We randomised pregnant women with metabolic risk factors to a Mediterranean-based dietary intervention or routine antenatal care using password protected internet-based computer system. We delivered the intervention over three sessions at 18, 20 and 28 weeks gestation. We assessed adherence using a validated short dietary questionnaire. Our primary outcome was a composite maternal outcome (pre-eclampsia and/or gestational diabetes) and a fetal composite outcome (stillbirth, small for gestational age fetus and/or admission to the neonatal intensive care unit).

Results In total, 1252 women were randomised. Both groups had similar basic characteristics with the majority of women being multigravidas, Asian and obese. The dietary intervention did not significantly reduce the primary maternal outcome (OR 0.99, 95% CI 0.72-1.36, p=0.95) or any of its composites (pre-eclampsia OR 1.48, 95% CI 0.87-2.50; GDM OR 0.86, 95% CI 0.60-1.24). Gestational weight gain was significantly lower in the intervention group (OR -1.24, 95% CI -2.27-0.21, p=0.018). There was no significant effect on the composite fetal outcome (OR 0.79, 95% CI 0.58-1.07, p=0.13) or its composites (SGA OR 0.72, 95% CI 0.51-1.04, p=0.07; stillbirth OR 0.49, 95% CI 0.04-5.57, p=0.56; admission to NICU OR 0.79, 95% CI 0.53-1.19, p=0.26). Delivering the intervention resulted in a significant change of dietary intake towards a Mediterranean-based diet.

Conclusions A Mediterranean-based dietary intervention is helpful to reduce gestational weight gain in pregnancy. The intervention did not improve maternal and fetal outcomes in a

high-risk population. Delivering a Mediterranean-based dietary intervention is feasible in a British pregnant population.

7.2 Introduction

The worldwide epidemic of maternal obesity continues to grow rapidly especially in high-income countries.(1,2) Almost every other women entering pregnancy in the UK and the USA is overweight or obese.(81) The adverse effect of obesity on pregnancy outcomes is well established.(5) Metabolic risk factors such as high BMI and dyslipidaemia significantly increase the risk of adverse maternal and fetal outcomes including pre-eclampsia (167), gestational diabetes (168), and fetal growth restriction.(169)

Dietary and lifestyle interventions can help to reduce pre-existing metabolic risk factors and improve pregnancy outcomes.(8) Mediterranean based dietary interventions have a protective effect against cardiovascular and metabolic disease in the non-pregnant population.(48) Mediterranean diet, characteristic for high intake of vegetables, fish, olive oil and nuts, promotes greater intake of unsaturated fatty acids and helps to reduce oxidative stress from fatty tissues.(170) The effect of Mediterranean diet on reducing metabolic risk factors in pregnant women with has been reported in observational studies (50) but no randomised trials exist to date.

We conducted a large multi-centre pragmatic randomised trial (ESTEEM) to evaluate the beneficial effect of a Mediterranean-based dietary intervention on composite maternal and fetal outcomes compared to routine antenatal care.

7.3 Methods

7.3.1 Study objectives

Our primary objective was to evaluate the effect of a simple, targeted Mediterranean-based diet, supplemented with extra-virgin olive oil and nuts, on a composite maternal and fetal outcome, compared to routine antenatal care within the National Health Service. Our secondary objectives were to assess the effect of the dietary intervention on various maternal and fetal clinical, dietary and biochemical outcomes.

7.3.2 Study design

I have discussed the study protocol and design in chapter 2. The protocol was registered and published prospectively.(146) The study was conducted as per the protocol with no recorded deviations.

The primary outcome was a composite maternal outcome defined as pre-eclampsia (new onset or superimposed) or gestational diabetes; and a composite fetal outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th centile) or admission to the neonatal intensive care unit. (Appendix 7)

The secondary outcomes were

maternal: pre-eclampsia, gestational diabetes, gestational weight gain, admission to high dependency unit or intensive care unit, antepartum haemorrhage, mode of delivery, preterm delivery (<37 weeks, and < 34 weeks), anaemia, and physical activity.

fetal and neonatal: small for gestational age (<10th centile), very small for gestational age (< 3^{rd} centile), large for gestational age (> 90^{th} centile), stillbirths, birth weight (in Kg using both customised and population centiles), admission to neonatal intensive care units, neonatal deaths, and hypoxic ischaemic encephalopathy.

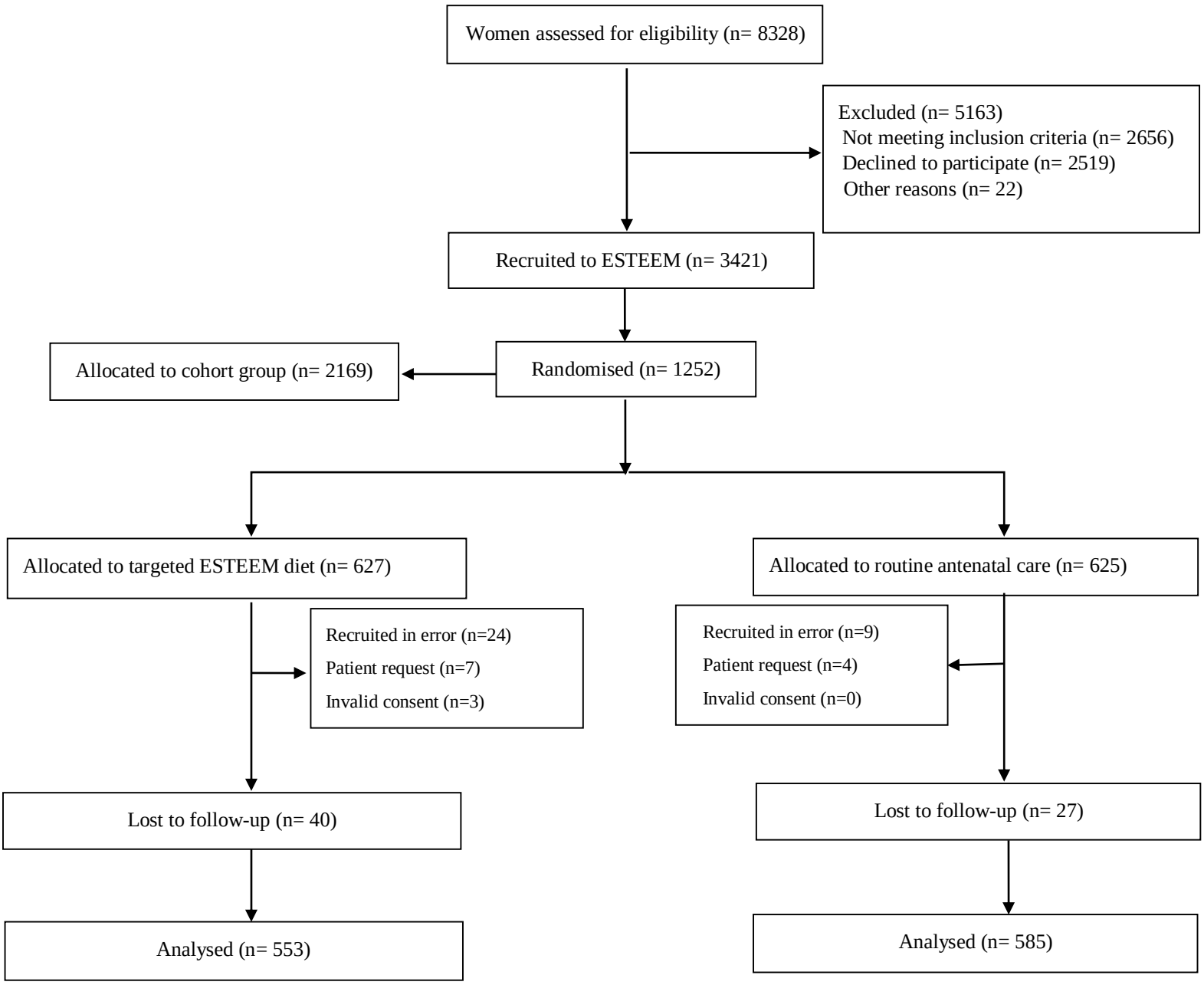
dietary: food intake for olive oil, nuts, vegetables, fish, fruits, pulses, red meat, white meat, butter/margarine, sugary drinks, commercial sweets, and micronutrients.

laboratory: maternal serum lipids including levels of triglycerides, high-density lipoproteins (HDL), the ratio of triglycerides (ratio of triglycerides to HDL) and non-high-density lipoprotein cholesterol (Non-HDL, cholesterol minus HDL).

7.4 Results

We screened 8328 pregnant women; 3421 met our inclusion criteria for ESTEEM (3421/8328, 41%). In total, 1252 women with metabolic risk factors and were randomised to the intervention or the control groups (1252/3421, 36%). (Figure 7.4.1).

Figure (7.4.1): The ESTEEM trial profile



7.4.1 Population characteristics

The baseline characteristics were similar in both groups. The average participant age was 31 and about 3% were above the age of 40. Both groups had similar basic characteristics with the majority of women being multigravidas, Asian and obese (Table 7.4.1). Serum lipids, previous clinical and family history were all comparable between the groups. Overall, 41% of the participants in the intervention group were compliant and attended all the planned intervention sessions. A summary of baseline dietary intake, physical activity and quality of life assessment is provided in Appendix (8).

Table (7.4.1): Baseline characteristics of participants in the ESTEEM trial.

Baseline characteristics	**Intervention**	**Control**
Demographics (584,610)		
Age (years)	31 (5.2)	31 (5.2)
Age > 40	23 (3.9%)	19 (3.1%)
Gravidity (593,612)		
Primigravida	162 (27.3%)	168 (27.5%)
Multigravida	431 (72.7%)	444 (72.5%)
Ethnicity (593,612)		
White	217 (36.6%)	217 (35.5%)
Asian	257 (43.3%)	270 (44.1%)
Black	97 (16.4%)	105 (17.2%)
Other	22 (3.7%)	20 (3.3%)
BMI (Kg/m^2) (593,612)		
Normal (18.5-24.9)	84 (14.2%)	84 (13.7%)
Overweight (25.0-29.9)	99 (16.7%)	102 (16.7%)
Obese (30.0-39.9)	410 (69.1%)	426 (69.6%)
Clinical history		
Pre-eclampsia / Eclampsia / HELLP	21 (3.7%)	29 (4.8%)
(575,600)	15 (2.7%)	22 (3.8%)
Gestational Diabetes (563,585)	8 (1.4%)	14 (2.3%)
Stillbirth / Neonatal Death (571,598)	5 (0.9%)	10 (1.8%)
Admission to ITU / HDU (530,557)	27 (4.9%)	31 (5.4%)
Chronic hypertension (554,575)	274 (51.1%)	276(51.5%)
Family history of hypertension/pre-	276 (51%)	303(54.6%)
eclampsia (537,536)		
Family history of Diabetes (541,555)		
Baseline serum lipids		

Triglycerides (mmol/L) (532,558)	1.6 (0.7)	1.7 (0.8)
HDL (mmol/L) (531,557)	1.7 (0.5)	1.6 (0.4)
Ratio of Triglycerides to cholesterol (527,553)	0.3 (0.2)	0.3 (0.2)
Non-HDL (mmol/L) (529,554)	3.2 (0.8)	3.3 (1.6)
Health Thermometer (400,222)	67.4 (18.7)	71.8 (18.7)
ESTEEM Q diet score (337,210)	5.0 (1.9)	5.0 (1.9)
Physical Activity (MET) (406, 241)	2579.5 (3335.9)	2591.7 (3306.9)

Data are mean (SD) or numbers (percentage)

ITU: intensive treatment unit, HDU: high dependency unit, HDL: high density lipoprotein, LDL: low density lipoprotein. MET: Metabolic Equivalent of Task minutes per week.

7.4.2 Primary outcomes

The intention to treat analysis demonstrated some protective effect of the dietary intervention on reducing the primary maternal outcome (OR 0.76, 95% CI 0.56-1.03, p=0.07) with more visible effect against GDM (OR 0.65, 95% CI 0.47-0.91, p=0.01) than pre-eclampsia (OR 1.43, 95% CI 0.84-2.43, p=0.19). This was further confirmed in our CACE analysis for primary maternal composite outcome (OR 0.55, 95% CI 0.29-1.05, p=0.06). In contrast, there was no major effect for the intervention to reduce the incidence of the composite fetal outcome (OR 0.79, 95% CI 0.58-1.08, p=0.14) or any of its composites (small for gestation age OR 0.78, 95% CI 0.53-1.15, p=0.21; stillbirth OR 0.49, 95% CI 0.04-5.57, p=0.56; admission to NICU OR 0.79, 95% CI 0.53-1.18, p=0.25). The protective effect of the intervention was more evident (OR 0.59, 95% CI 0.32-1.07, p=0.07) when accommodating for adherence with the intervention. (Table 7.4.2).

Table (7.4.2): Effects of Mediterranean diet on the primary composite maternal and fetal and neonatal outcomes, and its components

Primary outcomes	Intervention (n=553) N (%)	Control (n=585) N (%)	Crude OR (95% CI)	Crude p value	Adjusted OR (95% CI)	Adjusted P Value
Composite outcomes						

Composite maternal outcome (486,500)	111 (22.8%)	143 (28.6%)	0.74 (0.55, 0.98)	0.03	0.76 (0.56, 1.03)	0.07
Composite fetal outcome (550,583)	92 (17.3%)	118 (20.9%)	0.79 (0.59, 1.07)	0.13	0.79 (0.58, 1.08)	0.14
Primary outcome (CACE Analyses)						
Composite maternal Outcome (Pre-eclampsia and/or GDM)	111 (22.8%) [67]	143 (28.6%) [85]	0.50 (0.27, 0.93)	0.02	0.55 (0.29, 1.05)	0.06
Composite fetal Outcome (stillbirth and/or admission to NICU and/or small for gestational age.	92 (17.3%) [3]	118 (20.9%) [2]	0.61 (0.33, 1.12)	0.11	0.59 (0.32, 1.07)	0.07
Individual outcomes						
Gestational diabetes (477,497)	84 (17.6%)	124 (24.9%)	0.64 (0.47, 0.88)	0.00	0.65 (0.47, 0.91)	0.01
Pre-eclampsia (552,585)	34 (6.2%)	27 (4.6%)	1.36 (0.81, 2.28)	0.25	1.43 (0.84, 2.43)	0.19
Small for gestational age (550,583)	52 (9.8%)	69 (12.2%)	0.78 (0.53, 1.14)	0.20	0.78 (0.53, 1.15)	0.21
Stillbirth (552,585)	1 (0.2%)	2 (0.4%)	0.53 (0.05, 5.86)	0.60	0.49 (0.04, 5.57)	0.56
Admission to NICU (552, 584)	49 (9.2%)	64 (11.3%)	0.79 (0.54, 1.17)	0.25	0.79 (0.53, 1.18)	0.25

GDM: gestational diabetes mellitus NICU: neonatal intensive care unit

Subgroup analysis for obesity, raised Triglycerides and raised blood pressure at booking, did not demonstrate any major differences in the effect of the intervention on the primary outcome or its maternal and fetal composites (Table 7.4.3).

Table (7.4.3): The effect of the dietary intervention on primary outcomes across the different randomisation subgroups.

		Included in Analysis		Experienced Outcome		Adjusted Odds Ratio (95% CI)	P value
		Intervention	Control	Intervention	Control		
Primary Maternal Outcome							
	Obese	348	352	81 (23.3%)	104 (29.5%)	0.72 (0.50, 1.02)	0.55
	Not Obese	138	148	30 (21.7%)	39 (26.4%)	0.88 (0.50, 1.57)	
	Raised Triglycerides	199	212	50 (25.1%)	71 (33.5%)	0.68 (0.43, 1.08)	0.59
	Not Raised Triglycerides	243	245	51 (21.0%)	61 (24.9%)	0.81 (0.52, 1.26)	
	Raised Blood Pressure	30	27	10 (33.3%)	14 (51.9%)	0.60 (0.19, 1.89)	0.67
	Not Raised Blood Pressure	448	461	100 (22.3%)	125 (27.1%)	0.78 (0.57, 1.07)	

Pre-eclampsia						
Obese	386	409	26 (6.7%)	18 (4.4%)	1.65 (0.88, 3.11)	0.40
Not Obese	166	176	8 (4.8%)	9 (5.1%)	0.99 (0.37, 2.69)	
Raised Triglycerides	230	252	11 (4.8%)	11 (4.4%)	1.13 (0.47, 2.71)	0.91
Not Raised Triglycerides	270	280	18 (6.7%)	16 (5.7%)	1.21 (0.59, 2.46)	
Raised Blood Pressure	36	30	7 (19.4%)	2 (6.7%)	3.62 (0.65, 20.01)	0.25
Not Raised Blood Pressure	507	542	27 (5.3%)	24 (4.4%)	1.26 (0.71, 2.24)	
Gestational Diabetes						
Obese	341	349	61 (17.9%)	92 (26.4%)	0.58 (0.40, 0.86)	0.27
Not Obese	136	148	23 (16.9%)	32 (21.6%)	0.88 (0.47, 1.65)	
Raised Triglycerides	195	212	41 (21.0%)	63 (29.7%)	0.64 (0.39, 1.04)	0.86
Not Raised Triglycerides	238	242	36 (15.1%)	50 (20.7%)	0.68 (0.41, 1.11)	
Raised Blood Pressure	27	27	5 (18.5%)	13 (48.1%)	0.28 (0.07, 1.07)	0.19
Not Raised Blood Pressure	442	458	78 (17.6%)	107 (23.4%)	0.70 (0.50, 1.00)	
Primary Fetal Outcome						
Obese	373	392	61 (16.4%)	86 (21.9%)	0.69 (0.48, 1.01)	0.20
Not Obese	158	172	31 (19.6%)	32 (18.6%)	1.08 (0.61, 1.89)	
Raised Triglycerides	223	242	38 (17.0%)	45 (18.6%)	0.94 (0.58, 1.52)	0.37
Not Raised Triglycerides	258	270	46 (17.8%)	63 (23.3%)	0.69 (0.45, 1.07)	
Raised Blood Pressure	35	28	16 (45.7%)	6 (21.4%)	3.08 (0.97, 9.77)	0.018
Not Raised Blood Pressure	487	523	76 (15.6%)	108 (20.7%)	0.72 (0.52, 1.00)	
Small for Gestational Age[2]						
Obese[3]	375	397	33 (8.8%)	51 (12.8%)	0.65 (0.41, 1.03)	0.28
Not Obese	160	174	19 (11.9%)	21 (12.1%)	1.02 (0.52, 2.00)	
Raised Triglycerides[4]	218	239	20 (9.2%)	23 (9.6%)	1.00 (0.53, 1.91)	0.22
Not Raised Triglycerides	256	271	27 (10.5%)	42 (15.5%)	0.60 (0.35, 1.02)	
Raised Blood Pressure[5]	35	29	10 (28.6%)	5 (17.2%)	2.02 (0.58, 7.02)	0.093
Not Raised Blood Pressure	491	529	42 (8.6%)	66 (12.5%)	0.66 (0.43, 0.99)	
Admission to Neonatal ICU						
Obese	386	409	36 (9.3%)	45 (11.0%)	0.86 (0.53, 1.38)	0.60
Not Obese	166	175	13 (7.8%)	19 (10.9%)	0.67 (0.31, 1.45)	
Raised Triglycerides	230	251	20 (8.7%)	29 (11.6%)	0.74 (0.40, 1.37)	0.73
Not Raised Triglycerides	270	280	26 (9.6%)	32 (11.4%)	0.86 (0.49, 1.52)	
Raised Blood Pressure	36	30	6 (16.7%)	2 (6.7%)	2.43 (0.43, 13.79)	0.22

Not Raised Blood Pressure	507	541	43 (8.5%)	59 (10.9%)	0.78 (0.51, 1.20)

7.4.3 Secondary outcomes

Mothers in the intervention group had lower gestational weight gain compared to the control group (OR -1.18, 95% CI -2.27-0.15, p=0.02). All other secondary maternal outcomes were similar in both groups (Table 3). Using population charts, the incidence of small of gestational age was reduced in the intervention group (OR 0.73, 95% CI 0.51-1.04, p=0.08), this however was not the case when GROW charts were used (OR 0.78, 95% CI 0.53-1.15, p=0.21). None of the other secondary fetal outcomes were different between the two groups (Table 7.4.4).

Table (7.4.4): Secondary maternal and fetal outcomes in the ESTEEM trial on the effect of a Mediterranean-based dietary intervention in pregnant women with metabolic risk factors.

Maternal outcomes	**Intervention (n=553) n(%)**	**Control (n=585) n(%)**	**Crude OR (95% CI)**	**Crude p value**	**Adjusted OR (95% CI)**	**Adjusted P Value**
Gestational Weight Gain (Kg) (230,238)	6.8 (5.6)	8.3 (6.4)	-1.51 (-2.61, -0.42)	0.00	-1.18 (-2.21, -0.15)	0.02
Preterm Delivery <37 Weeks (545,579)	52 (9.5%)	64 (11.1%)	0.85 (0.58, 1.25)	0.41	0.82 (0.55, 1.22)	0.33
Preterm Delivery <34 Weeks(545,579)	23 (4.2%)	26 (4.5%)	0.94 (0.53, 1.66)	0.82	0.92 (0.51, 1.67)	0.79
Antepartum Haemorrhage(548,580)	9 (1.6%)	13 (2.2%)	0.73 (0.31, 1.72)	0.47	0.70 (0.29, 1.72)	0.44
Mode of Delivery						
Vaginal delivery vs. Caesarean Section	175 (32.6%) [14]	176 (30.8%) 112 (63.6%)	1.08 (0.84, 1.39) 1.07 (0.69, 1.65)	0.56 0.77	1.06 (0.82, 1.37) 1.28 (0.77, 2.12)	0.65 0.34
Emergency Vs Elective Caesarean Section	114 (65.1%)	56 (14.2%)	1.08 (0.72, 1.61)	0.72	1.15 (0.75, 1.76)	0.53
Spontaneous vs Instrumental Vaginal delivery	55 (15.1%)					
Anaemia (547,578)	114 (20.8%)	129 (22.3%)	0.92 (0.69, 1.22)	0.55	0.91 (0.66, 1.23)	0.53
Admission to HDU or ITU (527,566)	18 (3.4%)	24 (4.2%)	0.80 (0.43, 1.49)	0.48	0.79 (0.42, 1.50)	0.48
Fetal outcomes						
Hypoxic ischaemic encelopathy (550,580)	2 (0.4%)	4 (0.7%)	0.53 (0.10, 2.89)	0.46	0.56 (0.09, 3.46)	0.53
Neonatal Death (551,585)	3 (0.6%)	1 (0.2%)	3.20 (0.33, 30.90)	0.31	3.93 (0.33, 46.10)	0.28
Birth Weight (g) (550.584)	3340.1 (623.1)	3277.6 (599.4)	62.44 (-10.03, 134.90)	0.09	56 (-15.39, 127.39)	0.12
Small for Gestational Age (GROW)(550,584)	52 (9.8%)	69 (12.2%)	0.78 (0.53, 1.14)	0.20	0.78 (0.53, 1.15)	0.21
Small for Gestational Age (Population) (550,583)	61 (11.5%)	86 (15.2%)	0.72 (0.51, 1.03)	0.06	0.73 (0.51, 1.04)	0.08
Very small for Gestational Age (GROW)(550,583)	17 (3.2%)	21 (3.7%)	0.86 (0.45, 1.64)	0.64	0.84 (0.43, 1.63)	0.60
Very small for Gestational Age (Population) (550,583)	30 (5.6%)	33 (5.9%)	0.96 (0.58, 1.60)	0.89	0.96 (0.57, 1.61)	0.87
Large for Gestational Age (GROW) (550,583)	73 (13.7%)	64 (11.3%)	1.25 (0.87, 1.78)	0.23	1.23 (0.86, 1.78)	0.26
Large for Gestational Age (Population) (550,583)	59 (11.1%)	61 (10.8%)	1.03 (0.71, 1.51)	0.88	1.01 (0.69, 1.49)	0.94
Laboratory outcomes						
Triglycerides (mmol/L)(217,257)	3.0 (1.3)	2.9 (1.3)	0.08 (-0.15, 0.31)	0.50	0.04 (-0.15, 0.22)	0.70
HDL (mmol/L) (221,258)	1.8 (0.5)	1.8 (0.5)	0.03 (-0.06, 0.12)	0.54	0.02 (-0.05, 0.09)	0.51
Ratio of Triglycerides (215,255)	0.5 (0.2)	0.5 (0.2)	0.01 (-0.03, 0.04)	0.67	0.01 (-0.02, 0.04)	0.72
Non-HDL (mmol/L) (219,256)	4.4 (1.3)	4.3 (1.3)	0.03 (-0.21, 0.27)	0.82	0.01 (-0.18, 0.19)	0.93
Physical and dietary outcomes						
Physical Activity (MET) (262,270)	6.9 (1.6)	6.7 (2.0)	0.24 (-0.07, 0.56)	0.13	0.21 (-0.10, 0.51)	0.19
ESTEEM Q diet score (218,255)	7.2 (2.0)	5.1 (2.0)	2.06 (1.70, 2.43)	0.00	2.00 (1.66, 2.33)	0.00
Health Thermometer (257,252)	73.1 (16.9)	69.9 (18.6)	3.27 (0.19, 6.36)	0.03	2.98 (0.05, 5.91)	0.04

7.4.4 Dietary intake

Participants in the intervention group consumed more key foods in the Mediterranean diet including extra virgin olive oil (p=<0.001), nuts (p=<0.001), pulses (p=0.047), fish (p=<0.001), and white meat (p=<0.001). They also consumed less red meat (p=<0.001), and butter margarine (p=<0.001). Both groups reported similar GI symptoms with less bloatedness in the intervention group (p=0.03) (Table 7.4.5).

Table (7.4.5): Summary of participants' dietary intake at 36 weeks gestation

Question (threshold for one mark)	Intervention (n=553) n(%)	Control (n=585) n(%)	Crude OR (95% CI)	Crude P Value	Adjusted OR (95% CI)	Adjusted P Value
Do you use olive oil as the main fat to cook with? (Yes)	261 (93.2%) [273]	146 (49.0%) [287]	14.30 (8.52, 24.01)	<0.001	32.19 (16.03, 64.62)	<0.001
How many tablespoons do you consume of olive oil in a given day? (>=4)	63 (23.1%) [280]	28 (9.5%) [289]	2.87 (1.78, 4.64)	<0.001	2.81 (1.55, 5.09)	<0.001
How many servings of vegetable do you consume per day? (>=2)	185 (67.5%) [279]	189 (64.5%) [292]	1.14 (0.81, 1.62)	0.45	1.34 (0.85, 2.11)	0.21
How many fruit units do you consume per day? (>=3)	142 (51.4%) [277]	156 (52.7%) [289]	0.95 (0.68, 1.32)	0.76	1.10 (0.72, 1.68)	0.66
How many servings of red meat, processed meat or red meat products do you consume per day (<1)	206 (85.5%) [312]	156 (56.1%) [307]	4.60 (3.00, 7.07)	<0.001	3.42 (1.99, 5.86)	<0.001
How many servings of butter, margarine, or cream do you consume per day? (<1)	164 (61.2%) [285]	115 (39.5%) [294]	2.41 (1.72, 3.39)	<0.001	2.41 (1.55, 3.75)	<0.001
How many drinks containing sugar do you consume per day? (<1)	149 (55.4%) [284]	121 (41.0%) [290]	1.79 (1.28, 2.49)	<0.001	1.40 (0.92, 2.15)	0.12
How many servings of pulses do you consume per week? (>=3)	103 (37.5%) [278]	86 (29.1%) [289]	1.46 (1.03, 2.08)	0.033	1.56 (1.00, 2.44)	0.048
How many servings of fish or shellfish do you consume per week? (>=3)	101 (36.6%) [277]	67 (22.6%) [288]	1.98 (1.37, 2.86)	<0.001	2.57 (1.57, 4.21)	<0.001
How many times per week do you consume commercial sweets or pastries, such as	165 (59.8%) [277]	151 (51.7%) [293]	1.39 (1.00, 1.94)	0.053	1.42 (0.92, 2.19)	0.11

cakes, cookies, biscuits or custard? (<3)						
How many servings of nuts do you consume per week? (>=3)	192 (70.1%) [279]	67 (22.9%) [293]	7.86 (5.40, 11.45)	<0.001	6.75 (4.28, 10.62)	<0.001
Do you preferentially consume chicken or turkey instead of veal, pork, hamburger or sausage? (Yes)	221 (87.0%) [299]	224 (80.3%) [306]	1.64 (1.03, 2.63)	0.038	2.34 (1.26, 4.35)	0.007
Mean total Score	7.2 (2.0) [335]	5.1 (2.0) [330]	2.06 (1.70, 2.43)	<0.001	2.00 (1.66, 2.33)	<0.001
Symptoms Experienced						
Fullness of stomach	151 (56.8%) [287]	157 (62.5%) [334]	0.79 (0.55, 1.12)	0.18	0.93 (0.60, 1.43)	0.73
Bloatedness	76 (28.5%) [286]	92 (36.8%) [335]	0.68 (0.47, 0.99)	0.044	0.61 (0.39, 0.96)	0.032
Vomiting	35 (13.2%) [287]	44 (17.6%) [335]	0.71 (0.44, 1.15)	0.16	0.61 (0.33, 1.14)	0.12
Nausea	70 (26.2%) [286]	83 (32.9%) [333]	0.72 (0.50, 1.06)	0.09	0.82 (0.52, 1.31)	0.41
Indigestion	126 (47.2%) [286]	110 (44.0%) [335]	1.14 (0.80, 1.61)	0.47	1.08 (0.69, 1.69)	0.73
Constipation	70 (26.2%) [286]	82 (32.7%) [334]	0.73 (0.50, 1.07)	0.11	0.73 (0.46, 1.15)	0.17
Diarrhoea	32 (12.1%) [288]	39 (15.6%) [335]	0.74 (0.45, 1.23)	0.25	0.60 (0.34, 1.09)	0.093

Data are mean (SD) [missing value] or numbers (percentage) [missing values].

The EQ-5D questionnaire revealed similar quality of life status for both groups with an overall health mean difference score of 2.98 (p=0.04) (Table 7.4.6).

Table (7.4.6): Summary of the participants' quality of life using the EQ-5D questionnaire at 36 weeks gestation.

Quality of life dimension	Intervention (n=553)	Control (n=585)	Odds Ratio (95% CI)	P Value
Mobility	83 (29.6%) [273]	84 (28.1%) [286]	1.06 (0.68, 1.64)	0.80
Self-Care	25 (9.0%) [274]	36 (12.0%) [286]	0.73 (0.37, 1.46)	0.37
Usual Activities	88 (31.7%) [275]	102 (34.0%) [285]	0.88 (0.57, 1.35)	0.55
Pain/Discomfort	174 (62.4%) [274]	189 (63.2%) [286]	0.91 (0.60, 1.38)	0.65
Anxiety/Depression	53 (19.1%) [275]	59 (19.7%) [286]	1.07 (0.65, 1.78)	0.78
Health Thermometer	73.1 (16.9) [296]	69.9 (18.6) [333]	2.98 (0.05, 5.91)	0.04

Data are mean (SD) [missing value] or numbers (percentage).

7.5 Discussion

7.5.1 Summary of findings

Our findings demonstrate the overall beneficial effect of a Mediterranean-based diet in improving pregnancy outcomes in a high risk population particularly in reducing the incidence of gestational diabetes and gestational weight gain. This effect was more pronounced in those mothers who complied fully with the intervention and lead a gestational weight gain reduction by an average of 1.24 Kg. The effect on fetal outcome was less evident particularly when using GROW charts compared to standardised population charts. The uptake for the Mediterranean diet in our multi-ethnic population. Compared to baseline, the intervention group significantly consumed more for key food items such as fish, olive oil, nuts and chicken with less intake of meat and butter. Women approached to join the study were generally in favour of taking up the intervention with only 30% declining to participate (2519/8328, 30%). This was significantly

higher compared to similar studies evaluating lifestyle interventions in pregnancy with a decline to participate rate between 50-60%.(54,132,172) Delivering the intervention in the antenatal period, therefore, seems feasible.

7.5.2 Strengths and limitations

We used a prospective protocol that was registered and published prospectively. The large sample size provided enough power to detect a reduction in the primary outcome. This was supported by the small number of loss to follow-up cases. Our inclusion and randomisation criteria were relaxed, increasing the external validity of the findings. The generalisability of ESTEEM is high due to its pragmatic design and the large mix of ethnicities and socioeconomic backgrounds in our population. We performed an intention to treat analysis and supplemented it with a CACE analysis to accommodate for the participants' adherence to the intervention. We used minimisation to eliminate potential effect modifiers. We assessed the participants' physical activity and quality of life, two important elements for evaluating complex behavioural interventions. We adapted the intervention to local food culture by providing cooking recipes and used validated assessment tools to assess dietary intake.

Blinding the participants in nutritional studies is complex.(79) The lack of blinding in ESTEEM leaves a chance for the Hawthorne effect.(171) We did not introduce a control diet in the comparison group and some of the participants' might have followed a Mediterranean diet. We focused on increasing the intake of unsaturated fatty acids to reduce oxidative stress in pregnancy. However, due to limitations in the dietary assessment methods, we could not objectively compare the intake of these nutrients between the two groups. Furthermore, serum lipids assessment was only possible when performed randomly. Measuring fasting

serum values could arguably offer a more accurate view on the effect on lipids, however, this was not logistically possible within our trial settings. Our population was mainly obese and multigravida. The risk of pre-eclampsia and gestational diabetes might be different in lean nulliparous women. The adherence to the interception was suboptimal (41%), however, this is comparable to other dietary trials in pregnancy.(54,172)

7.5.3 Implications for future practice

Dietary and behavioural interventions in pregnancy were shown to improve maternal and fetal outcomes in a number of small trials, however, most suffer from methodological limitations.(8) Our findings, come in line with the results of recently published large trials suggesting some protective effect of dietary interventions on pregnancy outcomes.(54,132,172) However, our trial demonstrates a clear protective effect against gestational diabetes in contrast to these large trials.(54,132,172) This could be attributed to many factors.; the specific nature of Mediterranean diet might make it easier to follow by pregnant women leading to higher adherence and greater effect. Engaging mothers to be active in delivering the intervention could also have helped to improve adherence. Lastly, the criteria used to diagnose gestational diabetes varies as we used the the modified International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.(173)

In particular, ESTEEM supports the role of diet in reducing gestational weight gain, which is well established in available evidence.(8) Increased weight gain in pregnancy can act as a surrogate for adverse maternal and fetal outcomes such as gestational diabetes and small for gestation age.(174) However, establishing a linear link between diet, weight gain and pregnancy outcomes seems more complex.

The planned intervention sessions in ESTEEM were quite moderate in frequency and intensity. Delivering a more concentrated intervention might yield better health outcomes, however and quite possibly, it won't be feasible in modern health systems such as the NHS nor cost-effective.(175) Several studies have demonstrated a protective effect for Mediterranean diet on childhood obesity, asthma, and allergy.(176,177) The planned follow-up for ESTEEM mothers and babies will help to assess the long-term health outcomes and the feasibility of enrolling such intervention after pregnancy. The uptake for Mediterranean diet in a multi-ethnic British population was quite high leading to a significant change in the dietary habits of the intervention group. With its proven long-term health benefits, sustaining the adherence to Mediterranean diet can help to reduce maternal and childhood obesity.(30)

Much research evaluated the effect of dietary interventions on pregnancy outcomes with paradoxical findings.(83) This could be attributed to the methodological limitations and the large variations in the evaluated dietary regimes. Considering the findings of the ESTEEM trial, future studies should shift the focus to evaluating lifestyle interventions in different life periods such as pre-conception and postpartum. While ideal, delivering lifestyle interventions in the pre-conception period to optimise the pregnancy experience is not always feasible with more than 40% unplanned pregnancies in the UK.(173)

7.6 Conclusion

A Mediterranean-based dietary intervention in pregnant women with metabolic risk factors reduce the incidence of gestational diabetes and gestational weight gain. The implementation of Mediterranean diet in a multi-ethnic pregnant population is feasible and can improve pregnancy outcomes.

CHAPTER 8

DISCUSSION AND CONCLUSIONS

8.1 Summary of findings

Table (8.1) presents a summary of the findings of my work relevant to the highlighted objectives of each chapter**.**

Table (8.1): Summary of research findings for each chapter

Chapter	Population	Intervention / test	Outcome	Study design	Summary of results
	How to evaluate the effect of Mediterranean-based dietary intervention on maternal and fetal outcomes in high-risk pregnant population with metabolic risk factors?				
2	Pregnant women with metabolic risk factors	Mediterranean diet based	Maternal and fetal outcomes	Protocol of pragmatic randomised trial embedded in a cohort study	The ESTEEM study was conducted as per the published protocol. We randomised 1252 women to the trial and recruited 2169 women to the cohort study. The follow-up and future work on collected umbilical cord samples will help to evaluate the long-term effect of the dietary intervention on maternal and childhood outcomes.
	What are the methodological challenges of randomised trials evaluating dietary interventions in pregnancy and potential solutions?				
3	Randomised trials	Dietary interventions in pregnancy	Methodological challenges and solutions	Discussion and analysis of the ESTEEM trial experience	I identified five key challenges encountered in ESTEEM: recruitment, intervention delivery, clinical staff engagement, adherence assessment, and defining outcomes. The solutions applied to ESTEEM will help to guide future research on dietary interventions in pregnancy.
	What is the quality of online information on the risks and management of obesity in pregnancy?				
7	Websites with information about obesity in pregnancy	Credibility, accuracy, readability, content quality and technology	Quality assessment of information and technology	Systematic review	I reviewed 53 websites and assessed their information and technological quality. There were 12 commercial, 18 governmental and 23 NGO funded websites. The mean composite quality scores were not different among any of the websites groups. NGO funded websites that are obesity-specific and targeting healthcare users demonstrated higher overall quality scores.
	What dietary assessment tools are currently used in randomised trials evaluating dietary interventions in pregnancy?				
4	Dietary assessment tools in nutritional studies in pregnancy	Characteristics of used tools	Methodological choices, validity, reliability	Systematic review	Only two-thirds of available dietary trials in pregnancy assessed dietary intake using a specific tool. The most commonly used assessment tool was a multiple days' food diary followed by a food frequency questionnaire. The majority of used tools were adopted and not validated within the study population. The use of a pre-defined adherence criteria was not common. There was no association between the choice of dietary assessment tools and study quality, study sample size, year of publication, type of the publishing journal or the journal impact factor.

	What is the validity of a food frequency questionnaire and a short questionnaire to assess the dietary intake of pregnant women following Mediterranean diet compared to 24-hour dietary recalls?				
5	A semi-quantified food frequency questionnaire and short dietary questionnaire	Assessment of dietary intake in a randomised trial in pregnancy	Validity compared to 24-hour dietary recalls	Primary validation study	The food frequency questionnaire and ESTEEM Q are useful tools for assessing the intake of key food items in the Mediterranean diet compared to 24 hour recalls. The FFQ overestimated the intake of energy and key micronutrients such as unsaturated fatty acids. The short ESTEEM questionnaire offered a suitable substitution for the long questionnaire when assessing participants' adherence to the Mediterranean diet. Common gastro-intestinal disorders in pregnancy potentially increased the inter-rater variability for assessing dietary intake.
	What is the effect of a Mediterranean-based dietary intervention on maternal and fetal outcomes in a pregnant population with metabolic risk factors				
6	Pregnant women with metabolic risk factors	Mediterranean based diet	Composite maternal and fetal outcome	Primary pragmatic randomised trial	A Mediterranean-based dietary intervention in pregnant women with metabolic risk factors reduces the incidence of gestational diabetes and gestational weight gain. The implementation of Mediterranean diet in a multi-ethnic pregnant population is feasible and can improve pregnancy outcomes.

8.2 Strengths and limitations

The ESTEEM study was designed to provide an answer to an established gap in the literature on lifestyle interventions in pregnancy. The large sample size and pragmatic design provide high validity and generalisability to clinical practice. The tools used to evaluate dietary intake in the ESTEEM trial were validated and tailor-designed to increase accuracy within the study multi-ethnic population.

I conducted the systematic reviews following a well-established methodology, used a prospective protocol, and reported the findings as per the PRISMA. I have developed the online information assessment to include technology assessment following recent recommendations.(178)

The work presented suffers from certain limitations. The control group in the ESTEEM trial did not follow a neutral diet and some participants might already be following a Mediterranean lifestyle. The systematic review of online information included websites in

English language only. Other developed countries like France and Holland could have some reliable internet-based information sources. The work on dietary validation did not adjust for energy intake and included a high-risk sample only. The intention to screen for validation methods used in pregnancy was limited by the small number of available studies.

8.3 Implications for clinical practice

- Introducing a Mediterranean-based diet during the antenatal period is feasible in a multi-ethnic British population. The intervention reduced the incidence of gestational diabetes, gestational weight gain and had some protective effect on reducing small for gestational age. Clinician should counsel pregnant women on the benefits of dietary interventions in pregnancy. Providing dietary advice following a well-established health lifestyle is more consistent than current recommendation by NICE.(57)

- Delivering a Mediterranean-based dietary intervention in the second trimester of pregnancy might be insufficient to significantly improve maternal and fetal outcomes in a population with metabolic risk factors. Women at high risk of adverse outcomes should be counselled before conception on the benefits of lifestyle intervention and other preventive measures.

- Obesity-specific websites targeting healthcare users and funded by non-governmental bodies offer good quality information on obesity in pregnancy. Clinicians and healthcare professionals should advise women on the best available resources for information.

8.4 Implications for research

- The effect of dietary interventions on long-term maternal and fetal outcomes is not well investigated. In particular, the effect of Mediterranean diet on childhood asthma and allergy is equivocal. The ESTEEM cohort will provide a medium for future follow-up studies to provide more insights on such effect.

- The effect of dietary interventions on pregnancy outcomes is varied among existing studies due to differences in the choice of population, the intervention delivery, and the adherence. The ESTEEM findings will feed into a HTA funded individual patient data meta-analysis (IWIP) to enable high-quality evidence synthesis.

- Evidence on the best tools to assess dietary intake in pregnancy is limited. Comparative studies are needed to assess the accuracy, sensitivity, and applicability of the various dietary tools to a pregnant population.

- The use of novel technological and biochemical methods to assess dietary intake in pregnancy is limited. More studies are needed to investigate the role of such methods in pregnancy settings.

- Substituting long food frequency questionnaires with short, more focused questionnaire is feasible to assess the adherence to dietary intervention in a pregnant population in future studies.

Appendix (1): Contribution to each chapter

- Chapter (1): I wrote the whole chapter solely
- Chapter (2): I worked on drafting, updating and publishing the protocol for the ESTEEM study. I drafted the case report forms, dietary assessment questionnaires, and patient information sheet.
- Chapter (3): I conceived the idea, conducted the analysis and wrote the first manuscript to publish the work related to this chapter
- Chapter (4): I wrote the protocol for the systematic review, updated the search, analysed data and wrote the first manuscript.
- Chapter (5): I wrote the protocol and the statistical analysis plan, I helped to collect primary data, I entered and processed the data, and wrote the first manuscript.
- Chapter (6): I helped to manage the ESTEEM trial across 5 sites, I wrote site operational protocols, I recruited and randomised participants, I delivered the intervention at some centres, I collected outcomes and follow ups, I wrote the first draft of the manuscript.
- Chapter (7): I wrote the protocol for the systematic review, conducted the primary search, analysed data and wrote the first manuscript.
- ESTEEM study documents: I developed and revised the study case record file and the dietary assessment tools. The study information sheets, intervention documents, posters and consent forms were developed jointly with the study team 6 months before starting the recruitment. I revised and edited all documents.

Appendix (2): Patient information sheet for the ESTEEM study

Will information about me be kept confidential?

Yes, all information that is collected during this study will be anonymous and treated with complete confidentiality. Data will be handled, stored and destroyed in accordance with the Data Protection Act (1998).

Information held by the NHS may be used to follow your progress. Your GP and other doctors involved in your clinical care will be kept informed, but otherwise all information about you and your baby will be kept confidential.

If you take part in the study, your relevant medical records may be inspected by authorised individuals. They may also be looked at by regulatory authorities. The purpose of this is to check the trial is being carried out correctly.

Are there any risks to taking part in the study?

No.

What will happen if I don't want to continue with the study?

You are free to withdraw at any time without giving a reason. Your care will not be affected in any way. The data we have collected about you will be analysed, unless you specify otherwise.

What if I have a question or there is a problem?

If there is anything about the study you are not sure about, just ask a member of your care team at the hospital.

If you are unhappy about any aspect of the study and wish to make a complaint you can do this through the NHS complaints procedure. Your hospital will be able you give you information about how to do this. You can also contact the indepondent Patient Advice and Liaison Service (PALS) at your hospital.

What happens when the study finishes?

When the results of the study are known they will be published in medical journals and the results circulated to medical staff and the local communities. You won't be identified.

Involvement of the General Practitioner/Family doctor?

With your consent we will inform your GP of your participation in the trial.

Who has checked the study?

All research in the NHS is looked at by an independent group of people called the Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the National Research Ethics Service Committee East of England - Hatfield.

CONTACT

To find out more about ESTEEM, after having spoken to your local team, please contact the Trial Co-ordinator:

Trial Co-ordinator
0207 882 6049

Thank you for taking the time to read this patient information sheet.

the esteem trial

Patient Information Sheet

Effect of Simple, Targeted diEt in prEgnant women with Metabolic risk factors on pre-eclampsia

FOOD ACADEMY · Barts and The London School of Medicine and Dentistry · b+tlc Barts Charity · Barts Health NHS Trust

ESTEEM Patient Information Sheet Version 2 17.07.14

Would you like to be part of a dietary study on pregnant women?

This leaflet will tell you all about a diet based study called ESTEEM such as why it is done and what you will be asked to do if you decide to take part.

What is the ESTEEM study all about?

ESTEEM is a randomised controlled trial to help us find out whether particular dietary plan is effective in reducing pregnancy-related complications such as pre-eclampsia in pregnant women with raised body mass index, blood pressure or lipid levels.

A randomised controlled trial is when participants in a trial are randomly allocated to receive one or other of the alternative management plan under study (in this case particular diet or current care). Participants are randomly allocated to one of two groups because we do not know which method is the best.

What is pre-eclampsia?

Pre-eclampsia is a serious condition of pregnancy, where the mother develops high blood pressure and protein in the urine (proteinuria). Pre-eclampsia is associated with risks to the mother and baby. The treatment for pre-eclampsia is delivery. If pre-eclampsia develops before 34 weeks and the baby is born prematurely, he or she may need special care in a neonatal unit.

Why is this study needed?

A healthy diet has the potential to reduce complications in pregnancy and improve outcomes to the mother and baby. Compared to pregnant women on a standard western diet, women on a healthy diet had low risk of developing pre-eclampsia. Current studies are of poor quality, so it is difficult to reach a conclusion on the beneficial effect of diet in preventing pre-eclampsia. The ESTEEM study plans to assess if a diet based intervention could reduce the risk of complications such as pre-eclampsia in pregnancy.

ESTEEM Patient Information Sheet Version 2 17.07.14

Who is organising and paying for the study?

Queen Mary University of London is organising ESTEEM and the trial is funded by Barts and the London Charity. The pragmatic Clinical Trials Unit (PCTU) at Queen Mary, University of London will collect and analyse the data.

What will happen if I agree to take part?

You will be asked to fill in a consent form, which tells us you are happy to join.

1. Complete short questionnaires which will help us understand a little bit more about you, your diet and physical activity.
2. Give us a blood (and urine) sample.

If you do not fulfil the eligibility criteria for randomisation, we will not invite you for further visits. We will collect information on the outcomes of you and your baby after delivery from your hospital records.

If you fulfil the eligibility criteria for participation in the randomised control trial, we will then randomly allocate you to intervention or standard care. We will then request you to:

1. Complete a questionnaire on your diet.
2. Meet the ESTEEM team at regular intervals (no more than 4 visits in pregnancy, including your regular appointments).
3. Complete short questionnaires about you, your diet and physical activity before you have delivered your baby.

Why have I been chosen and do I have to take part?

As you are a pregnant woman we are asking you to take part. However, it is up to you whether you take part or not. If you decide you would rather not take part, your healthcare will not be affected in anyway. Also should you wish to participate you can withdraw at any time without giving any reason.

What happens to my sample?

Barts NHS trust will store and analyse your blood samples. Your blood samples will be stored for the lifetime of the trial and for 10 years after the completion of the trial. After this period, your sample will be destroyed.

We will obtain a separate consent on whether you are happy for cord blood to be taken at the time of delivery. We will store this sample for future ethically approved research purposes.

What kind of information will be collected about me?

We will record the results of your blood (and urine) samples and your response to the questionnaires. We will record information from your medical records. We will collect details about your current pregnancy, diet and condition.

What are the benefits to taking part in the study?

You'll be helping clinicians and policy makers decide whether current guidelines need to be changed. So it is an important study for all pregnant women in the UK.

Appendix (3): Participant consent forms for the ESTEEM study

UTIN: ☐☐|☐☐☐☐

Barts Health NHS
NHS Trust

Barts and The London
School of Medicine and Dentistry

PARTICIPANT CONSENT FORM

Title of project: Effect of simple, targeted diet in pregnant women with metabolic risk factors on pre-eclampsia (ESTEEM): A randomised trial

Please initial each box to confirm consent

1.	I confirm that I have read and understood the information sheet dated 17th July 2014 version 2.0 for the above study. I have had the opportunity to consider the information, ask questions about the study and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time, without giving a reason, and without my medical care or legal rights being affected	
3.	If in the course of the study I decide not to continue I understand that any collected data will be analysed, unless I specify otherwise.	
4.	I understand that the information and samples collected will be used for medical research only, including academic publications. I will be given a Unique Trial Identification Number (UTIN) in order to ensure that me and my baby's data are anonymous.	
5.	I understand that my healthcare professional will provide a copy of my consent form and personal information about me and my pregnancy, in confidence, to the central organisers at the Women's Health Research Unit at Queen Mary University London for use in the ESTEEM trial in accordance with the data protection act.	
6.	I understand that the information held by the NHS may be used to keep in touch with me and to follow up the health status of me and my baby and that I may be contacted by the research team in the future to be invited to take part in future studies. I agree to be contacted for these purposes	
7.	I understand that relevant sections of me or my baby's medical notes and data collected during the study may be looked at by individuals from the research team, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
8.	After entering the study, if I am found not to be at risk of pre-eclampsia, I give permission for my medical records to be accessed to obtain my delivery outcome data	
9.	I agree to my GP being informed of my participation in the ESTEEM trial.	
10.	I understand what is involved in the ESTEEM trial and agree to participate.	

You will be provided with a signed copy of this signed consent form.

Name of participant _____ Signature _____ Date _____

Name of person taking consent _____ Signature _____ Date _____

Statement of interpreter (where appropriate): I have interpreted the information above to the best of my ability and in a way in which the patient can understand.

Name of interpreter _____ Signature _____ Date _____

1 copy for Patient, 1 for hospital medical notes and original to be kept in ESTEEM Investigator Site File

Barts Health NHS
NHS Trust

Barts and The London
School of Medicine and Dentistry

CONSENT TO DONATION AND STORAGE OF TISSUE SAMPLES FOR FUTURE MEDICAL RESEARCH

Patient details (or affix pre-printed label)

Patient's full name:	Name of Investigator: Professor Shakila Thangaratinam
Date of birth:	Research Ethics Committee Ref: 14/EE/1048
Hospital number (or other identifier):	Description of tissue/sample to be taken: **Umbilical cord blood sample**

Tissue collected as part of the present research project and/or procedure may be stored and used by the Barts Health NHS Trust, Queen Mary's School of Medicine and Dentistry, and approved external research organisations for future medical research.

Samples used for research may contain personal information but all such information will be anonymised at the end of any project, when the results are published, and you will not receive the results of any future research project. All staff undertaking future studies will abide by the Data Protection Act 1998 with any medical information relating to you being kept confidential. The tissue may be given to external research organisations for approved medical research but tissue will not be sold, although costs will be recovered without any financial benefit to either you or to the researcher. All tissue will be disposed of lawfully when it is no longer required.

	Patient Initials
I understand that additional tissue (described above) will be taken during my treatment / investigation and will not be used for diagnostic purposes. I agree that this additional tissue will be stored in a Research Tissue Bank for future research.	☐
I accept that I have given my consent voluntarily to the storage of this additional tissue and that I am free to withdraw my consent at any time and the tissue to be destroyed.	☐
I agree that the tissue may be used for future genetic research but not for research that involves reproductive cloning, or be tested for inherited diseases (other than diabetes, obesity or cardiovascular disease) without my express consent.	☐
I agree that my health records may be used by authorised members of staff who are not directly involved in my clinical care and my hospital number is written above.	☐
I agree for cord blood samples taken from me to be stored for use in future ethically approved research	☐

If you have any preferences or exclusions for use of the donated tissue, or any other comments, please include them here:

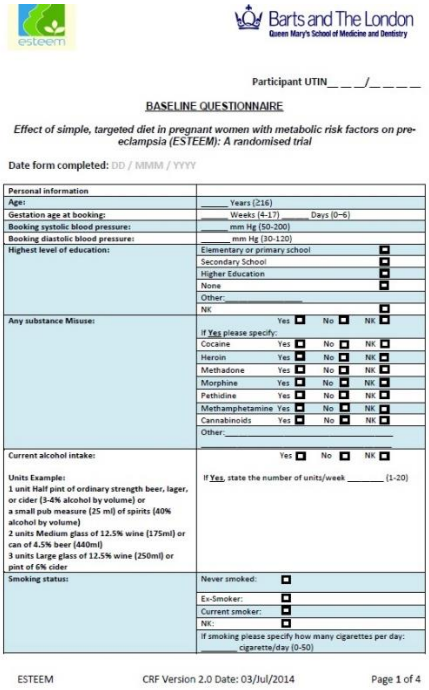
Name of Patient _____ Date _____ Signature _____

Name of Person taking consent _____ Date _____ Signature _____

1 copy for Patient, 1 for hospital medical notes and original to be kept in ESTEEM Investigator Site File

Appendix (4): Case report forms for the ESTEEM study

A: Baseline CRF



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Queen Mary's School of Medicine and Dentistry

Participant UTIN__ __ __/__ __ __ __

BASELINE QUESTIONNAIRE

Effect of simple, targeted diet in pregnant women with metabolic risk factors on pre-eclampsia (ESTEEM): A randomised trial

Date form completed: DD / MMM / YYYY

Personal information	
Age:	_____ Years (216)
Gestation age at booking:	_____ Weeks (4-17) _____ Days (0–6)
Booking systolic blood pressure:	_____ mm Hg (50-200)
Booking diastolic blood pressure:	_____ mm Hg (30-120)
Highest level of education:	Elementary or primary school ☐
	Secondary School ☐
	Higher Education ☐
	None ☐
	Other:_____
	NK ☐
Any substance Misuse:	Yes ☐ No ☐ NK ☐
	If Yes please specify:
	Cocaine Yes ☐ No ☐ NK ☐
	Heroin Yes ☐ No ☐ NK ☐
	Methadone Yes ☐ No ☐ NK ☐
	Morphine Yes ☐ No ☐ NK ☐
	Pethidine Yes ☐ No ☐ NK ☐
	Methamphetamine Yes ☐ No ☐ NK ☐
	Cannabinoids Yes ☐ No ☐ NK ☐
	Other:_____
Current alcohol intake:	Yes ☐ No ☐ NK ☐
Units Example: 1 unit Half pint of ordinary strength beer, lager, or cider (3-4% alcohol by volume) or a small pub measure (25 ml) of spirits (40% alcohol by volume) 2 units Medium glass of 12.5% wine (175ml) or can of 4.5% beer (440ml) 3 units Large glass of 12.5% wine (250ml) or pint of 6% cider	If Yes, state the number of units/week _____ (1-20)
Smoking status:	Never smoked: ☐
	Ex-Smoker: ☐
	Current smoker: ☐
	NK: ☐
	If smoking please specify how many cigarettes per day: _____ cigarette/day (0-50)

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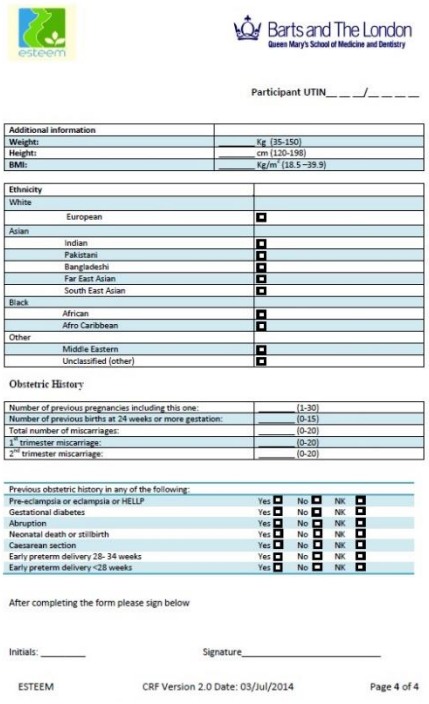

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Participant UTIN__ __ __/__ __ __ __

Additional information	
Weight:	_____ Kg (35-150)
Height:	_____ cm (120-198)
BMI:	_____ Kg/m² (18.5 –39.9)

Ethnicity	
White	
European	☐
Asian	
Indian	☐
Pakistani	☐
Bangladeshi	☐
Far East Asian	☐
South East Asian	☐
Black	
African	☐
Afro Caribbean	☐
Other	
Middle Eastern	☐
Unclassified (other)	☐

Obstetric History

Number of previous pregnancies including this one:	_____ (1-30)
Number of previous births at 24 weeks or more gestation:	_____ (0-15)
Total number of miscarriages:	_____ (0-20)
1st trimester miscarriage:	_____ (0-20)
2nd trimester miscarriage:	_____ (0-20)

Previous obstetric history in any of the following:			
Pre-eclampsia or eclampsia or HELLP	Yes ☐	No ☐	NK ☐
Gestational diabetes	Yes ☐	No ☐	NK ☐
Abruption	Yes ☐	No ☐	NK ☐
Neonatal death or stillbirth	Yes ☐	No ☐	NK ☐
Caesarean section	Yes ☐	No ☐	NK ☐
Early preterm delivery 28- 34 weeks	Yes ☐	No ☐	NK ☐
Early preterm delivery <28 weeks	Yes ☐	No ☐	NK ☐

After completing the form please sign below

Initials: _____ Signature_____

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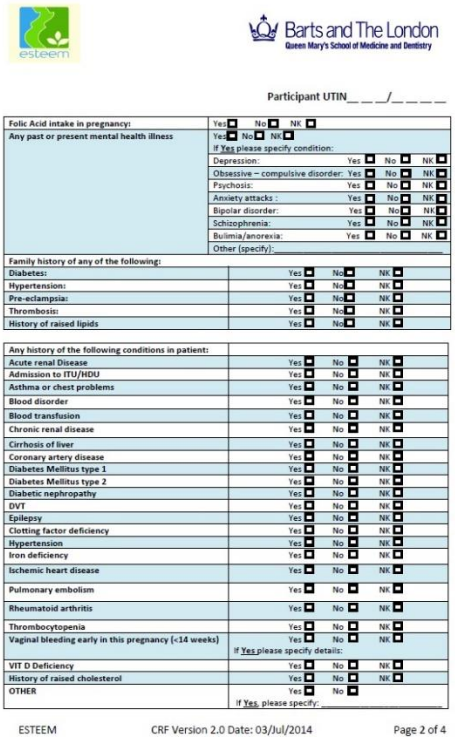

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Participant UTIN__ __ __/__ __ __ __

Folic Acid intake in pregnancy:	Yes ☐ No ☐ NK ☐
Any past or present mental health illness	Yes ☐ No ☐ NK ☐
	If Yes please specify condition:
	Depression: Yes ☐ No ☐ NK ☐
	Obsessive – compulsive disorder: Yes ☐ No ☐ NK ☐
	Psychosis: Yes ☐ No ☐ NK ☐
	Anxiety attacks : Yes ☐ No ☐ NK ☐
	Bipolar disorder: Yes ☐ No ☐ NK ☐
	Schizophrenia: Yes ☐ No ☐ NK ☐
	Bulimia/anorexia: Yes ☐ No ☐ NK ☐
	Other (specify):_____

Family history of any of the following:			
Diabetes:	Yes ☐	No ☐	NK ☐
Hypertension:	Yes ☐	No ☐	NK ☐
Pre-eclampsia:	Yes ☐	No ☐	NK ☐
Thrombosis:	Yes ☐	No ☐	NK ☐
History of raised lipids	Yes ☐	No ☐	NK ☐

Any history of the following conditions in patient:			
Acute renal Disease	Yes ☐	No ☐	NK ☐
Admission to ITU/HDU	Yes ☐	No ☐	NK ☐
Asthma or chest problems	Yes ☐	No ☐	NK ☐
Blood disorder	Yes ☐	No ☐	NK ☐
Blood transfusion	Yes ☐	No ☐	NK ☐
Chronic renal disease	Yes ☐	No ☐	NK ☐
Cirrhosis of liver	Yes ☐	No ☐	NK ☐
Coronary artery disease	Yes ☐	No ☐	NK ☐
Diabetes Mellitus type 1	Yes ☐	No ☐	NK ☐
Diabetes Mellitus type 2	Yes ☐	No ☐	NK ☐
Diabetic nephropathy	Yes ☐	No ☐	NK ☐
DVT	Yes ☐	No ☐	NK ☐
Epilepsy	Yes ☐	No ☐	NK ☐
Clotting factor deficiency	Yes ☐	No ☐	NK ☐
Hypertension	Yes ☐	No ☐	NK ☐
Iron deficiency	Yes ☐	No ☐	NK ☐
Ischemic heart disease	Yes ☐	No ☐	NK ☐
Pulmonary embolism	Yes ☐	No ☐	NK ☐
Rheumatoid arthritis	Yes ☐	No ☐	NK ☐
Thrombocytopenia	Yes ☐	No ☐	NK ☐
Vaginal bleeding early in this pregnancy (<14 weeks)	Yes ☐	No ☐	NK ☐
	If Yes please specify details:		
VIT D Deficiency	Yes ☐	No ☐	NK ☐
History of raised cholesterol	Yes ☐	No ☐	NK ☐
OTHER	Yes ☐	No ☐	
	If Yes, please specify: _____		

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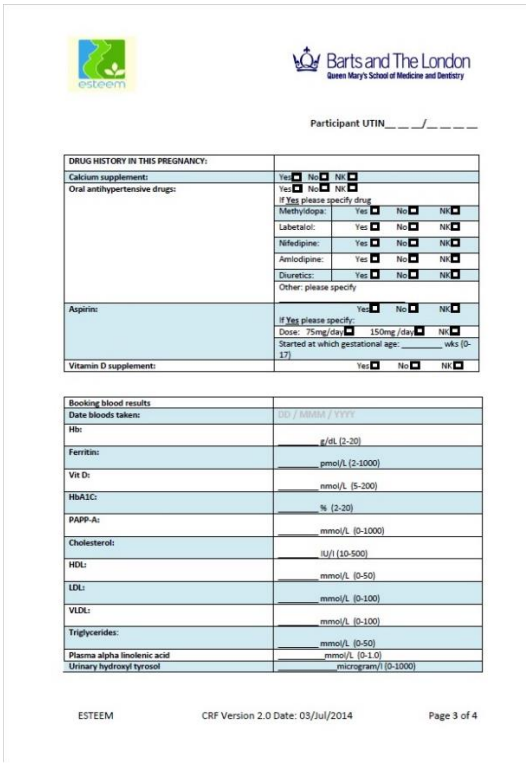

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DRUG HISTORY IN THIS PREGNANCY:			
Calcium supplement:	Yes ☐	No ☐	NK ☐
Oral antihypertensive drugs:	Yes ☐ No ☐ NK ☐		
	If Yes please specify drug		
	Methyldopa:	Yes ☐ No ☐ NK ☐	
	Labetalol:	Yes ☐ No ☐ NK ☐	
	Nifedipine:	Yes ☐ No ☐ NK ☐	
	Amlodipine:	Yes ☐ No ☐ NK ☐	
	Diuretics:	Yes ☐ No ☐ NK ☐	
	Other: please specify _____		
Aspirin:	Yes ☐ No ☐ NK ☐		
	If Yes please specify:		
	Dose: 75mg/day ☐ 150mg /day ☐ NK ☐		
	Started at which gestational age: _____ wks (0-17)		
Vitamin D supplement:	Yes ☐ No ☐ NK ☐		

Booking blood results	
Date bloods taken:	DD / MMM / YYYY
Hb:	_____ g/dL (2-20)
Ferritin:	_____ pmol/L (2-1000)
Vit D:	_____ nmol/L (5-200)
HbA1C:	_____ % (2-20)
PAPP-A:	_____ mmol/L (0-1000)
Cholesterol:	_____ IU/l (10-500)
HDL:	_____ mmol/L (0-50)
LDL:	_____ mmol/L (0-100)
VLDL:	_____ mmol/L (0-100)
Triglycerides:	_____ mmol/L (0-50)
Plasma alpha linolenic acid	_____ mmol/L (0-1.0)
Urinary hydroxyl tyrosol	_____ microgram/l (0-1000)

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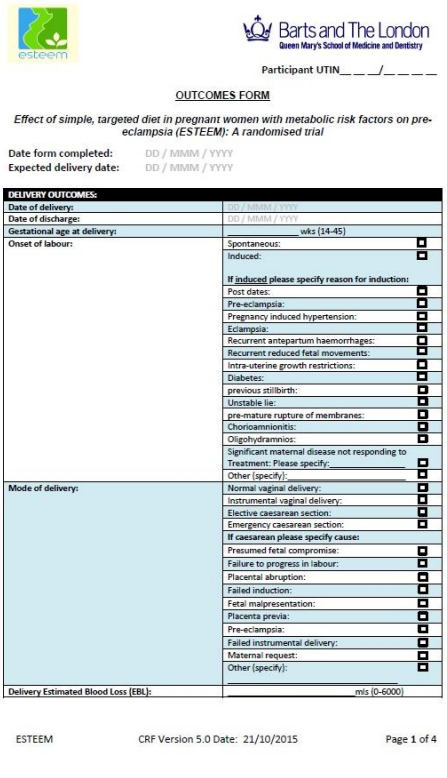
B: Outcomes CRF



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Participant UTIN__ __ __/__ __ __ __

OUTCOMES FORM

Effect of simple, targeted diet in pregnant women with metabolic risk factors on pre-eclampsia (ESTEEM): A randomised trial

Date form completed: DD / MMM / YYYY
Expected delivery date: DD / MMM / YYYY

DELIVERY OUTCOMES:	
Date of delivery:	DD / MMM / YYYY
Date of discharge:	DD / MMM / YYYY
Gestational age at delivery:	_____ wks (14-45)
Onset of labour:	Spontaneous: ☐
	Induced: ☐
	If induced please specify reason for induction:
	Post dates: ☐
	Pre-eclampsia: ☐
	Pregnancy induced hypertension: ☐
	Eclampsia: ☐
	Recurrent antepartum haemorrhages: ☐
	Recurrent reduced fetal movements: ☐
	Intra-uterine growth restrictions: ☐
	Diabetes: ☐
	previous stillbirth: ☐
	Unstable lie: ☐
	pre-mature rupture of membranes: ☐
	Chorioamnionitis: ☐
	Oligohydramnios: ☐
	Significant maternal disease not responding to Treatment: Please specify:_____ ☐
	Other (specify):_____ ☐
Mode of delivery:	Normal vaginal delivery: ☐
	Instrumental vaginal delivery: ☐
	Elective caesarean section: ☐
	Emergency caesarean section: ☐
	If caesarean please specify cause:
	Presumed fetal compromise: ☐
	Failure to progress in labour: ☐
	Placental abruption: ☐
	Failed induction: ☐
	Fetal malpresentation: ☐
	Placenta previa: ☐
	Pre-eclampsia: ☐
	Failed instrumental delivery: ☐
	Maternal request: ☐
	Other (specify): _____ ☐
Delivery Estimated Blood Loss (EBL):	_____mls (0-6000)

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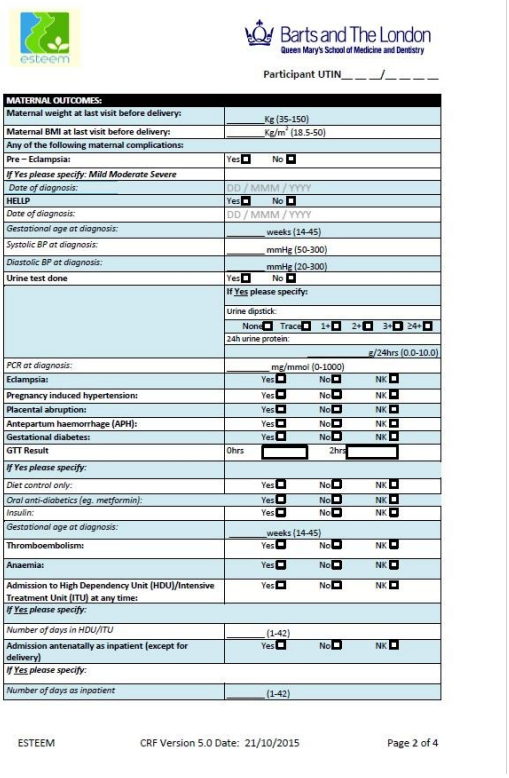

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Participant UTIN__ __ __/__ __ __ __

MATERNAL OUTCOMES:	
Maternal weight at last visit before delivery:	_____Kg (35-150)
Maternal BMI at last visit before delivery:	_____Kg/m² (18.5-50)
Any of the following maternal complications:	
Pre – Eclampsia:	Yes ☐ No ☐
If Yes please specify: Mild Moderate Severe	
Date of diagnosis:	DD / MMM / YYYY
HELLP	Yes ☐ No ☐
Date of diagnosis:	DD / MMM / YYYY
Gestational age at diagnosis:	_____weeks (14-45)
Systolic BP at diagnosis:	_____mmHg (50-300)
Diastolic BP at diagnosis:	_____mmHg (20-300)
Urine test done	Yes ☐ No ☐
	If Yes please specify:
	Urine dipstick: None ☐ Trace ☐ 1+ ☐ 2+ ☐ 3+ ☐ 24+ ☐
	24h urine protein: _____g/24hrs (0.0-10.0)
PCR at diagnosis:	_____mg/mmol (0-1000)
Eclampsia:	Yes ☐ No ☐ NK ☐
Pregnancy induced hypertension:	Yes ☐ No ☐ NK ☐
Placental abruption:	Yes ☐ No ☐ NK ☐
Antepartum haemorrhage (APH):	Yes ☐ No ☐ NK ☐
Gestational diabetes:	Yes ☐ No ☐ NK ☐
GTT Result	0hrs _____ 2hrs _____
If Yes please specify:	
Diet control only:	Yes ☐ No ☐ NK ☐
Oral anti-diabetics (eg. metformin):	Yes ☐ No ☐ NK ☐
Insulin:	Yes ☐ No ☐ NK ☐
Gestational age at diagnosis:	_____weeks (14-45)
Thromboembolism:	Yes ☐ No ☐ NK ☐
Anaemia:	Yes ☐ No ☐ NK ☐
Admission to High Dependency Unit (HDU)/Intensive Treatment Unit (ITU) at any time:	Yes ☐ No ☐ NK ☐
If Yes please specify:	
Number of days in HDU/ITU	_____ (1-42)
Admission antenatally as inpatient (except for delivery)	Yes ☐ No ☐ NK ☐
If Yes please specify:	
Number of days as inpatient	_____ (1-42)

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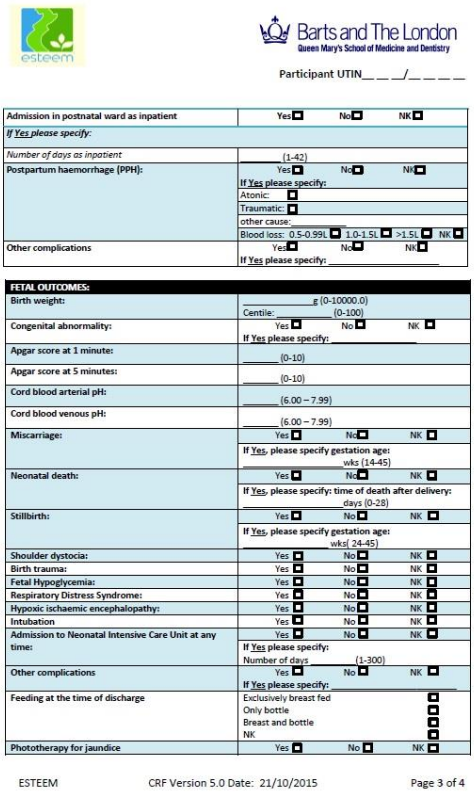

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Participant UTIN__ __ __/__ __ __ __

Admission in postnatal ward as inpatient	Yes ☐ No ☐ NK ☐
If Yes please specify:	
Number of days as inpatient	_____ (1-42)
Postpartum haemorrhage (PPH):	Yes ☐ No ☐ NK ☐
	If Yes please specify:
	Atonic: ☐
	Traumatic: ☐
	other cause:_____
	Blood loss: 0.5-0.99L ☐ 1.0-1.5L ☐ >1.5L ☐ NK ☐
Other complications	Yes ☐ No ☐ NK ☐
	If Yes please specify: _____

FETAL OUTCOMES:	
Birth weight:	_____g (0-10000.0)
	Centile: _____ (0-100)
Congenital abnormality:	Yes ☐ No ☐ NK ☐
	If Yes please specify: _____
Apgar score at 1 minute:	_____ (0-10)
Apgar score at 5 minutes:	_____ (0-10)
Cord blood arterial pH:	_____ (6.00 – 7.99)
Cord blood venous pH:	_____ (6.00 – 7.99)
Miscarriage:	Yes ☐ No ☐ NK ☐
	If Yes, please specify gestation age: _____ wks (14-45)
Neonatal death:	Yes ☐ No ☐ NK ☐
	If Yes, please specify: time of death after delivery: _____ days (0-28)
Stillbirth:	Yes ☐ No ☐ NK ☐
	If Yes, please specify gestation age: _____ wks(24-45)
Shoulder dystocia:	Yes ☐ No ☐ NK ☐
Birth trauma:	Yes ☐ No ☐ NK ☐
Fetal Hypoglycemia:	Yes ☐ No ☐ NK ☐
Respiratory Distress Syndrome:	Yes ☐ No ☐ NK ☐
Hypoxic ischaemic encephalopathy:	Yes ☐ No ☐ NK ☐
Intubation	Yes ☐ No ☐ NK ☐
Admission to Neonatal Intensive Care Unit at any time:	Yes ☐ No ☐ NK ☐
	If Yes please specify: Number of days _____ (1-300)
Other complications	Yes ☐ No ☐ NK ☐
	If Yes please specify: _____
Feeding at the time of discharge	Exclusively breast fed ☐ Only bottle ☐ Breast and bottle ☐ NK ☐
Phototherapy for jaundice	Yes ☐ No ☐ NK ☐

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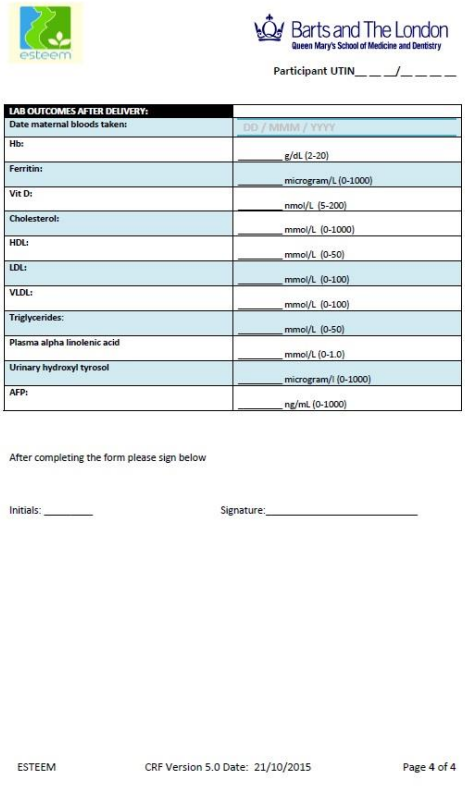

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Participant UTIN__ __ __/__ __ __ __

LAB OUTCOMES AFTER DELIVERY:	
Date maternal bloods taken:	DD / MMM / YYYY
Hb:	_____g/dL (2-20)
Ferritin:	_____microgram/L (0-1000)
Vit D:	_____nmol/L (5-200)
Cholesterol:	_____mmol/L (0-1000)
HDL:	_____mmol/L (0-50)
LDL:	_____mmol/L (0-100)
VLDL:	_____mmol/L (0-100)
Triglycerides:	_____mmol/L (0-50)
Plasma alpha linolenic acid	_____mmol/L (0-1.0)
Urinary hydroxyl tyrosol	_____microgram/l (0-1000)
AFP:	_____ng/mL (0-1000)

After completing the form please sign below

Initials: _____ Signature:_____

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Appendix (5): ESTEEM Q, EQ5D, IPAQ, FFQ, and 24 hour recall questionnaires for the ESTEEM study

A: ESTEEM Q

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Participant UTIN__ __ __/__ __ __ __

ESTEEM QUESTIONNAIRE

Effect of simple, targeted diet in pregnant women with metabolic risk factors on pre-eclampsia (ESTEEM): A randomised trial

Date completed: DD / MMM / YYYY Gestation age: _____weeks (12-45)

Are you vegetarian? Yes ☐ No ☐

If you are filling this out for the first time, please thinking about your food intake in the last week, otherwise think about your food intake since your last appointment:	Actual amount	*Office use only* YES=1 point NO=0 point
1. Do you use olive oil as the main fat to cook with? (Y/N)		
2. How many tablespoons do you consume of olive oil in a given day (including oil used for frying, salads, meals eaten away from home, etc.)?		
3. How many servings of vegetable do you consume per day? (1 serving = 200 g or palm size [consider side dishes as half a serving])		
4. How many fruit units (including natural fruit juices) do you consume per day (1 unit = 1 piece of fruit, or equivalent (10 grapes, slice of melon) or small glass of juice)?		
5. How many servings of red meat (lamb, beef, goat, pork), processed meat (sausages, hamburgers) or red meat products (bacon, ham) do you consume per day? (1 serving: 100–150 g or small palm-sized portion)		
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: One teaspoon)		
7. How many drinks containing sugar do you consume per day? (e.g. tea or coffee, canned fizzy drinks or sweetened fruit squash)		
8. How many servings of pulses (e.g. lentils, beans, dahl) do you consume per week? (1 serving : 150 g, fist size)		
9. How many servings of fish or shellfish (white fish, oily fish e.g. salmon, or shellfish like mussels) do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish, a palm-sized portion)		
10. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?		
11. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g, small handful)		
12. Do you preferentially consume chicken or turkey instead of veal, pork, hamburger, or sausage?		
FINAL SCORE: (Office use only)		

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Participant UTIN__ __ __/__ __ __ __

Have you experienced any of the following in the last month?

Symptoms	Yes	No	NK	Yes	No
Fullness of stomach					
Bloatedness					
Vomiting				Suspected stomach bug: ☐	☐
Nausea				Suspected stomach bug: ☐	☐
Indigestion					
Constipation					
Diarrhoea				Suspected stomach bug: ☐	☐

B: EQ-5D

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Participant UTIN__ __ __/__ __ __ __

EQ-5D

Effect of simple, targeted diet in pregnant women with metabolic risk factors on pre-eclampsia (ESTEEM): A randomised trial

Date form completed: DD / MMM / YYYY

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

***Mobility:**	I have no problems in walking about ☐ I have some problems in walking about ☐ I am confined to bed ☐
***Self-Care:**	I have no problems with self-care ☐ I have some problems washing or dressing myself ☐ I am unable to wash or dress myself☐
***Usual Activities (e.g. work, study, housework, family or leisure activities):**	I have no problems with performing my usual activities ☐ I have some problems with performing my usual activities ☐ I am unable to perform my usual activities ☐
***Pain/Discomfort:**	I have no pain or discomfort ☐ I have moderate pain or discomfort ☐ I have extreme pain or discomfort ☐
***Anxiety/Depression:**	I am not anxious or depressed ☐ I am moderately anxious or depressed ☐ I am extremely anxious or depressed ☐

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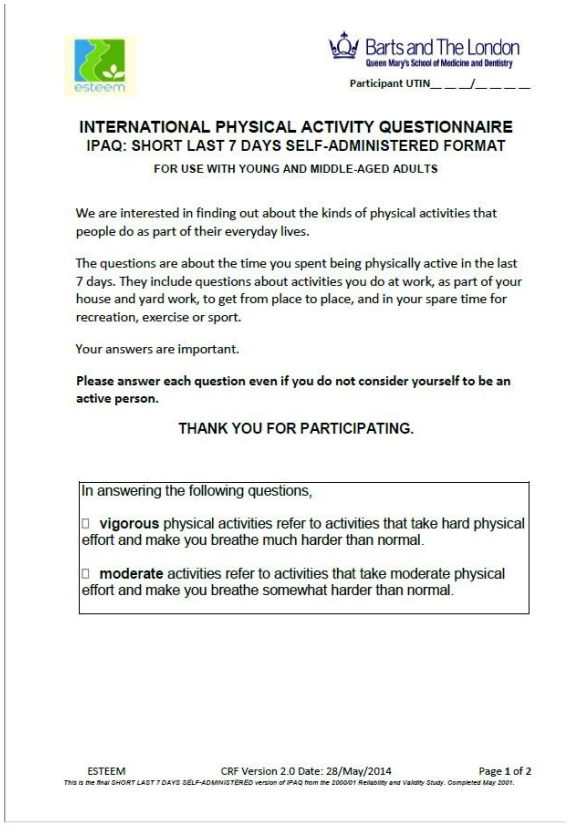
Participant UTIN__ __ __/__ __ __ __

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

C: IPAQ



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esteem

Participant UTIN__ __ __/__ __ __ __

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
IPAQ: SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT
FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives.

The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Your answers are important.

Please answer each question even if you do not consider yourself to be an active person.

THANK YOU FOR PARTICIPATING.

In answering the following questions,

- **vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.
- **moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

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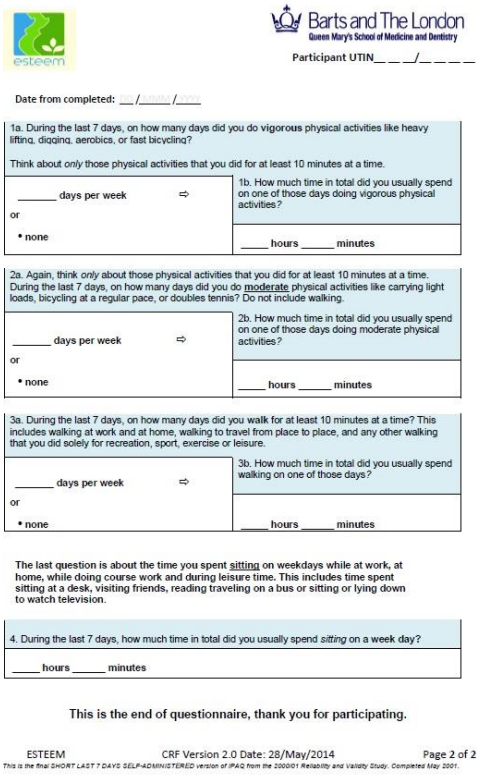
This is the final SHORT LAST 7 DAYS SELF-ADMINISTERED version of IPAQ from the 2000/01 Reliability and Validity Study. Completed May 2001.



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Barts and The London
Queen Mary's School of Medicine and Dentistry

Participant UTIN__ __ __/__ __ __ __

Date from completed: __ /MMM /____

1a. During the last 7 days, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

Think about *only* those physical activities that you did for at least 10 minutes at a time.

_____ days per week ⇨
or
• none

1b. How much time in total did you usually spend on one of those days doing vigorous physical activities?

____ hours _____ minutes

2a. Again, think *only* about those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ days per week ⇨
or
• none

2b. How much time in total did you usually spend on one of those days doing moderate physical activities?

____ hours _____ minutes

3a. During the last 7 days, on how many days did you **walk** for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure.

_____ days per week ⇨
or
• none

3b. How much time in total did you usually spend walking on one of those days?

____ hours _____ minutes

The last question is about the time you spent sitting on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.

4. During the last 7 days, how much time in total did you usually spend *sitting* on a week day?

____ hours _____ minutes

This is the end of questionnaire, thank you for participating.

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This is the final SHORT LAST 7 DAYS SELF-ADMINISTERED version of IPAQ from the 2000/01 Reliability and Validity Study. Completed May 2001.

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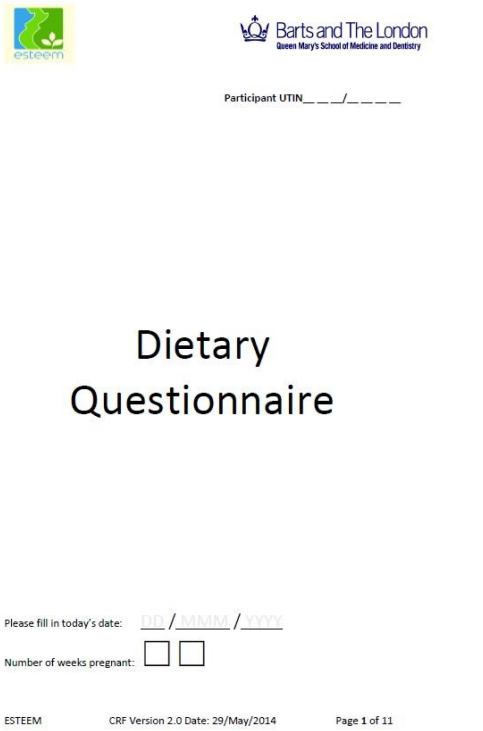

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Barts and The London
Queen Mary's School of Medicine and Dentistry

Participant UTIN__ __ __/__ __ __ __

Dietary Questionnaire

Please fill in today's date: DD /MMM /YYYY

Number of weeks pregnant: ☐☐

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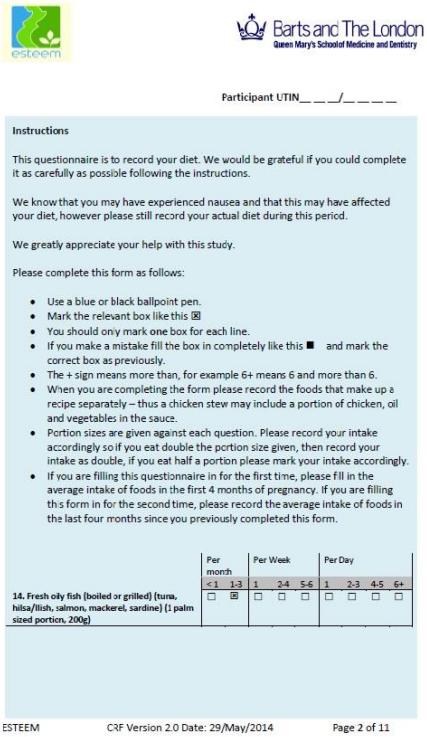

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Barts and The London
Queen Mary's School of Medicine and Dentistry

Participant UTIN__ __ __/__ __ __ __

Instructions

This questionnaire is to record your diet. We would be grateful if you could complete it as carefully as possible following the instructions.

We know that you may have experienced nausea and that this may have affected your diet, however please still record your actual diet during this period.

We greatly appreciate your help with this study.

Please complete this form as follows:

- Use a blue or black ballpoint pen.
- Mark the relevant box like this ☒
- You should only mark one box for each line.
- If you make a mistake fill the box in completely like this ■ and mark the correct box as previously.
- The + sign means more than, for example 6+ means 6 and more than 6.
- When you are completing the form please record the foods that make up a recipe separately – thus a chicken stew may include a portion of chicken, oil and vegetables in the sauce.
- Portion sizes are given against each question. Please record your intake accordingly so if you eat double the portion size given, then record your intake as double, if you eat half a portion please mark your intake accordingly.
- If you are filling this questionnaire in for the first time, please fill in the average intake of foods in the first 4 months of pregnancy. If you are filling this form in for the second time, please record the average intake of foods in the last four months since you previously completed this form.

	Per month		Per Week			Per Day			
	< 1	1-3	1	2-4	5-6	1	2-3	4-5	6+
14. Fresh oily fish (boiled or grilled) (tuna, hilsa/ilish, salmon, mackerel, sardine) (1 palm sized portion, 200g)	☐	☒	☐	☐	☐	☐	☐	☐	☐

ESTEEM CRF Version 2.0 Date: 29/May/2014 Page 2 of 11

Participant UTIN__ __ __/__ __ __ __

Please answer every question and don't leave any line blank. If you **NEVER** eat a food please mark the 0 or *<1 per month* box. Fill in your **average intake** over the last 4 months.

I. MILK or MILK PRODUCTS

How many times do you consume milk or milk products? Please consider the times when you consume milk products either alone or as part of other meals, including on cereals and in sauces and drinks.

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. Wholemilk (Full-fat), 1 glass or cup (approx. 200ml)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Semi-skimmed milk, 1 glass or cup (approx. 200ml)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Skimmed milk, 1 glass or cup (approx. 200ml)	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Condensed milk (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Cream or heavy cream (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Full-fat yoghurt (1 pot, 125g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Low-fat yoghurt (1 pot, 125g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Non-fat yoghurt: (1 pot, 125g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Cottage cheese or fresh soft cheese (100g, 1/3 large pot)	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Hard cheese (e.g. cheddar/paneer; small firger, 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Custard or dairy pudding (1 small)	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Kheer/shrikand (125g, small pot)	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Ice Cream (1 scoop)	☐	☐	☐	☐	☐	☐	☐	☐	☐

II. EGGS, MEAT, FISH

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. Hen/Chicken egg (2)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Chicken with skin (1 medium size breast or equivalent)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Chicken without skin (1 medium size breast or equivalent)	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Beef, pork, goat or lamb, or other red meat as a main dish (medium portion e.g. 1 pork chop, 2 small lamb chops, 3 0z steak)	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Game meat, rabbit, quail, duck, venison (medium portion)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Participant UTIN__ __ __/__ __ __ __

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
6. Liver (chicken, cow, pig) (medium portion)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Offal (tripe, brains, sweetbreads) (medium portion, 100g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Cured meats (ham, salami, chorizo) (50g portion, few small slices)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Sausages (2 sausages)	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Pate or Fois Gras (half portion, 50g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Burger (1 burger, 100g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Bacon (2 rashers)	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. White Fish (boiled or grilled) e.g. Hake, sole, bream, tilapia (1 palm sized portion, 200g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
14. Fresh oily fish (boiled or grilled) (tuna, hilsa/ilish, salmon, mackerel, sardine) (1 palm sized portion, 200g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
15. Tinned fish in brine (e.g tuna, salmon, sardines) (Small tin, 160g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
16. Tinned fish in oil (e.g. tuna, salmon, sardines) (Small tin, 160g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
17. Fish salted or smoked (salmon, cod, anchovy) (half portion, 50g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
18. Shellfish - Clams, mussels, oysters (1 serving, 100g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. Squid, Cuttlefish, Octopus (1 small plate)	☐	☐	☐	☐	☐	☐	☐	☐	☐
20. Seafood – shrimp, crab, lobster, prawns (1 small plate)	☐	☐	☐	☐	☐	☐	☐	☐	☐
21. Fried fish, mixed types (1 small plate)	☐	☐	☐	☐	☐	☐	☐	☐	☐

III. VEGETABLES

Please consider a portion of vegetables to be a palm-sized quantity or small bowl, unless specified.

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. Bitter gourd, bottle gourd (dudhi), white radish (mooli)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Cooked spinach or chard	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Cabbage, cauliflower, broccoli	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Lettuce, endive, rocket	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Tomato (5 medium sized tomatoes)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Onion (1/2 medium)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Starchy vegetables (excluding potatoes) e.g. carrots, pumpkin, squash, breadfruit	☐	☐	☐	☐	☐	☐	☐	☐	☐

Participant UTIN__ __ __/__ __ __ __

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
8. Cooked green beans, okra	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Aubergine/brinjal, courgette, cucumber	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Peppers	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Artichokes	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Asparagus	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Corn on the cob (roasted or grilled) (1 cob)	☐	☐	☐	☐	☐	☐	☐	☐	☐
14. Sweetcorn boiled or tinned	☐	☐	☐	☐	☐	☐	☐	☐	☐
15. Pulses (lentils, chickpeas, beans, dhal, rajama, channa)	☐	☐	☐	☐	☐	☐	☐	☐	☐

IV. FRUITS

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. Oranges, tangerines, Satsuma (1 fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Kiwi fruit (1 medium)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Banana (1 medium)	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Apple, pear (1 medium)	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Stone fruit - Peach, nectarine, apricot, plum (1 medium)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Melon (e.g cantaloupe, watermelon) (1 large slice)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Grapes (small handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Dried fruit – prunes, plums, apricots, figs, raisins (1 fruit or small handful raisins)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Mango or papaya (half fruit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Olives (small portion, approx. 15)	☐	☐	☐	☐	☐	☐	☐	☐	☐

V. BREADS, CEREAL AND SIMILAR

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. White bread (2 slices, quarter of a baguette)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Wholemeal bread (wheat, rye or other) bread (2 slices)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Roti/chappati (1 portion, tea plate sized)	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Naan/parotta (1 bread)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Participant UTIN__ __ __/__ __ __ __

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
5. Sweetened breakfast cereal (chocolate, sugar or honey coated) (1 small bowl 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Plain cereal (e.g. Weetabix, cornflakes, puffed wheat, muesli) (1 small bowl 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Porridge (corn or oatmeal) (1 small bowl 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Maize meal/mealy pap, polenta (1 small bowl)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Fried potatoes/chips (1 portion, large handful)	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Cooked white rice (2 large handfuls, 1 small bowl)	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Cooked whole grain, brown or red rice (2 large handfuls, 1 small bowl)	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Pasta (spaghetti, macaroni etc) (2 large handfuls, 1 small bowl)	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Pizza (2 slices, 200g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
14. Crispbread (e.g. ryvita, rice cake, oat cake) (2 crispbreads)	☐	☐	☐	☐	☐	☐	☐	☐	☐

VI. OILS, FATS, SWEETS AND SNACKS

	Per month		Per Week			Per Day			
	0 or <1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. Olive oil added at the table (e.g. on salad, bread or other dishes) (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Other vegetable oils e.g sunflower, corn, soy, rapeseed, peanut (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Ghee or palm oil (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Olive oil in cooking (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Other vegetable oils in cooking (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Margarine on bread or added to other food(1 teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Butter on bread or added to food (1 teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Plain biscuits e.g. digestive, rich tea (2 biscuits)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Biscuits with chocolate (1 biscuit)	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Pastries e.g. croissants, donut, cupcake etc (1 piece)	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Sweet desserts e.g cake, jalabi, barfi, gulab jamun, rasmalai, halwa, ladoo (1 small piece)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Participant UTIN__ __ __/__ __ __ __

	Per month		Per Week			Per Day			
	0 or < 1	1-3	1	2-4	5-6	1	2-3	4-5	6+
12. Confectionery – chocolate (1 small bar)	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Confectionery – boiled sweets etc (50g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
14. Chocolate powder (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
15. Potato or plantain crisps (1 packet 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
16. Walnuts (small handful, 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
17. Hazelnuts, almonds, Brazil nuts (small handful, 30g)	☐	☐	☐	☐	☐	☐	☐	☐	☐
18. Seeds (hemp, sunflower, sesame, pumpkin) (1 teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. Other snacks e.g. dumplings, samosa, pakora (1 piece)	☐	☐	☐	☐	☐	☐	☐	☐	☐

VII. DRINK AND OTHER

	Per month		Per Week			Per Day			
	0 or < 1	1-3	1	2-4	5-6	1	2-3	4-5	6+
1. Energy drinks e.g. Red bull (1 can)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Carbonated drinks e.g. Fanta, Sprite, Coca Cola, Supermalt, Rubicon (1 can or glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Diet Carbonated drinks e.g Pepsi or Coke *light)* (1 can)	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Tap water (1 glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Bottled still water (1 glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Bottled carbonated water (1 glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Fruit Juice (e.g. orange, apple, cranberry) (1 small glass, 125 ml)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Coffee (1 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Decaffeinated coffee (1 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Tea or infusion (1 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Indian Masala Chai	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Soup or Pureed vegetables (1 small bowl)	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Mayonnaise (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
14. Fresh tomato sauce (Cup full)	☐	☐	☐	☐	☐	☐	☐	☐	☐
15. Ketchup (1 tablespoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
16. Salt added to dishes on the tables (1 pinch)	☐	☐	☐	☐	☐	☐	☐	☐	☐
17. Garlic (1 clove)	☐	☐	☐	☐	☐	☐	☐	☐	☐
18. Jam, honey, marmalade (1 teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
19. Sugar added to drinks or food (1 teaspoon)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Participant UTIN__ __ __/__ __ __ __

VIII. OTHER FOOD ITEMS

It isn't possible to include every kind of food in a questionnaire. Could you please write down any foods that you have regularly eaten that you have not been asked about. Please write clearly.

	Per month		Per Week			Per Day			
	< 1	1-3	1	2-4	5-6	1	2-3	4-5	6+
Other food Items eaten	☐	☐	☐	☐	☐	☐	☐	☐	☐
Please specify									
1.	☐	☐	☐	☐	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	☐	☐	☐	☐	☐
3.	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐	☐	☐	☐	☐
5.	☐	☐	☐	☐	☐	☐	☐	☐	☐
6.	☐	☐	☐	☐	☐	☐	☐	☐	☐

IX OTHER QUESTIONS

Please circle one option on the following questions.

1. How often do you eat fried food?
a) Less than once a week
b) Once a week
c) 2-4 times a week
d) 5-6 times a week
e) Daily

2. When you are eating meat, how do you like it cooked?
a) I don't eat meat *(go to question 6)*
b) Rare
c) Medium to well done
d) Very well done

Participant UTIN__ __ __/__ __ __ __

3. When you eat meat, what do you do with the visible fat?
a) Remove it all
b) Remove a bit
c) Remove the majority
d) I do not usually remove any of the fat

4. How do you usually eat meat?

	Never	Monthly	Weekly	Daily
Roasted	☐	☐	☐	☐
Grilled	☐	☐	☐	☐
Fried	☐	☐	☐	☐
Stewed	☐	☐	☐	☐
Barbecued	☐	☐	☐	☐

5. How often do you eat barbecued or burnt meat?
a) Never or less than once a month
b) Once a month
c) 2-3 times a month
d) Weekly
e) More than twice a week

6. What kind of fat do you most often use for the following?
Please tick only one answer per line

	Margarine	Butter	Olive oil	Other vegetable oil e.g corn, sunflower oil	Ghee or palm oil	Other
For dressing	☐	☐	☐	☐	☐	☐
For cooking	☐	☐	☐	☐	☐	☐
For frying	☐	☐	☐	☐	☐	☐

Participant UTIN__ __ __/__ __ __ __

X. USE OF SUPPLEMENTS

1. Have you used supplements:
a) In the last month
b) Between one and three months ago
c) Over three months ago
d) Never

2. If you have used supplements during your pregnancy please can you specify the supplements you are using or have during this period (last 4 months).

	Brand	Dosage per week (number of spoonfuls or capsules/tablets)	Still taking? Yes	No
Liquid (spoonfuls)				
Supplements				
Cod liver oil	_____	_____	☐	☐
Omega-3	_____	_____	☐	☐
Liquid Iron	_____	_____	☐	☐
Capsules or tablets				
Cod liver oil	_____	_____	☐	☐
Omega 3 oil	_____	_____	☐	☐
Multivitamin	_____	_____	☐	☐
Vitamin D	_____	_____	☐	☐
Folic Acid	_____	_____	☐	☐
Vitamin C	_____	_____	☐	☐
B Complex	_____	_____	☐	☐
Calcium	_____	_____	☐	☐
Iron	_____	_____	☐	☐
Zinc	_____	_____	☐	☐
Healthy Start Vitamins	_____	_____	☐	☐
Other (List type)				
1.	_____	_____	☐	☐
2.	_____	_____	☐	☐
3.	_____	_____	☐	☐

Participant UTIN__ __ __/__ __ __ __

XI PREGNANCY RELATED NAUSEA

1. Have you experienced nausea or vomiting during your pregnancy?

Yes ☐
No ☐

2. Has the nausea or vomiting you have experienced had a significant impact on your food intake during the last 4 months?

Yes ☐
No ☐

E: 24 hour recall

ESTEEM 1:1 Consultation
24h Recall

Participant UTIN: ___/ ____
Date: __/ ___/ ____
Day of the week:

Quick list	Forgotten Foods	Meal Name & Time	Food Details	
"Could you list all food and drink items you had all day yesterday?"	*"Apart from the items you already listed, did you have anything else, like* • *Water, coffee, tea?* • *Juice, fizzy drinks or energy drinks?* • *Fruit and vegetables?* • *Bread? Any desserts or sweets?"*		• *Additions? (with coffee, tea, toast)* • *Cooking method & Cooking fat used?* • *If meat or dairy product - fat content?* • *If grain product - wholegrain or refined?* • *Brand?*	*Amount consumed?*

- Final Review & Last chance: *"Could you maybe think of any other food and drink you consumed yesterday?"*
- Usual intake: *"Was the amount of food you ate yesterday more than usual, usual or less than usual?"* usual ☐ more ☐ less ☐
  If more/less, please state a reason (nausea , vomiting):
- Supplements: Brand/type:..... Dosage:.....

Day 1

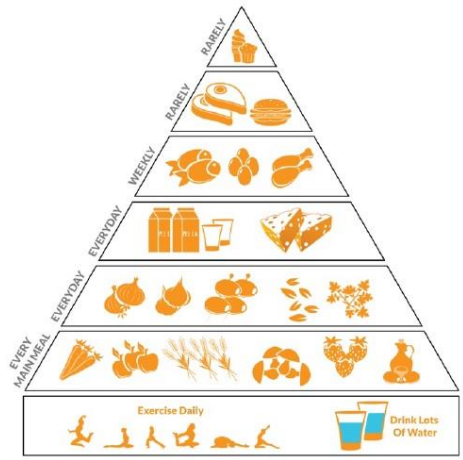
Version 1.0 Date: 18/Mar/2015

Appendix (6): Intervention factsheets for the ESTEEM trial

A: General information

10. **Limit these foods to no more than once a week:** Cream and butter; sweets, cakes, crisps, snacks and other convenience foods; sugary drinks (including sodas and teas).

This diagram can help you see how the balance of foods should look in your diet over all



Information Sources
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Simopoulos A, Visioli F. (2007) More on Mediterranean Diets: World Review of Dietetics (97);Published by Karger
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ESTEEM Dietary Information

This leaflet gives you some background information on how to follow the ESTEEM diet. You will also be given lots of advice and tips from the dietitians on the ESTEEM team.

esteem

The ESTEEM diet follows the principles of the Mediterranean diet, which has been associated with lots of health benefits including lower risk of heart disease, high blood pressure, obesity and diabetes.

This dietary pattern includes a high intake of monounsaturated fats from olive oil, some healthy fats from nuts, (particularly walnuts) and fish and a low intake of saturated fats. Olive oil is used to add to salads, cooked vegetables and soups. It is also used as a base to cook sauces with onions, garlic, tomatoes and herbs. Red meat, high-fat diary products and sugary foods are only consumed in small quantities.

Fruits, vegetables, nuts, whole grains, beans and pulses form the basis of every main meal. These foods provide important protective antioxidant nutrients like vitamin C, vitamin E and beta-carotene. You can get the benefit of all these important nutrients by eating brightly coloured fruits and vegetables like melon, strawberries, citrus fruits, red peppers, carrots, pumpkin and broccoli.

Tips for following the ESTEEM diet

The foods which form most of your diet and which you eat everyday should include whole grains, fruits, vegetables, beans and other legumes, herbs and spices and healthy fats like olive oil.

Low-fat dairy products like yoghurt and low-fat cheeses, can also be eaten daily in moderate amounts. Other sources of protein include poultry (chicken and turkey), fish and eggs.

Foods to limit as much as possible include red meat, processed meat like sausages and burgers, sweets, cakes and confectionery, cream, butter and sugary drinks.

1. **Use olive oil on salads and vegetables and as your main oil for cooking**. You will be provided with half a litre of oil per week for you and your family.

2. **Eat 2 servings of vegetables with each main meal.** Aim for variety in colour and texture. Eat highly coloured vegetables like tomatoes, peppers and broccoli as well as root vegetables like carrots, yams, cassava, beetroot and leafy green vegetables, to make sure you get a good range of the nutrients and other beneficial compounds. The less you cook the vegetables the better so eat some vegetables raw in salads, each day.

3. **Have at least 2/3 portions of fruit a day.**

4. **Eat whole grains everyday**. The fibre and nutrients in whole grains make them an important part of the ESTEEM diet. You can increase your intake by including wholegrain cereals in the morning like porridge and muesli and by having breads, including chappatis and rotis, made with wholegrain flour. Include whole grains in your main meals, for example by choosing brown rice, wholegrain pasta, barley, quinoa or wholewheat couscous as a side dish. You can also add grains such as barley or bulgur wheat to stews and casseroles.

5. **Eat legumes like peas, beans and lentils at least 3 times a week**. These can be eaten in curries, stews or soups, served as a side dish or eaten cold in salads.

6. **Replace red meat with poultry like chicken and turkey.** Avoid processed meats like sausages and burgers. Cut excess fat off meat to minimize your intake of animal fat.

7. **Eat fish around 2/3 times a week**. Eat both white fish and oily fish, like salmon, tuna, mackerel and sardines. These oily fish contain healthy omega 3 fatty acids which are good for your baby's development. However, restrict your intake of oily fish to a maximum of 2 (140g) portions or 4 medium cans of tuna per week as these fish can contain mercury.

8. **Eat the ESTEEM nuts every day**. You will be provided with 30g of mixed nuts to eat each day. They can be eaten as a snack or added to food.

9. **Low fat dairy foods, such as yoghurt and cheese** can be eaten each day in moderate portions, e.g. a pot of low fat natural yoghurt, a small cube of low fat cheese and a glass of semi-skimmed milk, will ensure you get the calcium you need. Non-diary sources of calcium include soy milk, tofu, fortified orange juice and some greens like bok choy.

B: Individual portion weekly plan

ESTEEM - Individual portion count - Weekly plan

This sheet is for your own personal use to give you a rough guide of whether you are following the ESTEEM dietary guidelines

Serving count	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Red meat																														
Sweets, sugary drinks and desserts																														
Eggs																														
Potatoes																														
Nuts																														
Legumes																														
Poultry (other white meat)																														
Fish (Max 2 oily fish																														
Dairy (low fat)																														
Olive oil	**Use olive oil as main cooking and added fat**																													
Fruits																														
Vegetables																														
Bread, rice, pasta (wholegrain)																														

There is no restriction on the amount of vegetables you can consume. Also remember to drink lots of water.

Cooking tips – ideally use grilling, baking or stir-frying as your main cooking methods.

Serving sizes: -

Vegetables – 1 cup full (approx. 100g)
Potatoes – 1 medium potato
Legumes – 1 cup full (approx. 150g cooked)

Meat– 100g-150g (cooked) palm-sized portion
Fish- 100-150g (cooked) palm-sized portion
Grains – 1 slice bread, 50g chapatti, 130g rice (cooked), 150g pasta (cooked)

Nuts – 30g
Fruit – 1 apple, banana, orange or slice of melon or small bunch of grapes

Dairy – 1 small glass skimmed milk, small cube of cheese (30g)
Eggs – 2

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C: Extra virgin olive oil

Information Sheet : Olive Oil

Olive oil is an important component in the diet of Mediterranean countries. In recent years medical studies have shown that populations that consume olive oil regularly as part of their normal diet have lower risk of chronic disease, including heart disease

About olive oil
Olive oil has many active components such as oleic acid, linoleic acid, Vitamin E and flavonoids, all of which contribute to its benefits.

Extra virgin olive oil and health
Scientific evidence has documented the beneficial effects of diets with a high intake of extra-virgin olive oil on cardiovascular risk factors, such as high blood pressure, high cholesterol, high blood lipids and atherosclerosis. It has been shown to also reduce inflammation and the risk of blood clots. Olive oil also improves the sensitivity to insulin making it helpful for those suffering from diabetes.

Olive oil is part of the ESTEEM diet because pre-eclampsia shares many of the same risk factors as cardiovascular disease and because a reduction in the diagnosis of pre-eclampsia has been observed amongst pregnant women who follow the Mediterranean dietary pattern of high monounsaturated oil and vegetable consumption.

Olive oil and the ESTEEM diet
Being enrolled on the ESTEEM trial you will have been given 0.6L per week of olive oil. Ideally you should try to consume around 2-4 tablespoons of olive oil each day.

This can be added to your own vegetables and salads or consumed in your share of meals made for the family. You should replace the oil you normally use for cooking, with olive oil.

Storing your olive oil
You can keep unopened olive oil for up to two years but once the container is opened it will degrade much faster so it should always be used within a few months. When storing oil keep the cap on and store away from heat and direct light.

Using olive oil in your diet
You will get the most benefits from your olive oil if you use it cold as a dressing on salads and vegetables.

Olive oil is more stable than many seed oils so it is also a good choice for cooking. The smoking point of Extra-virgin olive oil is between 186°C and 210°C depending on how the oil is produced. To get the maximum nutritional value from the oil it is best to avoid the oil smoking, therefore cook with the oil at lower temperatures and for a shorter time to preserve more of the health benefits of the oil.

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Use in dressings or added to food after cooking: This is the ideal way to get the maximum nutritional value out of your oil.

Pan-frying & stir-frying: Olive oil can be used to stir-fry and will still retain its benefits. Avoid heating to very high temperatures and add the food quickly to the pan to reduce the likelihood of the oil smoking.

Roasting: You can roast foods with olive oil, in the oven at 180°C for up to 2 hours.

Microwaving: Olive oil can be used in the microwave safely for cooking times of up to 10 minutes, however ideally add the oil after cooking.

Using olive oil to prepare a base for sauces, soups and curries
You can use olive oil to make a traditional Mediterranean sauce to accompany fish or pasta by frying onions and garlic gently in the oil, then adding tomatoes, herbs, salt and pepper. An alternative is to make a base for curry dishes.

Ingredients (for 4)*
2 tbsp olive oil
1 tsp cumin seeds
2 chopped medium onions
1 tsp ginger paste
1 tsp garlic paste
1 green chilli
1 tsp salt
1/2 tin canned chopped tomatoes
1 small bunch of coriander

Heat the olive oil in a pan on a medium heat and after 2 minutes add the cumin seeds. Add in the chopped onions and cook until golden brown.

Add ginger, garlic and green chilli finely chopped or made into a paste.

Cook this for 5 minutes and add 1 tsp of salt and 1 tsp of turmeric. Then add the 1/2 can of chopped tomatoes. Finally, add the finely cut coriander stalks into the base, keeping the leaves to use later.

To this base you can add any vegetables, meat or fish you wish, together with the coriander leaves.
* Recipe from www.foodacademy.co.uk

Information Sources

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D: Mixed nuts

Information Sheet : Nuts

Tree-nuts like almonds, walnuts and hazelnuts are rich in nutrients, including healthy fats, minerals such as calcium and potassium and important antioxidant vitamins like Vitamin E. Nuts have been shown to have wide-ranging cardiovascular and general health benefits.

Nuts are an important part of the Mediterranean diet pattern and eating nuts has been associated with beneficial effects on many aspects of health including reducing cardiovascular risk factors, reducing inflammation and improving obesity.

Nuts are high in healthy monounsaturated fats and low in saturated fats. Besides being a source of healthy fats nuts are a rich source of protein, fibre, vitamins E, B6, folic acid, and niacin, minerals magnesium, potassium and iron and healthy sterols that may help reduce cholesterol.

As nuts are high in fat, they are high in calories. However, consumption of nuts in the diet hasn't been shown to be associated with weight gain. This could be for a number of reasons, including the fact they are filling, reducing hunger for other foods but they also contain fibre and certain bioactive compounds, like polyphenols, which may help the body control weight.

You have been given 30g of nuts to eat each day as part of the ESTEEM diet.

During the study these nuts should be eaten every day.

The recommended daily amount is:

15 g of walnuts (about 3 nuts)
7.5 g of almonds (about 6 nuts)
7.5 g hazelnuts (about 8 nuts)

If you forget to eat the nuts you can eat two days worth the following day.

The nuts should be eaten whole and fresh, rather than cooked, in order to preserve the vitamins and other beneficial compounds the nuts contain. You can eat them as a snack or add them to food, salads or yoghurts.

Try to eat the nuts within 2 weeks of opening the bag and store open bags in the fridge. If this is not possible, store them in a dry dark place, closing the bags with a clamp or similar.

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The nuts in the ESTEEM diet have been selected to give you a range of different polyunsaturated fats, as well as other valuable nutrients. Aim to eat the nuts in the quantities suggested to get maximum benefit.

Almonds

Almonds are good for you because they are an excellent source of unsaturated fats, Vitamin E, dietary fibre and other healthy phytochemicals.

Walnuts

Walnuts are high in polyunsaturated fatty acids and in particular they are high in the plant omega-3 fatty acid alpha-linolenic acid (ALA). Essential fatty acids are important for your baby's development.

Hazelnuts

While you are pregnant you need to ensure an adequate intake of folic acid which is high in hazelnuts.

Nutrient/100g	Almonds	Walnuts	Hazelnuts
Monounsaturated fat (g)	32.2	8.9	45.7
Polyunsaturated fat (g)	12.2	47.2*	45.7
Fibre (g)	8.8	6.4	10.4
Protein	6.0	4.3	4.2
Folic Acid (microg)	29.0	98.0	113.0
Calcium	248.0	98.0	114.0
Potassium	728.0	441.0	680.0

** Walnuts are particularly high in beneficial omega 3 polyunsaturated fats*

Source: Ros E. (2010) Health benefits of nut consumption. Nutrients 2, 652-682

Appendix (7): Definition of the ESTEEM trial study outcomes.

New Onset pre-eclampsia:

New onset hypertension after 20 weeks gestation defined as systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mmHg, in at least two readings, taken 4-6 hours apart plus new onset proteinuria defined as spot urine PCR test greater than 30mg/mmol or >24 hour urine 300mg/24 hours or 2+ or more on standard urinary dipstick tests after 20 weeks gestation

Superimposed pre-eclampsia in women with chronic hypertension or chronic proteinuria:

In women with chronic hypertension and no proteinuria at baseline, the appearance of new onset proteinuria, (defined above) constitute a 'superimposed pre-eclampsia'.

Chronic hypertension is hypertension that is present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity.

In women who had proteinuria at base line, the diagnosis of superimposed preeclampsia requires an elevated serum alanine aminotransferase concentration (>70 U per litre) or worsening hypertension (either two diastolic BP of at least 110 mm Hg four hours apart or one diastolic measurement of at least 110 mm Hg or if the woman had been treated with an antihypertensive drug).

Women with eclamptic seizures with no hypertension or proteinuria are considered to have pre-eclampsia.

Gestational diabetes

Defined as per the modified International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria—ie, fasting venous glucose of 5·1 mmol/L or higher or 2 h venous glucose of 8·5 mmol/L or higher, or a combination of these.

Small for gestational age fetus

Defined as birth weight less than 10th centile using gestation related optimal weight customised charts (GROW).

Outcomes were collected as stated in the clinical notes by the supervising physician. We screened laboratory results to detect any abnormal biochemical results and link them to clinical notes. MEWS and drug charts were also screened to capture cases of pre-eclampsia in case a formal diagnosis has not been made in the clinical notes. Any ambiguity in capturing outcomes was resolved in consensus among the trial clinical management team.

Appendix (8): Baseline dietary and quality of life measurements for participants in the ESTEEM trial

A: ESTEEM Q

Question (threshold for one mark)	Intervention (n=593)	Control (n=612)
Do you use olive oil as the main fat to cook with? (Yes)	154 (36.7%) [173]	110 (42.3%) [352]
How many tablespoons do you consume of olive oil in a given day? (>=4)	45 (10.9%) [180]	28 (10.9%) [354]
How many servings of vegetable do you consume per day? (>=2)	195 (46.7%) [175]	150 (58.8%) [357]
How many fruit units do you consume per day? (>=3)	174 (41.3%) [172]	155 (59.4%) [351]
How many servings of red meat, processed meat or red meat products do you consume per day (<1)	293 (76.7%) [211]	123 (51.0%) [371]
How many servings of butter, margarine, or cream do you consume per day? (<1)	224 (54.1%) [179]	105 (40.2%) [351]
How many drinks containing sugar do you consume per day? (<1)	179 (42.6%) [173]	104 (40.3%) [354]
How many servings of pulses do you consume per week? (>=3)	104 (24.9%) [175]	64 (24.7%) [353]
How many servings of fish or shellfish do you consume per week? (>=3)	86 (20.6%) [175]	56 (21.5%) [352]
How many times per week do you consume commercial sweets or pastries, such as cakes, cookies, biscuits or custard? (<3)	225 (54.3%) [179]	146 (57.5%) [358]
How many servings of nuts do you consume per week? (>=3)	101 (24.3%) [178]	54 (20.8%) [353]
Do you preferentially consume chicken or turkey instead of veal, pork, hamburger or sausage? (Yes)	276 (73.0%) [215]	185 (79.7%) [380]
Mean total Score	5.0 (1.9) [256]	5.0 (1.9) [402]
Symptoms Experienced		
Fullness of stomach	255 (63.0%) [188]	147 (66.5%) [391]
Bloatedness	223 (54.9%) [187]	128 (58.7%) [394]
Vomiting	139 (34.2%) [187]	60 (26.9%) [389]
Nausea	209 (51.6%) [188]	127 (56.4%) [387]
Indigestion	182 (44.8%) [187]	95 (44.0%) [396]
Constipation	165 (40.7%) [188]	95 (44.2%) [397]
Diarrhoea	54 (13.4%) [189]	43 (19.5%) [392]

B: EQ-5D

Quality of life dimension	Intervention (n=551)	Control (n=586)
Mobility		
I have no problems in walking about	356 (86.0%)	220 (85.3%)
I have some problems in walking about	57 (13.8%)	37 (14.3%)
I am confined to bed	1 (0.2%)	1 (0.4%)
Missing data	179	354
Self-Care		
I have no problems with self-care	397 (95.9%)	252 (97.3%)
I have some problems with washing or dressing myself	15 (3.6%)	7 (2.7%)
I am unable to wash or dress myself	2 (0.5%)	0 (0.0%)
Missing data	179	353
Usual Activities		
I have no problems with performing my usual activities	348 (84.1%)	200 (77.8%)
I have some problems with performing my usual activities	63 (15.2%)	54 (21.0%)
I am unable to perform my usual activities	3 (0.7%)	3 (1.2%)
Missing data	179	355
Pain/Discomfort		
I have no pain or discomfort	221 (53.6%)	139 (53.5%)
I have moderate pain or discomfort	177 (43.0%)	116 (44.6%)
I have extreme pain or discomfort	14 (3.4%)	5 (1.9%)
Missing data	181	352
Anxiety/Depression		
I am not anxious or depressed	329 (79.5%)	213 (81.9%)
I am moderately anxious or depressed	80 (19.3%)	44 (16.9%)
I am extremely anxious or depressed	5 (1.2%)	3 (1.2%)
Missing data	179	352
Health Thermometer (0-100)	67.4 (18.7) [193]	71.8 (18.7) [390]

Appendix (9): Search Strategy for randomised trials using dietary assessment tools in pregnancy

Ovid MEDLINE(R) 1950 to Present with Daily Update

#	Searches	Results
1	Obesity/	88629
2	*obesity/	60169
3	*Obesity/	60169
4	obes*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	136045
5	1 or 2	88629
6	1 or 4	136045
7	3 or 4	136045
8	1 or 2 or 3 or 4	136045
9	Overweight/	4443
10	exp Overweight/	97104
11	*Overweight/	2653
12	overweight.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	21031
13	9 or 10	97104
14	10 or 11	97104
15	11 or 12	21031
16	exp Obesity/	97173
17	1 or 16	97173
18	4 or 16	137405
19	body weight.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	219574
20	(body adj weight).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	219574
21	(body adj2 weight).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	221994
22	(body and weight).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	258855

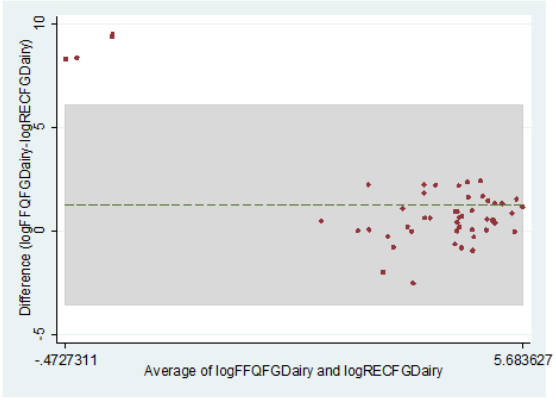
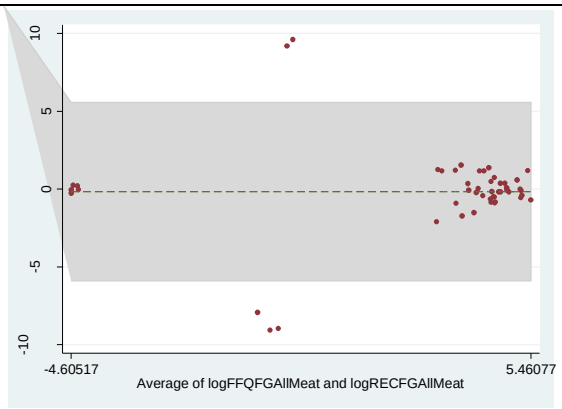
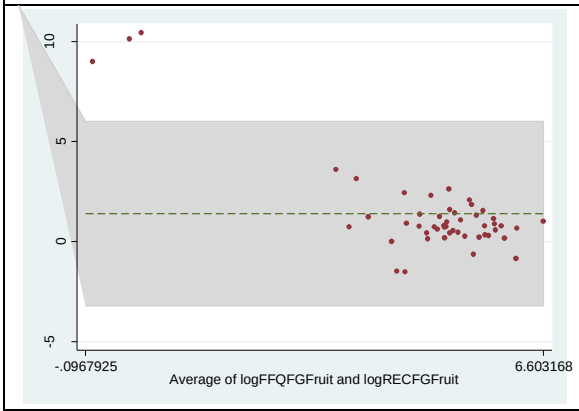
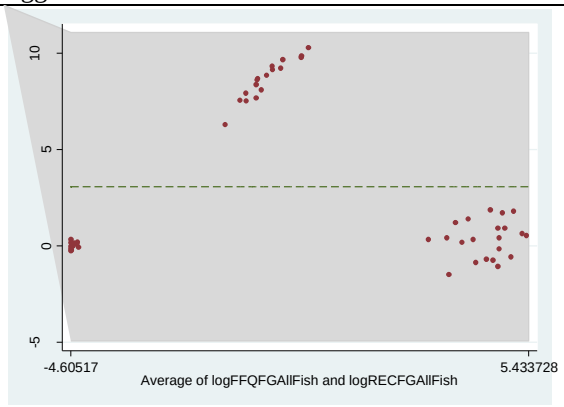
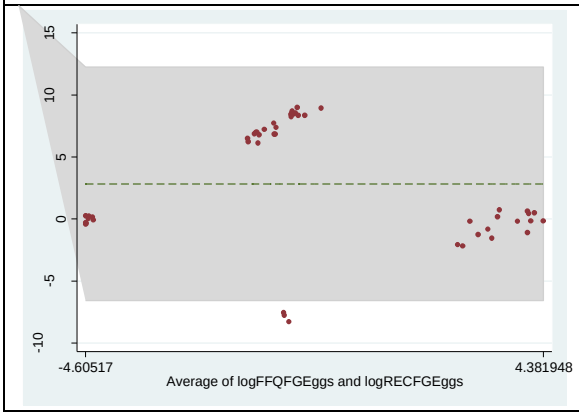
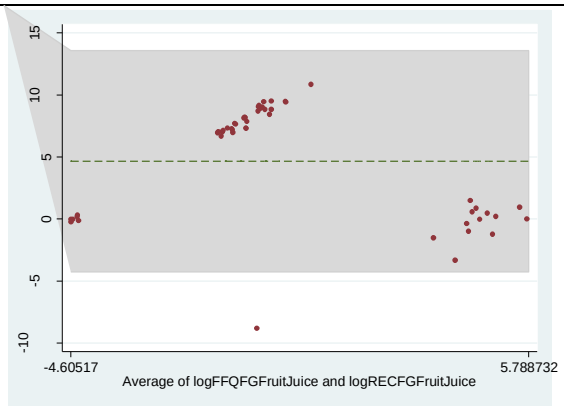
23	(body or weight).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1116567
24	20 or 21	221994
25	21 or 22	258855
26	21 or 23	1116567
27	22 or 23	1116567
28	9 or 10 or 11 or 12	103377
29	10 or 12	103377
30	1 or 2 or 3 or 4 or 16	137405
31	20 or 21 or 22 or 23	1116567
32	*body weight/	18917
33	body weight*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	223873
34	31 or 32	1116567
35	31 or 33	1116567
36	weight change.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2930
37	(weight adj2 change).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3831
38	weight change*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4937
39	weight chang*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4943
40	(weight adj2 chang*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7250
41	36 or 37	3831
42	36 or 38	4937
43	36 or 39	4943
44	36 or 40	7250
45	37 or 38	5816
46	37 or 39	5822
47	37 or 40	7250
48	38 or 39	4943

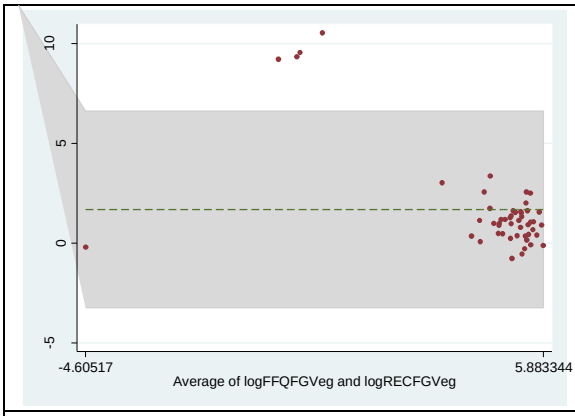
49	39 or 40	7250
50	38 or 40	7250
51	36 or 37 or 38 or 39 or 40	7250
52	weight lose.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	22
53	(weight adj2 lose).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1772
54	weight lose*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	78
55	(weight adj2 lose*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1841
56	weight los*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	42923
57	(weight adj2 los*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	46316
58	52 or 53	1772
59	52 or 54	78
60	52 or 55	1841
61	52 or 56	42923
62	52 or 57	46316
63	53 or 54	1821
64	53 or 55	1841
65	53 or 56	43645
66	53 or 57	46316
67	54 or 55	1841
68	54 or 56	42923
69	54 or 57	46316
70	55 or 56	43659
71	55 or 57	46316
72	56 or 57	46316
73	52 or 53 or 54 or 55 or 56 or 57	46316
74	excessive weight gain.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	463

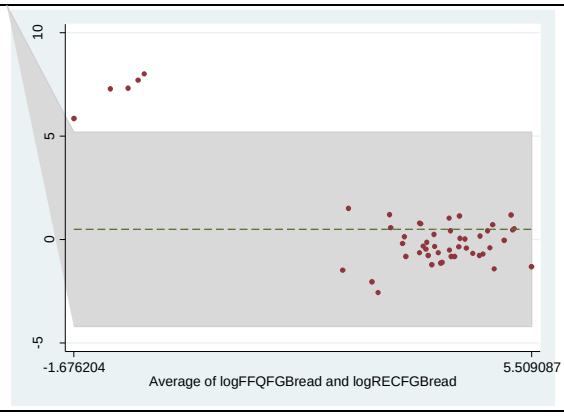
75	excessive weight gain*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	473
76	(excessive adj2 weight adj2 gain).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	571
77	(excessive adj2 weight adj2 gain*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	599
78	74 or 75	473
79	74 or 76	571
80	74 or 77	599
81	75 or 76	581
82	75 or 77	599
83	76 or 77	599
84	74 or 75 or 76 or 77	599
85	28 and 30 and 31 and 51 and 73 and 84	3
86	28 or 30 or 31 or 73 or 84	1187097
87	from 86 keep 1-100	100

Results of your search: from 86 [28 or 30 or 31 or 73 or 84] keep 1-100

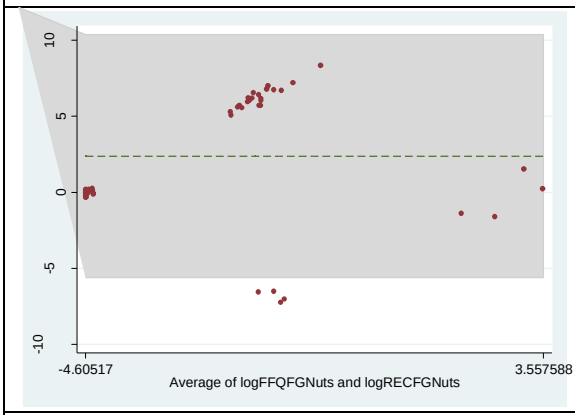
Appendix (10): Bland – Altman plots of estimated food and nutrients mean values from the FFQ and 24 hour recalls

Dairy	Meat
	
Fruit	**Eggs**
	
Fish	**Fruit Juice**
	
Vegetables	**Bread**

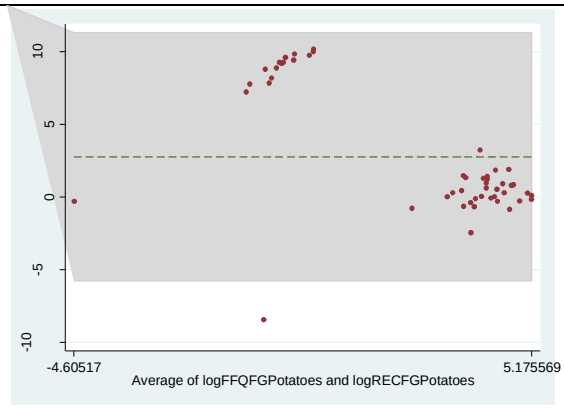




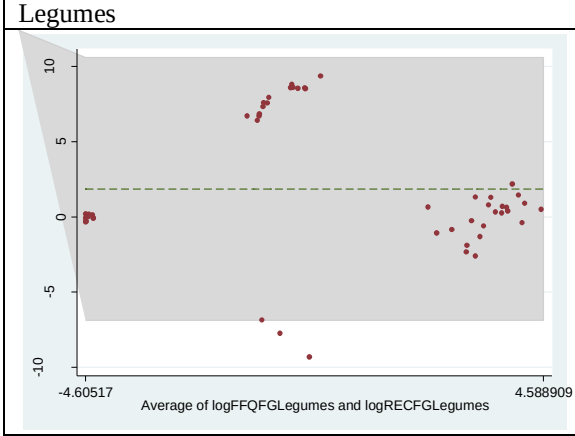
Nuts



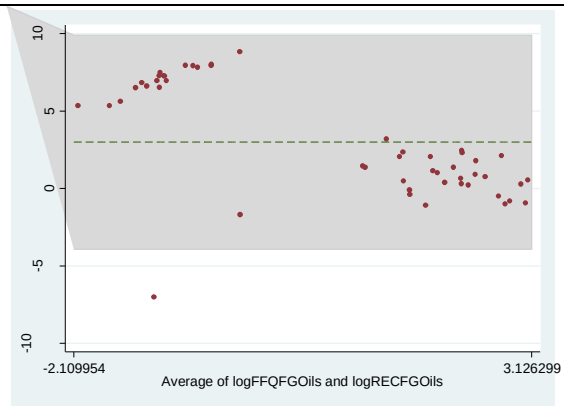
Potatoes



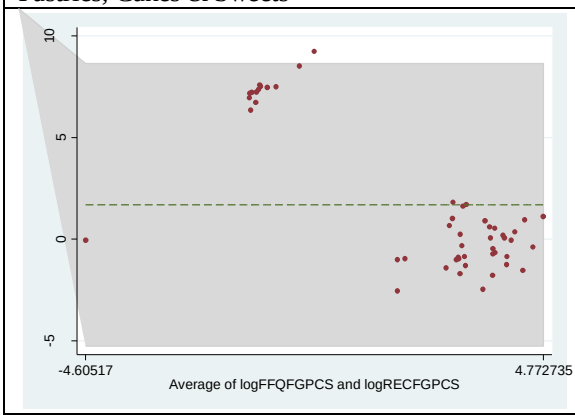
Legumes



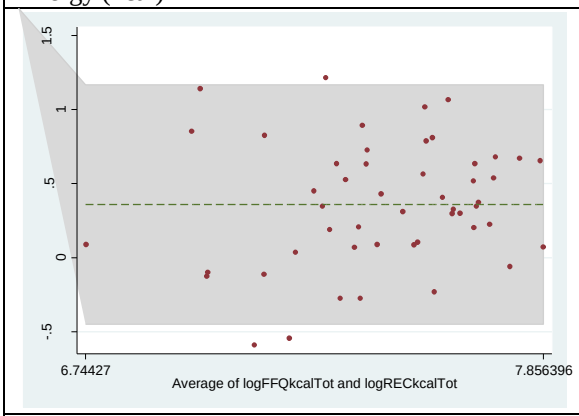
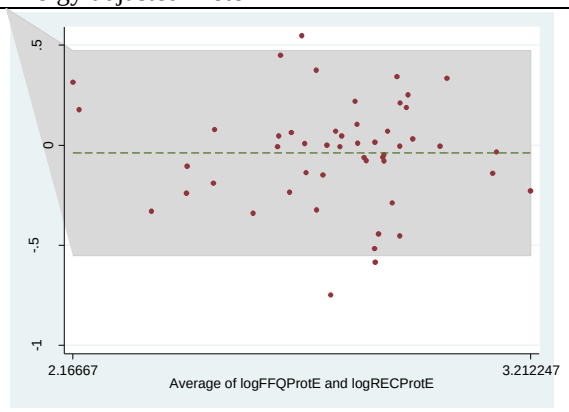
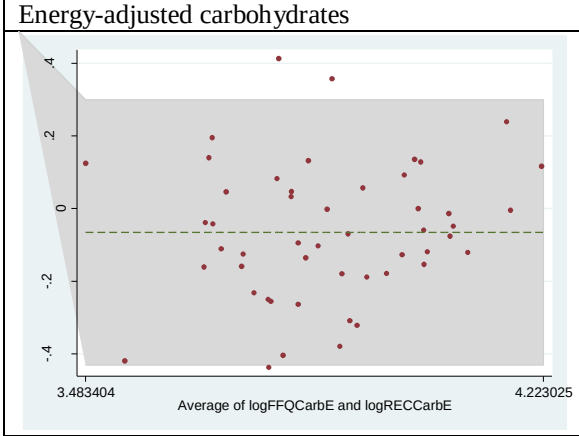
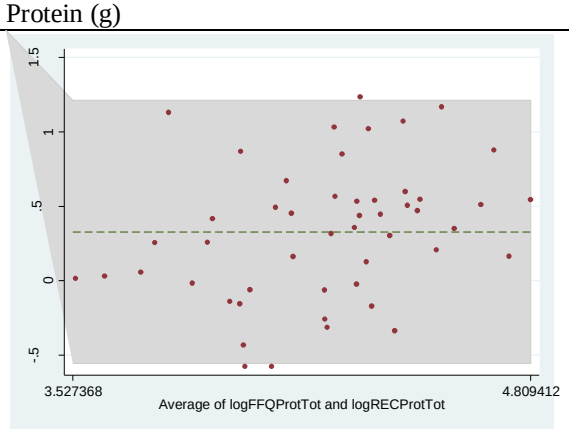
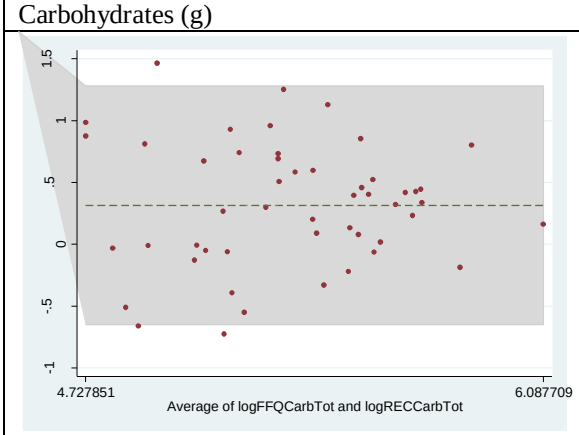
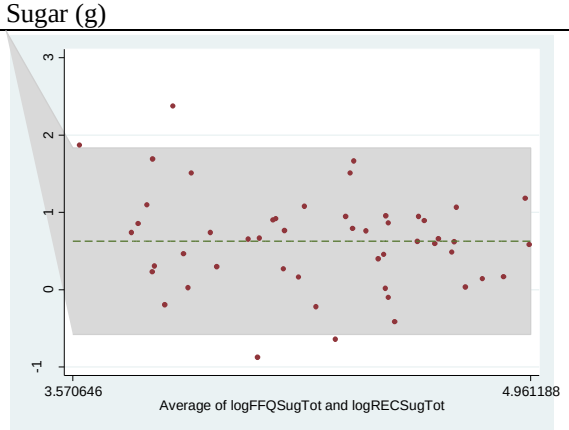
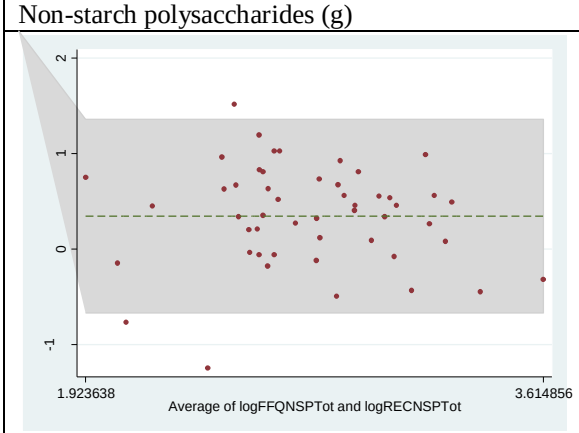
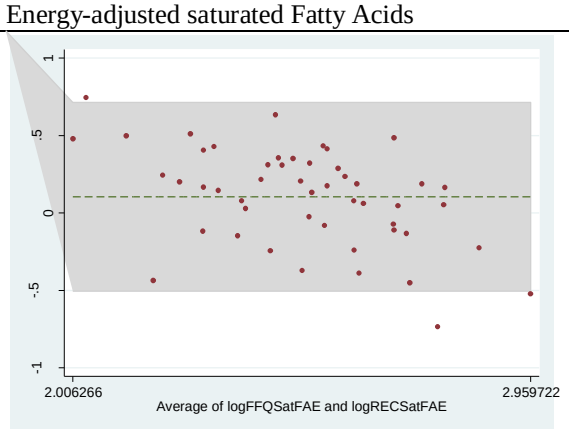
Oils

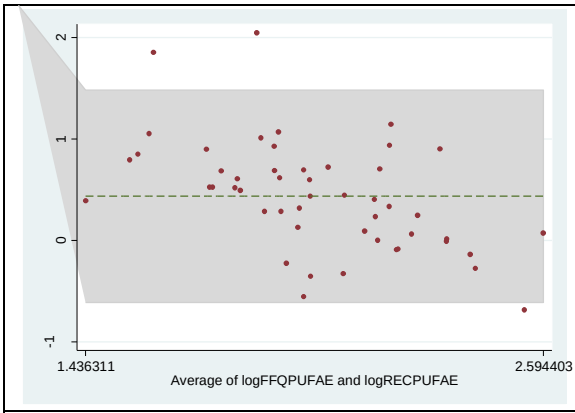


Pastries, Cakes & Sweets

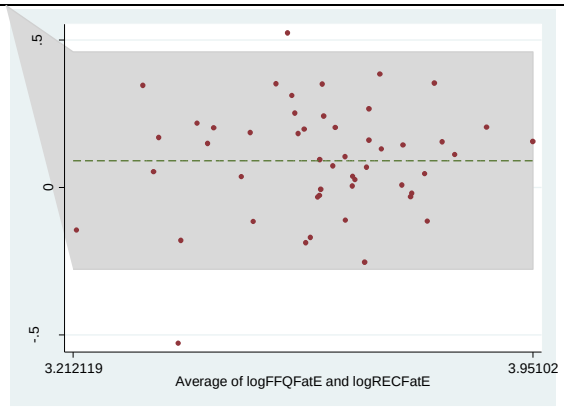


Micronutrients

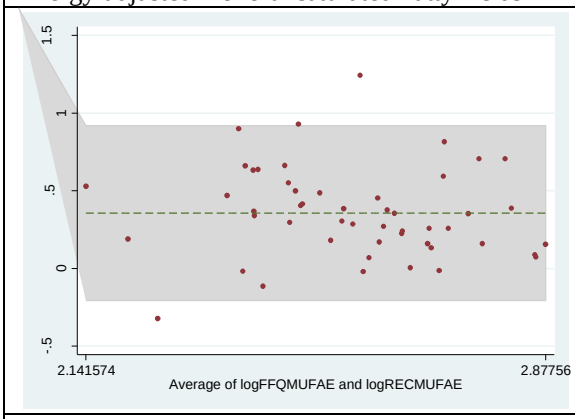
Energy (kcal)	Energy-adjusted Protein
	
Energy-adjusted carbohydrates	Protein (g)
	
Carbohydrates (g)	Sugar (g)
	
Non-starch polysaccharides (g)	Energy-adjusted saturated Fatty Acids
	
Energy-adjusted poly-unsaturated Fatty Acids	Energy-adjusted fat



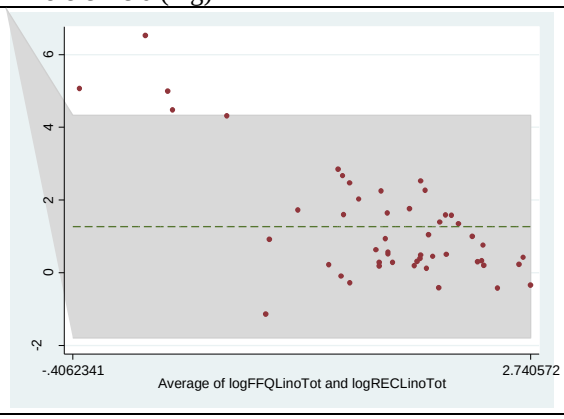
Energy-adjusted mono-unsaturated Fatty Acids



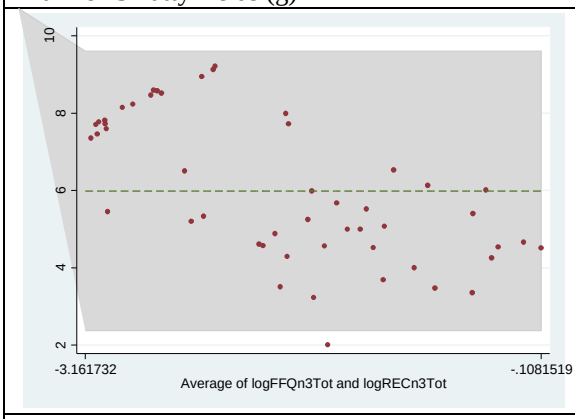
Linoleic Acid (mg)



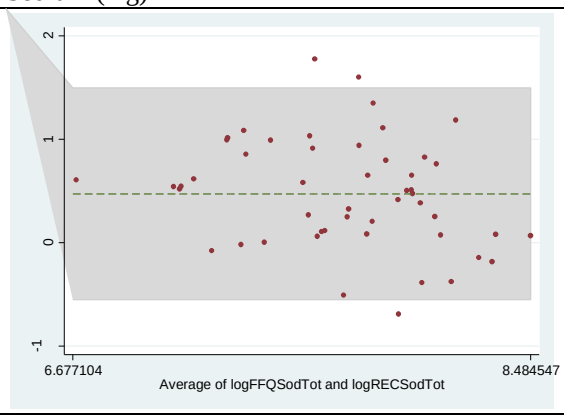
Marine n3 Fatty Acids (g)



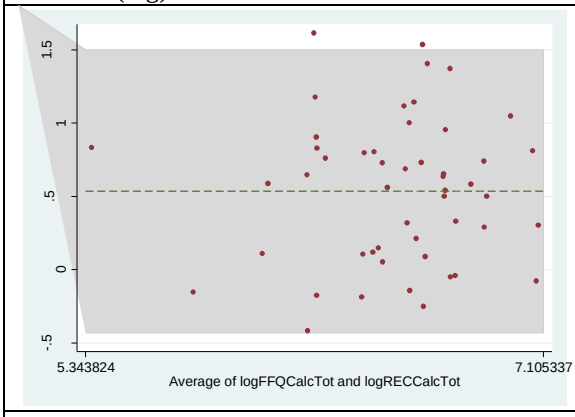
Sodium (mg)



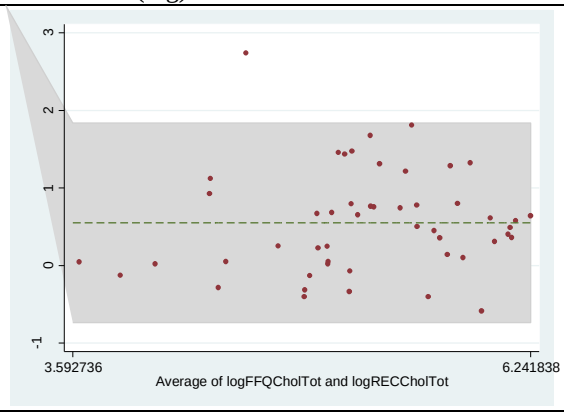
Calcium (mg)



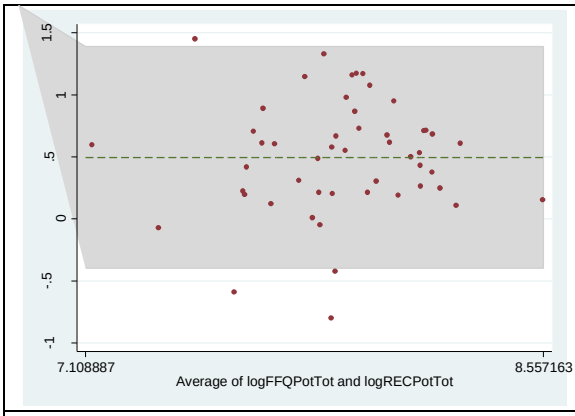
Cholesterol (mg)



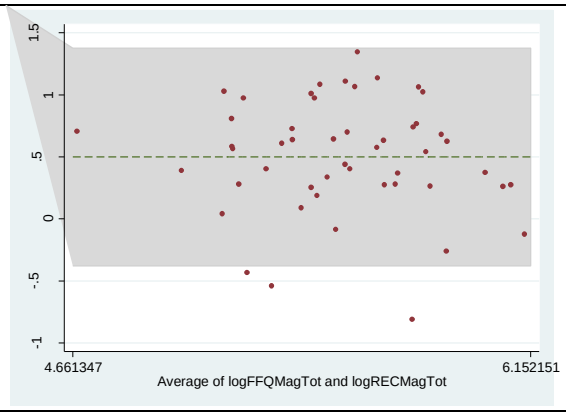
Potassium (mg)



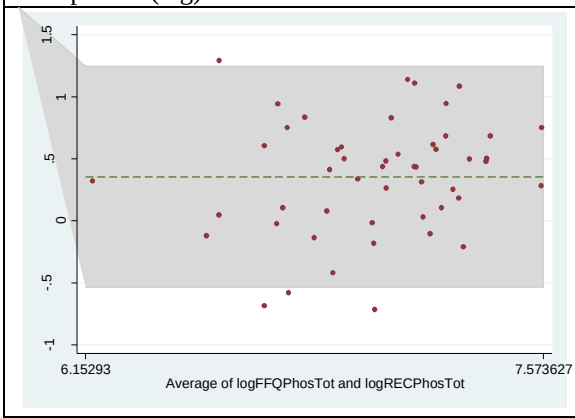
Magnesium (mg)



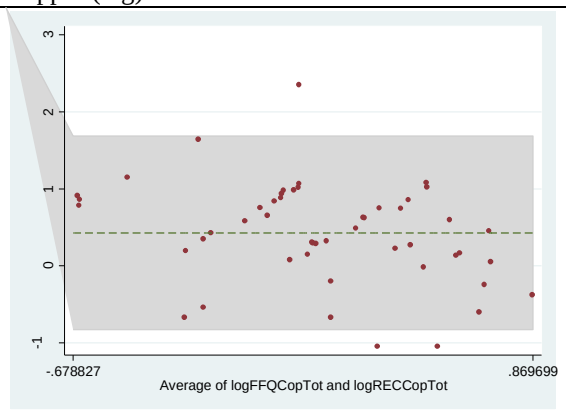
Phosphorus (mg)



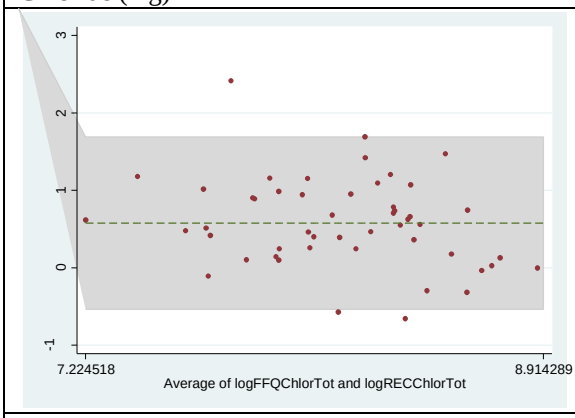
Copper (mg)



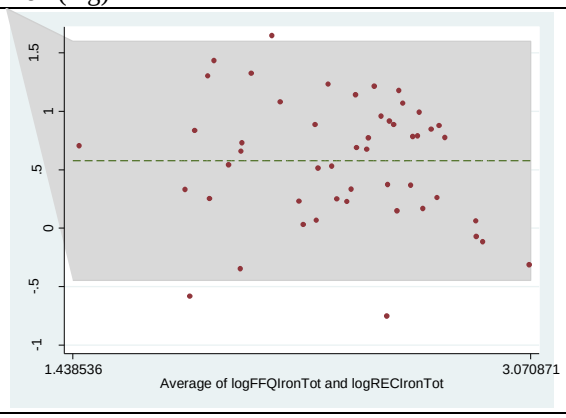
Chloride (mg)



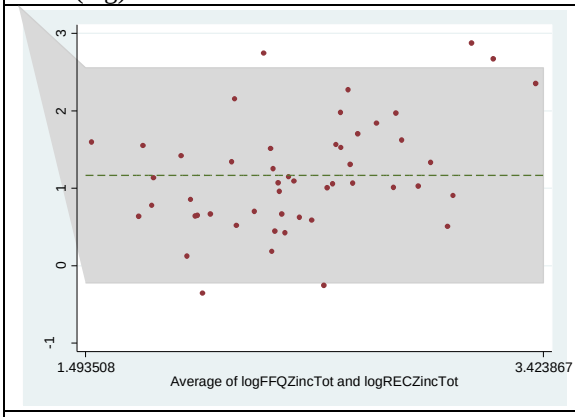
Iron (mg)



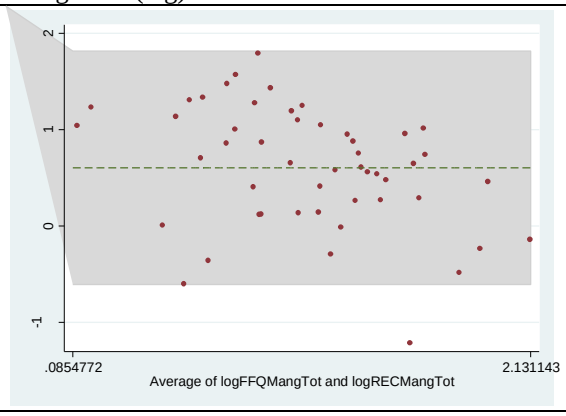
Zinc (mg)



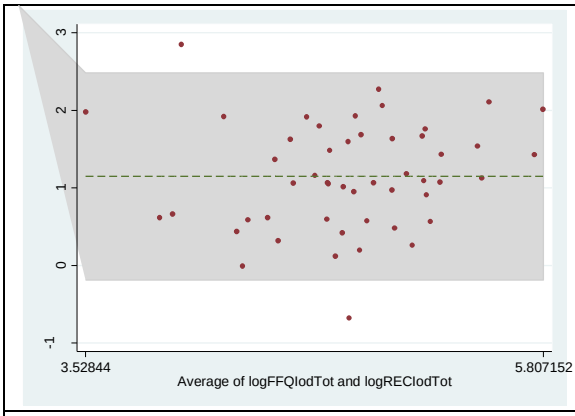
Manganese (mg)



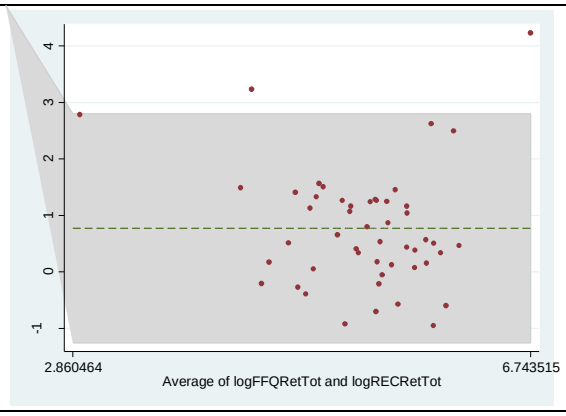
Iodine (µg)



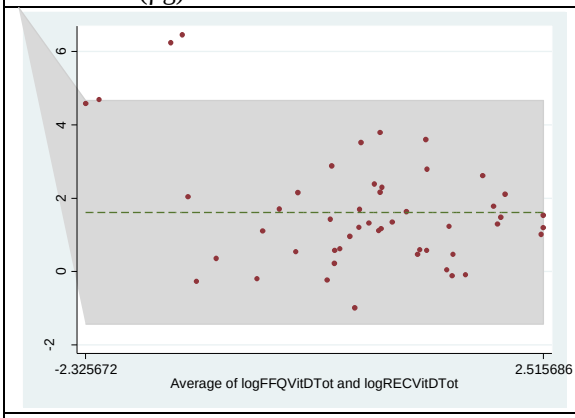
Retinol (µg)



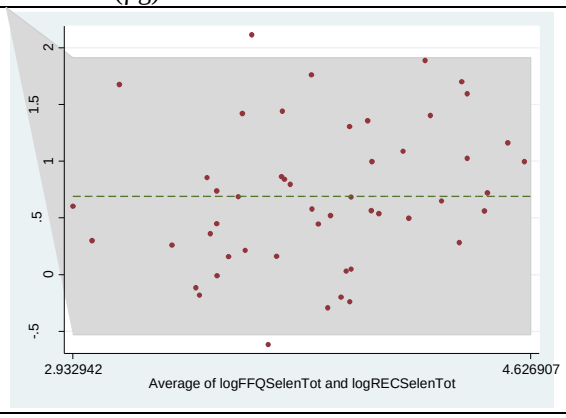
Vitamin D (µg)



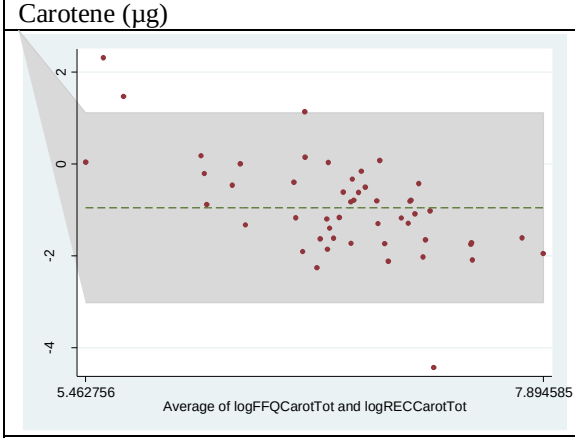
Selenium (µg)



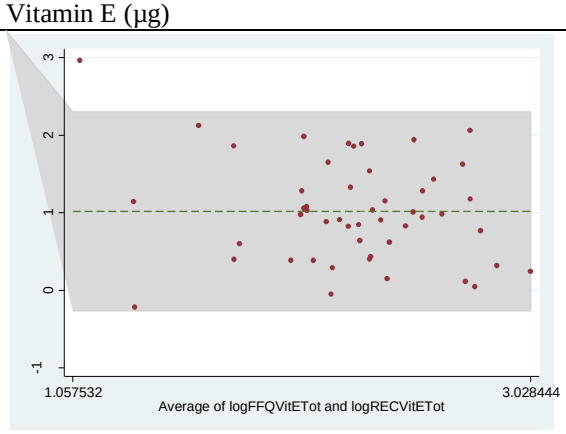
Carotene (µg)



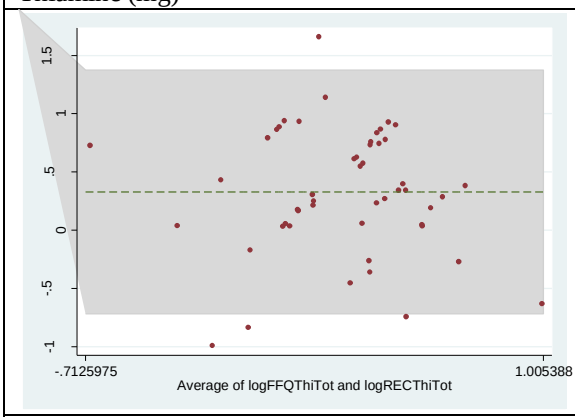
Vitamin E (µg)



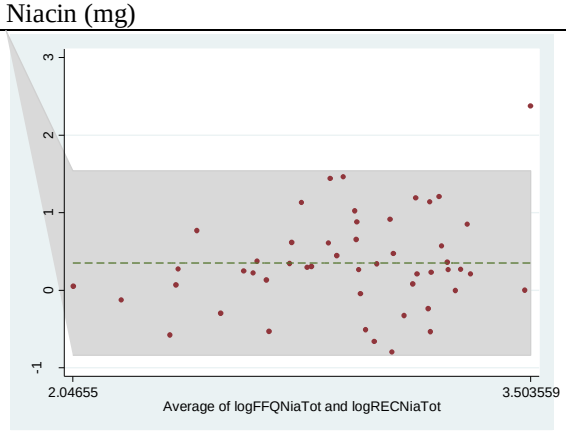
Thiamine (mg)



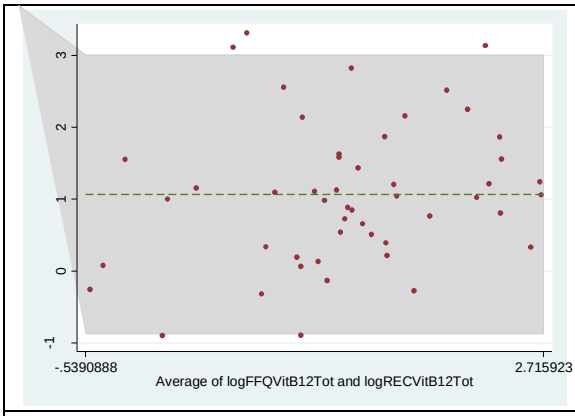
Niacin (mg)



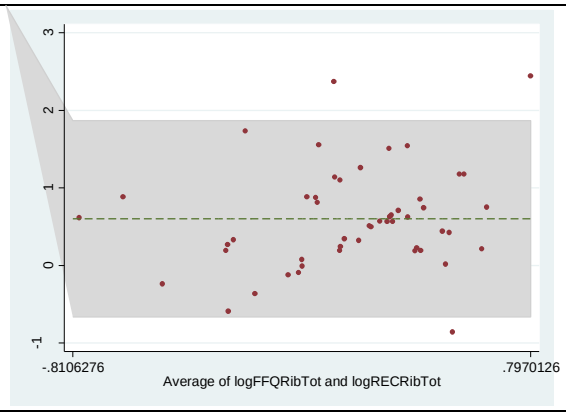
Vitamin B12 (µg)



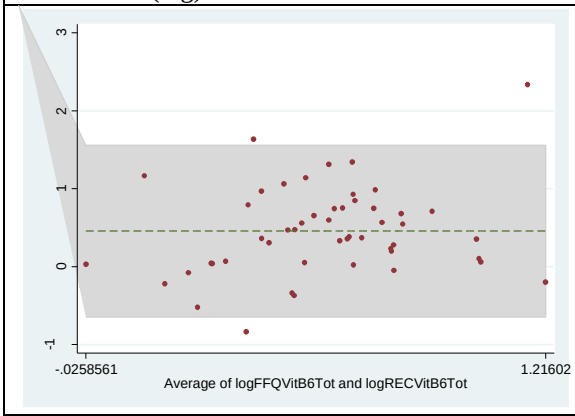
Riboflavin (mg)



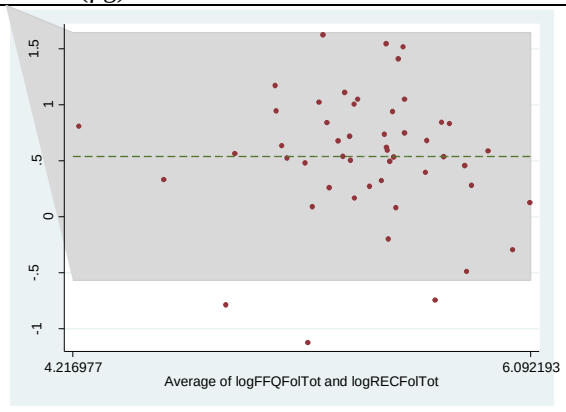
Vitamin B6 (mg)



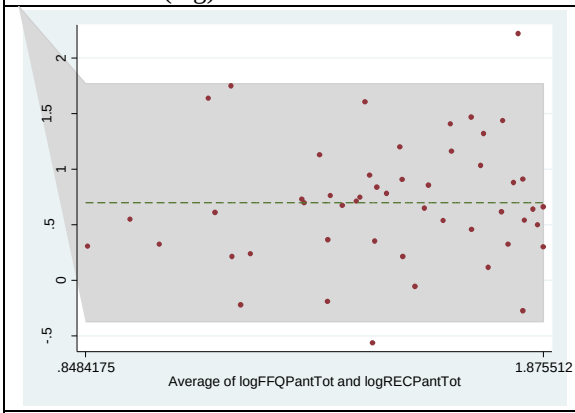
Folate (µg)



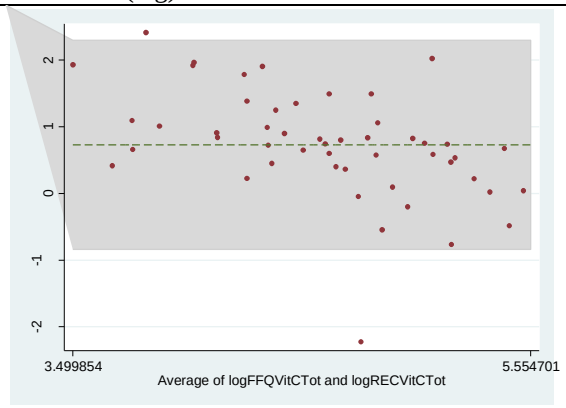
Pantothenate (mg)

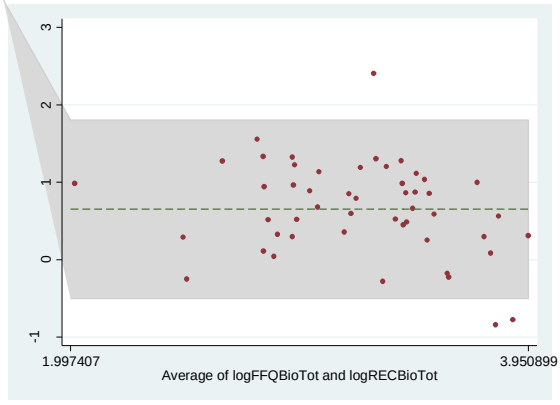


Vitamin C (mg)



Biotin (µg)





Appendix (11): Search Strategy used for online websites providing information on obesity in pregnancy.

[obese] OR [obesity] AND [pregnan*]

[overweight] AND [pregnan*]

[high BMI] AND [pregnan*]

[plus size] AND [pregnan*]

[healthy lifestyle] AND [pregnan*]

[diet] AND [pregnan*]

[obese] OR [obesity] AND [mother] OR [maternal]

[overweight] AND [mother] OR [maternal]

[high BMI] AND [mother] OR [maternal]

[plus size] AND [mother] OR [maternal]

[healthy lifestyle] AND [mother] OR [maternal]

[diet] AND [mother] OR [maternal]

Appendix (12): The PRISMA checklist for reporting systematic reviews

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

Section/topic	#	Checklist item

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix (13): Published articles in peer-reviewed journals

BMJ Open

Effect of simple, targeted diet in pregnant women with metabolic risk factors on maternal and fetal outcomes (ESTEEM): study protocol for a pragmatic multicentre randomised trial

Bassel H Al Wattar,[1] Julie Dodds,[1] Anna Placzek,[1] Eleni Spyreli,[1] Amanda Moore,[1] Richard Hooper,[1] Lee Beresford,[1] Tessa J Roseboom,[2,3] Maira Bes-Rastrollo,[4,5,6] Graham Hitman,[7] Khalid S Khan,[1,8] Shakila Thangaratinam,[1,8] for the ESTEEM study group

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ABSTRACT

Introduction: Women with metabolic risk factors are at higher risk of adverse pregnancy outcomes. Mediterranean-based dietary interventions have the potential to minimise these risks. We aim to evaluate the effectiveness of a simple, targeted intervention modelled on Mediterranean diet in preventing maternal and fetal complications in pregnant women with metabolic risk factors.

Methods and analysis: Pregnant women with a singleton pregnancy <18 weeks gestation, and without pre-existing diabetes, chronic renal disease and autoimmune diseases will be recruited. Women with metabolic risk factors will be randomised to receive a dietary intervention based on a Mediterranean pattern, supplemented with extra virgin olive oil and mixed nuts until delivery. The intervention will be delivered through a series of one to one and group sessions. The primary outcome is a composite maternal outcome of pre-eclampsia or gestational diabetes and a composite fetal outcome of stillbirth, small for gestational age fetus or admission to the neonatal intensive care unit. Secondary outcomes include maternal, fetal, dietary and laboratory outcomes. We aim to randomise 1230 eligible women with metabolic risk factors. We will also compare the outcomes in women with and without these risk factors. The sample size will provide us with 80% power at 5% significance, assuming a 20% loss to follow-up to detect a 30% reduction in maternal and fetal complications.

Ethics and dissemination: The ESTEEM trial is designed to provide a definitive estimate of the effects of Mediterranean dietary pattern in pregnancy on maternal and fetal outcomes. The pragmatic nature of ESTEEM ensures the applicability of its findings into clinical practice. The findings of the study will be published in peer-reviewed journals and presented at national and international scientific meetings and congresses. Ethical approval was granted by the NHS Research Ethics Committees (14/EE/1048).

Trial registration number: NCT02218931; Pre-results.

Strengths and limitations of this study

- Large sample size to provide adequate power to detect a reduction in composite maternal and fetal outcomes.
- Pragmatic design to facilitate the translation of findings into clinical practice.
- Advocating healthy lifestyle changes.
- Objective assessment of adherence.
- Unblinded intervention.
- Variations in care provision for the control group.

INTRODUCTION

Obesity is rapidly increasing worldwide adversely affecting public health.[1] Pregnant women with metabolic risk factors such as increased adiposity and dyslipidaemia are at high risk of adverse pregnancy outcomes.[2] About one in five women currently enter pregnancy as obese in the UK, leading to complications such as gestational diabetes, pre-eclampsia, stillbirth and neonatal death.[3] High levels of triglycerides and cholesterol are independent risk factors for pre-eclampsia and diabetes in pregnancy.[4 5] Poor dietary habits, sedentary lifestyle and underlying genetic predisposition all contribute to this phenomenon. Diet and physical activity based interventions have shown a beneficial effect on gestational weight gain, with varied effect on pregnancy outcomes.[6]

The Mediterranean dietary pattern has demonstrated a beneficial effect in reducing metabolic risk factors such as adiposity, hypertension and dyslipidemia.[7] In non-pregnant individuals with metabolic risk factors, a Mediterranean diet-based intervention supplemented with extra virgin olive oil

and nuts was shown to reduce cardiovascular mortality and morbidity.[8] Observational studies in pregnancy have reported a reduction in the risk of pre-eclampsia, gestational diabetes and fetal growth restriction in women with high compliance to a Mediterranean-based diet compared to those with low compliance.[9–11] However, the existing studies in this population are non-randomised, of poor quality, or focus on specific components of the diet, rather than modifying the overall dietary pattern.[6]

There is a need for an adequately powered pragmatic randomised trial to evaluate the beneficial effect of a Mediterranean diet in pregnancy that is simple, feasible and targeting women at most risk of complications.

OBJECTIVES

We aim to assess the effects of Mediterranean diet-based intervention in high-risk pregnant women to minimise maternal and fetal complications.

Our primary objective is to compare, in pregnant women with metabolic risk factors, the effect of a simple, targeted Mediterranean-based diet, supplemented with extra virgin olive oil and nuts, composed within culturally appropriate recipes and food options, on a composite maternal (pre-eclampsia or gestational diabetes) and fetal outcome (stillbirth, small for gestational age fetus or admission to neonatal intensive care unit), to current care.

The secondary objectives are to assess the effect of the dietary intervention on different individual maternal and fetal complications and on the participants' lipid profile in the two randomised groups. We will also evaluate the risk of complications in women with and without metabolic risk factors in the recruited cohort. Furthermore, we will study the effect of the dietary intervention on the risk of composite maternal and fetal outcomes in the following subgroups: obese women, women with raised triglycerides and women with chronic hypertension.

METHODS AND ANALYSIS

Study design

ESTEEM is a parallel group randomised trial embedded in a cohort study.

Setting

Secondary and tertiary care maternity units in England from September 2014 to September 2016.

Participants

Eligibility for recruitment

Women are eligible to participate in the ESTEEM study if they are pregnant with singleton fetus of <18 weeks gestation, are 16 years old or more, have a body mass index (BMI) between 18.5 and 40 kg/m^2, are able to consume nuts and olive oil, follow a Mediterranean dietary pattern and have a good understanding of written and spoken English. Participants are excluded if they have a history of pre-existing diabetes, chronic renal disease and autoimmune disease or if they are on any lipid-altering drugs, for example, statins

Eligibility for randomisation

Women will be randomised to the trial if they have any of the following risk factors: obesity (BMI ≥30 kg/m^2), raised serum triglycerides (≥1.7 mmol/L) or chronic hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic blood pressure).

Study conduct

Pregnant women will be provided with the ESTEEM Patient Information Sheet (PIS) at least 24 hours prior to the hospital booking visit to ensure that they have adequate time to consider the trial. If a participant has not read or received the PIS beforehand, the research team will explain the PIS in person. If the participant fully understands the study and is keen to join, a written consent form will be obtained. An additional written consent form will be completed prospectively to collect and store umbilical cord blood samples for use in future studies investigating the link between the maternal diet and the cord blood nutrients. Participants can still join the study if they decline the cord blood collection. Examples of both consent forms are submitted as supporting information (see online supplementary appendix 1).

Following consent, baseline information will be obtained from the participants, blood pressure will be measured, and an additional lipid profile test will be carried out to assess the participant's suitability for randomisation.

Women who fulfil the criteria for randomisation will be randomly allocated to the intervention group (Group A) or the control group (Group B). The randomisation and sequence allocation will be performed by the trial research staff via a password-protected internet-based data management system in a ratio of (1:1). Minimisation (with a random element to ensure allocation concealment) will be used to ensure balanced groups for maternal weight, gravidity and ethnicity. Women with no metabolic risk factors will be followed up as a non-randomised cohort and maternal and fetal outcomes will be obtained (Group C) (figure 1).

Women randomised to the intervention will be invited to the ESTEEM antenatal clinic to meet the study dietician or a trained allied health professional before 18 weeks, who will deliver the dietary intervention on a 1-1 basis. Women will be invited to two further sessions at 20 and 28 weeks gestation for delivery of the intervention in a group setting. Two follow-up phone calls will be made to the participants in the intervention group at 24 and 32 weeks gestation to check on their well-being, assess their compliance using the ESTEEM questionnaire and check for any adverse events (AEs).

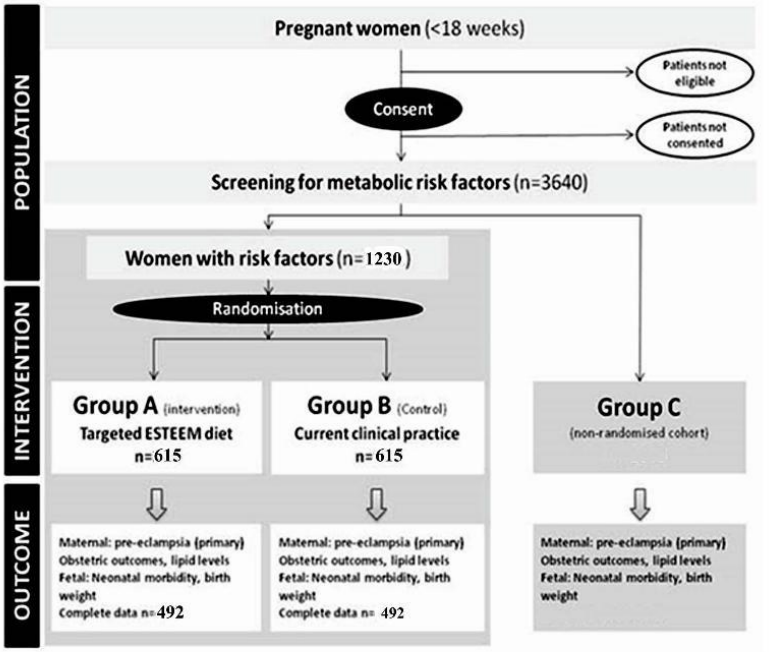

Figure 1 ESTEEM study design including the screening, recruitment and randomisation process.

Participants in the intervention group who miss the first appointment in which intervention is delivered will be given another appointment at 20 weeks of gestation. Any participant who fails to attend subsequent group sessions will be kept in the intervention group, if they continue to collect the nuts and olive oil and adhere to the intervention. Group sessions and telephone follow-ups will have a 2-week window for completion of tasks. Failure to complete the follow-up in time will be recorded as a deviation of protocol, and records will be updated accordingly.

Baseline information, as well as ESTEEM Q, IPAQ and EQ5D questionnaires, will be completed in person, over the telephone or posted to all participants in the intervention and the control groups. A final 1-1 follow-up session will be offered between 36 weeks gestation and delivery to women in both groups. The aim of this session is to assess dietary intake, physical activity, quality of life, repeat the serum lipids profile blood test and measure their weight and blood pressure (figure 2).

Health technology assessed

The ESTEEM dietary intervention is based on Mediterranean diet, with education to modify lifestyle choices. The key components of the diet include high intake of fruit and vegetables, non-refined grains, legumes, moderate to high consumption of fish, small to moderate intake of poultry and dairy products such as yoghurt and cheese, low consumption of red meat and processed meat and avoidance of sugary drinks, fast food and food rich in animal fat. In particular, ESTEEM advocates high intake of nuts (including walnuts, hazelnuts and almonds estimated at 30 g/day) and high intake of extra virgin olive oil as the main source of fat (estimated at 0.5 L/week). The intervention will include dietary education sessions, grocery shopping advice, cooking recipes for a healthy diet and advice for appropriate meal choices at restaurants.

At the first visit, the dietician or a trained allied health professional will assess the participant's dietary habits using 24 hours food recall followed by focused questions to estimate their basal dietary intake and identify elements for change towards a Mediterranean diet. Participants will be encouraged to set and record personalised goals following the SMART model (specific, measurable, achievable, relevant and time-specific) to implement the highlighted changes to their diet.[12] Women will also be asked to complete the ESTEEM questionnaire (a 12 items short dietary questionnaire specifically designed to assess the intake of Mediterranean food groups) to provide a baseline record. The participants' physical activity will be assessed using the IPAQ questionnaire,[13] and their quality of life will be assessed using the EQ-5D questionnaire.[14] The dietician or a trained allied health professional will also provide standardised education material on the benefits

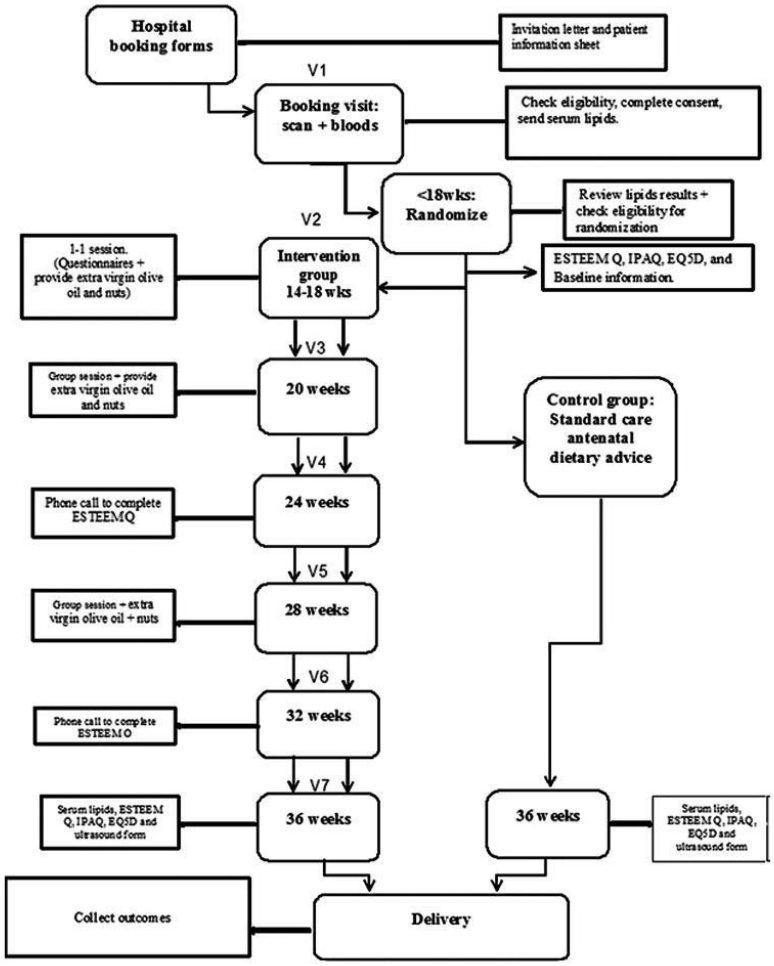

Figure 2 Flow chart of the ESTEEM study conduct.

of Mediterranean diet in pregnancy and supportive fact sheets on the benefits of nuts and extra virgin olive oil.

In the group sessions, mothers will be encouraged to involve their partners and the whole family in the dietary changes. Culturally adaptable recipes and grocery list for foods will be provided to promote intake of a Mediterranean lifestyle diet. Women will be advised to modify their current diet with a healthier option where possible, such as reducing the saturated fat and added sugar intake. Adherence to the intervention will be assessed primarily against the number of sessions attended, and if needed supplemented with dietary information collected using the ESTEEM Questionnaire at 20, 24, 28, 32 and 36 weeks gestation.

The control group will be provided with the usual antenatal dietary advice as per NICE guidelines on antenatal care, weight management in pregnancy and hypertension in pregnancy.[15–17] Folic acid and vitamin D supplementation will be provided as per national recommendations for all participants.

Umbilical cord blood samples collection and storage

Umbilical cord blood samples will be collected from all consented participants on delivery of the baby for use in future studies. Blood will be collected from the umbilical cord and the placenta using a syringe and a needle and saved in a 10 mL ethylenediaminetetraacetic acid (EDTA) dry tubes. All samples will be stored at an accredited Human Tissue Resource Centre (Barts and the London NHS Trust) and will be stored for a maximum of 72 hours at the site of collection. Samples will be then transferred to an accredited tissue bank facility (The Blizard Institute—Queen Mary University of London) to be stored in a −80°C freezer. All samples will be coded

anonymously with no information identifying the study participants. Samples will be stored in accordance with the institutional Data Protection Policy for the lifetime of the study and 10 years after its completion.

Proposed outcome measures

The primary outcome is a composite maternal outcome defined as pre-eclampsia (new onset or superimposed) or gestational diabetes; and a fetal composite outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th centile) or admission to the neonatal intensive care unit. The definitions are provided in online supplementary appendix.[2]

The secondary outcomes are as follows: maternal: pre-eclampsia, gestational diabetes, preterm delivery, gestational weight gain, antepartum haemorrhage, mode of delivery, anaemia and admission to high dependency unit or intensive care unit; fetal and neonatal: stillbirths, neonatal deaths, hypoxic ischaemic encephalopathy, birth weight (in kg using customised and population centiles) small for gestational age (<10th centile) and admission to neonatal intensive care units; dietary: nutrients and food intakes, food groups, including olive oil, vegetables, fruits, red meat, butter/margarine, sugary drinks, pulses, fish intake and commercial sweets; laboratory: levels of triglycerides, high-density lipoproteins, ratio of triglycerides and levels of non-high-density lipoprotein cholesterol.

Food frequency and ESTEEM questionnaires

The ESTEEM food frequency questionnaire (FFQ) is designed to assess habitual dietary intake over a specific reference period in a pregnant population. It was adapted from a validated FFQ specifically designed to assess the dietary intake in a pregnant Mediterranean population.[18] We adapted the ESTEEM FFQ to capture cultural foods commonly consumed in the study's multiethnic population. We obtained nutrients values from the McCance and Widdowson's Composition of foods integrated data set[19] and portion sizes from the Food Standards Agency UK portion sizes.[20] We will use the methodology reported in the EPIC FFQ design[21] to estimate dietary intake by capturing frequency data of the different nutrients and food groups.

We also developed a short food questionnaire of 12 items to assess the participants' adherence to the dietary intervention (The ESTEEM Q). The questionnaire was developed based on a similar 14 items questionnaire used in the PREDIMED trial to assess the adherence to a Mediterranean-based dietary intervention and was adopted to be used in a pregnant population.[22] We will collect both questionnaires at baseline and 36 weeks from the control and the intervention groups.

The FFQ will be validated in the pilot phase against multiple 24-hour food recalls using the multipass method in a subsample of 65 randomised participants. The agreement between daily intake of food groups, energy, macronutrients and micronutrients estimated, respectively, from the FFQ and from the 24-hour recalls will be evaluated using intraclass correlation coefficients. To graphically check the agreement between the two methods, we will use the analysis proposed by Bland and Altman,[23] using a plot of the differences between the measurements against their means. Evidence of consistent disagreement between the nutrients and food intakes will be investigated using paired t-tests. We will also identify the quintiles of intakes according to the 24-hour food recall data and the degree of gross misclassification (the proportion classified into opposite quintiles) and complete or adjacent agreement (the proportion classified into the same or an adjacent quintile) using the FFQ and 24-hour food recall data as additional indices of validity.

The FFQ will be also used to validate the ESTEEM questionnaire (ESTEEM Q) in the subsample of 65 participants. We will use reported food intakes from the FFQ to generate a response to each question on the ESTEEM. The resulting FFQ-generated ESTEEM Q total score will be compared against the actual ESTEEM Q total score.[22] The agreement between the two ESTEEM Q total scores will be evaluated using intraclass correlation coefficients. To assess the convergent validity of the ESTEEM Q total score, we will calculate the Pearson product moment correlations between the actual ESTEEM Q total score and nutrient intakes estimated from the FFQ. We will use Kappa statistics to determine the agreement between the scores for each of the 14 questions of the ESTEEM Q. We will also use the Bland–Altman method to illustrate the agreement between the scores of the FFQ and the ESTEEM Q total scores. We will use a paired t-test to investigate any consistent disagreement between the two scores.

Sample size

We expect the prevalence of the composite maternal outcome of pre-eclampsia or gestational diabetes to be 24% and expect the ESTEEM dietary intervention to reduce it by 30%. We will need 982 women to detect a 30% reduction in the primary outcome rate. After allowing for a 20% dropout, we will need to randomise 1230 eligible women to ensure an 80% power at the 5% significance level. We expect the above sample size to have an 80% power to detect a similar reduction in the composite fetal outcome rate at the 5% significance level, while allowing for a 20% loss to follow-up and a similar prevalence of 24%.

Statistical analysis

The effect of the treatment on the risk of composite maternal and fetal outcomes will be estimated as an OR with 95% CI, using a multivariable logistic regression. We will adjust for the minimisation factors, as well as age, history of previous gestational diabetes, family history of hypertensive disorders (hypertension and/or pre-eclampsia), family history of diabetes and history of stillbirth. These covariates have been selected based on prior

evidence. Secondary outcomes will be analysed using a multivariable logistic regression for binary outcomes and a linear regression for continuous outcomes, with a normalising transformation where necessary. Where a continuous outcome is also assessed at baseline, this will be adjusted for as an additional covariate. Analyses will be on an intention-to-treat basis. We do not anticipate any missing primary outcome data, as the selected outcomes should be recorded for all women and newborn infants. However, should any primary outcome data be missing, we will analyse participants with complete outcome data only. This approach is unbiased if data are 'Missing at Random'. If the primary outcome is missing for more than 5% of participants, then a sensitivity analysis will be conducted to explore the 'Missing at Random' assumption. Minimisation factors must also be non-missing for participants to be randomised.

Subgroup and secondary analysis

The primary analysis of the treatment effect on the risk of composite maternal and fetal outcomes will be repeated separately within three subgroups: obese women, women with raised triglycerides and women with chronic hypertension. These subgroups will be analysed by statistically testing for an interaction term. Subgroup-specific ORs will be reported with 95% CIs. These analyses will be secondary and given less weight in our conclusions than the primary analysis. Secondary to the intention-to-treat analysis we will perform analyses of the treatment effect which takes into account the participants' compliance with the intervention using a complier-averaged causal effect (CACE) analysis.

Internal pilot

We will dedicate the first 3 months of the study for an internal pilot to evaluate the rates of recruitment to the trial and test the trial's procedures. During the first 3 months of study's setup phase, we will obtain feedback from service users on the design of the patient information materials. During this period, we will also assess the number of pregnant women screened for recruitment, proportion of screened population who are eligible with metabolic risk factors, the adherence to the protocol, the fidelity of the follow-up, the reasons for exclusion from the trial, the proportion of eligible women participating in the trial and the reasons for which eligible women declined participation in the trial.

If more than half of eligible women are not recruited as anticipated by the end of the pilot phase, we will survey the clinical staff early to identify any issues that can be resolved to promote recruitment. Failure to recruit more than 50% of the target population over the first 6 months of recruitment will lead to a review of trial feasibility.

Data monitoring and confidential interim analysis

ESTEEM has a Trial Steering Committee (TSC) of four independent members, including a representative from APEC (Action on Pre-eclampsia), a charity dedicated to the well-being of women diagnosed to have pre-eclampsia and a service user with a history of pre-eclampsia. There are also three independent members on the Data Monitoring Committee (DMC). At the end of the pilot phase, all data will be presented to the DMC for confidential review. Recommendations of the DMC will be discussed with the TSC. There will be no gaps in recruitment to continue the momentum built-up during the pilot phase. All planned protocol amendments will be discussed and approved by the TSC, Main REC and the sponsor before taking action.

Data handling and confidentiality

The chief investigator has the overall responsibility to ensure that the participants' anonymity is protected and maintained at all times in the study. All information collected on the study participants will be kept confidential and managed in accordance with the Data Protection Act (1998-UK), NHS Caldicott Guardian (Health Service Circular: HSC 1999/012), The Research Governance Framework for Health and Social Care and the Research Ethics Committee Approval.

All data collected in the study will be entered onto a dedicated password-protected electronic database using a secure computer and internet connection. Paper case report forms (CRF) will be used as a backup if required. Data will be monitored centrally for consistency, viability, quality and screened for out-of-range errors. We will cross-check for conflicting data within and between the CRF using computerised logic checking screens. In the event of missing items or uncertainty in the records, data will be referred back to the relevant centre for clarification. Paper CRFs will be verified and processed on site by the trial coordinators or other delegated team members. Any data to be processed will be anonymised prospectively. All personal information obtained for the trial will be held securely and treated as strictly confidential. All staff members, at each hospital or the trials unit, share the same duty of care to prevent unauthorised disclosure of personal information to any unauthorised body. We will not publish any data that could lead to the identification of any study participants.

During the course of study, all records are the responsibility of the chief investigator and will be kept in secure conditions. On completion of the study, all records will be kept securely by the sponsor for a further 20 years.

Quality assurance and auditing

The chief investigator will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, good clinical practice (GCP), Trust and Research Office policies and procedures and any subsequent amendments.

Non-compliance may be captured from a variety of different sources including monitoring visits, CRFs,

communications and updates. The sponsor will maintain a log of any non-compliance to ascertain if there are any trends developing or escalating. The sponsor will assess the non-compliances and resolve it within a fixed time frame.

The study sites will perform remote trial monitoring as determined by the sponsor to verify the validity of source data. A random sample of cases will be monitored at source when site visits are performed. The documents to be verified will be randomly selected. Any major discrepancies found at a site visit would trigger a more extensive audit of trial data at the site involved.

Adverse events

Any AEs, defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities, will be recorded in the participant's individual study file, the medical notes and the CRF with appropriate follow-up by the research team.

Any serious adverse event (SAE), defined as an untoward occurrence of death, life-threatening condition, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, congenital anomaly or birth defect or any condition judged as medically significant by the investigator, will be reported to the study sponsor within 24 hours of learning of the event and to the main research ethics committee within 15 days.

ETHICS AND DISSEMINATION

NHS Research Ethics Committee approval was obtained in all centres (UK IRAS integrated research application system; reference 14/EE/1048). ESTEEM is registered online with clinicaltrials.gov (NCT02218931).

The study collaborators will hold a meeting on completing the study to discuss and evaluate the main results. The success of the study depends on the collaboration of a large number of stakeholders including doctors, nurses, midwives, nutritionists and others. Thus, the main credit for publishing the study's results will be dedicated to all collaborators equally. The trial management committee will be responsible for publishing the ESTEEM findings in high impact peer-reviewed journals. Open access publications will be sought where possible to maximise impact. All ESTEEM publications will follow the ICMJE authorship guidelines. Oral and poster presentations will be sought in national and international conferences of interest to the study topic to maximise dissemination. Individual study centres will not be permitted to publish partial data obtained from participants in the ESTEEM study without discussion with the chief investigator and/or the TSC.

DISCUSSION

Pregnancy offers an optimal period to motivate women to adhere to healthier diet and lifestyle changes.[24] The role of behavioural and dietary-based interventions has been increasingly evaluated to assess its benefit in preventing pregnancy complications. To date, no intervention has been shown to be significantly beneficial.[25]

The ESTEEM study is specifically designed to test the beneficial role of a Mediterranean-based dietary intervention in reducing metabolic risk factors in a high-risk pregnant population.

The high intake of beneficial food such as vegetables, fruits, non-refined grains, fish, extra virgin olive oil and nuts and the reduced intake of high-fat food and red meat characteristic of a Mediterranean diet have been shown to improve lipid profiles, insulin sensitivity and blood pressure.[8] This protective effect is linked to the increased intake of poly and mono-unsaturated fatty acids readily available in a Mediterranean diet compared to a modern Western diet.[26] A low ratio of unsaturated to saturated fatty acid in the diet has been linked to adverse outcomes in pregnancy such as pre-eclampsia and fetal growth restriction.[27] However, available studies are of poor quality and not sufficiently powered for specific pregnancy outcomes.[6]

The planned large study sample will provide ESTEEM with adequate power to detect a reduction in primary and secondary outcomes. The choice of the primary composite outcomes was agreed with the TSC based on input from multistakeholders in research on obesity in pregnancy.[28] Delivering the intervention via interactive educational sessions coupled with dedicated grocery lists and cooking recipes is aimed to improve the participants' adherence to the intervention.[29] Inducing and maintaining dietary changes in pregnancy and beyond could be challenging.[30]

Advocating a Mediterranean-based diet through educational intervention might not be sufficient to introduce a permanent change. Our strategy of providing cooking recipes specially developed to adopt local food culture and implement a Mediterranean cooking style could help the participants to better understand and comply with the intervention. The cost of acquiring nuts and olive oil is relatively high in the UK which could present a burden on the study participants. To improve adherence, we opted to provide the participants with extra virgin olive oil and mixed nuts throughout the study. This will also ensure the continuous availability of these nutrients throughout the lifetime of the study. The group sessions are aimed to reinforce the knowledge and the education on the benefits of Mediterranean diet, promote healthy eating habits, healthy shopping and sharing experiences among participants and will provide opportunities to explore obstacles and potential solutions.

Assessing adherence to the intervention is crucial to accurately interpret dietary trials' results. Using multiple food diaries is generally considered to be the golden standard tool for assessing dietary intake in dietary interventional trials.[31] However using this tool in a pregnant population can be quite cumbersome particularly for participants who care for large families and are in full-

time employment. While using an FFQ might offer a better and more efficient substitute, it still requires relatively high literacy, a characteristic not always available in our population of interest. It can also be less sensitive to detect subtle changes in the dietary intake compared to food diaries and 24 hour recalls.[32] FFQs must also be validated within the study population.[31] This might be a challenging task in ESTEEM due to the large variation in ethnic groups, food cultures and dietary habits in our population.

The use of a short screening tool such as the ESTEEM Q will offer an easy and sensitive tool to assess the intake of the nutrients of interest in the Mediterranean diet such as extra virgin olive oil and nuts. Introducing this short tool is far less complicated and can even be conducted over the phone which will help to improve returns. The limitation of using such tool is the limited information collected on the whole diet and the narrow focus on the Mediterranean nutrients' intake. Women will be recruited from multiple maternity units in the UK, which will allow us to recruit a multiethnic population with diverse food cultures. This will render ESTEEM findings more generalisable and transferable to clinical practice.

Some of the limitations in the design of the trial could affect the interpretation of its findings. The nature of the intervention makes it difficult to blind the participants and the clinicians, which could introduce bias. Furthermore, the control group will vary in the level of care available to mothers at various maternity units. For example, in some units, dietician support is provided for women with a BMI $\geq$30 kg/m^2 compared to >35 kg/m^2 or none in other units. It is also possible that knowledge of potential benefits of the study may motivate some women in the control group to follow the Mediterranean lifestyle, which could bias the results.

Poor adherence to the intervention is clearly an important factor that could bias the results of the trial. Using self-reporting dietary tools such as the FFQ and the ESTEEM Q will help us to estimate the adherence to the dietary intervention. We will conduct a sensitivity analysis of the treatment effect which takes account of the compliance rate defined by the attendance rate to the intervention sessions throughout the study.

A better assessment of the dietary intake could be achieved by using specific biomarkers such as hydroxytyrosol for olive oil intake and α-linolenic acids for nuts intake. Biomarkers offer an accurate and objective assessment of the nutritional intake. Their use, however, still has a number of limitations; it only offers a snapshot view of the intake over a limited time period and can be a relatively expensive and invasive tool.[33] Recording the return of empty packages can also provide a snapshot view of the consumption of provided nutrients, however, it is less specific and representative of the participant's individual intake.

There is increasing evidence on the possible benefit of Mediterranean diet on long-term childhood and maternal outcomes. Observational data have shown a potential reduction in childhood asthma and eczema following in utero exposure to the diet.[34] Furthermore, the effects of nut exposure to pregnant mothers on subsequent nut allergy in children needs evaluation. The effect of Mediterranean diet on future risk of type 2 diabetes in these women at high risk of metabolic factors is not known.

CONCLUSIONS

The ESTEEM trial will evaluate the benefit of a Mediterranean-based diet to reduce the risk of complications in pregnant women with high metabolic risk factors.

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Online health information on obesity in pregnancy: a systematic review

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ABSTRACT

Objective: To assess the quality of health information available online for healthcare users on obesity in pregnancy and evaluate the role of the internet as an effective medium to advocate a healthy lifestyle in pregnancy.

Study design: We used the poly-search engine Polymeta and complimented the results with Google searches (till July 2015) to identify relevant websites. All open access websites in English providing advice on the risks and management of obesity in pregnancy. Two independent reviewers assessed the quality of information provided in each of the included websites for credibility, accuracy, readability, content quality and technology. We compared websites 'quality according to their target population, health topic and source of funding'.

Results: Fifty-three websites were included. A third of websites were focused on obesity in pregnancy and two thirds targeted healthcare users. The median value for the overall credibility was 5/9, 7/12 for accuracy, 57.6/100 for readability, 45/80 for content quality and 75/100 for technology. Obesity specific websites provided lower credibility compared to general health websites ($p = 0.008$). Websites targeting health users were easier to read ($p = 0.001$). Non-governmental funded websites demonstrated higher content quality ($p = 0.005$). Websites that are obesity focused, targeting health users and funded by non-governmental bodies demonstrated higher composite quality scores ($p = 0.048$).

Conclusions: Online information on obesity in pregnancy is varied. Governmental bodies in particular need to invest more efforts to improve the quality of online health information.

Introduction

The epidemic of obesity continues to be a major health challenge worldwide [1], particularly in women of childbearing age [2]. About one in five women in this age group are obese with increased prevalence in high-income countries such as the USA (34%) and the UK (25%) [3]. Pregnant women with obesity have an increased risk of complications such as gestational diabetes, pre-eclampsia, stillbirth and cesarean section [2]. Early adoption of dietary and lifestyle interventions have the potential to reduce these risks in pregnancy [4,5]. The chief Medical Officer of England has emphasised the importance of encouraging women of childbearing age to adopt a healthier lifestyle to combat obesity before pregnancy [6].

Effective, cheap, innovative and widely adopted interventions are needed to improve women's health. The Internet is now one of the most consulted sources by women for health information in developed countries. The quality of health information provided online for healthcare users, in general, is inconsistent [7]. Poor quality information, particularly those targeting women, can adversely influence mother's behaviour leading to worse health outcomes [8].

The quality of health information available online on risks and management of obesity in pregnancy is not known. We systematically evaluated the quality of online information on the topic of obesity in pregnancy.

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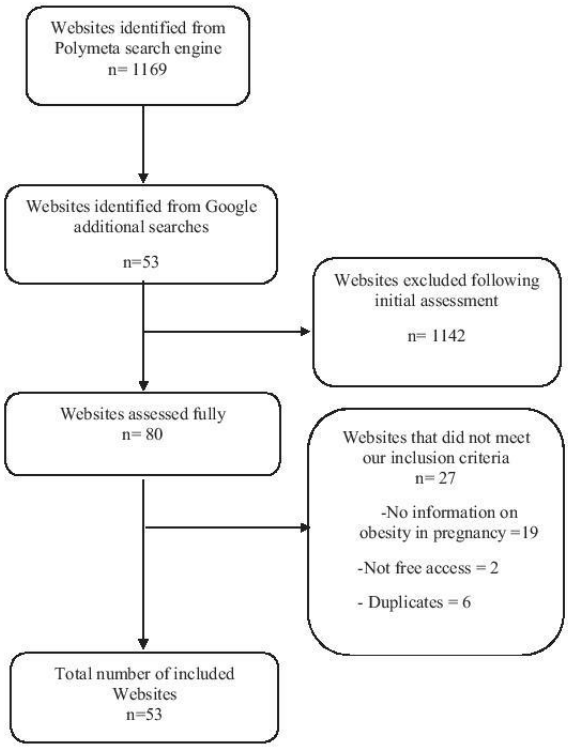

Fig. 1. Flow chart of the selection and inclusion process for websites providing health information on obesity in pregnancy.

for the overall credibility of websites was 5/9 (range 1–8), 7/12 for accuracy (range 2.5–11), 57.6/100 for readability (range 25–89.4) and 45/80 for content quality (range 20–62).

The overall median technology quality value was 75/100 (range 40–99). The value of the different technology assessment criteria included the following: 72/100 for accessibility (range 41–97), 72/100 for user experience (range 33–92), 73/100 for marketing score (range 11–98) and 62/100 for informatics (range 42–91).

Obesity specific websites had higher credibility scores compared to general health websites ($p = 0.008$). There was no statistically significant difference between those two groups for any of the remaining quality criteria. There were no significant differences in any of the quality criteria between websites targeting the general population and those targeting healthcare users, except for readability score which was higher in the latter group ($p = 0.001$). There was a significant association between the source of funding and the content quality with NGO funded websites scoring the highest compared to governmental and commercial websites ($p = 0.005$). None of the remaining quality criteria was affected by the source of funding. Table 2 summarizes the scores across the different quality criteria between websites groups.

The mean composite quality scores were not different between any of the websites groups.

Linear regression revealed that NGO websites that are obesity specific and targeting healthcare users were associated with higher composite quality compared to other websites ($\beta = 0.410$, $p = 0.048$). Table 3 summarises the composite quality scores of the different websites groups.

Comment

Summary of findings

Our review highlights the wide variation in the quality of online health information provided on obesity in pregnancy. We captured a relatively high number of websites addressing this health issue, with the majority of websites from the USA and the UK. This could be explained by the more developed role of online information in healthcare provision in these two countries compared to other English speaking countries. Most of the included websites were dedicated to women and healthcare consumers, emphasising the increasing role of the Internet in healthcare information provision [16]. There was a slightly higher number of NGO funded websites compared to governmental and commercial ones. However, the role of funding did not significantly affect the overall quality of health information provided by the included websites. We record an overall good level of technology quality in most included websites, this could be explained by an overall improvement in the available websites building tools [17]. Interestingly technological quality of NGO funded websites was comparable to governmental and commercial websites that traditionally enjoyed better funding. A number of included websites were started by individuals and small charities and had relatively good quality scores (e.g. whattoexpect.com). Such focused and dedicated websites were able to demonstrate higher quality on our scoring criteria compared to more general ones.

General health websites enjoyed better credibility compared to obesity focused ones. This could be attributed to the large investment and focus on quality enjoyed in the first group. Unsurprisingly websites targeting healthcare users employed much simpler and understandable language resulting in higher readability scores. This difference is to be expected as most of the general focus websites targeted health professionals such as GPs and obstetricians using complex medical language often difficult to comprehend fully by a lay person.

The DISCREN tool revealed better content quality in the NGO funded websites. This is a significant finding as governmental websites are expected to provide higher content quality in view of the high investment available. This highlights the lacking role of governmental health bodies in investing and developing online based innovative healthcare delivery systems.

The distribution of the composite quality scores was relatively wide. This echoes a general trend of mixed quality in portraying health information online and poor adherence to well-established guidelines on best methods to convey such information [7].

Strength and limitations

To our knowledge, this review is the first to assess the quality of information available online on obesity in pregnancy. We used a well-established methodology [10] to assess the quality of reported information. DISCREN is a valid and reliable questionnaire developed to help users and healthcare providers to assess the quality of provided information on treatment choices. Recent evidence advocates the important role of informatics in improving the usability of online health information [18]. This prompted us to assess the technological quality and correlate it with the overall quality of information reporting. We developed a comprehensive search strategy and used a multi search engine software to include the maximum number of websites available on the topic of interest. The high level of agreement between the two assessors' scores amplifies the validity of the information quality assessment process.

Our results were limited by the number of websites included. Using additional search engines might have revealed more

Table 1
Characteristics of included websites.

Website URL	Country	Obesity specific	Healthcare user focused	Listed authors	Patient forum	Privacy statement	Source of funding	Composite quality score
aafp.org	USA	No	No	Yes	No	Yes	NGO	0.16
acog.org	USA	No	Yes	No	No	Yes	NGO	0.53
babycenter.com	USA	No	Yes	Yes	No	Yes	NGO	0.96
babycentre.co.uk	UK	No	Yes	No	Yes	Yes	NGO	1.09
beststart.org	CAN	Yes	No	No	No	No	NGO	−0.32
cdc.gov	USA	No	Yes	No	No	Yes	GOV	−0.01
commonhealth.wbur.org	USA	No	Yes	Yes	Yes	Yes	NGO	0.07
contemporaryobgyn.modernmedicine.com	USA	No	No	Yes	No	Yes	NGO	0.12
cuh.org.uk	UK	Yes	No	No	No	No	GOV	0.01
esht.nhs.uk	UK	Yes	Yes	Yes	No	No	GOV	−0.04
fitpregnancy.com	USA	No	No	Yes	No	Yes	NGO	−0.08
gloshospitals.nhs.uk	UK	Yes	Yes	No	No	No	GOV	−0.19
gponline.com	UK	No	No	Yes	No	Yes	NGO	0.26
health.ny.gov	USA	No	No	No	No	Yes	GOV	−0.42
health.qld.gov.au	AUS	Yes	Yes	No	No	No	GOV	0.74
health.ucsd.edu	USA	No	Yes	No	No	Yes	COM	−0.42
hqip.org.uk	UK	No	No	Yes	No	No	NGO	0.34
hse.ie	IRE	No	No	No	No	No	GOV	0.35
instituteofmidwifery.org	USA	No	No	Yes	No	No	NGO	−0.43
ivfplus.com.au	AUS	No	Yes	No	No	No	COM	−0.67
keepingyouwell.com	USA	No	Yes	No	No	Yes	COM	−0.79
mainlinegi.com	USA	No	Yes	Yes	No	Yes	COM	0.38
marchofdimes.org	USA	No	Yes	No	Yes	Yes	NGO	0.62
markscrogginsmd.com	USA	No	Yes	No	No	No	COM	−0.67
mayoclinic.org	USA	No	Yes	No	No	Yes	COM	0.43
netmums.com	UK	No	Yes	No	Yes	Yes	NGO	−0.20
newkidscenter.com	USA	No	Yes	No	No	No	NGO	−0.39
nhs.uk	UK	No	Yes	No	Yes	No	GOV	0.70
nichd.nih.gov	USA	No	No	No	No	Yes	GOV	−0.30
noo.org.uk	UK	No	No	Yes	No	Yes	GOV	−0.10
obesityaustralia.org	AUS	Yes	Yes	Yes	No	Yes	NGO	−0.08
obfocus.com	USA	No	Yes	No	No	Yes	COM	−0.26
parents.com	USA	No	Yes	Yes	No	Yes	COM	0.33
patient.info	UK	No	Yes	Yes	Yes	No	NGO	0.04
plus-size-pregnancy.org	USA	Yes	Yes	No	No	Yes	NGO	−1.68
plymouthhospitals.nhs.uk	UK	Yes	Yes	No	No	No	GOV	−0.51
pwhce.ca	CAN	No	No	Yes	No	No	NGO	−0.33
qegateshead.nhs.uk	UK	Yes	Yes	Yes	No	No	GOV	−0.25
raisingchildren.net.au	AUS	No	Yes	Yes	Yes	Yes	NGO	0.80
rcog.org.uk	UK	Yes	Yes	No	No	No	NGO	0.96
rdehospital.nhs.uk	UK	Yes	Yes	No	No	No	GOV	0.03
royalberkshire.nhs.uk	UK	Yes	Yes	Yes	No	No	GOV	−0.19
sahealth.sa.gov.au	AUS	Yes	Yes	No	No	No	GOV	−0.93
seslhd.health.nsw.gov.au	AUS	No	Yes	No	No	No	GOV	0.14
stockport.nhs.uk	UK	Yes	Yes	No	No	No	GOV	0.62
tommys.org	UK	Yes	No	Yes	No	Yes	NGO	0.37
uhs.nhs.uk	USA	Yes	Yes	No	No	No	GOV	0.24
urmc.rochester.edu	USA	No	Yes	No	No	Yes	NGO	−0.69
webmd.boots.com	USA	No	No	Yes	No	Yes	COM	0.54
webmd.com	USA	No	No	Yes	No	Yes	COM	−0.23
whattoexpect.com	USA	No	Yes	Yes	No	Yes	NGO	0.74
womenandinfants.org	USA	No	Yes	No	No	Yes	COM	−1.02
yourplussizepregnancy.com	USA	Yes	Yes	No	No	Yes	COM	−0.36

AUS: Australia.
IRE: Ireland.
USA: United States of America.
UK: United Kingdom.
NGO: Non-governmental organisation.
GOV: Governmental.
COM: Commercial.

relevant websites. We only included websites written in English. The accuracy of information assessment was performed selectively against two peer-reviewed guidelines with no patients' input. Other aspects of managing obesity in pregnancy such as infertility and postpartum care might be equally interesting to women, but they were outside our scope.

Implications for practice

With the ever increasing rate of obesity worldwide, there is a great need for cheap and effective interventions to address this health issue [4]. The traditional health delivery model is failing to stop the progressive spread of obesity and more innovative, cheap

Table 2
Summary of information and technology scores per websites group. Quality is summarised per median and range for each domain.

	Credibility			Accuracy			Readability			Content quality			Technology		
	Median	Range	P value	Median	Range	P value	Median	Range	P value	Median	Range	P value	Median	Range	P value
Obesity specific	4	1–7	0.008	7	3–11	0.6	50	25–89	0.49	47	20–60	0.14	77	40–99	0.09
General health	5.5	2–8		7.5	3–11		58	40–70		44	20–62		72	47–83	
Healthcare user focused	5	1–8	0.97	7	3–11	0.32	60	31–89	0.001	44	20–62	0.56	75	50–89	0.69
General focus	5.2	4–7		8	5–11		45	25–67		49	35–62		77	40–99	
Commercial	5	2–7	0.12	6	4–11	0.43	54	31–89	0.61	37	20–45	0.005*	74	50–99	0.87
Governmental	4.5	3–7		7	3–11		55	36–70		47	30–62		75	60–89	
NGO	5.5	1–8		8	3–11		59	25–72		49	20–62		76	40–85	

* Post-hoc analysis: Com vs Gov p = 0.003. Gov vs NGO p = 0.47. Com vs NGO p = 0.004.

Table 3
Mean standardised composite quality scores and standard deviation per websites group.

	Composite score		P value
	Mean	SD	
Obesity specific	−0.09	0.62	0.30
General health	0.74	0.49	
Healthcare user focused	0.0019	0.63	0.97
General focus	−0.003	0.31	
Commercial	−0.22	0.53	0.206
Governmental	−0.0061	0.43	
NGO	0.12	0.63	

and effective systems are needed. Online sources have a number of advantages to facilitate the delivery of such interventions like easy accessibility, cheap set up, 24 h access and potentials to record individual patient data safely and interactively [16]. Care for obese women is shared among different medical specialists before, during and after pregnancy, this often leads to fragmented advice and poor continuity of care. Providing reliable and consistent health information online could help standardising the provided advice. This is particularly applicable in the postpartum period where often continuity of medical care is lost and the chance for retaining gained weight is higher [19].

Online healthcare information, in general, is still of mixed quality [7] and limited measurable applicability [20]. The American Medical association (AMA) has published a set of guidelines on best practice in developing healthcare dedicated websites [21]. However, the applicability of these guidelines is still limited [22]. Medical professionals have an important role to play in the process of improving the quality of online information by recommending good quality websites, promoting effective techniques in evaluating and searching for health information and getting involved in the development of standards for health websites [7]. Official and governmental bodies need to invest more efforts in improving the quality of information provided to the public to combat obesity in pregnancy and the society as a whole. Further involvement of the public and health charities in designing and providing health information online might help improve the quality of provided information. Healthcare professionals should guide their patients to good quality websites as reliable sources of information. The quality of NGO funded websites specifically targeting this health issue was associated with higher quality information than other sources and women should be encouraged to use them. Our review helps in identifying good quality websites to advise healthcare users and highlights the efforts needed to improve the quality of future work.

Conclusion

Online information on obesity in pregnancy is varied, more work is needed to standardise and improve the quality of reporting of online health information on this topic. Governmental bodies in particular need to invest more efforts to improve the quality of health information provided online on obesity in pregnancy.

Conflict of interest

The authors have nothing to declare.

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Authors' contribution

BHA conceived the idea, analysed the data and wrote first manuscript. CP and HL conducted the search and extracted data. ST and JZ provided vital input to the manuscript.

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Appendix A. Supplementary data

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REVIEW

Use of dietary assessment tools in randomized trials evaluating diet-based interventions in pregnancy: a systematic review of literature

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Purpose of review
Accurate assessment of dietary intake in interventional trials is the key to evaluate changes in dietary behaviour and compliance. We evaluated the use of dietary assessment tools in randomized trials on diet-based interventions in pregnancy by a systematic review.

Recent findings
We updated our previous search (until January 2012) on trials of diet and lifestyle interventions in pregnancy using Medline and EMBASE up to December 2015. Two independent reviewers undertook study selection and data extraction. We assessed the characteristics of dietary assessment tools, the timing and frequency of use and any validation undertaken.
Two-thirds (39/58, 67%) of the included studies used some form of tools to assess dietary intake. Multiple days' food diaries were the most commonly used (23/39, 59%). Three studies (3/39, 8%) validated the used tools for in a pregnant population. Three studies (3/39, 8%) prespecified the criteria for adherence to the intervention. The use of dietary assessment tools was not associated with study quality, year of publication, journal impact factor, type of journal and the study sample size.

Summary
Although self-reporting dietary assessment tools are widely used in interventional dietary trials in pregnancy, the quality and applicability of existing tools are low.

Keywords
assessment, diet, intervention, pregnancy, systematic review

INTRODUCTION

Maternal nutritional status before and during the pregnancy has a significant influence on pregnancy-related outcomes [1]. Diet and lifestyle interventions in pregnancy reduce gestational weight gain and have the potential to improve other outcomes such as gestational diabetes, preeclampsia and preterm delivery [2,3▪].

Dietary interventional trials use a variety of tools to evaluate participants' habitual dietary pattern, the effect of the intervention on dietary intake and participants' compliance with the intervention. Such tools have to be reliable, accurate and valid to improve the interpretation of the study findings [4]. Clinical trials in nonpregnant population traditionally use dietary histories as a gold standard to capture participants' dietary intake [4]. This is often time and cost consuming in large trial settings mandating the use of other short-term tools such as short food diaries and food frequency questionnaires (FFQs) [5–7].

Pregnancy poses unique challenges for reliable assessment of dietary intake, due to its physiological changes, pregnancy-related conditions such as excessive vomiting and variation in energy

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KEY POINTS

- Self-reporting dietary assessment tools are the most commonly used in dietary trials in pregnancy. This practice does not seem to correlate with the study quality, publication journal or study sample.
- Three days food diary is the most commonly used dietary assessment method in pregnancy.
- Pregnancy increases both the systematic and random reporting errors in dietary assessment tools.
- The role of objective biomarkers to assess dietary intake in pregnancy is still limited and further research is needed to determine their validity, reliability and applicability.

requirement per trimester [8]. These changes can significantly reduce the reliability of dietary assessment in pregnancy and increase the risk of bias in the trial's findings [9]. We undertook a systematic review to assess the characteristics and quality of dietary assessment tools used in randomized trials on pregnant women and the factors associated with their use.

METHODS

Literature search and study identification

We updated our previously published search for randomized studies on diet and lifestyle interventions in pregnancy (January 2012) using Medline and EMBASE until December 2015 to identify any new studies. The search strategy was designed in a multistep process by combining search terms related to pregnancy and diet [2]. There were no language restrictions (Appendix 1). AQ4

Study selection

We included all randomized trials of dietary interventions in a pregnant population. We obtained details of the dietary assessment tool and the outcomes measures. Two independent reviewers (B.H.A.W. and B.M.L.) performed the study selection process in two stages. First, we screened the full titles and abstracts of all identified citations for potentially relevant articles. Second, we obtained the full manuscripts of all potentially relevant articles and assessed their eligibility against our inclusion criteria. Any discrepancies were resolved by discussion with the third reviewer (S.T.). We excluded studies in animals and those in nonpregnant population.

Quality assessment of included studies

We assessed the quality of included randomized studies using the Jadad score [10]. One point was awarded for each of the following: study described as randomized, the randomization method was appropriate; the study was described as double blinded, the allocation method was appropriate; withdrawals and dropouts were described. Studies with a score above 3 were considered to be of high quality. A score of 3 was considered to be of moderate quality and studies with a score of 2 or less were considered to be of low quality.

Data extraction and analysis

Two independent reviewers extracted data using predesigned data extraction forms (C.M. and B.M.L.). We collected data on details such as the study design, country of study, journal impact factor, study population characteristics, type of dietary intervention evaluated and the outcomes. We recorded the type of dietary assessment tools used, time and frequency of use in pregnancy, and whether the authors evaluated the validity and reliability of the tool in the study population. Journals with an impact factor of more than 10 were considered to be of high impact.

We used logistic regression modelling to assess the effect of study quality, year of publication, journal impact factor, journal type (general vs. specialist) and study sample size on the probability of using dietary assessment tools in clinical trials. Statistical analysis was conducted using SPSS (V20) and Microsoft Excel (2007). AQ5

RESULTS

From 19 563 potentially relevant citations, 58 randomized trials assessed dietary intervention. Of these, only 39 studies used a dietary assessment tool and were included in our review. Figure 1 shows the details of the study selection process.

Characteristics of the studies using dietary assessment tools

Overall, 9728 pregnant women were included in 39 studies. Five studies targeted pregnant women with a BMI at least 30 (5/39, 13%), and 21 included pregnant women with any BMI (21/39, 54%). Three studies recruited women at high risk for gestational diabetes (3/39, 8%), and 10 evaluated the effect of diet on women with gestational diabetes (10/39, 26%). The intervention consisted solely of dietary counselling in 30/39 (77%) studies and a combination of dietary and physical activity advice in 9/39 (23%) studies.

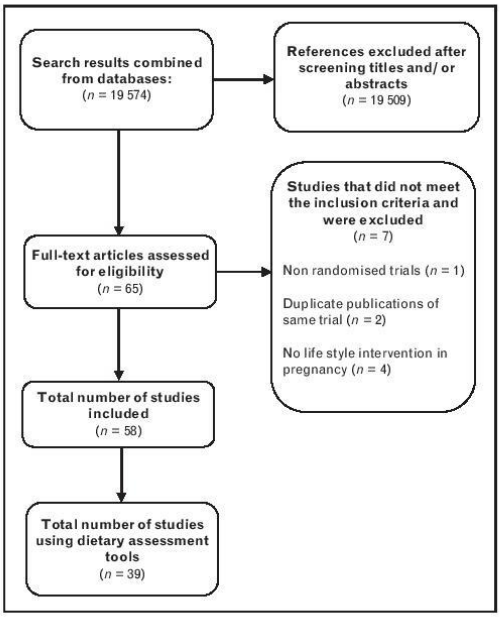

FIGURE 1. Identification and selection of studies that used dietary assessment tools to evaluate the effects of diet based interventions in pregnancy on maternal and fetal outcomes.

The majority of studies introduced the dietary intervention by the end of the second trimester (35/39, 90%).

Most studies were conducted in the United States of America (10/39, 27%), followed by Australia (6/39, 15%). Five studies (5/39, 13%) were published in general medical journals and the rest in specialist journals. Only two were published in high impact factor journals (impact factor >10). Table 1 provides a brief summary of the characteristics of the included studies.

Characteristics of dietary assessment tools

Short-term food diaries were most commonly used to assess dietary intake in trials (23/39, 59%), followed by FFQs (12/39, 31%) and 24-h recalls (8/39, 20%). Four studies used two assessment tools jointly [11–14]. The types of food diaries varied in duration: 3-day (13/23, 57%), 4-day (1/23, 4%), 5-day (1/23, 4%) and 7-day diaries (8/23, 35%). Only two studies used weighted food diaries [11,15] FFQs varied in the number of items included from 13 to 181. Six studies (6/39, 15%) used modified FFQs that were previously validated in a similar or different study population [16,17▪,18–21,22▪].

Three studies validated the dietary assessment tools used in the study population [13,23,24]. Of these, two (2/39, 5%) developed and validated the FFQ in the study population using nonweighted 5-day food diaries [24] and 24-h recall [13]. One study validated the content of the 24-h recall via a panel of experts [23]. Four trials (4/39, 10%) defined criteria for adherence to the dietary [24,25,26▪,27]. Three studies used biomarkers to assess the effectiveness of the intervention [11,15,19], and one used biomarkers to assess adherence to the intervention and change in dietary intake [22▪] (Table 1).

Quality assessment of studies using dietary assessment tools

The randomization method was appropriate in 72% of included studies (28/39, 72%). Only three studies were described as blinded (3/39, 8%) and of these blinding, and allocation was appropriate in only two (2/39, 5%). More than two-thirds of included studies described the losses of follow-up and withdrawals in the studies (32/39, 82%) (Fig. 2).

Factors associated with use of dietary assessment tools

The use of dietary assessment tools in trials was not associated with study quality ($P = 0.10$), year of publication (before or after 2005) ($P = 0.88$), journal impact factor ($P = 0.48$), type of journal (general vs. specialist) ($P = 0.33$) or the study sample size ($P = 0.19$).

DISCUSSION

Our review summarizes the use and quality of dietary assessment tools in randomized trials on dietary interventions in a pregnant population. Less than two-thirds of interventional studies included such an assessment tool. This practice did not seem to correlate with the study quality, publication journal or study sample. Self-reporting tools were the most commonly used, consistent with interventional dietary studies outside pregnancy [28].

Strengths and limitations

We performed a comprehensive review of the methods used to assess dietary changes in pregnancy. The trials were identified by a systematic review using a sound methodology, with no search limitations. We assessed the risk of bias and methodological quality of all included studies. We assessed the type of dietary tools, their validity and identified factors associated with their use in

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Table 1. Characteristics of randomized controlled trials on pregnant women using dietary assessment tools

Author and year	Country of study	Journal	Characteristics of intervention population	BMI	GA at intervention	Dietary intervention	Diet assessment tool
Asemi *et al.* (2014)	Iran	European Journal of Clinical Nutrition	Primigravida, age 18–40, diagnosed with GDM at 24–28 week gestation	Any	24–28 weeks	DASH diet was rich in fruits, vegetables, whole grains, low-fat dairy products, low in saturated fats and cholesterol, refined grains and sweets	Weekly 3-day dietary records (2 week day and one weekend day)
Bechtel-Blackwell *et al.* (2002)	USA	Clinical Nursing Research	African American primagravidas, age 13–18	Any	First trimester to early second trimester	Nutritional education	CASI (24 h dietary recall + general nutrition questions)
Bo *et al.* (2014)	Italy	Diabetes, Obesity and Metabolism	Age 18–50; GDM diagnosis, singleton pregnancy	<40	24–26 weeks	Individually prescribed diet + physical activity	FFQ
Bosaeus *et al.* (2015)	Sweden	Nutrional Journal	Age 20–45, European decent, nondiabetic, no neuroleptic drugs, and vegetarianism or veganism	18.5–24.9	12–18 weeks	Individualized dietary counselling	FFQ
Briley *et al.* (2002)	USA	Journal of The American Dietetic Association	African American with no preexisting health conditions or diet	Any	<24 weeks	In home, prenatal nutritional advice	24 h recalls
Ferrara *et al.* (2011)	USA	Diabetes Care	Singleton pregnancy with gestational diabetes, age ≥18, English speaking	Any	After diagnosis of GDM	DEBI for women with gestational diabetes	7 days dietary fat intake diary
Grant *et al.* (2011)	Canada	Diabetes Research and Clinical Practice	Age 18–45, diagnosed with GDM or IGT, no chronic illness affecting carbohydrate metabolism; No type 1 or type 2 diabetes; not using insulin before providing consent	Any	<34 weeks	Dietary counselling on nonstarchy food	3 days food diary
Grant *et al.* (2011)	Canada	Diabetes Research and Clinical Practice	Singleton pregnancy, age 18–45, diagnosed with GDM.	Any	28 weeks	Patients introduced to diabetes food guide and current Canadian dietary recommendations	3 days diary + FFQ
Guelinckx *et al.* (2010)	Belgium	The American Journal of Clinical Nutrition	Obese white pregnant women <15 weeks gestation	>29	15 weeks	Nutritional advice from a brochure ± lifestyle education by a nutritionist	7 days food diary
Hauner *et al.* (2012) (Infant)	Germany	The American Journal of Clinical Nutrition	Singleton pregnancy. Age 18–43. <15 weeks gestation, willing to implement the dietary recommendations, sufficient German language skills	18–30	15 weeks	Fish oil supplement + vitamin E daily during pregnancy and lactation + detailed nutritional counselling from trained research assistants	7 days food diary
Hawkins *et al.* (2015)	USA	Diabetic Medicine	Hispanic women age18–40, no history of Type 2 diabetes, hypertension, heart disease or chronic renal disease; no current medications adversely influence glucose tolerance; planning to continue the pregnancy to term	≥25	<18 weeks	In-person behavioural counselling sessions and 30 min of moderate-intensity activity per week	24 h recalls
Hui *et al.* (2011)	Canada	British Journal of Obstetrics and Gynaecology	Nondiabetic urban-living pregnant women (<26 weeks gestation)	Any	26 weeks	Community-based group exercise sessions + home exercise and dietary counselling	3 days food diary

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Table 1 (*Continued*)

Author and year	Country of study	Journal	Characteristics of intervention population	BMI	GA at intervention	Dietary intervention	Diet assessment tool
Ilmonen *et al.* (2011)	Finland	Clinical Nutrition	Pregnant women less than 17 weeks gestation and no metabolic diseases	Any	<17 weeks	Dietary counselling with probiotics or placebo	3 days food diary
Jackson *et al.* (2010)	USA	Patient Education and Counselling	English speaking, ≥18 years, <26 weeks gestation	Any	26 weeks	Teaching and counselling session about nutrition, exercise and weight gain using the (Video Doctor)	FFQ (18 items)
Jeffries *et al.* (2009)	Australia	Medical Journal of Australia	English speaking, ≤14 weeks gestation, age 18–45 years	Any	14 weeks	Nutritional advice	Eating habit questionnaire (used to distract from aim of project)
Jelsma *et al.* (2013)	Netherlands	BMC Pregnancy & Childbirth	Pregnant women at risk of GDM < 19 + 6 weeks. Singleton pregnancy, age <18 years	>29	<19 weeks + 6 days	Five Individual sessions and 4 optional telephone calls with lifestyle coach. Daily intake of Vitamin D	3 days food diary + FFQ (12 items)
Khoury *et al.* (2005)	Norway	American Journal of Obstetrics and Gynecology	Singleton pregnancy, nonsmoking, white ethnicity, age 21–38	19–32	17–18 weeks	Nutritional advice, low Cholesterol diet and supplement intake in pregnancy	7 days weighed dietary diary
Kiefferv *et al.* (2014)	USA	American Journal of Public Health	Hispanic pregnant women, age <18 years, resident in southwest Detroit residents, <20 weeks gestation	Any	<20 weeks	Healthy Mothers on the Move dietary program implemented in 2 home visits and 9 group meetings over 11 weeks	FFQ
Korpi-Hyovalti *et al.* (2012)	Finland	The British Journal of Nutrition	Pregnant women at high risk of gestational diabetes	Any	12 weeks	Dietary and lifestyle advice	4 days food diary
Luoto *et al.* (2011)	Finland	PLOS Medicine	Pregnant euglycaemic women, 8–12 weeks gestation, at least one risk factor for GDM	Any	8–12 weeks	Individual intensified counselling on physical activity, diet and weight gain	FFQ (181 items)
Man Shek *et al.* (2014)	China	Arch Gynecol Obstet	Chinese, residents in Hong Kong, age ≥18, diagnosed with IGT but otherwise in general good health, understand Chinese language	Any	28–30 weeks	Dietary advice, individual optimal caloric intake measured, individual counselling by a registered dietician	5 days food diary
Moreno-Castilla *et al.* (2013)	Spain	Diabetes Care	Age 18–45, singleton pregnancy, diagnosis of GDM <35 weeks	Any	<35 weeks	Individualized dietary advice	3 days food diary
Moses *et al.* (2009)	Australia	Diabetes Care	Age 18–45, singleton pregnancy, no previous GDM, nonsmoker, diagnosis of GDM	Any	28–32 weeks	Individualized dietary advice	3 days food diary
Moses *et al.* (2009)	Australia	American journal of Nutrition	<20 weeks gestation, singleton pregnancy, age >18, ability to read and understand English	Any	20 weeks	Detailed dietary education tailored for the assigned diet	3 days food diary
Moses *et al.* (2014)	Australia	The American Journal of Clinical Nutrition	<20 weeks gestation, singleton pregnancy, 18 years or older, read and understand English	Any	<20 weeks	Detailed dietary education tailored for assigned diet and individual requirements for pregnancy	3 days food diary
Petrella *et al.* (2013)	Italy	Journal of Maternal-Fetal & Neonatal Medicine	Age >18 years, singleton pregnancy	≥25	12 weeks	TLC Program	FFQ (158 items)

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Table 1 (*Continued*)

Author and year	Country of study	Journal	Characteristics of intervention population	BMI	GA at intervention	Dietary intervention	Diet assessment tool
Polley *et al.* (2002)	USA	International Journal of Obesity	Age >18 years, singleton pregnancy, gestation <20 weeks	≥19.8	20 weeks	Education about weight gain, healthy eating, and exercise	Short FFQ (13 items)
Poston *et al.* (2013)	UK	BMC Pregnancy & Childbirth	Obese, singleton pregnancy, gestation 15–18 weeks	≥30	15–18 weeks	One-to-one and group sessions with health trainer providing dietary and physical activity advice	24 h recalls + short FFQ
Quinlivan *et al.* (2011)	Australia	Australian and New Zealand Journal of Obstetrics and Gynaecology	Singleton pregnancies, obese or overweight, English speaking	≥25	Not reported	Dietary advice and clinical psychology	24 h itemized food consumption recalls
Rae *et al.* (2000)	Australia	Australian and New Zealand Journal of Obstetrics and Gynaecology	Pregnant women with GDM	>110% of ideal body weight	<28 + 1 weeks	Nutritional advice on a moderately energy restricted diabetic diet	3 days food diary
Rauh *et al.* (2013)	Germany	BMC Pregnancy & Childbirth	Age >18 years, singleton pregnancy, <18 weeks gestation with sufficient German language skills	≥18.5	18 weeks	Advice on healthy lifestyle, diet and physical activity with individualized goals	7 days dietary diary
Rhodes *et al.* (2010)	USA	American journal of Nutrition	BMI 25–45, age ≥25, singleton pregnancy.	25–45	13–28 weeks	Nutritional education, dietary counselling and food provision	24 h recalls
Rönö *et al.* (2014)	Finland	BMC Pregnancy & Childbirth	History of GDM/BMI ≥30, <20 weeks	≥30	20 weeks	Lifestyle counselling encouraging healthy diet and physical activity	3 day food diary
Sagedal *et al.* (2013)	Norway	BMC Public Health	Singleton pregnancy, >18 years old, <20 weeks gestation, fluent in Norwegian or English	>19	<20 weeks	Dietary counselling + pamphlets containing 10 dietary recommendations + hands-on cooking class + access to interactive website with information on nutrition during pregnancy	82 items FFQ + 24 h recalls
Thornton *et al.* (2009)	USA	Journal of the National Medical Association	Obese pregnant women with singleton pregnancy	≥30	12–18 weeks	Advised on a balanced nutritional regimen.	Daily food diary throughout pregnancy
Vesco *et al.* (2013)	USA	Obesity	Age >18, >8 weeks gestation (at first antenatal booking)	≥30	7–21 weeks	Combination of diet and exercise recommendation + behavioural self-management.	7 days food diary
Walsh *et al.* (2012)	Ireland	British Medical Journal	Secundigravid, singleton pregnancies, previous macrosomia of >4 kg, aged ≤18	Any	<18 weeks	Nutritional advice following a low glycaemic index diet	3 days food diary
Wang *et al.* (2015)	China	Asia Pac J Clin Nutr	Diagnosed with GDM, age 22–38, no pregnancy-related complications, no history of diabetes, hypertension or GDM	Any	24–28 weeks	Individualized dietary guidance	24 h recalls
Wolff *et al.* (2008)	Denmark	International Journal of Obesity	Nondiabetic, nonsmoking, white, aged 18–45	≥30	15 weeks	Nutritional advice and provision of supplements	7 days weighed food diary

DEBI, diet, exercise and breastfeeding intervention; FFQ, Food frequency questionnaire; GDM, Gestational diabetes mellitus; IGT, intolerance glucose test, TLC, therapeutic lifestyle changes.

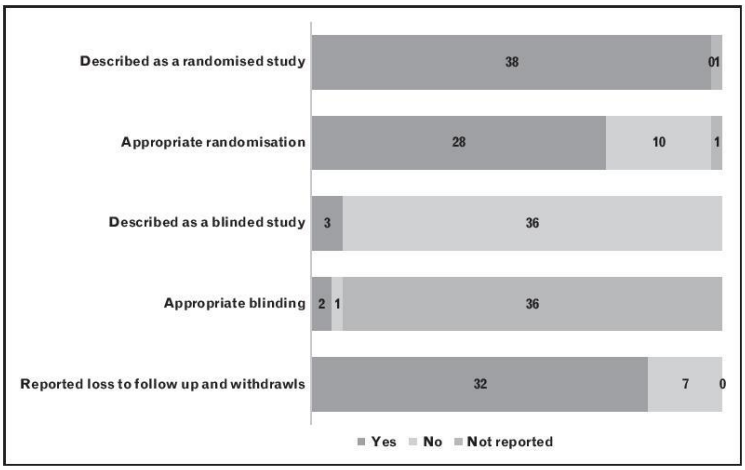

FIGURE 2. Summary of study quality assessment using the Jadad criteria.

a pregnant population. We were not able to provide details on the rationale for choosing various dietary tools in pregnancy and the methodology used due to the paucity of published information. Very few studies conducted validation studies, and the numbers were insufficient to generate any meaningful conclusions on validating SRTs in a pregnant population.

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Dietary tools in pregnancy

Food diaries were used in about two-thirds of included studies; traditionally diaries were the most commonly used tool to report dietary intake in epidemiological studies [29]. They, however, still suffer from a number of limitations, which may lead to misreporting or under-reporting of intake data. Food diaries are more likely to under-report certain nutrients in women and obese participants [30]. They can also vary largely in the accuracy of details provided particularly when portion sizes and meals' weight are not recorded [31]. Introducing food diaries over a long time (more than 3 days) is likely to lead to higher dropout rate, thus increasing the risk of bias [32]. In addition, participants are more likely to change their dietary habits when completing diaries for a long period reducing the diaries' ability to capture habitual intake [33]. Three-day food diary was the most commonly used method, and only two studies used weighed diaries [11,15]. However, we record no clear explanation for such practice.

A third of included trials used an FFQ to assess dietary intake. The decision to use these FFQs seemed arbitrary. FFQs' sensitivity to capture dietary changes in trial settings is generally trivial [34] and can be affected by a number of factors such as the sample size, population literacy, number of items in the FFQ, combination of food groups and the type of the dietary intervention introduced [9]. FFQs' reliability in pregnancy is further undermined because of the instability of dietary intake. Differences in dietary requirement per trimester and common eating disorders such as hyperemesis all increase the intrarater variability in a pregnant population [35]. Some observational studies have confirmed the relative ability of an FFQ to rank individuals according to their dietary intake in a pregnant population [36–38]. However, the generalizability of this to interventional trials is still arguable.

The majority of included studies in our review adopted an FFQ that was validated in a similar population, and only two validated their questionnaires in the study population against other SRTs [13,24]. Although this is a common practice in most dietary studies [39], the increased inter-rater variability in pregnancy is likely to result in a higher random error when SRTs are used in validation studies. Consequently, it might undermine the validation process requiring a larger study sample or more diaries collected [30]. Objective biomarkers could also be used in validation studies [40]; however, they also suffer from a number of limitations such as the effect of digestion and absorption between participants [41] which might be further exaggerated during pregnancy due to physiological changes such as the increased plasma volume.

Twenty-four-hour recalls were the least used tool in pregnancy studies. Similar to food diaries, they have the potential to capture day-to-day variability in dietary intake with reasonable sensitivity [31]. Some studies in our review have attempted to improve the quality of information collected via 24-h recalls by testing their content validity [25], combining them with FFQs [12] and by using the multipass method [13]. Recalls still have some limitations that could affect reliability such as the effect of participants' poor attention and memory gaps as well as the inconsistencies in reporting portion sizes [30].

Implication for future research

The increased systematic and random reporting errors from the use of dietary tools in pregnancy need to be minimized. The use of combined dietary assessment tools should be evaluated to reduce the under-reporting bias [42]. Regression models could also be used to correct measurement errors in dietary assessment studies [43]. Such tools take into consideration the presumed systematic and within-person random variations to allow for a more accurate estimate of effect [43]. The applicability of these tools in dietary studies in pregnancy is still limited, and more work is needed in this field.

The majority of available biomarkers assess specific nutrient intake rather than consumption of food items [41]. The applicability of biomarkers is still limited by the gap of knowledge on their validity, reliability and reproducibility [44]. In our review, biomarkers were used in four studies, but only one study used specific serum biomarkers to assess the dietary intake of particular nutrients [22▪]. Cost implications and invasiveness are other important factors to consider in trial settings [30].

Pregnancy imposes a number of specific challenges on dietary assessment in interventional studies. Establishing a link between diet and the condition of interest requires long-term follow-up before, during and after the pregnancy. Assessing dietary intake frequently might reduce patients' motivation in pregnancy settings particularly for multiparous women who have less free time to engage in laborious methods such as weighed diaries. Assessment tools need to address the objective of the trial and capture the effect of diet on both the mother and the foetus.

CONCLUSION

Although self-reporting dietary assessment tools are widely used in interventional dietary trials in pregnancy, the quality and applicability of existing tools are low with little consideration to the particularity of a pregnant population.

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Conflicts of interest

There are no conflicts of interest.

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