Obesity in pregnancy: Epidemiology and development of a lifestyle intervention

Eugene Oteng-Ntim

Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the
University of London

June 2015

Department of Non-Communicable Disease Epidemiology

Faculty of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

No Funding

DECLARATION OF OWN WORK

All students are required to complete the following declaration when submitting their thesis. A shortened version of the School's definition of Plagiarism and Cheating is as follows (*the full definition is given in the Research Degrees Handbook*):

"Plagiarism is the act of presenting the ideas or discoveries of another as one's own. To copy sentences, phrases or even striking expressions without acknowledgement in a manner which may deceive the reader as to the source is plagiarism. Where such copying or close paraphrase has occurred the mere mention of the source in a biography will not be deemed sufficient acknowledgement; in each instance, it must be referred specifically to its source. Verbatim quotations must be directly acknowledged, either in inverted commas or by indenting" (University of Kent).

Plagiarism may include collusion with another student, or the unacknowledged use of a fellow student's work with or without their knowledge and consent. Similarly, the direct copying by students of their own original writings qualifies as plagiarism if the fact that the work has been or is to be presented elsewhere is not clearly stated.

Cheating is similar to plagiarism, but more serious. Cheating means submitting another student's
work, knowledge or ideas, while pretending that they are your own, for formal assessment or evaluation.

Supervisors should be consulted if there are any doubts about what is permissible.

DECLARATION BY CANDIDATE

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook . I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

I have read and understood the School's definition and policy on the use of third parties (either paid or unpaid) who have contributed to the preparation of this thesis by providing copy editing and, or, proof reading services. I declare that no changes to the intellectual content or substance of this thesis were made as a result of this advice, and, that I have fully acknowledged all such contributions.

I have exercised reasonable care to ensure that the work is original and does not to the best of my knowledge break any UK law or infringe any third party's copyright or other intellectual property right.

To be completed by the candidate

NAME IN FULL (*Block Capitals*): ……

STUDENT ID NO: ……..

SIGNED: ……..... DATE: .....

Registry Last updated – 04/07/13

Acknowledgements

I would like to thank my supervisor Professor Pat Doyle for her valued guidance and mentorship and my advisory committee members Professor Oona Campbell and Tim Collier for their time and coaching throughout the project. I would also like to thank Professor Lucilla Poston, Marion Cable and Mr Paul Seed for their continual support. My sincere thanks go to my family, Linda, Samuel, David and Ruby.

Abstract

Obesity, defined as a body mass index of 30 kg/m^2 or more, has reached epidemic proportions globally, with more than one-and-a-half billion adults overweight and at least 500 million clinically obese. The prevalence of obesity in the UK has increased by over 300% since 1980. In the UK 24% of adult women are obese and one in six women at an antenatal booking clinic is obese.

Obesity has the potential for several detrimental effects on both the mother and the baby. Obese mothers are more likely to develop pre-eclampsia and eclampsia, gestational diabetes and venous thromboembolism. In addition, obese pregnant women are more likely to be induced, often resulting in complicated deliveries such as emergency Caesarean section and shoulder dystocia. Obesity significantly increases the risk of maternal mortality during or after pregnancy. Babies born to obese mothers are at an increased risk of congenital abnormalities, preterm deliveries and stillbirth, and children exposed to maternal obesity are at an increased risk of developing metabolic syndrome in later life.

The aim of this work was to assess the extent and potential for the prevention of adverse impacts of obesity in pregnancy. The specific objectives were to: summarise the literature on maternal obesity and adverse pregnancy outcome; perform an epidemiological analysis using local data of obesity in pregnancy; conduct a systematic review of existing evidence on lifestyle interventions for obesity in pregnancy; and to develop and evaluate a multi-component pilot study for a community-based intervention for maternal obesity in South London.

Analysis of delivery data from South London between January 2004 and May 2012 showed the overall prevalence of maternal obesity to be 15%, with considerable variation by ethnic group. There was a strong association between rising body mass index and risk of adverse pregnancy outcome, especially

diabetes. The effect of obesity on diabetes in pregnancy was more pronounced in Asians and Orientals compared to other ethnic groups. Calculations of population attributable risk fractions showed that, if we were able to prevent obesity before pregnancy in this population, around one-third of diabetes in pregnancy could be prevented. The data alluded to the fact that the benefit of obesity reduction would be greater in Blacks than in other ethnic groups because of the higher prevalence of obesity in this group.

A complex community-based lifestyle intervention called the Community Activity and Nutrition (CAN) programme was developed for delivery by health trainers in children's/Sure Start centres. The research showed that it is feasible to deliver the CAN intervention in children's/Sure Start centres (Effra in Brixton, Jessop in Herne Hill and Jubilee in Tulse Hill) in an Inner London socially deprived community. The pilot study encountered problems with recruitment resulting from understaffing and lack of participant time. However, once recruited, retention on the programme was good. There was some evidence that the intervention improved selected clinical outcomes. Further work is ongoing to establish the clinical and cost effectiveness of the intervention. If CAN is shown to be clinically effective and cost-effective, the translation of this research and adoption by policy makers into the wider community may help to ameliorate the adverse outcomes associated with obesity in pregnancy.

Table of Contents

List of Tables and Figures

Tables

Figures

CHAPTER 1: Introduction

1.1. Background

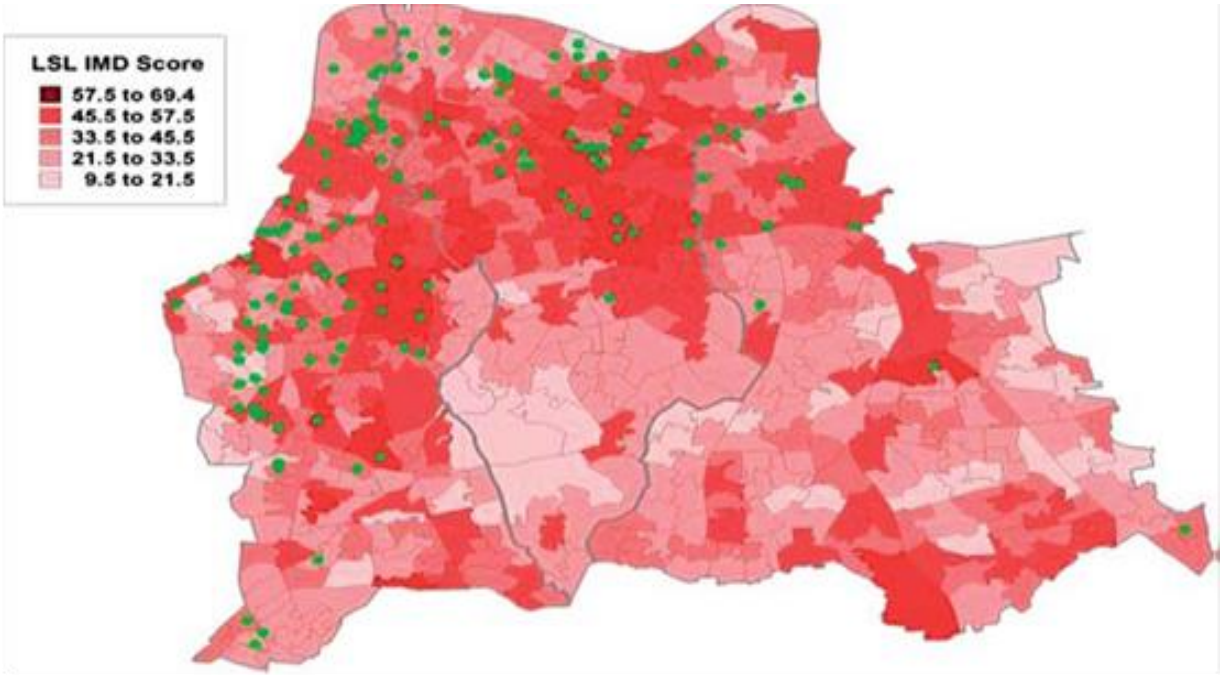
In the past three decades, the prevalence of overweight and obesity in women of reproductive age and in pregnant women has increased in most parts of the world (1-2) and trebled in the United Kingdom (3-4). Maternal obesity is associated with a plethora of complications for the mother, such as increased maternal mortality (5), gestational diabetes (6), pre-eclampsia (7), thromboembolism (8) and increased Caesarean section rate (9). It is also associated with adverse outcome in the newborn child such as macrosomia (10-12), preterm delivery (13) and admission to neonatal intensive care unit (14); and in later life in the adult offspring, it is associated with increased risk of obesity, insulin resistance, dyslipidaemia, hypertension and cardiovascular morbidity (15-18). If this adult offspring is a female, she is more likely to enter pregnancy obese and thus continue an intergenerational cycle of obesity and its adverse outcomes (19). It is of public health importance that interventions be developed to intercept this cycle.

1.2. Personal motivation for undertaking the research described in this thesis

I became a consultant in 2004 at Guy's and St Thomas' NHS foundation trust and served a community obstetric clinic based in Peckham, within the borough of Southwark, in South East London. I had clinical responsibility for looking after pregnant women from Southwark and Lambeth and, based on the number of bereaved patients that I needed to see, I assessed that the perinatal mortality in this area was higher than in other areas I had worked. In light of this, I carried out a study looking at the postcodes where mothers had had stillbirth and plotted these on the map of local communities (20). Pictorially (as displayed in Figure 1), this showed that there was a cluster of stillbirths in the Peckham area and other areas of high deprivation in the local communities that delivered

at Guy's and St Thomas' (20). At that time I did not relate these events to the populations at risk (all births), but I became interested in researching possible factors driving this apparent association. For example, I considered whether the apparently high stillbirth rate could be due to increasing age (women over 40 years), increased proportions of Black and ethnic minority groups, or whether this may be linked with increased maternal obesity. I had observed a high BMI in these deprived populations and became particularly interested in obesity as a possible risk factor for stillbirth and other adverse outcomes during pregnancy and at delivery.

Figure 1: The map of Lambeth and Southwark boroughs with the English indices of deprivation and distribution of stillbirths. The darker the area, the higher the deprivation index. The green dots represent each stillbirth.



.

In 2006 I proposed the establishment of a community-based obesity service. In view of the fact that the Women's Health Directorate at my trust had no new funding to set this up, I applied for a grant application to Guy's and St Thomas' Charity requesting funding to set up this new service. This grant was rejected and I was advised to reapply in partnership with the diabetic team. I reapplied six months later with the diabetic team and, yet again, the application was turned down. The reason given was that combining this service with the diabetic service would be too cumbersome.

I later reapplied in 2007 to conduct a health needs assessment of obese pregnant women in Lambeth and Southwark. I applied for £20,000 which was granted. I worked with a local public health group and the report concluded that there was an urgent need for an obesity service for obese pregnant women in the area and that it was important to develop an effective and feasible intervention within this community. I submitted a grant request to Guy's and St Thomas' Charity in 2008 for funding to develop and evaluate a community-based intervention for obese pregnant women called CAN (community activity and nutrition programme). Funding was awarded in 2009.

Around the same time, in 2009, Professor Lucilla Poston received a grant to do a similar but hospital-based study at Guy's and St Thomas' NHS Foundation Trust called UPBEAT (United Kingdom Better Eating and Activity Trial, Appendix F). Professor Poston and I then worked with a team to develop the intervention which consisted of nutritional advice and an activity programme (21). My role in this was to identify activity and nutrition programmes within the local area that obese pregnant women could take part in, and to identify all the leisure centres within the communities of Southwark and Lambeth, and the markets which have cheap and healthy foods. I attended all the meetings during the developmental phase and contributed intellectually, including producing a systematic review and meta-analysis of lifestyle interventions in pregnancy (22), as well as contributing to the write-up of the intervention manual. I set up the trial in the community - negotiating space at three children's centres in Lambeth

and Southwark which became the settings for the CAN intervention. The difference between the CAN and UPBEAT studies was that for CAN the intervention would be delivered in the community (Sure Start children's centres and participants' homes), without the collection of blood samples, while for UPBEAT the intervention would be delivered in the hospital setting and blood samples from participants were to be collected. To minimise competition for participants, CAN did not recruit patients from Guy's and St Thomas' NHS Foundation Trust. Hence, I approached King's College Hospital to recruit pregnant obese women for the CAN project.

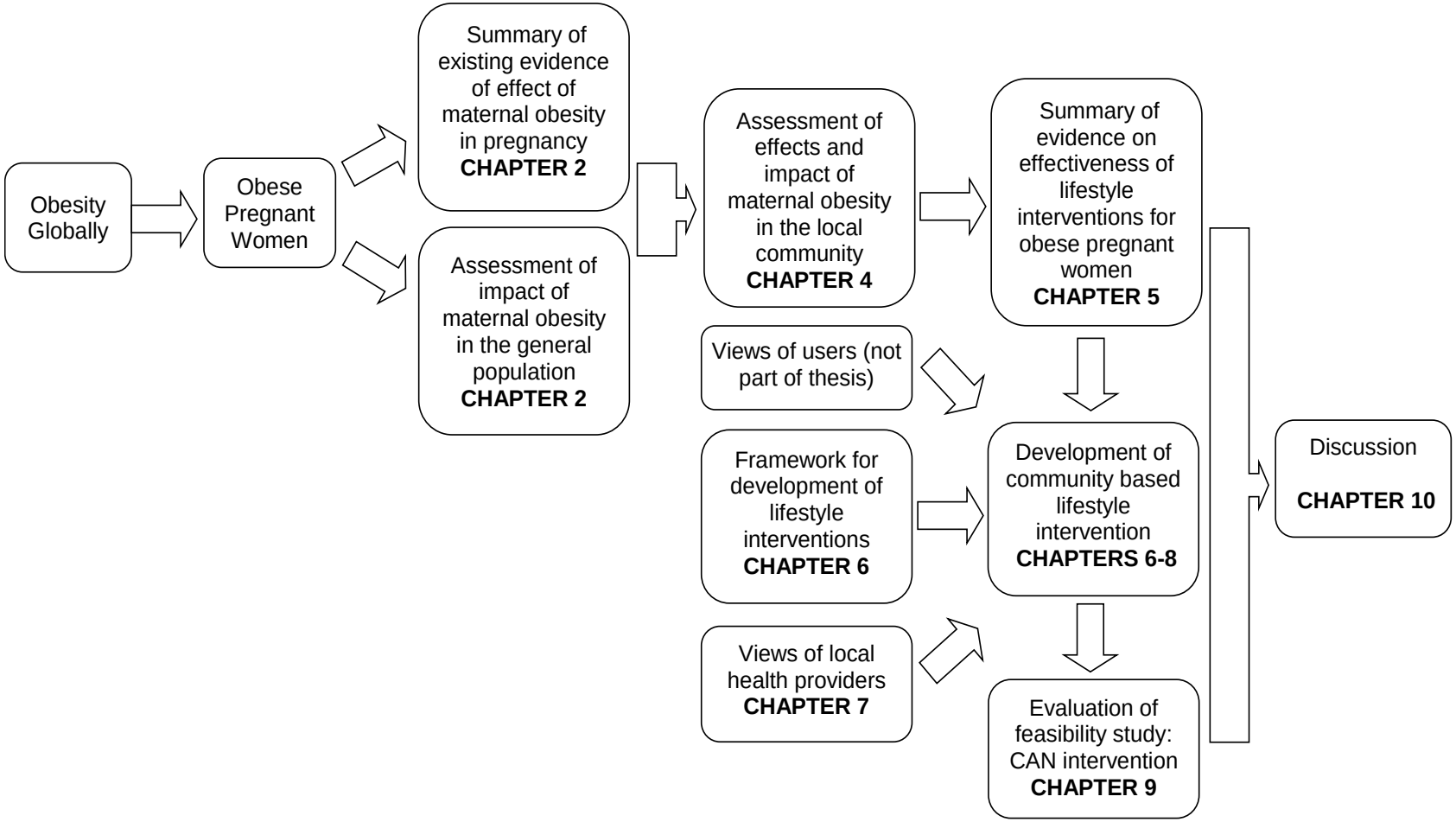
When I was awarded the grant for CAN, I felt the need to undertake further training in epidemiology to help me design the study and analyse the findings appropriately. I approached Professor Pat Doyle, who had been recommended by the public health team at Southwark. With encouragement and support from colleagues and family, I registered for a part-time PhD in 2009. I have funded the PhD part-time myself and have maintained the motivation with enormous support from my supervisor, Professor Pat Doyle, and the Divisional Head of Women's Health research professor, Lucilla Poston.

1.3. Structure of the thesis

A schematic diagram illustrating how the chapters link up is displayed below (Figure 2). This introductory chapter provides a short précis of my background and my motivation for doing this research. The second chapter provides a critical review of the literature on obesity and pregnancy, including its association with adverse outcomes and interventions that might mitigate these effects. Chapter Three provides a rationale for the thesis and presents the objectives of this research. Chapter Four describes an epidemiological analysis of local data, examining the determinants of obesity, and its effect and impact on pregnancy outcome. Chapter Five provides a systematic review of existing evidence on lifestyle interventions for obesity in pregnancy. Chapters Six and Seven describe the development of a multi-component pilot study for the

complex community-based activity and nutrition programme for maternal obesity in South London (CAN). Chapters Eight and Nine evaluate the study of the CAN intervention in South London. Each of these chapters has its own method and discussion sections. Chapter Ten presents a general overview of the findings together with the strengths and weaknesses of the research, appropriate interpretation and reflection, policy implications and recommendations for further research.

Figure 2: Schematic diagram of research presented in this thesis to illustrate how it all links up



RESEARCH PAPER COVER SHEET FOR CHAPTER 2

Please be aware that one cover sheet must be completed for each 'Research Paper' included in a thesis.

1. For a 'research paper' already published

1. 1.1. Where was the work published? ..... **Oteng-Ntim E** and Doyle P (2012). *Maternal outcomes in obese pregnancies in maternal obesity*. Edition 1, Chapter 4, ed Gillman MW, Poston L, Cambridge University Press, United States of America.

1.2. When was the work published? .....2012.....

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion …

1.3. Was the work subject to academic peer review? **Yes**

1.4. Have you retained the copyright for the work? **Yes**

If yes, please attach evidence of retention.
If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published? .....

2.2. Please list the paper's authors in the intended authorship order

2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments / In press

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary.)

…I conceived the idea and the plan of the chapter after an invitation to write the chapter. I wrote the chapter, which was supervised by Professor Pat Doyle. (Further sheets have been attached.)……

NAME IN FULL (Block Capitals) ……Eugene Oteng-Ntim……

STUDENT ID NO: ……235138……..

CANDIDATE'S SIGNATURE …… Date

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above)
……..……

CHAPTER 2: Literature Review: Maternal Obesity

Publication based on part of this work:

Oteng-Ntim E and Doyle P, (2012). *Maternal outcomes in obese pregnancies in maternal obesity*. Edition 1, Chapter 4, ed Gillman MW, Poston L, Cambridge University Press, United States of America.

2.1 Introduction

This chapter will introduce obesity and its influence on pregnancy outcomes. Short-term adverse effects of obesity on the pregnant woman, the fetus and the newborn infant, as well as complications in labour and delivery will be addressed. This material will encompass a specific focus on the population impact of obese pregnancies on maternal, fetal and neonatal outcomes, as well as introducing the concept of interventions to improve outcomes associated with maternal obesity.

This literature review is a critical personal overview. Online databases including Medline (Pubmed and OVID), EMBASE, the Cochrane Library, and obesity textbooks were used. Reports from the grey literature were searched, including the National Institute of Health and Clinical Excellence (NICE) and the Royal College of Obstetricians and Gynaecologists' websites. The terms used in the search are presented in Appendix E and included a wide range of adverse obstetric and neonatal outcomes. Restrictions were made with a focus on studies and reports written in English and references dating from 1960 to 2014. The search strategy for MEDLINE (the search strategy was the same for the other databases) is displayed in appendix E. Emphasis was placed on systematic reviews of evidence, where they existed.

2.2 Definition of obesity

Obesity is defined as 'an accumulation of excess body fat to such an extent that may impair health' (23). Total body fat can be measured by direct methods such as dual energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (24). Both are expensive, cumbersome and impractical to do during pregnancy. Moreover, DEXA has the added radiation risk (25).

Hence, obesity is usually measured using indirect methods such as the body mass index (BMI), which is an expression of body weight-for-height using the formula weight (in kilograms) divided by height (in metres) squared (kg/m^2). Overweight in adults is defined by the World Health Organisation (WHO) as body mass index (BMI) between 25 and less than $30kg/m^2$, and obesity as BMI greater than or equal to $30kg/m^2$ (Table 1).

Table 1: Definition of Obesity

BMI (Kg/m^2)	Weight Status
<18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-34.9	Mild Obesity
35.0-39.9	Moderate Obesity
≥40.0	Morbid Obesity

Adopted from http://www.who.int/nut/#obs (accessed 21st December, 2013)

BMI has been shown by WHO to correlate well with the accumulation of body fat and is a good reproducible indicator of metabolic risk (1). It is simple and easy to measure, requiring very simple, inexpensive tools for the measurement of height and weight. It is accepted as an accurate proxy for body fat in the individual, including in pregnancy (23, 26). The limitations are that it does not account for variation in body composition or fat distribution (24). Secondly, the relationship between the percentage of body fat and BMI is not

linear and may differ in the non-pregnant compared to the pregnant state or between one ethnic group and another, particularly the Asian population (27). As such, BMI as a measure of obesity can introduce misclassification problems that may result in a bias in estimating the effect related to obesity (28).

Despite these limitations, BMI is commonly used as the measurement of choice in the scientific literature and reports on obesity. Thus, throughout this thesis, I will be using the WHO classification of obesity as BMI≥30 kg/m^2.

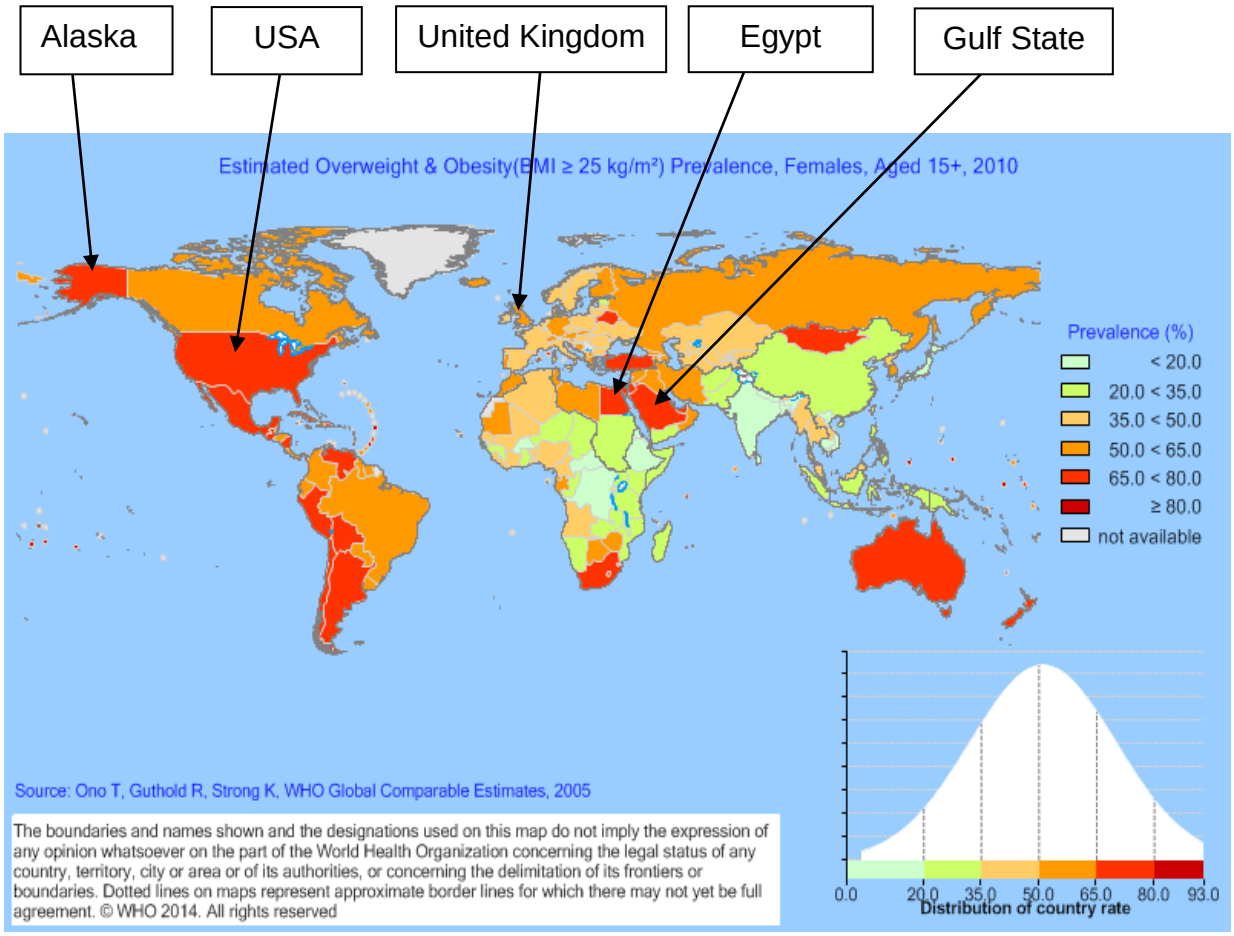
2.3 Global prevalence and trends in adult obesity

The latest projections from the World Health Organisation (WHO) indicate that obesity has more than doubled globally over the past 25 years. It is estimated that in 2008 approximately 1.5 billion adults (aged 20+) were overweight and at least 500 million were obese (WHO obesity and overweight website last updated in 2013) (29). Of the 500 million obese adults, 300 million were women. The figure of 1.5 billion is predicted to spiral to 2.3 billion in the overweight and 700 million in the obese groups by 2015. This phenomenon has been described as a global pandemic affecting all six continents. In most countries, including the United Kingdom (UK), the increasing trend is considered the most pertinent public health threat of this century (30). The proportion of obese adults in the United States rose from 15% in the late 1970s to approximately 33% in 2008 with the biggest rise being in Mexican women based in America (4). The prevalence of obesity in adult women (as depicted in Figure 3 and Appendix H) is already 40-70% in the Gulf States and over 20% in most of Europe (29-30).

In developing countries the prevalence of obesity is more common in urban than rural regions (31). This is because those in rural areas tend to eat a low glycaemic index diet, whereas those who live or move into urban areas tend to adopt western diets, high in refined sugars and fat. There is also reduced activity in the city and this sedentary lifestyle also contributes to the rising

obesity prevalence. Rising obesity prevalence also affects countries such as China and Mexico (31). Obesity is a major contributor to the emerging burden of non-communicable diseases in developing countries. Two-thirds of the global population now live in countries where high body mass index accounts for more mortality than underweight (32-34).

Figure 3: WHO, 2011, estimated overweight and obesity prevalence among adult women (2010)



World Health Organisation, 2013

2.4 Obesity in pregnancy

The prevalence of obesity in UK adults has increased by over 300% since 1980 (35-37). Furthermore, this increase has been seen in other countries too

(38). In 2008 around one-quarter of UK women aged 25-44 were obese (35, 39). There is also good evidence that obesity among pregnant women is increasing in the UK. A study in Glasgow showed a two-fold increase in obesity prevalence in pregnancy from 9.4% to 18.9% between 1990 and 2004 (40), and a similar trend was noted among pregnant women from Middlesbrough (9.9% to 16%) (41). A national sample study showed a rise from 7.6% in 1989 to 15.6% in 2007 of maternal obesity in England(3) . The Centre for Maternal and Child Enquiries (CMACE) study on maternal obesity in the UK, looking at the prevalence of pregnant women with BMI≥35 (severe obesity), showed that the prevalence of severe obesity was 5% in 2010. It noted a variation within the UK nations such that the prevalence was highest in Wales and lowest in England. Within the severe obesity cohort, it showed under-representation of Black and ethnic minority groups (representing 14% within the cohort as opposed to 20% in the general UK maternity population). It is possible that this could be due to a selection bias (42). There is also strong evidence that this picture is also true in the United States of America (43) and Australia (38).

2.4.1 Measurement

Most clinical and epidemiological studies use BMI in early pregnancy as a proxy for pre-conceptual BMI (44-45). This is for practical reasons, since early pregnancy is when height and weight are, or should be, routinely measured and recorded (RCOG recommendations 2010) (46). But a limitation of using BMI during, rather than before, pregnancy is that changes in maternal body composition following conception, as well as the products of conception, will be included in the weight measurement. This extra weight will result in an increase in BMI and the likelihood of being classified as obese. However, in early pregnancy, for example up to 10 weeks gestation, this extra weight is estimated to be around only 1.2 kg on average (47). This will increase maternal BMI by around 2% overall and will not have a major impact on the proportion of women wrongly classified as obese. However, as the pregnancy progresses and maternal weight increases, BMI will increase more markedly. For example, at

20 weeks, a maternal weight gain of 9kg will increase the BMI of the average UK woman of reproductive age by 12% (author's estimate). This will lead to a higher proportion of false positive obese pregnant women using the standard definition of obesity, which will increase as the pregnancy progresses. BMI is thus not considered a useful index in the second and third trimesters of pregnancy.

2.4.2 Excessive Gestational Weight Gain

Women who have excessive weight gain during pregnancy, without obesity in early pregnancy, may also be at risk of adverse outcome (48). Whilst pre-pregnancy BMI is undoubtedly an independent predictor of many adverse outcomes of pregnancy, there is also ample evidence which associates gestational weight gain with adverse outcomes for mother and baby (47). The influences of excessive weight gain on pregnancy outcome in women with normal pre-pregnancy BMI and those who are overweight or obese form the basis of the US Institute of Medicine (IOM) guidelines for weight management in pregnancy (48). However, most epidemiological research has focused on BMI and obesity in early pregnancy.

2.4.3 Determinants of obesity in pregnancy

Age

The prevalence of obesity rises with increasing age in both non-pregnant women (49) and pregnant women (41, 50). In a large sample of pregnant women in England, Heslehurst showed a trend of increasing age with increasing BMI category: from 26.3 years for pregnant women who were underweight to 30.2 years for pregnant women who were super morbidly obese (3). This data also displayed increasing mean parity with increasing BMI category.

Parity

Pregnancy is marked by changes to maternal metabolism, particularly in the second and third trimesters (51). There is increased insulin resistance. Insulin is responsible for controlling glycaemic load; thus, an insulin-resistant state results in increased glucose levels, facilitating increased transfer of glucose and nutrients to the fetus. The mother counteracts this by releasing more insulin into the blood stream, resulting in hyperinsulinaemia. The surplus glucose is then converted into fat, leading to weight gain, which may be retained, hence creating a phenomenon of rising BMI with each additional pregnancy. The interval between births may also have an influence on weight gain. Studies comparing women with one birth to those with no births within 10 years show 60 to 100% increased risk of becoming overweight (52).

Ethnicity

There is evidence that certain ethnic groups are more at risk of becoming obese than others. Obesity rates are higher amongst Black Africans and Black Caribbean women and lower for Whites and Orientals during pregnancy (3, 53). A recent study suggests that for the same BMI, gestational weight gain is more pronounced in Blacks than in Whites and it is associated with hypertensive disease (54).

Deprivation

There is an association between obesity and social class in the general population of the UK (35, 55), and it is recognised that deprived communities have a higher proportion of obesity than less deprived communities. In a study of antenatal women booking in Glasgow, those from the most deprived quintiles were almost 4 times more likely to be obese than those from the least deprived quintiles based on the Carstairs index (40). Another cross-sectional study of

women from Middlesbrough attending for antenatal booking showed a similar association (41).

Diet and lifestyle

Excessive weight gain results from daily increments of positive energy balance due to increased caloric intake and/or sedentary lifestyle leading to reduced activity. Recent large observational and interventional studies (56-57) have found that high glycaemic index diets contribute more to weight gain than fatty food consumption (58-60). Consumption of fruits, vegetables and whole grains is associated with a lower BMI (60). Excessive intake of sugar-sweetened beverages is associated with weight gain. Data from the Nurses' Health Study II in the USA showed that women between the ages of 24 and 74 years who consumed food high in refined sugars and starch were more likely to have increased weight gain (61). However, those who consumed predominantly high fibre foods such as grains, vegetables and fruits, as well as low glycaemia index diets, were less likely to be overweight or obese (56, 61).

Most of the data on diet and BMI comes from high income countries. Data from middle and low income countries, such as China and India, is now coming to light, alluding to the role of a Western-style diet contributing to a rapid rise in obesity and obesity-related diseases in these countries (34, 62).

Physical activity

Physical activity plays a major role in energy balance and maintaining weight, and many studies have assessed the link between physical activity and body mass index. Initial studies suggested that increasing physical activity restricted age-related weight gain but recent studies only demonstrated a moderate effect (63). The ideal physical activity necessary to prevent increased BMI in adults remains unknown. A recent systematic review concluded that increases in physical activity resulted in restricted age-related weight gain within

a four-year period (60). There could be multiple mechanisms to explain this but the most significant is likely to be increased energy expenditure. However, increased activity may also enhance appetite, and hence increased activity ought to be combined with dietary intervention to yield optimum effects on weight management.

Other behaviours that impact on weight control include a sedentary lifestyle, such as TV watching (64). A study from the United States found that each two-hour session of TV watching was associated with a 23% increase in the risk of obesity in adults (64). Prolonged TV watching may be associated with increased food intake and hence the association may be partly mediated through unhealthy diet, particularly as there is greater exposure to the advertisement of unhealthy foods. Many women report continuing exercising during pregnancy (65). Increased activity in pregnancy is said to improve glycaemic control and may play a role in the primary prevention of gestational diabetes (66-67).

Sleep

In the past ten years, evidence has accrued about sleep deprivation as a risk factor for obesity (68). A recent meta-analysis showed a link between length of sleep and increased BMI (60, 68). This association has a characteristic U-shaped pattern with those who sleep 6-8 hours during the night having lower BMI, and those who sleep less, or more, than this having higher BMI. This association persisted after adjusting for diet and other risk factors. Sleep disorder is also associated with adverse pregnancy outcome such as pre-eclampsia and diabetes (69). Assessment of sleeping habits and behaviour intervention designed to improve sleeping habits may be warranted to improve pregnancy outcome (69).

Social factors

There is ample evidence that changing social factors may reduce obesity prevalence (70). One explanation for this is that an individual's socioeconomic status may have an influence on his or her access to, and choice of, healthy foods. It is also clear (Foresight report, 2007) that an environment that makes activity difficult, or impossible, contributes significantly to the prevalence of obesity within a particular population (37) and hence the built environment is very pertinent to the prevention of obesity.

Psychological factors

Mental and psychological stress can result in the behaviour of comfort eating, and particularly increased intake of sugar-containing beverages and food (71). Anxiety and depression, which are common in pregnancy, can also make an affected individual lack interest in exercise and activity, eat more, or in extreme cases binge eat (72). In turn, obesity can result in depression (73), creating a vicious circle of poor eating and activity habits. This may well be exacerbated in pregnancy (74). Understanding more about the inter-relationship between depression and obesity will aid the development of effective interventions.

Genetic

Only a small percentage of obesity can be explained by genetics (75). Genomic work has demonstrated that obesity gene loci can explain less than three percent of obesity in the population (75). Behavioural and socio-environmental factors are the main drivers of BMI in a population and these, rather than genetic factors, offer opportunities for intervention. It is now thought that *in utero*, maternal over-nutrition may alter the fetal epigenetics and predispose the infant to become obese in adulthood (76).

Peripartum weight retention

Peripartum weight retention (i.e. extra weight gain over and above pre-pregnancy weight six months post-delivery) is associated with overweight and obesity long term (77). Peripartum weight retention is dependent on excessive weight gain during pregnancy. A recent systematic review alludes to 20% of women retaining 2.27kg of weight a year postpartum (52). Factors found to contribute to peripartum weight retention include maternal nutrition after delivery, activity and behaviour (e.g. television watching), sleep deprivation, no breastfeeding, and depression (78-81). Excessive weight retention at six months post-delivery was associated with increased weight of 10kg 15 years post-delivery (82).

Breastfeeding

Breastfeeding plays an important role in weight control post-delivery. Pregnancy increases fat stores, particularly visceral fat. Breastfeeding mobilises these fat stores after delivery and there is evidence that the longer a woman lactates, the more she mobilises these fat stores (83).

Observational studies looking at the association between breastfeeding and weight retention provide conflicting findings (83-84). This may be due to inconsistency in agreed measurements for breastfeeding (specifically duration and intensity), and variation in study design and analysis, particularly with regards to appropriate adjustment for confounding. Studies suggest that for the first three months, formula-feeding mothers consume fewer calories and hence lose more weight compared to breastfeeding mothers, but after that, up to a period of two years, breastfeeding mothers lose significantly more weight (85-87). Evidence from interventional studies in low income settings suggests that greater frequency of breastfeeding up to six months postpartum resulted in greater weight loss in women of normal birth weight infants. Long-term studies beyond 24 months are currently lacking (83).

2.5 Obesity-related outcomes in pregnancy: consequences for mother and baby

Obesity can seriously impact on the risk of developing a number of adult diseases such as type 2 diabetes, cardiovascular disease and respiratory problems, and can have an adverse effect on psychological health and wellbeing (29). The effect of obesity on pregnancy is similarly wide-ranging with a potentially serious impact on both the mother and the child. In the following sections I will provide a personal critical overview of the impact of obesity on the mother (Section 2.6), on the labour, delivery and postpartum period (Section 2.7) and on the fetus and newborn (Section 2.8) (Tables 2 and 3).

Table 2 summarises the maternal, labour and fetal complications associated with obesity during pregnancy.

Table 3 summarises the published evidence from large studies and reviews for the effect of maternal obesity on maternal, obstetric and neonatal outcome. The findings are discussed further on in this chapter.

Table 2: Maternal obesity and adverse pregnancy and fetal outcomes

Maternal complications associated with obesity during pregnancy	Maternal mortality Gestational diabetes Hypertensive disease, chronic hypertension and pre-eclampsia Thromboembolic disease Infection: wound infections, urinary tract infections and endometritis

Adverse outcomes in labour and delivery associated with obesity in pregnancy	Induction of labour Caesarean section Shoulder dystocia Anaesthetic complication Postpartum complications such as the association with postpartum haemorrhage and lactational dysfunction
Major fetal and neonatal complications associated with maternal obesity	Congenital defects Small for gestational age Intrauterine death Pre-term births Macrosomia

2.6 Maternal outcomes in obese pregnancies

2.6.1 Maternal mortality

Maternal obesity is over-represented in maternal deaths in developed countries (88-89). In the most recent confidential enquiry into maternal deaths in the United Kingdom, 27% of the 261 deaths occurring between 2006 and 2008 were in obese pregnant women (88). This compares to an estimated background obesity prevalence of 15% in pregnant women in the UK at that time (3, 90). Similarly, a maternal death review from California reported that 30% of the 386 women who died in pregnancy during 2002 and 2003 were obese, compared to 16% of women having live births in California in the same time period (90-91). These findings reflect the fact that the leading direct and indirect causes of mortality such as thromboembolism, pre-eclampsia and cardiovascular diseases have a higher prevalence in the obese, compared to the lean population. The UK maternal death enquiry reported that three-quarters of mothers who died from thromboembolism were overweight or obese, as were 61% of mothers dying from cardiac disease. For other causes, the percentage of women dying who were overweight or obese was around 40%, except for

those from suicide, haemorrhage and sepsis where the rates were lower at 20–25% (5). The importance of these findings has led to recommendations that obesity be recognised as a pre-existing medical condition requiring specific counselling and careful management from early pregnancy (46, 88).

In some parts of the developing world too, there is growing concern about rising BMI in women of childbearing age. Obesity is already a serious problem in Latin America, the Caribbean, the Middle East and North Africa (92). Rising national incomes in developing countries and increased 'Westernisation' will most likely lead to increased levels of obesity in the future with associated consequences for maternal mortality (93).

2.6.2 Gestational diabetes mellitus

Endocrine changes in pregnancy make the body more resistant to naturally produced insulin (94). These changes confer some physiological advantage to the fetus but some pregnancies – particularly in obese women who demonstrate enhanced insulin resistance – also increase the risk of hyperglycaemia and frank gestational diabetes. There is a strong correlation between obesity and gestational diabetes (6, 11, 95). A systematic review by Torloni et al. (95), estimates that moderate obesity (BMI above 30 and less than 40kg/m^2) in pregnancy results in a threefold (OR=3.01;CI=2.34-3.87) increase in the risk of gestational diabetes compared to women with healthy BMI. Morbid obesity (BMI≥ 40kg/m^2) is associated with over five times the increased risk of gestational diabetes (OR=5.55; 95% CI=4.27-7.21). Based on the definitions of diabetes which, until recently, were widely used (see below), about 3% to 7% of women develop diabetes in pregnancy overall, ranging from 1% to 3% of women of normal weight compared to 14% to 17% of obese women (11, 96). Other than pre-pregnancy weight, risk factors related to the development of gestational diabetes include ethnicity, previous history of gestational diabetes, age, parity and family history of diabetes (97).

Diabetes mellitus is a metabolic disorder characterised by persistent hyperglycaemia, with disturbance of carbohydrate metabolism resulting from a defect in insulin secretion, insulin action or both (98). The early definitions of gestational diabetes mellitus (GDM) were based on results from oral glucose tolerance tests (OGTT) which predicted later diabetes in the mother, a definition endorsed by WHO (98). More recently, it has become apparent that a definition of GDM would be more clinically relevant if it more precisely defined the degree of glycaemia at which outcomes of pregnancy such as neonatal health and Caesarean section worsen. Two recently published studies, the Hyperglycaemia and Pregnancy Outcome observational study (HAPO) (99) and the Australian Carbohydrate Intolerance Study (ACHOIS) have addressed this problem (100). The HAPO study showed that with increasing hyperglycaemia, there were increases in adverse outcomes in a continuous fashion. It also highlighted adverse outcome over a broader range of glycaemia. However the HAPO study did not investigate long-term outcomes. The ACHOIS, a randomised trial of standard antenatal care versus a more rigorous regime of control of glycaemia in women with GDM, showed that the rigorous protocol was associated with improved pregnancy outcomes. In a subset of the ACHOIS population, however, the intervention did not reduce offspring BMI at the age of 4 to 5 years (101).

Following HAPO and ACHOIS, the International Association of Diabetes in Pregnancy Study Group redefined gestational diabetes mellitus as fasting plasma glucose concentration greater than 5.1 mM, 1-hour greater than 10.0 mM, or 2-hour plasma glucose concentration greater than or equal to 8.5 mM following 75 g oral glucose challenge after fasting from midnight (53, 99). With the new HAPO definition about 30% of obese women will be classified as having GDM.

Women diagnosed with gestational diabetes have a higher risk of developing type 2 diabetes mellitus in later life. In a recent systematic review, Bellamy et al. (102) identified twenty studies that included over 675,000 women

and 10,800 cases of type 2 diabetes. They found that women with gestational diabetes had more than seven times the risk of developing type 2 diabetes compared to those who had normoglycaemic pregnancies (RR=7.43; CI=4.79-11.51).

Also of importance here is the recent hypothesis of the link between maternal obesity, plus macrosomia, and the child's risk of developing obesity in later life (17, 103). Thus, obesity in pregnancy is not only a modifiable risk factor for gestational diabetes but may also play a role in childhood obesity (see Section 2.8.4).

2.6.3 Hypertensive disease in pregnancy

Hypertensive disease in pregnancy, or gestational hypertension, is defined as new onset hypertension (systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg) after 20 weeks gestation (104-105). If gestational hypertension is associated with proteinuria as shown by one (measurement of 0.3 g/l) or more on proteinuria dipstick testing, or 300 mg or more per 24-hour urine collection, then the diagnosis is pre-eclampsia (11). Many studies show that maternal obesity is associated with increased risk of gestational hypertension (7, 12, 106-107). Two large population-based studies and a systematic review (see summary in Table 3) demonstrated clear and consistent strong positive associations between maternal pre-pregnancy BMI and the risk of pre-eclampsia (7, 11, 45). The systematic review concluded that the risk of pre-eclampsia typically doubled with each 5-7 kg/m^2 increase in pre-pregnancy BMI (7). Another recent study also addressed the dose-response effect of increasing body mass index and the rise in the prevalence of pre-eclampsia (108). With obesity prevalence rising throughout most countries (1), the role of pre-pregnancy body mass index as an independent risk factor for pre-eclampsia, and a target for pre-conceptual care, is a pertinent subject for research. Interestingly, a systematic review concluded that mothers who develop pre-eclampsia are more likely to develop

cardiovascular disease later on in life (109), raising the possibility that any preventive measure is likely to benefit health later in life as well as the more immediate adverse maternal and neonatal outcomes.

Mechanistically, the association between the rise in BMI and increasing pre-eclampsia prevalence may be explained by heightened inflammation in obese women, oxidative stress enhancement in the obese, or increased insulin resistance in the obese (103, 108, 110-111).

2.6.4 Thromboembolic complications

Venous thromboembolic (VTE) complications are a leading direct cause of maternal mortality in the United Kingdom and other developed countries (5, 112). Pregnancy-associated death from thromboembolism occurs once in around 7,000 pregnancies, a 12-fold increase compared to the non-pregnant state where the risk is around one in a million for women of reproductive age (113). A small case-controlled study in Denmark showed a significant association between venous thromboembolism in pregnancy and obesity, reporting an almost ten-fold increased risk for obese pregnant women compared to non-obese (114). A recent study from the UK Obstetric Surveillance System (UKOSS) found a more moderate effect; obese women were approximately two-and-a-half times more likely to develop thromboembolism compared to lean pregnant women (8). The possible mechanism underlying these observations may relate to elevated concentrations in the blood of pro-coagulant factors found in some studies (115). Contributing to this may be heightened inflammatory damage to the venous endothelium and sedentary lifestyle in the obese.

2.6.5 Infection

Infection accounts for substantial morbidity during pregnancy. There is strong evidence of an association between maternal obesity and wound

infection (99), genital tract infection and urinary tract infections (11, 44-45). The risk of an obese woman having an infection during pregnancy is three-and-a-half times higher than that for pregnant women with a normal body mass index (RR=3.34; CI=2.74-4.06). This finding is consistent with most studies (11, 44-45).

Even though influenza and the common cold are self-limiting conditions, pregnant women who develop complications are at increased risk of hospitalisation, intensive care unit admission and death compared to non-pregnant women (116-117). The recent pandemic spread of H1N1, demonstrated that pregnant women were at high risk of severe influenza-related complications and hence are a priority group for vaccination. Obesity, and in particular morbid obesity, has been shown to be a significant risk factor for severe disease in pregnancy in the 2009 influenza pandemic. A study by Yates et al. showed the odds of obese pregnant woman being hospitalised for H1N1 compared to non-obese pregnant woman are 2 (OR=2; CI=1.3-3). The study also showed that earlier treatment is associated with improved outcomes and hence identification of obesity as a risk factor for severe complication of H1N1 may necessitate earlier treatment for this group (118).

2.6.6 Anaesthetic complications

Obesity is a major risk factor for anaesthetic-related maternal mortality (5). In the 2002-2005 confidential enquiry into maternal death, 80% of the anaesthetic-related maternal deaths occurred in women who were obese. With obese pregnant women having increased risk of cardiac problems, thromboembolism, pre-eclampsia, diabetes and Caesarean section, it is not surprising that there is over-representation of obese pregnant women in anaesthetic-related maternal deaths. Secondly, the risk of failed epidural analgesia increases with increasing BMI. The risk of failed intubation is 1 in 280 in the obstetric population as a whole compared to 1 in 2230 in the general population (119-121). In contrast, the risk of difficult intubation in the obese

population is estimated to be 15.5% (122). This is attributed to soft tissue changes, oedema and fat deposition in the obese. It is important, therefore, for severely obese pregnant women to be referred to the obstetric anaesthetist for a clear plan for pain relief in labour and prior assessment with regard to how best to minimise the chances of failed regional analgesia and difficult intubations.

2.6.7 Intensive care unit admission and maternal obesity

Reasons for intensive care admission for pregnant women are varied. The common justifications are similar to indications for maternal mortality such as cardiac conditions (123), thromboembolism, postpartum haemorrhage (124) and, very recently, H1N1 infection (125). There is a greater preponderance of these conditions in obese pregnant women and in the case of H1N1 it has been shown that obesity confers increased severity of disease and hence increased likelihood of admission to an adult intensive care unit (117). Very few studies have looked directly at obesity and intensive care admission; however, of those that have looked at specific conditions such as H1N1 and cardiac conditions, there appears to be over-representation of obesity in these groups, highlighting that near-miss events are more likely to be common in the obese than the lean (123, 126).

2.7 Obesity-related adverse outcomes in labour and delivery

2.7.1 Induction of labour

Obese pregnant women have an increased incidence of labour induction. The estimated increase is between 1.7-fold and 2.2-fold, even after adjusting for associated antepartum complications (127). The evidence regarding labour duration is conflicting. Some investigators report higher incidences of prolonged labour and failure to progress but others do not (128). A better understanding of

the relationship between obesity and the labour mechanism is needed to prevent high rates of intervention during labour (129).

2.7.2 Caesarean section

Maternal obesity is an independent risk factor for Caesarean section (CS). Sheiner et al. (2004) investigated the pregnancy outcome of obese patients not suffering from hypertensive disorders or diabetes mellitus in women who delivered at Soroka Medical Centre in Israel between 1988 and 2002 (130). They found that the association between obesity and CS remained significant after controlling for variables recognised to coexist with obesity. It was suggested that this might be because of caregiver bias. Similarly, Sebire et al. (2001) showed that the CS rate for obese women was over 20% compared to the CS rate for normal weight women in London in the 1990s, which was nearer to 10% (11). Usha et al. reported the effect of maternal obesity on pregnancy complications with good control of confounding factors (127). The study supported previous evidence that obese women had double the risk of undergoing a Caesarean section compared with non-obese women. The researchers suggested that this may be an effect of the increased rate of large for gestational age infants leading to disproportion during labour, suboptimal uterine contractility, or that there may be increased fat deposition in the soft tissues of the pelvis. A recent systematic review by Poobalan et al. confirmed the consistency of this association and further showed that increasing BMI is associated with increasing likelihood of needing a Caesarean section (9). A study published by Hollowell et al in 2014 demonstrated a similar association in healthy women in England and went on to highlight the need to consider BMI with parity when assessing risks associated with birth (131).

2.7.3 Shoulder dystocia

Shoulder dystocia is defined as a delivery in which additional manoeuvres are required to deliver the fetus after normal gentle downward

traction has failed (132). It occurs when the fetal anterior shoulder impacts against the maternal symphysis pubis following delivery of the vertex (133). Shoulder dystocia complicates 0.13%–2.1% of all deliveries and is associated with adverse pregnancy outcome. The case-control study of Robinson et al. (2003) showed that the strongest predictors of shoulder dystocia are related to fetal macrosomia (134). Furthermore, they found that for obese non-diabetic women carrying fetuses whose weights are estimated to be within normal limits, there is no increased risk of shoulder dystocia. Therefore, for obese women, the predictors of shoulder dystocia are similar to those of non-obese women, i.e. macrosomia. Studies from Sweden (12) and Northwest Thames (11), London, showed the risk of macrosomia in obese pregnant women was two to three times higher than that for non-obese pregnant women (see Section 2.8.4).

2.7.4 Postpartum complications

Overall, the evidence indicates that obese women tend to have between 20% and 50% higher rates of postpartum haemorrhage (PPH) than non-obese women (53, 127, 130). The increased incidence of Caesarean section amongst obese women has been implicated as a causal factor. However, Usha et al. showed the increased rate of Caesarean section might not be the only factor influencing blood loss in this group; more obese women who had a vaginal delivery had a greater than 500 ml blood loss compared to those with a BMI of 20-30 (130). They suggested that this might be explained by excess bleeding from the relatively larger area of implantation of the placenta usually associated with a macrosomic fetus (135). Nuthalapaty and Rouse considered the possibility that the relatively large volume of blood related to obesity, and the resultant decreased bioavailability of uterotonic agents, could be an additional factor related to the increased risk of PPH (129).

2.7.5 Other postpartum complications

There is conflicting evidence regarding the relationship between obesity and failure to initiate breastfeeding, and/or a decreased duration of

breastfeeding. Maternal obesity is implicated in alteration of the hypothalamic-pituitary-gonadal axis and fat metabolism, resulting in lactational dysfunction; however, the exact mechanism remains to be determined (129).

In the postpartum period obese women have a significantly higher incidence of hospitalisation (more than 4 days) compared to non-obese women (127, 132). This has significant health resource implications and studies are needed to understand and prevent the high hospitalisation rate among obese women postpartum (133).

2.8 Obesity-related adverse outcomes on the fetus and newborn

2.8.1 Congenital defects

A congenital defect is defined as an abnormality in the development of the fetus resulting in structural, chromosomal and/or gene abnormality present at birth. The prevalence of major defects is around two percent of all deliveries and accounts for a more significant proportion of stillbirths in obese than non-obese women (136). Obese women are at a higher risk of delivering a baby with a congenital defect (137). Particular defects with increased prevalence in obese mothers are risk of neural tube defects (138), congenital heart defects and oro-facial defects such as cleft palate and/or lip (12, 137) (136, 139).

The mechanism for the observed association between obesity and NTD and congenital heart disease is likely to be that obesity can be defined as a pre-diabetic state, and diabetes has a strong association with neural tube defect and congenital heart disease (140-141). Hendricks et al. (2001) showed that hyperglycaemia and hyperinsulinaemia are a strong risk factor for neural tube defects and may be the driving force for the observed risk in obese women (142). Evidence from *in vitro* and *in vivo* studies shows that hyperglycaemia induces oxidative stress which alters gene expressions responsible for embryogenesis (143). There may be other mechanisms at play as some

observational studies suggest that when diabetic women are excluded from the data, the association between obesity and congenital defects remains (136-137).

Other mechanisms to explain the association may be deficiency in micronutrients such as folic acid at the periconceptional period (141). Folic acid provides a protective effect for the development of the neural tube as well as other major structures such as the heart (141). It is well recognised that obese women have lower folic acid levels in the blood (144-145). It may also be that folic acid metabolism is altered in the obese, compared to the lean. Obesity is associated with deficiencies in other micronutrients such as carotenoids, vitamin D and zinc (146). All of the above evidence emphasises the importance of preconceptional and early pregnancy nutrition and weight control (147).

2.8.2 Intrauterine death, neonatal and small for gestational age (SGA)

Miscarriage

Studies looking at the association of maternal obesity and first trimester fetal loss tend to be focused on women undergoing fertility treatment (148-149) where obesity has been found to be associated with increased risk of miscarriage (148, 150). These cannot be generalised to the general population as there may be confounding factors related to subfertility. In women who do not have fertility problems, the evidence of association between obesity and first trimester loss remains conflicting (151).

Stillbirth

Stillbirth is defined as death of the fetus after the accepted threshold of viability (24 completed weeks of pregnancy in the United Kingdom and 20 completed weeks in the United States) (152). Sebire et al. (2001) reported that obese pregnant women in London had a significantly increased risk of stillbirth

relative to women of normal weight (BMI 20–25) after adjustment for obesity-related diseases in pregnancy (11). Also, Cedergren (2004) found that morbidly obese women with a BMI >40 had an almost 3-fold increased risk of antepartum stillbirth (12). The study by Nohr et al. (2005) based in Denmark suggests that the increased risk of stillbirth could be related to rapid fetal growth due to fetal hyperglycaemia, which may place the fetus at risk of death by hypoxia if the placenta cannot transfer sufficient oxygen for metabolic requirements (153). A recent meta-analysis of epidemiological studies (observational studies) by Chu et al. showed the odds of stillbirth were doubled in obese women compared with normal BMI (OR=2.1; CI=1.59-2.74) (154). The risk was also high for overweight women but not as high as in the obese (154). A recent systematic review in the Lancet on modifiable risk factors for stillbirth worldwide highlighted overweight and obesity as the highest major modifiable risk factor contributing to 23%-40% of stillbirth in developed countries (152). An observational study on severe obesity by the Centre for Maternal and Child enquiry in the UK showed that mothers who were severely obese had double the risk of stillbirth compared to the general population (8.6/1000 compared to 3.9/1000) (42), a similar finding to that of the meta-analysis by Chu et al. (154). In summary, there is evidence of a doubling in the risk of stillbirth in the obese compared to lean pregnant women, and there appears to be increasing stillbirth with increasing BMI.

Neonatal Death

This is defined as the death of an infant in the first 28 days of life. Up until recently, all the studies on the association between obesity and neonatal death have been based on data from developed countries (155-156). A recent study focusing on cross-sectional demographic and health surveys (DHS) from 27 sub-Saharan African countries showed that obese women from sub-Saharan Africa were one-and-a-half times more likely to have a neonatal death compared to lean women (OR=1.46; 95% CI=1.11-1.91) (156). Studies have looked at the association between maternal obesity and neonatal death in developed countries and they report 1.5 to 2.6 increased odds of neonatal

mortality in obese mothers compared to women of normal BMI, similar to the findings from developing countries (12, 14, 153, 157-158). This association is more pronounced in the early neonatal period, suggesting the possible mechanism being related to medical conditions in pregnancy such as pre-eclampsia, diabetes in pregnancy, infection in pregnancy and congenital abnormality and premature delivery (156, 159-161).

Small for gestational age (SGA)

Cnattinguis et al. (1998) examined a large-population based cohort of Swedish pregnancies and found that the risk of delivering an SGA baby increased with increasing BMI (162). Cedergren (2004) also reported a similar finding from Sweden, although after excluding women with pre-eclampsia this increased risk was no longer statistically significant (adjusted OR 1.23; 95% CI=0.94, 1.60) (12). Rajasingham et al. (2009) also found a similar finding having used the customised growth charts (108). A study from the United Kingdom Obstetric Surveillance System (UKOSS) looking at super-morbidly obese pregnant women failed to find an association between body mass index of over 50kg/m^2 and SGA.

2.8.3 Preterm birth

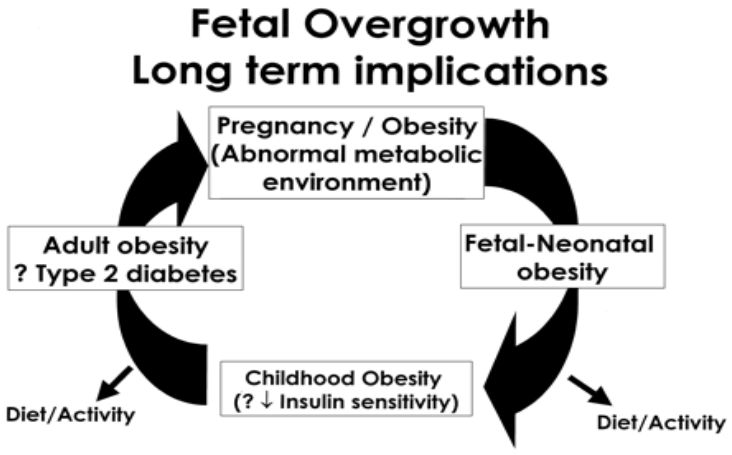
A prospective study by Hendler et al. (2005), the Maternal Fetal Medicine Units Network Preterm Prediction study, found that pre-pregnancy obesity was associated with fewer spontaneous preterm births (SPBs) than normal maternal weight (163). Conversely, a higher percentage of preterm births in obese women have been found because planned preterm births in association with early on-set pre-eclampsia are more predominant in obese, compared to lean women (13). Overall it seems that in obese pregnant women the increased risk of preterm birth is associated with obesity-related medical and antenatal complications and not some intrinsic predisposition to SPB (129).

2.8.4 Macrosomia

Increased maternal pre-pregnancy weight and increased pre-pregnancy insulin resistance are strongly correlated with increased fetal growth, in particular fat mass and weight at birth (99-100). It is thought that in early pregnancy increased maternal insulin resistance may be related to altered placental function, in addition to increased fetoplacental availability of glucose, free fatty acid, and amino acids, but the mechanism behind this is unknown (164).

Catalano et al. (2003) reported a significant increase in neonatal fat mass at birth in infants born to women with GDM (164). The strongest predictor of fat mass in infants of women with GDM was found to be maternal fasting glucose levels (99-100). This neonatal obesity is proposed to be a significant risk factor for adolescent/adult obesity (164). More importantly, obese female neonates have been shown to have higher rates of GDM in their own pregnancies (165); thus, a vicious cycle is created. Figure 4 shows the potential long-term effects of fetal overgrowth.

Figure 4: Potential long-term implications of fetal overgrowth



Adapted from Catalano (2003).

In light of evidence showing an abnormal metabolic state *in utero* in obese women, there seems a potential for *in utero* therapy/intervention to prevent the effects of maternal obesity on subsequent generations (103, 164). A recent study describes an association between maternal obesity and risk of adult offspring cardiovascular disease and mortality in mid-life. These observations make the development of an intervention to mitigate the effect of obesity *in utero* or pre-pregnancy highly pertinent (15).

2.9 The population impact of obese pregnancies on maternal, fetal and neonatal outcomes

The evidence presented thus far shows a markedly increased risk of adverse obstetric events in obese pregnancies, including gestational diabetes, hypertensive diseases, thromboembolism, infection, Caesarean section and postpartum haemorrhage. There are also clear indications that risks increase as BMI or the level of obesity increases. This is vitally important information for overweight or obese women considering pregnancy or in the early stages of pregnancy, and for the clinician managing her pregnancy. The evidence is sufficiently robust to consider an obese pregnancy as an at-risk pregnancy as reflected in the recent UK guidelines for the clinical management of women with obesity in pregnancy (42).

An important question to ask is: What proportion of the adverse obstetric events seen in the population, rather than the individual, can be attributed to obesity? A useful measure is the population attributable fraction (PAF). This can be thought of as the proportion of obstetric morbidity attributable to maternal obesity in the population, and also as the proportion of ‘potentially avoidable’ adverse outcomes if obesity was eliminated in the population; that is, avoidable if all pregnant women were of healthy BMI.

The proportion of potentially avoidable adverse outcomes increases with both the strength of association between obesity and the outcome, and the prevalence of maternal obesity in the population. For example, if maternal obesity is associated with an increased risk of 50% (relative risk 1.5) and the prevalence of maternal obesity in the population is low at 5%, the proportion of adverse obstetric events that could be avoided if obesity was eliminated is only 2%. However, if obesity is linked to a five-fold increased risk (relative risk of 5) of a particular outcome, and the prevalence of obesity in pregnancy is 50%, the proportion of potentially avoidable adverse outcome if obesity were eliminated is very high at 67%.

In most developed countries obesity is associated with two to three times increased risk of adverse outcome and the prevalence of obesity is around 20%. The best available estimates of relative risk measures from the literature, after adjustment for potential confounding factors such as age and parity, are used here. Using standard equations (PAF = P_1 (AOR-1)/AOR see page 81 for details of equations used) PAFs for obesity-related pregnancy outcomes were calculated and are depicted below in Figures 5 and 6. The calculations demonstrate that the contribution of maternal obesity to gestational diabetes and hypertension in pregnancy is around 30%, meaning that almost one-third of these outcomes could be prevented in the population if maternal obesity could be prevented. For CS, the figure is around one-fifth, and for postpartum haemorrhage, around 9%. If the prevalence of obesity were to increase to 50% in the future, the analogous PAF would be higher (Figure 6).

These are worrying estimates. They demonstrate the substantial impact of maternal obesity on obstetric health that currently exists in the population, and which is likely to increase further if there is no reversal in the trend of increasing maternal obesity. The figures also point to potentially huge savings in health service expenditure if maternal obesity could be eliminated, or at least reduced, in the population.

Figure 5: Proportion of potentially avoidable adverse obstetric events (in grey) if all mothers were normal weight in early pregnancy

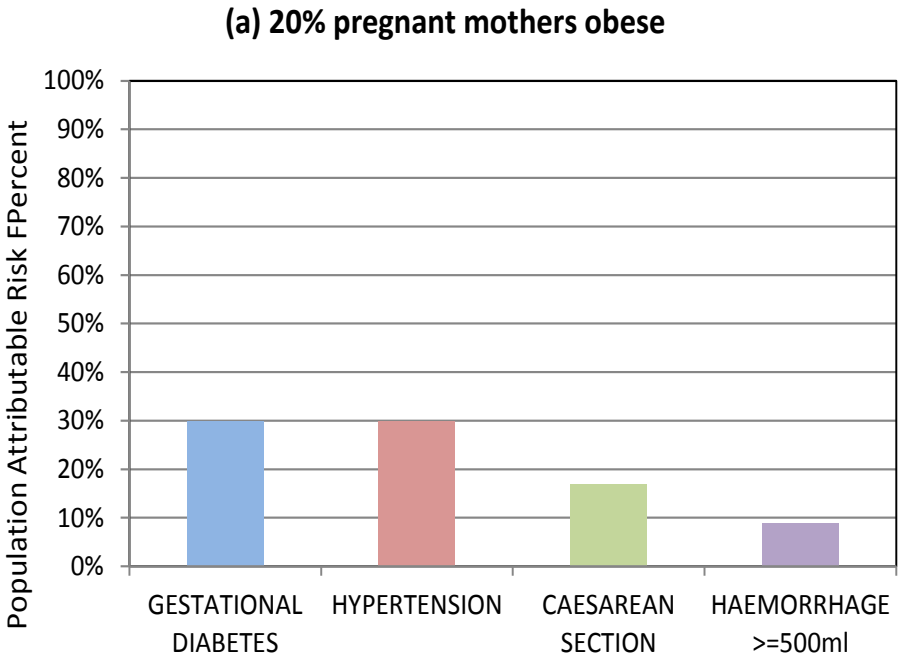


Figure 6: Proportion of potentially avoidable adverse obstetric events (in grey) if all mothers were normal weight in early pregnancy

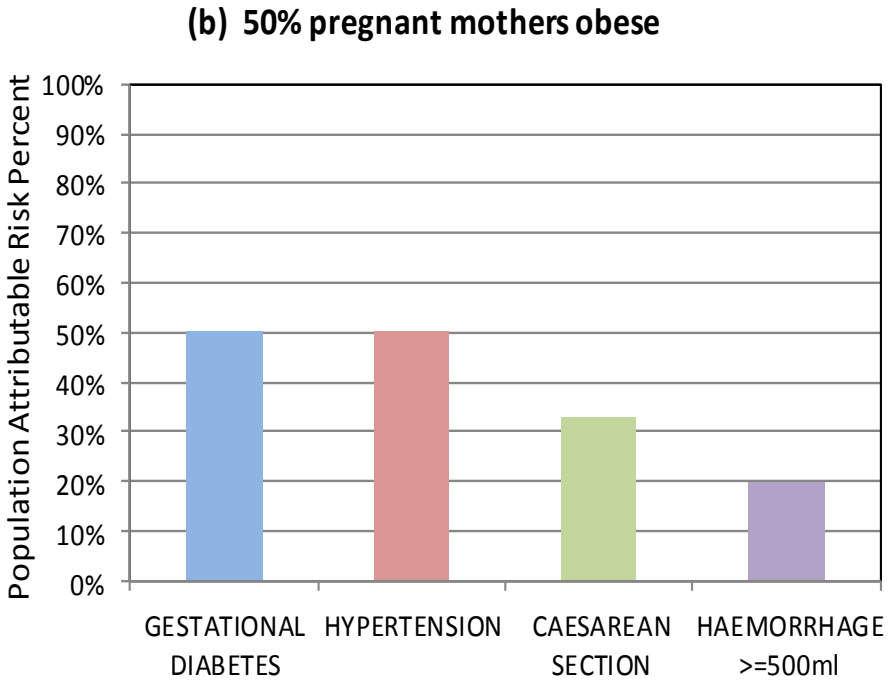


Table 3: Summary of evidence from systematic reviews and large-scale epidemiological studies on risk of maternal and fetal outcomes in obese pregnant women

Outcome	Reference	Setting	Study Design	Numbers in study	Estimated measure of effect (relative risk) (95% Confidence Interval) of obesity on outcome of interest
Gestational diabetes	Torloni et al., 2009 (95)	Worldwide	Systematic review of 59 cohorts and 11 case-control studies 1977 to 2007	70 studies involving 671945 women	Overweight: 1.97(1.77-2.19). Mild and moderate obesity: 3.01(2.34-3.87) Morbid obesity: 5.55 (4.27-7.21)
Hypertensive disorders in pregnancy	Obrien et al., 2003 (7)	Canada	Systematic review of cohort studies	13 cohort studies comprising 1.4 million pregnant women	The risk of pre-eclampsia doubled with each 5 to 7kg/m2 increase in pre-pregnancy BMI
	Sebire et al., 2001 (11)	UK	Cross-sectional analysis of North West Thames maternity database	287213 women with singleton pregnancies delivering 1989 to 1997	Overweight: 1.44 (1.28-1.62) Obese: 2.14 (1.85-2.47)
	Bhattacharya , 2007 (107)	UK	Cohort study	24241 nulliparous women with singleton pregnancies delivering 1976-2005	Overweight:1.6(1.2-1.8) Obese: 3.1 (2.8-3.5) Morbidly obese: 7.2(4.7-11.2)
Thrombo-embolism	Larsen et al., 2007 (114)	Denmark	Case control study nested in a cohort	129 cases with VTE in pregnancy and 258 controls who are pregnant without VTE	Obese: 9.7 (3.1-30.8)
	Knight et al., 2009 (8)	UK	Case control study	143 women who had thromboembolism antenatally between 2005-2006	Obese: 2.65 (0.9-6.45)
Induction of Labour	Sebire et al., 2001 (11)	UK	Cross-sectional study of deliveries in Liverpool Women's Hospital	287213 women with singleton pregnancies delivering 1989 to 1997	Overweight: 2.14(1.85-2.47) Obese: 1.70(1.64-1.76)
	Zhang et al., 2007 (128)	UK	Cross-sectional study	3913 completed singleton pregnancies who delivered in 2002	Overweight: 1.41 (1.21-1.66) Obese: 2.10 (1.73-2.55)
Caesarean section	Poobalan et al., 2009 (135)	UK	Systematic review and meta-analysis of publications 1996 to 2007	11 studies involving 166168 pregnant women	Combined: 2.1 (1.9-2.3) Overweight:1.53 (1.48-1.58) Mild and moderate obesity: 2.26 (2.04-2.51) Morbid obesity: 3.38 (2.49-4.57)

Outcome	Reference	Setting	Study Design	Numbers in study	Estimated measure of effect (relative risk) (95% Confidence Interval) of obesity on outcome
Postpartum haemorrhage	Sebire et al., 2001 (11)	UK	Cross-sectional analysis of North West Thames maternity database	287213 women with singleton pregnancies delivering 1989 to 1997	Obesity: 1.4 (1.2-1.6)
	Usha et al., 2005 (127)	UK	A population-based birth survey between 1990-1999	60167 women who delivered between 1990-1999	Obesity: 1.5 (1.2-18)
	Heslehurst et al., 2008 (44)	Europe and USA	Systematic review of publications 1990 to 2007 on BMI in pregnancy and pregnancy outcomes	6 studies included in meta-analysis	Obesity: 3.34 (2.74-4.06)
Maternal Infection	Heslehurst et al., 2008 (44)	Europe and USA	Systematic review of publications 1990 to 2007 on BMI in pregnancy and pregnancy outcomes	6 studies included in meta-analysis	Obesity: 3.34 (2.74-4.06)
Wound infection	Sebire et al., 2001 (11)	UK	Cross-sectional analysis of North West Thames maternity database	287213 women with singleton pregnancies delivering 1989 to 1997	Obesity: 2.24 (1.9-2.64)
Respiratory tract infection specifically H1N1	Yates et al., 2010 (117)	UK	National cohort study	1453 pregnant women of whom 241 admitted with H1N1	Obesity 1.5 (1.3-1.7)
Admission to ITU	Zwart et al., 2008 (126)	Netherlands	Cohort study	371,021 pregnant women with 2552 near misses	Obesity 1.5 (1.3-1.7)
Length of hospital stay	Heslehurst et al., 2008 (44)	Worldwide	Systematic review of publications 1990 to 2007 on BMI in pregnancy and pregnancy outcomes	4 studies included in meta-analysis	Healthy BMI: 2.4 days Mild and moderate obesity: 2.71days Morbid obesity: 3.28 days
Birth defects e.g. Neural tube defect	Stothard et al., 2009 (137)	UK	Systematic Review	39 studies were included in systematic review and 18 in meta-analysis	Overweight and obesity:1.8 (1.62-2.5)
Birth defects e.g. Cardio-vascular abnormality	Stothard et al., 2009 (137)	UK	Systematic Review	39 studies were included in systematic review and 18 in meta-analysis	Overweight and obesity:1.30 (1.12-1.51)

Outcome	Reference	Setting	Study Design	Numbers in study	Estimated measure of effect (relative risk) (95% Confidence Interval) of obesity on outcome
Elective Prematurity	Smith et al., 2007 (13)	Scotland, UK	Cross-sectional study	187290 of women who delivered their babies in Scotland; the data were collected when they were discharged	Obesity: 1.6 (1.2-1.8)
	McDonald et al., 2010 (166)	Canada	Systematic review	84 observational studies 1095834 women	Obesity:1.56 (1.42-1.71)
Spontaneous prematurity	Smith et al., 2007 (13)	UK	Cross-sectional study	187290 of women who delivered their babies in Scotland and the data were collected when they were discharged	Obesity:0.95 (.095-0.96)
	McDonald et al., 2010 (166)	Canada	Systematic review	84 observational studies 1095834 women	Obesity: 0.93 (0.85-1.01)
Macrosomia	Sebire et al. 2001 (11)	Lon UK	Cross-sectional analysis of North West Thames maternity database	287213	Obesity: 2.4 (2.2-2.5)
	Cedergren et al., 2004 (12)	USA	Cohort	805275	Morbid obesity: 3.82 (3.5-4.2)
Shoulder dystocia	Sebire et al., 2001 (11)	UK	Cross-sectional analysis of North West Thames maternity database	287213	Obesity: 3.14 (1.86-5.31)
Stillbirth	Chu et al., 2007 (154)	USA	Systematic review	Meta-analysis of 9 studies	Overweight and obesity: 2.1 (1.5-2.7)
	Flenady et al., 2011(152)	Australia	Systematic review	Meta-analysis of 4 studies	Overweight and obesity:1.63 (1.35-1.95)
Neonatal death	Kristensen et al., 2005 (14)	Denmark	Cohort study	24505 women receiving antenatal care in Aarhus University Hospital from 1989-1996	Overweight and obesity: 2.6 (1.2-5.8)

2.10 Interventions for maternal obesity

Approaches to prevent complications of obesity in pregnancy can be offered either pre-pregnancy or during pregnancy. The main approaches to obesity interventions in the general population which could be utilised pre-pregnancy include lifestyle changes (i.e. dietary, physical activity and behavioural therapy interventions), pharmacotherapy (for example, Orlistat and Metformin) and bariatric surgery (surgery whose sole purpose is to reduce the weight of the individual). During pregnancy, most of these interventions – in particular, bariatric surgery and some pharmacotherapies – are contra-indicated.

Interventions during pregnancy are discussed in Chapter 3 and a systematic review of the evidence on lifestyle interventions for obesity in pregnancy is presented in Chapter 5. Thus, the following sections will focus on pre-pregnancy interventions only.

Evidence from the literature shows the correlation between obesity pre-pregnancy and adverse outcomes, and so effective interventions pre-pregnancy to reduce BMI in the overweight and obese could be of enormous benefit. The options available pre-pregnancy are either at the population level or the individual level. At the population level political, economic, sociodemographic, technological, legislative or environmental strategies can be employed to reduce obesity prevalence. At the individual level, the options available are pharmacotherapy, bariatric surgery, lifestyle interventions, or combinations of these.

2.10.1 Pre-pregnancy interventions at the population level

Political

As there is now acceptance that there is a global obesity crisis, as alluded to in the recent United Nations high level meeting on non-communicable diseases, there is the political will to provide solutions and policies to support healthy lifestyles (improved diet and increased physical activities) (167-168). Political interventions such as mass media health promotion campaigns, for example Change for Life (169), legislating and imposing taxes on companies that sell unhealthy foods containing trans-fat, sugar-sweetened beverages, and government policies banning trans-fat, may serve to reduce obesity in the long term at the population level (170). A statement by Dame Sally Davies, Chief Medical Officer for England, recently intimated that if food companies do not reduce the amount of refined sugars in their food products, she might be forced to recommend imposing taxes as a last resort (171). Hungary already has measures in place that tax foods which are high in sugar and salt and France has recently done the same. The recent modelling evidence by Raynor and Mytton (2012) provides a comprehensive summary of this (172). It suggests that the level of tax levied on unhealthy foods in Hungary and France may not have much influence but provides a step in the right direction. It proposes that to see a marked change in behaviour or reduction in the consumption of sugar, salt and saturated fat-rich diet, the tax ought to result in price increases of at least 20%. A recent modelling study by Briggs et al. estimated a 20% tax on sugar-sweetened drinks would reduce the number of obese adults in the United Kingdom by 1.3%, with the greatest impact in the 16 to 29 year age group and hence would be likely to have a higher impact in the pregnancy population. A study from Australia calculated a saving of approximately 660,000 disability-adjusted life-years on a 10% reduction in salt, sugar and saturated fatty acid-rich food. Another approach is to impose tax on manufacturers who produce unhealthy foods in order to incentivise them to promote healthier options. This may provide a balance between influencing the market and maintaining

consumer choice (72). Legislation on food labelling, subsidies on healthy foods and market restriction could be important policy interventions that may reduce obesity prevalence (167). Political intervention that provides a clear agenda with the backing of national and international leaders such as WHO, World Bank and United Nations, with agreement from government leaders, may ensure that governments provide policies that align with healthy diets and improved levels of activity, thus contributing to reducing obesity pre-pregnancy.

While these policies may change behaviour in terms of eating healthily, and reducing the intake of sugar-sweetened drinks (168), the direct evidence that this results in a reduction in obesity prevalence is currently lacking. Thus, the political will to do this is proving difficult to secure as governments become concerned about taxes and strong lobbying by big cooperate organisations as well as being accused of being a “nanny state”.

Economic

Population-level interventions require adequate funding for implementation and international cooperation to provide adequate sustained funding for programmes that address obesity reduction. These policies are likely to be cost-effective as reduction in obesity prevalence could reduce morbidity and hence health care costs (170, 173). A recent report from the Academy of Royal Colleges led by Stevenson et al. highlights the importance of making every contact count, and the need for appropriate services to refer to (174). The report stresses that an investment of at least 100 million pounds in each of the next three financial years will be needed to address the shortfall in obesity services throughout the country. The evidence that this amount of funding will reduce obesity prevalence has been extrapolated from smoking cessation (174). A recent study in Science stresses that early years intervention from 0-5 (i.e. prenatal to aged five years) is extremely cost-effective compared to beyond aged 5 years (175).

Sociodemographic

In developed countries obesity is more common in the lower socioeconomic groups, whilst in developing countries the opposite is the case (176). Any population-based intervention should therefore engage and include targeting the sociodemographic groups most affected. In developed countries most published lifestyle interventions have under-representation of lower socioeconomic groups despite obesity being more common in these groups (177). This gap could be addressed by developing and trialling an intervention within a diverse community. A recent Marmot report, Fair Society Healthy Lives, alludes to the importance of early life intervention in addressing sociodemographic inequality (178)

Technological

With the advent of mass media and television there is ample opportunity for mass marketing and advertising unhealthy foods. Thus, banning the advertisement of unhealthy diets on television, particularly to children and adolescents, may contribute to reducing obesity pre-pregnancy (167, 173). However, the advertising industry employs around 300,000 people in the UK alone with a total expenditure of £16.1 billion. Global marketing needs to be regulated in order to protect children against the commercial promotion of unhealthy foods and beverages. Evidence that this approach may work is, however, lacking.

Environmental

Policies that incorporate town planning, such as the development of safe neighbourhoods, and increasing the number of local parks, walking areas and cycling routes, may improve physical activities (179). Secondly, reducing the number of fast food stores, shops and restaurants concentrated around schools and small localities by borough councils may also reduce the consumption of

unhealthy foods (180) (181). Environmental issues were alluded to in the Foresight report as promoting passive obesity (37). Thus, improving the environment may lead to improvements in physical activity levels and reduce the pre-pregnancy prevalence of obesity (182). Health impact assessment should be mandated when planning communities, as evidence from NICE alludes to its potential benefits (NICE (87) (183). This has been shown to be effective in some regions in France, the Netherlands and Denmark (184-185), and may also be true in the United Kingdom (186) (187).

2.10.2 Interventions for preventing obesity in children; targeting girls before reproductive years

Prevention of obesity in girls before they reach reproductive age is likely to be an effective strategy for the prevention of obesity in pregnancy. Over the last 30 years, the increase in obesity prevalence reported in adults has also been shown in children in many countries (e.g. China, India, Mexico and Canada) with evidence of some deceleration of the rate in the UK, the USA (188) and Australia (189). Once obesity is established, it is difficult to reverse.

A recent Cochrane systematic review meta-analysis, which assessed educational, health promotion and behavioural interventions in children of less than 18 years of age, demonstrated that childhood obesity lifestyle interventions may be effective in reducing adiposity (190). The results from this review should be interpreted with caution due to the level of heterogeneity observed between studies and the potential biases noted in many of the studies. Most of the included interventions combined dietary and activity modification strategies which may be limited in their approach and it is suggested that consideration ought to be given to other approaches such as advertising, obesogenic environment and school policies. Further synthesis of the included studies demonstrated that school curricula, including healthy eating and physical activity, may be effective. The review highlights that childhood obesity lifestyle

interventions can be both safe and effective, and from the limited data on indicators of equity, appear to be equitable.

Of the 37 studies included, 19 analysed the effect of the outcome based on gender. Eight showed no gender difference in outcome, four showed more of an effect on males than on females and seven showed more of an effect on females than males. Of the 18 studies which did not analyse gender, five of the studies included only females. The Cochrane review did not meta-regress on gender.

There are strengths in focusing on childhood obesity prevention. If shown to be cost-effective and not harmful to girls, then such interventions may reduce adult obesity in women and hence pre-pregnancy obesity, which may improve outcomes for mother and infant and minimise the intergenerational increase in obesity prevalence and its associated co-morbidity. The weakness of lifestyle interventions in children is that they may be deemed stigmatising, highlighting the problem to be the child's fault. It is well recognised that most of the beneficial effects of childhood interventions have not been sustained (191) and this may be due to the general obesogenic environment in which there is aggressive marketing or advertising of the unhealthy lifestyle to children at school, in the community and at home via television or sports sponsors of companies that sell unhealthy foods such as Coca-Cola. Also, introducing interventions in childhood may be far too late. With evidence of fetal programming, focusing on dietary or activity changes during the intra-uterine environment, such as interventions during pregnancy, may be more effective with possibly greater uptake and sustainability (190).

While it is extremely important to tackle the obesity epidemic at the population level by changing the environment, the fact that obesity is rising in most countries and most populations implies that interventions also ought to focus on the individual as well as the population.

2.10.3 Pre-pregnancy interventions focusing on the individual

Bariatric surgery pre-pregnancy

Surgery whose purpose is to reduce weight (bariatric surgery) may offer an effective treatment modality. There is an increasing trend in bariatric surgery being offered and performed in the UK for cases in which lifestyle interventions have not worked, particularly for those with morbid obesity (192). Obstetricians are increasingly seeing pregnant women who have had bariatric surgery (193).

The operation can either be classified as restrictive or malabsorptive; some patients may have both. Restrictive surgery is focused on reducing the size of the stomach; for example, gastric banding performed through keyhole surgery, i.e. laparoscopically. The restrictive method is intended to reduce the capacity of the stomach and hence ensure reduced food intake and the feeling of fullness. The malabsorptive procedure involves diversion of part of the gullet; for example, biliopancreatic diversion or jejunoileal bypass, which then reduces food absorption and in so doing reduces uptake of nutrients. Most of these procedures are now performed through keyhole surgery as it has minimal complications and reduced length of hospital stay (194); nevertheless, this can be very expensive (194).

Evidence suggests that weight loss associated with these operations is substantial compared to the non-intervention group (192). A ten-year follow-up of such patients showed a sustained weight loss marked with improvement such as diabetes, hypertension, sleep apnoea and abnormal lipids (195-196). However, it is important to note that these operations are not free of side effects or indeed complications. There is about 0.1% mortality associated with these operations and other complications such as bowel hernia, blockage of the bowel, and infection (197). Additionally, patients who have had such operations are at risk of deficiencies in micro-nutrients such as B12, folates and zinc (198). The success of the operations is dependent on the surgeon's skill level, type of

surgery, patient indication, psychological support and the back-up lifestyle intervention afterwards, emphasising the importance of follow-up.

Weight loss following bariatric surgery may improve fertility, either because of improved confidence and sexual interest, or due to improved hormonal endocrine function which is favourable to fertility (199-200). There is little high quality evidence of the benefits of bariatric surgery on later pregnancy. However, some studies show that such pregnancies have a reduced prevalence of maternal complications such as gestational diabetes and pre-eclampsia compared to pregnancies of obese women without surgery (201). Currently, there are no data to answer the question of whether bariatric surgery prior to pregnancy reduces perinatal mortality in subsequent pregnancies.

In view of the micro-nutrient deficiency and the concern that rapid weight loss following bariatric surgery may contribute to fetal growth restriction, most guidelines recommend that pregnancy is deferred for at least a year to 18 months (198).

Drugs: weight loss agents

Weight reducing agents have been around for over twelve years but most have been deemed ineffective and there have been questions over their safety, particularly for women of reproductive age because of the concern about teratogenicity (202). As such, most of these drugs, such as Orlistat, are contra-indicated in pregnancy. A newly licenced anti-obesity drug, Toperamate, has been associated with increasing the risk of oral cleft (cleft lip and cleft palate) (203). Moreover, extreme weight loss peri-conception has been associated with adverse outcome and a recent NICE guideline advises against this (204).

Drugs: Insulin sensitive agents

Metformin, a drug used in the treatment of type 2 diabetes and an example of an insulin sensitive agent, is becoming commonly used in obese women pre-pregnancy, particularly in women with polycystic ovarian syndrome where the pathophysiology is thought to be insulin resistance. In diabetic patients, metformin sensitises the insulin receptors to insulin and reduces endogenous insulin production. Its use in obese non-diabetic and non-PCOS women for weight loss has not yet been investigated. (205).

2.10.4 Lifestyle interventions focusing on the individual

Preventive medicine aims to undertake measures to prevent disease. The National Institute for Clinical Excellence (NICE), the RCOG study group on Obesity and Reproductive Health, the American Dietetic Association, and the American Society of Nutrition (2009) advocate weight loss pre-pregnancy for obese women and recommend randomised trials to evaluate pre-pregnancy interventions (206-209). Weight loss can be achieved by lifestyle interventions incorporating the combination of a healthy low caloric intake, low glycaemic index diet, increased physical activity and behavioural modification (210).

Few studies have evaluated weight changes pre-pregnancy. One study reported that women with BMI increase between pregnancies from normal weight to obese, and normal weight to overweight, were at increased risk of medically indicated preterm birth (211). Inter-pregnancy weight gain was associated with a dose-response increase in the risk of gestational and type 2 diabetes (212). A nationwide Swedish study of 151,025 women evaluating inter-pregnancy BMI change and adverse outcome reported that compared to women whose BMI changed between -1.0 and 0.9kg/m^2, the odds for adverse outcomes for those who gained 3kg/m^2 or more over two years were approximately doubled for pre-eclampsia, gestational hypertension, gestational diabetes, large for gestational age babies and stillbirth (213).

There is an urgent need for studies in both the UK and internationally to evaluate interventions that address obesity pre-pregnancy and during pregnancy. These periods have been deemed the critical and sensitive periods for the primary prevention of obesity (214). This thesis will focus on lifestyle intervention during pregnancy. A summary of interventional approaches during pregnancies is presented in Chapter 3. A systematic review and meta-analysis of lifestyle interventions during pregnancy is presented in Chapter 5.

CHAPTER 3: Rationale, aims and objectives of proposed research

3.1 Introduction

Prior to pregnancy, interventions described in Section 2.10.2 above, including pharmacotherapy and bariatric surgery, could be considered as part of planning for pregnancy. However, around half of pregnancies in the United Kingdom are unplanned (215) and only a small proportion of women planning pregnancy follow the recommendations for nutrition and lifestyle (215). Thus, an intervention which is developed pre-pregnancy may only reach a small proportion of women who could benefit from it. This may be due to difficulty in identifying a pre-pregnancy point of care in that there is no obvious contact point for most women planning pregnancy.

In contrast, during pregnancy, there is sufficient evidence to suggest that mothers are more motivated to adapt healthy lifestyle changes - for example, stoppage of alcohol and smoking (216) - and this could also be true for lifestyle behaviour change during pregnancy (217). Current government policy and the Royal College of Obstetricians and Gynaecologists support a life-course approach to tackling the obesity epidemic and a safe effective intervention during pregnancy may provide benefit for mother and baby as well as generations to come (218-219). However, recent systematic reviews concluded that interventions for obese pregnant women to improve maternal and perinatal health outcomes remain unclear and equivocal (177, 220). A recent National Institute of Health and Clinical Excellence guideline on weight management before, during and after pregnancy recommended the need for randomised controlled trials (RCTs) on lifestyle interventions in pregnancy in the United Kingdom to inform safe and effective means of improving outcomes and to define optimal gestational weight gain for pregnant women (221).

3.2 Outcome measures used in maternal obesity interventions

A recent study by Thangaratinam which analysed lifestyle interventions for restricting weight gain in pregnancy asked clinicians what they would deem appropriate as a primary outcome for lifestyle interventions in pregnancy. They recommended focussing on gestational diabetes, pre-eclampsia, Caesarean section, preterm delivery and birth weight, as well as gestational weight gain based on BMI of the mother pre-pregnancy (222). The Institute of Medicine (IOM) in the United States of America (USA) has recommended gestational weight gain relative to each BMI category, as shown in Table 4 below, and this is used as a reference range. This advice has been based on observational studies. Data from interventional studies may confirm or refute these recommendations being used as optimum weight gain in pregnancy for each BMI category (223).

Table 4: 2009 IOM gestational weight gain recommendations USA

Pre-pregnancy BMI category	Total weight gain range(kg)	Rate of weight gain 2nd and 3rd trimester mean range in kg/week
Underweight (<18.5kg/m^2)	12.5-18	0.51 (0.44-0.58)
Normal weight (18.5-24.9kg/m^2)	11.5-16	0.42(0.35-0.50)
Overweight (25.0-29.9kg/m^2)	7-11.5	0.28(0.23-0.33)
Obese (≥30.0kg/m^2)	5-9	0.22 (0.17-0.27)

3.3 Behavioural interventions in obese pregnant women

There are two approaches commonly adopted to improve pregnancy outcome. One focuses on restriction of gestational weight gain and the other on improvement of insulin sensitivity. Both interventions focus on behavioural change but with different emphases and different dietary recommendations.

The rationale underpinning the focus on insulin sensitivity is that pre-pregnancy obesity and excessive weight gain in pregnancy are associated with exaggeration of the physiological state of insulin resistance in pregnancy, leading to associated postprandial hyperglycaemia and other related metabolic sequelae (103, 224). Obese women gain less weight during pregnancy compared to the lean, but they also have a lower recommended weight gain during pregnancy and hence a greater proportion do not meet the USA Institute of Medicine recommended weight gain compared to the normal or overweight women (Table 4) (223). While a significant number of observational studies conclude that there is an association between adverse pregnancy outcome and excessive weight gain (223, 225), because of the lack of appropriately powered interventional studies, the National Institute of Health and Clinical Excellence guideline 'dietary intervention and physical activity intervention for weight management before, during and after pregnancy' recommended that more robust and appropriately powered interventional studies are required which focus on improved clinical outcomes and not only gestational weight (204). A recent meta-analysis which undertook a systematic review of all the studies which have attempted to restrict weight gain showed that although a modest restricted weight gain can be achieved (1.42kg less in weight gain compared to control) (CI=0.95-1.89kg) (222), there is no good quality evidence yet for a clear beneficial effect on clinical outcomes. This might suggest that the focus on gestational weight gain is inappropriate. However, most of the studies reviewed were of a small size and underpowered to assess clinical outcomes and larger, better designed studies are required.

The strategies employed to date to restrict gestational weight gain are varied and include either diet alone or diet and physical activity. Thangaratinam et al.'s review suggests that diet is more effective (222). Dietary advice varied between calorific restriction and portion control. The frequency and mode of delivery of the intervention varied widely from study to study and at present there seems to be no pattern of relationship between intensity and outcome (226).

There are several relevant and large ongoing trials undertaking behavioural interventions in overweight and obese women during pregnancy which are adequately powered to assess clinical outcomes and their findings are awaited with interest. These include a study from Australia, the LIMIT randomised controlled trial (limiting gestational weight gain for overweight and obese women to improve health outcomes) study (Clinical trial register ACTRN 12607000161426), the HELP study (UK), and the United Kingdom pregnancy better eating and activity trial (UPBEAT study). Although gestational weight gain (GWG) is not the primary outcome in these studies, it is assessed in all and will provide important information on the relationship between restriction of weight gain and pregnancy outcome (227). The recently published LIMIT study did not show improvement in primary clinical outcome such as gestational diabetes and large for gestational age infant (67); however, as a secondary outcome measure, it showed reduction in the proportion of infants who were macrosomic.

3.3.1 Prevention of GDM and macrosomia

Other studies have focused on the role of abnormal glucose tolerance in adverse outcomes in obese pregnancies. Recent evidence from the HAPO study shows that there is a dose-response association between maternal hyperglycaemia and perinatal morbidity (228). As mentioned above, the predominant metabolic change associated with obesity and pregnancy is heightened insulin resistance, which predisposes women to GDM (224). Thus, lifestyle interventions currently used in managing diabetes, whether type 2 diabetes or indeed gestational diabetes, are likely to be effective in obese pregnant women without co-morbidities in preventing diabetes and other associated adverse outcomes (97, 229). The lifestyle intervention used focuses on the individual changing their diet to a low glycaemic index diet with a reduced glycaemic load, combined with improved physical activity (229). A low glycaemic index diet results in diminished glycaemic response after oral intake relative to the same amount of carbohydrate from a reference food (230-231). Glycaemic load includes the total amount of carbohydrate within food consumed and the glycaemic index of the food, thus measuring both the quantity and

quality of the carbohydrate ingested and an indicator of total glycaemic response. There is strong evidence that maternal dietary glycaemic load has an inverse relationship with pregnancy outcome even in non-diabetics (231). This association may be more pronounced in the overweight and obese (231). Also, interventional studies which utilise low glycaemic index diets have resulted in improved pregnancy outcome in non-diabetics irrespective of body mass index (232), (233-235).

3.3.2 Physical activity

An increase in physical activity has been employed as an intervention in both GWG restriction studies and in current trials focusing on improvement of insulin sensitivity. Some concerns may arise about the safety of the fetus during physical activity in pregnancy, but there is ample evidence which suggests that low impact exercises and activities such as walking, swimming and cycling are safe in pregnancy (65, 236). High impact activities during the first trimester may be associated with early miscarriage but from mid-pregnancy onwards there is no data to suggest that exercise is associated with a deleterious pregnancy outcome. If anything, it may well be protective (81-84).

Several studies have demonstrated that physical activity in pregnancy is not associated with reduced birth weight except in association with high impact intensive exercises where growth restriction may occur (237-239) (240-241). However, a lower birth weight in those at risk of large for gestational age delivery could potentially be positive for the baby and reduce the incidence of birth trauma. Several studies have reported that physical activity during pregnancy may prevent adverse outcomes, particularly in women who have gestational diabetes (100, 242). A study which looked at moderate physical activity for a period of two hours per week showed a reduced chance of large for gestational age delivery and reduced birth weight in gestational diabetics, which was associated with improved neonatal outcome (243). Yet currently there are very few robust studies evaluating the role of physical activity

intervention in the prevention of gestational diabetes. Physical activity may improve insulin sensitivity and increased skeletal muscle glucose uptake (63).

3.3.3 Theoretical approach to intervention delivery

Whatever the intervention, it is important to evaluate the impact of lifestyle intervention on maternal behaviours (diet and physical activity) and to show that these are modified. Development of the intervention and potential success in achieving behavioural change depends on a detailed understanding of barriers to behavioural change. Addressing these barriers within interventions could contribute to the success of that intervention. Most studies fail to incorporate the theory of behaviour change within the design of their intervention and this may explain the difference between a successful or failed intervention (226).

The distinctive factors that obese pregnant women may not be motivated and may have low self-esteem could explain why they may not comply with a lifestyle intervention (244). They may come from a cultural background which views obesity as a form of affluence and may not accept the association of obesity with adverse health outcomes. They may have a partner or other important persons in their life who may restrict their motivation for behaviour change. They may also be stigmatised by their weight which may compromise changes in behaviour, or indeed they may have limited education and hence understanding the implications may be a challenge. A feasibility study which addresses these barriers, and assesses the glycaemic load as well as the physical activity, before embarking on a bigger main randomised trial will be an important pre-requisite to a successful intervention.

Obese women can be identified and are being identified at booking, as all women who book during pregnancy in the United Kingdom are recommended to be weighed and have their BMI calculated and documented (46, 204). Interventions that could help improve the outcome in this group of

patients are urgently needed. Whilst it is ideal for interventions to be offered pre-pregnancy or even in childhood or adolescence, the fact that adolescent obesity, childhood obesity and maternal obesity are all increasing alludes to the fact that this is not easily achieved (218).

In conclusion, the global obesity epidemic in adults, in childhood and in pregnancy highlights the importance of developing interventions that will be effective in reducing obesity. Evaluating these lifestyle interventions should be based on a robust framework such as the MRC framework for evaluating complex interventions (245). Any new interventions should incorporate detailed understanding of the metabolic milieu in pregnancy and evaluate possible implications for the wellbeing of the mother and baby.

3.4 Aim and objectives of PhD

The aim of this work was to assess the extent and the potential for the prevention of adverse impacts of obesity in pregnancy.

Specific objectives were:

(i) To summarise the literature on adverse effects of obesity on maternal and child health outcomes in the UK and elsewhere and to estimate the population attributable fraction (Chapter Two). This is a personal critical review.
(ii) To examine the determinants of maternal obesity and its effect and impact on different ethnic groups attending Guy's and St Thomas' NHS Foundation in South London (Chapter Four).
(iii) To conduct a systematic review and meta-analysis of lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcomes (Chapter Five).
(iv) To use the results of the systematic review as a platform to develop a multi-component lifestyle change (Community-based Activity and

Nutrition, CAN) intervention for maternal obesity to be piloted in the South London boroughs of Lambeth and Southwark (Chapters Six, Seven and Eight).

(v) To evaluate the feasibility of the CAN intervention in South London (Chapter Nine).

RESEARCH PAPER COVER SHEET FOR CHAPTER 4

Please be aware that one cover sheet must be completed for each 'Research Paper' included in a thesis.

1. For a 'research paper' already published

1.1. Where was the work published? **Oteng-Ntim E**, Kopeika J, Seed P, Wandiembe S, Doyle P. *Impact of obesity on pregnancy outcome in different ethnic groups: Calculating population attributable fractions*. Plos One; 2013: 8(1):e53749

1.2. When was the work published? **2013**

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion

1.3. Was the work subject to academic peer review? **Yes**

1.4. Have you retained the copyright for the work? **Yes**

If yes, please attach evidence of retention.
If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published?

2.2. Please list the paper's authors in the intended authorship order

2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments / In press

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)
I extracted the data and performed the analyses. I wrote the first draft of the paper.
……

NAME IN FULL (Block Capitals) …EUGENE OTENG-NTIM……

STUDENT ID NO: ……235138……..

CANDIDATE'S SIGNATURE …….. Date

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) ……..……

CHAPTER 4: The determinants and effect of maternal obesity in a South London population

Publication based on part of this work:

Oteng-Ntim E, Kopeika J, Seed P, Wandiembe S, Doyle P. *Impact of obesity on pregnancy outcome in different ethnic groups: Calculating population attributable fractions*. Plos One; 2013: 8(1):e53749

The above publication included births from 2004-2008. The study described below relates to a complete re-analysis of data on births from 1st January 2004 to 31st May 2012 performed in late 2013 and early 2014.

4.1 Introduction

Before developing and evaluating a lifestyle intervention for obese pregnant women in South London, it is important to establish the public health need for it. The prevalence of maternal obesity, as well as adverse associations and impact of maternal obesity on obstetric and neonatal outcome, in South London is undocumented.

Whilst the literature described in Chapter One alludes to adverse outcomes associated with obesity in pregnancy generally, this may not necessarily be the case in South London (a multi-ethnic deprived Inner London community) where I work and where the developed intervention is being trialled.

Over half of the women of childbearing age in most developed countries are either overweight (BMI 25-29.9kg/m^2) or obese (≥30kg/m^2) (1). It has been estimated that at the start of pregnancy around one in six women in England is obese (3). Women who are obese pre-pregnancy face an increased risk of adverse obstetric outcomes (12, 44). These risks include gestational diabetes (95), pre-eclampsia (7), thromboembolism (8), increased likelihood of

Caesarean section (135) and perinatal morbidity and mortality (11, 162). However, most of the published research has been conducted in predominantly White populations with less than 10% Black and ethnic minorities (44). Some studies conclude that obesity is more common in Blacks (3), while others conclude it is less prevalent (46), and ethnic susceptibility to obesity is not fully documented in the United Kingdom. An understanding of the independent impact of obesity in pregnant women in general, and in Blacks or ethnic minorities in particular, is important in identifying relevant interventions (246). Some recent evidence suggested that there might be a substantial difference between ethnic groups in the association of obesity with adverse outcomes (247).

Population attributable fractions (PAFs) are useful in assessing the impact of disease risk factors in populations. They take into account both the strength of the association between a risk factor and an outcome, and the prevalence of the risk factor in the population. There have been only a limited number of studies looking at PAFs for maternal obesity; two in the United States population (248) (249) and one in Western Europe (250). The latter has examined PAFs for the effect of obesity in a cohort of women living in the Netherlands on perinatal outcome, the majority of the population being white. No comparable studies have been published in the UK. The importance of PAFs in obstetrics was made poignant in a recent publication in the Lancet which concluded that overweight and obesity may contribute to 40% of stillbirths in developed countries (152).

The overall aim of this study is to examine the determinants of maternal obesity and its effect and impact on adverse pregnancy and neonatal outcomes in a large, ethnically diverse Inner London obstetric population.

The specific objectives of this work were:

a. To measure the prevalence of maternal obesity in a multi-ethnic community in South London over the period from 1st January 2004 to 31st May 2012, using deliveries at hospitals within Guy's and St Thomas' NHS Foundation Trust, part of King's Health partners.
b. To examine the determinants of obesity in women delivering at this group of hospitals.
c. To investigate the association between maternal obesity and obstetric and neonatal outcome in these data.
d. To measure the impact of maternal obesity on obstetric and neonatal outcome in this data by calculating population attributable fractions.

4.2 Methods

4.2.1 Study design and setting

This was a cross-sectional analysis of a routine clinical dataset. Data were obtained from all singleton deliveries at Guy's and St Thomas' NHS Foundation Trust between 1st January 2004 and 31st May 2012.

4.2.2 Data source and extraction

Data on all deliveries between January 1st 2004 and May 31st 2012 were identified and extracted from the maternity information system database (Terranova Pacific Services (UK) Ltd, Healthware system). Information is routinely entered by midwives in charge of each case. The software has some prompts, standardised clinical definitions and mandatory fields. In 2008 the BMI field was made mandatory to minimise missing BMI data as identified in a previous analysis. All midwives were given formal training before they were issued with login access to the database. To ensure the accuracy of the entries, two dedicated information technology midwives performed daily data quality checks, and cross-checks with clinical notes in some cases. The daily electronic

Birth and Discharge Notifications sent to South East London Shared Services Partnership also acted as a further data quality check.

Data items extracted for this research study included the patient identification number and date of birth, postcode of residence, maternal age at delivery, height, weight, BMI, parity, ethnicity, estimated date of delivery based on last menstrual period and/or ultrasound dating, smoking at booking, medical conditions at booking and during pregnancy, mode of delivery, liquor grading, estimated blood loss and infant's gestation at delivery, outcome of the infant at delivery, gender and birth weight, Apgar scores, cord pH and admission to special care baby unit (SCBU) or neonatal intensive care unit.

4.2.3 Data cleaning

The data were extracted from the maternity information system and imported into STATA 13. The following steps were taken in order to clean the data:

a. The data were sorted by patient identification number and date and time of delivery. Duplicate records were removed.
b. The number of individuals with a record for each variable in the dataset was checked.
c. Suspected recording errors for each variable were changed to missing value codes. For example, adjustments were made with regard to birth weight, such that birth weight greater than 15kg was thought to be unrealistic and hence was removed.
d. Consistency between pairs of variables was checked to identify extreme and unreasonable values. The pairs of variables examined included gestational age at delivery and birth weight.
e. Each variable was explored in depth to assess the extent of missing data. Methods for addressing missing data for BMI are described in Section 4.2.6.

4.2.4 Data management

Inclusion criteria

All singleton deliveries after 24 completed weeks of gestation born between January 2004 and May 2012 were included in the study dataset.

Exclusion criteria

Deliveries which ended in miscarriage, or termination, and multiple pregnancies were excluded from the study database.

Defining and recoding variables

BMI was calculated as weight (kg) at first antenatal visit (booking), divided by height (m) squared. In cases where information on weight and height were missing, the original notes were retrieved. BMI was recorded as missing when information on height and weight was missing from the original notes or the booking BMI was unrealistic (<13 kg/m^2). The subjects were categorised into the following groups of BMI: underweight <18.5 kg/m^2; normal 18.5 to 24.9 kg/m^2; overweight 25 to 29.9 kg m^2; and obese ≥ 30 kg/m^2. Obese mothers were further categorised into mildly obese (30-34.9kg/m^2); moderately obese (35-39.9kg/m^2); and morbidly obese (≥40kg/m^2).

All postcodes obtained from the electronic database were converted into Indices of Multiple Deprivation (251) using the Department of communities and Local Government data base and Centre for Maternal and online electronic converting system. The Index of Multiple Deprivation (IMD) brings together 7 different indicators which cover specific aspects or dimensions of deprivation: Income, Employment, Health and Disability, Education, Skills and Training, Barriers to Housing and Services, Living Environment and Crime. These are

weighted and combined to create the overall IMD 2010 (251). Obtained indices were then categorised into quintile groups for the United Kingdom with 1 being the least and 5 being the most deprived groups.

Information on ethnic group was classified as White (White British, White Irish and Other White), Asian (Bangladeshi, Indian, Pakistani, other Asian and Asian British), Black (Black Caribbean, Black African, other Black and Black British), Oriental (Chinese, Japanese, Korean and Vietnamese), Others and Missing (no information recorded).

Parity, defined as the number of deliveries beyond 24 weeks of gestation, was categorised into 0 (nulliparous), 1-3 (one to three previous deliveries) and ≥4 (four or more previous deliveries).

Maternal age was calculated as exact age in years on the day of delivery and then categorised into the following groups: <20 years; 20-24 years; 25-29 years; 30-34 years; 35-39 years; 40+ years. Smoking status at booking was documented and taken to represent the smoking status of the mother throughout pregnancy. Binary variables for hypertension and diabetes were generated using data from the following categorical variables: antenatal conditions; pregnancy complication; and problems at delivery. Women were considered to be a diabetes case when pre-existing type 1 or 2, or gestational diabetes, was recorded in any of the above variables at any level of gestation.

Data were also collected for other obstetric parameters, including Caesarean section, gestation at delivery, postpartum haemorrhage (blood loss after delivery greater than or equal to 500mls) and for neonatal parameters including birth weight, admission to neonatal intensive care and special care baby unit (NICU & SCBU).

4.2.5 Outcome variables

For objective (a), the primary outcome variable was the prevalence of maternal obesity in this population. For objective (b) the primary outcome variable was obesity, with the exposure variables being ethnicity, age, parity, smoking and deprivation.

For objectives (c) and (d), the primary outcome variables were diabetes in pregnancy (which includes pre-existing diabetes and gestational diabetes (defined by WHO) (252), Caesarean section (elective and emergency), instrumental delivery, postpartum haemorrhage status (greater than or equal to 500mls), preterm delivery (delivery less than 37 completed weeks); and for neonatal parameters low birth weight (<2.5kg), macrosomia (>4kg), admission to neonatal intensive care unit (NICU) or special care baby unit (SCBU), and perinatal death.

4.2.6 Statistical analysis

Stata 13 software was used for all analyses. Unless specified otherwise, a probability of 0.05 was used as the limit of statistical significance for all tests. All reported p-values are two-sided.

The prevalence of obesity was derived from the number of deliveries to obese pregnant women as a proportion of the total number of deliveries (with complete BMI data).

Data were summarised and displayed in cross-tabulations. The proportions of missing data for each variable were examined. Since BMI had a high proportion of missing data, the issue of potential selection bias was further investigated by cross-tabulating BMI with other variables and compared using the chi-squared test.

Associations between exposures and outcome were assessed using univariate and multivariate logistic regression. Potential confounders were identified by a statistically significant ($p<0.05$) association with the outcome in univariate analysis. For multivariate models, each potential confounder was added to the logistic regression model in turn. Confounding was assumed if adjusting for each potential confounder changed the odds ratio by 10% or more.

Imputation for missing BMI was not used in the multivariate models because there was evidence that missing data were not missing at random (see Section 4.3.2). To further investigate the possible bias resulting from missing data for BMI, two sensitivity tests were performed. Firstly, “BMI missing” was used as a dummy category in the multivariate logistic regression analysis and the results were compared with those obtained when women with missing BMI data were omitted (the standard approach). Secondly, since there was a reduction in the proportion of missing data in more recent years, models were re-run for births in more recent years (2008 onwards) and compared to the results for the whole dataset (January 2004 to May 2012).

It was anticipated before the analysis that there may be statistical interaction (effect modification) between factors, such as ethnicity and BMI, in their effects on obstetric and neonatal outcomes based on evidence outside pregnancy (27). To test for potential ethnic variation in the association between obesity and adverse obstetric outcomes, the analyses were stratified by ethnicity and formally tested for interaction by adding an ethnicity-obesity interaction term to the logistic regression model. Effect modification was confirmed by a p-value of <0.05 in a likelihood ratio test.

Adjusted population attributable fractions (PAFs) for the impact of obesity on different obstetric outcomes were also computed for the whole group and separately for each ethnic group. The formula used for calculating the PAF was:

$$PAF = P_1 (AOR-1)/AOR$$

where:

P_1 = proportion of women with the outcome of interest who are obese

AOR = Adjusted odds ratio for the association between obesity and the outcome of interest.

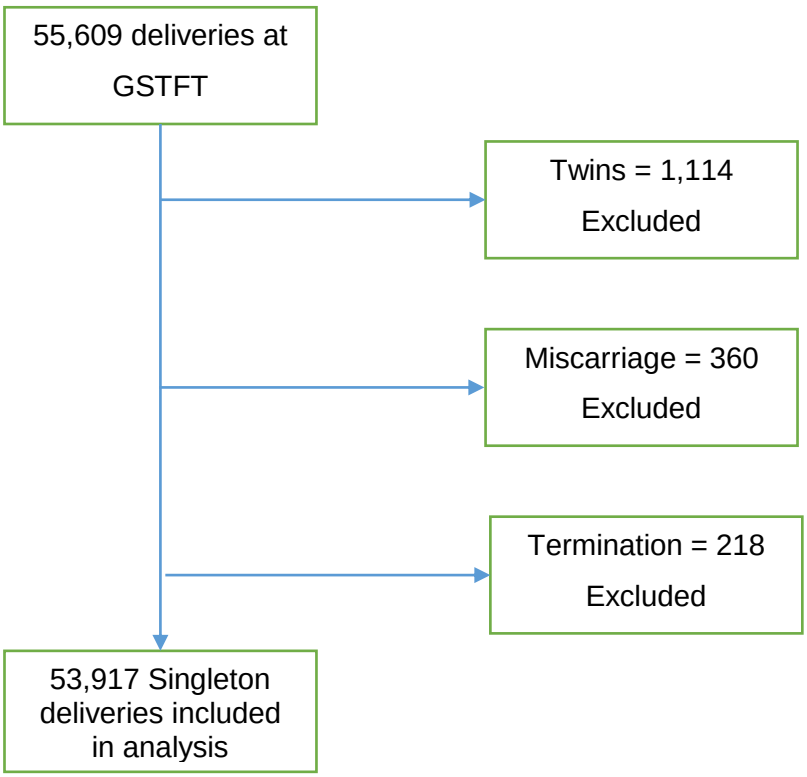
The study was approved by Guy's and St Thomas' ethics committee and it did not require consent.

4.3 Results

4.3.1 Description of study population

53,917 singleton deliveries between the 1st of January 2004 and the 31st of May 2012 were included in this analysis. Figure 8 describes the number and type of exclusions.

Figure 8: Figure illustrating the number of deliveries included in the analysis and the number of excluded deliveries by category



There was an average of 6,304 singleton deliveries per year to 2011 (see Table 5). Complete data on BMI was available for 43,249 women (80.2%) and of these 25% were classified as overweight and 15% were classified as obese. Fifty-five percent of mothers were aged between 25 and 34 years (mean age 31 years) and almost two-thirds (58%) were nulliparous. Seventy-eight percent of the population lived in deprived communities (4^{th} or 5^{th} quintiles IMD) and 46% were from ethnic minority groups: 35% Black; 6% Asian; 4% Oriental; and 0.5% Other (Table 5). For all variables other than BMI, smoking and gestation at delivery, the proportion of missing data was below 2% (Table 5). Missing data for BMI was examined in more detail below (Section 4.3.2).

With regard to the obstetric outcomes, 2.3% of the population had diabetes, 8.7% and 19.7% had elective and emergency Caesarean section respectively, 13.6% had instrumental delivery and 32.3% had postpartum haemorrhage (Table 6). In relation to neonatal outcomes, 6.5% of the infants were delivered preterm, 10.1% were macrosomic, 6.7% had low birth weight, 5.7% were admitted to either special care or neonatal intensive care unit and the proportion that resulted in perinatal death was 0.8% (Table 6).

4.3.2 Missing data for BMI

The proportions of individuals with missing BMI data by year of delivery, maternal characteristics and outcome categories were compared (Tables 7 and 8). Most of the variables showed little difference in the group with missing BMI data compared to the group with recorded BMI data. However, despite these small differences, in light of the large sample size, low P-values were obtained. Individuals with missing data for BMI were more likely to be delivered before 2008, were more likely to be nulliparous, slightly older, less deprived and much less likely to have diabetes (Tables 7 and 8). These maternal characteristics are associated with a lower prevalence of obesity (see Section 4.3.3). This provided evidence that BMI data were more likely to be missing for non-obese, rather than obese women, and was thus not missing at random.

4.3.3 Determinants of obesity

There was evidence of a weak trend of increasing obesity prevalence with calendar year, although the effect was not marked until 2012 when the odds of obesity were 20% higher than in 2004 (Table 9). The prevalence of obesity was 10% in Whites, 24% in Blacks, 10% in Asians and 5% in Chinese (Table 9). After adjusting for confounding factors, the odds of maternal obesity were found to be 2.4 times higher in Blacks compared to Whites (AOR=2.37; CI=2.27-2.52) and less than half in Chinese compared to Whites (AOR=0.44; CI=0.35-0.56) (Table 9). The odds of obesity increased steadily with increasing age and parity. An association between deprivation and obesity was present at the highest two quintiles of deprivation (AOR=1.56; CI=1.39-1.75 for level 4 and AOR=1.89; CI=1.68-2.13 for level 5, the most deprived group) (Table 9).

4.3.4 Association between BMI and pregnancy outcome

Increasing maternal BMI was strongly associated with increasing risk of adverse pregnancy outcome including diabetes, Caesarean section (elective and emergency) and postpartum haemorrhage (Table 10). The trend was strongest for diabetes with odds ratios increasing from 2.32 (95% CI=1.96-2.72) for overweight women to 8.74 (95% CI=6.62-11.55) for morbidly obese women compared to women with normal BMI. For emergency Caesarean section, odds ratios increased from 1.37 (95% CI=1.29-1.45) for overweight women to 1.96 (95% CI=1.64-2.34) for morbidly obese women compared to women of normal BMI. Postpartum haemorrhage showed a similar pattern and magnitude of effect. In these examples risks were lowest for underweight women compared to women of normal weight (Table 10). A weaker association was seen for preterm delivery, reaching statistical significance in the morbidly obese group (OR=1.66; CI=1.271-2.16). For neonatal outcomes, there was a clear association between maternal BMI and macrosomia, with odds ratios increasing from 1.53 (95% CI=1.41-1.65) for overweight women to 2.33 (95% CI=1.89-2.88) for morbidly obese women, compared to women with normal BMI.

Increasing maternal BMI was associated with increasing odds of admission of the baby to a neonatal intensive care or special care baby unit: odds ratios of 1.41 (95% CI=1.23-1.62) for obese women and 1.63 (95% CI=1.22-2.17) for morbidly obese women compared to women with normal BMI.

There were relatively few perinatal deaths (347), making the numbers in each BMI category small. Categorising obesity as BMI≥30kg/m^2, obese women were 57% more likely to lose their babies through stillbirth or early neonatal death (OR=1.57; CI=1.21-2.04) than women with BMI less than 30kg/m^2 (Table 11, sixth column); this finding reached statistical significance. The influence of obesity as a categorical variable is summarised in Table 11 (third column).

4.3.5 Association between obesity and pregnancy outcome within ethnic groups

Table 11 shows the effect of obesity on obstetric outcomes within each ethnic group. Obesity was associated with diabetes in all four ethnic groups, and there was evidence of statistical interaction (P=0.004). Odds ratios were highest for the Asian group (OR=5.82; CI=3.90-8.70) and the Chinese group (OR=4.51; CI=2.28-8.93), and lowest for the Black group (OR=3.12; CI=2.61-3.73). There was evidence of interaction between obesity and ethnicity in the likelihood of both elective (p=0.02) and emergency (p<0.001) Caesarean section, odds ratios being highest for the Chinese population (AOR=3.38; CI=1.81-6.31 for elective CS and AOR=2.01; CI=1.19-3.44 for emergency CS). The odds ratios for admission of the neonate to a neonatal unit also showed significant variation according to ethnic group (p=0.004): odds ratios were highest for the White group (OR=1.75; CI=1.49-2.06) and lowest for the Chinese group (OR=0.98; CI=0.30-3.22). The effect of maternal obesity on other outcomes showed variability across the ethnic groups, but this variation did not reach statistical significance.

4.3.6 Sensitivity analyses

Two sensitivity analyses were performed to investigate the impact of missing BMI data. Firstly, logistic regression analyses were repeated using "BMI missing" as a category in the logistic regression model. The results are presented in Table 12. The findings are very similar to the findings presented in Table 11 (using the standard analysis method). A second sensitivity analysis was conducted repeating the analysis using more recent births, from 2009 to 2012, for which the proportion of missing BMI data was around 15%. The findings are presented in Table 13. Again, the findings are similar to those in Table 11.

4.3.7 Population attributable risk fractions

Adjusted odds ratios and proportions of obesity were used to calculate population attributable risk fractions (PAFs) for obesity in the total population and in each ethnic group. In order of magnitude, PAFs for the total study population were 30% for diabetes, 12% for Caesarean section (elective and emergency combined), 9.3% for perinatal death, 8.1% for macrosomia, 5% for admission to a neonatal unit, 4.2% for postpartum haemorrhage, and 3.7% for preterm delivery (Table 14).

There were substantial differences in PAFs between different ethnic groups, reflecting both differences in the strength of associations between obesity and the outcome, and the prevalence of obesity in the different ethnic groups. The contribution of excessive weight to diabetes in the population was highest in the Black group (35.3%), followed by that in the White group (26%), the Asian group (26.3%), and the Chinese group (13.6%) (Table 14). For elective Caesarean section the PAF was highest in the Black group (13.3%), followed by 9.6% for the Chinese, 3.4% for the White, and no impact for the Asian group. For emergency Caesarean section, PAFs were lower for Asian women (2%) and Chinese women (2.8%) compared to Black (4.8%) and White

(5.6%) women. A similar pattern was seen for postpartum haemorrhage (PAFs in order of magnitude 6% for the Black group, 3% for the White, 1.6% for the Asian group, and 1.9% for the Chinese group), and preterm delivery (PAFs in order of magnitude 3.6% for the Black group, 3.1% for the White, 3% for the Asian group, and 1% for the Chinese group).

For the neonates, PAFs for macrosomia are 14.2% for the babies of Black mothers, 12.1% for the babies of Asian mothers, 6.2% for babies of Chinese mothers and 6.1% for babies of White mothers (Table 14). For admission to a neonatal care unit PAFs are, in order of magnitude, 6% for the babies of White mothers, 3.5% for the babies of Black mothers, 0.5% for Asian mothers and no impact for the babies of Oriental mothers (Table 14).

4.4 Discussion

4.4.1 Summary of findings

This research estimates the prevalence of obesity in pregnancy in a South London population (deliveries between 2004 and 2012) to be 15%. This shows that Black people, are 2.4 times more likely to be obese compared to Whites (OR=2.37; CI=2.27-2.52) and that Chinese people are less than half as likely to be obese as Black people (OR=0.44; CI=0.35-0.56). Maternal body mass index increased with increasing age and parity. There was a weak association between deprivation and obesity except at the two most deprived quintiles of deprivation where the association was strong (for fifth quintile OR=1.89; CI=1.68-2.13 and fourth OR=1.56 (1.39-1.75).

The findings presented here show a strong association between maternal obesity and adverse obstetric and neonatal events, including diabetes, Caesarean section, preterm birth, postpartum haemorrhage, macrosomia and admission to neonatal intensive care unit or special care baby unit. This work confirms previous findings on the adverse effects of maternal obesity (44).

Interestingly, the association between obesity and diabetes showed significant variation according to the ethnicity of the mother, being strongest for Asian women and lowest for Black women. This observation has been reported only once previously in the United Kingdom (247), when it was concluded that body mass index interacts with racial group with regard to the prevalence of gestational diabetes, particularly in South Asian women (247).

A relevant question to ask is: How much of the burden of adverse obstetric and neonatal events could be avoided if obesity was eliminated, or at least reduced, in the population? In this study, it was shown that 30% of diabetes in pregnancy, 12% of Caesarean section, 4.2% of postpartum haemorrhage, 3.7% of preterm delivery, 8% of macrosomia, 5% of admissions to a neonatal intensive care unit or special care baby unit, and 9.3% of perinatal deaths could potentially be avoided if there was no maternal obesity in the population. These are, of course, theoretical calculations, but they illustrate the important role obesity plays in determining obstetric morbidity in this population. They also demonstrate the opportunity for substantial cost savings in obstetric health services in this area of South London.

The impact of obesity varied by ethnic groups and reflected differences in the prevalence of obesity, and the strength of the association between obesity and the outcomes. This variation was most marked for diabetes, as it was estimated that 35.3% of diabetes could be attributed to obesity in the Black population compared to only 13.6% in the Chinese population. In fact, most outcomes examined showed higher population attributable risk fractions for obesity in Black women, driven by the very high prevalence of maternal obesity in this group (24.4%). Although at the individual level obesity had a greater effect for some outcomes in Asian or Chinese women than in Black women, attributable risk fractions were lower for these groups because of the lower prevalence of obesity in these groups (4.7% Chinese and 9.7% Asian).

4.4.2 Interpretation of findings

The magnitude of the impact of obesity on diabetes (30%) and Caesarean section (12%) found in this study was similar to findings reported for the US population of pregnant women (248), which was 30% and 15% respectively. However, the PAF for macrosomia is lower in the current study (8.1%) in comparison with others (248, 250) (19% and 15%). This difference could be due to differences in the definition of macrosomia as well as differences in the underlying characteristics of the populations.

Obesity is associated with insulin resistance (224, 253). Insulin resistance predisposes to diabetes, pre-eclampsia (254), and macrosomia (255). Macrosomia tends to make vaginal delivery very difficult because of the size of the fetus; it is associated with an increase in Caesarean section rate. Following delivery of a macrosomic infant, the uterus is more likely to be atonic and hence predisposed to postpartum haemorrhage. Also, with a higher Caesarean section rate this also predisposes to postpartum haemorrhage. Recent guidelines from RCOG/CMACE and NICE emphasise the importance of managing obesity in pregnancy (26, 204). This study provides a strong indication that if we are able to reduce obesity pre-pregnancy, it would have a significant impact on maternal and perinatal morbidity and mortality. It also highlights that policies should address the demographic inequality associated with obesity in that it is more common in women from deprived communities, as well as from minority ethnic groups; thus, it has a greater impact on the Black population compared to other ethnic groups.

4.4.3 Limitations

This chapter has highlighted important new findings in obstetrics but it has some limitations.

Missing BMI data

Missing data is unfortunately common in studies where routine data sets have been used. In the dataset used for this research 19.8% of BMI data were missing. There could be several reasons for this. It could be because midwives who are meant to measure women and record height, weight and BMI in the healthware database were not aware that BMI was important and thus were not recording it as a matter of priority. This problem was recognised in 2008 and the BMI field on the database was made mandatory before the midwives could progress to the next data field. Another reason could be missing notes; however, this data is routinely recorded at booking directly into the healthware database, and hence missing notes are unlikely to be a significant reason for the missing BMI data, especially in more recent years.

Missing data can be classified as 'missing completely at random', 'missing at random' or 'missing not at random'. If it is assumed that the missing BMI data was missing completely at random or missing at random, then analysing the data using multiple imputation techniques can be advantageous as it ensures that the data are handled in an unbiased way and improves statistical validity (256). In order to assess whether the population whose BMI data were missing were similar to those with complete BMI data, the demographic profiles of women with and without BMI data were compared. It was found that BMI was more likely to be missing for women with a lower likelihood of obesity e.g. low parity, low level of deprivation and no diabetes. Thus, it is reasonable to assume that the missing BMI data were missing not at random. This is a well-recognised finding for parameters such as BMI which are visible to the clinician and which can vary between otherwise similar patients (256). It is possible that BMI was more likely to be measured and recorded for overweight or obese women because the midwife appreciated the clinical importance of this, and hence the distribution of BMI is likely to be on the lower side in the missing BMI group and higher in the recorded group. Missing data for women with low BMI will tend to inflate the prevalence, but we estimate that

even if all the women with missing data were not obese, the prevalence would fall to 12% (from 14.8%). The actual prevalence is likely to be somewhere between 12 and 14.8%.

There is a concern that missing BMI data - which is non-random - may bias the analyses. However, a sensitivity analysis, which used logistic regression analyses with a BMI missing dummy variable, and an analysis using data from 2008 onwards (where the proportion of missing BMI data was lower), showed a similar pattern of results to those obtained from the standard analyses. This provides evidence that any bias is likely to be minimal.

Confounding factors

Confounding is defined as a variable which is independently associated with the exposure variable and also independently associated with the outcome variable while at the same time the variable is not in the causal pathway. Not addressing confounding in studies is likely to lead to bias and every effort was made in this study to address important confounding factors such as the age, ethnicity, and parity of the patient, smoking, and deprivation quintile. This analysis also considered the calendar year at delivery as a confounder.

I accept that there may have been a confounding that was not addressed. For example, the study could not address confounding at the individual socioeconomic level, but it could be argued that individual socioeconomic level has a narrow definition limited only to the employment and education of the patient or partner. Hypertension may be an important confounding factor or effect modifier, or on the causal pathway to adverse outcome, and in future work I will be looking at this in more detail in prospective data collection in order to ensure that hypertension and other co-morbidity can be investigated in more detail. Finally, in this study I was unable to distinguish pre-existing diabetes from gestational diabetes so there was some degree of misclassification of outcome. Gestational diabetes accounts for 90% of all

diabetes in pregnancy. Of the remaining 10%, five percent is type 2 diabetes and the other five percent is type 1 diabetes (97). Thus, only a small proportion of diabetes in pregnancy existed pre-pregnancy, and while I accept that the data are not ideal, I would argue that it would have been unethical to wait for prospective longitudinal data before publishing the findings.

In conclusion, this chapter confirms that maternal obesity is linked to maternal and perinatal morbidity for both the individual and the population as a whole. Reducing the prevalence of obesity will reduce the likelihood of adverse events for the obese woman herself and the burden of adverse events in the population. The greatest population impact was seen for diabetes, where 30% of cases could potentially be avoided if all pregnant women were of normal BMI at the start of pregnancy. The impact of obesity is highest for Black women, reflecting the high prevalence of obesity in this group. Policies and strategies to address obesity in pregnancy will have the greatest impact if they target the whole population but with a proportionate emphasis on Black women.

Table 5: Summary table for background characteristics of the mothers

Description	Number of women	Percentage
All singleton deliveries	53917	100%
Year of delivery		
2004	5537	10.27%
2005	5826	10.81%
2006	6162	11.43%
2007	6188	11.48%
2008	6818	12.65%
2009	6423	11.91%
2010	6762	12.54%
2011	6716	12.46%
2012	3485	6.45%
Total	**53917**	**100%**
Maternal BMI at booking		
Underweight (<18.5 kg/m^2)	1430	3.3%
Normal weight (18.5-24.9 kg/m^2)	24743	57.2%
Overweight (25.0-29.9 kg/m^2)	10647	24.6%
Class I obese (30.0-34.9 kg/m^2)	4239	9.8%
Class II obese (35.0-39.9 kg/m^2)	1498	3.5%
Class III obese(≥40.0 kg/m^2)	692	1.6%
Total of obese ≥30	*6429*	*14.9%*
Total (non-missing)	**43249**	**100%**
Missing data	*10668*	*19.8%*
Mean BMI (SD) kg/ m^2	25.0 (5.3)	
Maternal age at delivery		
<20	2042	3.8%
20-24	7260	13.5%
25-29	12250	22.7%
30-34	17695	32.8%
35-40	11590	21.5%
>40	3080	5.7%
Total (non-missing)	**53917**	**100%**
Missing data	*0*	-
Mean Age at delivery (SD) years	31 (6)	
Parity		
0	31210	58%
1-3	21282	39.5%
4 plus	1351	2.5%
Total (non-missing)	**53843**	**100%**
Missing data	*74*	0.1%
Ethnicity		
White	28799	54.3%
Asian or Asian British	3004	5.6%
Black or Black British	19076	35.9%
Chinese	1926	3.6%
Other	288	0.5%
Total (non-missing)	**53093**	**100%**
Missing data	*824*	*1.5%*

Description	Number of women	Percentage
Smoking	3357	7.0%
Non-smoking	44753	93.0%
Total non-missing	**48110**	**100%**
Missing	5807	10.8%
Index of Deprivation		
1 (least deprived)	1663	3.2%
2	3094	5.8%
3	6148	11.4%
4	24269	45.3%
5 (most deprived)	18351	34.3%
Total (non-missing)	**53525**	**100%**
Missing data	*392*	*0.7%*

Table 6: Summary table of obstetric and neonatal outcomes

Outcomes	Number of women	Percentage
Diabetic Non-diabetic Total non-missing *Missing*	1213 52704 **53917** 0	2.25% 97.75% **100%** 0%
Elective Caesarean section Vaginal deliveries and non-elective Caesarean section Total non-missing *Missing*	4694 49223 **53917** 0	8.71% 91.29% **100%** 0%
Emergency Caesarean section Vaginal deliveries and non-emergency Caesarean section Total non-missing *Missing*	10592 43325 **53917** 0	19.65% 80.35% **100%** 0%
Instrumental delivery Non-instrumental delivery Total non-missing *Missing*	7333 46584 **53917** 0	13.60% 86.40% **100%** 0%
Postpartum haemorrhage Normal blood loss Total non-missing *Missing*	17345 36257 **53602** 315	32.36% 67.64% **100%** 0.58%
Preterm delivery Term delivery Total non-missing *Missing*	3476 47819 **51295** 2622	6.78% 93.22% **100%** 4.86%
Macrosomic Non-macrosomic Total non-missing *Missing*	5444 48473 **53917** 0	10.10% 89.90% **100%** 0%
Low birth weight Non-low birth weight Total non-missing *Missing*	3605 50312 **53917** 0	6.69% 93.31% **100%** 0%
NICU/SCBU No NICU/SCBU admission Total non-missing *Missing*	3089 50828 **53917** 0	5.73% 94.27% **100%** 0%
Perinatal death Live births surviving 7 days Total non-missing *Missing*	438 53479 **53917** 0	0.81% 99.19% **100%** 0%

Table 7: Table comparing maternal characteristics for deliveries with and without BMI measurement

Year of delivery	Non-missing BMI n(Column%)[Row%]	Missing BMI n(Column%)[Row%]
2004	3681(8.51)[66.5]	1856 (17.40)[33.5]
2005	4172(9.65)[71.6]	1654(15.50)[28.4]
2006	4579(10.59)[74.3]	1583(14.84)[25.7]
2007	4569(10.56)[73.8]	1619(15.18)[26.2]
2008	5362(12.40)[78.6]	1456(13.65)[21.4]
2009	5521(12.77)[86.0]	902(8.46)[14.0]
2010	6063(14.03)[90.0]	699(6.55)[10.0]
2011	6135(14.19)[91.3]	581(5.45)[8.7]
2012	3137(7.30)[90.8]	318(2.97)[9.2]
Total	43249(100)[80.2]	10668 (100)[19.8]
		P<0.001
Ethnicity ONS	**Non-missing BMI n(Column%)[Row%]**	**Missing BMI n(Column%)]Row%]**
White N %	23140 (54.23)[80.4]	5659 (54.28)[19.6]
Black N %	15288 (35.83)[80.1]	3788 (36.34)[19.9]
Asian N %	2410 (5.65)[80.2]	594 (5.70)[19.9]
Chinese N %	1598 (3.75)[83.0]	328 (3.15)[17.0]
Other N %	232 (0.54)[80.6]	56 (0.54)[19.4]
Total N %	42668 (100)[80.2]	10425 (100)[19.8]
		P=0.06
Maternal Age	**Non-missing BMI n(Column%)[Row%]**	**Missing BMI n(Column%)[Row%]**
<20 N %	1605 (3.71)[78.6]	437 (4.10)[21.4]
20-24 N %	5911(13.67)(81.4)[18.6]	1349 [12.65]
25-29 N %	9933 (22.97)[81.1]	2317 (21.72)[18.9]
30-34 N %	14286 (33.03)[80.7]	3409 (31.96)[19.3]
35-40 N %	9110 (21.06)[78.6]	2480 (23.25)[21.4]
>40 N %	2404 (5.56)[78.1]	676 (6.34)[21.9]
Total	43249 (100)[80.2]	10668 (100)[19.8]
Mean SD	31	31
		P<0.001
Parity- Cat	**Non-missing BMI**	**Missing BMI**

	n(Column%)[Row%]	n(Column%)[Row%]
0	24397 (56.48)[78.2]	6813 (63.97)[21.8]
1-3	17721 (41.03)[83.3]	3561 (33.43)[16.7]
4 or more	1074 (2.49)[79.5]	277 (2.60)[20.5]
Total	43192 (100)[80.2]	10651 (100)[19.8]
		P<0.001
Smoking	**Non-missing BMI n(Column%)[Row%]**	**Missing BMI n(Column%)[Row%]**
Smoking	2959 (93.13)[88.1]	398 (92.15)[11.9]
Non-smoking	40084 (6.87)[89.6]	4669 (7.85)[10.4]
Total	43192 (100)[89.5]	5067 (100)[10.5]
		P=0.01
IMD quintile	**Non-missing BMI n(Column%)[Row%]**	**Missing BMI n(Column%)[Row%]**
1 (least deprived)	1143 (2.66)[68.7]	520 (4.93)[31.3]
2	2245 (5.22)[72.5]	850 (8.06)[27.5]
3	4779 (11.12)[77.7]	1371 (12.99)[22.3]
4	19861 (46.22)[81.8]	4403 (41.73)[18.2]
5 (most deprived)	14943 (34.77)[81.4]	3407 (32.29)[18.6]
Total	42971 (100)[80.3]	10551 (100)[19.7]

Table 8: Table comparing clinical and obstetric outcomes for deliveries with and without BMI measurement

	Non missing BMI n(Column%)[Row%]	Missing BMI n(Column%)[Row%]
Non-diabetic	42098(97.3)[79.9]	10606(99.4)[20.1]
Diabetic	1151(2.7)[94.9]	62(0.6)[5.1]
Total	43249(100)[80.2]	10668(100)[19.8]
		P<0.001
Instrumental delivery	39871(92.2)[81.0]	9352(87.7)[19.0]
Elective Caesarean section	3378(7.81)[72.0]	1316(12.34)[28.0]
Total	43249(100)[80.2]	10668(100)[19.8]
		P<0.001
Non Em Caesarean section	34847(80.6)[80.4]	8478(79.5)[19.6]
Emergency Caesarean section	8402(19.4)[79.3]	2190(20.5)[20.7]
Total	43249(100)[80.2]	10668(100)[19.8]
		P=0.01
Non Instrumental delivery	37349(86.4)[80.2]	9235(86.6)[19.8]
Instrumental	5900(13.6)[80.5]	1433(13.4)[19.5]
Total	43249(100)[80.2]	10668(100)[19.8]
		P=0.57
Non-PPH	28805(67.0)[79.5]	7452(70.2)[20.6]
PPH	14185(33.0)[81.8]	3160(29.8)[18.2]
Total	42990(100)[80.2]	10612(100)[19.8]
		P<0.001
Non-macrosomic	38873(89.9)[80.2]	9600(90.0)[19.8]
Macrosomic	4376(10.1)[80.4]	1068(10.0)[19.6]
Total	43249(100)[80.2]	10668(100)[19.8]
		P=0.7
Non-NICU	40753(94.2)[80.2]	10075(94.4)[19.8]
NICU	2496(5.8)[80.8]	593(5.6)[19.2]
Total	43249(100)[80.2]	10668(100)[19.8]
		P=0.04
Live birth	42907(99.2)[80.2]	10577(99.2)[19.8]
Perinatal death	347(0.8)[79.2]	91(0.9)[20.8]
Total	43249(100)[80.2]	10668(100)[19.8]
		P=0.6

Table 9: Association of year of delivery, maternal ethnicity, age, deprivation and parity with obesity

	Obese n (%)	Non-obese n (%)	Crude OR (95%CI)	Adjusted* OR (95%CI)	P Value
Birth Year					
2004	567 (15.4)	3114 (84.6)	1	1	
2005	595 (14.3)	3577 (85.7)	0.91 (0.81-1.03)	0.92 (0.81-1.05)	0.22
2006	635 (13.9)	3944 (86.1)	0.88 (0.78-1.00)	0.92 (0.81-1.04)	0.19
2007	671 (14.7)	3898 (85.3)	0.95 (0.84-1.07)	1.00(0.89-1.14)	0.94
2008	773 (14.4)	4589 (85.6)	0.93 (0.82-1.04)	1.00 (0.89-1.14)	0.95
2009	805 (14.6)	4716 (85.4)	0.94 (0.83-1.05)	1.01 (0.90-1.14)	0.81
2010	866 (14.4)	5197 (85.6)	0.91 (0.82-1.02)	0.97 (0.86-1.10)	0.64
2011	968 (15.8)	5167 (84.2)	1.03 (0.92-1.15)	1.08 (0.96-1.22)	0.19
2012	549 (21.0)	2618 (79.0)	1.15 1.01-1.31)	1.21 (1.06-1.39)	0.01
Maternal ethnicity					
White	2313 (10.0)	20827 (90.0)	1	1	
Black	3725 (24.4)	11563 (73.6)	2.99 (2.74-3.07)	2.37 (2.27-2.52)	<0.0005
Asian	234 (9.7)	2176 (90.3)	0.97(0.84-1.12)	0.91 (0.79-1.05)	0.21
Chinese	76 (4.7)	1522 (98.3)	0.45 (0.36-0.57)	0.44 (0.35-0.56)	<0.0005
Other	22 (9.5)	210 (90.5)	0.94 (0.61-1.47)	0.88 (0.56-1.37)	0.56
Maternal age					
<20	145 (9.0)	1460 (91)	0.55 (0.46-0.66)	0.61 (0.51-0.73)	<0.0005
20-24	792 (13.4)	5119 (86.6)	0.86 (0.78-0.94)	0.86 (0.78-0.94)	0.001
25-29	1520 (15.3)	8413 (84.7)	1	1	
30-34	1955 (13.7)	12331 (86.3)	0.88 (0.82-0.94)	1.00 (0.92-1.07)	0.95
35-40	1475 (16.2)	7635 (85.8)	1.07 (0.99-1.16)	1.15 (1.06-1.25)	<0.001
>40	542 (22.5)	1862 (77.5)	1.61 (1.44-1.80)	1.49 (1.33-1.68)	<0.0005
Parity					
0	2537 (10.4)	21860 (89.6)	1	1	

1-3	3496 (19.7)	14225 (80.3)	2.12 (2.0-2.24)	1.68 (1.59-1.79)	<0.0005
≥4	389 (36.2)	685 (73.8)	4.89 (4.29-5.58)	2.92 (2.54-3.37)	<0.0005
Smoking					
Smoking	472 (16.0)	2487 (84.0)	1.09 (0.99-1.21)	1.22 (1.10-1.37)	<0.0005
No Smoking	5926 (14.8)	34158 (85.2)	1		
Deprivation					
1 Least deprived	79 (6.9)	1064 (93.1)	0.83 (0.64-1.07)	0.94 (0.72-1.21)	0.6
2	137 (6.1)	2108 (93.9)	0.73 (0.60-0.89)	0.81 (0.66-0.99)	0.8
	Obese n (%)	**Non-obese n (%)**	**Crude OR (95%CI)**	**Adjusted* OR (95%CI)**	**P Value**
3	391 (8.2)	4388 (91.8)	1	1	
4	2917 (14.7)	16944 (85.3)	1.93 (1.73-2.16)	1.56 (1.39-1.75)	<0.0005
5 Most deprived	2865 (23.7)	12078 (76.3)	2.66 (2.38-2.98)	1.89 (1.68-2.13)	<0.005

*Adjusted for birth years, maternal ethnicity, maternal age, parity, smoking and deprivation.

Table 10: Adjusted odds ratios (95% CI) for obstetric and child outcomes according to maternal body mass index (excluding missing BMI data category)

Characteristic	In whole population N (%)	BMI Category (Kg/m^2)					
		Underweight <18.5 N (%) OR[1] (95%CI)	Normal 18.5-24.9 N (%) OR[1]	Overweight 25.0-29.9 N (%) OR[1] (95%CI)	Mildly obese 30-34.9 N (%) OR[1] (95%CI)	Moderately obese 35-39.9 N (%) OR[1] (95%CI)	Morbidly obese>40
Diabetes	1151 (2.66)	9(0.63) 0.47(0.24-0.92)	327(1.32) 1.0	337(3.17) 2.32(1.97-2.72)	254(5.99) 4.48(3.75-5.36)	151(10.08) 7.80 (6.29-9.69)	73(10.55) 8.74(6.62-11.55)
Elective CS	3378(7.81)	79(5.52) 0.99(0.78-1.26)	1659(6.70) 1.0	891(8.37) 1.19(1.09-1.30)	461(10.88) 1.52(1.35-1.71)	182(12.15) 1.65(1.39-1.97)	106(15.32) 2.37(1.90-2.97)
Emergency CS	8402(19.43)	180(12.59) 0.69(0.59-0.82)	4305(17.40) 1.0	2322(21.81) 1.37(1.29-1.45)	1019(24.04) 1.61(1.48-1.75)	389(25.97) 1.84(1.62-2.10)	187(27.02) 1.96(1.64-2.34)
Instrumental delivery	5900(13.64)	246(17.2) 1.07(0.92-1.24)	3972(16.05) 1.0	1192(11.20) 0.89(0.82-0.96)	349(8.23) 0.77(0.68-0.86)	91(6.07) 0.59(0.47-0.74)	50(7.23) 0.72(0.53-0.97)
Postpartum haemorrhage	14185(33)	354(24.91) 0.78(0.68-0.88)	7515(30.55) 1.0	3746(35.42) 1.32(1.25-1.39)	1634(38.74) 1.55(1.44-1.67)	628(42.23) 1.85(1.66-2.87)	308(44.64) 2.08(1.78-2.43)
Preterm delivery	2694 (6.34)	90(6.44) 1.16(0.93-1.44)	1345(5.56) 1.0	733(6.97) 1.18(1.07-1.30)	319(7.59) 1.24(1.09-1.42)	139(9.34) 1.53(1.26-1.85)	68(9.88) 1.66(1.27-2.16)
Macrosomia	4376(10.12)	55(3.85) 0.47(0.36-0.62)	2153(8.70) 1.0	1239(11.64) 1.53(1.41-1.65)	563(13.28) 1.83(1.64-2.03)	251(16.76) 2.42(2.09-2.81)	115(16.62) 2.33(1.89-2.88)
Low birth weight	4376(10.12)	149(10.42) 1.65(1.38-1.980)	1493(6.03) 1.0	688(6.46) 0.96(0.87-1.06)	257(6.06) 0.87(0.75-1.00)	111(7.41) 1.04(0.85-1.29)	61(8.82) 1.26(0.95-1.66)
NICU/SCBU[2]	2496(5.77)	72(5.03) 0.94(0.74-1.21)	1306(5.28) 1.0	653(6.13) 1.20(1.08-1.33)	296(6.98) 1.41(1.23-1.62)	114(7.61) 1.57(1.28-1.94)	55(7.95) 1.63(1.22-2.17)
Perinatal Death	347(0.8)	9(0.63) 1.05(0.53-2.06)	154(0.62) 1.0	97(0.91) 1.20(0.91-1.57)	58(1.37) 1.74(1.26-2.40)	15(1.00) 1.17(0.66-2.04)	14(2.02) 2.65(1.51-4.64)

1. Odds ratios adjusted for maternal age, parity, deprivation, smoking and ethnic group.
2. NICU/SCBU: Neonatal Intensive Care Unit or Special Care Baby Unit

Table 11: Adjusted odds ratios (95% CI) for obstetric and child outcomes according to maternal obesity[1], presented for the whole population and separately by ethnic group of the mother

Obstetric and perinatal outcome	Whole population n %	Whole population OR [2] (95% CI)	Maternal ethnic group				
			WHITE OR [2] (95% CI)	BLACK OR [2] (95% CI)	ASIAN OR [2] (95% CI)	CHINESE OR [2] (95% CI)	Interaction P-value
Diabetes	1151 (2.66)	3.86 (3.38-4.40)	4.74 (3.83-5.88)	3.12 (2.61-3.730)	5.82 (3.90-8.70)	4.51 (2.28-8.93)	0.004
Elective CS	3378(7.81)	1.53 (1.39-1.68)	1.44 (1.24-1.67)	1.61 (1.42-1.83)	1.00 (0.61-1.63)	3.38 (1.81-6.31)	0.019
Emergency CS	8402(19.43)	1.52 (1.42-1.63)	1.90 (1.71-2.11)	1.30 (1.19-1.43)	1.29 (0.92-1.82)	2.01 (1.19-3.44)	<0.001
Instrumental delivery	5900(13.64)	0.74 (0.67-0.83)	0.79 (0.69-0.90)	0.66 (0.55-0.78)	0.90 (0.59-1.36)	1.07 (0.53-2.17)	0.233
Postpartum haemorrhage	14185(33)	1.52 (1.43-1.61)	1.58 (1.44-1.73)	1.49 (1.38-1.61)	1.27 (0.95-1.69)	1.84 (1.15-2.94)	0.390
Preterm Delivery	2694(6.34)	1.26 (1.14-1.40)	1.37 (1.15-1.64)	1.19 (1.04-1.36)	1.44 (0.91-2.29)	1.26 (0.49-3.22)	0.573
Macrosomia	4376(10.2)	1.74 (1.60-1.89)	1.67 (1.48-1.89)	1.74 (1.54-1.97)	2.44 (1.53-3.88)	2.38 (1.27-4.46)	0.353
Low birth weight	2759(6.38)	0.94 (0.84-1.06)	1.02 (0.83-1.24)	0.93 (0.81-1.08)	0.87 (0.54-1.40)	0.20 (0.03-1.43)	0.191
NICU/SCBU	2496(5.77)	1.38 (1.24-1.55)	1.75 (1.49-2.06)	1.18 (1.01-1.37)	1.08 (0.63-1.85)	0.98 (0.30-3.22)	0.004
Perinatal Death	347(0.8)	1.57 (1.21-2.04)	1.41 (0.81-2.44)	1.43 (1.04-1.96))	3.42 (1.49-7.84)	1.95 (0.25-15.45)	0.315

1. BMI 30≥ Kg/m^2.
2. Odds ratios adjusted for maternal age, parity, and deprivation
3. P = interaction evidence

Table 12: Sensitivity analysis 1 using dummy variable for "BMI missing". Adjusted odds ratios (95% CI) for obstetric and child outcomes according to maternal obesity[1], presented for the whole population and separately by ethnic group of the mother

Obstetric and perinatal outcome	Whole population n %	Whole population OR [2](95% CI)	Maternal ethnic group			
			WHITE OR [2] (95% CI)	BLACK OR [2] (95% CI)	ASIAN OR [2] (95% CI)	CHINESE OR [2] (95% CI)
Diabetes	1213 (2.25)	3.84 (3.38-4.38)	4.73 (3.82-5.87)	3.11 (2.60-3.8.66) P=0.03	5.80 (3.89-8.66) P=0.38	4.50 (2.27-8.91) P=0.89
Elective CS	4694 (8.71)	1.56 (1.42-1.71)	1.46 (1.26-1.70)	1.61 (1.42-1.82) P=0.92	1.01 (0.62-1.65) P=0.16	3.39 (1.81-6.33) P=0.01
Emergency CS	10592 (19.65)	1.51 (1.41-1.62)	1.89 (1.70-2.10)	1.30 (1.19-1.42) P<0.01	01.29 (0.92-1.81) P=0.03	2.01 (1.18-3.43) P=0.83
Instrumental delivery	7333 (14.90)	0.75 (0.68-0.83)	0.79 (0.69-0.90)	0.66 (0.55-0.78) P=0.11	0.90 (0.59-1.36) P=0.55	1.07 (0.53-2.17) P=0.41
Postpartum haemorrhage	17345 (32.36)	1.51 (1.43-1.60)	1.57 (1.43-1.72)	1.49 (1.38-1.62) P=0.38	1.27 (0.95-1.68) P=0.16	1.84 (1.15-2.94) P=0.53
Preterm Delivery	3476 (6.78)	1.25 (1.13-1.39)	1.36 (1.13-1.39)	1.18 (1.03-1.35)	1.44 (0.91-2.29)	1.26 (0.49-3.22)
Macrosomia	5444 (10.1)	1.72 (1.58-1.87)	1.66 (1.48-1.87)	1.75 (1.55-1.97) P=0.63	2.43 (1.53-3.87) P=0.12	2.38 (1.27-4.46) P=0.28
Low birth weight	3605 (6.69)	0.94 (0.84-1.05)	1.01 (0.83-1.24)	0.93 (0.81-1.07) P=0.51	0.87 (0.54-1.39) P=0.56	0.20 (0.03-1.42) P=0.11
NICU/SCBU	3089 (5.73)	1.36 (1.22-1.51)	1.74 (1.48-2.04)	1.16 (0.99-1.35) P<0.001	1.07 (0.63-1.83) P=1.08	0.97 (0.29-3.19) P=0.35
Perinatal Death	438 (0.8)	1.58 (1.22-2.04)	1.41 (0.81-2.44)	1.44 (1.04-1.97) P=0.96	3.49 (1.53-8.00) P=0.08	1.95 (0.25-15.47) P=0.76

1. BMI≥ 30Kg/m^2.
2. Odds ratios adjusted for maternal age, parity, and deprivation
3. P = interaction evidence

Table 13: Sensitivity analysis 2 using data from 2008 to 2012. Adjusted odds ratios (95% CI) for obstetric and child outcomes according to maternal obesity, presented for the whole population and separately by ethnic group of the mother

Obstetric and perinatal outcome	Whole population n %	Whole population OR [2](95% CI)	Maternal ethnic group			
			WHITE OR [2] (95% CI)	BLACK OR [2] (95% CI)	ASIAN OR [2] (95% CI)	CHINESE OR [2] (95% CI)
Diabetes	769 (3.29)	4.02 (3.41-4.73)	4.61 (3.55-6.00)	3.44 (2.74-4.32)	6.28 (3.75-10.51)	2.97 (1.08-8.19)
Elective CS	2459 (10.51)	1.55 (1.37-1.76	1.52 (1.25-1.85)	1.62 (1.36-1.92)	0.78 (0.38-1.60)	2.80 (1.09-7.22)
Emergency CS	4379 (18.72)	1.46 (1.33-1.61)	1.94 (1.67-2.25)	1.19 (1.04-1.35	1.40 (0.87-2.25)	1.98 (0.89-4.42)
Instrumental delivery	3260 (15.58)	0.76 (0.66-0.88)	0.80 (0.66-0.97)	0.69 (0.54-0.88)	0.95 (0.54-1.66)	0.64 (0.19-2.21)
Postpartum haemorrhage	8535 (36.74)	1.51 (1.3-1.64)	1.54 (1.36-1.75)	1.49 (1.34-1.67)	1.41 (0.96-2.08)	1.96 (0.98-3.92)
Preterm Delivery	1401 (6.34)	1.21 (1.03-1.41)	1.29 (1.00-1.67)	1.17 (0.95-1.44)	1.21 (0.61-2.40	0.95 (0.21-4.13)
Macrosomia	2402 (10.3)	1.74 (1.54-1.95)	1.64 (1.39-1.94)	1.73 (1.46-2.06)	2.94 (1.62-5.35)	3.72 (1.60-8.66)
Low birth weight	3605 (6.69)	0.89 (0.75-1.05)	0.92 (0.69-1.24)	0.93 (0.75-1.16)	0.61 (0.29-1.30)	0.92 (0.69-1.24)
NICU/SCBU	1268 (5.42)	1.26 (1.06-1.49)	1.60 (1.26-2.03)	1.08 (0.85-1.38)	0.84 (0.36-1.97)	1.60 (1.26-2.03)
Perinatal Death	168 (0.72)	1.35 (0.90-2.02)	0.71 (0.26-1.99)	1.45 (0.89-2.36)	3.48 (0.91-13.36)	0.71 (0.26-1.99)

1. BMI≥ 30 Kg/m^2.
2. Odds ratios adjusted for maternal age, parity, and deprivation

Table 14: Population attributable risk fraction (PAF %) for the impact of obesity on obstetric and perinatal outcome

Obstetric and perinatal outcome	Whole population PAF % (95% CI)	Maternal ethnic group			
		WHITE PAF % (95% CI)	BLACK PAF % (95% CI)	ASIAN PAF % (95% CI)	CHINESE PAF % (95% CI)
Diabetes	30.05 (26.59-33.35)	25.92 (20.87-30.65)	35.26 (29.19-40.82)	26.28 (17.14-34.41)	13.62 (3.89-22.36)
Elective CS	6.82 (5.19-8.44)	3.40 (1.76-5.01)	13.31 (9.63-16.83)	-0.46 (-5.00-3.94)	9.62 (2.87-15.90)
Emergency CS	5.20 (4.32-6.07)	5.55 (4.46-6.47)	4.84 (3.08-6.56)	1.97 (-0.74-4.61)	2.83 (0.06-5.52)
Instrumental delivery	-2.39 (-3.16, -1.62)	-1.68 (-2.48—0.88)	-7.75 (-10.47—5.10)	-0.45 (-3.04-2.07)	-0.52 (-2.75-1.66)
Postpartum haemorrhage	4.17 (3.57-4.77)	3.06 (2.41-3.71)	6.13 (4.81-7.43)	1.58 (-0.27-3.40)	1.86 (0.40-3.29)
Preterm delivery	3.74 (1.94-5.51)	3.12 (1.00-5.23)	3.60 (0.26-6.84)	3.04 (-0.25-8.24)	1.05 (-4.14-5.99)
Macrosomia	8.13 (6.77-9.48)	6.12 (3.77-6.46)	14.17 (10.68-17.62)	12.11 (4.06-19.49)	6.17 (0.01-10.06)
Small for gestational age	-0.84 (-2.50-0.77)	-0.21 (-2.22-1.77)	-1.74 (-4.76-1.19)	-1.67 (-5.49—1.80	-4.38 (-6.71-2.10)
NICU-SCBU	4.91 (3.10-6.69)	6.00 (3.86-8.04)	3.48 (0.35-7.16)	0.54 (-5.56-4.25)	-0.60 (-6.33-4.83)
Perinatal death	9.25 (3.25-14.88)	5.97 (3.86-8.04)	3.48 (0.35-7.16)	3.02 (-2.78, 8.50)	1.18 (-1.11, 3.41)

RESEARCH PAPER COVER SHEET FOR CHAPTER 5

Please be aware that one cover sheet must be completed for each 'Research Paper' included in a thesis.

1. For a 'research paper' already published

1. 1.1. Where was the work published? **Oteng-Ntim E**, Varma R, Croker H, Poston L, Doyle P. *Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis*. BMC Med. 2012; 10(1):47

1.2. When was the work published? **2012**

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion

1.3. Was the work subject to academic peer review? **Yes**

1.4. Have you retained the copyright for the work? **Yes**

If yes, please attach evidence of retention.
If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published? .....

2.2. Please list the paper's authors in the intended authorship order ……

2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments / In press

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

I conceived and designed the study. I conducted the literature search with one other person and supervised the meta-analysis. I wrote the first draft of the paper.

NAME IN FULL (Block Capitals) ……EUGENE OTENG-NTIM…….

STUDENT ID NO: ……235138……..

CANDIDATE'S SIGNATURE …Eugene Oteng-Ntim…… Date …….

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) ……..……

CHAPTER 5: Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis

Publication based on this work:

Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. *Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis*. BMC Med. 2012; 10(1):47

Following the publication of the above paper, this systematic review was updated. It now includes material published up to February 2014. There follows a transcript of the published study updated as appropriate to include relevant recent publications. I led all aspects of this work and performed the meta-analysis.

5.1 Introduction

Both developed and developing countries are experiencing a rapid increase in the prevalence of obesity (1, 3, 30, 257). Twenty-four percent of women of reproductive age in the United Kingdom are now obese (BMI equal to or greater than 30kg/m^2) and the prevalence appears to be increasing (37). Studies in UK women show that the rates of obesity in pregnancy have almost doubled in the last two decades (40-41). Recent estimates suggest the prevalence of obesity in pregnancy in the UK is at least 20% with 5% having severe or morbid obesity (3, 42).

Observational study data has linked obesity in pregnancy with adverse maternal and infant outcomes (3, 11, 17, 42). Obesity increases the risks of gestational diabetes (17, 42, 95, 258), hypertensive disease (including pre-eclampsia) (6-7, 42), thromboembolism (8, 114), infection (7, 127), Caesarean section (9, 42), congenital fetal anomalies (137), macrosomia (6), induction

(128), stillbirth (95), shoulder dystocia (7) and preterm delivery (13). Moreover, maternal obesity may impact on long-term outcomes such as the increasing weight of the child in infancy and the severity of obesity in future generations (17, 103, 259).

As most of the adverse outcomes of obese pregnancies show strong associations with pre-pregnancy BMI, it is reasonable to assume that the ideal intervention would be to reduce obesity prior to pregnancy (161). However, this is difficult to achieve because 50% of pregnancies in the UK are unplanned and a recent study concluded that only a small proportion of women planning pregnancy follow nutrition and lifestyle recommendations (215). As such, an intervention pre-pregnancy may reach only a small proportion of the intended women.

Alternatively, pregnancy itself may represent an ideal opportunity to target lifestyle change as women have increased motivation to maximise their own health and that of their unborn child (215). However, evidence of benefit from published intervention studies appears limited and inconsistent (260-278). We therefore sought to determine the efficacy of combined dietary activity and behaviour support interventions in overweight and obese pregnant women by undertaking a systematic review and meta-analysis according to PRISMA criteria for maternal clinical outcomes of weight gain, gestational diabetes and Caesarean section, and infant outcomes such as large for gestational age and macrosomia. The aim was to generate data of the highest statistical power and sensitivity. Therefore, in comparison to previous similar-themed systematic reviews (177, 279-281), we chose to interrogate multiple databases (not restricted to English) and also to separately meta-analyse randomised and non-randomised clinical trials, evaluating relevant clinical outcomes including gestational diabetes and Caesarean section, which had not been attempted in prior meta-analyses.

5.2 Methods

5.2.1 Eligibility criteria

The eligible studies included randomised and non-randomised controlled clinical trials that evaluated antenatal dietary and lifestyle interventions in obese and overweight pregnant women whose outcome measures included quantitative maternal and fetal health outcomes. Trials of women with existing gestational diabetes and trials of pre-conception or postpartum interventions were not included. Inclusion of trials was not restricted by language, publication date or country. Systematic reviews and observational studies were excluded.

5.2.2 Information sources

Literature searches were performed using five mainstream electronic databases [Cochrane Library, MEDLINE, EMBASE, CINAHL, Maternity and Infant care] and nine other databases [PsyclINFO via OVID SP, PyscLNFO via OVID SP, Science Citation Index via Web of Science, Social Science Citation Index via Web of Science, Global Health, Popline, Medcarib, Nutrition database, RCOG website, opensigle.inist.fr].

5.2.3 Search strategy

The following medical subject headings (MeSH) terms, words and combinations of words were used in constructing the systematic search: overweight or obesity; pregnancy or pregnancy complications or pregnancy outcome or prenatal care; lifestyle, early intervention, education, health education, education, patient education hand-out, patient education, exercise, exercise therapy, health promotion, diet, carbohydrate-restricted, diet, fat-restricted, diet, reducing, diet therapy, weight loss. Full details of the search strategy are shown in Table 15. The searches were unlimited by time up to

February 2014 and limited to human studies and clinical trials. The systematic search was undertaken in the mainstream databases and targeted searches were conducted in the other databases. The grey literature was not searched.

5.2.4 Study selection

Electronic literature searches, study selection, methodology, appropriateness for inclusion and quality appraisal were performed. Disagreements between reviewers were resolved by consensus. Included studies were divided into two groups (RCTs and non-RCTs) and separately meta-analysed.

5.2.5 Data collection process

Two independent reviewers extracted the data. As a first step, each paper was screened using the title and the abstract. In the next round studies were assessed for methodological quality and appropriateness for inclusion by two reviewers working independently from the full text of the manuscript. This was done without consideration of the results.

5.2.6 Data items

For each included trial data was extracted on: maternal gestational weight gain, gestational diabetes, Caesarean section, large for gestational age baby (>4kg) and birth weight.

5.2.7 Risk of bias in individual studies

The quality of the studies was assessed based on how the studies had minimised bias and error in their methods. We categorised the studies according to criteria based on PRISMA guidelines (282) and the Cochrane Library (283). For example, high quality trials reported: study aims, control

comparison similar to the intervention group, relevant population demographics pre-and post-intervention and data on each outcome. These study characteristics are tabulated in Tables 18 and 19. A final assessment categorised the studies as high, medium or low quality.

5.2.8 Summary and analysis of studies that met the criteria

This is shown in Figure 7 and in a tabulated format contained within Tables 16 and 17.

5.2.9 Summary measures and data synthesis

The meta-analyses were performed by calculating the risk ratios as the main measure of effect. Quantitative analysis was performed on an intention-to-treat basis focused on data derived from the period of follow-up. There was heterogeneity between studies because of the smaller sample size of some of the studies (poor quality), variation of the study population, and the intensity and duration of the interventional strategies being evaluated. In light of these reasons, statistical meta-analysis with random effects model was used to combine effect sizes using STATA 12. The degree of heterogeneity was expressed using Tau^2 rather than I^2 as recommended by Rucker et al (284) .

5.3 Results

5.3.1 Study characteristics

The review process is outlined in Figure 7 and the selected papers are summarised in Tables 16 and 17.

Twenty-one trials met the inclusion criteria: 15 RCTs (260-268) and 6 non-randomised controlled trials (217, 269-270, 272-273, 285). All 21 trials were performed in developed countries: USA 5, Canada 3, Denmark 2,

Netherlands 1, Sweden 1, Spain 1, Brazil 1, Finland 2, Belgium 1, Australia 4 (Tables 11 and 12). Six RCTs were judged to be of medium quality and one was judged to be of high quality (261, 263, 268). The rest were deemed to be low quality (Tables 18 and 19).

The pooled RCTs included a total of 4835 participants and the pooled non-randomised controlled trials included 1534 participants. Participants were predominantly of White ethnicity except in the studies by Asbee (261), Gray Donaldson (272) and Hui (267). In the Asbee study the majority were described as being of Hispanic ethnicity (261).

For all included RCTs the control group received no intervention or standard care. In the non-randomised controlled trials, most used non-parallel controls (217, 269, 272-273) or controls from another centre (270). The outcomes investigated in the trials were gestational weight gain, gestational diabetes, Caesarean section delivery, large for gestational age baby, and birth weight.

5.4 Intervention characteristics

The nature of the interventions varied widely between studies; some of the key features of the interventions are outlined in Tables 19 and 20. In summary, for the six non-randomised studies, three of the interventions comprised individual and group/ seminar components (270, 272-273, 286), two were individual (269, 285) and one was unclear (217). Of the fifteen randomised studies, one comprised individual and group components (267), ten were individual (261-264, 266, 268) and three were group-based (260). Where there were individual and group components, the latter were usually physical activity sessions. All of the non-randomised trials included dietary and physical activity guidance, as did the majority of the randomised studies. Exceptions were two studies which included only nutritional guidance (263-264) and one which included guidelines about weight gain and weight monitoring only (262). The

majority of studies included dietary or physical activity guidance with one of the non-randomised studies (269) and three of the randomised studies (263, 266-268) specifying that guidance was personalised.

5.5 Effects of the intervention on outcomes

Of the 21 trials: 17 measured gestational weight gain (12 randomised, 5 non-randomised); 10 measured gestational diabetes (8 randomised, 2 non-randomised) 12 measured Caesarean deliveries (8 randomised, 4 non-randomised); 12 measured large for gestational age (8 randomised, 4 non-randomised); and 8 measured birth weight (8 randomised). Meta-analyses for the different outcomes are shown in Tables 20 and 21 and Figures 8 to 16.

Meta-analysis of randomised trials showed that combined antenatal lifestyle, dietary and activity intervention had a borderline effect on restricting gestational weight gain (Table 20 and Figure 8). There was no difference in the prevalence of gestational diabetes in overweight and obese women (Table 20 and Figure 9). Meta-analysis of non-randomised trials only showed weak evidence that lifestyle intervention reduces gestational weight gain (Table 21 and Figure 16) and there was no evidence for reduction in the prevalence of gestational diabetes (Table 21 and Figure 15). There was no robust evidence that lifestyle intervention is associated with a lower prevalence of Caesarean delivery or large for gestational age or any alteration in birth weight (Tables 20 and 21, Figures 8 to 16).

5.6 Discussion

5.6.1 Summary of main findings

This review provides weak evidence that antenatal lifestyle, dietary and activity advice for overweight and obese pregnant women restricts maternal weight gain during pregnancy and has no effect on the prevalence of

gestational diabetes in women who are overweight or obese. However, the quality of the study designs was generally poor. The reduction in gestational weight gain was observed to be statistically significant in the meta-analysis of randomised trials [12 RCTs; n=4835; -0.29kg (95% CI=-0.57 to -0.01kg)] but non-significant in the meta-analysis of non-randomised trials (6 trials, n=1534). No effects of antenatal lifestyle interventions were identified in obese and overweight pregnant women in relation to Caesarean delivery, large for gestational age, birth weight and macrosomia (>4kg).

5.6.2 Interpretation

There is evidence to suggest antenatal lifestyle interventions may mildly restrict gestational weight gain and have no statistical effect on other important clinical outcomes, possibly due to inadequate power of the combined sample size. The effect on restricted weight gain was not consistent across all the trial populations and therefore cannot be generalised. There was also wide variation in the types of interventions evaluated in the studies. The majority were individual-based and most provided generic guidance comprising mainly of dietary and physical activity information, with few tailoring guidelines. There was considerable heterogeneity in intervention design and no obvious patterns between intervention type and study outcomes. For the gestational weight gain and gestational diabetes outcomes, both the successful and non-successful studies included those which were personalised, combined physical activity and dietary guidance and were individualised. Moreover, the degrees of weight gain restriction achieved were modest overall. It is even harder to draw conclusions regarding the specific behaviour change strategies included (e.g. monitoring and goal setting) or theoretical basis of interventions since these were typically poorly reported.

Identifying specific components of successful interventions aids understanding of how interventions are having an effect and clear reporting of intervention design allows for easier replication (287). Previous reviews have

attempted to draw conclusions regarding specific effective components of interventions. Suggestions have been made that weight monitoring and setting weight goals could be useful (279), and also monitoring, along with education counselling and physical activity sessions (217, 288). Another review suggested that interventions be based on the 'Theory of Planned Behaviour', but the rationale for using this model over others in this population was unclear (289). None of these reviews examined intervention components systematically. A more recent review assessed interventions targeting gestational weight gain from a psychological perspective and specifically examined intervention content and delivery methods (226). This review comprised ten controlled trials, all included in the current review; only two of the studies reported based interventions on theory and studies used on average five behaviour change strategies (self-monitoring, feedback provision and setting behavioural goals were the most common), but no conclusions could be drawn as to their contribution to study outcomes. Broadly consistent with this were the six studies in the current review which were not reviewed by Gardner et al. (226). The review by Gardner et al. questioned the evidence supporting the benefits of weight monitoring, but tentatively suggested that information provision had been under-used and that it might be of benefit to have a narrower focus of intervention targets (226).

5.6.3 Comparison with other systematic reviews and strengths

This study adds to a growing body of evidence that aims to evaluate lifestyle intervention as a means to minimise the adverse outcomes associated with obese pregnancy. In comparison to other published reviews (177, 279, 289), I have adopted an original approach by broadening the literature source (multiple data sources, no language restriction), focusing on relevant clinical outcomes (such as Caesarean section, gestational diabetes, macrosomia), and improving sensitivity by meta-analysing both randomised and non-randomised trials. Furthermore, to minimise bias, the review methodology was registered *a priori* (Prospero number CRD420111122

http://www.crd.york.ac.uk/PROSPERO). I therefore believe this review provides a comprehensive and reliable analysis of the current evidence and for the first time highlights that lifestyle intervention in pregnancy may reduce the prevalence of gestational diabetes.

5.6.4 Limitations of this systematic review

The evidence summarised in this work comes from available studies of which most are of low quality, with only four studies attaining a medium quality score and one achieving a high quality score. Hence, the evidence base is weak and calls for more robust studies. Our trial population is relatively small, the intensity and duration of the interventions of trials varied and trials were predominantly USA in origin, a phenomenon common to many public health reviews, especially on obesity. There was significant evidence of heterogeneity between studies and this was appropriately addressed by using a random effect model to establish pooled effect estimates as well as using Tau^2 (to measure levels of heterogeneity), which has the added advantage that it considers variation between studies as a normal distribution and takes account of this. Secondly, the forest plots have been sub-grouped in terms of the level of quality of the studies which may also help in addressing heterogeneity.

Although our focus was on antenatal lifestyle intervention for obese and overweight pregnant women, our search yielded some studies that contained a mixed group of obese and normal weight women and we excluded all the non-obese from our analysis. Still, this may lead to inconsistencies in measuring the effect of the intervention as well as under- or over-estimating the treatment effect. Furthermore, even though our search was systematic and rigorous, we could have missed eligible studies inadvertently. This study may have a limitation of publication bias as it does not include unpublished data. The assumption with publication or information bias is that negative findings are often not published. For this systematic review, this is not the case as most of the studies, including the biggest studies to date, were published in reputable

journals with null results (67). I reviewed the grey literature on the opensigle.inist.fr in order to incorporate interventional studies which may have been published in the grey literature, and while there were twelve articles published on obesity and pregnancy, none of them were interventional studies. Thus, none of them met the criteria to be included in the systematic review meta-analysis.

5.6.5 Conclusions and policy implications

This review reveals that lifestyle intervention for obese and overweight women during pregnancy had a borderline effect on restricting gestational weight gain but the quality of the published studies is mainly poor. This then highlights a paradox. At a time when solutions to address adverse outcomes associated with maternal overweight and obesity are identified as a public health priority, we find that most of the research evidence lacks robustness to inform future evidence-based lifestyle interventions for obese pregnant women. There is thus a research gap regarding the effectiveness of lifestyle intervention in pregnancy. It is unlikely that further meta-analysis will help to refine the quality of evidence since studies demonstrated significant heterogeneity in relation to demography, outcome measurement, follow-up and degrees of intervention. Hence, I conclude that there is the need for a well-designed large-scale prospective trial which examines combined antenatal lifestyle interventions in obese pregnant women that is suitably powered and incorporates robust methodology in accordance with standards set by the Medical Research Council's framework for evaluating complex interventions (290). There are two such studies which are currently ongoing, called LIMIT (ACTRN 12607000161426) and UPBEAT (ISRCTN89971375). LIMIT has recently been published, showing that lifestyle intervention does not improve pregnancy outcome and it does not result in any harm. The criticism with the LIMIT study was that the intervention was not intensive enough (i.e. six sessions with two face-to-face contact sessions and four telephone contact sessions). UPBEAT, which utilises eight sessions, with all eight offering face-to-

face contact, focused on obese pregnant women, and may be intense enough to show a difference. Both of these studies are appropriately powered to show convincingly whether lifestyle intervention is most likely to improve pregnancy outcomes or not. Neither of these studies is delivered in a community setting, which will ensure easy translation of the intervention to a wider population, including deprived and diverse communities.

Table 15: Search strategy utilised for MEDLINE from 1946 to February 2014

Batch	Search term (MESH)	Combination	Result
1	Pregnancy Complications/ OR Pregnancy/ OR Pregnancy Outcome/ OR Pregnancy, High Risk/		646055
2	Prenatal Care/ OR Pregnancy/ OR Pregnancy Complications		647726
3	Antenatal.mp.		18393
4	Gestation intervention.mp.		4
5		1 OR 2 OR 3 OR 4	651321
6	Overweight.mp. OR Obesity/ OR Overweight/ OR Body Weight/		249097
7	Obesity/ OR Obesity, Morbid/ or Obesity.mp.		145882
8	Body Weight/ OR Obesity/ OR Body Mass Index/ or BMI.mp. OR Overweight/		293584
9		6 OR 7 OR 8	328089
10		5 AND 9	21583
11	Diet, Fat-Restricted/ OR Diet/ OR Diet, Protein-Restricted/ OR Diet, Carbohydrate-Restricted/ OR Diet.mp. OR Diet, Reducing/ OR Diet Therapy/		255985
12	Life Style/		36837
13	Health Education/		48625
14	Patient Education as Topic/		63238
15	Exercise.mp. OR Exercise/ OR Exercise, Therapy/		192937
16	Health Promotion/		43967
17	Weight Loss/		19434
18		11 OR 12 OR 13 OR 14 OR 15 OR	601919

Batch	Search term (MESH)	Combination	Result
		16 OR 17	
19		10 AND 18	3769
20		LIMIT 19 TO (female or humans or pregnancy) and (clinical trial, all OR clinical trial, phase i OR clinical trial, phase ii OR clinical trial, phase iii OR clinical trial, phase iv OR clinical trial OR controlled clinical trial OR RCT)	154

Table 16: A summary of the studies that met the criteria of the systematic review on lifestyle interventions in overweight and obese pregnant women: randomised trials

Author (year)	Ethnic group/ Country	Participant/ setting	Sample size	Intervention	Outcome measure(s)	Conclusion
Polley et al. (2002) (266)	31% Black and 61% White/USA	Recruited before 20 weeks of pregnancy (normal BMI >19.5 to 24.9; overweight BMI ≥25 to <30 kg/m^2)/ Hospital based	120, including 49 overweight 59 in control arm; 61 in intervention arm	Exercise and nutrition information (oral and newsletter) Personalised graphs and behavioural counselling	Gestational weight gain; gestational diabetes; Caesarean section; birth weight	No statistically significant reduction in gestational weight, prevalence of gestational diabetes, Caesarean section, or large for gestational age baby
Hui et al. (2006) (267)	Predominantly Caucasian/ Canada	Less than 26 weeks pregnant (community-based and antenatal clinics). All BMI categories. Mean BMI of non-intervention arm = 25.7 (SD = 6.3) and for intervention arm = 23.4 (SD = 3.9)	45 21 in non-intervention arm; 24 in intervention arm	Physical exercise (group-sessions home-based exercise) Individualised nutrition plans	Gestational weight gain	No statistically significant reduction in gestational weight gain
Wolff et al., 2008 (264)	100% Caucasian/Denmark	Obese (BMI ≥30 kg/m^2) women enrolled at 15 weeks gestation	50 analysed 23 in control arm; 27 in intervention arm	Intensive intervention with 10 one-hour visits with a dietician at each antenatal visit, dietary guidance provided	Gestational weight gain; gestational diabetes; Caesarean section; birth weight	Statistically significant reduction in gestational weight gain, no statistically significant reduction in prevalence of gestational diabetes or Caesarean section, or birth weight
Jeffries et al., 2009 (262)	>90% Caucasian/Australia	Women at or below 14 weeks gestation. All BMI categories included	286 138 in control arm; 148 in intervention arm	Personalised weight measurement card (based on Institute of Medicine guidelines) Control had only single measurement at enrolment	Gestational weight gain	No statistically significant reduction in gestational weight gain.
Ong et al., 2009 (276)	Predominantly Caucasian/Australia	Pregnant obese women recruited at 18 weeks gestation	12 six in control arm; six in intervention arm	Personalised 10 weeks of home-based supervised exercise (three sessions per week)	Maternal aerobic fitness and gestational diabetes	No statistically significant difference in aerobic fitness or gestational diabetes
Barakat et al., 2011 (291)	100% Caucasian/Spain	All BMI categories	160 80 in control arm; 80 in intervention arm	Three group-based sessions per week, light resistance and toning exercise from the second trimester	Gestational weight gain and birth weight	No statistically significant difference in gestational weight gain and birth weight. Exercise intervention might attenuate adverse consequences of maternal BMI on newborn birth size
Asbee et al., 2009	26% African	Pregnant women recruited	100	One session of dietetic counselling	Gestational weight gain;	Statistically significant reduction in

Author (year)	Ethnic group/ Country	Participant/ setting	Sample size	Intervention	Outcome measure(s)	Conclusion
(261)	American/USA	before 16 weeks gestation. All BMI categories except those of BMI >40 kg/m^2	43 in control arm; 53 in intervention arm	and activity	pregnancy outcome	gestational weight gain. No effect on pregnancy outcome
Thornton et al., 2009 (263)	41% African American/USA	Obese pregnant women (BMI ≥30 kg/m^2) recruited between 12 and 28 weeks gestation	257 randomised. 25 lost to follow up. 116 in control arm; 116 in intervention arm	Nutritional regime for gestational diabetes	Gestational weight gain; gestational diabetes; Caesarean section; pregnancy outcome	Statistically significant reduction in gestational weight gain, no statistically significant reduction in prevalence of gestational diabetes, Caesarean section or birth weight
Guelinckx et al., 2010 (260)	100% Caucasian/Belgium	Obese (BMI >30kg /m^2) women enrolled at 15 weeks gestation.	195 randomised 85 analysed 65 in control arm; 65 in passive arm, 65 in intervention arm	Three arms: group sessions with a dietician; written brochures; and standard care Dietary and physical activity guidance provided by dietician and in written brochures	Nutritional habits; gestational weight gain; gestational diabetes; Caesarean section; birth weight	Improved nutritional habits; no statistically significant reduction in gestational weight gain, prevalence of gestational diabetes, Caesarean section or birth weight.
Phelan et al., 2011 (268)	67% White/USA	Pregnant women BMI between 19.8 and 40 kg/m^2 recruited between 10 and 16 weeks gestation	401 randomised. 201 in non-intervention arm; 200 in intervention arm	Exercise and nutrition information (oral and newsletter) Personalised graphs and behavioural counselling	Gestational weight gain; gestational diabetes; Caesarean section; pregnancy outcome	Significant reduction in gestational weight gain; no statistically significant reduction in prevalence of gestational diabetes, Caesarean section or birth weight
Quinlivan et al., 2011 (292)	73% White, 19% Asian/ Australia	Pregnant women: overweight (BMI 25 to 29.9 kg/m^2) and obese (BMI ≥30 kg/m^2)	132 randomised. 65 in non-intervention arm; 67 in intervention arm	Attended a study- specific antenatal clinic providing continuity of care, weighing on arrival, brief dietary intervention by food technologist and psychological assessment and intervention if indicated	Gestational weight gain; gestational diabetes; birth weight	Statistically significant reduction in gestational weight gain and prevalence of gestational weight gain. No statistically significant reduction in birth weight.
Luoto et al., 2011 (277)	Predominantly White/Finland	Pregnant women at risk of gestational diabetes. All BMI ranges	399 cluster random-ised. 219 in non-intervention arm; 180 in intervention arm	Attended a study-specific individual antenatal lifestyle counselling clinic including group exercise	Gestational diabetes; gestational weight gain; birth weight	Statistically significant reduction in birth weight and macrosomia but no statistically significant difference in gestational diabetes
Nascimento et al., 2011 (278)	Predominantly White/Brazil	Pregnant women of all BMI categories	82 randomised. 42 in non-intervention arm; 40 in intervention arm	Attended a group-based exercise under supervision and received a home exercise counselling	Gestational weight gain; raised blood pressure; perinatal outcome	No statistically significant difference in gestational weight gain in terms of gestational weight gain, raised blood pressure or perinatal outcome
Vinter et al., 2011	White/Denmark	Pregnant women who are obese	360 randomised. 154 in non-intervention arm; 150 in intervention arm	Attended a 6 group-based exercise under physiotherapist supervision and 4 grouped based dietician advice Free membership to a gym for 6 months	Gestational weight gain; raised blood pressure; perinatal outcome	Statistically significant reduction in restricted gestational weight gain and no change in other obstetric and perinatal outcomes
Dodd et al., 2014	White/Australia	Pregnant women who are	2512 randomised.	Comprehensive dietary and exercise	Gestational diabetes and	No statistically significant difference in

Author (year)	Ethnic group/ Country	Participant/ setting	Sample size	Intervention	Outcome measure(s)	Conclusion
		obese	1104 in the non-intervention arm;1108 in intervention arm	and behaviour change advice delivered by research dietician and trained research assistants. Attended 2 individual sessions one at planning stage, the other face to face at 36 weeks by the research dietician. 4 telephone contacts by research assistants in order to re-enforce the lifestyle advice.	large for gestational age infant	gestational diabetes and large for gestational age infants. There was a significant reduction in macrosomia in the intervention group compared to the control group otherwise all other secondary outcomes showed no statistically significant difference.

1. BMI: body mass index
2. SD: standard deviation

Table 17: Summary of the studies that met the criteria of the systematic review on lifestyle interventions in overweight and obese pregnant women: non-randomised trials

Author (year)	Ethnic group/country	Participants/setting	Sample size	Intervention	Outcome measure(s)	Conclusion
Gray-Donald et al. (2000) (272)	Native Americans/ Canada	Recruited before the 26th week of pregnancy, non-parallel recruitment of control and intervention arms. Mean BMI = 29.6 kg/m^2 (SD = 6.45) in non-intervention arm and mean BMI = 30.8 kg/m^2 (SD = 6.85) in intervention arm at baseline.	219 107 in non-intervention arm; 112 in intervention arm	Dietary and weight counselling Exercise groups provided	Gestational weight gain; gestational diabetes; Caesarean section; birth weight; postpartum weight retention	No statistically significant difference in gestational weight gain, prevalence of gestational diabetes, Caesarean section or large for gestational age baby
Olson et al. (2004) (293)	96% white/USA	Recruited before third trimester. Hospital and clinic setting BMI range: 19.8 to 29 kg/m^2	498 381 in non-intervention arm;	Used the Institute of Medicine recommended guidelines on weight gain; 'health book'	Gestational weight gain ; birth weight	No statistically significant reduction in gestational weight gain or prevalence of large for

Author (year)	Ethnic group/country	Participants/setting	Sample size	Intervention	Outcome measure(s)	Conclusion
			117 in the intervention arm	used to record diet and exercise and contained healthy eating and exercise information		gestational age baby
Claesson et al. (2007) (270)	Not stated. Predominantly Caucasian/ Sweden	Obese and registered at antenatal care clinic. BMI ≥30 kg/m^2	348 193 in non-intervention arm; 155 in intervention arm	Nutritional habits interview, weekly counselling and aqua aerobic sessions	Gestational weight gain; Caesarean section.	Statistically significant reduction in gestational weight gain; no difference in prevalence of Caesarean section
Kinnunen et al. (2007) (285)	Over 90% Caucasian/Finland	First-time pregnant women who were obese (BMI ≥30 kg/m^2)	196 95 in non-intervention arm; 101 in intervention arm	Individual counselling at each antenatal visits. Dietary guidance and optional activity sessions.	Gestational weight gain; diet change; birth weight	No statistically significant reduction in gestational weight gain or prevalence of large for gestational age baby. Statistically significant reduction in dietary glycaemic load.
Shirazian et al., 2010 (273)	33% Blacks; 67% Latino/ USA	Singleton obese (≥30 kg/m^2) pregnant women recruited in the first trimester. Historical non-intervention group.	54 28 in non-parallel control arm; 28 in intervention arm)	One-to-one counselling; six structured seminars on healthy living (healthy eating and walking)	Gestational weight gain; gestational diabetes; Caesarean section	Statistically significant reduction in gestational weight gain; no difference in prevalence of gestational diabetes
Mottola et al., (2010) (269)	Not stated/ Canada	Overweight (BMI ≥25 to 29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) pregnant women recruited before 16 weeks gestation; historical non-intervention group.	65 matched non-parallel control of 260	Individualised nutrition plan; exercise consisted of walking (three to four times per week, used pedometers)	Gestational weight gain; Caesarean section; birth weight; peripartum weight retention	Possible reduction in gestational weight gain; no difference in prevalence of Caesarean section or large for gestational age baby; minimal effect on peripartum weight retention

1. BMI: body mass index
2. SD: standard deviation

Table 18: Assessment of the quality of the included trials: non-randomised trials

Author (year)	Population representa-tiveness	Adequacy of sequence generation	Masking/ selection bias	Incomplete outcome data	Contamination	Sample size	Grade of quality
Gray-Donald et al. (2000) (272)	Yes: Registered from clinic	No	No	No	No: non-parallel control	219	Low
Olson et al. (2004) (293)	Yes	No	No	No	No: non-parallel control	560	Low
Claesson et al. (2007) (270)	Yes: Registered from clinic	No	No	Yes	No: selected from nearby city	315	Low
Kinnunen et al. (2007) (285)	Yes	No	No	No	Yes	55	Low
Shirazian et al. (2010) (273)	Yes	No	No	Yes	No: non-parallel control	28	Low
Mottola et al. (2010) (269)	Yes	No	No	Yes	No: non-parallel control	65	Low

Table 19: Assessment of the risk of bias of the included trials: randomised trials

Author (year)	Population representa-tiveness	Adequacy of sequence generation	Masking/ selection bias	Intention to treat	Incomplete outcome data	Loss to follow up	Sample size	Grade of quality
Polley et al. 2002 (266)	Yes	Yes:	No	Not reported	No	Yes	120	Low
Hui et al. (2006) (267)	Yes: from clinic	Exact method not described	No	Not reported	No	Yes	52	Low
Wolff et al., 2008 (264)	Yes	Yes: computer generated	No	Not reported	Yes	Yes	50	Low
Jeffries et al., 2009 (262)	Yes	Yes: opaque envelope	Yes	Not reported	Yes	Yes	286	Low
Ong et al., 2009 (276)	Yes	Exact method not described	No	Not reported	No	No	12	Low
Barakat et al., 2011 (291)	Yes	Yes	Yes	Yes	Yes	Yes	160	Medium
Asbee et al. 2009 (261)	Yes	Yes	No	Not reported	Yes	No	100	Low
Thornton et al., 2009 (263)	Yes	Yes	Yes	Not reported	Yes	Yes	257	Medium
Guelinckx et al., 2010 (260)[26]	Not reported	Randomised but not reported how	Not reported	Not reported	Yes	Not reported	99	Low
Phelan et al., 2011 (268)	Yes	Yes: opaque envelope	Yes	Yes	Yes	Yes	401	Medium,
Quinlivan et al., 2011 (292)	Yes	Yes: opaque envelope	Yes	Yes	Yes	Yes	124	Medium
Luoto et al., 2011 (277)	Yes	Yes	Yes	Yes	Yes	Yes	399	Medium
Nascimento et al., 2011 (278)	Yes	Yes: opaque envelope	Yes	Yes	Yes	Yes	82	Low
Vinter, 2012	Yes	Yes: opaque envelope	Yes	Yes	Yes, big	Yes, but big	360	Medium
Dodd et al., 2014	Yes	Yes. Computer generated	No	Yes	Yes but small	Yes, but small	2152	High

Table 20: Effect estimates for randomised trials of lifestyle advice versus standard care

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Gestational weight gain (kg)	12	4835	Mean difference (Tau^2, 95% CI)	-1.67 (-3.34- 0.01)
Gestational diabetes	8	4231	Odds ratio (Tau^2, 95% CI)	0.92 (0.65-1.30)
Caesarean delivery	8	3977	Odds ratio (Tau2, 95% CI)	0.98 (0.88-1.09)
Large for gestational age	8	4326	Odds ratio (Tau^2, 95% CI	0.95 (0.77-1.18)
Birth weight (g)	8	1876	Mean difference (Tau^2, 95% CI)	-.01 (-0.09-0.07)

[a] Statistically significant pooled estimates. CI: confidence interval

Table 21: Effect estimates for non-randomised trials of lifestyle advice versus standard care

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Gestational weight gain (kg)	5	1534	Mean difference (Tau^2, 95% CI)	-1.41 (-3.36-0.55)
Gestational diabetes	2	233	Odds ratio (Tau^2, 95% CI)	1.42 (0.76-2.63)
Caesarean delivery	4	1246	Odds ratio (Tau^2, 95% CI)	1.13 (0.82-1.55)
Large for gestational age	3	1199	Odd ratio (Tau^2, 95% CI)	0.92 (0.64-1.32)

CI: confidence interval

Figure 7: Flow diagram of study selection

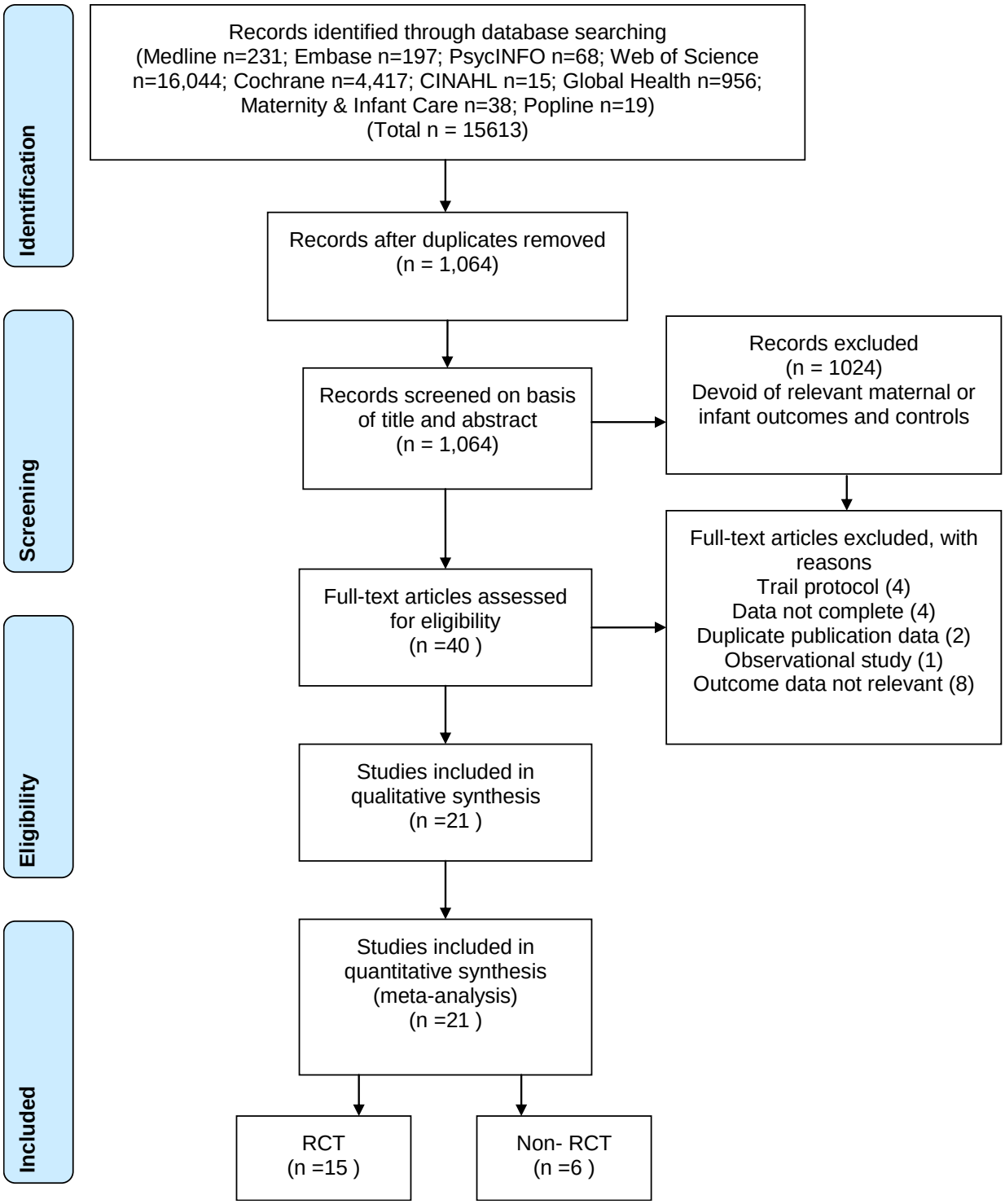


Figure 8: Forest plot of randomised trials investigating the effect of lifestyle advice versus standard care on gestational weight gain (kg)

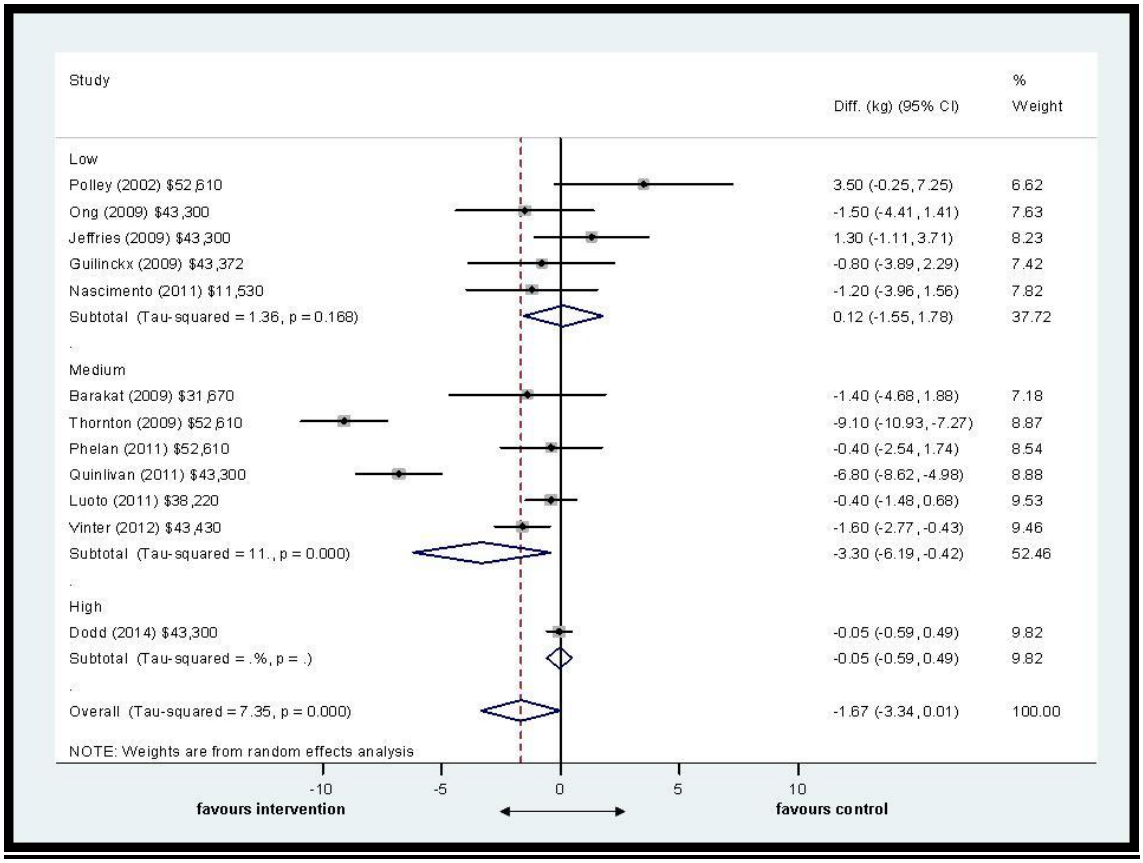


Figure 9: Forest plot of randomised trials investigating the effect of lifestyle advice versus standard care on risk of gestational diabetes

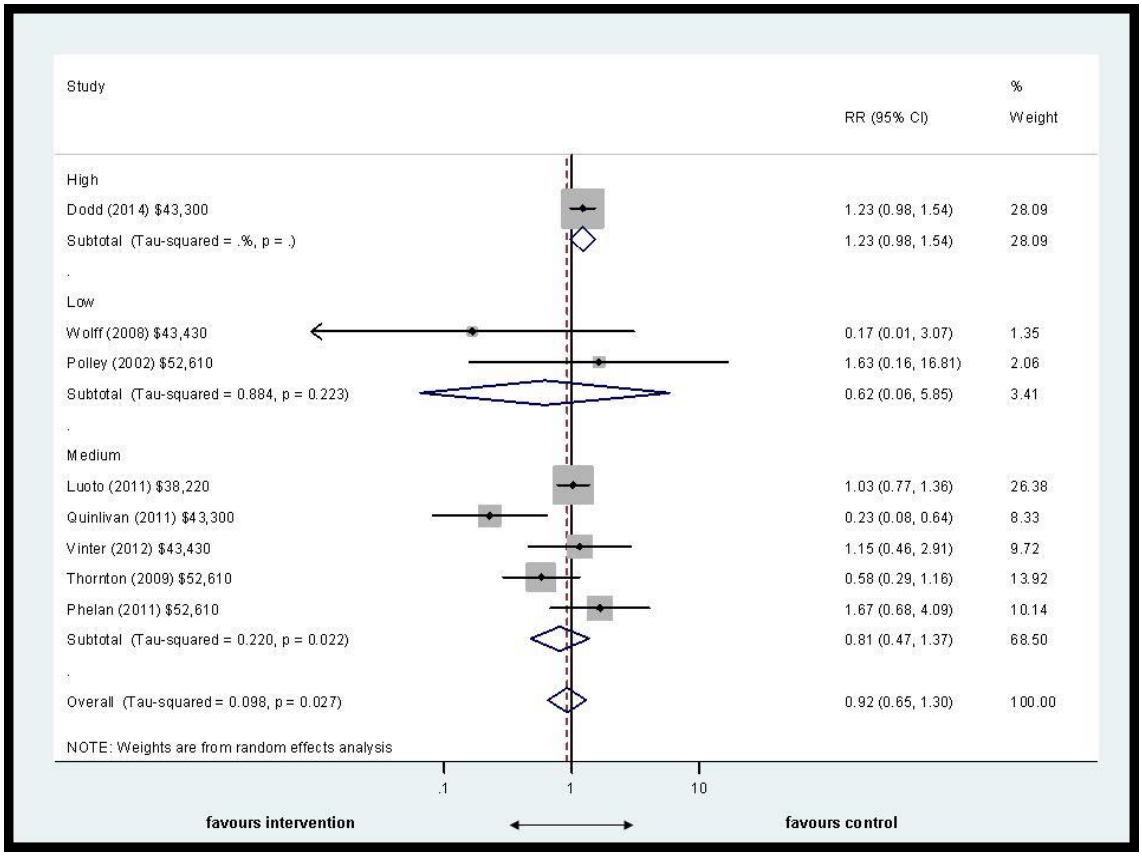


Figure 10: Forest plot of randomised trials investigating the effect of lifestyle advice versus standard care on risk of Caesarean delivery

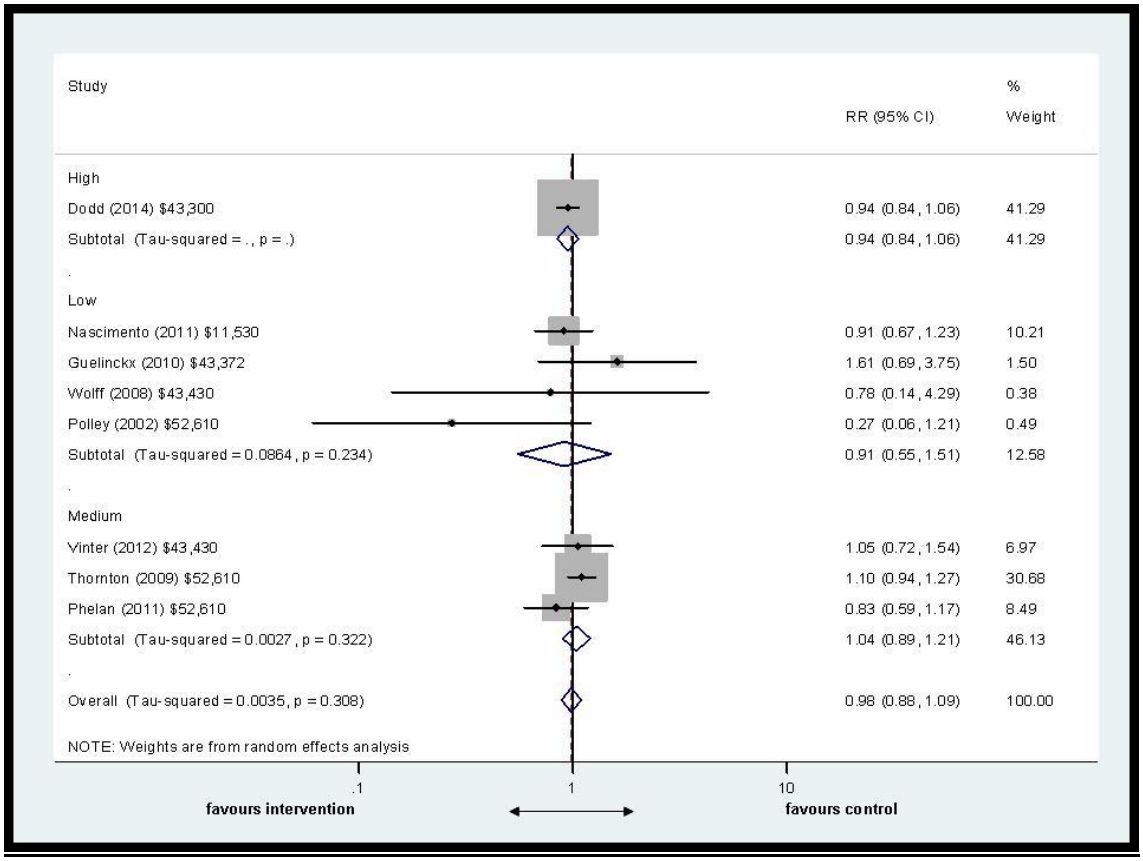


Figure 11: Forest plot of randomised trials investigating the effect of lifestyle advice versus standard care on risk of large for gestational age baby

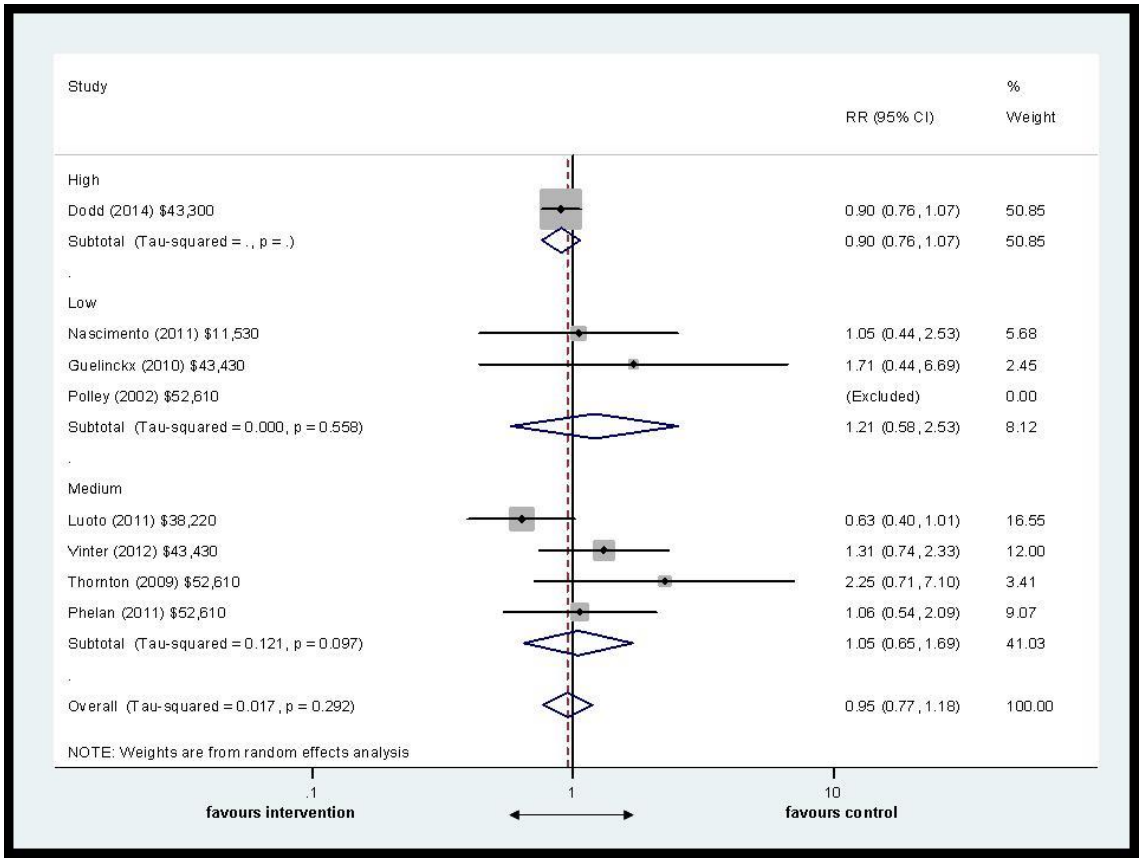


Figure 12: Forest plot of randomised trials investigating the effect of lifestyle advice versus standard care on birth weight

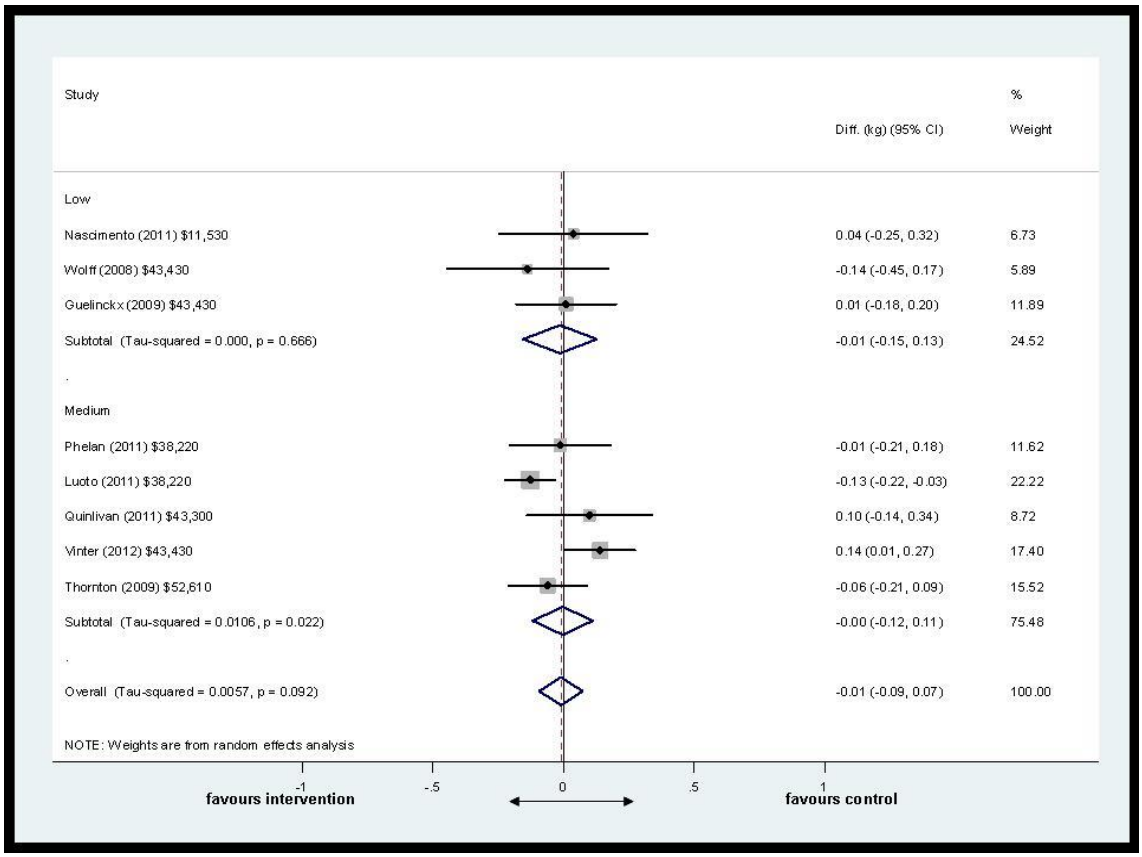


Figure 13: Forest plot of non-randomised trials investigating the effect of lifestyle advice versus standard care on risk of large for gestational age baby

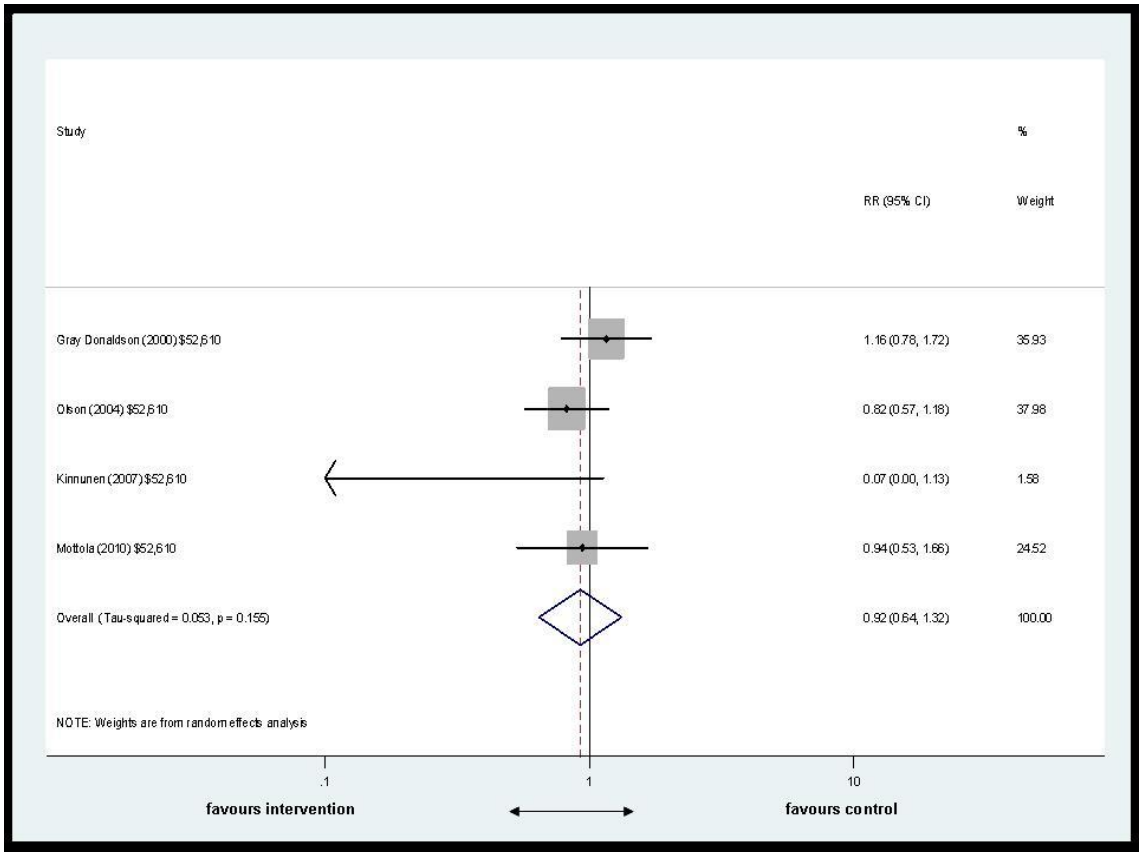


Figure 14: Forest plot of non-randomised trials investigating the effect of lifestyle advice versus standard care on risk of Caesarean section

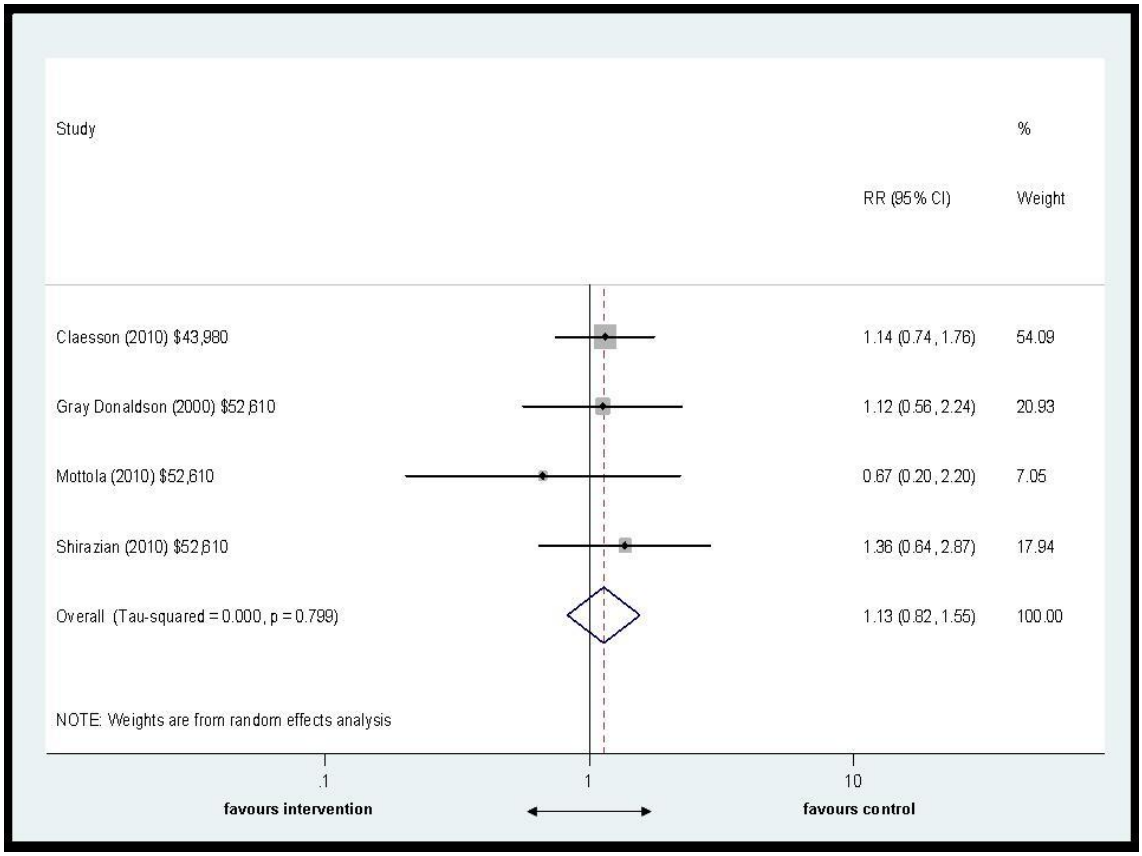


Figure 15: Forest plot of non-randomised trials investigating the effect of lifestyle advice versus standard care on risk of gestational diabetes

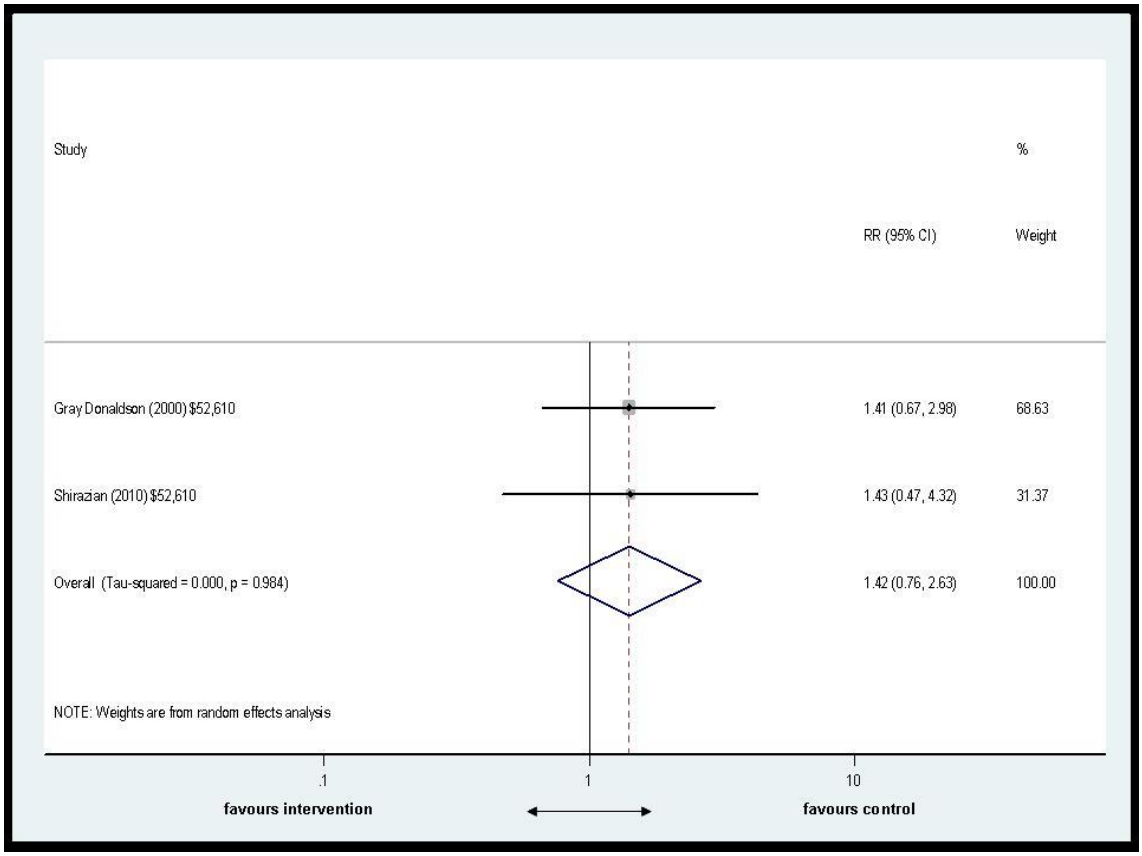
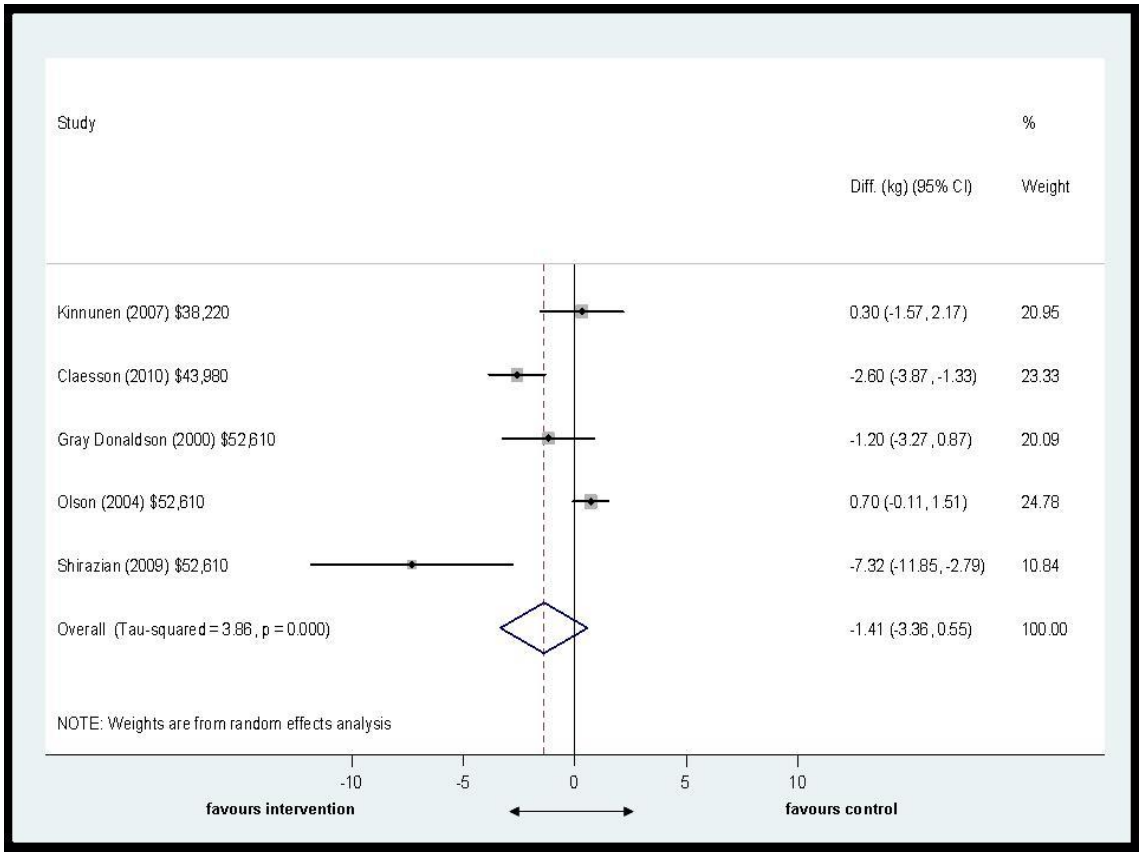


Figure 16: Forest plot of non-randomised trials investigating the effect of lifestyle advice versus standard care on gestational weight gain (kg)



CHAPTER 6: Development of the CAN intervention using the MRC framework for designing a complex intervention to improve health

6.1 Introduction

Previous chapters explored the challenge posed by overweight and obesity in pregnancy worldwide and provided evidence from the literature to explain why obesity is viewed by both the public and professionals as one of the most important public health problems in pregnancy. The challenge is even greater at the local South East London level, as shown by the data in Chapter Four, which establishes that the impact of obesity (on the mother, the delivery and the infant) is higher in Blacks than in other ethnic groups.

As demonstrated in Chapter Five, there is so far insufficient evidence that lifestyle interventions result in improved pregnancy outcomes. Despite obesity having more of an impact on Blacks, none of the published interventional studies had a sufficient number of black participants to assess effectiveness in this population (67). There has been a recommendation for well-designed interventional studies for obese pregnant women that engage with diverse multi-ethnic deprived communities with a view to preventing racial and ethnic disparities in obesity risk (76, 221). Obese pregnant women from all backgrounds deserve evidence-based lifestyle advice which will aid them to make informed lifestyle decisions. Pregnancy may be a critical period in which to provide interventions that may lead to restricted postpartum weight retention in women and prevent macrosomia and hence future obesity in the offspring (18, 76). A series of animal studies involving rodents and nonhuman primates provides the evidence that a dietary change that takes place prenatally may orchestrate alterations in infant adiposity and metabolism which may be long-lasting. This phenomenon has been attributed to epigenetic mechanisms (253). Thus, timely prenatal interventions instituted during a period of plasticity in fetal development (as opposed to corrective attempts made later in life) may result in improved health outcomes which are lasting. If these interventions reach out to

deprived and ethnically diverse pregnant obese populations, as highlighted by the Marmot report, it may also be the best time to address the inequality associated with obesity (178).

6.2 Aim

The aim of this work was to develop a multi-component community-based activity and nutrition (CAN) programme for obese pregnant women in a deprived diverse community setting in South East London.

6.3 Framework and method for designing the CAN intervention

The development of the CAN intervention used the framework for design and evaluation of complex interventions to improve health. (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC004871; BMJ, 2000, www.mrc.ac.uk/complexpackages.html, http://www.mrc.ac.uk/utilities/documentrecord/index.htm?d=MRC004871) (290)

Complex interventions are those that include several components (www.mrc.ac.uk/complex interventions guidance). CAN is a complex intervention because it meets the criteria of the Medical Research Council's guidelines on what constitutes a complex intervention: it has three components of physical activity improvement, nutritional advice, and behavioural support by professionals (with health trainers delivering the intervention) (245).

The development of the intervention was undertaken by the author and Professor Lucilla Poston (Head of Division for Women's Health Research, King's College, London group). This intervention was used in two separate pilot studies: UPBEAT and CAN. The intervention study called UPBEAT (United Kingdom Better Eating Activity Trial) is a multi-centred hospital-based study, a complex behavioural intervention comprising dietary and physical activity change in obese pregnant women. This is led by Lucilla Poston. CAN

(Community, Activity and Nutrition programme) piloted the same intervention in a community setting at Sure Start/children's centres in order to establish the feasibility and translation of this multi-component intervention in a deprived diverse community in South East London. The author is leading this study. My role in developing the intervention was to contribute intellectually to the debate and formulation of the interventions. I was present at all of the meetings and during the writing up of the intervention manual. I also sought the views of local experts involved in providing lifestyle intervention services in both Lambeth and Southwark boroughs and identified places where mothers could obtain healthy and cheap food in the boroughs. I also identified all the leisure centres in these communities where mothers would be able attend to improve their activities.

Table 22 describes the steps taken in the development and evaluation of UPBEAT/CAN as a complex intervention using the MRC framework for complex interventions, including my personal role in each step. Professor Poston has written a letter confirming my role in this process (appendix J).

Pre-clinical or theoretical phase

The theoretical phase looked at the evidence (E) available for doing the study, the population and the problem (P) being studied, the intervention (I), the comparator (C), outcome (O) and design of study, in this case a trial (T) i.e. EPICOT.

Evidence

Chapters Two, Three and Four provide strong evidence for the effect and impact of obesity on adverse pregnancy outcomes, particularly in a diverse, deprived community. This justifies and provides a robust evidence for the need to develop an intervention to mitigate these adverse associations. The developmental over-nutrition hypothesis highlights that over-nutrition results in excessive glucose being transferred through the placenta to the fetus, resulting

in fetal insulinaemia and ultimately large for gestational age delivery and macrosomia (294). Chapter Three provides a robust rationale for a behaviour intervention incorporating low glycaemic index diets and increased activity (100).

Population and problem

The intervention focuses on obese pregnant women. The theory and reason for this is fully described in previous chapters. Obesity has a strong effect and impact on adverse pregnancy outcomes. Moreover, Chapter Four alludes to obesity being over-represented in Blacks and deprived groups; hence, any intervention should make an attempt to engage with the users and ensure the sample population is representative of the population for which the intervention is eventually intended.

Intervention

The CAN community activity and nutrition programme incorporates low glycaemic index diet, improved activity, and behavioural support during pregnancy. The theory behind the intervention is described in Chapter Three incorporating SMART goals (226, 295-296). The intervention itself is described in Chapter Eight.

Comparator

The comparator group is a non-intervention group following a local clinical guideline.

Outcomes

The outcome selected for the pilot is changed behaviour in terms of reduced glycaemic load in the diet and improved activity. For the main CAN trial

the outcomes are macrosomia for the infant and gestational diabetes for the mother.

The design of the trial

The design of the trial is a pragmatic randomised controlled trial.

Phase I: Defining the components of the intervention

The components of nutrition, activity and behavioural support were developed by a multidisciplinary team, of which I was a member. Having decided that the intervention would incorporate eight behaviour change sessions focused on a low glycaemic index diet and improved activity (see Chapter Eight for details), it was important to conduct qualitative studies to ask providers and users (obese women from South East London) how they envisaged or would engage with an ideal service. The findings and details of these qualitative studies form the basis of Chapter Seven. Findings from these studies were incorporated into the development of the CAN intervention, described in Chapter Eight.

Phase II: Pilot study

In Phase II, I evaluated whether the intervention (CAN) delivered in a community Sure Start/children's centre setting was feasible, and secondly, whether it resulted in a change of behaviour. Methods and findings of the pilot study are presented in Chapter Eight.

Table 22: Steps taken in the development and evaluation of CAN as a complex intervention using the MRC framework

Steps MRC 2000, BMJ 2004 and MRC 2008	CAN	My role
Theory or preclinical phase	Evidence was identified for CAN by performing a literature review on two aspects of maternal obesity. a. The problems of obesity and reproductive health (297). This has been updated for my thesis in Chapter Two. b. A comprehensive review of the effectiveness on lifestyle interventions during pregnancy, pre-pregnancy and post-delivery (289).	I came up with the idea, conducted the literature review and led the writing of the papers (289, 297). I applied for a grant to address the question of whether a community-based maternal obesity programme was needed. I came up with the idea and co-wrote the manuscript for publication (296). I applied and was successful in acquiring a grant to conduct a health needs assessment of maternal obesity in South East London. I have compiled and written a report on this (296). An executive summary is attached as Appendix A.
Phase I: Defining the components of the intervention	The components of nutrition, activity and behavioural support used for CAN and UPBEAT were developed by a multidisciplinary expert group (including myself) led by Professor Lucilla Poston.	I obtained a second grant to develop and evaluate a lifestyle intervention for maternal obesity. As reported above, I compiled and co-authored a report on health needs assessment for maternal obesity in Lambeth (296). The executive summary is appended and the full report is on the CAN website.

Steps MRC 2000, BMJ 2004 and MRC 2008	CAN	My role
	The feasibility of delivering the intervention in the community was evaluated, the acceptability to providers was tested and the providers' views were published (Chapter Seven). Local guideline on the management of maternal obesity was written to establish agreed uniform care that we provide for obese pregnant women and this was altered appropriately in agreement with NICE guidelines.	This was performed by me from the secured grant and two manuscripts for publication on this (298-299). I wrote and produced local evidence-based clinical guidelines for the care we provide for obese women in pregnancy. This is used as the care in the control group (Appendix B).
Phase II: Pilot study	The intervention in a Sure Start/children's centre community setting was trialled in order to establish whether it was feasible and whether it would change behaviour in terms of reported low glycaemic index diet and improved activity.	I performed the implementation of this trial in the community. I established the translation of this intervention into the community.
The intervention itself	The intervention itself (used in CAN) is based on Phases I and II above and, collaborating with the United Kingdom Better Eating and Activity trial (UPBEAT) team, an agreed intervention was decided upon.	Using the findings from the health needs assessment and as part of the UPBEAT group, the CAN/UPBEAT intervention was developed which is described in detail in the CAN participant manual (attached at the back of this thesis in the form of a CD as Appendix G).

RESEARCH PAPER COVER SHEET FOR CHAPTER 7

Please be aware that one cover sheet must be completed for each 'Research Paper' included in a thesis.

1. For a 'research paper' already published

1.1. Where was the work published? **Oteng-Ntim E**, Pheasant H, Khazaezadeh N, Mohhidin A, Bewley S, Wong J, Oke B. *Developing a community based maternal obesity intervention: a qualitative study of service providers' views*. British Journal of Obstetrics and Gynaecology. 2010. 117(13):1651-5

I had lead responsibility for this work.

1.2. When was the work published? **2010**

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion:

In preparation for the PhD and also for applying for a grant, I undertook this study to seek service providers' views which would contribute to the development of the Community Activity and Nutrition programme for obese pregnant women. Apart from this piece, all of the major substantial parts of my work, which form the thesis, have been done after registering for the PhD.

1.3. Was the work subject to academic peer review? **Yes**

1.4. Have you retained the copyright for the work? **Yes**

If yes, please attach evidence of retention.
If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published? .....

2.2. Please list the paper's authors in the intended authorship order ……

2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments / In press

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)
I conceived and designed the study. I conducted the literature search with one other person and supervised the meta-analysis. I wrote the first draft of the paper.

NAME IN FULL (Block Capitals) ……EUGENE OTENG-NTIM…….

STUDENT ID NO: ……235138……..

CANDIDATE'S SIGNATURE …Eugene Oteng-Ntim…… Date …….

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above)
……..……

CHAPTER 7: Developing a community-based maternal obesity intervention: a qualitative study of service providers' views

Publication based on this work:

Oteng-Ntim E, Pheasant H, Khazaezadeh N, Mohhidin A, Bewley S, Wong J, Oke B. *Developing a community-based maternal obesity intervention: a qualitative study of service providers' views*. British Journal of Obstetrics and Gynaecology. 2010. 117(13):1651-5

There follows below an expanded and updated version of the published paper.

7.1 Introduction

Obesity is a global epidemic and, if current trends continue, 50% of the UK adult female population is predicted to be obese by 2050 (300). An escalating proportion of pregnant women are obese (301) and obesity is associated with an increase in maternal and perinatal complications (Chapters One, Two and Four). Maternal obesity is also a contributor to childhood obesity (17-18). The national prevalence of maternal obesity is estimated to be 18% (41). However, the confidential enquiry into maternal and child health (CEMACH) found that 27% of pregnant women who died between 2003-2005 were obese and that 30% of mothers who had a stillbirth or neonatal death were obese, suggesting that obesity is a contributor to poor outcome (5). In response to these findings, CEMACH provided recommendations for the management of maternal obesity including the need for the development of national guidelines (5). The English government has put in place a strategy to tackle obesity (Healthy Weight, Healthy Lives), recognising the challenge posed by obesity in pregnancy and making recommendations to mitigate its effect. At the local level, Primary Care Trusts (PCTs) are expected to commission or develop services that assist with the identification and treatment of pregnant obese women. However, recent systematic reviews on weight management in pregnancy

concluded that there is no evidence on the effectiveness of dietary and/or physical activity interventions in pregnancy (177, 302). No published study could be found in the literature on providers' views of interventions to address obesity in pregnancy. The aim of this study was to gain insight into the thoughts and views of health care providers managing obese pregnant women in order to help inform the development of an intervention for obese pregnant women.

7.2 Method

This was a qualitative study using personal telephone interviews with providers of care and advice for people with obesity. These providers are referred to here as stakeholders. Stakeholder interviews were organised with both internal service providers and external private providers. Internal stakeholders were consulted in order to understand the current service provision for the target population groups, to record improvements that could be made to meet the unmet needs of these service users, and to note recommendations for the design of the proposed Phase II intervention. External stakeholder interviews involved detailed discussions around their existing provision of obesity services, the potential to adapt the programme where necessary to tackle maternal obesity, and recommendations for the development of a service to meet health needs.

7.2.1 Selection of study sample

Internal service providers were identified within the borough of Lambeth (inner city London borough with high levels of deprivation) using lists of employees (303). Internal service providers were consulted in order to identify and understand the current service provision for obese women who are pregnant, and to record current provision and recommendations for any proposed intervention to improve services. A sample was selected using purposive sampling provided by the public health team for Southwark and Lambeth. Purposive sampling may not produce a representative sample of all

service providers, but this method of sampling is acceptable in qualitative research within the context of exploratory study (303). External stakeholders (third sector/private providers) of obesity services were identified using snowball (network) sampling (snowball sampling starts with known providers who are asked to recommend further providers who can be interviewed, so that the sample builds up like a snowball) (303). The external stakeholders were involved in order to understand their existing provision of obesity services and the potential for adaptation to tackle maternal obesity and to obtain their recommendations for the development of a new maternal obesity service. A total of 22 service providers were identified. Twelve were internal to the National Health Service (NHS), eight of whom were clinical. Ten were external, three of whom were experienced in tackling maternal obesity (Table 23).

7.2.2 Interviews

All stakeholders were contacted to ask whether they would consent to be interviewed and to agree a convenient time for the interview to take place. The interviews were semi-structured, based upon an agreed topic guide (as shown in the table below), and undertaken as telephone interviews, each lasting approximately one hour. The interviews were not recorded but detailed notes were taken throughout the discussions.

The interview guide used was as follows:

1. What services are available to improve physical activity and healthy living for obese pregnant women?
2. What services are available to improve healthy nutrition for obese pregnant women?
3. What pathways are available for obese pregnant women?
4. What are the challenges to tackling obesity pre-pregnancy and during pregnancy?
5. What should the development of a new intervention entail?

6. What should the content be?
7. What should the structure be?
8. Who should deliver the intervention?
9. Where could the intervention be delivered?
10. How often, and with what time interval?
11. How could a developed intervention be incorporated into existing pathways and interventions?

The topic guide used for service provider interviews was as follows:

Theme	Details
1. Current practice	a. Identification b. Management
2. Challenges to tackling maternal obesity	a. Patient b. Health care system and environment c. Evidence and guidance
3. Developing a new intervention	a. Content b. Structure c. Staff d. Setting e. Frequency f. Stage of pregnancy and recruitment g. Integrating the new intervention within existing services

Table 23: Internal and external service providers interviewed

Internal service providers	**External service providers** (indicating the specific service they usually provide)
• Community midwife • Community dietician • Consultant obstetrician • Clinical director for maternity services • Head of obstetrics • Fertility treatment lead	• MEND (childhood obesity) • Traffic Light programme (childhood obesity) • Empower (preventing childhood obesity but links with treating maternal obesity postnatally) • Watch It (childhood obesity)

• Clinical health psychologist • General practitioner • Obesity lead at the PCT • Maternity services manager at the PCT • Head of family support and children's services • Director of nursing (health visitor)	• Shape-Up (adult obesity) • Counterweight programme (adult obesity) • Slimming-on-referral (adult obesity) • Slimming World for pregnant mothers (maternal obesity – antenatal) • Weight Watchers referral scheme (adult obesity) • Pushy Mothers (maternal obesity – postnatal)

7.2.3 Data Analysis

The semi-structured interviews were analysed in detail using a modified version of 'Framework Analysis', i.e. charting and collating the interview responses under headings and subheadings, followed by thorough analysis and mapping of the grids to allow identification of key themes (e.g. current practice, challenges to tackling maternal obesity and development of a new intervention) (304). It is acknowledged that saturation was not achieved for the stakeholder interviews.

7.3 Results

7.3.1 Theme 1: Current practice – lack of existing services

All stakeholders said that a number of services and projects currently exist in Lambeth to increase physical activity, improve healthy eating and manage obesity in adults and children. They all alluded to the fact that limited services within the borough have been established to tackle maternal obesity and there is no maternal obesity care pathway for the structured management of pregnant women. All stakeholders provided information that midwives provide

first line healthy eating and physical activity advice for those women identified as obese but the external stakeholders reported inconsistency in the advice given and lack of available written resources for patients to support the verbal information. Dietetic and psychology provision is available for cases that are considered specialist or high-risk, e.g. patients developing gestational diabetes or those experiencing severe mental health issues. Overall, all stakeholders acknowledged the inadequate service provision and management of pregnant obese women.

7.3.2 Theme 2: Challenges to tackling maternal obesity (pregnant obese women and obese women trying to conceive)

One external stakeholder (from Slimming World) considered cultural and language barriers as potential issues to take into account when designing a new service (e.g. meeting the needs of all ethnic groups). All internal stakeholders also commented on the need for attempting to tackle maternal obesity in different cultural groups and reinforced the issue by explaining that Lambeth is an ethnically diverse community. Clinical stakeholders expressed concern that some women, in particular Black and Minority Ethnic (BME) groups, do not attend antenatal appointments on a regular basis and therefore 'slip through the net'. In addition, a clinical stakeholder (midwife) noted the issue of managing weight in Afro-Caribbean women who regard weight as a sign of beauty in their culture.

Half of the external stakeholders (Slimming World, Counterweight, MEND, Weight Watchers and Traffic Light) said that lack of motivation and readiness to change handicapped the effectiveness of any interventions introduced to tackle maternal obesity. However, they also commented that pregnancy may be a time when patients are more receptive and motivated to change. This was highlighted as being particularly important for obese women trying to conceive. Two external stakeholders (Weight Watchers and Shape Up) suggested adopting a screening tool to ensure that only motivated patients are

recruited to any new services. Three of the four non-clinical stakeholders and six of the eight clinical stakeholders also mentioned lack of motivation as a barrier to tackling obesity but one suggested that younger women may be more motivated to change than older women. In addition, a clinical stakeholder (obstetrician) confirmed that obese women wanting to become pregnant do not lack motivation as they are aware that if they lose weight they will be able to receive fertility treatment.

Health care professional engagement was raised as a challenge by two clinical stakeholders (midwife and GP) who doubted that all professionals were aware that tackling obesity should be a priority area. Comparison was made with smoking as all health care professionals now recognise the risks associated with smoking, particularly whilst pregnant, and are aware of the need to prevent smoking in pregnant women. They considered that a similar approach should be pursued to tackle obesity. This links with the concern over raising the issue of weight, which was mentioned by three internal stakeholders, who explained that health care professionals may not feel comfortable broaching the subject of obesity with patients. A clinical stakeholder (GP) suggested investigating how to raise the issue of weight with obese women and what terminology and language should be used. A non-clinical stakeholder (Weight Watchers) suggested running training for all health care professionals.

7.3.3 Theme 3: Developing a proposed new intervention

Content

Sixteen stakeholders recommended some form of multi-component intervention that incorporates nutrition, physical activity and behavioural change elements. The key features of the nutrition component included providing culturally specific healthy eating advice adapted for women during pregnancy and encompassing advice for breastfeeding and weaning for the mother and baby (postnatal phase). Key features of the physical activity component

included advice and exercise sessions that are tailored for women during pregnancy such as low impact exercises, e.g. walking, aquanatal and yoga/pilates. The key feature of the behavioural change component involved some form of motivational interviewing technique to assist with adopting improved behaviour around eating and activity. In addition, one stakeholder (GP) highlighted the need for practical interactive sessions, e.g. supermarket tours, practising reading food labels and shopping on a budget.

Six stakeholders did not recommend a multi-component intervention and advised a focus mainly on diet. These were the midwife, dietician, director of nursing, head of family support, maternity services manager and fertility lead. They were all concerned about exercising in pregnancy and the fact that this may be associated with miscarriage.

Structure of intervention

Stakeholders expressed different views regarding whether the service should be one-to-one or group-based or a combination of the two types of sessions. One-to-one sessions were favoured for their ability to provide individualised and personal care and the sensitivity of the subject area requiring a confidential and closed environment. In comparison, group-based sessions were deemed advantageous because of the peer support factor that helps to motivate patients.

Staff to deliver intervention

Stakeholders agreed unanimously that a multidisciplinary team to manage any new interventions with health trainers should be considered key because they already provide healthy weight and healthy lifestyle intervention to women who are not pregnant. Different views were expressed by stakeholders regarding the use of specialist and non-specialist staff to deliver the programme. Stakeholders who suggested using specialist staff mentioned

dieticians, exercise specialists and psychologists, whereas all of the other stakeholders recommended non-specialist staff, e.g. health trainers and community food workers, supported by midwives and health visitors. The reasons expressed for favouring specialist staff included the fact that maternal obesity is a condition associated with additional risks and therefore specialist staff may be better placed to manage these issues and risks. In comparison, reasons for supporting non-specialist staff included increased cost effectiveness, limited time and capacity of specialist staff and the need to reserve specialist staff for high-risk cases. All stakeholders commented on the fact that staff would need to be trained in the delivery of the intervention with non-specialist staff requiring more intensive training. The need for standardised resources to support the training of the staff and dissemination to all patients was highlighted by three stakeholders.

Setting for delivery of intervention

A number of settings were identified by the stakeholders, ranging across community, primary and secondary care. Community clinics (e.g. children's centres) are particularly useful when involving women in weight management programmes, because they are already used and are easy to access; 18 of the 22 interviewees suggested the community-based setting in Sure Start children's centres.

Frequency of sessions

Some stakeholders suggested a regular service, e.g. using the same venue and time every week as consistency maximises attendance. The recommended length of the programme suggested by all of the stakeholders was between 8-12 weeks to ensure that drop-out rates are kept to a minimum, although stakeholders acknowledged the programme length would need to be longer to incorporate both the antenatal and postnatal phases.

Stage of pregnancy and recruitment

All stakeholders discussed recruitment, stating that obese pregnant women should be identified and targeted using their pre-pregnancy weight or BMI at first booking appointment.

Integrating the new intervention within existing services

All stakeholders recommended developing a local maternal obesity care pathway to improve and standardise both the identification and management of obese pregnant women. This would incorporate any proposed new interventions, thus assisting with the identification and recruitment of women into the programme. Lastly, all stakeholders agreed the need to pilot the service and also to ensure that effective monitoring and evaluation mechanisms are put in place to make incremental improvements to the design and to increase the currently limited evidence base.

7.4 Discussion

7.4.1 Main findings

The London borough of Lambeth is an inner city London borough with high levels of deprivation; 82% of the population live in areas in the top two UK quintiles of deprivation and 46% of the pregnant population are from BME backgrounds. It lacks dedicated services for tackling maternal obesity, and therefore many obese pregnant women have unmet health needs. Service providers recognise and support the need for the design and implementation of a multi-component (healthy eating, physical activity and behaviour change) intervention, both antenatally and postnatally. New services should be established at community-based settings and administered by trained non-health care professionals supported by midwives and health visitors. The

sessions could be flexible to meet the needs of the women, incorporating either group-based, one-to-one or telephone support as stakeholders favoured all of these options. Monitoring and evaluation should be included as part of the intervention to enable continuous service improvement and to add to the currently limited evidence base. This was alluded to by all stakeholders. All stakeholders highlighted that interventions require improved identification of obese pregnant women using BMI calculation at the booking appointment.

7.4.2 What is already known on this topic?

Maternal obesity is now being acknowledged as a serious public health problem (180). Health care professionals are aware that programmes need to be implemented to tackle obesity in pregnant women but few Primary Care Trusts (PCTs) are developing care pathways or protocols. Those PCTs trying to address the unmet health needs of their population are faced with inadequate evidence and guidelines to support their decisions.

7.4.3 What this study adds

A limited number of studies have already been published on interventions for maternal obesity, but none have reported the thoughts, views and recommendations of stakeholders. This article reports a qualitative study from the perspectives of those managing obese pregnant women, both in the NHS and the voluntary/private sectors. The findings will inform the development of maternal obesity programmes and should be of value to people from a broad range of disciplines including academics, researchers, clinicians, public health professionals, commissioners, and governmental organisations.

7.4.4 Strengths and limitations

Strengths

This study interviewed a broad group of stakeholders, both within the NHS and in the private sector, hospital-based as well as community-based and from a broad range of disciplines. Hence, the findings from the study may be transferable (305). In this study, there has been clear description of the method by which the data was collected (306). The selection of stakeholders could be considered fair due to its inclusion of both public and private sectors and the widened nature of the selection. At the time of completing this work, there were very few publications in the literature about providers' views on developing obesity interventions and hence, despite the limitations, its acceptance for publication was based mainly on its originality. The sampling methods adopted, i.e. purposive sampling and snowball samplings, are well recognised in qualitative methods in initial exploratory studies. It allowed information to be gained for the development of a new service or for a complex intervention and its evaluation to be performed (245). This study not only focuses on positive case analysis but also on negative case analysis; it reported on both and thus attempts to provide a balanced perspective of the findings. The author's knowledge of the area being studied may be a positive stimulus to performing this study and may have contributed to the data being obtained successfully (307). This study allowed the author to gain knowledge that contributed to the design of a lifestyle intervention as recommended by the MRC framework (245).

Limitations

The design and conduct of the study had several limitations, including possible biases associated with the method of sample selection, data collection and interpretation of findings. It is important to consider how my presence in the research setting contributed to the data collected, for example. As the researcher, my values could have tainted the research, particularly in the

selection of who to interview, and the way in which I asked the questions may have encouraged a particular answer (296, 303). In qualitative research, it is almost impossible for the researcher to remain completely outside the values and subjectivity of the study. It is, however, essential to the principle of reflexivity that I subject my own research practices to the same critical analysis deployed in the study. For example, why did I choose to do purposive sampling instead of random sampling of subjects? Random sampling would have ensured that I reduced systematic bias and that each subject would have the same chance of being selected, hence making the results more likely to be representative of the population being studied. Random sampling in this case may have been impossible as a sampling frame did not exist at the primary care trust, public health Lambeth and the acute Trusts. The ability to create one was limited as the study population was widely dispersed and there were no denominator data. Random sampling would have been more expensive in terms of both resources and time.

I may also have chosen not to interview a stakeholder because of a preconceived view that he/she might be difficult. The second impact I may have had was on how I was perceived by the responders; especially, being a consultant obstetrician, I may be deemed influential, which may attract certain responses or restrict the interviewee from saying what he/she genuinely wants to say. There may have been similar issues regarding my being male. I could have overcome these issues by allowing another researcher to repeat the interviews to see if the interviewees gave the same responses (308).

The medium through which the information was collected was transcription, which may be open to bias. The author may have been selective regarding which information to transcribe and which to omit. The high-standard medium for collecting verbal data is either audio-recording or video recording. These methods minimise data misrepresentation or misinterpretation (309-310). In scenarios where transcription is used, it would have been most appropriate to

use standardised rules for transcribing, as recommended by Waitzkin et al. (309).

I interviewed by telephone, instead of conducting face-to-face interviews. Telephone interview may deter subjects from disclosing sensitive information, as there is less chance of developing a good rapport and building the appropriate level of trust to disclose information freely. On the other hand, the subject, not knowing the interviewer and communicating through telephone, may arrive at the conclusion that it is unlikely that a true response to the answers may be traced back to the interviewee, and hence might be happy to freely share any sensitive information. Furthermore, telephone interviews were convenient for both the interviewers and interviewees. The information was not recorded because I did not have the ethical permission to do so and the assumption was that this would have been intrusive. It is, however, acknowledged that recorded information may reduce information bias as the reference material or information is there to be referred to at any time. With a planned interview guide and detailed transcription of notes, this may have diminished information bias and may also have allowed the point of saturation to be clearly identified.

Another important issue to consider in the conduct of the study is that the principle of saturation was not applied. Once the point of saturation is reached in a study, additional stakeholders no longer provide extra information or insight. The study had limited funding and time and hence it was not possible to wait for saturation to be reached. The fact that saturation was not reached in this study may limit the interpretation as more stakeholders could have provided new information relevant for setting up the intervention. However, despite this, a wide range of stakeholders from a broad spectrum of disciplines was interviewed.

Finally, although a sample of service providers was identified, the views of pregnant service users will be essential when developing any new service.

Further and more extensive research should take place with women at different stages of pregnancy; pre-conception, antenatally and postnatally (299). In addition, the responses of the service providers (internal stakeholders) are specific to Lambeth which limits the generalisability to diverse inner city areas in the UK and elsewhere.

7.4.5 Conclusions

This qualitative study sought the views of stakeholders and, despite its limitations, highlights providers' views that an intervention to tackle maternal obesity is needed. The existing evidence shows that the effectiveness of services provided to this target population group is limited and therefore the design of any new programme requires consultation with service users.

CHAPTER 8: The CAN intervention

8.1 Introduction

Having followed the MRC framework for developing a complex intervention to establish the burden of obesity in pregnancy; having developed a strong theoretical rationale for the nature of a lifestyle intervention that can be utilised; having performed a systematic review and meta-analysis of the lifestyle intervention; having explored users' (299) and providers' views on how they envisage such a service and having secured their engagement; and working with an expert group of researchers, the CAN intervention was developed.

8.2 The CAN intervention

Details of the CAN intervention programme in the form of a participant manual are presented in Appendix as the last appendix. A brief summary of the intervention is given below.

CAN is an integrated diet and activity behaviour-change intervention which is delivered over 8 weeks starting at 17+0-18+6 weeks and finishing at 26-28 weeks of gestation. Participants are followed for up to 6 months post-delivery. The intervention is delivered using a combination of one-to-one and group-based activities (weekly), as well as telephone contacts, SMS text messages, e-mail and web-based support. Dietary advice focuses on decreasing glycaemic load, restricting saturated fatty acid and free sugar intake, and increasing fruit and vegetable consumption. The advice also includes spacing meals evenly to attenuate change in plasma glucose levels. Diets include foods with low glycaemic index (GI). Subjects are advised to spread their intake of food over smaller meals but with substitutions of starchy foods with a lower glycaemic index, including brown bread, basmati rice in place of white long grain rice, pasta in place of potatoes, and low glycaemic index breakfast cereals rather than high ones. Activity focuses on increasing total

activity such as walking, swimming, step aerobics and gym-based exercises. The intervention is delivered by a trained health facilitator in a community health/leisure centre setting in South East London. The stakeholders (users and providers) recommended the setting to be in the community (Chapter 7).

The programme comprises of sessions combining group-based activity (nutrition and exercise components) lasting two hours and one-to-one sessions lasting ninety minutes to provide motivational support and personalised goal-setting, tailored to meet the needs of the individual.

Information leaflets and a participant manual are given to the applicants. The information and activities that comprise the intervention are culturally specific and sensitive to the needs of obese women and their partners and families.

The components of the programme include the following:

8.3 Nutrition

At the group sessions healthy eating topics include recommendations for:

- Low glycaemic index food which is patient and culturally focused
- Fruits and vegetables
- Reduced saturated fat intake
- Food label reading
- Appropriate portion sizes
- Eating less, more often, rather than three big meals a day
- Reduced free sugar intake (especially sugar-rich beverages)

8.4 Physical activity

A menu of exercise choices, based on the participant's wishes and local availability, is offered. A participant may choose, for example, weekly exercise

sessions (land-based low impact exercise such as cycling and dancing, and water-based exercise such as swimming and aqua-aerobics) which are provided in Lambeth by such organisations as Aqua Natal and Sport England. Group exercise sessions are planned to be fun, structured and non-competitive. For those who prefer exercising alone, walking is one of the menu options as the means to achieving agreed personal goals.

Postnatal women are referred on to existing and well-established resources in the children's centres including breastfeeding cafés, mother and baby exercise classes, and baby massage courses.

8.5 Behavioural change

This psychology-based component helps women to change their lifestyle through both one-to-one and group-based motivational sessions using a solution-based problem-solving approach. The theory behind this is based on social cognitive theory and behavioural self-management approaches designed to help participants set SMART goals (311-313).

At the one-to-one sessions SMART goals are agreed between each woman and the programme leader. These are reviewed at one-to-one sessions during the course of the programme/pregnancy/post-natal maintenance period. SMART goals are Specific, Measurable, Achievable, Relevant, and Timely; for example: "I will walk to the children's centre, which takes 30 minutes, three days a week on Monday, Wednesday and Friday instead of taking the bus" or "I will eat three portions of fruit and vegetables every day over the next week". The goal can then be reviewed and reset, for example to five portions a day, always ensuring each goal is achievable. One or two SMART goals are set at each session, relevant to the improvement needed for each woman. One woman may need to increase her physical activity levels whilst another woman may need to focus on reducing her high calorie snack intake. The programme

leaders use a variety of prompts (e.g. meetings, telephone calls, texts, letters) to encourage the maintenance of improved lifestyle choices.

The peer support arising from group sessions motivates women to have contact with other women. The programme offers weekly sessions for each participant at the same time of day and on the same day of the week. Evidence on the effectiveness of adult and childhood obesity interventions, and stakeholder interviews with private providers, suggests that regular weekly sessions maintain motivation. The evidence suggests that programmes that are held more frequently have lower rates of attendance.

There are two main contact points for data collection, at 17+6 and 28 weeks gestation. The programme commences at approximately 17+6 weeks into pregnancy. The programme lasts for approximately 8 weeks. The community-based programme finishes at 27 weeks gestation. Following completion of the programme there will be motivational support (for example, via mobile texts, podcasts or mail) for a further period until delivery.

8.6 Staff

The programme is delivered by health care professionals who co-ordinate the programme, working in partnership with the existing health trainers and peer educators in Lambeth. We recruited staff with the desire, ability and personality to motivate and act as role models for the women. All staff were trained to ensure that they are competent at organising and leading the programme.

8.7 Settings at which the intervention was delivered

The intervention was delivered within the community at Sure Start and children’s centres. The pictures below show one of the children’s centres where

the intervention is being delivered, with two of the health trainers appointed to deliver the intervention.


Jessop Children's Centre

CHAPTER 9: Pilot study for the CAN intervention in South London

9.1 Introduction

This chapter describes a pilot study undertaken to assess the feasibility of the CAN (community activity and nutrition) programme designed to help obese pregnant women in a disadvantaged community (South London) to eat more healthily and become more active. CAN incorporates dedicated health trainers who set up and run one-to-one and group-based sessions for a period of 8 weeks starting from 18-20 weeks of gestation.

The objectives of the pilot were to:

1. Measure the feasibility of the study; and
2. Make preliminary assessments regarding whether the intervention is associated with changes in behaviour (dietary or activity behaviour), and, where possible, clinical outcomes.

9.2 Trial method and protocol

This method builds on the findings and recommendations of studies undertaken in 2009, the primary outcome of which was stakeholder agreement that a community-based service targeting obese pregnant women was both desirable and theoretically feasible (Chapter Seven).

The intervention was developed jointly by the author and Professor Lucilla Poston with a King's College, London team trialling a hospital-based intervention called UPBEAT (United Kingdom Pregnancy, Better Eating and Activity Trial).

9.2.1 Study design

Pilot RCT of community-based multi-component (activity, nutrition, behavioural support) programme for obese pregnant women (BMI>/=30 kg/m2) aged between 18 and 40 years with no co-morbidity.

9.2.2 Study hypothesis

A community-based intervention of dietary and physical activity advice combined with behavioural support (CAN) for obese singleton pregnant women will alter dietary and activity behaviour and have a positive impact on maternal glucose homeostasis and birth weight.

The study was designed by the author, and the setting up in the community and recruitment from King's College Hospital were both organised by the author. The initial recruitment of the pilot population was done by the author and a research midwife. The setting in selected children's centres was to attract participants from Black and ethnic minorities, identified as a risk group (Chapter 4). The method and protocol for CAN was developed by the author, as well as seeking ethical approval. All the analyses in this chapter were performed by the author apart from the nutritional analysis, for which the author sought help from the nutritionist involved in the study.

9.2.3 Study population

Women were recruited from King's College Hospital Foundation Trust maternity unit. In total 4700 pregnant women deliver at KCH per year, approximately 14% of whom are obese.

The study population was comprised of pregnant singleton women at less than 17 weeks and six days' gestation, attending the KCH maternity unit, who were obese and had no co-morbidity. Obese women with multiple

pregnancies or with medical co-morbidity (diabetes, thyroid disease, hypertension, stroke or myocardial infarction) were excluded from the study.

9.2.4 Recruitment and randomisation

All new patients fulfilling the inclusion criteria were approached by the research midwife, and given an information leaflet about the study. An opt-out approach was taken, and each patient was contacted the next day by the research midwife via telephone and recruited into the study if consent was given and if eligibility was confirmed. All essential information (age, address, postcode, ethnicity, cigarette smoking, GP address), including weight, height and BMI, was recorded on the study database (web-based).

Once consent was given, intervention was allocated using a randomisation procedure incorporated within the online database to minimise treatment groups by ethnicity (ONS categories: Black, White, Asian, Other), BMI group (30-35 kg/m^2, 36-40, greater than 40) and age (18-25, 26-30, 31-40, >40). The computer software informed the midwife of the next study number and allocation. The research midwife arranged appropriate visits and training sessions.

9.2.5 The intervention

This study used the intervention developed in conjunction with the trial for pregnant obese women, which uses a hospital-based intervention (UPBEAT), and findings from provider consultation (Chapter seven). Details of the intervention are described in Chapter Eight and in the CAN participants' manual attached (the last Appendix).

9.2.6 Care in the control group

Patients allocated to the non-intervention group had routine antenatal care, which was referral to their linked consultant. The local guideline for managing obese pregnant woman is attached as an appendix (Appendix B).

9.2.7 Follow-up and outcome measurement

a) Assessment of behavioural change. Physical activity was measured by an accelerometer over the previous week before randomisation, at 28 to 30 weeks, at 34 weeks and at 6 months post-delivery (details in Section 9.2.9). Diet was assessed at recruitment, 28 weeks, 36 weeks of gestation and 6 months post-delivery using the 24 hour recall developed for the CAN and UPBEAT studies (details in Section 9.2.8). In the non-intervention group, diet and physical activity were assessed in the same way and at similar time points.

b) Glucose homeostasis. Glucose tolerance tests were performed in all women at 27+0 to 28+6 weeks, which included fasting glucose, 1 hour after 75 g of glucose challenge and 2 hours after glucose challenge in both the intervention and non-intervention arms.

c) Weight change was assessed in study-specific visits to the research midwife at recruitment, 28+6 and 34+0 to 36+6 weeks gestation and 6 months post-delivery. In the non-intervention group, weight was measured at the same time points.

d) Evaluation of the feasibility, acceptability and fidelity of delivery of the intervention: The success, accessibility and acceptability of the intervention delivery and compliance with the protocol of the intervention were assessed by monitoring attendance at contact points 18+6 weeks and 28 weeks and via telephone calls. The proportion recruited and

declining was assessed. The reasons for refusal and drop-out, plus adverse events and attitudes were recorded and assessed.

e) Obstetric outcome was assessed during pregnancy and delivery. These include gestational diabetes, pre-eclampsia and severe pre-eclampsia, Caesarean section (elective and emergency) and reasons for section, induction of labour, blood loss at delivery (ml), birth weight, prematurity, death (stillbirths and neonatal deaths up to 28 days), gestational age at delivery, placental weight, inpatient nights (antenatal and total), breastfeeding initiation rates and smoking cessation rates.

9.2.8 Methods for assessing dietary change

Dietary data analysis was undertaken to assess dietary intake at baseline in all women before randomisation (15+0 to 17+6 weeks gestation) and again, to evaluate the effect of the intervention, in both control and intervention arms at 26-28+6 weeks gestation. Dietary recalls were performed by midwives trained in dietary assessment techniques, using a triple pass 24-hour dietary recall method performed at baseline and again following the intervention. The quality of dietary data was checked within a web-based database (MedSciNet™) by a research dietician. Dietary coding was inputted by the same research dietician using food codes from McCance and Widdowson's Composition of Foods (Summary Edition [6th Edition]) within the MedSciNet database. Dietary composition analysis was undertaken by the research dietician using the dietary analysis software WISP version 3.0 (Tinuviel software). Mean (SD) and percentage macronutrient and selected micronutrient intakes (of particular relevance to pregnancy) were reported.

A wide range of dietary variables were assessed. To determine whether the intervention had influenced dietary intake according to the dietary advice given, and without detriment to micronutrient intake, the following relevant parameters are reported: 1) energy intake; 2) the glycaemic index (GI) and the

glycaemic load (GL); 3) carbohydrate intake; 4) protein intake; 5) fat intake - total, monounsaturated, saturated and polyunsaturated; 6) sugar intake; 7) dietary fibre; and 8) dietary iron, zinc, vitamin D, folate and calcium.

The GI is a system for classifying carbohydrate-containing foods according to their glycaemic response, whereas GL also takes into account the amount of carbohydrate consumed. Mean dietary GI and GL were calculated within the WISP version 3.0 software which contains previously published GI values (Atkinson et al., 2008) (314). Where GI values were missing, additional UK published values (Henry *et al.,* 2005; Aston et al., 2008) were inputted, where available, using glucose as the standard reference value of 100 (315-316). Where dietary GI values were not available, values were inputted according to previously published methodology (Aston et al., 2010), developed for consistent assignment of GI values to foods (317).

9.2.9 Method for assessing activity change

Physical activity was assessed using an actigraph accelerometer (www.theactigraph.com) for a week, seven days before randomisation. To assess the effect of the intervention, participants in both the intervention and non-intervention arms were also asked to wear the accelerometer for a week following the OGTT (28 to 29+6 weeks). Accelerometers allow objective evaluation of physical activity, providing information on the frequency, intensity and duration of both physical activity and sedentary behaviour (ONS, 2010). They also have the advantage of providing standardised measures when compared to self-reporting of activity, hence, reducing recall bias and subjectivity. The disadvantage is that when the monitor is not being worn activity is missed, and also the accelerometer fails to measure water activities such as swimming. Sedentary activity was defined as <100 counts per minute (cpm), light activity 100-1951cpm, moderate activity as 1952-5725 cpm and vigorous activity as >5725cpm. As periods of vigorous activity were low, minutes for moderate to vigorous activities were combined (MVPA).

9.2.10 Data management

All data were entered onto a dedicated study database shortly after being obtained and checked for consistency and accuracy at regular intervals. Back-up copies of the database were made and confidentiality of access and storage of both electronic and paper information was ensured.

9.2.11 Statistical analysis

For assessment of dietary behaviour change, data analysis was undertaken using the Predictive Analytics SoftWare (PAWS) Statistics 18 (Statistical Package for the Social Sciences Inc.). Normality of data was checked using standard distributional plots. The independent samples t-test and the Mann-Whitney U test were used to determine differences in dietary intake between control and intervention groups at 28 weeks gestation.

For binomial outcomes, analysis compared proportions of women with the outcomes of interest in the intervention and the non-intervention arms of the study. For example, the proportions of women in the two arms of the study who achieved a restricted weight gain following randomisation were compared. Similar analysis include comparisons of the proportion of women with improved glycaemic control at 28 weeks, changes in activity and dietary habits and measures of improved wellbeing at 28 weeks and 6 months post-delivery. Mean age, BMI, IMD scores and activity levels in the two groups were compared using t tests.

9.2.12 Sample size and power

The aim of the pilot was to measure the feasibility of the study rather than estimate the effect of the intervention on health outcomes.

For the eventual main trial, the primary outcome for the mother will be abnormal oral glucose tolerance test at 27+0 to 28+6 weeks of gestation and for the infant, large for gestational age delivery (>90th customised birth weight centile). The sample size for the eventual study will be calculated to have at least 80% power to detect a statistically significant difference in the proportion of women who have an abnormal glucose tolerance test at 28 weeks and also large for gestational age baby at delivery in the intervention arm, compared to the control arm.

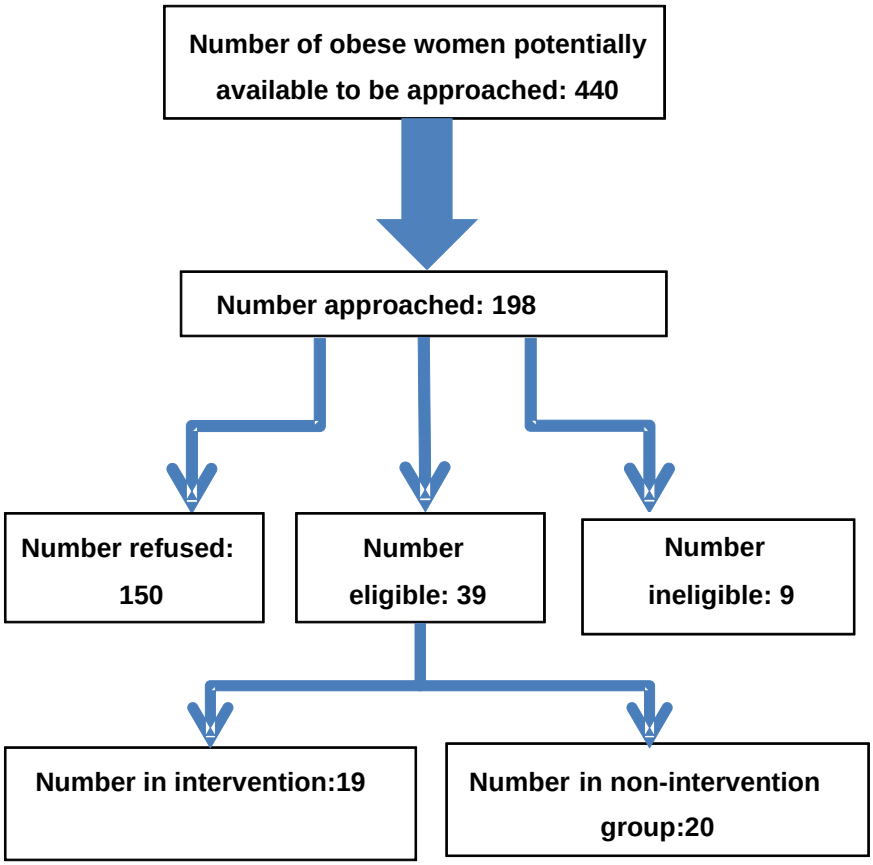
The rationale for using abnormal glucose tolerance test is that it has been shown to correlate with important clinical outcomes that affect the mother (e.g. gestational diabetes, pre-eclampsia) and the baby (e.g. congenital defect) (127). The rationale for using large for gestational age delivery is that it has been shown to correlate with adverse delivery outcome (e.g. Caesarean section, dystocia and shoulder dystocia).

9.3 Results

9.3.1 Recruitment and retention

Figure 21 shows patient flow through the trial for a period of eight months. Potentially it was estimated that 440 obese patients would be available over the eight-month period of the study (4700×14% obese×8/12=440). Of these, 45% were approached (198 women). Of those who were approached, 75% declined to take part in the trial (150 women). Of those who agreed to take part, 19% were ineligible (9 women). Of the 39 eligible women, all of them were randomised with 19 in the intervention arm and 20 in the non-intervention arm.

Figure 21: Patient flow through the trial over an 8-month period



Reasons for low approach rate

The number of eligible participants was not a limiting factor. In interviewing the eligible women and the research midwives, the main reason cited for the low number of eligible women being approached was too few staff involved with recruitment i.e. the relative lack of research midwifery time available for recruitment. The clinical midwives were also either unaware of the study or lacked time to mention the study to the patients, leading to fewer referrals from the clinical midwives. The referral pathway has mainly been organised through the fetal medicine centre in order to approach women having their first trimester scan, and was not used via the midwives doing the booking, hence reaching less than half the number of potential participants. As there was only one part-time midwife (three days/week) working on the study, the amount of research midwifery time focused on recruiting was low, as a considerable

proportion of available time was spent on acquiring outcome data rather than on recruitment.

Reasons given by patients for declining to take part in the study when asked by the research midwife at the time they declined

Several reasons were given by participants for refusing. Thematically these can be grouped into: finding time during the day to come to yet more appointments and inflexibility with the time that the intervention is delivered, as children's centres open between 0900 and 1700, which is likely not to be conducive to the requirements of working mothers. In addition, a high proportion of mothers who declined turned down entry into the study because of difficulty finding childcare. Some participants were concerned about stigma and being labelled as obese once they joined the study. A few of the participants who declined did not view obesity as high-risk in pregnancy and so did not see the need for the study (table 24)

Table 24: Summary of reasons for declining by obese pregnant women who refused to take part in the study

Reasons for refusal (Where two or more reasons are given, the first answer is included here)	**Number out of 150**	**Proportion**
Not able to find time because of travel, too many antenatal appointments or patient being a carer	24	16%
Work commitment	47	31%
Not able to get childcare	37	25%
Away on holidays	5	3%
Stigma	4	3%
Refusal from significant other (partner)	9	6%
No reason given	24	16%

Sociodemographic characteristics of those who refused and those who accepted

There were no major demographic differences between those who declined and those who agreed to come into the study. Black and ethnic minorities were well represented in the recruitment (Table 25).

Table 25: Socioeconomic characteristics of those who agreed and did not agree to come into the study

	Refused N=150	**Recruited N=39**	**P Value**
Mean age (SD)	30.07(5.96)	30.13 (5.41)	0.96
Mean BMI (SD)	35.09 (4.10)	36.68 (5.37)	0.08
Ethnicity			
White N(%)	40(29)	14 (36)	0.73
Black N(%)	89 (64)	22(56)	
Asian N(%)	4(3)	2(5)	
Other N(%)	5(4)	1(3)	
English Quintiles of Index multiple deprivation- English			0.18
1 (Least deprived)	0 (0%)	0 (0%)	
2	0 (0%)	0 (0%)	
3	3 (2%)	3 (8%)	
4	52 (34%)	12 (32%)	0.18
5 (Most deprived)	99 (64%)	23 (61%)	

Retention and drop-out results

Of the 19 participants in the intervention arm, 17 participated in at least 4 sessions and 15 in at least 6 or more (80%) (Table 26). The mean number of sessions attended per woman was 5.5 out of a total of eight.

Table 26: Attendance at each session of the intervention: in total eight sessions (S1-S8) for 19 participants

Total number of sessions attended									
i.d	Centre	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6	Session 7	Session 8
1	CAN	0	1	0	1	1	0	1	0
2	CAN	1	1	0	1	1	1	1	1
3	CAN	1	1	0	1	1	1	0	1
4	CAN	0	1	1	1	0	0	1	0
5	CAN	1	1	1	1	0	1	1	1
6	CAN	1	1	1	1	1	1	0	1
7	CAN	1	1	0	1	0	1	1	0
8	CAN	1	1	1	1	1	1	1	1
9	CAN	2	2	2	2	2	2	2	2
10	CAN	2*	0	2	2	2	2	0	0
11	CAN	4	4	4	4	4	4	4	4
12	CAN	2	2	2	2	2	2	2	
13	CAN	2*	2	0	2	2	2	2	0
14	CAN	2	2	4	4	4	4	4	4
15	CAN	2	2	2	2	2	2	2	2
16	CAN	2*	2*	2*	2*	0	2*	0	2*
17	CAN	1	2*	2*	0	2*	0	0	2*
18	CAN	2	2	2	2	2	0	0	2
19	CAN	1	4	4	4	4	4	4	4

Code: 0=Did not attend, 1=Group session, 2=1:1 session, 2*=Only 1 woman possible, 3=Phone sessions only, 4=Drop-out

9.3.2 Characteristics of intervention and control groups

Sociodemographic description of the CAN pilot study group is shown in Table 27. There were no major differences between groups in terms of age, BMI, ethnicity, parity or index of multiple deprivations.

Table 27: Sociodemographic characteristics of subjects at baseline by randomised group

	Control Group N=20	Intervention Group N=19	P Value
Age (Years) Mean (SD)	29.60 (4.66)	30.68 (6.17)	0.55
BMI Mean (SD)	36.61 (6.45)	36.75 (6.14)	0.95
Ethnicity			0.81
White N (%)	7 (35)	7 (37)	
Black N (%)	11 (55)	11 (58)	
Asian N (%)	1 (5)	1 (5)	
Other N (%)	1 (5)	0 (0)	
Parity			0.39
Primip N(%)	9 (45)	6 (32)	
Multip N (%)	11 (55)	13 (68)	
IMD (Index of Multiple Deprivation) - English addresses only			
N	19	19	
Mean (SD)	37.60 (7.81)	33.31 (11.65)	
English Quintiles of IMD			
1 (Least deprived)	0 (0%)	0 (0%)	0.18
2	0 (0%)	0 (0%)	
3	0 (0%)	3 (16%)	
4	6 (32%)	6 (32%)	
5 (Most deprived)	13 (68%)	10 (53%)	

Although the sample sizes were small, resulting in low power to detect statistically significant differences, these data provide some evidence that randomisation and minimisation were robust.

9.3.3 Dietary behaviour change

Conformity to dietary advice was assessed using structured questionnaires and validation was assessed using 24 hour dietary diaries. In order to minimise bias due to misreporting, the differences in the respective

food intakes were compared prior to randomisation and at 28 weeks of gestation, hence assessing the difference pre-intervention and post-intervention compared to the difference in the same time points in the non-intervention group.

The results presented in Table 28 demonstrate a significant reduction in dietary glycaemic load at 28 weeks gestation in the intervention group compared to the control group ($P<0.05$). This reduction in GL is concurrent with a reduction in total energy intake in the intervention group, with no differences found in percentage carbohydrate intake between the control and intervention groups. Although not statistically significant, there was a trend for a reduction in saturated fatty acid (SFA) (%E) intake ($P=0.07$) and improvement to the polyunsaturated fatty acid: saturated fatty acid ratio ($P=0.085$) in the intervention group only. Dietary glycaemic load remained unchanged. Despite a reduction of energy intake in the intervention group, no significant changes to key micronutrients were found between groups (Table 28).

Table 28: Dietary glycaemic index, glycaemic load, energy, macro- and micronutrient intake following dietary and lifestyle intervention (28 weeks gestation) adjusted to baseline

	Control (N=15) *Mean (SD)*	Intervention (N=14) *Mean (SD)*	P Value
Energy intake (kcal)	2115 (325)	1647 (554)	***0.01****
Dietary GI	54.7 (8.1)	56.7 (7.1)	0.89
Dietary GL	147 (30)	117 (38)	***0.03****
Dietary GL (%E)	26.3 (5.7)	27.7 (8.2)	0.59
Carbohydrate (%E)	48.3 (9.8)	50.3 (7.5)	0.55
Protein (%E)	16.3 (3.7)	15.7 (5.1)	0.71
Total fat (%E)	35.1 (9.0)	33.9 (7.2)	0.69
SFA (%E)	13.4 (4.0)	10.7 (3.8)	0.07
MUFA (%E)	10.6 (3.5)	10.0 (3.0)	0.64
PUFA (%E)	6.0 (3.7)	7.5 (4.2)	0.30
P:S ratio	0.45 (0.25)	0.87 (0.88)	0.09
Total sugar (%E)	22.0 (11.3)	18.7 (7.4)	0.38

	Control (N=15) *Mean (SD)*	Intervention (N=14) *Mean (SD)*	P Value
Fibre (NSP) (g)	10.3 (4.1)	11.9 (6.3)	0.43
Iron (mg)	11.6 (4.0)	10.7 (5.1)	0.60
Zinc (mg)	9.6 (2.7)	7.5 (3.7)	0.09
Vitamin D (µg)	3.0 (3.6)	2.0 (2.1)	0.39
Folate (µg)	224 (123)	223 (96)	0.98
Calcium (mg)	857 (329)	723 (391)	0.33

*Significant *P*<0.05. SFA: saturated fatty acid, PUFA: polyunsaturated fatty acid, MUFA: monounsaturated fatty acid, GI: glycaemic index, GL: glycaemic load, PS: polyunsaturated fatty acid: saturated fatty acid ratio, NSP: non-starch polysaccharide. %E: estimated percentage contribution to total energy intake.

9.3.4 Physical behaviour change

The accelerometer data was available for 12 out of the 39 participants (30%). Pregnant women found the accelerometers uncomfortable to wear and hence only a small proportion provided any results at all. There was no observed difference between the participants in the intervention versus the non-intervention group, although little can be concluded because of lack of power (Table 29).

Table 29: Physical activity measurements for the intervention and control subjects

Level of activity Counts/minute	**Control group N=7 Mean minutes/day (SD)**	**Intervention group N=5 Mean minutes/day (SD)**	**P Value**
<100 (Sedentary)	1159 (53.11)	1140 (51.73)	0.55
Total activity	214 (69.88)	223 (41.84)	0.79
100-1951 (Light activity)	171 (51.12)	188 (38.36)	0.53

Level of activity Counts/minute	Control group N=7 Mean minutes/day (SD)	Intervention group N=5 Mean minutes/day (SD)	P Value
1952-5724 (moderate activity)	43 (30.84)	35 (15.26)	0.57
5725-9498 (vigorous activity)	0.4 (0.37)	0.2 (0.16)	0.24
≥9499 (very vigorous activity)	0.00 (0.00)	0.01 (0.02)	0.33
Combined moderate and vigorous activity	44 (30.80)	36 (15.29)	0.57

9.3.5 Clinical Outcomes

Obstetric outcomes of the pilot study are presented in Table 30. Overall, 37% of women developed gestational diabetes according to the HAPO criteria and 8% had large for gestational age babies (LGA) (99). There was evidence of a trend towards lower prevalence of gestational diabetes in the intervention group compared to non-intervention as well as lower prevalence of large for gestational age babies although these differences were not statistically different. This being a pilot study, it was not powered to demonstrate effectiveness of the intervention.

Table 30: Clinical outcome (maternal and neonatal) data of participants in the intervention and control arm

	Control	Intervention	P Value
Weight at trial entry Mean(SD)	99.64 Kg (14.61) N=20	98.28 kg (15.1) N=19	
Weight at 28 weeks Mean(SD)	105.49 (15.09) N=15	102.16 (15.70) N=16	0.10
Fasting glucose at 28 weeks (mM) Mean(SD)	5.13 (0.94) N=15	4.72 (1.30) N=15	0.33
1 hour glucose at 28 weeks (mM) Mean (SD)	8.66 (2.90)	8.48 (3.30)	0.88
2 hour glucose at 28 weeks (mM) Mean (SD)	6.11 (2.50)	6.47 (3.06)	0.73
Gestational diabetes based on HAPO definition (%)	7/12 (46.7%)	3/15 (20%)	0.12
Gestation at delivery Weeks(SD)	39.73 (1.38) N=18	39.50 (0.92) N=16	0.57
Newborn birth weight (kg) Mean (SD)	3.429 (0.6) N=18	3.370 (0.4) N=16	0.74
Customised birth weight centile Mean (SD)	40.52 (33.01) N=17	38.30 (26.61) N=14	0.84
LGA (greater than 90th birth weight centile (%) for gestation at delivery	2/17 (11.8%)	0/14 (0.0)	0.19

9.4 Discussion

9.4.1 Summary of findings

This pilot trial has demonstrated that it is feasible to carry out the CAN intervention in Sure Start/children's centres. However, fewer than expected potential participants were approached. A reason for this is that research midwifery time was focused on data collection, which was intensive, as opposed to recruitment. The proportion of those approached who agreed to take part in

the study was also small. Difficulty finding time because of work, inflexibility of the timing of the intervention and childcare were cited as major barriers. Of those who agreed, acceptability and attendance was good. Drop-out was due to lack of flexibility with regard to timing of the intervention, holidays or childcare. Assessment of activity using the accelerometer was very uncomfortable for obese women. It may be necessary to drop this assessment for the main trial. The dietary assessment yielded strong evidence of reduced glycaemic load and saturated fatty acid intake in those in the intervention arm compared to those in the non-intervention arm. Assessment of obstetric outcome, while not appropriately powered for this pilot study, showed a trend towards reduction in gestational diabetes and large for gestational age babies in the intervention compared to the non-intervention arm.

9.4.2 Challenges

Despite widespread evidence of maternal obesity being associated with adverse outcome, there is as yet no proven effective intervention to alleviate these associated adverse outcomes (22). This might be because none of the studies evaluating these interventions followed the MRC framework for developing a complex intervention (318).

This chapter, which has focused on Phase II of the MRC framework, has demonstrated that it is feasible to deliver the complex lifestyle intervention CAN in community Sure Start children's centres. But this has not been without challenges, particularly in the assessment of physical activity. With the published lifestyle interventions not showing a proven benefit, it may well be that these interventions did not result in a behaviour change in terms of improved dietary behaviour and improved physical activity. These published interventions failed to address the question of whether the intervention actually changed behaviour. This pilot focused on assessing behaviour change in terms of diet as well as activity and, despite the small sample size, provides some evidence that the CAN intervention may have changed behaviour in terms of

reduced glycaemic load (P=0.03) and reduced energy intake (p=0.01). This was assessed based on 24-hour dietary recall, which is an established validated tool for assessing dietary behaviour change. Recall may be a problem as pregnant women may be selective in recalling their dietary behaviour. Indeed, a recent systematic review and meta-analysis by Thangaratinam et al. showed that dietary interventions may be more significant in terms of improving outcome in obese overweight pregnant women compared to physical activities (222). In this chapter it has been demonstrated that it was difficult for participants to wear the accelerometers and because of the discomfort the results shown here are very sparse. Also, during the study timeframe media coverage of obesity and the need for improved lifestyles may have contaminated the behaviour of the non-intervention group, bringing it closer to that of the intervention group. This may have diminished any true effect.

Recruiting obese pregnant women in deprived communities is very challenging, and hence these populations feature less in published articles. A recent study concluded that programmes are needed to curb the excessive gestational weight gain in all racial groups and to help some subgroups ensure adequate weight gain (54). Due to perhaps the setting of this study i.e. in Sure Start children's centres with the focus on local communities, the study was able to attract diverse applicants and findings from this work when completed may be able to be utilised in urbanised diverse communities. Findings from this pilot study have led to some recommendations for the follow-on study, as highlighted below.

9.4.3 Implications and recommendations:

From this pilot study, the following recommendations for the main trial are as follows:

1. Increase the number of midwives to improve recruitment and to promote the study by giving talks to midwife groups who run the booking clinics about the importance of the study and the eligibility criteria.
2. Provide posters and leaflets about the study in all of the antenatal clinics, including those in the community.
3. Follow the same process of randomisation and minimisation of participants in the main trial.
4. Reduce the time required for qualitative measurements, such as dietary questionnaires and accelerometer measurements, so that research midwives have sufficient time to focus on recruitment and the merging of first and second visits.
5. Allow flexibility of the timing of the sessions, particularly in the evening, being scheduled after working hours so that working mothers can attend.
6. Allow flexibility with the delivery of the intervention i.e. via phone calls, texts and emails, or one-to-one or group-based sessions.
7. Provision of crèche facilities to ensure that those with children will also be able to attend. Hopefully this will also reduce drop-out rates.
8. Find alternative methods for the assessment of physical activity. Women found wearing the accelerometer uncomfortable and alternative approaches will be needed for the main trial.
9. Regarding the sample size needed for main trial, and erring on the conservative side, the following calculation was made: Assuming an incidence of GDM of 30% in the control arm and 23% in the intervention arm (relative risk reduction of 30%), and a 20% lost to follow-up, it is estimated that approximately 770 women in each arm of the study (1540 in total) will provide the study with 80% to detect this risk reduction using a p value of <0.05%.

9.4.4 Conclusions

This pilot study has demonstrated that the CAN intervention is feasible in a high-risk diverse, low socioeconomic status population but that it is important

to make some adjustments to the protocol. The adjustments to be made include focusing the research midwives' time on recruitment, and ensuring flexibility for the participants in terms of the way in which the intervention is delivered and the timing of the intervention delivery. Following this pilot study, sessions have been established out of hours, i.e. starting at 18.00, ensuring flexibility for participants who are working, while maintaining sessions in the morning and afternoon. More research midwives have been employed to aid with recruitment, so that recruitment within the main trial has improved.

I found evidence that the CAN intervention results in a change of dietary behaviour in terms of reduced reported glycaemic load ($p=0.03$) and dietary energy intake ($p=0.01$) but it did not demonstrate a change in activity, possibly because of reduced uptake in the use of the accelerometer.

CHAPTER 10: Discussion

This thesis aimed to assess the extent and potential for the prevention of adverse impacts of obesity in pregnancy. The work culminating from the thesis has gone some way to addressing this. The objectives of the thesis were as follows:

(i) To summarise the literature on maternal obesity and the adverse impacts of maternal obesity on maternal and child health outcomes in the UK and elsewhere, as reported in Chapter Two.

(ii) To perform a descriptive epidemiological analysis of available local data on obesity in pregnancy. This would help to establish the association and impact of obesity on pregnancy outcomes in an ethnically diverse Inner London population using Guy's and St Thomas' data, as reported in Chapter Four.

(iii) To conduct a systematic review of existing evidence on lifestyle interventions for obesity in pregnancy, as performed in Chapter Five.

(iv) To develop a multi-component pilot study for a complex community-based activity and nutrition (CAN) intervention for maternal obesity in South London, as shown in Chapters six, seven, and eight.

(v) To conduct a pilot study of the CAN intervention in South London, as reported in Chapter Nine.

10.1 Summary of main findings

10.1.1 Maternal obesity and maternal and infant outcomes

The evidence presented in Chapter Two confirmed that obesity represents a major public health problem for the United Kingdom and most other countries. It showed that obesity is strongly associated with increased maternal and perinatal mortality and morbidity and that reducing the prevalence of obesity in pregnancy could markedly reduce adverse outcomes. The evidence clearly indicated that interventions to address the adverse outcomes associated with maternal obesity are urgently needed and remain a public health priority.

10.1.2 The epidemiology of maternal obesity in a South London population

The work described in this thesis estimated the prevalence of obesity in pregnancy in a South London population to be 15% (with some evidence of increasing prevalence over time). It demonstrated that Black pregnant women are over twice as likely to be obese compared to White women and that maternal BMI increased with increasing age and parity. The data showed a weak association between deprivation and obesity except at the highest quintile of deprivation, where the association was strong. These are new observations from a diverse community in South London.

In accordance with the established literature, this study showed a marked increase in adverse obstetric events in obese pregnant women including diabetes, Caesarean section, preterm delivery, postpartum haemorrhage and significant neonatal morbidity. The risks paralleled the increase in BMI. This showed that not only was obesity associated with adverse outcome but that BMI values in the overweight range were also associated with increased risk of adverse outcome. Of note, and a novel finding, is that the

association of obesity with gestational diabetes was more marked in obese women of Asian ethnic origin compared to the other ethnic groups.

In this thesis, by calculating population attributable fractions, analysis showed that if it were possible to prevent or mitigate the effect of obesity in pregnancy, then approaching one-third of diabetes cases, one in eight Caesarean sections, one in 20 cases of postpartum haemorrhage and one in 12 cases of macrosomia could theoretically be prevented in this population. Of particular importance, at a population level, is the differential impact of obesity on pregnancy outcome in particular ethnic groups. For example, for diabetes the avoidable proportion of cases is higher in Blacks (35%) compared to Whites (26%) due to the higher prevalence of obesity in this ethnic group.

10.1.3 Systematic review on lifestyle interventions for obesity in pregnancy

Findings from the systematic review and meta-analysis in Chapter Five showed that antenatal lifestyle, dietary and activity advice for overweight and obese pregnant women modestly restricts maternal weight gain during pregnancy but has no significant effect on other clinical outcomes such as the prevalence of gestational diabetes in women who are overweight or obese. However, the quality of the study designs was generally poor and did not support an evidence-based intervention programme at the time of publication. The review showed that no lifestyle interventions had been trialled in the United Kingdom and a very small percentage of participants were from Black and ethnic minorities. This review was published in 2013, and the high number of citations (22) reflects the current interest in obesity amongst pregnant women because of the increasing health care burden.

10.1.4 Development and evaluation of the CAN intervention

From stakeholder consultation, it was found that South London lacked dedicated services for tackling maternal obesity. Service providers recognised

and supported the need for the design and implementation of a multi-component (healthy eating, physical activity and behaviour change) intervention both pre-pregnancy and antenatally. It was evident that obese pregnant women and those trying to conceive may benefit from a service dedicated to addressing the heightened adverse outcomes associated with obesity. Working in partnership with Professor Lucilla Poston and using the MRC framework for designing a complex intervention, the CAN intervention was developed prior to undertaking a pilot study in a community children's centre /Sure Start setting.

Evaluation of this intervention in a pilot study on 39 obese pregnant women, randomised to the CAN intervention versus non-intervention in a diverse South East London population, showed that the CAN intervention was feasible when delivered in a community setting within an area of deprivation. The trial attracted participants from diverse ethnic backgrounds as well as the highest levels of deprivation, and showed a trend towards improvement of clinical outcomes. The pilot study also showed that the CAN intervention was associated with behaviour change as evidenced by reducing glycaemic load and energy intake, but it did not demonstrate a change in physical activity. Objective assessment of activity was difficult because of poor uptake in the use of the accelerometer.

Pilot data were used to perform a power calculation for a definitive study which will address the effectiveness of the CAN intervention in improving two primary clinical outcomes, gestational diabetes for the mother and macrosomia for the baby. This trial is currently underway.

10.2 What is already known?

It is well recognised that obesity is a significant global health problem (1, 319). It is also known that obesity is a major health issue for women during pregnancy, with approximately 15-20% of pregnant women said to be obese (3, 44). The associated risks of obesity to the mother, fetus and infants has been

well reported (44, 320-321). There have been many publications on gestational weight gain and pregnancy outcomes which have been comprehensively summarised by the Institute of Medicine (48).

However, despite the numerous publications and reports on the adverse effects of obesity on pregnancy outcomes, there have been limited attempts to estimate the population attributable fraction for obesity and to establish the differential effect and impact of obesity on particular ethnic groups. There have also been limited reports on effective interventions that may be implemented to mitigate the adverse effects of obesity in pregnancy.

10.3 What does this research add?

This project has estimated the proportions of avoidable adverse outcomes associated with obesity in pregnancy, and has demonstrated that obesity has a differential effect and impact on Blacks and other ethnic groups. It has produced a detailed, contemporary systematic review and meta-analysis which showed limited effects of lifestyle interventions in pregnancy. Similar studies have been published by others (177, 222) but none of them is current enough to incorporate the biggest and the most recent study (67).

This research developed a feasible community-based lifestyle intervention, designed with a multidisciplinary group of stakeholders in the setting of Sure Start/children's centres delivered by health trainers. The initial pilot study has demonstrated that it has potential to alter the dietary behaviour of obese pregnant women to reduce glycaemic load and caloric intake. The pilot study has led to nine recommendations, shown in Section 9.4.3, which may help other researchers designing an intervention for obese pregnant women as well as the design and conduct of the main CAN trial. The main trial to establish the effectiveness of the intervention is currently underway in a combination of hospital and community settings, and I will be responsible for undertaking a comparison of intervention delivery in the two settings.

10.4 Successes and shortcomings of this research

10.4.1 Successes

The research described in this thesis demonstrates the ability to take a clinical problem, such as obesity in pregnancy within a local setting, to identify the extent and impact of the problem using local data, and to develop an intervention that attempts to mitigate or alleviate the impact of the problem.

One of the main strengths of the project is the large sample size of the healthware database used for Chapter Four. This has created an opportunity to study and analyse rare outcomes such as perinatal mortality and to demonstrate its association with obesity with reasonable statistical power. The opportunity to analyse pregnancies from such an ethnically and socially diverse population was important and novel. The research identified ethnic differences in the impact of obesity in pregnancy and the interaction between ethnicity and obesity with regard to diabetes. The latter is a novel finding in the United Kingdom. Performing a systematic review and meta-analysis of lifestyle interventions in overweight and obese pregnant women contributed to the development of a local community-based intervention and a publication from this work has been well accessed by researchers and has provided a useful contribution to the literature (22).

Conducting a pilot study for a complex intervention of activity and dietary behaviour change for obese pregnant women in a deprived diverse setting in London was not an easy task. To have conducted this pilot and demonstrated that it is feasible is a modest success and highlights useful lessons for the main trial and for other researchers who may want to consider similar work. The ability of the pilot study to show a favourable dietary behaviour change, in terms of reduced glycaemic load, may be considered a success as none of the studies included in the systematic review and meta-analysis took this approach for assessing behaviour change.

Evidence from the Marmot report, Fair Society Healthy Lives, (178) highlights the importance of early life intervention (*in utero* to three years) in addressing inequality in health outcomes and improving the life chances of an individual. Thus, an early-life *in utero* intervention such as CAN performed within the setting of diverse deprived communities may provide a proportionate engagement and benefit for Black and ethnic minorities who, as the study shows, are more afflicted with obesity than Whites. The most recent data from the ongoing main trial shows that 54% of the participants who have been recruited into the CAN study are Black. At a time when early life interventions and investment into *in utero* and early life programmes substantially boost adult health (175), CAN may play a role in the arena by addressing healthy nutritional behaviour in obese pregnant women with an aim to improve the health of children. Funding has been provided by the EU Framework 7 study Early Nutrition to undertake an evaluation of the health of children from the main trial, including all children born to the CAN participants. The CAN programme for delivery of the intervention in the community has also been incorporated into the recent successful Big Lottery bid by Lambeth council, which focuses on interventions *in utero* and in early childhood to prevent obesity and improve early learning, known as the LEAP study (Lambeth Early Action Partnership: Appendix D).

10.4.2 Shortcomings

There are important limitations in this research.

Chapter Two is a personal critical review and as such I could have inadvertently left out some publications which might compromise the comprehensiveness of the review. However, I have made every effort to review all of the available literature. I acknowledged the possibility of a publication bias and a lower contribution from the ‘grey’ literature, but I have attempted to add

the grey literature according to the recommendations of the relevant RCOG and Cochrane websites.

The third chapter provides a robust rationale of the thesis. My research does not include animal studies, which may be considered a limitation, but I hope the review of the human studies provides a clear rationale for the research, without the need to review animal studies. However, where appropriate, animal studies have been referenced.

The fourth chapter has some limitations which have been acknowledged, with attempts made to minimise these. The major limitation of Chapter Four is the fact that almost one-fifth of BMI data were missing. Efforts have been made to minimise the impact of missing BMI data on the findings. I have shown that the missing BMI data were missing 'not at random' (322), and hence, imputation was not used. The recognition of this problem and my insistence that the BMI field on the Healthware system was made mandatory have reduced the proportion of missing BMI data since 2008.

The shortcomings of Chapter Five relate to the fact that some of the included studies in the systematic review are of low quality and the review does not include unpublished data. Whilst I searched for publications from the 'grey' literature, this did not yield any new intervention studies. However, I may have inadvertently left out potentially eligible studies, which could bias the findings.

Chapter Six focused on the development of the lifestyle intervention for obese women in pregnancy using the MRC framework. The development of a complex lifestyle intervention for dietary and nutrition behaviour change requires input from many disciplines, including the social sciences, psychology, obstetrics and gynaecology and nutrition. The intervention was therefore jointly developed within a multidisciplinary team led by Professor Lucilla Poston. I played a major role from the outset as obstetric lead, and lead for the community-led delivery. The CAN programme, delivered in Sure Start children's

centres, allowed the trial to be as closely embedded as possible in real early years pathways and practices in the community.

However, working in a multidisciplinary team, whilst necessary, has the shortcomings of lack of clarity regarding ownership and external visibility of leadership. No individual ‘owns’ the intervention, and it may not be clear who leads what. Chapters One and Six make clear my role in developing the intervention. Following the development of the intervention, I set up CAN in three children’s centres and negotiated the recruitment of patients for the CAN intervention at King’s College Hospital. The initial recruitment was performed by myself until I employed a research midwife based at King’s College Hospital who helped to strengthen the recruitment pathway.

Chapter Seven, which sought the views of service providers, has limitations in the methodology, as the interviews were not recorded. The sample size was also small and did not clearly delineate the point of saturation. However, despite the major shortcomings of this chapter, at the time it was published (298), it was amongst one of the first studies in the UK to have sought the views of providers in developing maternal obesity interventions in the community.

Chapter Nine evaluates the pilot study. To the best of my knowledge, this describes the pilot study results of the first community-based lifestyle intervention for obese pregnant women in the UK. The limitations are mainly to do with numbers. The number of potential participants contacted was very small and only one-quarter of potentially eligible obese pregnant women was recruited to the study. This may raise questions about the external validity of the study. According to the MRC framework for evaluating a complex intervention, the purpose of a pilot study is to identify problems early and resolve them at an early stage before the main trial. Thus, the recommendations included in Chapter Nine provide solutions for improving the reach of the study to potential eligible patients. This challenge is not unusual when recruiting obese pregnant women to interventional studies (271).

Together, these shortcomings and my attempts to address them provide important lessons with regard to future work and may benefit other researchers.

10.4.3 A summary of lessons learnt from the pilot study

There is a value in doing pilot trials to highlight the important lessons for the future and also for other studies. The pilot study described here has provided clarity on how to bring about dietary behaviour change in obese pregnant women in terms of reduced glycaemic load and energy intake. It has also revealed barriers to recruitment which, if I had started the main trial straight away, could have resulted in failure in terms of recruitment and cost. The study did not measure adherence to the behaviour change advice or collection of blood profiles which could have contributed to the knowledge and understanding on mechanisms of the lifestyle intervention. The pilot study highlighted the need for flexibility of timing of the appointments for participants in order to aid recruitment and retention, and this was subsequently implemented. It also highlighted the importance of research midwifery time dedicated to recruitment, which is likely to improve the number of potential participants reached.

Development of the intervention and the pilot in a community setting has demonstrated the importance of including ethnically diverse participants, particularly from Black and other minority groups, for whom there are very scanty data in the literature.

Recent data from the ongoing main trial show that, of the 256 obese women recruited into CAN by 31st July 2014, 132 were Black, 78 were White, 4 Asian, 1 Chinese and 55 Other. Thus, over half of participants in the current interventional study are Blacks, which is substantially different from other published trials (22). The development and evaluation of the trial has followed the MRC framework for developing and evaluating a complex intervention and,

importantly, the findings showed that once participants were recruited compliance to attendance was good. Almost three-quarters of participants attended 5 or more sessions, which is much higher than most previous interventions which did not show an effect on clinical outcomes (67). Lack of compliance may be the reason why the published studies did not show a major change in terms of outcome.

This pilot study demonstrated the importance of refining the protocol for delivery of the intervention, continuing with some aspects, and abandoning others in order to improve the delivery in the main trial.

10.5 Research recommendations from national policy documents

Policy documents from the National Institute for Health and Clinical Excellence have highlighted several public health research recommendations including:

1. A maternal child and nutrition guideline recommending research on dietary interventions which recognise the specific circumstances facing mothers from minority ethnic or disadvantaged groups as well as studies which provide contextual details (323). The research described in this thesis addresses this research gap.
2. A cardiovascular disease prevention guideline recommending research on reducing population consumption of saturated fat including in children (324). This study showed that in a population of obese pregnant women the CAN intervention may reduce saturated fatty acid intake.
3. The general obesity guideline stressing that multi-component intervention is the treatment of choice. The work from this thesis utilises a multi-component intervention (325).
4. The NICE obesity guideline also recommends the need for research into the effectiveness of interventions to manage obesity in varied population groups, including obese pregnant women, as well as the setting and the

source of delivery (326). This research has focused on obese women who are pregnant.

5. A recent Department of Health White Paper on “Healthy Weight, Healthy People" recommends the life-course approach to tackling the obesity epidemic, starting from pregnancy, through to early life and into adulthood. This work has addressed the effect of obesity in pregnancy and the feasibility of a community-based intervention at the beginning of the life-course (219).
6. The guideline on weight management before, during and after pregnancy has highlighted research gaps in the evidence, such as a lack of well-designed UK intervention studies on weight management in pregnancy and after birth. The findings described in this thesis will contribute to addressing this gap. The guideline also stresses limited evidence of the effectiveness of weight management interventions in pregnancy and after childbirth for women from disadvantaged, low income and minority ethnic groups. The work from this thesis addresses this gap.

10.6 Policy implications and research recommendations from this research

Policy makers in obstetrics and maternity care need to focus on obesity in pregnancy if they are to address its associated adverse outcomes, such as maternal and perinatal mortality and morbidity. Interventions to address the adverse outcomes associated with obesity need to be treated as a priority and need to be appropriately evaluated using the MRC framework for evaluating complex interventions.

This research suggests that in South East London interventions that target Black and ethnic minority groups may have more of an impact because the burden of obesity differentially affects these groups and they make up a considerable proportion of the population.

Funding bodies need to prioritise funding for evaluating interventions that will improve outcomes in the obese population during pregnancy. These interventions will need to engage users and providers, including the third sector, in order to ensure the seamless translation of the interventions into standard practice if shown to be effective. Moreover, interventions that target deprived communities are urgently needed to address the inequality associated with maternal obesity.

Studies focusing on nutrition pertinent to specific ethnic groups may be needed, so that appropriate education with regard to healthy eating in the different ethnic groups can be effectively provided. Studies which focus on barriers to healthy eating and improved activity may need to be prioritised. Studies that address how cultural barriers, with regard to healthy lifestyle, can be addressed are likely to make a difference to the obesity prevalence in different ethnic groups. Research should also explore the education of partners or other significant persons in the lives of obese women as they may provide motivation for a favourable behaviour change for the mother and her family. At a time when WHO and world leaders are focusing on non-communicable diseases globally (319), with obesity contributing to a significant part of the burden, there is no earlier time to start intervention than *in utero* and pregnancy as this may hold the key to trans-generational change.

Future work should focus on seeking evidence on the effectiveness of lifestyle interventions in the pregnant obese woman, particularly in Black and ethnic minorities. The ongoing work with CAN will go some way to addressing this. Research should also investigate health literacy in pregnancy, particularly in the obese population, and we have recently been awarded a grant to explore this in detail, particularly in different ethnic groups during pregnancy.

It is recommended that more studies should focus on lifestyle interventions pre-pregnancy. Attached in Appendix C is a proposal to evaluate a

lifestyle intervention in the pre-pregnant, overweight and obese group, particularly in women with subfertility.

All of these studies and interventions highlight a future work programme which follows on from this work and which would engage users, particularly those from Black and ethnic minorities and those from deprived communities, ensuring that social inequality associated with obesity is proportionately considered and addressed. The cost-effectiveness of these interventions will be an essential part of the evaluation if in the future the intervention is to be implemented.

10.7 Conclusion

In conclusion, the research described in this thesis has shown that pregnant women who are obese are at an increased risk of adverse outcomes to themselves and their offspring. The most significant adverse outcome to the mother is diabetes and to the offspring is macrosomia. Data from a population in South London showed that the effect of obesity on the risk of diabetes was most pronounced in Asians. At the population level, eliminating obesity in pregnancy could potentially reduce diabetes in pregnancy by almost one-third, and slightly more in the Black population because of the high prevalence of obesity in this group. From the systematic review and meta-analysis, the evidence shows that a dietary and activity lifestyle intervention has a weak effect in terms of restricted weight gain but otherwise has no other benefit. The pilot study of CAN, a community-based activity and nutrition programme for obese pregnant women consisting of eight sessions delivered by health trainers, showed that recruitment was difficult but retention was good. Despite the small sample size, the intervention resulted in a significant reduction in the intake of carbohydrates rich in refined sugar as well as reduced energy intake. Measuring change in activity with an accelerometer was difficult as obese pregnant women found it uncomfortable to wear them.

Having shown the study was feasible, with evidence of a change in behaviour in terms of reduced glycaemic load, the trial is continuing to recruit. The trial will establish the effectiveness of the intervention in a diverse deprived community setting with engagement of the Black population, a group shown in this thesis to be disproportionately impacted by obesity in pregnancy. If effective, it is hoped the intervention will be adopted into mainstream obstetric care for obese pregnant women in this community and elsewhere.

References

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011 Feb 12;377(9765):557-67.
2. WHO WHO. Obesity and overweight fact sheet 311. 2013.
3. Heslehurst N, Rankin J, Wilkinson JR, Summerbell CD. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989-2007. Int J Obes (Lond). 2010 Mar;34(3):420-8.
4. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012 Feb 1;307(5):491-7.
5. CEMACH. saving mothers lives 2003-2005. 2007.
6. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007 Aug;30(8):2070-6.
7. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology. 2003 May;14(3):368-74.
8. Knight M. Antenatal pulmonary embolism: risk factors, management and outcomes. BJOG. 2008 Mar;115(4):453-61.
9. Poobalan AS, Aucott LS, Precious E, Crombie IK, Smith WC. Weight loss interventions in young people (18 to 25 year olds): a systematic review. Obes Rev. 2010 Aug;11(8):580-92.
10. Atkinson RL, Pietrobelli A, Uauy R, Macdonald IA. Are we attacking the wrong targets in the fight against obesity?: the importance of intervention in women of childbearing age. Int J Obes (Lond). 2012 Oct;36(10):1259-60.
11. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1175-82.
12. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol. 2004 Feb;103(2):219-24.
13. Smith GC, Shah I, Pell JP, Crossley JA, Dobbie R. Maternal obesity in early pregnancy and risk of spontaneous and elective preterm deliveries: a retrospective cohort study. Am J Public Health. 2007 Jan;97(1):157-62.
14. Kristensen J, Vestergaard M, Wisborg K, Kesmodel U, Secher NJ. Pre-pregnancy weight and the risk of stillbirth and neonatal death. BJOG. 2005 Apr;112(4):403-8.
15. Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. BMJ. 2013;347:f4539.
16. Reynolds RM. Excess maternal weight gain during pregnancy is associated with overweight/obesity in offspring at age 16 years, but maternal

pre-pregnancy obesity has a greater effect. Evid Based Nurs. 2013 Apr;16(2):43-4.
17. Poston L. Developmental programming and diabetes - The human experience and insight from animal models. Best Pract Res Clin Endocrinol Metab. 2010 Aug;24(4):541-52.
18. Cunningham SA, Kramer MR, Narayan KM. Incidence of childhood obesity in the United States. N Engl J Med. 2014 Jan 30;370(5):403-11.
19. Reynolds RM, Osmond C, Phillips DI, Godfrey KM. Maternal BMI, parity, and pregnancy weight gain: influences on offspring adiposity in young adulthood. J Clin Endocrinol Metab. 2010 Dec;95(12):5365-9.
20. Tezcan B, Khazaezadeh N, Ash A, Oteng-Ntim E. Social disparity and intrauterine death: from politics to policies. J Obstet Gynaecol. 2011 Aug;31(6):507-8.
21. Briley AL, Barr S, Badger S, Bell R, Croker H, Godfrey KM, et al. A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. BMC Pregnancy Childbirth. 2014;14:74.
22. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Med. 2012;10:47.
23. WHO. obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organisation Technical Report Series. 2000; Available from: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/index.html.
24. Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. BMJ. 2001 Mar 24;322(7288):716-20.
25. Han TS, Sattar N, Lean M. ABC of obesity. Assessment of obesity and its clinical implications. BMJ. 2006 Sep 30;333(7570):695-8.
26. RCOG/CMACE. 2010.
27. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ. 2002 Jul 20;325(7356):157-60.
28. Rothman KJ. BMI-related errors in the measurement of obesity. Int J Obes (Lond). 2008 Aug;32 Suppl 3:S56-9.
29. WHO. fact sheet.
30. Haslam DW, James WP. Obesity. Lancet. 2005 Oct 1;366(9492):1197-209.
31. Caballero B. The global epidemic of obesity: an overview. Epidemiol Rev. 2007;29:1-5.
32. WHO. Available from: http://www.who.int/nutrition/en/.
33. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2013 Dec 15;380(9859):2095-128.
34. Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990-2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2013 Dec 15;380(9859):2144-62.

35. DOH. Health survey for England. 2008.
36. Abayomi JC, Watkinson H, Boothby J, Topping J, Hackett AF. Identification of 'hot spots' of obesity and being underweight in early pregnancy in Liverpool. J Hum Nutr Diet. 2009 Jun;22(3):246-54.
37. Aylott J BI, Copeland R, Johnson D. tackling obesity: the foresight report and implication for local government
2008; Available from: http://www.idea.gov.uk/idk/aio/8268011.
38. Cameron AJ, Welborn TA, Zimmet PZ, Dunstan DW, Owen N, Salmon J, et al. Overweight and obesity in Australia: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Med J Aust. 2003 May 5;178(9):427-32.
39. Vlad I. Obesity costs UK economy 2bn pounds sterling a year. BMJ. 2003 Dec 6;327(7427):1308.
40. Kanagalingam MG, Forouhi NG, Greer IA, Sattar N. Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. BJOG. 2005 Oct;112(10):1431-3.
41. Heslehurst N, Ells LJ, Simpson H, Batterham A, Wilkinson J, Summerbell CD. Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. BJOG. 2007 Feb;114(2):187-94.
42. Centre for maternal and child enquiriesFitzsimmons K SA. Maternal obesity in the United Kingdom: Findings from a national project. 2010; Available from: http://www.oaa-anaes.ac.uk/assets/_managed/editor/File/CMACE/CMACE_Obesity_Report_2010_Final%20for%20printing.pdf.
43. ACOG Committee opinion no. 549: obesity in pregnancy. Obstet Gynecol. 2013 Jan;121(1):213-7.
44. Heslehurst N, Simpson H, Ells LJ, Rankin J, Wilkinson J, Lang R, et al. The impact of maternal BMI status on pregnancy outcomes with immediate short-term obstetric resource implications: a meta-analysis. Obes Rev. 2008 Nov;9(6):635-83.
45. Bhattacharya S. Higher BMI in pregnant women associated with a greater likelihood of pre-eclampsia, caesarian delivery and higher offspring birth weight and body fat. Evid Based Med. 2010 Oct;15(5):152-3.
46. CMACE/RCOG. management of women with obesity in pregnancy. 2010; Available from: http://www.rcog.org.uk/files/rcog-corp/CMACERCOGJointGuidelineManagementWomenObesityPregnancya.pdf.
47. Rasmussen KM, Catalano PM, Yaktine AL. New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. Curr Opin Obstet Gynecol. 2009 Dec;21(6):521-6.
48. Rasmussen KM, Abrams B, Bodnar LM, Butte NF, Catalano PM, Maria Siega-Riz A. Recommendations for weight gain during pregnancy in the context of the obesity epidemic. Obstet Gynecol. 2010 Nov;116(5):1191-5.
49. Satter N PL, Baker P. Obesity and reproductive health: age and ethnic variation. 2008;1:31-6.
50. Heslehurst N, Lang R, Rankin J, Wilkinson JR, Summerbell CD. Obesity in pregnancy: a study of the impact of maternal obesity on NHS maternity services. BJOG. 2007 Mar;114(3):334-42.

51. Knopp RH, Bergelin RO, Wahl PW, Walden CE, Chapman M, Irvine S. Population-based lipoprotein lipid reference values for pregnant women compared to nonpregnant women classified by sex hormone usage. Am J Obstet Gynecol. 1982 Jul 15;143(6):626-37.
52. Rooney BL, Schauberger CW. Excess pregnancy weight gain and long-term obesity: one decade later. Obstet Gynecol. 2002 Aug;100(2):245-52.
53. Yu CK, Teoh TG, Robinson S. Obesity in pregnancy. BJOG. 2006 Oct;113(10):1117-25.
54. Liu J, Gallagher AE, Carta CM, Torres ME, Moran R, Wilcox S. Racial differences in gestational weight gain and pregnancy-related hypertension. Ann Epidemiol. 2014 Mar 3.
55. DOH. 2005.
56. Field AE, Willett WC, Lissner L, Colditz GA. Dietary fat and weight gain among women in the Nurses' Health Study. Obesity (Silver Spring). 2007 Apr;15(4):967-76.
57. Heitmann BL, Lissner L, Sorensen TI, Bengtsson C. Dietary fat intake and weight gain in women genetically predisposed for obesity. Am J Clin Nutr. 1995 Jun;61(6):1213-7.
58. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA. 2002 Nov 27;288(20):2569-78.
59. Ma Y, Li Y, Chiriboga DE, Olendzki BC, Hebert JR, Li W, et al. Association between carbohydrate intake and serum lipids. J Am Coll Nutr. 2006 Apr;25(2):155-63.
60. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011 Jun 23;364(25):2392-404.
61. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004 Aug 25;292(8):927-34.
62. organisation. Wh. WHO global infobase. Data for saving lives. . accessed September 11, 2012.
63. Wareham NJ, van Sluijs EM, Ekelund U. Physical activity and obesity prevention: a review of the current evidence. Proc Nutr Soc. 2005 May;64(2):229-47.
64. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA. 2003 Apr 9;289(14):1785-91.
65. RCOG Gt. excercise in pregnancy. statement number 4. 2006;1.
66. Bung P, Artal R, Khodiguian N, Kjos S. Exercise in gestational diabetes. An optional therapeutic approach? Diabetes. 1991 Dec;40 Suppl 2:182-5.
67. Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, et al. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. BMJ. 2014;348:g1285.
68. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. Obesity (Silver Spring). 2008 Mar;16(3):643-53.
69. Nodine PM, Matthews EE. Common sleep disorders: management strategies and pregnancy outcomes. J Midwifery Womens Health. 2013 Jul-Aug;58(4):368-77.

70. Bennett GG, Wolin KY, James SA. Lifecourse socioeconomic position and weight change among blacks: The Pitt County study. Obesity (Silver Spring). 2007 Jan;15(1):172-81.
71. Block JP, He Y, Zaslavsky AM, Ding L, Ayanian JZ. Psychosocial stress and change in weight among US adults. Am J Epidemiol. 2009 Jul 15;170(2):181-92.
72. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. The associations of anxiety and depression symptoms with weight change and incident obesity: The HUNT Study. Int J Obes (Lond). 2012 Dec 11.
73. Laborde JE, Saez-Santiago E. Association between obesity and symptoms of depression of adults in Puerto Rico. P R Health Sci J. 2013 Sep;32(3):132-7.
74. Molyneaux E PL, Howard LM. . Obesity and mental disorders during pregnancy and postpartum: a systematic review and meta-analysis. Obstetrics & Gynecology. Obstetrics and Gynaecology. 2014;123(4):857-67.
75. Herrera BM, Keildson S, Lindgren CM. Genetics and epigenetics of obesity. Maturitas. 2011 May;69(1):41-9.
76. Gillman MW, Ludwig DS. How early should obesity prevention start? N Engl J Med. 2013 Dec 5;369(23):2173-5.
77. Gunderson EP. Childbearing and obesity in women: weight before, during, and after pregnancy. Obstet Gynecol Clin North Am. 2009 Jun;36(2):317-32, ix.
78. Stuebe AM, Michels KB, Willett WC, Manson JE, Rexrode K, Rich-Edwards JW. Duration of lactation and incidence of myocardial infarction in middle to late adulthood. Am J Obstet Gynecol. 2009 Feb;200(2):138 e1-8.
79. Stuebe AM, Kleinman K, Gillman MW, Rifas-Shiman SL, Gunderson EP, Rich-Edwards J. Duration of lactation and maternal metabolism at 3 years postpartum. J Womens Health (Larchmt). 2010 May;19(5):941-50.
80. Herring SJ, Rich-Edwards JW, Oken E, Rifas-Shiman SL, Kleinman KP, Gillman MW. Association of postpartum depression with weight retention 1 year after childbirth. Obesity (Silver Spring). 2008 Jun;16(6):1296-301.
81. Oken E, Taveras EM, Popoola FA, Rich-Edwards JW, Gillman MW. Television, walking, and diet: associations with postpartum weight retention. Am J Prev Med. 2007 Apr;32(4):305-11.
82. Rooney BL, Schauberger CW, Mathiason MA. Impact of perinatal weight change on long-term obesity and obesity-related illnesses. Obstet Gynecol. 2005 Dec;106(6):1349-56.
83. Stuebe AM, Rich-Edwards JW. The reset hypothesis: lactation and maternal metabolism. Am J Perinatol. 2009 Jan;26(1):81-8.
84. Martin RM, Patel R, Kramer MS, Guthrie L, Vilchuck K, Bogdanovich N, et al. Effects of promoting longer-term and exclusive breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: a randomized trial. JAMA. 2013 Mar 13;309(10):1005-13.
85. van Raaij JM, Schonk CM, Vermaat-Miedema SH, Peek ME, Hautvast JG. Energy cost of lactation, and energy balances of well-nourished Dutch lactating women: reappraisal of the extra energy requirements of lactation. Am J Clin Nutr. 1991 Mar;53(3):612-9.

86. Sadurskis A, Kabir N, Wager J, Forsum E. Energy metabolism, body composition, and milk production in healthy Swedish women during lactation. Am J Clin Nutr. 1988 Jul;48(1):44-9.
87. Dewey KG, Heinig MJ, Nommsen LA. Maternal weight-loss patterns during prolonged lactation. Am J Clin Nutr. 1993 Aug;58(2):162-6.
88. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG. 2011 Mar;118 Suppl 1:1-203.
89. Hauger MS, Gibbons L, Vik T, Belizan JM. Prepregnancy weight status and the risk of adverse pregnancy outcome. Acta Obstet Gynecol Scand. 2008;87(9):953-9.
90. Main EK. Decisions required for operating a maternal mortality review committee: the California experience. Semin Perinatol. 2012 Feb;36(1):37-41.
91. health Cdop. The california pregnancy associated mortality review report from 2002 and 2003. Maternal death review. 2011.
92. WHO. Global database on body mass index. accessed 2012.
93. Campbell OM, Graham WJ. Strategies for reducing maternal mortality: getting on with what works. Lancet. 2006 Oct 7;368(9543):1284-99.
94. Waugh N, Royle P, Clar C, Henderson R, Cummins E, Hadden D, et al. Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee. Health Technol Assess. 2010 Sep;14(45):1-183.
95. Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obes Rev. 2009 Mar;10(2):194-203.
96. Yogev Y, Catalano PM. Pregnancy and obesity. Obstet Gynecol Clin North Am. 2009 Jun;36(2):285-300, viii.
97. NICE. Diabetes in pregnancy. 2008; Available from: http://www.nice.org.uk/nicemedia/pdf/CG063Guidance.pdf.
98. WHO. 1999; Available from: http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf.
99. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008 May 8;358(19):1991-2002.
100. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005 Jun 16;352(24):2477-86.
101. Gillman MW, Oakey H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA. Effect of treatment of gestational diabetes mellitus on obesity in the next generation. Diabetes Care. 2010 May;33(5):964-8.
102. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009 May 23;373(9677):1773-9.
103. Poston L, Harthoorn LF, Van Der Beek EM. Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. Pediatr Res. 2011 Feb;69(2):175-80.

104. Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J, et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ. 2009;339:b3129.
105. NICE. Hypertension in pregnancy. The management of hypertensive disorders during pregnancy. 2010.
106. Walsh SW. Obesity: a risk factor for preeclampsia. Trends Endocrinol Metab. 2007 Dec;18(10):365-70.
107. Bhattacharya S, Campbell DM, Liston WA. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health. 2007;7:168.
108. Rajasingam D, Seed PT, Briley AL, Shennan AH, Poston L. A prospective study of pregnancy outcome and biomarkers of oxidative stress in nulliparous obese women. Am J Obstet Gynecol. 2009 Apr;200(4):395 e1-9.
109. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007 Nov 10;335(7627):974.
110. Denison FC, Roberts KA, Barr SM, Norman JE. Obesity, pregnancy, inflammation, and vascular function. Reproduction. 2010 Sep;140(3):373-85.
111. Poston L, Igosheva N, Mistry HD, Seed PT, Shennan AH, Rana S, et al. Role of oxidative stress and antioxidant supplementation in pregnancy disorders. Am J Clin Nutr. 2011 May 25.
112. Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. Pulmonary embolism in pregnancy. Lancet. 2010 Feb 6;375(9713):500-12.
113. Drife J. Thromboembolism. Br Med Bull. 2003;67:177-90.
114. Larsen TB, Sorensen HT, Gislum M, Johnsen SP. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. Thromb Res. 2007;120(4):505-9.
115. Lippi G, Franchini M. Pathogenesis of venous thromboembolism: when the cup runneth over. Semin Thromb Hemost. 2008 Nov;34(8):747-61.
116. Rodriguez-Bano J, Pano-Pardo JR, Munez Rubio E, Segura Porta F. Pregnancy, obesity and other risk factors for complications in influenza A(H1N1) pdm09 infection. Enferm Infecc Microbiol Clin. 2012 Oct;30 Suppl 4:32-7.
117. Yates L, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, et al. Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant. Health Technol Assess. 2010 Jul;14(34):109-82.
118. Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ. 2011;342:d3214.
119. Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. Anaesthesia. 1987 May;42(5):487-90.
120. Barnardo PD, Jenkins JG. Failed tracheal intubation in obstetrics: a 6-year review in a UK region. Anaesthesia. 2000 Jul;55(7):690-4.
121. Saravanakumar K, Rao SG, Cooper GM. The challenges of obesity and obstetric anaesthesia. Curr Opin Obstet Gynecol. 2006 Dec;18(6):631-5.

122. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, et al. Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg. 2003 Aug;97(2):595-600, table of contents.
123. Small MJ, James AH, Kershaw T, Thames B, Gunatilake R, Brown H. Near-miss maternal mortality: cardiac dysfunction as the principal cause of obstetric intensive care unit admissions. Obstet Gynecol. 2012 Feb;119(2 Pt 1):250-5.
124. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ. 2001 May 5;322(7294):1089-93; discussion 93-4.
125. Van Kerkhove MD, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med. 2011 Jul;8(7):e1001053.
126. Zwart JJ, Richters A, Ory F, de Vries JI, Bloemenkamp KW, van Roosmalen J. Eclampsia in the Netherlands. Obstet Gynecol. 2008 Oct;112(4):820-7.
127. Usha Kiran TS, Hemmadi S, Bethel J, Evans J. Outcome of pregnancy in a woman with an increased body mass index. BJOG. 2005 Jun;112(6):768-72.
128. Zhang J, Bricker L, Wray S, Quenby S. Poor uterine contractility in obese women. BJOG. 2007 Mar;114(3):343-8.
129. Nuthalapaty FS, Rouse DJ. The impact of obesity on obstetrical practice and outcome. Clin Obstet Gynecol. 2004 Dec;47(4):898-913; discussion 80-1.
130. Sheiner E, Edri A, Balaban E, Levi I, Aricha-Tamir B. Pregnancy outcome of patients who conceive during or after the first year following bariatric surgery. Am J Obstet Gynecol. 2011 Jan;204(1):50 e1-6.
131. Hollowell J, Pillas D, Rowe R, Linsell L, Knight M, Brocklehurst P. The impact of maternal obesity on intrapartum outcomes in otherwise low risk women: secondary analysis of the Birthplace national prospective cohort study. BJOG. 2014 Feb;121(3):343-55.
132. RCOG Gt. Shoulder dystocia guidelines. 2005.
133. Baxley EG, Gobbo RW. Shoulder dystocia. Am Fam Physician. 2004 Apr 1;69(7):1707-14.
134. Robinson H, Tkatch S, Mayes DC, Bott N, Okun N. Is maternal obesity a predictor of shoulder dystocia? Obstet Gynecol. 2003 Jan;101(1):24-7.
135. Poobalan AS, Aucott LS, Gurung T, Smith WC, Bhattacharya S. Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women--systematic review and meta-analysis of cohort studies. Obes Rev. 2009 Jan;10(1):28-35.
136. Rankin J, Tennant PW, Stothard KJ, Bythell M, Summerbell CD, Bell R. Maternal body mass index and congenital anomaly risk: a cohort study. Int J Obes (Lond). 2010 Sep;34(9):1371-80.
137. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009 Feb 11;301(6):636-50.
138. Rasmussen SA, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity and risk of neural tube defects: a metaanalysis. Am J Obstet Gynecol. 2008 Jun;198(6):611-9.

139. Blomberg MI, Kallen B. Maternal obesity and morbid obesity: the risk for birth defects in the offspring. Birth Defects Res A Clin Mol Teratol. 2010 Jan;88(1):35-40.
140. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006 Jul 22;333(7560):177.
141. Carmichael SL, Rasmussen SA, Shaw GM. Prepregnancy obesity: a complex risk factor for selected birth defects. Birth Defects Res A Clin Mol Teratol. 2010 Oct;88(10):804-10.
142. Hendricks KA, Nuno OM, Suarez L, Larsen R. Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. Epidemiology. 2001 Nov;12(6):630-5.
143. Zabihi S, Loeken MR. Understanding diabetic teratogenesis: where are we now and where are we going? Birth Defects Res A Clin Mol Teratol. 2010 Oct;88(10):779-90.
144. Mojtabai R. Body mass index and serum folate in childbearing age women. Eur J Epidemiol. 2004;19(11):1029-36.
145. Ortega RM, Lopez-Sobaler AM, Aparicio A, Bermejo LM, Rodriguez-Rodriguez E, Perea JM, et al. Vitamin D status modification by two slightly hypocaloric diets in young overweight/obese women. Int J Vitam Nutr Res. 2009 Mar;79(2):71-8.
146. Kimmons JE, Blanck HM, Tohill BC, Zhang J, Khan LK. Associations between body mass index and the prevalence of low micronutrient levels among US adults. MedGenMed. 2006;8(4):59.
147. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. Pediatrics. 2003 May;111(5 Part 2):1152-8.
148. Rittenberg V, Sobaleva S, Ahmad A, Oteng-Ntim E, Bolton V, Khalaf Y, et al. Influence of BMI on risk of miscarriage after single blastocyst transfer. Hum Reprod. 2011 Oct;26(10):2642-50.
149. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online. 2011 Oct;23(4):421-39.
150. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online. 2011 Jul 28.
151. Turner MJ, Fattah C, O'Connor N, Farah N, Kennelly M, Stuart B. Body Mass Index and spontaneous miscarriage. Eur J Obstet Gynecol Reprod Biol. 2010 Aug;151(2):168-70.
152. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet. 2011 Apr 16;377(9774):1331-40.
153. Nohr EA, Bech BH, Davies MJ, Frydenberg M, Henriksen TB, Olsen J. Prepregnancy obesity and fetal death: a study within the Danish National Birth Cohort. Obstet Gynecol. 2005 Aug;106(2):250-9.

154. Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, et al. Maternal obesity and risk of stillbirth: a metaanalysis. Am J Obstet Gynecol. 2007 Sep;197(3):223-8.
155. Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. JAMA. 2014 Apr 16;311(15):1536-46.
156. Cresswell JA, Campbell OM, De Silva MJ, Filippi V. Effect of maternal obesity on neonatal death in sub-Saharan Africa: multivariable analysis of 27 national datasets. Lancet. 2012 Aug 8.
157. Tennant PW, Rankin J, Bell R. Maternal body mass index and the risk of fetal and infant death: a cohort study from the North of England. Hum Reprod. 2011 Jun;26(6):1501-11.
158. Chen A, Feresu SA, Fernandez C, Rogan WJ. Maternal obesity and the risk of infant death in the United States. Epidemiology. 2009 Jan;20(1):74-81.
159. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension. 2003 Jul;42(1):39-42.
160. Wolf M, Kettyle E, Sandler L, Ecker JL, Roberts J, Thadhani R. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol. 2001 Nov;98(5 Pt 1):757-62.
161. Nohr EA, Vaeth M, Baker JL, Sorensen T, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. Am J Clin Nutr. 2008 Jun;87(6):1750-9.
162. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med. 1998 Jan 15;338(3):147-52.
163. Hendler I, Goldenberg RL, Mercer BM, Iams JD, Meis PJ, Moawad AH, et al. The Preterm Prediction Study: association between maternal body mass index and spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2005 Mar;192(3):882-6.
164. Catalano PM. Obesity and pregnancy--the propagation of a viscous cycle? J Clin Endocrinol Metab. 2003 Aug;88(8):3505-6.
165. Kral JG. Preventing and treating obesity in girls and young women to curb the epidemic. Obes Res. 2004 Oct;12(10):1539-46.
166. McDonald SD, Han Z, Mulla S, Beyene J. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. BMJ. 2010;341:c3428.
167. Beaglehole R, Bonita R, Alleyne G, Horton R, Li L, Lincoln P, et al. UN High-Level Meeting on Non-Communicable Diseases: addressing four questions. Lancet. 2011 Jul 30;378(9789):449-55.
168. Geneau R, Stuckler D, Stachenko S, McKee M, Ebrahim S, Basu S, et al. Raising the priority of preventing chronic diseases: a political process. Lancet. 2010 Nov 13;376(9753):1689-98.
169. Hancock C. Change4life campaign. Lancet. 2009 Feb 28;373(9665):721.
170. Gortmaker SL, Swinburn B, Levy D, Carter R, Mabry PL, Finegood D, et al. Changing the Future of Obesity: Science, Policy and Action. Lancet. 2011 Aug 27;378(9793):838-47.

171. Daives DS. Annual report of the chief medical officer. 2013.
172. Mytton OT, Clarke D, Rayner M. Taxing unhealthy food and drinks to improve health. BMJ. 2012;344:e2931.
173. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P, et al. Priority actions for the non-communicable disease crisis. Lancet. 2011 Apr 23;377(9775):1438-47.
174. stephenson T. Measuring up: The medical professions' prescription to the obesity crisis. 2012(1):1-60.
175. Campbell F, Conti G, Heckman JJ, Moon SH, Pinto R, Pungello E, et al. Early childhood investments substantially boost adult health. Science. 2014 Mar 28;343(6178):1478-85.
176. Poston GMWa. Maternal Obesity. 2012(1).
177. Dodd JM, Grivell RM, Crowther CA, Robinson JS. Antenatal interventions for overweight or obese pregnant women: a systematic review of randomised trials. BJOG. 2010 Oct;117(11):1316-26.
178. Michael M. fair society, healthy lives. 2010.
179. Walpole SC, Prieto-Merino D, Edwards P, Cleland J, Stevens G, Roberts I. The weight of nations: an estimation of adult human biomass. BMC Public Health. 2012;12:439.
180. Davies DS. Annual report of the chief medical officer. 2013.
181. Burgoine T, Forouhi NG, Griffin SJ, Wareham NJ, Monsivais P. Associations between exposure to takeaway food outlets, takeaway food consumption, and body weight in Cambridgeshire, UK: population based, cross sectional study. BMJ. 2014;348:g1464.
182. Wilding J. Are the causes of obesity primarily environmental? Yes. BMJ. 2012;345:e5843.
183. Pineo H. Health and the built environment. Lancet. 2012 Sep 29;380(9848):1146-7.
184. Casey R, Chaix B, Weber C, Schweitzer B, Charreire H, Salze P, et al. Spatial accessibility to physical activity facilities and to food outlets and overweight in French youth. Int J Obes (Lond). 2012 Jul;36(7):914-9.
185. Ward PW. Inactivity, not gluttony, causes obesity. BMJ. 2014;348:g2717.
186. Mayor S. Children living near fast food outlets in England are more likely to be overweight, study shows. BMJ. 2014;348:g1557.
187. Howard SJ, Davies SC. Chief medical officer urges action to tackle overweight and obesity. BMJ. 2014;348:g2375.
188. Rokholm B, Baker JL, Sorensen TI. The levelling off of the obesity epidemic since the year 1999--a review of evidence and perspectives. Obes Rev. 2010 Dec;11(12):835-46.
189. Nichols MS, Silva-Sanigorski A, Cleary JE, Goldfeld SR, Colahan A, Swinburn BA. Decreasing trends in overweight and obesity among an Australian population of preschool children. Int J Obes (Lond). 2011 Jul;35(7):916-24.
190. Waters E, de Silva-Sanigorski A, Hall BJ, Brown T, Campbell KJ, Gao Y, et al. Interventions for preventing obesity in children. Cochrane Database Syst Rev. 2011(12):CD001871.
191. Zhou YE, Emerson JS, Levine RS, Kihlberg CJ, Hull PC. Childhood obesity prevention interventions in childcare settings: systematic review of

randomized and nonrandomized controlled trials. Am J Health Promot. 2014 Mar-Apr;28(4):e92-103.
192. Buchwald H, Ikramuddin S, Dorman RB, Schone JL, Dixon JB. Management of the metabolic/bariatric surgery patient. Am J Med. 2011 Dec;124(12):1099-105.
193. Kominiarek MA. Preparing for and managing a pregnancy after bariatric surgery. Semin Perinatol. 2011 Dec;35(6):356-61.
194. Hezelgrave NL, Oteng-Ntim E. Pregnancy after bariatric surgery: a review. J Obes. 2011;2011:501939.
195. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004 Oct 13;292(14):1724-37.
196. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007 Aug 23;357(8):741-52.
197. Buchwald H. Consensus conference statement bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. Surg Obes Relat Dis. 2005 May-Jun;1(3):371-81.
198. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol. 2009 Jun;113(6):1405-13.
199. Merhi ZO. Impact of bariatric surgery on female reproduction. Fertil Steril. 2009 Nov;92(5):1501-8.
200. Shah DK, Ginsburg ES. Bariatric surgery and fertility. Curr Opin Obstet Gynecol. 2010 Jun;22(3):248-54.
201. Bennett WL, Gilson MM, Jamshidi R, Burke AE, Segal JB, Steele KE, et al. Impact of bariatric surgery on hypertensive disorders in pregnancy: retrospective analysis of insurance claims data. BMJ. 2010;340:c1662.
202. Ornoy A, Zvi N, Arnon J, Wajnberg R, Shechtman S, Diav-Citrin O. The outcome of pregnancy following topiramate treatment: a study on 52 pregnancies. Reprod Toxicol. 2008 Apr;25(3):388-9.
203. Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. N Engl J Med. 2012 Oct 25;367(17):1577-9.
204. NICE. Weight management , before during and after pregnancy.
205. Levri KM, Slaymaker E, Last A, Yeh J, Ference J, D'Amico F, et al. Metformin as treatment for overweight and obese adults: a systematic review. Ann Fam Med. 2005 Sep-Oct;3(5):457-61.
206. 53rd RCOG Study group (2007) Obesity and reproductive Health. 2007.
207. . 2004 Feb.
208. Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. Fertil Steril. 1994 Apr;61(4):598-604.
209. American Dietetic Association (2009) Position of American Dietetic Association 2009.
210. Oldroyd JC, Unwin NC, White M, Mathers JC, Alberti KG. Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. Diabetes Res Clin Pract. 2006 May;72(2):117-27.

211. Whiteman VE, Rao K, Duan J, Alio A, Marty PJ, Salihu HM. Changes in prepregnancy body mass index between pregnancies and risk of preterm phenotypes. Am J Perinatol. 2011 Jan;28(1):67-74.
212. Whiteman VE, Aliyu MH, August EM, McIntosh C, Duan J, Alio AP, et al. Changes in prepregnancy body mass index between pregnancies and risk of gestational and type 2 diabetes. Arch Gynecol Obstet. 2011 Jul;284(1):235-40.
213. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet. 2006 Sep 30;368(9542):1164-70.
214. Lawlor DA, Chaturvedi N. Treatment and prevention of obesity--are there critical periods for intervention? Int J Epidemiol. 2006 Feb;35(1):3-9.
215. Inskip HM, Crozier SR, Godfrey KM, Borland SE, Cooper C, Robinson SM. Women's compliance with nutrition and lifestyle recommendations before pregnancy: general population cohort study. BMJ. 2009;338:b481.
216. Rode L, Nilas L, Wojdemann K, Tabor A. Obesity-related complications in Danish single cephalic term pregnancies. Obstet Gynecol. 2005 Mar;105(3):537-42.
217. Olson CM. A call for intervention in pregnancy to prevent maternal and child obesity. Am J Prev Med. 2007 Nov;33(5):435-6.
218. RCOG Sac. Why should we consider a life course approach to women's health care? RCOG Opinion paper. 2011;27(1):1-8.
219. Government H. Healthy life, healthy people, our strategy for public health in England. 2010 2010.
220. scharr.
221. nice. dietary intervention and physical activity interventions for weight management in pregnancy and after childbirth. 2011.
222. Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ. 2012;344:e2088.
223. Rasmussen KM YA. Committee to Reexamine IOM Pregnancy Weight Guidelines, Institute of Medicine, National Research Council: . The National Academic Press. 2009.
224. Nelson SM, Matthews P, Poston L. Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. Hum Reprod Update. 2010 May-Jun;16(3):255-75.
225. Siega-Riz AM, Viswanathan M, Moos MK, Deierlein A, Mumford S, Knaack J, et al. A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. Am J Obstet Gynecol. 2009 Oct;201(4):339 e1-14.
226. Gardner B, Wardle J, Poston L, Croker H. Changing diet and physical activity to reduce gestational weight gain: a meta-analysis. Obes Rev. 2011 Apr 27.
227. Dodd JM, Turnbull DA, McPhee AJ, Wittert G, Crowther CA, Robinson JS. Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes: the LIMIT randomised controlled trial. BMC Pregnancy Childbirth. 2011;11:79.

228. group Hsrc. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG. 2010 Apr;117(5):575-84.
229. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev. 2009(1):CD006296.
230. Lock DR, Bar-Eyal A, Voet H, Madar Z. Glycemic indices of various foods given to pregnant diabetic subjects. Obstet Gynecol. 1988 Feb;71(2):180-3.
231. Knudsen VK, Heitmann BL, Halldorsson TI, Sorensen TI, Olsen SF. Maternal dietary glycaemic load during pregnancy and gestational weight gain, birth weight and postpartum weight retention: a study within the Danish National Birth Cohort. Br J Nutr. 2012 Aug 21:1-8.
232. Walsh JM, McGowan CA, Mahony R, Foley ME, McAuliffe FM. Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. BMJ. 2012;345:e5605.
233. Moses RG, Luebcke M, Davis WS, Coleman KJ, Tapsell LC, Petocz P, et al. Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. Am J Clin Nutr. 2006 Oct;84(4):807-12.
234. Oostdam N, van Poppel MN, Wouters MG, van Mechelen W. Interventions for preventing gestational diabetes mellitus: a systematic review and meta-analysis. J Womens Health (Larchmt). 2011 Oct;20(10):1551-63.
235. Clapp JF. Influence of endurance exercise and diet on human placental development and fetal growth. Placenta. 2006 Jun-Jul;27(6-7):527-34.
236. Artal R, O'Toole M. Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period. Br J Sports Med. 2003 Feb;37(1):6-12; discussion
237. Lokey EA, Tran ZV, Wells CL, Myers BC, Tran AC. Effects of physical exercise on pregnancy outcomes: a meta-analytic review. Med Sci Sports Exerc. 1991 Nov;23(11):1234-9.
238. Kramer MS. Aerobic exercise for women during pregnancy. Cochrane Database Syst Rev. 2002(2):CD000180.
239. Leet T, Flick L. Effect of exercise on birthweight. Clin Obstet Gynecol. 2003 Jun;46(2):423-31.
240. Bell RJ, Palma SM, Lumley JM. The effect of vigorous exercise during pregnancy on birth-weight. Aust N Z J Obstet Gynaecol. 1995 Feb;35(1):46-51.
241. Clapp JF, 3rd, Dickstein S. Endurance exercise and pregnancy outcome. Med Sci Sports Exerc. 1984 Dec;16(6):556-62.
242. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009 Oct 1;361(14):1339-48.
243. Alderman BW, Zhao H, Holt VL, Watts DH, Beresford SA. Maternal physical activity in pregnancy and infant size for gestational age. Ann Epidemiol. 1998 Nov;8(8):513-9.
244. Laraia BA, Siega-Riz AM, Dole N, London E. Pregravid weight is associated with prior dietary restraint and psychosocial factors during pregnancy. Obesity (Silver Spring). 2009 Mar;17(3):550-8.

245. Bond L, Craig P, Egan M, Skivington K, Thomson H. Evaluating complex interventions. Health improvement programmes: really too complex to evaluate? BMJ. 2010;340:c1332.
246. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Inequalities in maternal health: national cohort study of ethnic variation in severe maternal morbidities. BMJ. 2009;338:b542.
247. Makgoba M, Savvidou MD, Steer PJ. An analysis of the interrelationship between maternal age, body mass index and racial origin in the development of gestational diabetes mellitus. BJOG. 2012 Feb;119(3):276-82.
248. Lu GC, Rouse DJ, DuBard M, Cliver S, Kimberlin D, Hauth JC. The effect of the increasing prevalence of maternal obesity on perinatal morbidity. Am J Obstet Gynecol. 2001 Oct;185(4):845-9.
249. Hulsey TC, Neal D, Bondo SC, Hulsey T, Newman R. Maternal prepregnant body mass index and weight gain related to low birth weight in South Carolina. South Med J. 2005 Apr;98(4):411-5.
250. Djelantik AA, Kunst AE, van der Wal MF, Smit HA, Vrijkotte TG. Contribution of overweight and obesity to the occurrence of adverse pregnancy outcomes in a multi-ethnic cohort: population attributive fractions for Amsterdam. BJOG. 2012 Feb;119(3):283-90.
251. David McLennan HB, Michael Noble, Joanna Davies, Elisabeth Garratt , Chris Dibben. The English Indices of Deprivation 2010. 2011.
252. WHO. WHO guidelines for the management of postpartum haemorrhage and retained placenta. World Health Organization. 2009.
253. Poston L. Intergenerational transmission of insulin resistance and type 2 diabetes. Prog Biophys Mol Biol. 2011 Jul;106(1):315-22.
254. Carr DB, Newton KM, Utzschneider KM, Faulenbach MV, Kahn SE, Easterling TR, et al. Gestational diabetes or lesser degrees of glucose intolerance and risk of preeclampsia. Hypertens Pregnancy. 2011;30(2):153-63.
255. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG. 2010 Apr;117(5):575-84.
256. Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? Int J Epidemiol. 2014 Aug;43(4):1336-9.
257. Low S, Chin MC, Deurenberg-Yap M. Review on epidemic of obesity. Ann Acad Med Singapore. 2009 Jan;38(1):57-9.
258. Yogev Y, Visser GH. Obesity, gestational diabetes and pregnancy outcome. Semin Fetal Neonatal Med. 2009 Apr;14(2):77-84.
259. Ludwig DS, Currie J. The association between pregnancy weight gain and birthweight: a within-family comparison. Lancet. 2010 Sep 18;376(9745):984-90.
260. Guelinckx I, Devlieger R, Mullie P, Vansant G. Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: a randomized controlled trial. Am J Clin Nutr. 2010 Feb;91(2):373-80.
261. Asbee SM, Jenkins TR, Butler JR, White J, Elliot M, Rutledge A. Preventing excessive weight gain during pregnancy through dietary and lifestyle counseling: a randomized controlled trial. Obstet Gynecol. 2009 Feb;113(2 Pt 1):305-12.

262. Jeffries K, Shub A, Walker SP, Hiscock R, Permezel M. Reducing excessive weight gain in pregnancy: a randomised controlled trial. Med J Aust. 2009 Oct 19;191(8):429-33.
263. Thornton YS, Smarkola C, Kopacz SM, Ishoof SB. Perinatal outcomes in nutritionally monitored obese pregnant women: a randomized clinical trial. J Natl Med Assoc. 2009 Jun;101(6):569-77.
264. Wolff S, Legarth J, Vangsgaard K, Toubro S, Astrup A. A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women. Int J Obes (Lond). 2008 Mar;32(3):495-501.
265. Yeo S. A randomized comparative trial of the efficacy and safety of exercise during pregnancy: design and methods. Contemp Clin Trials. 2006 Dec;27(6):531-40.
266. Polley BA, Wing RR, Sims CJ. Randomized controlled trial to prevent excessive weight gain in pregnant women. Int J Obes Relat Metab Disord. 2002 Nov;26(11):1494-502.
267. Hui al lS, Gardiner P, Sevenhuysen G et al. community based excercise and dietary intervention during pregnancy: a pilot study. Canadian Journal of diabetes. 2006;30(2):169-75.
268. Phelan S, Phipps MG, Abrams B, Darroch F, Schaffner A, Wing RR. Randomized trial of a behavioral intervention to prevent excessive gestational weight gain: the Fit for Delivery Study. Am J Clin Nutr. 2011 Apr;93(4):772-9.
269. Mottola MF, Giroux I, Gratton R, Hammond JA, Hanley A, Harris S, et al. Nutrition and exercise prevent excess weight gain in overweight pregnant women. Med Sci Sports Exerc. 2010 Feb;42(2):265-72.
270. Claesson IM, Sydsjo G, Brynhildsen J, Cedergren M, Jeppsson A, Nystrom F, et al. Weight gain restriction for obese pregnant women: a case-control intervention study. BJOG. 2008 Jan;115(1):44-50.
271. Kinnunen TI, Aittasalo M, Koponen P, Ojala K, Mansikkamaki K, Weiderpass E, et al. Feasibility of a controlled trial aiming to prevent excessive pregnancy-related weight gain in primary health care. BMC Pregnancy Childbirth. 2008;8:37.
272. Gray-Donald K, Robinson E, Collier A, David K, Renaud L, Rodrigues S. Intervening to reduce weight gain in pregnancy and gestational diabetes mellitus in Cree communities: an evaluation. CMAJ. 2000 Nov 14;163(10):1247-51.
273. Shirazian T, Monteith S, Friedman F, Rebarber A. Lifestyle modification program decreases pregnancy weight gain in obese women. Am J Perinatol. 2010 May;27(5):411-4.
274. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes. 2009 Feb;58(2):453-9.
275. Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R. Exercise during pregnancy improves maternal glucose screen at 24-28 weeks: a randomised controlled trial. Br J Sports Med. 2011 Sep 26.
276. Ong MJ, Guelfi KJ, Hunter T, Wallman KE, Fournier PA, Newnham JP. Supervised home-based exercise may attenuate the decline of glucose tolerance in obese pregnant women. Diabetes Metab. 2009 Nov;35(5):418-21.

277. Luoto R, Kinnunen TI, Aittasalo M, Kolu P, Raitanen J, Ojala K, et al. Primary prevention of gestational diabetes mellitus and large-for-gestational-age newborns by lifestyle counseling: a cluster-randomized controlled trial. PLoS Med. 2011 May;8(5):e1001036.
278. Nascimento SL, Surita FG, Parpinelli MA, Siani S, Pinto e Silva JL. The effect of an antenatal physical exercise programme on maternal/perinatal outcomes and quality of life in overweight and obese pregnant women: a randomised clinical trial. BJOG. 2011 Nov;118(12):1455-63.
279. Streuling I, Beyerlein A, von Kries R. Can gestational weight gain be modified by increasing physical activity and diet counseling? A meta-analysis of interventional trials. Am J Clin Nutr. 2010 Oct;92(4):678-87.
280. Tanentsapf I, Heitmann BL, Adegboye AR. Systematic review of clinical trials on dietary interventions to prevent excessive weight gain during pregnancy among normal weight, overweight and obese women. BMC Pregnancy Childbirth. 2011;11:81.
281. Sui Z, Grivell RM, Dodd JM. Antenatal exercise to improve outcomes in overweight or obese women: a systematic review. Acta Obstet Gynecol Scand. 2012 Jan 10.
282. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
283. collaboration c. cochrane handbook for systematic reviews of interventions. 2011; Available from: http://www.cochrane.org/training/cochrane-handbook.
284. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol. 2008;8:79.
285. Kinnunen TI, Pasanen M, Aittasalo M, Fogelholm M, Hilakivi-Clarke L, Weiderpass E, et al. Preventing excessive weight gain during pregnancy - a controlled trial in primary health care. Eur J Clin Nutr. 2007 Jul;61(7):884-91.
286. Claesson IM, Brynhildsen J, Cedergren M, Jeppsson A, Sydsjo A, Josefsson A. Weight gain restriction during pregnancy is safe for both the mother and neonate. Acta Obstet Gynecol Scand. 2009;88(10):1158-62.
287. Michie S, Abraham C, Eccles MP, Francis JJ, Hardeman W, Johnston M. Strengthening evaluation and implementation by specifying components of behaviour change interventions: a study protocol. Implement Sci. 2011;6(1):10.
288. Olson CM. Achieving a healthy weight gain during pregnancy. Annu Rev Nutr. 2008;28:411-23.
289. Birdsall KM, Vyas S, Khazaezadeh N, Oteng-Ntim E. Maternal obesity: a review of interventions. Int J Clin Pract. 2009 Mar;63(3):494-507.
290. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
291. Barakat R, Pelaez M, Montejo R, Luaces M, Zakynthinaki M. Exercise during pregnancy improves maternal health perception: a randomized controlled trial. Am J Obstet Gynecol. 2011 May;204(5):402 e1-7.

292. Quinlivan JA, Lam LT, Fisher J. A randomised trial of a four-step multidisciplinary approach to the antenatal care of obese pregnant women. Aust N Z J Obstet Gynaecol. 2011 Apr;51(2):141-6.
293. Olson CM, Strawderman MS, Reed RG. Efficacy of an intervention to prevent excessive gestational weight gain. Am J Obstet Gynecol. 2004 Aug;191(2):530-6.
294. Armitage JA, Poston L, Taylor PD. Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity. Front Horm Res. 2008;36:73-84.
295. Gardner B, Cane J, Rumsey N, Michie S. Behaviour change among overweight and socially disadvantaged adults: a longitudinal study of the NHS Health Trainer Service. Psychol Health. 2012;27(10):1178-93.
296. oteng-Ntim E KN, Mohiddin A,, Bewley S OB. http://www.gsttcharity.org.uk/grants/obesitypreg.pdf. 2008.
297. Vyas S GKN, Oteng-Ntim E. Pregnancy and obesity. Progress in obstetrics and Gynaecology. 2008;18:11-8.
298. Oteng-Ntim E, Pheasant H, Khazaezadeh N, Mohidden A, Bewley S, Wong J, et al. Developing a community-based maternal obesity intervention: a qualitative study of service providers' views. BJOG. 2010 Dec;117(13):1651-5.
299. Khazaezadeh N pH, Bewley S, Oteng-Ntim E et al. Using service users views to design a maternal obesity intervention. BJM. 2011;19(1):49-59.
300. report f. 2007.
301. Chereshneva M HL, Oteng-Ntim E. The effects of booking body mass index on obstetric and neonatal outcomes in inner city tertiary referral centre. Obstetric Medicine. 2008;1:88-91.
302. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Med. 2012;10(1):47.
303. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ. 2000 Jan 8;320(7227):114-6.
304. Green J, Waters E, Haikerwal A, O'Neill C, Raman S, Booth ML, et al. Social, cultural and environmental influences on child activity and eating in Australian migrant communities. Child Care Health Dev. 2003 Nov;29(6):441-8.
305. LeCompte M GJ. Problems of reliability and validity in ethnographic research. Rev Educ Res. Rev Educ Res. 1982;52:31-60.
306. Murphy E DR, Greatbatch, Parker S, Watson P. Qualitative research methods in health technology assessment: a review of the literature. 1998;2(16).
307. Prasad B, Costello AM. Impact and sustainability of a "baby friendly" health education intervention at a district hospital in Bihar, India. BMJ. 1995 Mar 11;310(6980):621-3.
308. D S. Qualitative methodology and sociology. 1985(First edition).
309. Jensen GM. Qualitative methods in physical therapy research: a form of disciplined inquiry. Phys Ther. 1989 Jun;69(6):492-500.
310. Beck CT. Qualitative research: the evaluation of its credibility, fittingness, and auditability. West J Nurs Res. 1993 Apr;15(2):263-6.

311. Carver CS, Scheier MF. Scaling back goals and recalibration of the affect system are processes in normal adaptive self-regulation: understanding 'response shift' phenomena. Soc Sci Med. 2000 Jun;50(12):1715-22.
312. Wrosch C, Scheier MF, Miller GE, Schulz R, Carver CS. Adaptive self-regulation of unattainable goals: goal disengagement, goal reengagement, and subjective well-being. Pers Soc Psychol Bull. 2003 Dec;29(12):1494-508.
313. Rasmussen HN, Wrosch C, Scheier MF, Carver CS. Self-regulation processes and health: the importance of optimism and goal adjustment. J Pers. 2006 Dec;74(6):1721-47.
314. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. Diabetes Care. 2008 Dec;31(12):2281-3.
315. Henry CJ, Lightowler HJ, Strik CM, Storey M. Glycaemic index values for commercially available potatoes in Great Britain. Br J Nutr. 2005 Dec;94(6):917-21.
316. Aston LM, Gambell JM, Lee DM, Bryant SP, Jebb SA. Determination of the glycaemic index of various staple carbohydrate-rich foods in the UK diet. Eur J Clin Nutr. 2008 Feb;62(2):279-85.
317. Aston LM, Jackson D, Monsheimer S, Whybrow S, Handjieva-Darlenska T, Kreutzer M, et al. Developing a methodology for assigning glycaemic index values to foods consumed across Europe. Obes Rev. 2010 Jan;11(1):92-100.
318. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. BMJ. 2006 Feb 18;332(7538):413-6.
319. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. Lancet. 2014 Jul 5;384(9937):45-52.
320. Athukorala C, Rumbold AR, Willson KJ, Crowther CA. The risk of adverse pregnancy outcomes in women who are overweight or obese. BMC Pregnancy Childbirth. 2010;10:56.
321. Dodd JM, Grivell RM, Nguyen AM, Chan A, Robinson JS. Maternal and perinatal health outcomes by body mass index category. Aust N Z J Obstet Gynaecol. 2011 Apr;51(2):136-40.
322. Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? Int J Epidemiol. 2014 Apr 4.
323. (NICE) Nifhace. maternal and child nutrition. NICE PH11. 2008.
324. (NICE) NIfHacE. Prevention of cardiovascular disease. NICE 2010;PH25.
325. NICE. Obesity-working with local people. 2012.
326. NICE. Obesity. NICE. 2006.
327. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet. 2005 Sep 24-30;366(9491):1059-62.
328. Kopelman P, Jebb SA, Butland B. Executive summary: Foresight 'Tackling Obesities: Future Choices' project. Obes Rev. 2007 Mar;8 Suppl 1:vi-ix.
329. Health Survey For England. The information centre for health and social science. 2008.

330. Foresight. Tackling Obesities: Future Choices – Modelling Future Trends in Obesity & Their Impact on Health. London: Government Office for Science, 2007. 2007.
331. Stamatakis E, Zaninotto P, Falaschetti E, Mindell J, Head J. Time trends in childhood and adolescent obesity in England from 1995 to 2007 and projections of prevalence to 2015. J Epidemiol Community Health. 2010 Feb;64(2):167-74.
332. DOH. Forecasting obesity to 2010. 2006.
333. Stamatakis E, Primatesta P, Chinn S, Rona R, Falascheti E. Overweight and obesity trends from 1974 to 2003 in English children: what is the role of socioeconomic factors? Arch Dis Child. 2005 Oct;90(10):999-1004.
334. Modder J, Fitzsimons KJ. CMACE/RCOG Joint Guideline. Management of Women with Obesity in Pregnancy. RCOG. 2010.
335. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J, et al. Outcomes of maternal weight gain. Evid Rep Technol Assess (Full Rep). 2008 May(168):1-223.
336. Langford A, Joshu C, Chang JJ, Myles T, Leet T. Does Gestational Weight Gain Affect the Risk of Adverse Maternal and Infant Outcomes in Overweight Women? Matern Child Health J. 2008 Feb 5.
337. Scholl TO, Hediger ML, Schall JI, Ances IG, Smith WK. Gestational weight gain, pregnancy outcome, and postpartum weight retention. Obstet Gynecol. 1995 Sep;86(3):423-7.
338. Cedergren M. Effects of gestational weight gain and body mass index on obstetric outcome in Sweden. Int J Gynaecol Obstet. 2006 Jun;93(3):269-74.
339. Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab. 2004 Jun;89(6):2583-9.
340. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006 Dec 14;444(7121):860-7.
341. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol. 1999 Feb;180(2 Pt 1):499-506.
342. Balen AH, Anderson RA. Impact of obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. Hum Fertil (Camb). 2007 Dec;10(4):195-206.
343. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B, et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ. 1993 Feb 20;306(6876):484-7.
344. Crosignani PG, Ragni G, Parazzini F, Wyssling H, Lombroso G, Perotti L. Anthropometric indicators and response to gonadotrophin for ovulation induction. Hum Reprod. 1994 Mar;9(3):420-3.
345. Gillett WR, Putt T, Farquhar CM. Prioritising for fertility treatments--the effect of excluding women with a high body mass index. BJOG. 2006 Oct;113(10):1218-21.
346. Farquhar CM, Gillett WR. Prioritising for fertility treatments--should a high BMI exclude treatment? BJOG. 2006 Oct;113(10):1107-9.
347. Lintsen AM, Pasker-de Jong PC, de Boer EJ, Burger CW, Jansen CA, Braat DD, et al. Effects of subfertility cause, smoking and body weight on the success rate of IVF. Hum Reprod. 2005 Jul;20(7):1867-75.

348. Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, et al. Physical activity, body mass index, and ovulatory disorder infertility. Epidemiology. 2002 Mar;13(2):184-90.
349. Mulders AG, Laven JS, Eijkemans MJ, Hughes EG, Fauser BC. Patient predictors for outcome of gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis. Hum Reprod Update. 2003 Sep-Oct;9(5):429-49.
350. Jacobs HS, Conway GS. Leptin, polycystic ovaries and polycystic ovary syndrome. Hum Reprod Update. 1999 Mar-Apr;5(2):166-71.
351. Shah DK, Missmer SA, Berry KF, Racowsky C, Ginsburg ES. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. Obstet Gynecol. 2011 Jul;118(1):63-70.
352. Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res. 2002 Jun;10(6):551-4.
353. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod. 2004 Jul;19(7):1644-6.
354. Ray JG, Wyatt PR, Vermeulen MJ, Meier C, Cole DE. Greater maternal weight and the ongoing risk of neural tube defects after folic acid flour fortification. Obstet Gynecol. 2005 Feb;105(2):261-5.
355. Mills JL, Troendle J, Conley MR, Carter T, Druschel CM. Maternal obesity and congenital heart defects: a population-based study. Am J Clin Nutr. 2010 Jun;91(6):1543-9.
356. Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, et al. Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med. 2007 Aug;161(8):745-50.
357. Hendler I, Blackwell SC, Bujold E, Treadwell MC, Wolfe HM, Sokol RJ, et al. The impact of maternal obesity on midtrimester sonographic visualization of fetal cardiac and craniospinal structures. Int J Obes Relat Metab Disord. 2004 Dec;28(12):1607-11.
358. Maresh M, Beard RW, Bray CS, Elkeles RS, Wadsworth J. Factors predisposing to and outcome of gestational diabetes. Obstet Gynecol. 1989 Sep;74(3 Pt 1):342-6.
359. CEMACH. The Confidential Enquiry into Maternal and Child Health (CEMACH).Saving mothers' lives: reviewing maternal deaths to make motherhood safer, 2003–2005. The seventh report of the confidential enquiries into maternal deaths in the United Kingdom. London: CEMACH. 2007.
360. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. Am J Obstet Gynecol. 2004 Apr;190(4):1091-7.
361. Nohr EA, Vaeth M, Bech BH, Henriksen TB, Cnattingius S, Olsen J. Maternal obesity and neonatal mortality according to subtypes of preterm birth. Obstet Gynecol. 2007 Nov;110(5):1083-90.
362. Galtier-Dereure F, Boegner C, Bringer J. Obesity and pregnancy: complications and cost. Am J Clin Nutr. 2000 May;71(5 Suppl):1242S-8S.

363. Oddy WH, Li J, Landsborough L, Kendall GE, Henderson S, Downie J. The association of maternal overweight and obesity with breastfeeding duration. J Pediatr. 2006 Aug;149(2):185-91.
364. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. Pediatrics. 2004 Jul;114(1):e29-36.
365. Rasmussen KM, Yaktine AL. Institute of Medicine. Weight gain during pregnancy: reexamining the guidelines,The National Academies Press, Washington, DC. 2009.
366. Herring SJ, Platek DN, Elliott P, Riley LE, Stuebe AM, Oken E. Addressing obesity in pregnancy: what do obstetric providers recommend? J Womens Health (Larchmt). 2010 Jan;19(1):65-70.
367. McDonald SD, Pullenayegum E, Taylor VH, Lutsiv O, Bracken K, Good C, et al. Despite 2009 guidelines, few women report being counseled correctly about weight gain during pregnancy. Am J Obstet Gynecol. 2011 May 27.
368. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Hum Reprod. 2006 Jan;21(1):80-9.
369. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod. 1995 Oct;10(10):2705-12.
370. Paramsothy P, Lin YS, Kernic MA, Foster-Schubert KE. Interpregnancy weight gain and cesarean delivery risk in women with a history of gestational diabetes. Obstet Gynecol. 2009 Apr;113(4):817-23.
371. Amorim AR, Linne YM, Lourenco PM. Diet or exercise, or both, for weight reduction in women after childbirth. Cochrane Database Syst Rev. 2007(3):CD005627.
372. Mutsaerts MA, Groen H, ter Bogt NC, Bolster JH, Land JA, Bemelmans WJ, et al. The LIFESTYLE study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. A randomised controlled trial. BMC Womens Health. 2010;10:22.
373. UPBEAT: UK Pregnancies: Better Eating and Activity Trial. http://www.medscinet.net/upbeat.
374. Public Health Observatory. Lambeth Community Health Profile, 2007. 2007.
375. Oteng-Ntim E, Khazaezadeh N, Mohiddin A, Bewley S, Oki B, Pheasant H, et al. Health Needs Assessment for Maternal Obesity in Lambeth
Public Health Action Support Team (PHAST) on behalf of, and supported by, Lambeth Primary Care Trust (PCT) and Guy's and St Thomas' Hospital NHS Trust (GSTT). 2008.
376. Swanton K, Frost M. Lightening the load: tackling overweight and obesity: London: HM
Government, 2007. 2007.
377. Chereshevna M. A study to investigate the effects of pre-pregnancy BMI on obstetric
outcomes and caesarean delivery in the UK in an inner city setting. SSMYr4: King's

College London, 2005. 2005.
378. Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertil Steril. 2004 Aug;82(2):421-9.
379. Costacou T, Mayer-Davis EJ. Nutrition and prevention of type 2 diabetes. Annu Rev Nutr. 2003;23:147-70.
380. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007 Feb 10;334(7588):299.
381. Tuomilehto J. Counterpoint: Evidence-based prevention of type 2 diabetes: the power of lifestyle management. Diabetes Care. 2007 Feb;30(2):435-8.
382. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403.
383. National Statistics. National Diet and Nutrition Survey: young people aged 4 to 18 years.http://www.statistics.gov.uk/ssd/surveys/national_diet_nutrition_survey_children.asp.
384. Jones LR, Wilson CI, Wadden TA. Lifestyle modification in the treatment of obesity: an educational challenge and opportunity. Clin Pharmacol Ther. 2007 May;81(5):776-9.
385. Jones LR, Wadden TA. State of the science: behavioural treatment of obesity. Asia Pac J Clin Nutr. 2006;15 Suppl:30-9.
386. Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. Cochrane Database Syst Rev. 2007(3):CD005105.
387. Marsh KA, Steinbeck KS, Atkinson FS, Petocz P, Brand-Miller JC. Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. Am J Clin Nutr. 2010 Jul;92(1):83-92.
388. Riserus U. Fatty acids and insulin sensitivity. Curr Opin Clin Nutr Metab Care. 2008 Mar;11(2):100-5.
389. National Institute for Health and Clinical Excellence 29. PH2 Four commonly used methods to increase physical activity: guidance. March 2006; 37. 2006.
390. Jakicic JM, Winters C, Lagally K, Ho J, Robertson RJ, Wing RR. The accuracy of the TriTrac-R3D accelerometer to estimate energy expenditure. Med Sci Sports Exerc. 1999 May;31(5):747-54.
391. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Apr 16;377(9774):1341-52.
392. McTigue KM, Harris R, Hemphill B, Lux L, Sutton S, Bunton AJ, et al. Screening and interventions for obesity in adults: summary of the evidence for

the U.S. Preventive Services Task Force. Ann Intern Med. 2003 Dec 2;139(11):933-49.

Appendix A: Health Needs Assessment for Maternal Obesity in Lambeth

Compiled by: Eugene Oteng-Ntim, Nina Khazaezadeh, Abdu Mohiddin, Susan Bewley, Bimpe Oki

Hannah Pheasant, Katie Enock and Kerry Lonergan (PHAST)

Date: June 2008

This study was funded by Guy's and St Thomas' Charity

Registered Charity Number 251983

EXECUTIVE SUMMARY

Obesity is increasingly becoming a matter of concern in both the general population and in relation to pregnancy, but maternal obesity has received limited emphasis compared to adult and childhood obesity. In order to fully understand and identify whether unmet health and health care needs exist within the maternal obese population of Lambeth (obese pregnant women and obese women trying to conceive), a health needs assessment was conducted.

The borough of Lambeth is densely populated with high levels of deprivation. The population is ethnically diverse with 38% of the population comprising of Black and Minority Ethnic groups. Although national or local data do not exist for the prevalence of maternal obesity, the overall synthetic prevalence of adult obesity amongst women in Lambeth is 21% and there are estimated to be approximately 14,195 obese women of childbearing age in Lambeth. Obesity rates are known to be higher in deprived areas and in certain ethnic groups (Black African and Black Caribbean). The prevalence of adult obesity in Lambeth is therefore likely to be above the estimated level of 21%. In addition, the prevalence of childhood obesity in Lambeth is higher than both the London and national average with 13.1% obese in reception year and 25.2% obese in year 6. The percentage of obese women trying to conceive and obese pregnant women in Lambeth is expected to increase as the current proportion of obese children reach childbearing age. Finally, the fertility rate in Lambeth is predicted to increase although projected figures on births must be interpreted with caution.

The increased obesity levels within women of childbearing age impact negatively on the health of both the woman and baby during the pre-conceptual, antenatal, and postnatal periods. Pre-conceptually, women are less likely to conceive naturally and the effectiveness of infertility treatment is reduced. During the antenatal period, obesity has been linked to an increased risk of pre-eclampsia, gestational diabetes, prolonged gestation, and Caesarean delivery. In addition, high maternal weight is associated with an increased risk of neonatal mortality. Postnatally, it has been reported that obese women are less likely to lactate and thus breastfeed their newborns.

The current service provision for obese women trying to conceive and obese pregnant women in Lambeth is limited and maternal obesity care pathways are not in place. Although obese women trying to conceive are being identified accurately within the fertility clinic, a high percentage of obese pregnant women (36%) are not having their BMI recorded accurately at their booking appointment. Furthermore, neither of the population groups receives adequate first line healthy eating and physical activity advice, and both groups receive either limited or no additional support to assist with weight management. In addition, prevention of maternal obesity via the promotion of pre-conceptual weight loss for all women of childbearing age is not supported across the borough.

There is some evidence on the effectiveness and cost effectiveness of interventions to treat maternal obesity. Extending the literature to include interventions that assist with tackling either childhood or adult obesity contributed to identifying successful elements that should be included in the design of new interventions to treat obese pregnant women and obese women trying to conceive. Furthermore, semi-structured interviews with key stakeholders (service providers and service users) provided insight into their views and recommendations, both of which enhance the evidence base. The recommendations focus on expanding existing services and developing new services to meet the unmet health needs of obese women trying to conceive

and obese pregnant women living in Lambeth. The key recommendations are outlined below:

1. Implement pre-conceptual counselling and weight management services in primary care to ensure that obese women of childbearing age lose weight prior to conceiving.
2. Develop and implement evidence-based maternal obesity care pathways.
3. Implement protocols to improve the identification of obese pregnant women using the BMI measurement at the booking appointment (10-12 weeks).
4. Implement protocols to improve the identification of obese women trying to conceive in primary care prior to being referred for fertility treatment.
5. Coordinate training for all relevant health care professionals involved with obese pregnant women and obese women trying to conceive to ensure that women receive accurate and consistent weight management advice.
6. Develop and implement two new interventions: one for obese women trying to conceive and one for obese pregnant women.
    a. Both interventions should be multi-component to include interactive healthy eating, physical activity and behavioural change sessions.
    b. The information and activities provided should be culturally specific with particular emphasis on the Black African and Black Caribbean women to reduce inequalities between ethnic groups.
    c. The interventions should be group-based and in a community setting equitably distributed across the borough.
    d. A health care professional should be involved with the intervention (for example, a midwife) but non-health care professionals (for example, health trainers) should be recruited and trained to organise and lead the sessions. This is more cost-effective and increases the sustainability of the intervention.
    e. Robust monitoring and evaluation strategies should be developed during the design phase of the interventions to enable continuous

improvements to the service to take place and to increase the overall evidence base for managing maternal obesity.

Recent government publications, namely '*Healthy Weight, Healthy Lives'* and the *'Confidential Enquiry into Maternal and Child Health'* (CEMACH), have highlighted the issues associated with obesity in pregnancy, and the national recommendations from CEMACH and the National Institute for Health and Clinical Excellence guidance (Fertility, Diabetes in Pregnancy, Maternal and Child Nutrition, and Antenatal Care) will be incorporated into new national public health policies. At the local level, PCTs are expected to commission services which meet the recommendations set out in national guidance. The recommendations from the national guidance have, therefore, been incorporated into this current needs assessment. Finally, whilst specific maternal obesity targets do not currently exist, a number of related Public Service Agreement targets will benefit from interventions directed at reducing the prevalence of maternal obesity, such as reducing the childhood obesity rate, increasing breastfeeding initiation rates, and reducing health inequalities to tackle infant mortality by optimising maternal nutrition.

The full report can be found at:
http://www.gsttcharity.org.uk/grants/awarded_results.html

Appendix B: Obesity and low BMI in pregnancy

Clinical Guidance

Obesity and Low BMI in Pregnancy

Summary

Management of women with either high or low BMI in pregnancy. Focusing on high BMI, risks to the mother, referral for anaesthetic support, dietary advice, investigation for diabetes and hypertension. Ensuring appropriate equipment is available.

Document Detail	
Document Type	Guidelines
Document name	Obesity and Low BMI in Pregnancy
Document location	GTi Clinical Guidance Database
Version	2.0
Effective from	*2012*
Review date	
Owner	Clinical Lead, Obstetrics and Gynaecology
Author	Eugene Oteng-Ntim, Consultant Obstetrician and Gynaecologist
Approved by date	Clinical Guidance Group, *2012*
Superseded documents	
Related documents	
Keywords	Obesity, pregnancy, BMI, morbidly obese
Relevant external law, regulation, standards	

Change History		
Date	Change details, since approval	Approved by

Pregnancy & BMI

Introduction 1

The prevalence of obesity, defined as a body mass index (BMI) greater than or equal to 30kg/m^2, is estimated at 25% of the female population in England. 1.8% of these women can be described as morbidly obese; that is, BMI ≥ 401.
Body mass index is a tool used to classify whether a person is a healthy weight for their height. It is calculated by dividing weight in kilograms by the square of the height in metres.

Body mass index BMI = weight in kg/height in metres²

Classification of Obesity

WHO Classification	**Popular description**	**BMI Kg/m2**
Underweight	Thin	<18.5
Normal range	Normal	18.5-24.9
Overweight		>25
Pre-obese	Overweight	25-29.9
Obese Class I	Obese	30-34.9
Obese Class II	Moderately Obese	35-39.9
Obese Class III	Morbidly Obese	>40

Women with a BMI > 30 are at increased risk of pregnancy complications and morbidity.

Risks include:

Pre-eclampsia[3]

Thromboembolism[4, 5]

Gestational diabetes

Failed induction

Increased risk of instrumental deliveries[6] and Caesarean section[7]

Failed spinal/epidural[8]

Failed intubation[9]

Postpartum haemorrhage[10]

Post-operative infection

Poor wound healing[3]

Increased risk of birth weight > 4 kg[7]

Increased perinatal loss

Increased maternal mortality

The triennial report by the Confidential Enquiry into Maternal and Child Health (CEMACH) "Why Mothers Die 2003-2005"[11] indicates that 27% of women who had a pregnancy-related death were obese. Accurate risk assessment, early detection, appropriate referral and ongoing monitoring should minimise the preventable risks.

ANTENATAL care for all women:

BMI should be calculated at booking and documented in the hand-held maternity notes.

There is no need to re-weigh women of normal weight or those who are pre-obese (BMI between 18.5-30) once their BMI has been calculated from their booking weight.

Guidelines for women with a low body mass index (BMI) <18.5 kg/m2

Women with BMI <18 should be referred to their link consultant for discussion and development of an individual plan. The importance of taking a detailed history and then serially measuring BMI is to distinguish anorexia (and bulimia) from slim body habitus.

Most of these women will have slim body habitus genetically and will be eating and gaining weight normally in pregnancy. So long as they are well and the SFH is normal they can be reassured that the pregnancy outcome is likely to be normal.

Pregnant women with past or current eating disorders should be regarded as having high-risk pregnancies (Franko et al., 2001). Anorexia is not a temporary condition of adolescents, but can be a serious chronic disorder with a significant mortality rate. Anorexia is associated with an increased risk of IUGR, Caesarean section and postpartum depression. In extreme cases women may

induce vomiting, purge themselves, abuse laxatives and develop electrolyte disorders or cardiac failure. Outcomes appear to be worse if women are symptomatic of their eating disorder during the pregnancy.

It is important to enquire carefully whether the patient is currently experiencing symptoms. Asking questions about body image, food avoidance, food rules and dieting behaviours has effectively distinguished women with eating disorders from healthy controls (Franko et al. 2000). Examination findings may include excoriation of the hands or lanugo hair.

Women with a past or current history of anorexia or bulimia (sufficient to be under the care of a psychiatrist) should be referred to MAPPIM. Some women may be seen by their previous psychiatrist or referred to the eating disorder service (at St Georges). MAPPIM should be aware of all women attending a previous psychiatrist or eating disorder service even if they do not review directly. It is important for the link midwife and consultant to liaise with the GP. Postpartum recurrence may be a problem.

If BMI <18, it is worth monitoring weight monthly to observe normal weight gain – but beware that some anorexics resist and avoid weighing and it is important to develop a trusting relationship with maternity services.

References

Franko DL & Spurrell B. Detection and management of eating disorders in pregnancy. Am J Obstet Gynaecol 2000;95:942-946

Franko DL, Blais MA, Becker AE et al. Pregnancy complications and neonatal outcomes in women with eating disorders. Am J Psych. 2001; 158:1461-6

Guidelines for women with a normal body mass index (BMI) 19-25 kg/m2

Women should have their attention drawn to the usual dietary and exercise advice given in the Health Education Pregnancy Book.

Guidelines for women with a pre-obese body mass index (BMI) 25-30kg/m2

Patients should be given the usual dietary and exercise advice from the Sensible Eating leaflet/Health Education booklet.

Guidelines for women with a body mass index (BMI) >30kg/m2

If BMI >30kg/m^2, these issues should be discussed during the antenatal consultation:

1. What healthy diet is necessary to control sugar in pregnancy and for the mother's long-term health
2. The importance of 30 minutes' regular daily activity for the mother's health
3. Regular attendance for BP and urinalysis
4. Monitoring fetal movement/changes in fetal movement
5. Difficulty in assessing fetal growth by palpation
6. Imaging difficulty at ultrasound scan
7. The possibility of the need for EFM in labour and possible failure in obese women
8. Risk associated with thrombosis and prophylactic measures
9. Difficulties associated with insertion of epidural

A referral should be made to the patient's consultant. Following antenatal consultation, an individualised plan of care should be clearly documented in the woman's hand-held maternity notes.

Where there are concerns regarding the assessment of fetal wellbeing and where fetal heart monitoring is not possible an ultrasound assessment should be considered.

For women whose weight is above 150 kg, the HBC manager and senior birth centre ODP should be notified by email and a copy of the woman's care plan and EDD should be included. This will ensure that the specialist equipment required is made available in a timely manner.

Care pathway relating to the three categories of obesity

INTRAPARTUM CARE

	Obese Class I BMI 30-34.9	**Obese Class II BMI 35.0-39.9**	**Obese Class III Morbidly obese BMI>40.0**
Obstetric	Consultant referral 12 See before 24 weeks		
Anaesthetic		Anaesthetic referral 24-34 weeks	
Diet	Advice re healthy diet. Referral to dietician if woman agrees >35		
Nutritional supplements	1. Advise 5mg folic acid supplementation daily at least one month before conception and continuing during first trimester of pregnancy 2. Advise 10mcg of vitamin D supplementation daily during pregnancy and while breastfeeding		
Scans	Detailed anomaly scan 18-20+6 weeks and uterine artery Doppler		
	Growth and wellbeing scan at 32 weeks for those with BMI greater than or equal to 35kg/m^2		
Aspirin	Not routine - only if other indication	Commence low-dose aspirin at booking	
GDM	Random blood glucose and HbA1C at booking and at 26 weeks (Refer to diabetic screening form)		
PET Screening	BP and urinalysis should be assessed as per low-risk guideline in the absence of other risk factors for pre-eclampsia 13,14	Blood pressure and urinalysis should be assessed every 3 weeks (24-32 weeks gestation) and every 2 weeks after 32 weeks gestation 13,14	
> 30 weeks		Consultant review 32-34 weeks Obstetric review at 37 weeks to discuss delivery	
Place of birth	Home-from-home only if no other risk factors	Advise Hospital Birth Centre for safety	
Fetal monitoring in labour	Usual	Electronic fetal heart rate monitoring. Consider FSE if monitoring difficult	
Iv access	Iv access on admission where clinician feels it may be difficult to do in emergency		

Antacid	Ranitidine 150mg should be administered 6-hourly throughout labour	
Eating	Usual	Women should **not eat** in labour. They may drink water and isotonic 'sports drinks'
Admission	Usual	Inform coordinator, obstetric registrar, anaesthetic registrar
Anaesthetics	Treat as normal	Anaesthetic alert when patient in labour
Thrombopro-phylaxis	Thromboprophylaxis risk assessment should be carried out as per (RCOG green top guideline)	Thromboprophylaxis required for all modes of delivery. 90-130kg = enoxaparin 60mg od 130-170kg = enoxaparin 80 mg od

INTRAPARTUM CARE

Each woman should be managed as an individual, considering her expressed wishes, her medical/obstetric history and her level of risk for surgery.

Women with a BMI >35 at booking should be advised to be delivered in the Hospital Birth Centre.

On admission the HBC co-ordinator, obstetric registrar and anaesthetist should be informed of all women with BMI of 35 or above. They may wish to inform the consultant obstetrician and anaesthetist.

Electronic fetal monitoring should be recommended for women with a BMI >34.915. It may be necessary to use a fetal scalp electrode.

Maintaining normality during labour minimises the risk of complications3. However, there is an increased risk of Caesarean section with increased BMI and therefore women with a BMI of >40 should not eat in labour. They may drink water and isotonic 'sports drinks'.

The Trust's guidelines relating to moving and handling should be adhered to at all times.

The following aids for moving the patient are available:

1. Patient transfer device – theatre
2. Sliding sheet
3. Hoist

Pain relief:

If an epidural is anticipated insertion is made easier if the woman is able to maintain one position during the procedure i.e. before labour becomes advanced. Therefore, the catheter may be inserted in early labour. It is important to ensure that the epidural is fully effective throughout labour.

Tissue Viability:

Six-hourly risk assessment for BMI>35 should be carried out using the maternity risk assessment scoring system and action should be taken where appropriate. Advice may be sought from the tissue viability nurse if required (available by bleep via the switchboard). The Trust Tissue Viability guidance should be followed.

INDUCTION OF LABOUR:

Serious consideration should be given to avoiding induction of labour unless absolutely necessary. Induction of labour is only recommended when delivery is of greater benefit to the woman or baby than if the pregnancy continues.[17] Following induction of labour with vaginal prostaglandins (PGE2) fetal wellbeing should be established once contractions are detected or reported.[18] See induction of labour guidelines. Consideration should be given to maternal size and the effectiveness of methods of monitoring fetal wellbeing.

Where adequate assessment of fetal wellbeing is not possible and delivery is required, Caesarean section should be considered.

Induction in women with BMI of >40

Consider the following prior to deciding upon induction of labour:

- Mobility of the woman
- If immobile, use of TED stockings
- Follow STH guidelines on thromboprophylaxis.

If induction of labour has been agreed, consideration should be given to the following:

1. Induction should be arranged for a weekday morning (Mon-Thurs).
2. The consultant on call should be informed.
3. The consultant anaesthetist should be informed. The patients will have been assessed antenatally by a consultant anaesthetist. The feasibility of performing a crash Caesarean section (category 1) will have been assessed at this time.
4. All staff involved in the care provision should be made aware of the forward plan and the possibility of Caesarean section should induction of labour fail.
5. The induction of labour guidelines should be followed.[21]

CAESAREAN SECTION for women with BMI >40

Elective Caesarean section should be for the usual obstetric indications.
Elective Caesarean section should be scheduled from Monday to Friday.
The date and time must be agreed following discussion with the consultant obstetrician who will be doing the list; a specific care plan should be written and the MPL for theatre informed. A senior person (ST3 or above) should do the operation.

The mode of anaesthesia should be discussed and decided antenatally. The appropriate arrangements should be made for specialist equipment i.e. long instruments prior to the procedure to avoid delay or distress to the woman.

Any emergency Caesarean section carries an increased risk of morbidity and mortality. Therefore, the most senior person available should perform the surgery (i.e. ST 3 or above). At the anaesthetic assessment the feasibility of an emergency Caesarean must be considered and documented and the woman must be informed if it will be difficult to deliver her baby within 20 minutes (see HBC anaesthetic guidelines).

POSTPARTUM

It is recommended that early mobilisation is encouraged and thromboprophylaxis is given in line with current guidelines, as the risk of thrombosis is increased. All women with BMI >40 require thromboprophylaxis regardless of the mode of delivery (enoxaparin 60mg od if 90-130kg, 80 mg od if 130-170kg). All women with BMI >30 having a Caesarean section require enoxaparin, with the dose depending on their weight (40mg od if < 90kg or 60 mg od if 90-130kg). There is an increased risk of pressure sores, so they should therefore be closely monitored. Where necessary, the opinion of the tissue viability nurse should be sought (available by bleep via the switchboard).

In addition, there is an increased risk of wound infection, so it is imperative that all wounds should be observed and advice given regarding care. Medical opinions on the ward (or from GP if in the community) should be sought immediately if wound infection/breakdown is suspected.

Equipment

Blood pressure cuffs:

All clinical areas (including all community clinics) should have access to large blood pressure cuffs.

Scales:

The scales in the hospital antenatal clinic should go up to 180kg.

All pregnant women should be weighed at booking. If the scales are inadequate it is likely that their BMI is >30 and they need to be referred to their link obstetric consultant. They can be weighed at this visit (or referred to the hospital if their consultant clinic is in the community). If the patient weighs >180kg, discuss with the site practitioner how to weigh.

Beds:

Normal beds can take women weighing <170kgs; the birthing beds can take <227kgs. For women weighing >170 kgs contact Huntleigh on *2282 to hire the contura1080 which takes up to 450kgs and has integral weighing scales.

Theatre Table:

The theatre tables can take women <220kgs. For a larger theatre table contact the main theatres. For other equipment such as armchairs, commode, and wheelchairs, these can also be hired from Huntleigh. It is the responsibility of the midwifery manager for each area (wards, day unit, clinic and in the community) to ensure that suitable equipment is available for women of any size. Monthly spot checks will be done.

Department of health (2000). Health survey for England 2000. D.O.H publications.

1. Caro JF (2002) Definitions and Classification of Women with Obesity http://www.endotext.org/obesity1.htm
2. Kabiru W, Raynor B.D. (2004) Obstetric outcomes associated with increase in BMI category during pregnancy. American Journal of Obstetrics and Gynaecology 191(3) 928-932.
3. Stevens H (2002). Blood pressure patterns through consecutive pregnancies are influenced by body mass index. American Journal of Obstetrics and Gynaecology 187 (5) 134-138.
4. Royal College of Obstetrics and Gynaecology (2001). Clinical green top guidelines. Thromboembolic disease in pregnancy and the puerperium. Acute Management (28).
5. Singhal T, Vogiatzi M, Parmeshwaran S, Howarth E.S. (2005) Maternal obesity and its impact on pregnancy outcome. Journal of Obstetrics and Gynaecology 25 S39.
6. Cooley S.M, Donnelly J, Walsh T, Sarkar R, Munaza S, Geary M, Gillan J, Macmaron C. (2005). The influence of body mass index (BMI) on maternal and fetal wellbeing. A prospective study. Journal of Obstetrics and Gynaecology 25 S43.
7. Nicoll AE, Young D, Bow E, Brennand J, Cameron (2005). Maternal body mass index and parturition. Journal of Obstetrics and Gynaecology 25 S68.

8. Grange C. (2000). Medical emergencies in pregnancy. In Russell R (ed) Anaesthesia for obstetrics and gynaecology LONDON BMJ Books 239-280.
9. Hamer M (1997). Difficulty and failed intubation in obstetrics. International Journal Obstetrics Anaesthetists 6:245
10. Thorsdottir I (2002). Weight gain in women of normal weight before pregnancy: complications in pregnancy or delivery and birth outcome. In Obstetrics and Gynaecology 799-806
11. Confidential Enquiry into Maternal and Child Health (CEMACH) 'Why Mothers Die '2000-2002', RCOG Press
12. Action on pre-eclampsia. (2004) Promoting safer pregnancy. Pre-eclampsia
community guidelines. APEC
13. Nawar-Youssef M.N, Iqbal F, Odukoya O.A (2005). Pregnancy care in obese women. An observational study in a district general hospital. Journal of Obstetrics and Gynaecology 25 (1) 538.
14. NICE (2003) National Institute of Clinical Excellence. Antenatal Care. Routine Care for the Healthy Pregnant Woman. NICE London.
15. National Institute for Clinical Excellence (2001). Inherited clinical guidance. The use of electronic fetal monitoring. NICE 2001
16. Induction of labour (2001) RCOG Evidence-based guideline number 9 RCOG press
17. NICE (2001) Inherited Clinical Guideline D. Induction of labour
18. National Institute for Clinical Excellence (NICE) April 2004 Clinical Guideline 13. Caesarean Section. NICE London
19. National Collaborative Centre for Women's and Children's Health. April 2004 Caesarean Section Clinical Guideline RCOG London
20. Department of Health (DOH) 2001 Reference Guide to Consent for Examination or Treatment. DOH London
21. RCOG Green top guideline 37a: Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. RCOG 2009

Appendix C: A community-based lifestyle intervention for weight loss in overweight and obese women planning pregnancy

Study Protocol

Scientific Title: A multi-component Community-based Lifestyle Intervention for weight loss in overweight and obese women planning pregnancy: CLIO Pre-Pregnancy Randomised Controlled Trial

Public Title: Community-based Lifestyle Intervention for weight loss in overweight and obese women planning pregnancy

Acronym: CLIO

Study Type	Randomised Controlled Trial
Chief Investigator	Mr Eugene Oteng-Ntim
	Principle Investigators
	Dr Jacqueline E.A.K. Bamfo
	Dr Shree Datta
	Ms Nina Khazaezadeh
	Mr Arri Coomarasamy
	Dr Raj Mitra
	Dr Suzanne Barr
	Professor Pat Doyle

Correspondence Mr Eugene Oteng-Ntim
Eugene.Oteng-Ntim@gstt.nhs.uk

Expertise of Applicants

Mr Eugene Oteng-Ntim MB BS PGDip FRCOG – Consultant in Obstetrics and Gynaecology at Guy's and St Thomas' NHS Foundation Trust. Area of expertise is obesity in pregnancy, currently doing a PhD in Obesity and Reproductive Health at the London School of Hygiene and Tropical Medicine (LSHTM). Coordinator of the project.

Professor Pat Doyle, PhD – Professor of Epidemiology. Area of expertise is Reproductive Epidemiology, London School of Hygiene and Tropical Medicine, University of London.

Mr Arri Coomarasamy, MD, MRCOG - Consultant in Obstetrics and Gynaecology. Area of expertise is Reproductive Medicine and HTA grant holder on obesity intervention during pregnancy. Birmingham Women's Hospital.

Nina Khazaezadeh MSc – Consultant midwife. Area of expertise is Public Health and Women's Health, Guy's and St Thomas' NHS Trust.

Dr Raj Mitra – General Practitioner, Lambeth. Member of Lambeth Clinical Commissioning Collaborative Board, Honorary Senior Lecturer in General Practice, King's College London.

Dr Jacqueline E. A. K. Bamfo, BSc, MRCOG, DFFP, MD, Diploma in Obstetric Ultrasound. Specialty Training Registrar in Obstetrics and Gynaecology, University College Hospital.

Dr Shree Datta, MRCOG, Diploma in Leadership and Management, Leadership and Management, LLM, Medical Law and Ethics, Co-Chair, Junior Doctors

Committee at BMA, Specialist Registrar in Obstetrics and Gynaecology at Queen Mary's Hospital, Sidcup.

Suzanne Barr PhD, Lecturer in Nutrition and Reproductive Health, King's College, London. Expertise in Nutrition.

Study Centres: Guy's and St Thomas' NHS Foundation Trust
King's College Foundation Trust
Birmingham Women's Hospital

Statistics: The Maternal and Fetal Research Unit
Division of Reproductive Health Endocrinology, and Development, KCL
Stata (version 7.0; Stata Corp, College Station, Texas)

Laboratory: The Maternal and Fetal Research Unit
Division of Reproductive Health Endocrinology, and Development, KCL.

Table of Contents

Summary and the rationale for the trial

We propose a multicentre randomised controlled trial in overweight and obese women which will examine the effectiveness and costs of a six-month structured multi-component community-based lifestyle programme for weight loss.

We are asking the following questions:

1. Will dietary intervention based upon reduction of dietary glycaemic load, reduced caloric intake, reduced saturated fats and reduced free sugars result in weight loss?
2. What are the changes to dietary and physical activity behaviours from 0-6 months?
3. Will the interventions lead to:
    1. A ≥5% weight reduction over 6 months as the primary outcome?
    2. A change in insulin sensitivity using the HOMA model from 0-6 months?
    3. Improved glucose homeostasis?
    4. Pregnancy rate within 12 months?
    5. A change in wellbeing and depression scores using the short form 36 version 2 tool?
4. Will one-to-one counselling or behavioural support increase physical activity, improve glucose haemostasis and cause weight loss?

    We aim to evaluate the process and cost-effectiveness of the intervention.

Background

Obesity is a global epidemic and a major public health issue in today's society. It is defined as 'an accumulation of excess body fat to an extent that may impair health'. It is now commonly evaluated as body mass index (BMI, kg/m^2). The World Health Organisation (WHO) defines a BMI of 18.5–24.9 kg/m^2 as normal

weight, BMI of < 18.5 kg/m^2 as underweight, BMI of 25–29.9 kg/m^2 as overweight, and BMI ≥ 30 kg/m^2 as obese. A BMI ≥ 40 kg/m^2 indicates morbid obesity. Obesity can also be classified by the presence of central obesity, as a waist circumference ≥ 80 cm for Europid women, with ethnicity-specific values (327).

By 2050 the UK could be a mainly obese society (328). The cost of obesity to the UK Government was nearly £7 billion in 2002 and could reach £45 billion by 2050 (328). There is a recognised health inequality associated with obesity, with obesity being higher in those of low socioeconomic status. There also appears to be a high prevalence in some groups such as African and Black Caribbean women. Recent data from the Health Survey for England (HSE) suggests that 24% of women aged 16-44 years in the UK are obese and 3% are morbidly obese (BMI>40) (329). Childhood obesity is becoming an increasing problem. Twenty-two percent of UK schoolgirls aged 11-15 had BMI>30kg/m2 in 2003; however, this number is predicted to rise to 27% in 2012 (330-332). Childhood overweight and obesity prevalence rates of children from manual social classes and children from lower income households appears to be increasing more rapidly than children from non-manual classes and higher income households, respectively (333).

Obesity is related to adverse outcomes during pregnancy. In the recent 2006-2008 confidential enquiries into maternal deaths, 47% of mothers who died from direct deaths were overweight or obese. Furthermore, in cardiac disease, the commonest cause of indirect deaths and deaths overall, 60% of those who died were overweight or obese (88). Whilst there was a fall in deaths from congenital heart lesions, a significant number of deaths were due to sudden adult death syndrome (SADS) and myocardial infarction (88). Obese pregnant women are at increased risk of pre-term labour, pre-eclampsia, gestational diabetes, thromboembolism, operative delivery and postpartum haemorrhage. The fetuses are at risk of miscarriage, congenital abnormalities, macrosomia and stillbirth (334). Furthermore, excessive weight gain in pregnancy is associated

with postpartum maternal overweight, which further compounds long-term obesity (335-338).

Inflammation and obesity

Obesity not only leads to cardiovascular disease and diabetes but also affects every major organ in the human body (339). It is a component of metabolic syndrome, a group of disorders characterised by visceral obesity, insulin resistance, dyslipidaemia, and hypertension. The literature suggests that the pathogenesis of the cellular and organ damage seen in obesity may instigate a complex process involving chronic low-grade inflammation with upregulation of proinflammatory cytokines, proatherogenic mediators and prothrombotic cells (340). Normal pregnancy is characterised by an increase in the systemic inflammatory response (341). Inflammation is common to obesity and pregnancy and if its effects are additive, this could possibly increase the risks of adverse outcomes.

Obesity and pregnancy

Subfertility and miscarriage

Obesity impacts pregnancy from conception to the pastpartum period. Compared with women of normal weight, there is a lower natural and assisted conception rate in obese women (342-347). At Guy's and St Thomas' Foundation Trust, 30% percent of women seeking treatment for infertility were either overweight or obese (unpublished). Obesity-related subfertility may be a consequence of infrequent ovulation or anovulation, which occurs three times as commonly in obese women (348). A common cause of anovulation is polycystic ovarian syndrome (PCOS), a condition associated with obesity. Obese PCOS women are less likely to conceive compared to lean PCOS women (349-350). Miscarriage is frequent in obese women (351-352). Obese women have fewer normally fertilised oocytes and lower estradiol levels (351).

A study of 1644 obese women compared to 3288 age-matched normal weight controls found a higher risk of early miscarriage and recurrent miscarriage in obese patients with odds of 1.2 and 3.5, respectively (353).

We have recently conducted a systematic review on the effect of BMI on the chance of pregnancy and risk of miscarriage following assisted conception treatment (accepted for poster presentation at the British Fertility Society meeting in January 2011). The literature search was conducted on MEDLINE and EMBASE from 1966-2010. Twenty-two studies, including 22733 patients having IVF treatment, were included in our review. Meta-analysis of these studies showed that women who were overweight or obese (BMI ≥25 kg/m^2, n=7072) had significantly lower clinical pregnancy (RR = 0.87, 95% CI: 0.80-0.94, P = 0.0006)) and live birth rates (RR = 0.81, 95% CI: 0.72-0.92, P = 0.0006) and a significantly higher miscarriage rate (RR = 1.29, 95% CI: 1.14-1.45, P<0.0001) compared to women with a normal BMI (18.5-25 kg/m^2, n= 15661), following IVF treatment. A subgroup analysis comparing women who had normal weight with women who were overweight (n=4062) revealed lower clinical pregnancy (RR=0.91, 95% CI: 0.86-0.96, P=0.0006) and live birth rates (RR=0.91, 95% CI: 0.84-0.99, P= 0.02) and higher miscarriage rates (RR= 1.20, 95% CI: 1.07-1.35, P=0.002) in overweight women.

Fetal congenital anomalies

Maternal obesity increases the risk of fetal congenital abnormalities. These include neural tube defects and congenital heart disease (atrial septal defects, hypoplastic left heart syndrome, aortic stenosis, pulmonic stenosis, and tetralogy of fallot (354-355). Furthermore, a multicentre study has reported that maternal obesity doubles the risk of spina bifida, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele (356). The increased maternal habitus of obesity may limit visulisation during ultrasonography and therefore reduce the detection of fetal anomalies (357).

Adverse obstetric outcomes

The confidential enquiries into maternal deaths and numerous studies have clearly shown that maternal mortality and morbidity are high in overweight and obese women (88, 154, 358). In addition to acquired heart disease, thromboembolism remains a risk for obese women. In the 2003-2005 confidential enquiries into maternal deaths, 57% of the women who died from thromboembolism were obese (359).

The FASTER Trial involving a database of 16,102 patients reported that obesity and morbid obesity were associated with increased odds of gestational hypertension (odds ratios [ORs] 2.5 and 3.2), preeclampsia (ORs 1.6 and 3.3), gestational diabetes (ORs 2.6 and 4.0), birth weight > 4000 g (ORs 1.7 and 1.9) and birth weight > 4500 g (ORs 2.0 and 2.4). In nulliparous women, Caesarean section rates for obese and morbidly obese women were 33.8% and 47.4% respectively, compared to 20.7% for women with normal weight (360). These findings are supported by others (358). Preterm delivery is also increased for obese women. One study reported that neonatal mortality in infants born after preterm premature rupture of membranes (PROM) was significantly higher if infants were born to an overweight or obese mother (adjusted hazard ratios 3.5, CI 1.4-8.7, and 5.7, CI 2.2-14.8), respectively (361). Clearly, these adverse outcomes will have a huge cost and service provision commitment.

Strong evidence now links obesity to stillbirth. A recent systematic review and meta-analysis involving 96 population-based studies identified obesity as the highest-ranking modifiable risk factor for stillbirth. Maternal overweight and obesity had PARs (population attributable risk) of 8—18% across five countries. Five studies assessed overweight and four studies assessed obesity, revealing an increase in the odds of stillbirth of 23% and 60%, respectively. BMI higher than 40 kg/m^2 doubled the odds of stillbirth (aOR 2·08 [95% CI 1·58–2·73])(152) (154).

Neonatal and childhood complications

Breastfeeding is impaired in obese women. Obesity increases short-term neonatal morbidity from hypoglycaemia and metabolic disturbance and increases admission to neonatal care (255, 362-363). In the long term, there is evidence of a link between health inequality and obesity. A recent retrospective cohort study of 8400 children found that among low-income children, maternal obesity in early pregnancy doubled the risk of childhood obesity at 2 to 4 years of age (364).

Weight management and strategies

Weight gain

Currently, the National Institute for Clinical Excellence recommends that women normalise their weight before becoming pregnant. In pregnancy, there is a lack of clear recommendations for appropriate weight gain. Here, NICE cites recommendations from the American Institute of Medicine (IOM). In 2009, the IOM modified their original 1990 recommendations, in light of the increased prevalence of obesity. They suggest that healthy American women at BMI of 18.5 to 24.9 should gain 11.5–16 kg (25–35 pounds) during pregnancy, underweight women (BMI less than 18.5) should gain 13-18 Kg (28 to 40 pounds), and overweight women (BMI of 25 to 29.9) should gain 7– 11.5 kg (15 to 25 pounds). Obese (BMI greater than 30) women should limit weight gain to 5–9 kg (11-20 pounds) (365).

Obstetricians need to be informed about what advice to give patients about appropriate weight gain (366). The Southampton Women's Survey (SWS), a longitudinal survey of 12,583 women living in Southampton, U.K), evaluated the gestational weight gain of 948 women, finding that 49% gained more weight in pregnancy than that recommended by the 2009 IOM guidance. A recent study surveyed 310 women at prenatal clinics in Ontario, Canada. Twenty-eight

percent of women recalled being informed about recommended weight gain and only 12.0% of the women achieved the recommended weight gain according to the IOM guidelines. Only one in four women recalled being told about the risks of excessive weight gain (367).

Strategies

The purpose of preventive medicine is to undertake measures to prevent disease. Historically, it is an effective method of health care and is potentially cost-effective. In the UK, NICE fertility guidelines published in 2004 recommended that 'Women with BMI ≥30 are likely to take longer to conceive and those in this group who are anovulatory should be advised that losing weight is likely to increase their chance of conceiving'. The evidence for this is level 2b, being based on small studies; therefore, randomised trials are recommended (206-208). In infertile women, lifestyle intervention could improve spontaneous conception rates and prevent unnecessary fertility treatment as well as obstetric complications (368). Guidelines from NICE and the RCOG study group on Obesity and Reproductive Health recommend 'investment into weight reduction programmes before providing fertility treatment' (206). A combined position document from the American Dietetic Association and the American Society of Nutrition (2009) supports the importance of nutrition and activity intervention prior to pregnancy, whether the planned pregnancy is natural or through assisted conception (209).

Observational and small interventional studies show that modest weight loss is associated with restoration of ovulation in anovulatory women and improves the chances of pregnancy. Weight loss can be achieved through lifestyle intervention incorporating the combination of a healthy low caloric intake, low glycaemic index diet, increased physical activity and behavioural modification (210). Weight loss has been advised for the improvement of reproductive function in overweight women, specifically those suffering from polycystic

ovarian syndrome (PCOS) (369). However, the evidence of the effectiveness of lifestyle weight reduction intervention is still limited.

Few studies have evaluated pregnancy outcomes after weight loss pre-pregnancy. A population-based, retrospective cohort analysis of data between 1978 and 2005 evaluated the effects of pre-pregnancy changes in BMI between successive pregnancies on the risk of preterm birth. Compared with women who maintained normal inter-pregnancy BMI, women with BMI changes from normal weight to obese (OR 1.4, 95% CI 1.2 to 1.6) and normal weight to overweight (OR 1.2, 95% CI 1.1 to 1.3) were at increased risk of medically indicated preterm birth (211). Inter-pregnancy weight gain was associated with a dose-response increase in the risk of gestational and type 2 diabetes. Women moving from normal pre-pregnancy weight in the first pregnancy to obese pre-pregnancy weight in the second pregnancy tripled their risk of developing diabetes. However, mothers who maintained their inter-pregnancy BMI weight category or who moved to a lower BMI category had reduced risk for gestational and type 2 diabetes (212). Inter-pregnancy weight gain of more than 10 lb in women with a history of gestational diabetes almost doubles the risk of Caesarean section in a future pregnancy (370).

In a large nationwide Swedish study of 151 025 women, Vilamor et al. studied the association between inter-pregnancy BMI change from the first to the second pregnancies, and the risk of adverse outcomes. Compared with women whose BMI changed between -1.0 and 0.9 units, the odds for adverse outcomes for those who gained 3 or more units over two years were approximately doubled and were: pre-eclampsia, 1.78 (95% CI=1.52-2.08); gestational hypertension 1.76 (1.39-2.23); gestational diabetes 2.09 (1.68-2.61); Caesarean delivery 1.32 (1.22-1.44); stillbirth 1.63 (1.20-2.21); and large for gestational age birth 1.87 (1.72-2.04). The authors concluded that even a moderate increase in BMI could significantly increase poor pregnancy outcomes (213).

These studies strongly suggest weight control between pregnancies and pre-

pregnancy would be beneficial for reducing adverse outcomes and that this would even out the health disparities. Weight loss after pregnancy will improve the long-term health of the mother and the infant and reduce the impact of obesity-related complications on public health and health provision services.

Currently, there is little in the literature to guide the best method of weight loss, either pre-pregnancy or in pregnancy. A Cochrane review of six trials involving 245 women after childbirth found that dieting and exercise together were more effective than diet alone in achieving weight loss. There was insufficient evidence to comment about breastfeeding women (371). Careful nutritional monitoring in obese women during pregnancy has not been found to have deleterious effects (263).

There have been few randomised trials evaluating weight loss pre-pregnancy and during pregnancy. The LIFESTYLE study is a randomised trial in the Netherlands for overweight and obese subfertile women, which will compare a six-month structured weight loss lifestyle programme followed by conventional fertility care (intervention group) to conventional fertility care only (control group). The delivery of a healthy term singleton beyond 37 weeks gestation, pregnancy complications, the need for fertility treatment and cost analysis will be the outcome measures (372). There is an ongoing pregnancy intervention trial in the UK. The UK Pregnancies Better Eating and Activity Trial (UPBEAT) trial aims to develop an intervention based on diet and physical activity to reduce adverse pregnancy outcomes in obese pregnant women and also improve maternal glucose sensitivity during pregnancy (373).

There is a need for studies in the UK and internationally to evaluate the best interventions that address obesity pre-pregnancy and during pregnancy. Health disparity may exacerbate the problems of obesity, and this provides an added incentive for reducing the prevalence of obesity. The obstetric unit at St Thomas' Hospital is a tertiary referral centre for South East England; it also serves the boroughs of Southwark and Lambeth. The community of Lambeth

includes areas of high deprivation, with 16 out of its 21 wards in the most deprived areas in England (374). The population is ethnically diverse with a high percentage of Black African and Black Caribbean people. In 2008 approximately 62% of the Lambeth populations were White and 38% were from Black and Minority Ethnic communities (GLA 2005 Round Interim Ethnic Group Projections). In future, these proportions are predicted to remain stationary. By 2008, the overall synthetic prevalence of adult obesity amongst women in Lambeth was 21% and there were an estimated 14,195 obese women of childbearing age. In view of the increasing rates of obesity, the prevalence of adult obesity is likely to be well above this by now (375). Notably, the prevalence of obesity in women is currently greatest in the Black Caribbean and Black African populations and lowest in the Chinese (376). In the 2008 confidential enquiries into maternal deaths, 42% of direct maternal deaths and 24% of indirect deaths were in women of Black and Minority Ethnic groups (88). Whilst there were multiple factors involved in the cases, this still highlights that women in these communities have increased risks of adverse outcomes.

A study of the Maternity and Gynaecology database at Guy's and St Thomas' Hospital NHS Trust (GSTT) in 2005 (377) evaluated the effects of pre-pregnancy BMI on obstetric outcomes. Obesity was not only an independent risk factor for adverse obstetric outcomes and Caesarean delivery, but a cost analysis also revealed that for every woman requiring a Caesarean delivery instead of a normal delivery there was an additional cost of £1,693. Prevention of obesity will reduce poor obstetric outcomes, positively impact health inequality and reduce costs to the health system. Reducing maternal obesity in these groups can only have added benefit.

Hypothesis

In this proposal, we hypothesise that combined intervention with dietary and physical advice combined with behavioural support will alter dietary and exercise behaviour in overweight and obese women, which will result in weight

reduction of at least 5% in 6 months and have a positive impact on glucose tolerance and wellbeing in 6 months as well as pregnancy rates over one year. We propose a multicentre randomised controlled trial to test this hypothesis.

We will examine the effectiveness and costs of a six-month structured multi-component lifestyle programme for weight loss and improvements in pregnancy. The dietary intervention to be used in this study is based upon reduction of dietary glycaemic load, reduced caloric intake and reduced saturated fats and reduced free sugars. Restriction of dietary 'non-milk extrinsic sugars', especially sugar rich beverages, will not only reduce calorific intake but also improve insulin sensitivity, particularly since the consumption of these beverages is so high amongst women living in the UK (378). Lowering dietary saturated fatty acids will have similar effects and increased consumption of fibre-rich foods or complex carbohydrates will also reduce insulin resistance (379-381); the intervention will also include recommendations for greater physical activity which will promote weight loss and also improve glucose homeostasis.[34] One-to-one counselling will be included as this form of behavioural support increases physical activity and is effective in improving glucose haemostasis and weight loss (210, 382-383). We shall also offer group counselling which can play an important role in a model of combined diet and physical activity intervention (384-386).

Study design

The aims of this research are to:

i. Implement a low glycaemic index dietary intervention alongside increased physical activity for delivery to obese women attending subfertility services.
ii. Assess patient acceptability to the intervention.
iii. Evaluate changes to dietary and physical activity behaviours from 0-6 months.

iv. Evaluate the effectiveness of the intervention using the following outcome measures:
    a. ≥5% weight reduction over 6 months as the primary outcome
    b. A change in insulin sensitivity using the HOMA model from 0-6 months
    c. Pregnancy rate within 12 months with or without fertility treatment
    d. A change in wellbeing and depression scores using the short form 36 version 2 tool
    e. Process evaluation
v. Evaluate the cost effectiveness of the intervention

Population

Women will be recruited through General Practitioners or from among women attending pre-pregnancy planning clinics or gynaecology clinics in the catchment area of Guy's and St Thomas' NHS Foundation Trust, King's College Foundation Trust and Birmingham Women's Hospital. The study population will be women who are overweight and obese, defined according to the WHO criteria.

Ethics

Securing all necessary ethical review and regulatory approvals is planned in the pre-recruitment phase over a period of at least three months through the Local Research Ethics Committees.

With at least 100 women in the active treatment arm, we will be able to estimate the likely rate of compliance to within 10% of the true value with 95% confidence. With regard to pregnancy, this study will have 90% power to detect a trebling in the proportion of women becoming pregnant in the 12-month follow-up period, estimated to be around 10% in the control arm. We will include

pregnancies resulting from both natural and assisted conception, but will stratify the data by type of conception.

Inclusion criteria: Women aged 18-40 years, BMI>/=30kg/m2, healthy women, normotensive women (BP<140/90 mmHg), premenopausal.

Exclusion criteria: Contraindications to dietary intervention or exercise, obese women with other indicators of infertility (e.g. tubal disease or male factor infertility, azoospermia). Medical co-morbidity such as hypercholesterolemia, diabetes, hypertension, stroke or myocardial infarction, systemic lupus erythematosus, chronic infectious disease or overt psychiatric condition. Endocrine disorders such as thyroid dysfunction or hyperprolactinaemia. Medication use or substance misuse. History of bariatric surgery.

Data Collection and Analysis

The study will have three phases; the first two are for data collection and the last is for analysis and writing-up (Figure 1).

PHASE ONE

Months 1 to 6. The first 3 months will consist of preliminary work. The objective of this phase is to assess the appropriateness and acceptability of the intervention in a target group to inform the content and delivery of the intervention. During this period the study will be set up, and semi-structured qualitative interviews will be conducted with 10 obese volunteers from the clinics to assess the acceptability of the proposed intervention (see below). Interviews will explore obese women's beliefs about diet and activity while trying to conceive.

A Standard Operation Procedure Manual, Patient Information Leaflet and training packages to support the intervention delivery will be developed and modified if required and piloted during Phase One.

PHASE TWO

Months 7 to 31. The objective of this phase is to trial a combined diet and activity intervention using established behaviour-changing principles. Randomisation will start in month 7 and continue to month 16, depending on the rate of accrual. Follow-up (at 6 and 12 months following recruitment) will be completed between months 23 and 31.

(i) Recruitment and randomisation

The study will recruit obese women attending these clinics (see later section on sample size and power). We will also recruit women who are planning pregnancy from GP surgeries, gynaecology clinics and fertility clinics. We estimate that 40 new patients per month with anovulatory or unexplained infertility, and who are obese, will be seen. All new patients fulfilling these inclusion criteria will be approached by the nursing sister in charge of the clinic, and given an information leaflet about the study. An opt-in approach will be taken, and the patient will be contacted the next day by the research nurse via telephone and recruited into the study if consent is given and if eligibility is confirmed. All essential information (age, address, postcode, ethnicity, cigarette smoking, GP address) including weight and height and BMI will be recorded on the study database (web-based).

Once consent is given, intervention will be allocated using a randomisation procedure incorporated within the online database to balance treatment groups by ethnicity (ONS categories: Black, Caucasian, Asian, Other), BMI group (30-35kg/m2, 36-40, greater than 40) and age (18-25, 26-30, 31-35, 36-40). The computer software will inform the health trainer of the next study number and

allocation. The research nurse will arrange appropriate visits and training sessions.

(ii) The intervention

We will use an integrated diet and activity behaviour-change intervention which will be delivered over three months followed by a nine-month follow-up period (Figure 1). The intervention will be delivered using a combination of one-to-one (six one-to-one sessions, every other week) and group-based activities (six sessions fortnightly, as well as telephone contacts, SMS text message, e-mail and web-based support provided in a structured and systematic way. Dietary advice will focus on 1) reduction of dietary glycaemic index (GI), 2) reduction of saturated fat and 3) restriction on added sugars. In addition, the diet will be designed as reduced-energy (caloric restricted diet). No specific energy restriction will be prescribed; however, guided information on reduction in portion sizes will be provided with the aim of leading to weight loss. All dietary advice will be given in the context of Department of Health dietary recommendations.

Restriction of added sugars, especially sugar-sweetened beverages, will reduce calorific intake as consumption is high amongst UK women (386). The glycaemic index classifies carbohydrate-containing foods based on their potential to raise blood glucose. The Cochrane review, which investigated the use of low GI diets on weight management, concluded that mean reduction in weight was significantly greater in participants receiving low GI diets compared to control diets (standard low fat diet) (387). This is confirmed in a recent controlled trial in subfertile women (with PCOS) comparing a low-GI energy restricted diet or a conventional energy restricted diet (387). Both diets resulted in weight loss; however, insulin sensitivity and menstrual cyclicity improved to a greater extent following the low GI diet compared to the conventional diet. Reduction of dietary GI will be provided in the context of exchanging high GI foods and drinks for low GI alternatives. Examples include using granary bread or basmati rice in place of white bread or white rice, new potatoes in place of

old potatoes (due to amylose: amylopectin ratio), and recommending low glycaemic index breakfast cereals rather than high. Reduction of added sugars will be achieved both in the context of low glycaemic index and by the exchange of sugar-sweetened beverages for non-sugar containing varieties (386). A reduction in dietary saturated fats will be acheived by instructing participants to reduce consumption of foods with high saturated fat content and partially replacing these with unsaturated fats sources, leading to a reduced total fat intake and concurrently reduced energy intake. Lowering dietary saturated fatty acids has also been shown to improve insulin sensitivity (388).

Dietary compliance will be monitored by a registered dietitian using 24-hour dietary recalls at three timepoints on six occasions (two pre-intervention, two post-intervention and two halfway through the intervention phase, one week apart) and by the use of a validated food frequency questionnaire at three timepoints. Levels of under-reporting will be calculated. Energy, nutrient and GI data will be assessed using dietary analysis software (WISP version 3.0 (Tinuviel software)) to provide percentage and absolute (kilocalorie/ gram/ miligram) energy and nutrient intakes. This will include, for example, dietary intake of folate and other nutrients relevant to pre-conception. The researcher will be blinded to the arm of the study in which the participant is enrolled.

Activity advice will be targeted towards increasing total activity levels and reducing time spent in sedentary activities. Advice will be individualised and tailored to participants' interests and lifestyle and delivered by a trained health facilitator in a community health/leisure centre setting. It is anticipated that walking, in particular, and swimming will be the preferred activities but strategies will also include discussion of how activity can be incorporated into routine lifestyle such as at work and at home. The activity intervention will aim to achieve 30 minutes' moderate intense activity on at least 5 days per week. This is similar to strategies used in other studies and in line with general population guidance (389). They will be given individualised tailored guidance and support to achieve increases in activity and encouraged to set goals. Monitoring will be addressed through accelerometry and self-reporting.

The most practical and widely used form of objective activity measure is the accelerometer, a motion sensor worn over several days. Accelerometers have been used extensively to objectively measure activity levels in diverse free-living settings. Accelerometry has a high degree of validity for quantifying activity duration and intensity, but only moderate correlation with total energy expenditure (390).

(iii) Care in the control group

Patients allocated to the non-intervention group will have routine existing care which consists of referral by the fertility specialist to a hospital-based dietician for diet and healthy lifestyle advice.

(iv) Follow-up and outcome measurement (see later).

Biomarkers of metabolic syndrome

Blood will be sampled through randomisation, three months and six months after the intervention in both arms. Insulin sensitivity will be determined using the HOMA model from and fasting blood glucose and insulin. Markers of metabolic syndrome such as C-reactive protein, lipid levels, blood pressure, waist circumference and blood pressure will be assessed.

PHASE THREE

Months 32 to 35. The objective of this phase of the study is to complete data entry, data checking and analysis.

(i) Data management

All data will be entered onto dedicated study databases shortly after being obtained and will be checked for consistency and accuracy at regular intervals. A member of the research team will be responsible for making back-up copies of the database and ensuring confidentiality of access and storage of both electronic and paper information.

(ii) Analysis

The main analysis will compare proportions of women with the outcomes of interest in the intervention and the control arms of the study. For example, the proportions of women in the two arms of the study who achieved a 5% reduction in weight 6 months following randomisation will be compared. Appropriate adjustments for confounding will be made using multiple regression. Similar analysis will include comparisons of the proportions of women achieving a pregnancy within 12 months of follow-up, and the proportion of women with improved glycaemic control, changes in activity and dietary habits and measures of improved wellbeing 6 months after recruitment. All analysis will be conducted using STATA.

Outcomes

a. The primary RCT outcome will be a 5% reduction in weight 6 months following randomisation to the intervention arm. Weight change will be assessed in study-specific visits to the research nurse at recruitment and every two weeks (at group sessions). In the control group, women's weight will be measured at recruitment and at 6 months.
b. The secondary RCT outcome will be a change in insulin sensitivity using the HOMA model from 0-6 months. Fasting blood glucose and insulin will be evaluated through randomisation, three months and six months after the intervention in both arms, including markers of metabolic syndrome.
c. Evaluation of the intervention acceptability and fidelity of delivery: the success, accessibility and acceptability of the intervention delivery and compliance with the protocol of the intervention will be assessed by monitoring attendance at contact points and via telephone calls. Semi-structured qualitative interviews will be conducted for the proposed sample of around 20 in the intervention group and 10 in the control group to obtain feedback regarding interviews, aiming to explore the women's views, their understanding of the advice provided in both arms of the trial, and their

experience of the implementation. Data will be taped and transcribed and analysed using framework analysis using Nvivo CAQDAS package.

d. Progesterone: At day 21 post-menstruation plasma progesterone will be measured as part of routine clinical care prior to the intervention and six months through randomisation in all women.
e. All pregnancies based on first trimester ultra-sound and fertility treatments occurring in the year following randomisation will be recorded for all women. Data will be obtained via telephone interview and transcription from clinic records. Term live birth rate and adverse pregnancy outcomes will be evaluated.
f. Wellbeing will be assessed prior to randomisation and 6 months after the intervention in all women using the SF36 health status measure. A change in wellbeing and depression scores using the short form 36 version 2 tool will be evaluated.
g. An estimate of health care costs (delivery of the intervention only) will be evaluated. The whole process and cost-effectiveness of the intervention will be evaluated.

Budget and justification

The total requested budget is £486,699.83. A detailed description of the budget is outlined in Appendix 3.

Research nurses are required to identify, recruit and follow up eligible women for the study. Due to the pressure of services provision, clinic nurses cannot fulfil these roles. The clinics run on different days for the 2 London-based centres; hence, the research nurse will work at both units. A full-time salary is requested for the two research nurses. Two health trainers are required to deliver the intervention in Phase Two. A nutritionist and research assistant with nutritional background will be employed on a part-time basis to analyse the dietary and physical activity questionnaires. Statistical support is requested at the onset of the study (Phase 1) for writing the data analysis plan, and in the

final stage to work with the nutritionist and physical activity assistants, and to undertake the final analyses. All samples will be analysed; therefore, technical assistance is requested for the final stages of the study. Database design and maintenance cost is requested as well as costs for consumables.

The findings of this trial will provide an evidence-based intervention to facilitate weight loss in obese women, which we believe is likely to be generalisable, at least to urban populations in the UK and other countries. This will benefit the NHS because not only will it improve the women's health, but it will also improve their fertility, particularly for those with obesity-related anovulatory cycle infertility. This will avoid assisted reproductive techniques, which can cost the NHS large amounts of money with their associated risk of multiple pregnancy and preterm delivery and the need for neonatal special care cots. Those who become pregnant with a reduced BMI as a result of the intervention will benefit from reduced risk of miscarriage, gestational diabetes, pre-eclampsia, macrosomia, shoulder dystocia and difficult deliveries, Caesarean section, and long hosptial stays. For the babies born, a reduced risk of macrosomia and associated insulin resistance implies a lower probability of obesity in childhood, and in turn, in adult life. A reduction in this transgenerational obesity risk has profound implications for improvements in health, and reduced costs to the NHS of obesity-related morbidity.

Supporting this trial, which has incorporated a detailed user and stakeholder consultation, could ensure a feasible, effective, multi-component community-based intervention to address obesity in women of reproductive age.

Sample size and power calculation

This study is powered to be sufficient to detect a statistically significant difference in the proportion of women who achieve a 5% reduction in weight in the intervention arm, compared to the control arm, after 6 months' follow-up. The rationale for using a 5% weight reduction is that this has been shown to

improve fertility (44, 208, 369, 380). Gadde et al. assessed the efficacy and safety of two doses of phentermine plus topiramate controlled-release combination as an adjunct to diet and lifestyle modification for weight loss and metabolic risk reduction in individuals who were overweight and obese, with two or more risk factors. Twenty-one percent of subjects randomised to placebo achieved at least a 5% weight loss. Rates in the active arm were 62% and 70%, depending on the dose of phentermine (391). We believe similar rates can be achieved by a lifestyle intervention (392). We therefore set out to achieve at least a doubling of the rate of 5% weight loss in the active arm (21% compared to 42%). Complete data on 111 women in each arm would give 90% power to detect such an effect at the 5% significance level. Eleven women per arm are needed. To allow for a maximum 20% loss to follow-up, we will recruit 278 in total (139 in each arm). This is fewer than we hope to achieve, but represents an estimated minimum clinically important difference.

Timetable of the Project (Gantt chart)

The detailed timetable is outlined in Appendix 2.

Phase 1: 0 - 6months.

Preliminary and pilot phase. To determine the best approach and delivery for the proposed intervention. To develop and standardise the content and delivery method and assess the feasibility and acceptability to obese women and providers with a view to optimising the intervention for use in Phase 2.

Phase 2: 7-31 months.

RCT of overweight and obese women

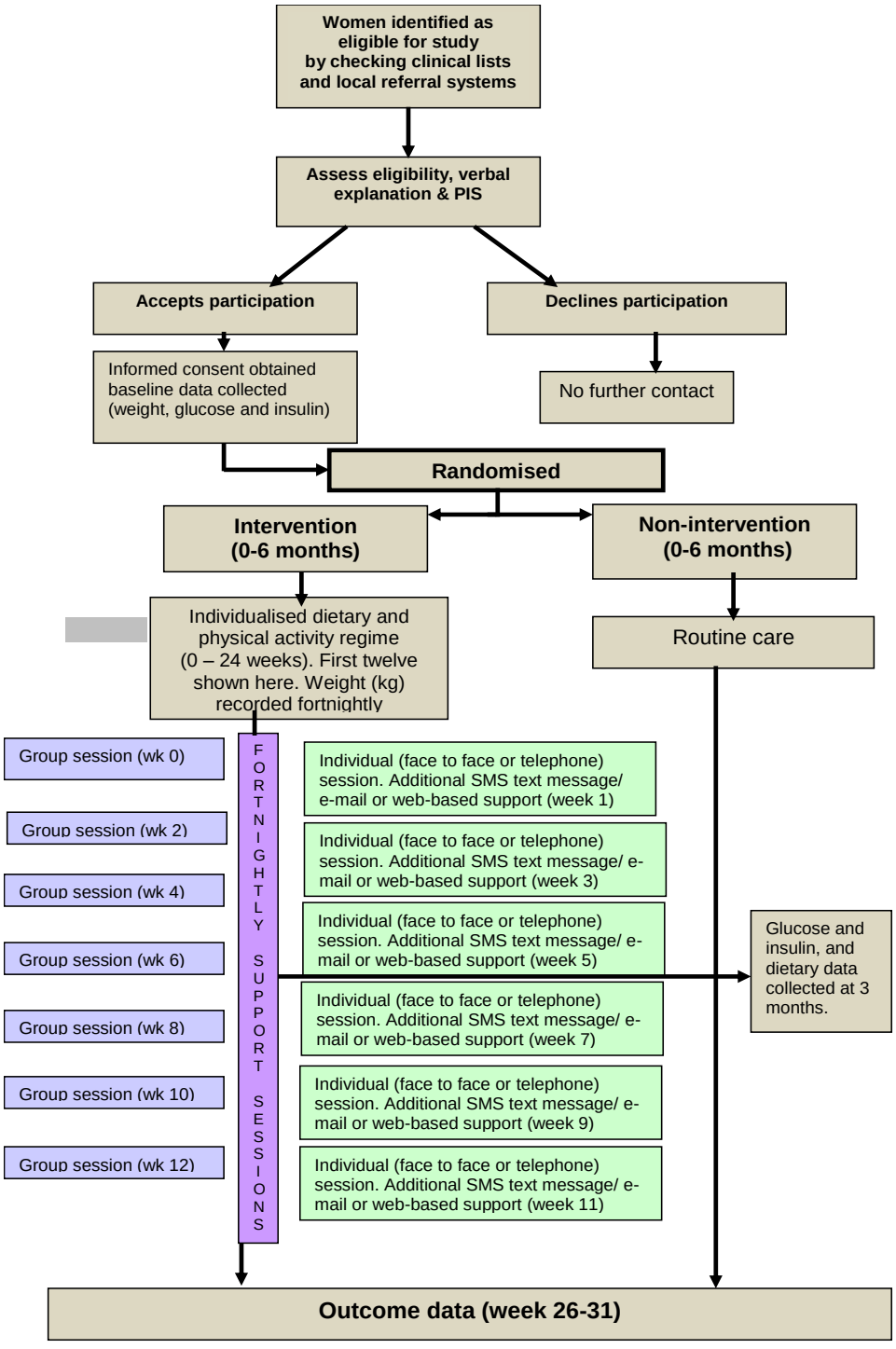
Phase 3: 32-35 months. Analysis and report writing.

With at least 100 women in the active treatment arm, we will be able to estimate the likely rate of compliance to within 10% of the true value with 95% confidence. With regard to pregnancy, this study will have 90% power to detect a trebling in the proportion of women becoming pregnant in the 12-month follow-up period, estimated to be around 10% in the control arm. We will include pregnancies resulting from both natural and assisted conception, but will stratify the data by type of conception.

Conflict of interest

There are no conflicts of interests to declare.

Figure 1: Protocol Timeline



Appendix D: Lambeth Early Action Partnership

Lambeth Early Action Partnership

Bid for the BIG Lottery Fulfilling Lives; Better Start bid

Executive Summary

Our vision is for Lambeth to be the best place in the world for children to be born and grow up and we will accept no less than for all of our children to be healthy, happy, confident, safe and able to achieve their aspirations.

We, the ***Lambeth Early Action Partnership,*** are delighted to have the opportunity to submit our LEAP partnership bid which we believe offers a tremendous opportunity to transform the lives of children and families in Lambeth. The Lambeth Early Action Partnership comprises parents and carers, their babies, infants and children, practitioners, academics, community groups and senior leaders from across the voluntary sector, local authority, police, health and schools with the National Children's Bureau as the lead voluntary sector organisation.

The vision reflects our belief that in order for babies and children to be healthy, happy and confident we need to look at all aspects of their lives. It is impossible to separate the social and emotional development of babies and children, their language and communication skills and their health from the wellbeing of their parents, their social networks, the strength of their communities and the wider environment. Therefore our vision is to work together following a public health approach to improve all aspects of life for children, their parents and the wider community.

The LEAP area comprises four neighbouring wards in the centre of the borough: Coldharbour, Stockwell, Tulse Hill and Vassall. They are home to a fifth of Lambeth's population and a quarter of our children under 18 (25% of whom are under four). Three quarters of children under-18 in the LEAP area are from black and minority ethnic communities and over half of five year olds have English as an additional language. Social cohesion is an issue that we want to address through the LEAP programme as Lambeth becomes increasingly diverse in terms of ethnicity and language and more polarised in terms of socio-economic groups.

Through our transformational Strategy we will reduce inequalities and improve health, social and economic outcomes so that all of our children have the opportunity to lead fulfilling lives. Around 1,000 babies are born each year in our LEAP wards and the number of under-fives is expected to increase by 10% in the next decade. Our focus is improving the lives of over 10,000 babies who will be born in the ten-year period of the LEAP programme.

Our agreed priorities are:

- **Diet and nutrition**
  - Improve breastfeeding initiation and continuation.
  - Reduce childhood obesity.
  - Reduce maternal obesity.
- **Social and emotional development**
  - Reduce the prevalence and impact of domestic violence and injury.
  - Improve social and emotional development and close the gaps for under-achieving groups.
- **Communication and language**
  - Improve level of communication and language development and close the gaps for under achieving groups.
- **Systems change**
  - Family Centred support: families have a good experience of joined up support with consistent messages and relationships based on mutual respect.
  - Governance: organisations work together around the family and shared information supports this.
  - Prevention: resources are focussed on prevention with parents and the community as active participants and a focus on a wide range of factors affecting family health and wellbeing

Over the ten year programme we will:

- improve the rates of children achieving a good level of social and emotional development in the target wards from 45% to 81%.
- improve the rates of children achieving a good level of communication and language development in the target wards from 63 % to 95%
- eliminate the gaps in achievement for boys, children on free school meals and particular ethnic groups for social and emotional development and communication and language development.
- reduce obesity rates at school entry by from 15% to 9%
- halt rising rates of obesity for all groups at age 11 in the target wards.

We have developed a transformative strategic approach which is based on six key elements:

- Community champions who support new parents to improve the better start outcomes and reduce isolation.
- A workforce which includes community champions and understands the better start outcomes and how to form respectful, positive and equal relationships with parents.
- Developing the role of General Practice as the trusted central point for child health with continual responsibility from birth to under-4 in liaison with a range of other professionals.
- A commitment to shift resource to early intervention from specialist services.
- Evidence based programmes and innovation, co-produced and evaluated with families that will provide learning to disseminate across the borough and more widely.

- An ambitious public health approach and a gold standard enhanced Healthy Child Programme which is accessible for all.

The LEAP partnership has a commitment to shift 3% of total spend on children and babies) into early intervention as the financial returns from Big Lottery investment are realised. The Lambeth fund map gives us a detailed understanding of how we currently invest in children's services and the 3 % equates to approximately £3m per annum, starting from when cost benefits are realised. This is a significant shift that shows our commitment to lasting systems change. We propose to jointly fund our planned interventions in the first three years of the Programme to ensure that improved outcomes and the benefits of our interventions are secured at pace.

We firmly believe that we have the means to deliver our vision because of:

- The strength and vitality of our partnership across local people and professionals and across statutory and third sector organisations
- the assets we have within and available to our community
- the commitment of our leadership, at all levels
- our good understanding of the issues to be addressed and of the evidence of what works
- our experience and capability to deliver transformational change and drive improvement

In the first 18 months our commitment is that the LEAP programme will make an immediate and visible impact.

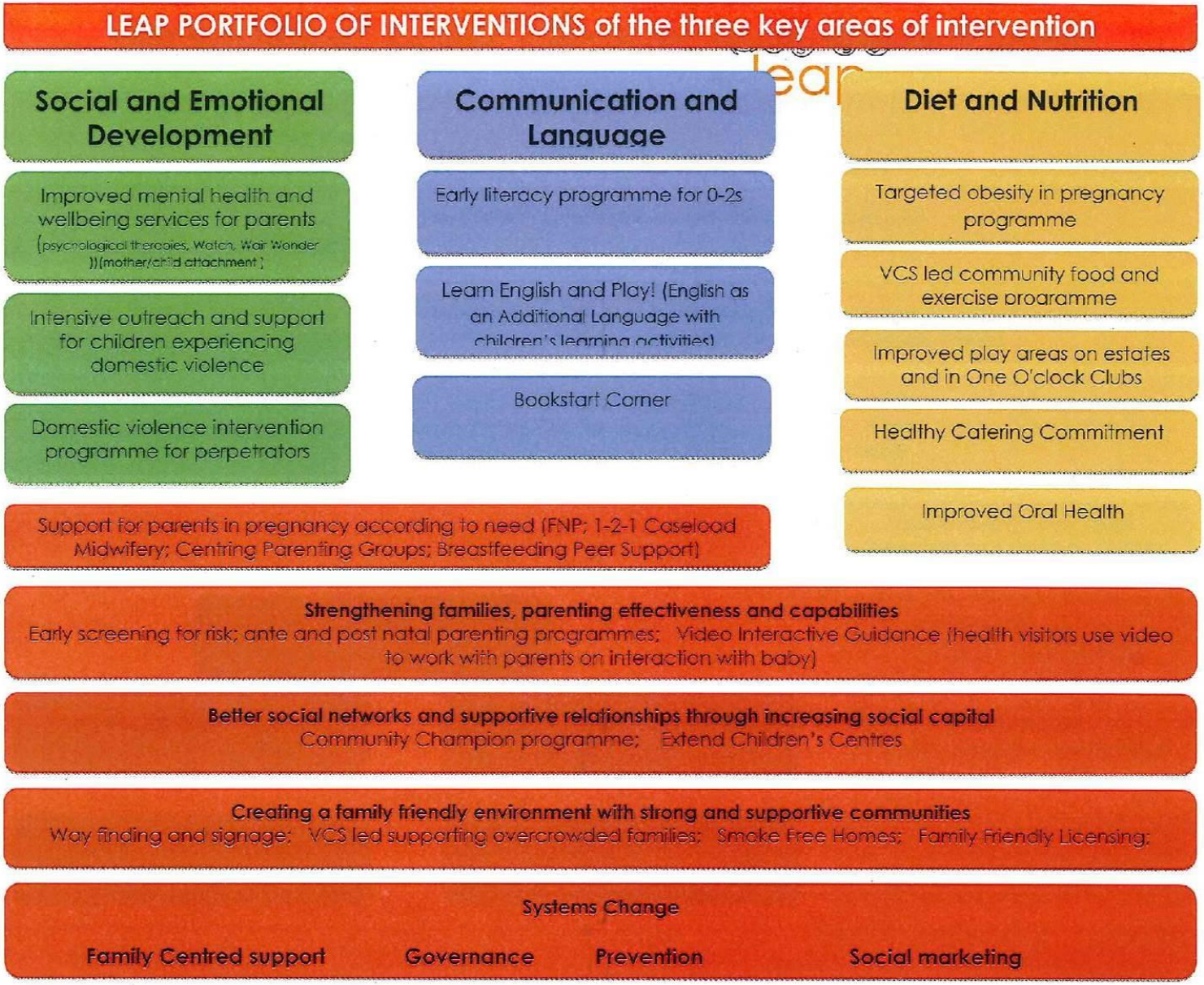
- 150 parents will be invited to attend an ante natal or post natal parenting programme.
- 84 obese pregnant women will be invited to take part in the programme to reduce risk of complication in pregnancy and birth.
- 270 of our workforce will be trained in Brief Encounters to support parents experiencing relationship difficulties.
- 169 of our workforce will be trained in the Family Partnership Model to develop 'helper' qualities and skills that enable families to overcome difficulties and build strengths and resilience.
- 234 parents experiencing mild to moderate mental health problems will receive support through our community service
- 150 parents and their babies and children will receive support through the Watch, Wait, Wonder programme, to improve parent child bonding
- 75 parents with English as an additional language will complete a tailored LEAP course
- 120 babies and young children will benefit from the increased support around early language and literacy.
- 104 community champions will be recruited and trained to support parents and families to be healthy, happy and confident

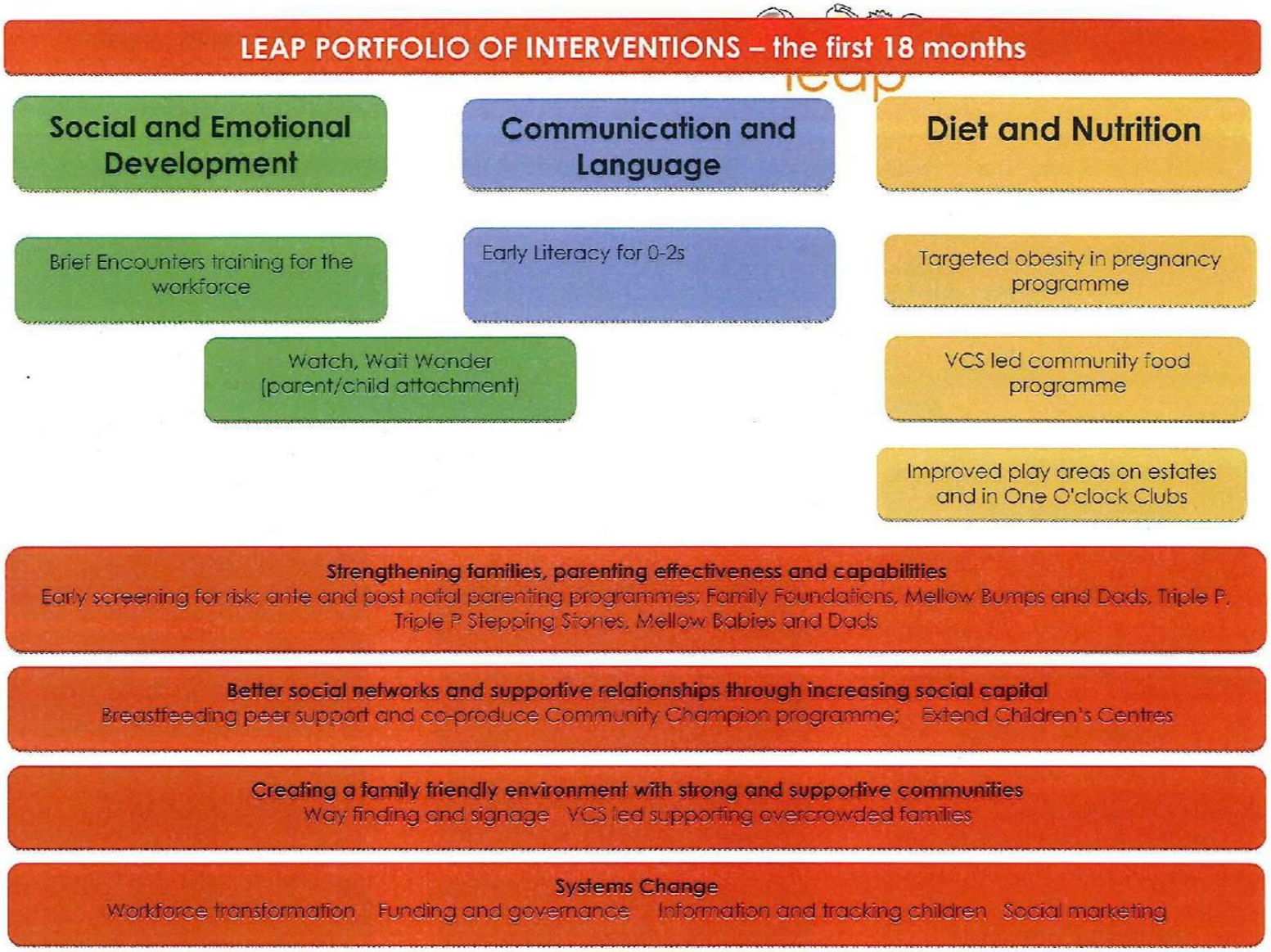
- 400 families will be offered support to alleviate the impact of living in overcrowded accommodation.
- All first time young parents in the area will be offered the Family Nurse Partnership programme by the end of the first 18 months.
- New play areas on 4 estates and 4 one o clock clubs will be created and new spaces in 5 children's centres will be built.
- 'Way-finding' will help families find services through highly visible and imaginative signage throughout the LEAP area, linking early years and health facilities to each other.
- People who live and work in the LEAP area will be told about the programme and invited to participate.

We would like to express our thanks to the Big Lottery and to the Social Research Unit at Dartington. We have found the process itself rewarding and it has contributed significantly to our approach. We have built a true, consensual and lasting partnership with commitment and collaboration at all levels with a strong and central voice for parents.

"We've been developing partnership working here in Lambeth for quite some time ... but I've never encountered a process like this; people from all sorts of backgrounds, and everyone talking as equals. To have the on-the-ground observations of the parents has been very valuable." Ruth Wallis, Director of Public Health

We are all very excited about our bid. We are looking forward to hearing your feedback and to engaging with you further in May. In the meantime, for further information on our bid please contact Annamarie Hassall, NCB Director of Programmes (ahassall@ncb.org.uk).


LEAP PORTFOLIO OF INTERVENTIONS of the three key areas of intervention
Social and Emotional Development
Improved mental health and wellbeing services for parents (psychological therapies, Watch, Wait Wonder)(mother/child attachment)
Intensive outreach and support for children experiencing domestic violence
Domestic violence intervention programme for perpetrators
Communication and Language
Early literacy programme for 0-2s
Learn English and Play! (English as an Additional Language with children's learning activities)
Bookstart Corner
Diet and Nutrition
Targeted obesity in pregnancy programme
VCS led community food and exercise programme
Improved play areas on estates and in One O'clock Clubs
Healthy Catering Commitment
Improved Oral Health
Support for parents in pregnancy according to need (FNP; 1-2-1 Caseload Midwifery; Centring Parenting Groups; Breastfeeding Peer Support)
Strengthening families, parenting effectiveness and capabilities
Early screening for risk; ante and post natal parenting programmes; Video Interactive Guidance (health visitors use video to work with parents on interaction with baby)
Better social networks and supportive relationships through increasing social capital
Community Champion programme; Extend Children's Centres
Creating a family friendly environment with strong and supportive communities
Way finding and signage; VCS led supporting overcrowded families; Smoke Free Homes; Family Friendly Licensing;
Systems Change
Family Centred support
Governance
Prevention
Social marketing


LEAP PORTFOLIO OF INTERVENTIONS – the first 18 months
Social and Emotional Development
Communication and Language
Diet and Nutrition
Brief Encounters training for the workforce
Early Literacy for 0-2s
Targeted obesity in pregnancy programme
Watch, Wait Wonder (parent/child attachment)
VCS led community food programme
Improved play areas on estates and in One O'clock Clubs
Strengthening families, parenting effectiveness and capabilities
Early screening for risk; ante and post natal parenting programmes; Family Foundations, Mellow Bumps and Dads, Triple P, Triple P Stepping Stones, Mellow Babies and Dads
Better social networks and supportive relationships through increasing social capital
Breastfeeding peer support and co-produce Community Champion programme; Extend Children's Centres
Creating a family friendly environment with strong and supportive communities
Way finding and signage VCS led supporting overcrowded families
Systems Change
Workforce transformation Funding and governance Information and tracking children Social marketing

Appendix E: Search Strategy

Box 1 Search strategy
1. *pregnancy/
2. pregnan$.ti,ab.
3. matern$.ti,ab.
4. gravid$.ti,ab.
5. mother.ti,ab.
6. parent.ti,ab.
7. or/1–5
8. or/1–6
9. *obesity/ or *obesity, morbid/
10. obes$.ti,ab.
11. *Weight Gain/ph [Physiology]
12. (overweight or over weight or weight gain).ti,ab.
13. (bmi or body mass index).ti,ab.
14. or/9–13
15. (cohort or observation$ or prospective or
longitudinal).ti,ab.
16. 7 and 14
17. 8 and 14
18. 16 and 15
19. 17 and 15
20. animal/
21. humans/
22. 20 not (20 and 21)
23. 18 not 22
24. 19 not 22
25. fertil$.ti,ab.
misc
hypertension

pre-eclampsia
diabetes
thromboembolism
caesarean section
postpartum haemorrhage
anaesthetics
H1N1
Intensive care admission
28. or/25–27
29. 23 not 28
30. 24 not 28
31. limit 29 to english language
32. limit 30 to english language
33. limit 31 to year = 1990–2013
34. limit 32 to year = 1990–2013

Appendix F: A complex intervention to improve pregnancy outcomes in obese women; the UPBEAT randomised controlled trial

Briley *et al. BMC Pregnancy and Childbirth* 2014, **14**:74
http://www.biomedcentral.com/1471-2393/14/74

BMC Pregnancy & Childbirth

STUDY PROTOCOL Open Access

A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial

Annette L Briley[1], Suzanne Barr[2], Shirlene Badger[1], Ruth Bell[3], Helen Croker[4], Keith M Godfrey[5,6], Bridget Holmes[2], Tarja I Kinnunen[3], Scott M Nelson[7], Eugene Oteng-Ntim[1], Nashita Patel[1], Stephen C Robson[8], Jane Sandall[1], Thomas Sanders[2], Naveed Sattar[7], Paul T Seed[1], Jane Wardle[4] and Lucilla Poston[1*]

Abstract

Background: Despite the widespread recognition that obesity in pregnant women is associated with adverse outcomes for mother and child, there is no intervention proven to reduce the risk of these complications. The primary aim of this randomised controlled trial is to assess in obese pregnant women, whether a complex behavioural intervention, based on changing diet (to foods with a lower glycemic index) and physical activity, will reduce the risk of gestational diabetes (GDM) and delivery of a large for gestational age (LGA) infant. A secondary aim is to determine whether the intervention lowers the long term risk of obesity in the offspring.

Methods/Design: Multicentre randomised controlled trial comparing a behavioural intervention designed to improve glycemic control with standard antenatal care in obese pregnant women.
Inclusion criteria; women with a BMI ≥30 kg/m^2 and a singleton pregnancy between 15^{+0} weeks and 18^{+6} weeks' gestation. Exclusion criteria; pre-defined, pre-existing diseases and multiple pregnancy. Randomisation is on-line by a computer generated programme and is minimised by BMI category, maternal age, ethnicity, parity and centre.
Intervention; this is delivered by a health trainer over 8 sessions. Based on control theory, with elements of social cognitive theory, the intervention is designed to improve maternal glycemic control. Women randomised to the control arm receive standard antenatal care until delivery according to local guidelines. All women have a 75 g oral glucose tolerance test at 27^{+0}- 28^{+6} weeks' gestation.
Primary outcome; Maternal: diagnosis of GDM, according to the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria. Neonatal; infant LGA defined as >90th customised birth weight centile.
Sample size; 1546 women to provide 80% power to detect a 25% reduction in the incidence of GDM and a 30% reduction in infants large for gestational age.

Discussion: All aspects of this protocol have been evaluated in a pilot randomised controlled trial, with subsequent optimisation of the intervention. The findings of this trial will inform whether lifestyle mediated improvement of glycemic control in obese pregnant women can minimise the risk of pregnancy complications.

Trial registration: Current controlled trials; ISRCTN89971375.

Keywords: Study protocol, Pregnancy, Obesity, Complex intervention, Randomised controlled trial, Glycemic index, Physical activity, Gestational diabetes, Large for gestational age

* Correspondence: lucilla.poston@kcl.ac.uk
[1]Division of Women's Health, Women's Health Academic Centre, King's College London and King's Health Partners, 10th floor, North Wing, St. Thomas' Hospital, London SE1 7EH, UK
Full list of author information is available at the end of the article

Background

The rise in the global incidence of obesity has reached pandemic proportions [1]. In 2008, the World Health Organisation (WHO) estimated there were 1.5 billion individuals with a body mass index (BMI) ≥ 25 kg/m^2 including nearly 300 million obese women (BMI ≥ 30 kg/m^2) [2]. The United Kingdom (UK) has seen a sharp increase in the proportion of obese women; as reported in a recent survey, approximately one in five women aged between 16 and 44 are obese [3]. The UK Confidential Enquiry into Maternal and Child Health identified that overweight and obesity, was either directly or indirectly the cause of over half of maternal mortality [4]. The adverse effects of obesity on reproductive health and childbearing are manifold. Obesity reduces fertility, and in pregnancy is associated with a heightened risk of gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy including pre-eclampsia, and failure to progress in labour. Caesarean section rates are high, and infants of obese mothers are at greater risk of congenital malformation, large for gestational age at delivery (LGA) (>90th centile), macrosomia, shoulder dystocia and stillbirth. Following delivery, obese women are more likely to suffer a postpartum haemorrhage, and have longer hospital stays than women with a normal BMI (18.5-24.9 kg/m^2) [5,6]. The effects of obesity may extend beyond health in pregnancy; increasing evidence suggests that the children of obese women or of those whose gestational weight gain (GWG) was excessive, may be at greater risk of obesity because of antenatal exposure to adverse metabolic influences *in utero*, or in the early postnatal period [7,8].

In the UK, in contrast to the United States (US), women are no longer routinely weighed in pregnancy, except at their first antenatal appointment. The US Institute of Medicine (IOM) guidelines for weight gain during pregnancy provide recommendations for women according to their pre-pregnancy BMI, recommending that obese women should gain less weight in pregnancy (11-20 lb; 5-9 kg) than those with a lower pre-pregnancy BMI [9]. This advice is based on observational studies suggesting improved outcomes with lower weight gain. The UK National Institute for Health and Clinical Excellence (NICE) guidelines on weight management in pregnancy concluded that more evidence of improved outcomes from interventional studies is required before the US or similar guidelines for limitation of GWG are adopted [10]. Whilst review of the literature suggests that intervention studies designed to limit GWG may sometimes be effective in achieving a reduction in GWG, there is at present, no evidence for improvement of pregnancy outcome amongst obese women. However most studies, including those in overweight and obese pregnant women, have been small, not powered for clinical outcomes and have had limitations in the design [11,12].

The role of insulin resistance in obese pregnancies

An alternative approach to restricting GWG is to focus on the adverse clinical outcomes associated with obesity, and to develop interventions which are directly associated with known underlying mechanisms. A pre-pregnancy BMI ≥30 kg/m^2 irrespective of the amount of weight gained during pregnancy, is the most important independent determinant of the risk of caesarean section, delivery of a LGA infant and postpartum weight retention [13]. Also, the evidence linking GWG with GDM, in contrast to the strong association with pre-pregnancy BMI, is relatively weak [14]. This is, at least in part, likely to be a reflection of the strong association between maternal fat mass and insulin resistance [7]. There is a physiological increase in insulin resistance during normal pregnancy and the obese pregnant woman is at greater risk of developing GDM. Maternal hyperglycemia and, more recently, maternal hypertriglyceridemia are strongly implicated in the development of fetal macrosomia [15-18]. Using the method of continuous blood glucose monitoring, Harmon *et al.* have shown, as might be anticipated, that obese pregnant women have an exaggerated *post prandial* glucose response [17]. As the magnitude of the *post prandial* response was directly implicated in increasing fetal adiposity and birth weight through fetal hyperinsulinemia, a dietary intervention focusing on reducing *post prandial* hyperglycemia by lowering the dietary glycemic load could improve maternal glucose control, reduce the incidence of GDM and lower the incidence of LGA infants. Similarly, pre-eclampsia is associated with maternal insulin resistance, and improved glucose homeostasis might lower the risk of pre-eclampsia in obese women [19].

Improving glycemic control in pregnancy

Specific dietary advice and increased physical activity could contribute to improved maternal glucose homeostasis [20]. In a study of 50 obese Danish women designed to limit GWG, Wolff *et al.* [21] found that an intense dietary regime (10 one-hour sessions with a dietician) focusing on healthy eating, resulted in a reduction of plasma insulin compared to women in the control arm of the study. Another study reported that a diet and exercise regime led to a reduction in GWG and a decrease in the incidence of GDM in 126 overweight and obese Australian women [22], but no difference in birth weight (3.5 kg versus 3.4 kg). In non-obese women with mild GDM, in whom improved glucose homeostasis is achieved through a strict regime of dietary intervention and insulin treatment when required, a reduction in the risk of adverse pregnancy outcome is achievable, as shown in two randomised controlled trials [23,24]. Higher levels of physical activity in normoglycemic pregnant women and those with GDM have also been shown to improve insulin sensitivity [7], but

limited data of adequate power is available for the obese pregnant population. A recent meta-analysis of eight prenatal physical activity intervention studies however, showed that there was a lack of consistent evidence regarding the benefits of exercise combined or not combined with dietary advice for improving glucose tolerance in obese pregnant women, which was interpreted to reflect the limited power of current evidence and poor intervention compliance [25].

Systematic review of the literature

Louie *et al.* conducted a systematic review of the influence of lowering dietary glycemic index (GI) in pregnancies across all BMI categories [26]. Of the eight studies included, two suggested that a low GI diet can reduce the risk of LGA infants in healthy pregnancies, but one reported an increase in small for gestational age (SGA) infants. In the three studies in which pregnancies were complicated by GDM the evidence supported the overall advantages of a low GI diet. This review recommended that until larger scale intervention trials are completed, a low GI diet should not replace the current dietary recommendations from government and health agencies, and that further research regarding the optimal time to start a low GI diet for maximum protection against adverse pregnancy outcomes is warranted.

In a systematic review of nine randomised trials including 743 overweight and obese pregnant women, Dodd *et al.* reported that there was no significant effect of interventions designed to limit GWG on weight gain or on delivery of a LGA infant [11]. In a later systematic review of thirteen randomised clinical trials of lifestyle interventions in overweight and obese pregnant women (n = 1228) we concluded that there was a modest influence on GWG (-2.21 kg; 95% confidence interval (CI) -2.86 kg to -1.59 kg), but no significant effect on any relevant clinical outcome [27]. We have also reviewed dietary and physical activity interventions in normal BMI and obese pregnant women (n = 1656 women) for the purpose of limiting GWG; in a systematic review we assessed 12 trials. Overall, diet and physical activity change was effective in reducing GWG, but there was considerable heterogeneity in outcomes [28]. The analysis highlighted differences in sample characteristics and aspects of intervention design, content, delivery and evaluation which might explain variation in effectiveness. Furthermore, failure to evaluate changes in behaviour or its psychological determinants could have obscured identification of the processes by which weight change is effective, and limited the ability to discern active intervention ingredients. We concluded that interventions should be more systematically designed and built on insights from behavioural science.

More recently, Thangaratinam *et al.*, in a meta-analysis evaluated 44 clinical trials using lifestyle or dietary interventions or a combination of both during pregnancy across all BMI ranges, found a reduction in GWG (1.42 kg reduction) with any intervention in comparison to the control [12]. Physical activity alone, was associated with a reduction in birth weight (mean difference -60 g, 95% CI -120 g to -10 g). Interventions based on diet were the most effective, being associated with reductions in maternal GWG (3.84 kg, 95% CI 2.45 to 5.22 kg) and a modest improvement of obstetric outcomes. However, the combination of intervention methods did not result in a reduction in the incidence of LGA between the groups (RR 0.85, 95% CI 0.66 to 1.09). Amongst obese women, there was no evidence for an improvement of any clinical outcome. In an editorial, to this review, we highlighted that there remains a paucity of information regarding intensity, duration and compliance of the interventions, all of which could account for the lack of efficacy, as well minimal evidence for any effect of the intervention on the targeted behaviours. If the intervention does not achieve a change of behaviour in the anticipated direction, it follows that there will be no influence on clinical outcomes [29].

The protocol presented here describes a complex behavioural intervention comprising dietary and physical activity changes which we have developed with the aim of improving glycemic control in obese pregnant women. The intervention is based on established control theory with elements of social cognitive theory [30,31]. The primary hypothesis being tested is that an antenatal intervention package of low glycemic dietary advice combined with advice on increased physical activity will reduce the incidence of maternal GDM and LGA infants. A secondary hypothesis is that the intervention will reduce the risk of obesity in the child. Prior to undertaking a trial adequately powered to investigate clinical outcomes, we completed a pilot study (n = 183 women) to determine whether the intervention changed dietary and physical behaviours as anticipated [32]. This pilot study showed that diet but not physical activity (as objectively measured) changed with the intervention and that all aspects of the protocol were feasible. A process evaluation led to optimisation of intervention delivery. The trial steering committee recommended continuation with recruitment for the randomised controlled trial (RCT), and it was decided that the physical activity aspect of the intervention should remain, as this follows standard guidelines for pregnant women [33].

Methods/Design

Study design

Multicentre RCT. For participating centres see the UPBEAT trial website: http://www.medscinet.net/upbeat/.

Ethical approval

NHS Research Ethics Committee approval was obtained in all centres (UK IRAS integrated research application

system; reference 09/H0802/5). *Inclusion Criteria:* Women with a singleton pregnancy, 15^{+0}- 18^{+6} weeks' gestation and body mass index ≥30 kg/m^2 at first antenatal appointment.

Exclusion criteria

Women unable or unwilling to give informed consent; $<15^{+0}$ weeks or $>18^{+6}$ weeks' gestation; essential hypertension requiring treatment either pre-pregnancy or in index pregnancy; pre-existing renal disease; systemic lupus erythematosus; antiphospholipid syndrome; sickle cell disease; thalassemia; coeliac disease; thyroid disease; current psychosis; multiple pregnancy; currently prescribed metformin.

The protocol for the study is shown in Figure 1.

Trial entry

Eligible women are identified in antenatal clinics and from general practitioner and midwives referral letters. Verbal and written information is given. Research midwives contact potential recruits, obtain verbal consent and arrange the first appointment. For those who decline to participate, permission is sought to collect minimal pregnancy outcome data.

15^{+0}-18^{+6} weeks' appointment: baseline and randomisation

At the first appointment, written informed consent is obtained. Baseline demography, medical and family history and current pregnancy information is collected. A short validated food frequency questionnaire (FFQ) [34] is completed to evaluate dietary glycemic load, dietary glycemic index, saturated fat and total sugar intake and other dietary variables. Women are weighed, pulse and blood pressure are checked, anthropometric measurements obtained and blood and urine samples taken. Behavioural and psychological measures include; the EuroQuol Quality of life (EQ-5D) [35], the Edinburgh Postnatal Depression Scale (EPDS) [36], the International Physical Activity Questionnaire (IPAQ) [37], and a 'binge eating' screening questionnaire [38]. Randomisation occurs at this visit via a secure internet based data management system (MedSciNet™), which is the repository for all trial data. The randomisation schedule is minimised according to ethnicity, parity (0 *versus* ≥ 1), age, BMI (BMI 30-34.9 kg/m^2 *versus* 35-39.9 kg/m^2 and >40 kg/m^2) and centre. Randomised women are allocated sequential study numbers, regardless of allocation to the intervention or standard care group.

Intervention

Women randomised to the intervention group attend a one-to-one interview with the health trainer, which includes discussion of the potential benefits of attending the weekly sessions. In the UK, health trainers help people to change their behaviour to achieve personal choices and goals, and generally do not have pre-specified health professional qualifications, but relevant experience. All health trainers in this trial receive study-specific training in all aspects of the intervention and ongoing support throughout the trial. Women in the intervention group receive a participant handbook, a DVD of an exercise regime safe for pregnancy, a pedometer and a logbook for recording weekly SMART (Specific, Measurable, Achievable, Relevant and Time specific) goals, and steps as assessed by pedometer. They are invited to attend 8 sessions with the health trainer on a weekly basis, each lasting 1 to 1.5 hours. Women are encouraged to attend all sessions, but are strongly recommended to attend a minimum of five. For the sessions not attended in person, the health trainer covers the session material by phone or email. Attendance and coverage of session material are documented in the study database. Following a review of the dietary and physical intervention, each session is designed to focus on different approaches in achieving the goals set. These include SMART goals, self monitoring, and provision of feedback regarding goal attainment, identification and problem solving of barriers, enlisting social support and providing opportunities for social comparison. At each session, review of the previous weeks' goals is undertaken.

The dietary intervention aims to promote a healthier pattern of eating, similar to that used in diabetes prevention studies, but does not aim to restrict energy intake. In order to decrease the glycemic load, dietary advice includes exchanging starchy foods with a medium/high GI for those with a lower dietary GI, and restricting the consumption of sugar-sweetened beverages (including fruit juice) but not fruit. Participants are also given dietary advice to reduce saturated fatty acid intake.

Advice regarding physical activity focuses on increasing the daily step count incrementally, and being more active in daily life. Pedometers are used for monitoring and motivation. The emphasis is on walking at a moderate intensity with additional options included, especially for those who are already engaging in some physical activity. This degree of activity accords with that recommended by the UK Royal College of Obstetricians and Gynaecologists [33].

Standard care

Women randomised to the standard care group attend routine antenatal care according to local health care provision. UK recommendations state that women with a BMI ≥ 30 kg/m^2 should be advised by a health professional at the earliest opportunity of the risks of obesity in pregnancy and be given advice about a healthy diet and safe levels of physical activity. Recommendations for referral to a registered dietician are infrequently implemented. Women are only weighed at their first antenatal visit [10].

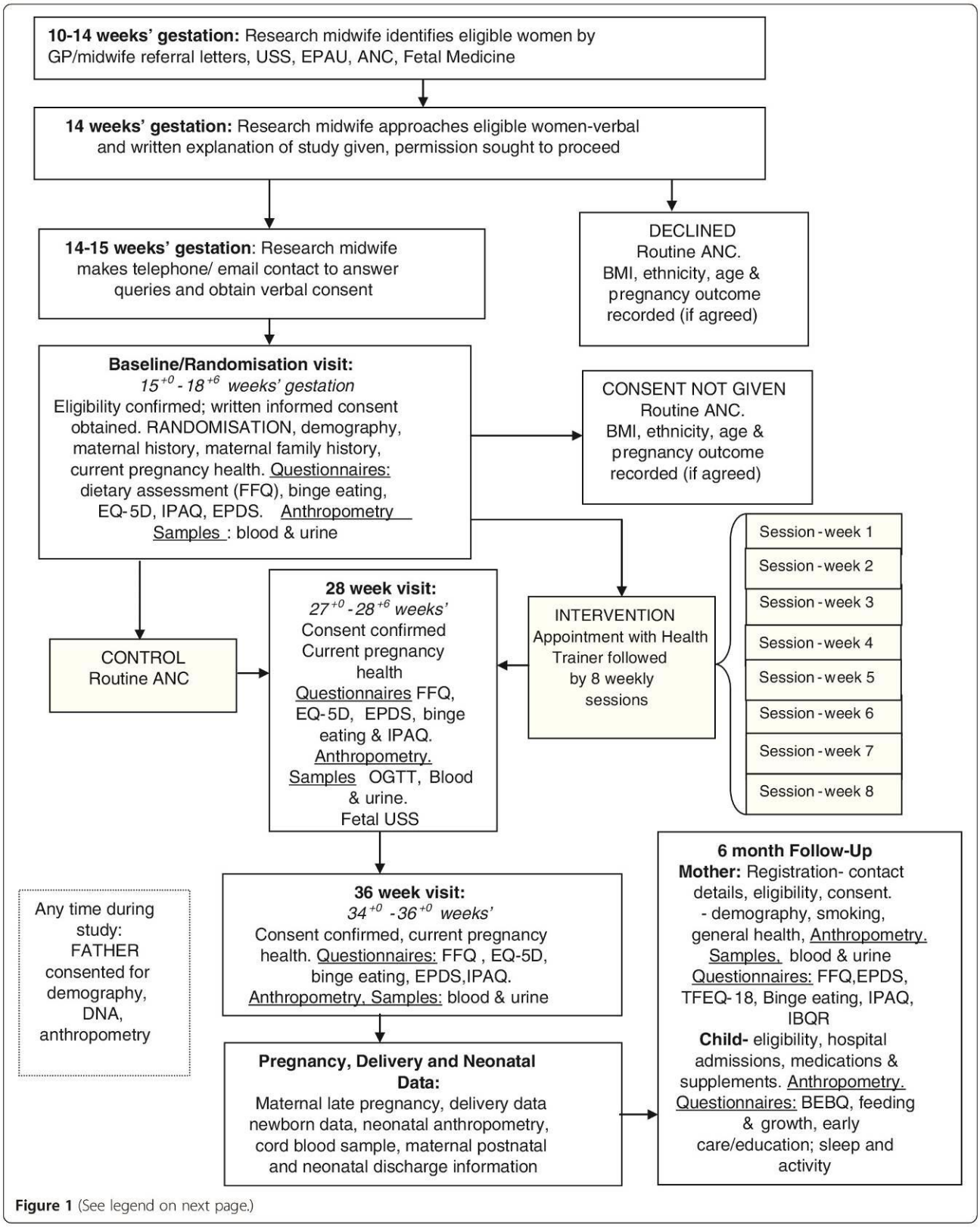


Figure 1 (See legend on next page.)

(See figure on previous page.)
Figure 1 UPBEAT protocol summary. Abbreviations: ANC; Antenatal clinic, BEBQ; baby eating behaviour questionnaire, BMI; Body mass index, DNA; Deoxyribonucleic acid, EPAU; Early pregnancy assessment unit, EPDS; Edinburgh postnatal depression score questionnaire. EQ-5D; EuroQuol 5 dimension quality of life questionnaire FFQ; Food frequency questionnaire, GP; General Practitioner, IBQ-R: Infant behaviour questionnaire revised; IPAQ; International physical activity questionnaire; LGA; Large for gestational age OGTT; Oral glucose tolerance test, SGA; Small for gestational age, TFEQ-18; Three-factor eating questionnaire-R18, USS; Ultrasound scanning.

27^{+0}- 28^{+6} weeks' appointment

All women in both groups attend for an oral glucose tolerance test (OGTT) at 27^{+0}- 28^{+6} weeks' gestation (fasting for a minimum of 10 hours, 75 g glucose load). At this visit weight and anthropometric measurements are taken, health in current pregnancy noted, additional blood and urine samples taken, dietary FFQ, EQ-5D, EPDS, IPAQ and 'binge eating' questionnaires completed. Early pregnancy data including blood pressure, blood chemistry and anomaly scan reports are entered from routine clinical records.

34^{+0}- 36^{+0} weeks' appointment

Women in both arms of the study attend the research appointment at 34^{+0}- 36^{+0} weeks' gestation. Current health in pregnancy is recorded, weight and anthropometric measurements taken, blood and urine samples collected and dietary FFQ, EQ-5D, EPDS, IPAQ and 'binge eating' questionnaires completed.

Unexpected adverse events are reported in accordance with good clinical practice guidance.

Pregnancy outcome data

Following delivery, information is collected from maternal medical records regarding health in late pregnancy, labour onset, mode of delivery, blood loss, antenatal and postnatal inpatient nights. Where possible a cord blood sample is taken.

Neonatal and postnatal outcome data includes Apgar scores, admission to special care baby unit and inpatient nights. To address the influence of the intervention on fetal growth and adiposity, neonatal anthropometry and length measurements are undertaken within 72 hours of birth.

Six months postpartum

To determine whether the intervention has led to sustained change in maternal dietary and physical activity behaviours, diet is assessed by FFQ and physical activity by IPAQ. Maternal demographic data, health since pregnancy and smoking history is obtained. Maternal anthropometric measures are taken. EPDS, Three Factor Eating Questionnaire R18 (TEFQ-18) [39] and 'binge eating' questionnaires are completed. To address safety and the influence of the intervention on the long term health of the child, details regarding the child's health from birth are obtained. If cord blood was not taken, and if the parents provide consent, a buccal cell sample is taken from the child's mouth for DNA extraction (Oragene™). To address the potential influence of the intervention on infant adiposity at 6 months and obtain information on known determinants of childhood obesity, infant length and other anthropometric measures are taken. The mother provides information for an infant feeding and growth questionnaire [40] and a validated questionnaire addressing appetite (Baby Eating and Behaviour Questionnaire (BEBQ) [41]. Information on activity using questions from the Infant Behaviour Questionnaire -Revised (IBQ-R) [42] and sleep patterns are obtained [43] and information on childcare (kindergarten, other carers) collected.

Paternal data

At any point during the pregnancy or at the 6 month postnatal appointment the father of the baby is asked to consent to taking part in the study to provide information which may influence the health of the child. A brief medical history, blood pressure and pulse are checked, anthropometric measurements taken and a blood samples collected for the provision for DNA. In the absence of direct paternal measurement, women are asked to recall their partner's height and weight and brief medical and smoking history.

Study endpoints

Primary maternal outcome

GDM diagnosed by OGTT at 27^{+0} – 28^{+6} weeks' gestation according to the criteria recommended by IADPSG. Diagnosis of GDM; fasting capillary glucose ≥ 5.1 mmol/L and/or 1 hour glucose ≥10 mmol/L and/or 2 hour glucose ≥8.5 mmol/L [44].

Primary neonatal outcome

LGA delivery defined as adjusted birth weight >90^{th} centile [45] for gestational age adjusting for maternal height, corrected maternal weight, ethnicity, parity, and sex of baby.

Secondary outcomes

Maternal - Pre-eclampsia, severe pre-eclampsia; mode of delivery: caesarean section (elective, emergency, pre-labour, in labour), vaginal delivery, operative vaginal delivery; induction of labour; blood loss at delivery (>1000 ml; >2000 ml); inpatient nights (antenatal, postnatal); GWG, trimester specific GWG; fasting plasma glucose, fasting plasma insulin, insulin resistance calculated by homeostatic model assessment 2 (HOMA2-IR) [46] at 28 weeks'

gestation; diagnosis of GDM by local criteria; referral to GDM antenatal service following OGTT; requirement for insulin or metformin during pregnancy; fetal growth at 28 weeks. Health related quality of life as assessed by EQ-5D. At 27^{+0}- 28^{+6} and 34^{+0}- 36^{+0} weeks' gestation and 6 months postpartum; mid-arm, neck, hip, thigh and wrist circumference and skinfold thickness (subscapular, triceps, biceps, supra-iliac); plasma fructosamine, triglycerides, LDL, VLDL and HDL cholesterol, plasma insulin, C-reactive protein, other relevant epigenetic and metabolomic biomarkers, and urinary biomarkers; dietary measures including glycemic load, saturated fat and total sugar intake; dietary feeding patterns; physical activity scores; measures of depression; maternal smoking. At 6 months postpartum, postnatal weight retention, existing maternal morbidity (diabetic status, hypertension, thromboembolism, low mood [47]).

Neonatal; Gestational age at delivery, delivery at <37 weeks', delivery at <34 weeks'; birth weight, birth weight >4,000 g, <2,500 g; birth weight >95^{th} <10th and <5^{th} customised birth weight centile, distribution of birth weight, neonatal death, days in special care baby unit, total inpatient days, need for mechanical ventilation and duration, discharge home on O_2, suspected and confirmed infection, evidence of intraventricular haemorrhage and other complications, (pulmonary haemorrhage, necrotizing enterocolitis), retinopathy of prematurity, hypoglycaemia. Occipitofrontal head circumference, abdominal circumference, mid-arm circumference, chest circumference, crown-rump length and crown-heel length (neonatometer), triceps and subscapular skin fold thicknesses and estimated fat mass.

Key epigenetic and metabolomic biomarkers will be investigated using cord blood or whole blood (maternal and fetal) and their relation to specific outcomes.

Infant at 6 months; duration of breast feeding, choice of formula milk, weaning history (introduction of foods and frequency/timing of foods), a general measure of appetite, and four specific scales: enjoyment of food, food responsiveness, slowness in eating, and satiety responsiveness, anthropometric measurements (occipitofrontal circumference, abdominal circumference, mid-arm circumference, chest circumference, crown-rump length and crown-heel length by infantometer, subscapular and triceps skin fold thicknesses and estimated fat mass; activity (total number of 14 standard milestones reached) and sleeping patterns (time spent sleeping; morning, afternoon and night; health care resource use (hospital admissions and medications); frequency of use of kindergarten/mother's help.

Sub-group analysis

Women who are treated for GDM; differences in diagnostic thresholds between centres will be accommodated by minimisation by centre. Other subgroups likely to be of interest include demographic and socio-economic status (assessed by Index Multiple Deprivation), ethnic groups, BMI categories, groups of different parity and smokers.

Interaction tests will be used to determine whether treatment is particularly effective in individual subgroups. Performance of subgroup analysis will be dependent on sufficient data. Because of the well known risk of false positives, both main effects and interaction tests will be performed before considering results for subgroups.

Sample size

In the pilot RCT [32], 30% of women in the standard care arm developed GDM according to the IADPSG criteria [39]. 1546 women (including allowance for 20% drop out) (773/arm) will be recruited to provide 80% power to detect a 25% reduction in the incidence of GDM. Considering LGA deliveries, for a 30% relative risk reduction (RRR) from an estimated 17.2% of LGA to 12.0% in the intervention arm; 1546 women would give 80% power [48,49].

Analysis

To determine whether the trial participants are representative of the general population, relevant parameters available from electronic summary patient records will be compared between eligible women agreeing and declining to take part. Analyses will follow the intention-to-treat principle.

Following CONSORT guidelines, risk ratios and risk differences will be estimated by binary regression for Yes/No outcomes. Where measurements are repeated over time, results [mean (SD) or n (%)] will be presented separately at each time point. Randomised comparisons with 95% confidence intervals will be made using linear regression with robust standard errors, adjusting for the baseline value where appropriate.

Multiple regression models will be used to address the influence of maternal exposures on neonatal and infant (6 months) body composition and the role of paternal factors.

Discussion

This RCT will determine whether a complex intervention addressing diet and physical activity will reduce the incidence of GDM and LGA infants in a population of obese pregnant women receiving antenatal care in the UK. The study will inform guidelines on the management of obesity in pregnancy, and if successful, is designed to be rapidly transferrable to clinical practice. Determination of infant anthropometry at 6 months of age will assess whether the intervention in pregnancy can influence body composition of the infant. Further studies on childhood body composition at 3 years of age will also be undertaken.

Abbreviations

BMI: Body mass index; FFQ: Food frequency questionnaire; EPDS: Edinburgh Postnatal Depression Scale; EQ-5D: EuroQuol-5D; GDM: Gestational diabetes mellitus; GI: Glycemic index; GL: Glycemic load; GWG: Gestational weight gain; HOMA2-IR: Homeostatic Model Assessment-Insulin resistance; IADPSG: International Association of Diabetes Pregnancy Study Group; IPAQ: International Physical Activity Questionnaire; LGA: large for gestational age; O_2: Oxygen; OGTT: Oral glucose tolerance test; PE: Pre-eclampsia; RCT: Randomised controlled trial; RRR: Relative risk reduction; SGA: Small for gestational age; SMART (goals): Specific, Measurable, Achievable, Relevant and Time-Specific.

Competing interests

None of the authors disclosed any financial or non-financial competing interests.

Authors' contributions

LP, ALB and KMG contributed to all aspects design of the study and LP and ALB had overall responsibility for the study. LP, ALB, NP drafting of the manuscript; BH, TS and SB(Barr) contributed to development of the dietary elements of the intervention; RB, TIK and SCR contributed to the development of the physical activity elements of the intervention; HC and JW contributed to development of the behavioural elements of intervention, SMN and NS contributed to assessment of maternal glucose homeostasis and biochemical analyses; EO-N contributed to the development of the final protocol; JS and SB(Badger) through process evaluation of the pilot trial contributed to development of the final protocol; PTS developed the data analysis protocol. All authors were involved in drafting of the manuscript and gave approval for the final version of the manuscript.

Authors' information

LP is Professor of Maternal and Fetal Health, TS is Professor of Nutritional Science, SB(Badger) a Research Associate and SB(Barr) a Research Dietician at King's College London; RB is a Senior Lecturer in Public Health Medicine, and SCR Professor of Fetal Medicine at Newcastle University; KMG is Professor of Epidemiology & Human Development and Director Centre for the Developmental Origins of Health and Disease at Southampton University; SMN is Professor of Reproductive and Maternal Medicine, and NS Professor of Metabolic Medicine at Glasgow University; EO-N is a Consultant Obstetrician and ALB a Consultant Midwife at Guy's and St. Thomas' NHS Foundation Trust, London; PTS is a Senior Lecturer in Medical Statistics at King's College London and JW is Professor in Clinical Psychology and Director of the Health Behaviour Unit at University College London. TIK, HC and NP are research fellows.

Acknowledgements

This paper presents independent research funded by the National Institute of Health Research (NIHR) under the Programme Grants for Applied Research programme (RP-PG-0407-10452). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health. The study is also part funded Guys and St. Thomas' Charity and the Chief Scientist Office, Scottish Government Health Directorates, Edinburgh, UK. LP, PTS and ALB is part funded by Tommy's Charity. KG is supported by the National Institute for Health Research through the Southampton NIHR Nutrition, Diet & Lifestyle Biomedical Research Unit.

Author details

[1]Division of Women's Health, Women's Health Academic Centre, King's College London and King's Health Partners, 10th floor, North Wing, St. Thomas' Hospital, London SE1 7EH, UK. [2]Division of Diabetes and Nutritional Sciences, King's College London and King's Health Partners, London, UK. [3]Institute of Health & Society, Newcastle University, Newcastle, UK. [4]Epidemiology and Public Health, University College London, London, UK. [5]MRC LifeCourse Epidemiology Unit, University of Southampton, Southampton, UK. [6]NIHR Biomedical Research Unit in Nutrition, Diet and Lifestyle, University of Southampton Hospital NHS Foundation Trust, Southampton, UK. [7]Centre for Population and Health Sciences, School of Medicine, University of Glasgow, Glasgow, UK. [8]Institute of Cellular Medicine, Newcastle University, Newcastle, UK.

Received: 28 January 2014 Accepted: 10 February 2014
Published: 18 February 2014

References

1. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL: **The global obesity pandemic: shaped by global drivers and local environments.** *Lancet* 2011, **378:**804–814.
2. World Health Organization: **WHO Global Database 2008.** 2011. N311, http://www.who.int/mediacentre/factsheets/fs311/en/. Date accessed 09.01.2014.
3. Sutton R: **Adult anthropometric measures, overweight and obesity.** *Health Surv Engl* 2012, **1:**1–37.
4. Centre for Maternal and Child Enquiries: **Saving Mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008.** *BJOG* 2011, **118:**1–203.
5. Heslehurst N, Simpson H, Ells LJ, Rankin J, Wilkinson J, Lang R, Brown TJ, Summerbell CD: **The impact of maternal BMI status on pregnancy outcomes with immediate short-term obstetric resource implications: a meta-analysis.** *Obes Rev* 2008, **9:**635–683.
6. Tsoi E, Shaikh H, Robinson S, Teoh TG: **Obesity in pregnancy: a major healthcare issue.** *Postgrad Med J* 2010, **86:**617–623.
7. Nelson SM, Matthews P, Poston L: **Maternal metabolism and obesity: modifiable determinants of pregnancy outcome.** *Hum Reprod Update* 2010, **16:**255–275.
8. Poston L, Harthoorn LF, van der Beek EM: **Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement.** *Pediatr Res* 2011, **69:**175–180.
9. Institue of Medicine and National Research Council: *Weight Gain During Pregnancy: Reexamining the Guidelines.* Washington DC: The National Academies Press; 2009.
10. National Institute for Health and Clinical Excellence: **Dietary interventions and physical activity interventions for weight management before, during and after pregnancy.** *Public Health Guid* 2010, **27.** http://www.nice.org.uk/nicemedia/live/13056/49926/49926.pdf. Date accessed 05.12.2013.
11. Dodd JM, Grivell RM, Crowther CA, Robinson JS: **Antenatal interventions for overweight or obese pregnant women: a systematic review of randomised trials.** *BJOG* 2010, **117:**1316–1326.
12. Thangaratinam S, Rogozińska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, Kunz R, Mol BW, Coomarasamy A, Khan KS: **Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence.** *BMJ* 2012, **344:**e2008.
13. Nohr EA, Vaeth M, Baker JL, Sørensen TI, Olsen J, Rasmussen KM: **Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy.** *Am J Clin Nutr* 2008, **87:**1750–1759.
14. Viswanathan MS-RA, Moos MK, Deierlein A, Mumford S, Knaack J, Thieda P, Lux LJ, Lohr KN: **Outcomes of maternal weight gain.** In *Evidence reports/technology assessments, No 168.* United States: Agency for Healthcare Research and Quality; 2008.
15. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TRJ, Trimble ER, Coustan DR, Hadden DR, Hod M, *et al*: **Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: associations of maternal a1c and glucose with pregnancy outcomes.** *Diabetes Care* 2012, **35:**574–580.
16. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarinder U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks SA: **Hyperglycemia and adverse pregnancy outcomes.** *N Engl J Med* 2008, **358:**1991–2002.
17. Harmon KA, Gerard L, Jensen DR, Kealey EH, Hernandez TL, Reece MS, Barbour LA, Bessesen DH: **Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth.** *Diabetes Care* 2011, **34:**2198–2204.
18. Vrijkotte TGM, Algera SJ, Brouwer IA, van Eijsden M, Twickler MB: **Maternal triglyceride levels during early pregnancy are associated with birth weight and postnatal growth.** *J Pediatr* 2011, **159:**736–742.
19. Parretti E, Lapolla A, Dalfrà M, Pacini G, Mari A, Cioni R, Marzari C, Scarselli G, Mello G: **Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes.** *Hypertension* 2006, **47:**449–453.
20. Zhang C, Ning Y: **Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence.** *Am J Clin Nutr* 2011, **94:**1975S–1979S.

21. Wolff S, Legarth J, Vangsgaard K, Toubro S, Astrup A: **A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women.** *Int J Obes* 2008, **32:**495–501.
22. Quinlivan JA, Lam LT, Fisher J: **A randomised trial of a four-step multidisciplinary approach to the antenatal care of obese pregnant women.** *Aust N Z J Obstet Gynaecol* 2011, **51:**141–146.
23. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS: **Effect of treatment of gestational diabetes mellitus on pregnancy outcomes.** *N Engl J Med* 2005, **352:**2477–2486.
24. Landon MB: **Is there a benefit to the treatment of mild gestational diabetes mellitus?** *Am J Obstet Gynecol* 2010, **202:**649–653.
25. Ruchat SM, Mottola MF: **The important role of physical activity in the prevention and management of gestational diabetes mellitus.** *Diabetes Metab Res Rev* 2013, **29:**334–346.
26. Louie JCYBJ, Makovic TP, Ross GP, Moses RG: **Glycemic index and pregnancy: a systematic literature review.** *J Nutrit Metab* 2010, **2010:**1–8.
27. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P: **Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis.** *BMC Med* 2012, **10:**47.
28. Gardner B, Wardle J, Poston L, Croker H: **Changing diet and physical activity to reduce gestational weight gain: a meta-analysis.** *Obes Rev* 2011, **12:**e602–e620.
29. Poston LCL: **How should women be advised on weight management in pregnancy?** *BMJ* 2012, **344:**e2774.
30. Carver CS, Scheier MF: **Origins and functions of positive and negative affect: a control-process view.** *Psychol Rev* 1990, **97:**19–35.
31. Bandura A: **Health promotion by social cognitive means.** *Health Educ Behav* 2004, **31:**143–164.
32. Poston L, Briley A, Barr S, Bell R, Croker H, Coxon K, Essex H, Hunt C, Hayes L, Howard L, *et al*: **Developing a complex intervention for diet and activity behaviour change in obese pregnant women (the UPBEAT trial); assessment of behavioural change and process evaluation in a pilot randomised controlled trial.** *BMC Pregnancy Childbirth* 2013, **13:**148.
33. **Royal college of obstetricians and gynaecologists: exercise in pregnancy. 2006, RCOG statement 4.** http://www.rcog.org.uk/womens-health/clinical-guidance/exercise-pregnancy. Date accessed 12.12.2013.
34. Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, Lubin R, Thurnham DI, Key TJ, Roe L, *et al*: **Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers.** *Int J Epidemiol* 1997, **26:**S137.
35. EuroQol: **EuroQol- A New facility for the measurement of health-related quality of life.** *Health Policy* 1990, **19:**199–208.
36. Cox JLHJ, Sagovsky R: **Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale.** *Br J Psychiatry* 1987, **150:**782–786.
37. Ekelund USH, Brage S, Becker W, Jakes R, Hennings M, Wareham NJ: **Crierion-related validity of the last 7 Day, short form of the international physical activity questionnaire in swedish adults.** *Public Health Nutr* 2006, **9:**258–265.
38. Stice E, Fisher M, Martinez E: **Eating disorder diagnostic scales: additional evidence of reliability and validity.** *Psychol Assess* 2004, **16:**60–71.
39. Stunkard AJ, Messick S: **The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger.** *J Psychosom Res* 1985, **29:**71–83.
40. Robinson S, Marriott L, Poole J, Crozier S, Borland S, Lawrence W, Law C, Godfrey K, Cooper C, Inskip H: **Dietary patterns in infancy: the importance of maternal and family influences on feeding practice.** *Br J Nutr* 2007, **98:**1029–1037.
41. Llewellyn CH vJC, Johnson L, Carnell S, Wardle J: **Development and factor structure of the baby eating behaviour questionnaire in the gemini birth cohort.** *Appetite* 2011, **57:**388–396.
42. Gartstein MARM: **Studying infant temperament via the revised infant behaviour questionnaire.** *Infant Behav Dev* 2003, **26:**64–86.
43. Sadeh A: **A brief screening questionnaire for infant sleep problems: validation and findings for an internet sample.** *Pediatrics* 2004, **113:**e570–e577.
44. International Association of Diabetes Pregnancy Study Groups Consensus Panel: **International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy.** *Diabetes Care* 2010, **33:**676–682.
45. Gardosi J, Francis A: **Software program for the calculation of customised birth weight percentiles.** 2002-2007. [Accessed January 2010]. www.gestation.net.
46. Wallace TM, Levy JC, Matthews DR: **Use and abuse of HOMA modeling.** *Diabetes Care* 2004, **27:**1487–1495.
47. Gibson JM-MK, Shakespeare J, Price J, Gray R: **A systematic review of studies validating the edinburgh postnatal depression scale in antepartum and postpartum women.** *Acta Psychiatr Scand* 2009, **119:**350–364.
48. Sebire N, Jolly M, Harris J, Wadsworth J, Joffe M, Beard R: **Maternal obesity and pregnancy outcome: a study of 287, 213 pregnancies in london.** *Int J Obes (Lond)* 2001, **25:**1175–1182.
49. Ehrenberg H, Durnwald C, Catalano P, Mercer B: **The influence of obesity and diabetes on the risk of cesarean delivery.** *Am J Obstet Gynaecol* 2004, **191:**969–974.

doi:10.1186/1471-2393-14-74
Cite this article as: Briley *et al.*: A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. *BMC Pregnancy and Childbirth* 2014 **14**:74.

Submit your next manuscript to BioMed Central and take full advantage of:

- **Convenient online submission**
- **Thorough peer review**
- **No space constraints or color figure charges**
- **Immediate publication on acceptance**
- **Inclusion in PubMed, CAS, Scopus and Google Scholar**
- **Research which is freely available for redistribution**

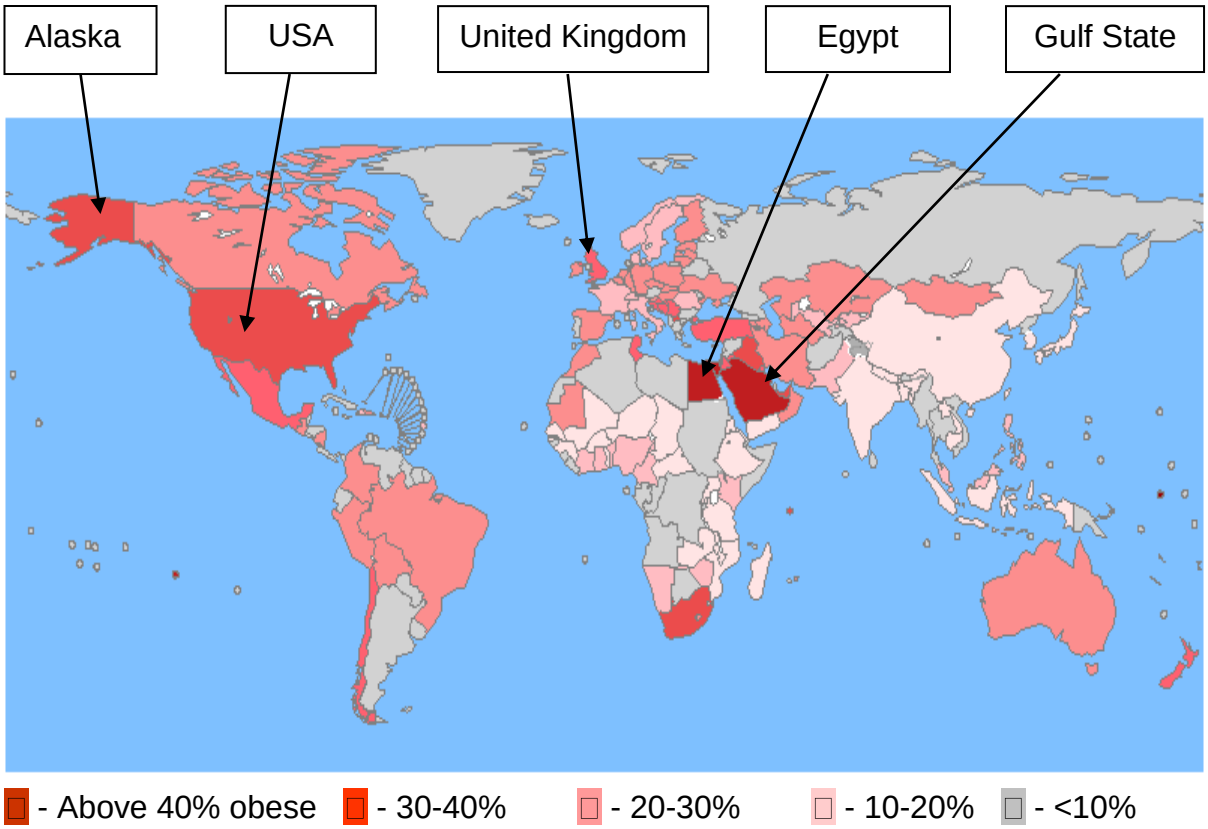
Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

Appendix G: CAN Participant Manual

Details of the CAN intervention programme participant manual are attached to this electronic thesis submission.

Appendix H: Figure showing the prevalence of obesity (BMI≥30 kg/m2) among adult women (WHO) 2008



Appendix I: Table of background characteristics of the mothers by year of delivery

BMI category	Year 2004 N(%)	Year 2005 N(%)	Year 2006 N(%)	Year 2007 N(%)	Year 2008 N(%)	Year 2009 N(%)	Year 2010 N(%)	Year 2011 N(%)	Year 2012 N(%)	Total N(%)
<18.5 N	113	159	188	160	175	153	171	204	107	1430
%	3.1	3.8	4.1	3.5	3.3	2.8	2.8	3.3	3.4	3.3
18.5-24.9	2082	2392	2630	2642	3083	3214	3527	3438	1735	24743
	56.6	57.3	57.4	57.8	57.5	58.2	58.2	56.0	54.7	57.2
25-29.9	919	1026	1126	1096	1331	1349	1499	1525	776	10647
	25.0	24.6	24.6	24.0	24.8	24.4	24.7	24.8	24.5	24.6
30-34.9	359	381	408	449	523	522	579	650	368	4239
	9.8	9.1	8.9	9.8	9.8	9.5	9.5	10.6	11.6	9.8
35-39.9	151	153	148	164	164	189	193	214	122	1498
	4.0	3.5	3.2	3.6	3.1	3.4	3.2	3.5	3.9	3.5
>40	57	61	79	58	86	94	94	104	59	692
	1.5	1.4	1.7	1.3	1.6	1.7	1.6	1.7	1.9	1.6
Obese	567	595	635	671	773	805	866	968	549	6429
category	15.4	14.3	13.9	14.7	14.4	14.6	14.3	15.8	17.3	14.9
Total Non-missing	**3681**	**4172**	**4579**	**4569**	**5362**	**5521**	**6063**	**6135**	**3167**	**43249**
Missing	1856	1654	1583	1619	1456	902	699	581	318	10668
	33.5	28.4	25.7	26.2	21.4	14	10.3	8.7	9.1	19.8
Total	5537	5826	6162	6188	6818	6423	6762	6716	3485	53917
	100	100	100	100	100	100	100	100	100	100
Maternal age	**Year 2004**	**Year 2005**	**Year 2006**	**Year 2007**	**Year 2008**	**Year 2009**	**Year 2010**	**Year 2011**	**Year 2012**	**Total**
<20 N	275	285	270	277	278	223	190	163	81	2042
%	5.0	4.9	4.4	4.5	4.1	3.5	2.8	2.4	2.3	3.8
20-24 N	821	868	911	863	950	824	849	788	382	7260
%	14.8	14.9	14.8	14	13.9	12.9	12.6	11.7	10	13.5
25-29 N	1300	1381	1420	1433	1553	1454	1423	1494	792	12250
%	23.5	23.7	23	23.2	22.8	22.6	21	22.2	22.7	22.7
30-34 N	1742	1810	1919	1981	2225	2149	2355	2313	1201	17695
%	31.5	31.1	31	32	32.6	33.5	34.8	34.4	34.5	32.8
35-39 N	1131	1173	1280	1314	1440	1434	1525	1520	773	11590
%	20.4	20.1	20.8	21.2	21.1	22.3	22.6	22.6	22.2	21.5
>40 N	268	309	362	320	372	335	420	438	256	3080
%	4.8	5.3	5.9	5.2	5.5	5.2	6.2	6.5	7.4	5.7
Total N	5537	5826	6162	6188	6818	6423	6762	6716	3485	53917
%	100	100	100	100	100	100	100	100	100	100
Parity	**Year 2004**	**Year 2005**	**Year 2006**	**Year 2007**	**Year 2008**	**Year 2009**	**Year 2010**	**Year 2011**	**Year 2012**	**Total**
0 N	3050	3218	3467	3710	4084	3889	3977	3811	2004	31210
%	55.1	58.3	56.3	60	60	60.1	58.8	56.8	57.5	58

1-3	2304	2424	2528	2311	2541	2378	2631	2755	1410	21282
%	41.6	43.9	41.0	37.4	37.3	37.0	38.9	41.0	40.5	39.5
4 plus N	173	180	163	158	178	150	142	143	64	1351
%	3.1	3.3	2.7	2.6	2.6	2.3	2.1	2.1	1.8	2.5
Total non-missing (%)	**5527 (100)**	**5522 (100)**	**6158 (100)**	**6179 (100**	**6813 (100)**	**6417 (100)**	**6750 (100)**	**6709 (100)**	**3478 (100)**	**53843 (100)**
Missing N	10	4	4	9	15	6	12	7	7	74
%	0.2	0.1	0.1	0.2	0.2	0.1	0.2	0.1	0.2	0.1
Total N	5537	5826	6162	6188	6818	6423	6762	6716	3485	53917
Ethnicity	**Year 2004**	**Year 2005**	**Year 2006**	**Year 2007**	**Year 2008**	**Year 2009**	**Year 2010**	**Year 2011**	**Year 2012**	**Total**
White N	2908	2985	3212	3240	3668	3546	3731	3662	1847	28799
%	52.6	51.9	5.1	52.3	55.1	55.9	55.8	55.3	53.8	54.3
Asian N	288	299	294	307	373	377	413	404	249	3004
%	5.2	5.2	4.8	5.0	5.6	5.9	6.2	6.1	7.2	5.7
Black N	2092	2217	2310	2241	2334	2157	2274	2263	1188	19076
%	37.8	38.6	38.2	36.2	35.0	34.0	34.0	34.2	34.6	35.9
Chinese N	201	212	203	207	237	231	236	258	141	1926
%	3.6	3.7	3.3	3.4	3.6	3.6	3.5	3.9	4.1	3.6
Other N	40	35	30	28	48	34	32	31	10	288
%	0.7	0.6	0.5	0.5	0.7	0.5	0.5	0.5	0.3	0.5
Total non-missing	**5529 100**	**5748 100**	**6049 100**	**6023 100**	**6660 100**	**6345 100**	**6686 100**	**6618 100**	**3435 100**	**53093 100**
Missing N	8	78	113	165	158	78	76	98	50	824
%	0.1	1.3	1.8	2.7	2.3	1.2	1.1	1.5	1.4	1.5
Total N	5537	5826	6162	6188	6818	6423	6762	6716	3485	53917
Smoking	**Year 2004**	**Year 2005**	**Year 2006**	**Year 2007**	**Year 2008**	**Year 2009**	**Year 2010**	**Year 2011**	**Year 2012**	**Total**
Smoking N	459	365	422	375	339	365	437	400	195	3357
%	10.6	7.2	7.7	7.1	5.7	6.4	7.0	6.4	6.0	7.0
Non-smoking N %	4313 90.4	4723 92.8	5**08**9 92.3	4939 92.9	5623 94.3	5370 93.6	5811 93	5847 93.6	3038 94.0	44753 93.0
Total non-missing %	**4772 100**	**5088 100**	**5511 100**	**5314 100**	**5962 100**	**5735 100**	**6248 100**	**6247 100**	**3233 100**	**48110 100**
Missing N	765	738	651	874	856	688	514	469	252	5807
%	13.8	12.7	10.6	14.1	12.6	10.7	7.6	7.0	7.2	10.8
Total N	5537	5826	6162	6188	6818	6423	6762	6716	3485	53917
IMD Quintile	**Year 2004**	**Year 2005**	**Year 2006**	**Year 2007**	**Year 2008**	**Year 2009**	**Year 2010**	**Year 2011**	**Year 2012**	**Total**
1 N	126	165	179	208	226	213	213	216	117	1663
%	2.3	2.8	2.9	3.4	3.3	3.3	3.2	3.2	3.4	3.2
2 N	277	298	350	358	416	400	406	395	194	3,094
%	5.0	5.2	5.7	5.8	6.2	6.3	6.0	5.9	5.6	5.8
3 N	570	595	631	696	857	760	862	765	412	6,148

	%	10.4	10.3	10.3	11.3	12.7	11.8	12.8	11.5	11.9	11.4
4	N	2,573	2,662	2,741	2,730	3,000	2,869	3,034	3,100	1,560	24,269
	%	46.9	46.1	44.8	44.5	44.4	44.9	45.1	46.4	45.0	45.3
5	N	1,943	2,050	2,214	2,144	2,262	2,148	2,208	2,202	1,180	18,351
	%	35.4	35.5	36.2	34.9	33.5	33.6	32.8	33.0	34.1	34.3
Total non-missing	%	**5489**	**5770**	**6115**	**6136**	**6761**	**6390**	**6723**	**6678**	**3463**	**53525**
		100	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Missing	N	48	56	47	52	57	33	39	38	22	392
	%	0.9	1.0	0.8	0.8	0.8	0.5	0.6	0.6	0.6	0.7
Total	N	5,537	5,826	6,162	6,188	6,818	6,423	6,762	6,716	3,485	53,917

Appendix J: Development of the CAN Project

KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

Women's Health Academic Centre

Division of Women's Health
King's College London
Women's Health Academic Centre KHP
St Thomas Hospital
10th Floor, North Wing
Westminster Bridge Road
London SE1 7EH
Tel: 020 7188 3639
Fax: 020 7620 1227
www.kcl.ac.uk

6th June 2014

Professors Marian Knight and David Williams

Dear Marian and David

Re Eugene Oteng Ntim; PhD Thesis

Eugene has asked that I clarify for you his role in the development of the CAN project and how this relates to the UPBEAT trial, for which I am PI.

The original concept for the CAN intervention in obese women was developed by Eugene i.e. the idea of developing an intervention to be delivered in the community. I suggested that as we were simultaneously developing an intervention for delivery in the hospital that he became a member of the UPTEAT trial team, thus contributing his substantial knowledge in the field of obstetrics and obesity. With my encouragement he applied for, and was successful in obtaining, independent funding for the community based project to be based at King's College Hospital from the Guy's and St Thomas' Charity, Thus CAN became the community arm of the UPBEAT trial with the same primary outcomes, but with study specific goals which were the subject of Eugene's thesis.

In terms of his contribution, Eugene had substantial input into the final protocol for the intervention, development of the trial database, and writing of the intervention manual. He contributed to all the meetings where the intervention was devised. Specifically for his thesis, he was responsible for all the practical aspects of setting up the trial in the community centres, He negotiated delivery of the community-based intervention in three Sure Start Children's Centres: Jubilee, Effra, and Jessop Children's Centres. He recruited the first participants himself before appointing a Research Midwife at King's College Hospital this establishing a successful pathway for recruitment. Eugene developed the provider questionnaires and put together the CAN specific trial literature. He also personally conducted the analysis of the data for the CAN participants in the pilot study reported in the thesis,

The concept for CAN, the successful application for a grant, and recruitment in community setting at another hospital were thus all led by Eugene.

This was an important study as it has shown the feasibility and acceptability of delivering a lifestyle intervention in obese pregnant women in Sure Start Children's Centres in an ethnically diverse and deprived population of pregnant women. I am pleased to say that as result of his efforts that Eugene has been instrumental in a new award of £35M from the National Lottery to Lambeth Council which includes establishing a service for obese pregnant women in the community.

With kind regards

Yours sincerely

Professor Lucilla Poston BSc, PhD, FRCOG, FMedSc
Head of Division of Women's Health

Appendix K: Publication List and Confirmation of Copyright

Publications

1. **Oteng-Ntim E** and Doyle P, (2012). *Maternal outcomes in obese pregnancies in maternal obesity*. Edition 1, Chapter 4, ed Gillman MW, Poston L, Cambridge University Press, United States of America.
2. **Oteng-Ntim E**, Kopeika J, Seed P, Wandiembe S, Doyle P. *Impact of obesity on pregnancy outcome in different ethnic groups: Calculating population attributable fractions*. Plos One; 2013: 8(1):e53749
3. **Oteng-Ntim E**, Varma R, Croker H, Poston L, Doyle P. *Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis*. BMC Med. 2012; 10(1):47
4. **Oteng-Ntim E**, Pheasant H, Khazaezadeh N, Mohhidin A, Bewley S, Wong J, Oke B. *Developing a community-based maternal obesity intervention: a qualitative study of service providers' views*. British Journal of Obstetrics and Gynaecology. 2010. 117(13):1651-5
5. Khazaezadeh N, Pheasant H, Bewley S, Mohiddin A, **Oteng-Ntim E**. *Using service users' views to design maternal obesity intervention.* British Journal of Midwifery. 2011;19(1):49-56
6. Rowlands G, Khazaezadeh N, **Oteng-Ntim E**, Seed P, Barr S, Weiss BD. *Development and validation of a measure of health literacy in the UK: the newest vital sign*. BMC Public Health. 2013;13(1):116
7. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, **Oteng-Ntim E**, El-Toukhy T. *Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis*. Reprod Biomed Online. 2011;23 (4):421-39.
8. Rittenberg V, Sobaleva S, Ahmad A, **Oteng-Ntim E**, Bolton V, Khalaf Y, Braude P, El-Toukhy T. *Influence of BMI on risk of miscarriage after single blastocyst transfer.* Hum Reprod. 2011; 26(10):2642-50

9. Hezelgrave NL, **Oteng-Ntim E**. *Pregnancy after bariatric surgery: a review*. J Obes. 2011;2011:501939
10. Birdsall KM, Vyas S, Khazaezadeh N, **Oteng-Ntim E**. *Maternal obesity: a review of interventions.* Int J Clin Pract. 2009 Mar;63(3):494-507

Copyright Confirmation - Chapter 2 publication

CAMBRIDGE UNIVERSITY PRESS

The Edinburgh Building
Shaftesbury Road
Cambridge CB2 8RU, UK

www.cambridge.org

Telephone +44 (0)1223 312393
Fax +44 (0)1223 315052
Email information@cambridge.org

Eugene Oteng-Ntim

via email: Eugene.Oteng-Ntim@gstt.nhs.uk

August 2, 2013

Dear Eugene

Eugene Oteng-Ntim and Pat Doyle, "Maternal outcomes in obese pregnancies" pp 35-44 in Matthew W. Gillman , Lucilla Poston (Eds) Maternal Obesity, 2012

Thank you for your recent permission request, to include the above extract/s in:
Your PhD Thesis.

Non-exclusive permission is granted free of charge for this specific use on the understanding that you have checked that we do not acknowledge another source for this material.

Please ensure full acknowledgement (author, title, publication date, and Cambridge University Press).

Yours sincerely

Linda Nicol
Permissions Manager
email lnicol@cambridge.org

Copyright Confirmation - Chapter 5 publication

-----Original Message-----
From: "Alexandre Francois" <alexandre.francois@biomedcentral.com>
[mailto:alexandre.francois@biomedcentral.com]
Sent: 31 July 2013 12:17
To: Oteng-Ntim Eugene
Subject: 00477045 re:

Dear Dr. Oteng-Ntim,

Thank you for contacting BioMed Central.

I can confirm that copyright on any research article in all journals published by BioMed Central is retained by the author(s).

Authors grant BioMed Central a license to publish the article and identify itself as the original publisher.

Authors also grant any third party the right to use the article freely as long as its integrity is maintained and its original authors, citation details and publisher are identified.

The BioMed Central Copyright and License Agreement (identical to the Creative Commons Attribution License) formalizes these and other terms and conditions of publishing research articles.

For more information please go to: http://www.biomedcentral.com/info/about/copyright

If you have any questions please do not hesitate to contact me.

Best wishes

Alexandre Francois
Customer Services
alexandre.francois@biomedcentral.com
www.biomedcentral.com
----------Your Question/Comment ----------

Dear Alexandre

Could you kindly provide me with a proof on a BMC medicine headed paper that I retained the copy right of this article in order that I will be able to use for my PhD thesis.
Research article Open Access
<http://www.biomedcentral.com/about/access> Highly Accessed
<http://www.biomedcentral.com/about/mostviewed>
<http://www.biomedcentral.com/1741-7015/10/47>

Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis

Eugene Oteng-Ntim, Rajesh Varma, Helen Croker, Lucilla Poston, Pat Doyle
BMC Medicine 2012, 10:47 (10 May 2012)

With kind regards
Eugene Oteng-Ntim
Head Of Obstetrics

License Agreement - Chapter 7 publication

This is a License Agreement between Eugene Oteng-Ntim ("You") and John Wiley and Sons ("John Wiley and Sons"). The license consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

Get the printable license.

License Number	3199290513337
License date	Jul 31, 2013
Licensed content publisher	John Wiley and Sons
Licensed content publication	BJOG: An International Journal of Obstetrics and Gynaecology
Licensed content title	Developing a community-based maternal obesity intervention: a qualitative study of service providers□™ views
Licensed copyright line	Â© 2010 The Authors Journal compilation Â© RCOG 2010 BJOG An International Journal of Obstetrics and Gynaecology
Licensed content author	E Oteng-Ntim,H Pheasant,N Khazaezadeh,A Mohidden,S Bewley,J Wong,B Oke
Licensed content date	Sep 24, 2010
Start page	1651
End page	1655
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No