Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial

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Summary

Background Behavioural interventions might improve clinical outcomes in pregnant women who are obese. We aimed to investigate whether a complex intervention addressing diet and physical activity could reduce the incidence of gestational diabetes and large-for-gestational-age infants.

Methods The UK Pregnancies Better Eating and Activity Trial (UPBEAT) is a randomised controlled trial done at antenatal clinics in eight hospitals in multi-ethnic, inner-city locations in the UK. We recruited pregnant women (15–18 weeks plus 6 days of gestation) older than 16 years who were obese (BMI ≥30 kg/m²). We randomly assigned participants to either a behavioural intervention or standard antenatal care with an internet-based, computer-generated, randomisation procedure, minimising by age, ethnic origin, centre, BMI, and parity. The intervention was delivered once a week through eight health trainer-led sessions. Primary outcomes were gestational diabetes (diagnosed with an oral glucose tolerance test and by criteria from the International Association of Diabetes in Pregnancy Study Groups) and large-for-gestational-age infants (≥90th customised birthweight centile). Analysis was by intention to treat. This trial is registered with Current Controlled Trials, ISCRTN89971375. Recruitment and pregnancy outcomes are complete but childhood follow-up is ongoing.

Findings Between March 31, 2009, and June 2, 2014, we assessed 8820 women for eligibility and recruited 1555, with a mean BMI of 36·3 kg/m² (SD 4·8). 772 were randomly assigned to standard antenatal care and 783 were allocated the behavioural intervention, of which 651 and 629 women, respectively, completed an oral glucose tolerance test. Gestational diabetes was reported in 172 (26%) women in the standard care group compared with 160 (25%) in the intervention group (risk ratio 0·96, 95% CI 0·79–1·16; p=0·68). 61 (8%) of 751 babies in the standard care group were large for gestational age compared with 71 (9%) of 761 in the intervention group (1·15, 0·83–1·59; p=0·40). Thus, the primary outcomes did not differ between groups, despite improvements in some maternal secondary outcomes in the intervention group, including reduced dietary glycaemic load, gestational weight gain, and maternal sum-of-skinfold thicknesses, and increased physical activity. Adverse events included neonatal death (two in the standard care group and three in the intervention group) and fetal death in utero (ten in the standard care group and six in the intervention group). No maternal deaths were reported. Incidence of miscarriage (2% in the standard care group *vs* 2% in the intervention group), major obstetric haemorrhage (1% *vs* 3%), and small-for-gestational-age infants (≤5th customised birthweight centile; 6% *vs* 5%) did not differ between groups.

Interpretation A behavioural intervention addressing diet and physical activity in women with obesity during pregnancy is not adequate to prevent gestational diabetes, or to reduce the incidence of large-for-gestational-age infants.

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Introduction

In 2013, an estimated one in five women in the world aged 20 years or older was obese (BMI ≥30 kg/m²).[1] Obesity in women was most widespread in high-income countries, with a prevalence of 25% in the UK and 34% in the USA.[1]

Pregnant women with obesity are at risk of many complications, with insulin resistance and gestational diabetes being major concerns because they beget important adverse outcomes. These include stillbirth, large-for-gestational-age infants, and associated complications at birth.[2] Children born to women with gestational diabetes could themselves be at risk of metabolic disease in later life.[3]

The increasing global problem of obesity in maternity care has led to national guideline recommendations for the development of interventions to improve pregnancy outcomes.[4,5] This advice stimulated many clinical trials, predominantly of behavioural interventions addressing

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See Online for appendix

Research in context

Evidence before this study

Obesity is a risk factor for complications in pregnancy, particularly gestational diabetes, large-for-gestational-age babies, and associated adverse outcomes. In a systematic review of 44 randomised controlled trials of behavioural interventions in pregnant women, irrespective of BMI, lifestyle interventions were shown to possibly improve clinical outcomes for both mother and baby. We and others have undertaken systematic reviews restricted to behavioural interventions in women with obesity, suggesting the potential for prevention of gestational diabetes. The contributing trials were mostly small scale and not powered for robust detection of differences in clinical outcomes. In the LIMIT trial of more than 2000 overweight and obese women, no reduction in gestational diabetes was recorded in individuals who took part in a lifestyle intervention, although gestational diabetes was not the primary endpoint of the trial.

Added value of this study

Our study compared a theory-based and intensive behavioural intervention with standard antenatal care for obese pregnant women from communities of ethnic diversity and high levels of socioeconomic deprivation. The intervention improved diet and physical activity, and modest reductions were noted in maternal weight gain and fat mass, but it had no effect on the incidence of gestational diabetes or large-for-gestational-age infants. Use of an oral glucose tolerance test and diagnosis of gestational diabetes with the stringent IADPSG diagnostic criteria (also used by WHO) was associated with a lower than anticipated incidence of large-for-gestational-age infants in the trial population.

Interpretation

An intervention addressing diet and physical activity in high-risk women with obesity does not prevent gestational diabetes or reduce the incidence of large-for-gestational-age infants. We recommend a shift in research focus towards improved screening for and treatment of gestational diabetes, in addition to renewed efforts towards effective public health measures that prevent obesity in women of reproductive age.

diet and physical activity. However, most trials have been underpowered for clinical outcomes such as gestational diabetes, focusing instead on restriction of gestational weight gain.[6] Nonetheless, systematic reviews of these mostly small trials suggest the potential for prevention of gestational diabetes in women with obesity by behaviour change interventions in pregnancy.[7,8]

Here, we report the results of the UK Pregnancies Better Eating and Activity Trial (UPBEAT), a randomised controlled trial of a complex behavioural intervention addressing diet and physical activity versus standard antenatal care. The behavioural intervention was designed to prevent maternal gestational diabetes and reduce the incidence of large-for-gestational-age infants. By contrast with interventions tested in many previous small-scale studies,[6] the intervention was more intensive in design. Findings of a pilot study have shown feasibility, acceptability, and efficacy of the intervention to change lifestyle behaviours.[9]

Methods

Study design

We did this multicentre, randomised controlled trial at antenatal clinics in eight inner-city NHS Trust Hospitals in the UK—London (three centres), Bradford, Glasgow, Manchester, Newcastle, and Sunderland. The detailed study design and protocol have been published elsewhere.[10] A flow chart of the protocol is shown in the appendix (p 1). We did the study according to the UK's National Institute for Health and Care Excellence (NICE) guidelines for diabetes in pregnancy, in which early pregnancy biochemistry screening for glucose intolerance and risk of gestational diabetes is not recommended.[11] The NHS research ethics committee approved the study protocol for all centres (UK integrated research application system, reference 09/H0802/5). The trial steering committee approved the protocol and the analysis plan and provided oversight of all aspects of the trial, including safety.

For the **protocol** see http://www.kcl.ac.uk/lsm/research/divisions/wh/clinical/open/UPBEAT-protocol.pdf

For more on the **randomisation website** see http://medscinet.com

Participants

We recruited women older than 16 years with a BMI of 30 kg/m² or higher and a singleton pregnancy between 15 weeks and 18 weeks plus 6 days of gestation. We excluded individuals if they were unwilling or unable to give informed consent; if they had underlying disorders, including a pre-pregnancy diagnosis of essential hypertension, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle-cell disease, thalassaemia, coeliac disease, thyroid disease, and current psychosis; or if they were currently being prescribed metformin. All participants provided written informed consent. For women who declined to participate, we recorded age, BMI, ethnic origin, socioeconomic status, and outcome data if permission was granted.

Randomisation and masking

We randomly allocated participants to either standard antenatal care or the behavioural intervention plus standard antenatal care. We used a computer-generated randomisation procedure via a password-protected website. Allocation to study groups was done by the centre's UPBEAT trial midwife. We used minimisation, according to ethnic origin (black, white, Asian, other), parity (primiparous, multiparous), age (≤24, 25–29, 30–34,

≥35 years), BMI (30·0–34·9, 35·0–39·9, ≥40 kg/m²), and centre. In view of the nature of the intervention, participants and staff were aware of allocations.

Procedures

Within 1 week of randomisation, women in the intervention group attended an individual interview at their trial centre with a health trainer (a person with skills in assisting behavioural change, but not necessarily a health professional) who received coaching in all aspects of the intervention and ongoing support throughout the study period.[10] The intervention, which was informed by control theory and elements of social cognitive theory, consisted of eight further health trainer-led group or individual sessions of 1 h duration once a week for 8 weeks.[10] If a participant could not attend a session in person, the material was covered by telephone or email, providing flexibility in intervention delivery. Every session addressed approaches to achieving SMART goals (ie, specific, measurable, achievable, relevant, time-specific) and reviewed the previous week's goals. Women assigned to the intervention received advice on: self-monitoring, identification, and problem-solving of barriers to behaviour change; enlisting social support; and providing opportunities for social comparison. We encouraged participants to attend all sessions and provided them with a handbook in which information was included about the intervention and the theory behind it, with recommended foods and recipes, and suggestions for physical activity. We also gave the women a DVD of an exercise regimen that was safe for pregnancy, a pedometer, and a log book for recording their weekly SMART goals. The intention of the intervention was to improve glucose tolerance through dietary and physical activity behaviour change. With the dietary intervention we aimed to promote a healthy pattern of eating but not necessarily to restrict energy intake. We tailored recommendations to the woman's habitual diet and cultural preference, and suggested exchanging carbohydrate-rich foods with a medium-to-high glycaemic index for those with a lower glycaemic index to reduce the glycaemic load, and restricting dietary intake of saturated fat. With respect to advice on physical activity, we focused on incremental increases in walking from a pedometer-assessed baseline, tailored to pre-existing activities. The emphasis of the exercise intervention was on walking at a moderate intensity, with additional options included, particularly for women already engaging in some physical activity. Further details are available in the protocol.[10] Women in the intervention group continued with their routine antenatal care appointments.

Women who were allocated to the standard antenatal care group continued to attend routine antenatal appointments at their trial centre, in accordance with local practice. Typically, women would attend nine appointments. Recommendations of UK guidelines are for women with obesity to be advised, at first contact with a health professional, and at no other time, about a healthy diet and the benefits of physical activity.[5,11] We did not provide any additional information, including any details of the nature of the intervention.

For diagnosis of gestational diabetes, we gave all participants an oral glucose tolerance test (75 g load) between 27 weeks and 28 weeks plus 6 days of gestation. We used diagnostic criteria recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)—ie, fasting venous glucose of 5·1 mmol/L or higher, 1 h venous glucose of 10·0 mmol/L or higher, 2 h venous glucose of 8·5 mmol/L or higher, or a combination of these.[12] We used these criteria not only because of their increasing adoption globally (and by WHO) but also because of differences in routine diagnostic criteria used by trial centres. We referred women who were diagnosed with gestational diabetes for antenatal diabetic services, according to local practice at every centre.

To assess the efficacy of the behavioural intervention, we gathered maternal dietary data and physical activity scores, calculated gestational weight gain, and took maternal anthropometric measurements. We used standard laboratory methods to measure biochemical outcomes between 27 weeks and 28 weeks plus 6 days of gestation.

We used a food frequency questionnaire[10,13] to assess the diet of participants for the month before randomisation and for the month before the study visit at between 27 weeks and 28 weeks plus 6 days of gestation. We adapted this questionnaire from one used in the UK arm of the European Prospective Investigation into Cancer Study.[13] We used WISP 3.0 (Tinuviel Software, Llanfechell, Anglesey, UK) to calculate nutritional composition and glycaemic load per 100 g of food and beverage items. We excluded from the analysis data for participants who we estimated were under-reporting (≤4·5 MJ/day) and over-reporting (≥20 MJ/day).[14]

We measured physical activity at randomisation and at the study visit between 27 weeks and 28 weeks plus 6 days of gestation. We used the International Physical Activity Questionnaire (IPAQ) and summarised data according to established methods.[10] We calculated physical activity (min/week) as metabolic equivalents (METs)—ie, the ratio of energy expenditure for an activity to energy expenditure at rest—with the formula 8·0×vigorous activity + 4·0×moderate activity + 3·3×light activity (walking).

At delivery of the infant, we measured and weighed the baby. We calculated customised birthweight centiles with Gestation Related Optimal Weight (GROW) software, version 6.7.5.1 (Gestation Network, Perinatal Institute, Birmingham, UK).

For more on **GROW software** see http://www.gestation.net

Outcomes

The primary maternal outcome was gestational diabetes. Prespecified secondary outcomes included dietary measures, physical activity scores, gestational weight gain, maternal anthropometric measurements (mid-arm and

thigh circumference and subscapular, triceps, biceps, and suprailiac skinfold thicknesses), and biochemical outcomes (maternal fasting plasma glucose, fasting plasma insulin, insulin resistance [calculated by homoeostatic model assessment, HOMA2-IR],[15] fasting triglycerides, LDL cholesterol, HDL cholesterol, and VLDL cholesterol). We prespecified several other secondary clinical maternal outcomes: pre-eclampsia (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both, on at least two occasions 4 h apart, with proteinuria ≥300 mg/24 h or spot urine protein:creatinine ratio ≥30 mg/mmol creatinine, or urine dipstick protein ≥2+); severe pre-eclampsia (defined as systolic blood pressure ≥170 mm Hg, diastolic blood pressure ≥110 mm Hg, or both, with proteinuria ≥500 mg/24 h or spot urine protein:creatinine ratio ≥50 mg/mmol creatinine, or urine dipstick protein ≥3+); mode of delivery (elective or emergency caesarean section, vaginal delivery, or operative vaginal delivery); induction of labour; blood loss at delivery (>1000 mL or >2000 mL); inpatient nights (antenatal and postnatal); referral to diabetic antenatal service after oral glucose tolerance test; and a requirement for insulin or metformin during pregnancy. Prespecified maternal secondary outcomes not reported here are listed in the appendix (p 2).

The primary neonatal outcome was delivery of a large-for-gestational-age infant, which we defined as the 90th or higher customised birthweight centile for gestational age, adjusting for maternal height and weight, ethnic origin, parity, and sex of the baby. We prespecified several secondary neonatal outcomes: gestational age at delivery; delivery at less than 37 weeks and less than 34 weeks; birthweight; birthweight 4·0 kg or heavier, 2·5 kg or lighter, or 1·5 kg or lighter; customised birthweight centile (≥95th, ≤10th, and ≤5th); neonatal death; days in special care baby unit; total inpatient days; discharge home on oxygen; confirmed infection; retinopathy of prematurity; neonatal hypoglycaemia; intraventricular haemorrhage; need for mechanical ventilation and duration; necrotising enterocolitis; pulmonary haemorrhage, skinfold thicknesses and circumferences; and birthweight centiles as population centiles (≥90th, ≥95th, ≤10th, and ≤5th). Prespecified neonatal secondary outcomes not reported here are listed in the appendix (p 2).

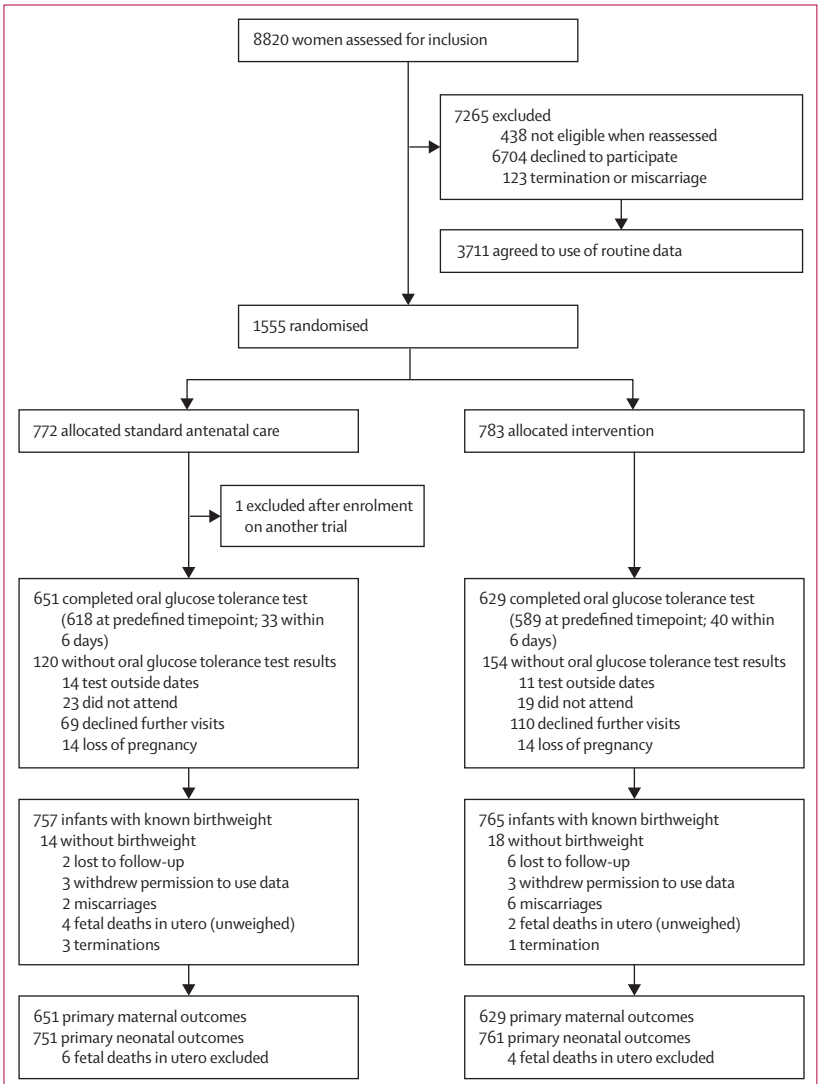

Figure: **Trial profile**

	Standard care (n=772)	Intervention (n=783)
Age (years)	30·4 (5·6)	30·5 (5·5)
BMI (kg/m²)	36·3 (4·6)	36·3 (5·0)
Ethnic origin	..	..
White	483 (63%)	490 (63%)
Black	200 (26%)	202 (26%)
Asian	48 (6%)	47 (6%)
Other	41 (5%)	44 (6%)
Parity	..	..
Primiparous	338 (44%)	336 (43%)
Multiparous	434 (56%)	447 (57%)
Current smoker	60 (8%)	48 (6%)
Previous history of gestational diabetes (multiparous only)	13/434 (3%)	19/447 (4%)
Family history of type 2 diabetes	181/767 (24%)	194/772 (25%)
Family history of gestational diabetes	20/742 (3%)	38/760 (5%)
Index of multiple deprivation*	..	..
1 (least deprived)	36/771 (5%)	29/778 (4%)
2	44/771 (6%)	59/778 (8%)
3	84/771 (11%)	93/778 (12%)
4	289/771 (37%)	245/778 (31%)
5 (most deprived)	318/771 (41%)	352/778 (45%)

Data are mean (SD) or number of women/total (%). *Scores were calculated for the region of residence, by fifths of the population. UK-wide scores were developed from English and Scottish data relating to employment and income domains.

Table 1: **Baseline characteristics of women**

Adverse events other than those prespecified as secondary outcomes included miscarriage, late termination of pregnancy, maternal accident, placental abruption, antenatal and postnatal sepsis, iatrogenic premature birth, intrauterine complications (fetal cardiac, renal, respiratory, and neurological), fetal death in utero, unspecified neonatal complications at birth, and confirmed neonatal sepsis.

Statistical analysis

We calculated that a sample size of 1546 women (allowing for 20% dropout) would provide at least 80% power to detect a clinically important 25% reduction in the incidence of gestational diabetes, from 30% (observed in the pilot study of 183 women)[9] to 23%. From a review of published population birthweight centiles in obese UK women,[16] 1546 infants provided 80% power to detect a 30% relative risk reduction for large-for-gestational-age infants (17·2% to 12·0%).

Our analysis was by intention to treat. We expressed treatment effects for binary endpoints as risk ratios (relative risk) with 95% CIs, using binomial regression and adjusting for maternal BMI, ethnic origin, and parity (ie, minimisation variables for intervention allocation). We calculated risk differences and did significance tests for both primary endpoints. For continuous measurements, we used linear regression with robust SEs, adjusting for baseline data or the variables used for minimisation. For physical activity data, we did median regression. For biochemical data, we did log transformations for normality, as appropriate. To check for the potential of a variable response to the intervention, we did subgroup analyses with interaction tests for BMI, ethnic origin, socioeconomic status, parity, and smoking. Moreover, to ascertain whether attendance at intervention sessions affected outcome, we did further interaction tests.

For the main analysis, we followed the missing-at-random assumption. Predictors of missingness, which we included to ensure an unbiased measure of treatment effect, were maternal BMI, ethnic origin, and parity. To test the possibility of undetectable bias attributable to missing data, we did a series of analyses under different missing-not-at-random assumptions for the primary

	Standard care	Intervention	Effect of intervention		p
			Risk ratio (95% CI)	Mean difference (95% CI)	
Gestational diabetes	172/651 (26%)	160/629 (25%)	0·96 (0·79–1·16)	–1·2% (–5·8 to 3·8)*	0·68
Fasting blood glucose (mmol/L)	4·71 (0·6), n=651	4·68 (0·6), n=629	..	–0·02 (–0·09 to 0·04)	0·49
1 h blood glucose (mmol/L)	8·02 (2·1), n=605	7·91 (2·1), n=584	..	–0·10 (–0·33 to 0·14)	0·43
2 h blood glucose (mmol/L)	5·94 (1·5), n=650	5·96 (1·5), n=628	..	0·02 (–0·15 to 0·19)	0·81
Treatment of gestational diabetes†	..	..	..	..	..
Dietary advice	69/146 (47%)	62/127 (49%)	1·03 (0·81–1·32)	..	0·80
Metformin	35/146 (24%)	34/127 (27%)	1·12 (0·74–1·68)	..	0·60
Metformin and insulin	16/146 (11%)	14/127 (11%)	1·01 (0·51–1·98)	..	0·99
Insulin	26/146 (18%)	17/127 (13%)	0·75 (0·43–1·32)	..	0·32
All pre-eclampsia	27/752 (4%)	27/753 (4%)	1·00 (0·59–1·69)	..	>0·99
Severe pre-eclampsia	10/752 (1%)	6/753 (1%)	1·64 (0·60–4·49)	..	0·33
Labour and delivery	..	..	..	..	..
Induction of labour	275/757 (36%)	251/765 (33%)	0·90 (0·79–1·04)	..	0·15
Unassisted vaginal delivery	399/757 (52%)	400/765 (52%)	0·99 (0·90–1·09)	..	0·87
Operative vaginal delivery	84/757 (11%)	94/765 (12%)	1·11 (0·84–1·46)	..	0·47
Caesarean section	274/757 (36%)	271/765 (35%)	0·98 (0·86–1·12)	..	0·75
Elective caesarean section	136/757 (18%)	160/765 (21%)	1·16 (0·95–1·43)	..	0·15
Emergency caesarean section	138/757 (18%)	111/765 (14%)	0·80 (0·63–1·00)	..	0·051
Post partum haemorrhage (mL)	..	..	..	..	..
≥1000	91/747 (12%)	109/755 (14%)	1·19 (0·91–1·54)	..	0·20
≥2000	10/747 (1%)	20/755 (3%)	1·98 (0·93–4·20)	..	0·075
Inpatient nights (n)	2·3 (1·8), n=691	2·4 (1·9), n=691	..	0·14 (–0·06 to 0·34)	0·16
Antenatal	2·9 (2·5), n=65	2·9 (3·5), n=74	..	–0·02 (–0·98 to 0·95)	0·98
Postnatal	2·2 (1·7), n=685	2·3 (1·6), n=684	..	0·08 (–0·09 to 0·25)	0·37
Gestational weight gain (kg)‡	..	..	..	..	..
Total	7·76 (4·6), n=567	7·19 (4·6), n=526	..	–0·55(–1·08 to –0·02)	0·041
Before pregnancy to 27–28 weeks + 6 days	5·40 (3·3), n=664	4·97 (2·9), n=637	..	–0·42(–0·75 to –0·09)	0·013

(Table 2 continues on next page)

	Standard care	Intervention	Effect of intervention		p
			Risk ratio (95% CI)	Mean difference (95% CI)	
(Continued from previous page)					
Mid-arm circumference (cm)	..	..	..	..	..
15–18 weeks + 6 days	36·8 (4·0), n=766	36·7 (4·1), n=775	..	..	..
27–28 weeks + 6 days	36·9 (4·2), n=663	36·6 (4·0), n=634	..	−0·19 (−0·39 to 0·01)	0·063
34–36 weeks + 0 days	36·6 (4·1), n=567	36·5 (3·9), n=526	..	−0·10 (−0·32 to 0·13)	0·40
Thigh circumference (cm)	..	..	..	..	..
15–18 weeks + 6 days	68·6 (6·5), n=766	68·6 (6·8), n=775	..	..	..
27–28 weeks + 6 days	69·2 (6·8), n=662	68·9 (6·6), n=635	..	−0·10 (−0·54 to 0·33)	0·64
34–36 weeks + 0 days	69·3 (6·7), n=566	68·9 (7·0), n=526	..	−0·48 (−1·01 to 0·05)	0·078
Sum of skinfold thicknesses (mm)§	..	..	..	..	..
15–18 weeks + 6 days	123 (27), n=763	123 (29), n=771	..	..	..
27–28 weeks + 6 days	127 (26), n=661	124 (27), n=632	..	−2·3 (−4·3 to −0·3)	0·022
34–36 weeks + 0 days	125 (27), n=561	122 (26), n=520	..	−3·2 (−5·6 to −0·8)	0·0081
Plasma fasting insulin (mU/L)	23·2 (2·4), n=510	22·5 (2·3), n=480	..	0·97 (0·87 to 1·08)¶	0·57
HOMA2-IR (units)	3·04 (2·1), n=496	2·99 (2·1), n=471	..	0·98 (0·89 to 1·07)¶	0·60
Plasma triglycerides (mmol/L)	..	..	..	..	..
27–28 weeks + 6 days	1·98 (1·41), n=505	1·92 (1·40), n=478	..	0·99 (0·96 to 1·02)¶	0·39
Plasma LDL cholesterol (mmol/L)	..	..	..	..	..
27–28 weeks + 6 days	3·66 (1·31), n=509	3·66 (1·35), n=479	..	1·01 (0·99 to 1·04)¶	0·27
Plasma HDL cholesterol (mmol/L)	..	..	..	..	..
27–28 weeks + 6 days	1·80 (1·29), n=509	1·80 (1·28), n=479	..	1·00 (0·98 to 1·02)¶	0·93
Plasma VLDL cholesterol (mmol/L)‖	..	..	..	..	..
27–28 weeks + 6 days	0·40 (1·41), n=505	0·38 (1·40), n=478	..	0·99 (0·96 to 1·02)¶	0·39

Data are number of women/total (%) or mean (SD), number of women. HOMA2-IR=homoeostatic model assessment. *For the primary maternal outcome, the risk difference (95% CI) is presented. †Treatment was recorded in women with gestational diabetes diagnosed according to predefined study criteria. ‡Gestational weight gain calculated using estimated weight before pregnancy. §Calculated by addition of biceps, triceps, suprailiac, and subscapular skinfold thicknesses. ¶For biochemistry data, the ratio of means (95% CI) is presented. ‖Calculated by Friedewald formula (triglycerides/5).

Table 2: **Maternal outcomes**

maternal and neonatal endpoints, with the Stata command rctmiss. We tested the assumptions that the odds of disease in participants with missing data were variously half or double that for women with complete data, in both study groups or in one group only. We did all analyses with Stata version 13.1.

This trial is registered with Current Controlled Trials, ISCRTN89971375.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From March 31, 2009, to June 2, 2014, 8820 pregnant women with a BMI of 30 kg/m² or higher were assessed for inclusion. Of 8259 eligible individuals, 1555 (19%) gave informed consent to participate and were randomly allocated to either standard antenatal care (n=772) or the behavioural intervention (n=783; figure). The mean BMI of participants was 36·3 kg/m² (SD 4·8); three-quarters of women were in the two highest quintiles of the index of multiple deprivation (table 1). Compared with 3711 individuals who declined to participate but agreed to use of routine data, participants were on average 10 months older and had a BMI that was 0·7 kg/m² higher (appendix p 3).

On average, women who were assigned the intervention attended seven (SD 3) of eight health trainer-led sessions, including four in person, and a further three by telephone or email. For sessions attended in person, 30% of women attended only one session, and 46% attended fewer than four. For sessions delivered by any method, 10% of women received only one session and 17% had fewer than four.

629 (80%) women in the intervention group and 651 (84%) in the standard care group had an oral glucose tolerance test and could be assessed for the primary maternal outcome. Demographic variables were similar between groups for women with primary outcome data (appendix p 4). The main reason for missing outcome data was that participants declined to attend further study

visits (figure). 129 (16%) women in the intervention group failed to complete the oral glucose tolerance test compared with 92 (12%) in the standard care group (p=0·02).

The incidence of gestational diabetes was similar between groups (table 2). Of women who had an oral glucose tolerance test, ten women in the intervention group and eight in the standard care group had their test done outside the predefined period. A sensitivity analysis excluding all data obtained outside this period gave similar results to the main analysis (intervention 150 [25%] of 589 *vs* standard care 164 [27%] of 618; risk ratio 0·96, 95% CI 0·79–1·16; p=0·67).

Compared with women assigned standard antenatal care, glycaemic index was reduced in participants assigned the intervention, as was mean intake of total energy, carbohydrate, saturated fat, and total fat; protein and fibre intake was increased (table 3). Physical activity was higher at 27–28 weeks plus 6 days of gestation in women in the intervention group versus the standard care group, which was attributable to more time spent walking (table 3).

Women in the intervention group had less gestational weight gain than did those in the standard care group at the time of the oral glucose tolerance test, and over the entire pregnancy (table 2). The sum of maternal skinfold thicknesses was also lower with the intervention at 27–28 weeks plus 6 days of gestation and at 34–36 weeks of gestation (table 2). Mode of delivery, post partum haemorrhage, or treatment of gestational diabetes did not differ between groups; likewise, no differences were noted between groups in fasting glucose, fasting insulin, or HOMA2-IR, or in any other biochemical variables measured at 27–28 weeks plus 6 days of gestation (table 2).

761 infants born to women allocated the intervention and 751 infants born to mothers in the standard care group had a known birthweight and could be assessed for the primary neonatal outcome (≥90th customised birthweight centile; table 4). The incidence of large-for-gestational-age infants did not differ between groups. Similar results were recorded in a sensitivity analysis allowing for possible selective bias in missing data (odds ratio 0·95, 95% CI 0·72–1·25, assuming a halving of the odds of large-for-gestational-age infants in the intervention group with missing data).

By population birthweight centiles (secondary outcome), 12% of infants were in the 90th centile or higher, and there was no difference between groups. Similarly, other neonatal secondary outcomes did not differ between groups, with the exception of neonatal hypoglycaemia, which was increased in the intervention group (table 4). As neonatal hypoglycaemia is treatable, it is not judged a severe adverse event. Neonatal anthropometric measures were evaluated in a subgroup of infants and did not differ between groups (appendix p 5).

Table 5 shows adverse events that were not prespecified as secondary outcomes. Adverse events did not differ between intervention and standard care groups.

Interaction tests for prespecified maternal demographic variables (BMI, ethnic origin, socioeconomic status, parity, and smoking) did not differ between standard care and intervention groups for the primary maternal or neonatal

	Standard care	Intervention	Mean difference (95% CI)	p
Nutrition				
Total energy (MJ/day)				
15–18 weeks + 6 days	7·8 (2·6)	7·6 (2·5)	..	..
27–28 weeks + 6 days	7·5 (2·3)	6·8 (1·9)	−0·70 (−0·96 to −0·45)	<0·0001
Glycaemic index (0–100)				
15–18 weeks + 6 days	56·9 (4·1)	56·8 (3·9)	..	..
27–28 weeks + 6 days	57·0 (3·9)	54·3 (3·9)	−2·6 (−3·0 to −2·1)	<0·0001
Glycaemic load per day				
15–18 weeks + 6 days	141 (56)	135 (51)	..	..
27–28 weeks + 6 days	133 (47)	112 (38)	−21 (−26 to −16)	<0·0001
Carbohydrate (% energy)				
15–18 weeks + 6 days	49·4 (7·4)	49·0 (7·4)	..	..
27–28 weeks + 6 days	48·6 (6·6)	47·2 (7·2)	−1·4 (−2·2 to −0·58)	0·0011
Protein (% energy)				
15–18 weeks + 6 days	19·7 (4·4)	20·1 (4·5)	..	..
27–28 weeks + 6 days	20·1 (4·0)	22·3 (4·6)	2·05 (1·5 to 2·5)	<0·0001
Total fat (% energy)				
15–18 weeks + 6 days	31·0 (5·5)	31·0 (5·3)	..	..
27–28 weeks + 6 days	31·5 (5·1)	30·5 (5·2)	−0·88 (−1·49 to −0·26)	0·0011
Saturated fat (g/day)				
15–18 weeks + 6 days	26·5 (11·5)	25·4 (11·0)	..	..
27–28 weeks + 6 days	26·4 (10·9)	22·0 (8·3)	−4·3 (−5·4 to −3·1)	<0·0001
Saturated fat (% energy)				
15–18 weeks + 6 days	12·7 (3·0)	12·5 (2·9)	..	..
27–28 weeks + 6 days	13·1 (3·0)	12·1 (2·8)	−0·85 (−1·2 to −0·51)	<0·0001
Fibre (g/day)				
15–18 weeks + 6 days	13·6 (6·0)	13·1 (5·3)	..	..
27–28 weeks + 6 days	12·6 (5·3)	13·4 (5·3)	0·83 (0·17 to 1·48)	0·013
Physical activity				
MET (min/week)				
15–18 weeks + 6 days	1386 (660–3052)	1386 (594–2982)	..	..
27–28 weeks + 6 days	1386 (639–3363)	1836 (792–4158)	295 (105 to 485)*	0·0015
Moderate or vigorous activity (min/week)				
15–18 weeks + 6 days	0 (0–180)	0 (0–180)	..	..
27–28 weeks + 6 days	0 (0–240)	30 (0–240)	0 (−18 to 18)*	>0·99
Walking (min/week)				
15–18 weeks + 6 days	280 (140–600)	280 (140–540)	..	..
27–28 weeks + 6 days	300 (132–630)	420 (180–840)	77 (28 to 126)*	0·0018

Data are mean (SD) or median (IQR). Women with reported total energy ≤4·5 MJ/day or ≥20 MJ/day at 15–18 weeks + 6 days of gestation were excluded from analyses of diet. Thus, in the standard care group, 571 women were assessed at 15–18 weeks + 6 days of gestation and 511 were assessed at 27–28 weeks + 6 days of gestation; corresponding figures in the intervention group were 574 and 435. Dietary intervention estimates were calculated by multiple regression and adjusted for pretrial values. For analyses of physical activity, in the standard care group, 678 women were included at 15–18 weeks + 6 days of gestation and 588 were assessed at 27–28 weeks + 6 days of gestation; in the intervention group, 683 and 559 women, respectively, were analysed. Physical activity estimates were calculated by bootstrapped (1000 replications) median regression, adjusting for pretrial values. MET is defined as the energy expenditure ratio of activity to rest; one MET is roughly equal to an individual's resting energy expenditure. MET, vigorous activity, moderate or vigorous activity, and walking were not prespecified endpoints. MET=metabolic equivalent of task. *Median difference (95% CI).

Table 3: **Maternal nutritional and physical activity outcomes, by period of gestation**

	Standard care	Intervention	Effect of intervention		p
			Risk ratio (95% CI)	Mean difference (95% CI)	
Large for gestational age (customised birthweight centiles)	..	..	..	..	..
≥90th	61/751 (8%)	71/761 (9%)	1·15 (0·83–1·59)	1·2% (–1·6 to 4·1)*	0·40
≥95th	32/751 (4%)	39/761 (5%)	1·20 (0·76–1·90)	..	0·43
≤10th	76/751 (10%)	95/761 (13%)	1·24 (0·93–1·64)	..	0·15
≤5th	43/751 (6%)	36/761 (5%)	0·83 (0·54–1·27)	..	0·39
Population birthweight centiles	..	..	..	..	..
≥90th	83/750 (11%)	96/761 (13%)	1·14 (0·87–1·50)	..	0·35
≥95th	42/750 (6%)	51/761 (7%)	1·20 (0·81–1·78)	..	0·37
≤10th	38/750 (5%)	53/761 (7%)	1·38 (0·92–2·06)	..	0·12
≤5th	19/750 (3%)	22/761 (3%)	1·14 (0·62–2·09)	..	0·67
Birthweight (kg)	3450 (580), n=751	3420 (580), n=761	..	–27 (–85 to 31)	0·37
≥4	105/751 (14%)	105/761 (14%)	0·99 (0·77–1·27)	..	0·93
≤2·5	36/751 (5%)	31/761 (4%)	0·85 (0·53–1·36)	..	0·50
≤1·5	9/751 (1%)	7/761 (1%)	0·77 (0·29–2·05)	..	0·60
Gestational age at birth (weeks)	39·5 (2·4), n=751	39·5 (2·0), n=761	..	0·02 (–0·2 to 0·2)	0·89
Delivery ≤37 weeks	48/751 (6%)	45/761 (7%)	0·93 (0·62–1·37)	..	0·70
Delivery ≤34 weeks	16/751 (2%)	15/761 (2%)	0·93 (0·46–1·86)	..	0·83
Hospital admission	..	..	..	..	..
Admission to neonatal unit	57/751 (8%)	65/761 (9%)	1·13 (0·80–1·58)	..	0·49
Time spent in neonatal unit, if admitted (days)	16·8 (30·2), n=52	11·6 (23·5), n=61	..	–0·26 (–9·65 to 9·13)	0·96
Time spent in hospital after birth, if admitted (days)	3·0 (9·0), n=733	2·8 (7·3), n=743	..	–0·06 (–0·86 to 0·74)	0·88
Neonatal death	2/771 (<1%)	3/783 (<1%)	0·98 (0·14–6·97)	..	0·99
Intraventricular haemorrhage, grade 3–4	2/751 (<1%)	0/760	..	..	..
Retinopathy of prematurity	1/751 (<1%)	1/760 (<1%)	0·99 (0·06–15·70)	..	0·99
Discharged home on oxygen	4/751 (1%)	2/760 (<1%)	0·49 (0·09–2·69)	..	0·41
Neonatal hypoglycaemia	12/751 (2%)	27/760 (4%)	2·22 (1·13–4·36)	..	0·020
Confirmed infection	14/751 (2%)	7/760 (1%)	0·49 (0·20–1·22)	..	0·13
Congenital abnormalities	6/751 (1%)	5/760 (1%)	0·82 (0·25–2·69)	..	0·75
Mechanical ventilation	21/751 (3%)	19/760 (3%)	0·89 (0·48–1·65)	..	0·72
Duration of mechanical ventilation (h)	500 (885), n=20	330 (573), n=16	..	–170 (–667 to 327)	0·49
Necrotising enterocolitis	2/751 (<1%)	0/760	..	..	..
Pulmonary haemorrhage	2/751 (<1%)	1/760 (<1%)	0·49 (0·04–5·43)	..	0·56

Data are number of children/total (%) or mean (SD), number of children. Population centiles were calculated with WHO centiles. *For the primary neonatal outcome, the risk difference (95% CI) is presented.

Table 4: **Neonatal outcomes**

outcomes (appendix p 6). Furthermore, no differences were recorded in maternal and neonatal primary outcomes with respect to whether the intervention had been delivered mainly in person or by telephone or email (maternal p=0·39; neonatal p=0·54), nor for women who attended more versus less than half the health trainer-led sessions (maternal p=0·56; neonatal p=0·59).

Discussion

Our findings suggest that a complex intervention addressing diet and physical activity in pregnant women with obesity is effective at improving diet quality and physical activity, reducing gestational weight gain, and decreasing surrogate measures of maternal body fatness. However, the intervention does not prevent development of gestational diabetes nor change the incidence of large-for-gestational-age infants in this population. Neither was evidence noted of a benefit on other pregnancy outcomes, including pre-eclampsia, which is associated with raised BMI.

By contrast with previous systematic reviews and meta-analyses of studies on a smaller scale to ours,[7,8] our null finding extends some observations. In particular, in two Danish studies of lifestyle interventions,[17,18] more than 350 obese pregnant women in each study were screened with an oral glucose tolerance test. Although analysis was not by intention-to-treat, a reduction in the primary outcome of gestational weight gain of around 1·5 kg was

recorded in both studies, but gestational diabetes was not decreased. In the Australian LIMIT randomised controlled trial in 2212 overweight and obese pregnant women,[19] a lifestyle intervention less intense than ours (in terms of frequency and personal contact) had no effect on gestational diabetes (a secondary outcome). Furthermore, no difference was noted in the proportion of large-for-gestational-age infants (the primary outcome) or in gestational weight gain, but the proportion of babies 4 kg or heavier at birth was lower in the intervention group.[19] The inference from systematic reviews that pregnancy lifestyle interventions might be an effective means to prevent gestational diabetes in women with obesity seems to have been biased by small-scale studies and methodological limitations.[6,7]

On average, seven of the eight intervention sessions were attended by women assigned to the intervention, whether in person or by telephone or email. There was no indication that failure of adherence, mode of session delivery, ethnic origin, or socioeconomic status of the women affected the primary outcomes. Further planned analyses will ascertain whether coverage of sessions affected specific elements of dietary and physical activity behavioural change. Measurement of several biomarkers of glucose intolerance and insulin resistance, as well as the metabolome, at study entry and after the intervention will also establish whether early risk stratification can identify a subgroup of women in whom the intervention could show clinical benefit.

Our study was set in UK inner-city settings of ethnic diversity and high socioeconomic deprivation. Black women were the predominant minority ethnic subgroup (26%); individuals of this ethnic origin have a high risk of obesity in pregnancy in the UK,[20] which, as elsewhere, is strongly related to socioeconomic deprivation. Similar to previous studies,[17–19] large numbers of women had to be approached to meet our recruitment target, and the drop-out rate in our study for oral glucose tolerance testing was similar to previous studies.[17,18] The reluctance of pregnant women with obesity to take part in a complex behavioural intervention suggests that lifestyle interventions can improve healthy behaviours, but only in a subgroup of motivated individuals. Likewise, the 5% higher proportion of women who dropped out of the study from the intervention group than the standard care group, although a limitation, was not unexpected. Despite small numerical differences, participants were similar to individuals who declined participation with respect to demographic characteristics, suggesting generalisability of outcomes to populations of this demographic complexity.

The self-reported reduction in glycaemic load in the intervention group was larger than that noted in previous similar pregnancy intervention studies,[21,22] a potential reflection of the intensity of our intervention, which included motivational interviewing every week for 8 weeks, goal setting, and behavioural self-monitoring.[23] Together with reduced intake of saturated fat and total energy in the intervention group, these outcomes could be the reasons for the modest lowering of gestational weight gain and measures of fat mass noted in our study. Although we acknowledge the limitations of dietary assessment by self-report, the size of the improvement was similar to that recorded in the pilot trial,[9] in which a more rigorous assessment method was used. Thus, we conclude that the behavioural intervention increases healthy dietary behaviours, but that the modest size of the effect is inadequate to reduce the risk of gestational diabetes or improve insulin sensitivity in women who are obese at the time of conception.

The incremental rise in physical activity achieved with the intervention was also inadequate to improve glucose tolerance. A minimum of 16 MET h/week of physical activity has been suggested to be needed to reduce the risk of gestational diabetes,[24] which equates to 41 min/day of walking; this amount is well above the 12–13 min increase (or <1 mile) reported by women in our study, which was similar to the increase in physical activity reported in the LIMIT trial intervention group.[22] Again, we are aware of the limitations in accuracy of self-report; indeed, in the pilot trial, physical activity was assessed by accelerometry, and no increase in exercise levels was reported in the intervention group compared with women in the standard care group.[9] However, this method of objective assessment is recognised to be ineffective at measuring low-intensity activity that, as we report here, was increased by self-report.

Although not the primary maternal outcome of this study, the 0·55 kg lower gestational weight gain in the intervention group compared with the standard care group adds to growing evidence from other studies that a substantial reduction in gestational weight gain is unlikely to be achievable in women with obesity through interventions adressing diet, physical activity, or both.[17,18] The reduction achieved was less than that reported in a meta-analysis of previous studies (–2·41 kg),[6] which

	Standard care (n=772)	Intervention (n=783)	p*
All miscarriage	14	18	0·50
Late termination of pregnancy	3	1	..
Maternal accident	1	0	..
Placental abruption	0	1	..
Maternal antenatal sepsis	1	0	..
Maternal postnatal sepsis	1	0	..
Iatrogenic preterm birth	2	2	..
Intrauterine complications (cardiac, neurological, renal, respiratory)	2	3	..
Fetal death in utero	10	6	0·30
Unspecified neonatal complications at birth	2	1	..
Neonatal sepsis	1	0	..

*p values were only calculated if data were sufficient.

Table 5: **Adverse events not prespecified as secondary outcomes**

could reflect our rigorous trial method (ie, intention-to-treat analysis), the high mean BMI, ethnic diversity, and low socioeconomic status of the UPBEAT participants, or that gestational weight gain was not the main focus of this study.

Ongoing follow-up of mothers and their children in the UPBEAT study will ascertain whether the changes recorded in diet, physical activity, and maternal anthropometric measures are sustained or extended and can benefit maternal and child health in the longer term. Although gestational diabetes was not prevented, the behavioural intervention has the potential to reduce the risk of obesity and adverse metabolic risk in the child, because excessive gestational weight gain, high maternal fat mass, and increased glycaemic load are all associated independently with greater adiposity in the offspring, potentially through epigenetic pathways.[3,25,26]

We had anticipated that 17% of babies in our study would be in the 90th centile or higher, whereas the recorded incidence was 9% and 12% by customised and population centiles, respectively. This incidence is well below the 16% reported in UK women with similar BMI (range 35·0–39·9 kg/m²),[27] and roughly half of that noted in the LIMIT trial (20%), which included women who had a lower BMI.[19] Our use of IADPSG criteria for diagnosis of gestational diabetes could partly explain the low incidence of large-for-gestational-age babies in our study. To our knowledge, no previous study of women with obesity has diagnosed gestational diabetes with these criteria, and a quarter of women in both groups in our trial had gestational diabetes. Only 9% would have had a diagnosis of gestational diabetes had we used the previous WHO guidelines.[11] Diagnosis and treatment of more women with gestational diabetes in this study compared with current clinical practice in the UK could, therefore, account for the lower incidence of large-for-gestational-age infants to roughly population levels (10%). In line with this notion, a 50% reduction in large-for-gestational-age infants was reported after treatment of women with mild gestational diabetes[28] that fell below conventional diagnostic thresholds but would have been treated by the new criteria. Women were treated according to local practice at trial centres, 83% receiving treatment after a diagnosis of gestational diabetes. Although local practice might have differed, randomisation was minimised to centre, and variable practice is unlikely to have affected primary trial outcomes. Indeed, had all women been treated, as recommended by the IADPSG, the incidence of large-for-gestational-age infants might have been reduced further. Universal testing of all participants in our study for gestational diabetes, independent of the diagnostic criteria, might have contributed to the difference between trial and population incidences of large-for-gestational-age infants because, despite NICE recommendations, universal testing of women with obesity is not adopted across the UK.[11]

Several neonatal outcomes, including birthweight and inpatient days, were lower than UK outcomes for women with obesity,[27] although caesarean section rates were similar, potentially a reflection of current management of women with a diagnosis of gestational diabetes. Participation in a clinical trial is in itself unlikely to be a cause of lower than anticipated incidence of large-for-gestational-age infants because no evidence for such an effect was noted in the LIMIT trial, in which the incidence of large-for-gestational-age infants was 20%.[19] Comparison of the incidence of large-for-gestational-age infants with eligible women who declined participation was precluded because those with available birthweight data had a significantly lower BMI than did the group as a whole.

Our study highlights the need for randomised controlled trials in women with obesity that do universal testing and formally compare IADPSG and older diagnostic criteria for gestational diabetes. In the UK, comparison should be made with the most recent NICE criteria, which do not align with IADPSG.[11]

More infants born to mothers in the intervention group developed neonatal hypoglycaemia than did those in the standard care group, but statistical power for this outcome was low. This finding contrasts with that of a meta-analysis of smaller lifestyle intervention studies, which showed no effect.[6] Ten infants in the intervention group with hypoglycaemia were fed formula milk from birth, compared with two in the standard care group (37% *vs* 16%; p=0·04). Since early introduction of formula feeding has been associated with neonatal hypoglycaemia,[29] this factor could be contributory. The rates of exclusive breastfeeding (p=0·73) or formula feeding (p=0·63) did not differ at neonatal discharge between the two study groups; therefore, this finding is likely to be attributable to chance.

The behavioural intervention we assessed in this study could provide a means to improve healthy behaviours in obese pregnant women. It offers an alternative to current UK NICE guidelines,[5] which recommend general healthy eating and physical activity for pregnant women with obesity with little evidence for proven change in behaviours. The potential benefit of the intervention on post-pregnancy infant health and on maternal and infant long-term health needs further investigation, which is under way. Increasing the intensity and duration of the intervention, which is already greater than that adopted in previous studies,[6,17,19,23] is likely to be impractical for most women with obesity.

The current focus on behavioural interventions to prevent gestational diabetes would seem to be misplaced. The intervention we assessed could be used as an evidence-based method to encourage healthy dietary and physical activity behaviours in women with obesity. However, efforts to prevent gestational diabetes should be diverted towards not only trials of targeted interventions, including pharmacotherapy but also establishing optimum diagnostic criteria for gestational diabetes to reduce risk of adverse outcomes. Importantly, renewed efforts are needed at the population level to prevent obesity in women of reproductive age.

Contributors

LP, NS, SMN, and EO-N devised the original proposal and secured funding. LP had overall responsibility for the study and ALB for trial management. LP, ALB, RB, HC, KMG, LH, NK, SMN, JS, PTS, NS, JW, and TABS drafted the protocol. SCR and MKW contributed to data collection. PTS, NP, and DP contributed to the statistical analysis plan and data analysis. LG and ACF were responsible for dietary data and analysis. LP, NS, SMN, and KMG wrote the original draft of the report. All authors contributed to data interpretation and approved the final report.

Declaration of interests

LP reports a research grant from Abbott Nutrition, outside the submitted work. TABS reports personal consultancy fees from the Natural Hydration Council, Heinz Foods, Archer Daniels Midland, the Global Dairy Platform, and GlaxoSmithKline, outside the submitted work; and is a trustee and scientific governor for the British Nutrition Foundation, outside the submitted work. KMG reports reimbursement of travel and accommodation expenses from Nestle Nutrition Institute, outside the submitted work; research grants from Abbott Nutrition and Nestec, outside the submitted work; and patents pending for phenotype prediction, predictive use of CpG methylation, and maternal nutrition composition, outside the submitted work. All other authors declare no competing interests.

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