Infant adiposity following a randomised controlled trial of a behavioural intervention in obese pregnancy.

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Clinical Trial Registry Name and Registration Number

The UPBEAT trial is registered with Current Controlled Trials, ISRCTN89971375.

Abbreviations

BISQ- Brief Infant Sleep Questionnaire; BMI- Body Mass Index; CDM- Covariate-dependent Missing ; FFQ- Food Frequency Questionnaire; GDM- Gestational Diabetes; GI- Glycaemic Index; GL- Glycaemic Load; GWG- Gestational Weight Gain; IPAQ- International Physical Activity Questionnaire; MET- Metabolic Equivalent of Energy Expenditure; MAR- Missing at Random; MNAR- Missing not at Random; UPBEAT-UK Pregnancies Better Eating and Activity Trial.

Contributors' Statement Page

Dr Nashita Patel, Mr Paul Seed, Dr Dharmintra Pasupathy and Professor Lucilla Poston conceptualized and designed the study, drafted and carried out the initial analyses, critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr Louise Hayes, Ms Julia Levin, Dr Sara White and Ms Angela Flynn carried out the initial dietary and physical activity analyses. All these authors critically reviewed and approved the final manuscript as submitted.

Dr Annette Briley, Dr Eugene Oteng-Ntim, Professor Stephen Robson, Professor Scott M Nelson, Ms Claire Singh designed the data collection instruments, and coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

Professors Ruth Bell, Keith Godfrey, Debbie Lawlor, Naveed Sattar and Jane Wardle designed the data collection instruments, critically reviewed the manuscript and approved the final manuscript as submitted.

Abstract

Objective.

Randomised controlled trials are required to address causality in the reported associations between maternal influences and offspring adiposity. The aim of this study was to determine whether an antenatal lifestyle intervention in obese pregnant women associated with improved maternal diet and reduced gestational weight gain leads to a reduction in infant adiposity and sustained improvements in maternal lifestyle behaviours at 6 months postpartum.

Subjects and Methods.

We conducted a planned postnatal follow up of a randomised controlled trial (UPBEAT) of a complex behavioural intervention targeting maternal diet (glycemic load and saturated fat intake) and physical activity in 1555 obese pregnant women. The main outcome measure was infant adiposity, assessed by subscapular and triceps skinfold thicknesses. Maternal diet and physical activity, indices of the familial lifestyle environment, were assessed by questionnaire.

Results.

698 (45.9%) infants (342 intervention, 356 standard antenatal care) were followed up at mean age 5.92 months. There was

no difference in triceps skinfold thickness z-scores between the intervention vs. standard care arms (difference -0.14 SD, 95% CI -0.38 to 0.10, p=0.246), but subscapular skinfold thickness z-score was 0.26 SD (-0.49 to -0.02; p=0.03) lower in the intervention arm. Maternal dietary glycemic load (-35.34; -48.0 to -22.67; p<0.001) and saturated fat intake (-1.93% energy; -2.64 to -1.22; p<0.001) were reduced in the intervention arm at 6 months postpartum. Causal mediation analysis suggested that lower infant subscapular skinfold thickness was mediated by changes in antenatal maternal diet and gestational weight gain rather than postnatal diet.

Conclusion.

This study provides evidence from follow-up of a randomised controlled trial that a maternal behavioural intervention in obese pregnant women has the potential to reduce infant adiposity and to produce a sustained improvement in maternal diet at 6 months postpartum.

Introduction

The high prevalence of childhood obesity is a major health concern, with 27.3% of children estimated to be overweight or obese in the USA[1]. A combination of antenatal and postnatal exposures including environmental factors have been implicated in the development of childhood obesity[2,3], which has been shown to track into adulthood[1]. Observational studies suggest that manipulation of maternal metabolism through diet and/or physical activity in the antenatal period has the potential to reduce childhood obesity[2,4] and this has been unequivocally achieved in pregnant obese experimental animals and their offspring[5]. These observations have led to a consensus that obesity is in part 'programmed' *in-utero*, in keeping with the 'developmental programming' hypothesis[5]. Recent analyses using Mendelian randomisation methods have provided evidence for a causal relationship between maternal pregnancy body mass index (BMI) and glucose with birth weight[6], but any lasting causal effect on later infant adiposity is unknown. Well-designed randomized controlled trials in pregnant women and their offspring are required to infer causality through minimising selection bias and confounding[5,7].

We undertook an RCT, the UK Pregnancies Better Eating and Activity Trial (UPBEAT) of a dietary and physical activity intervention in 1555 obese pregnant women[8]. Women were randomised to standard antenatal care or standard antenatal care with an intense behavioural intervention that focussed on improving insulin sensitivity through reducing dietary glycemic load and saturated fat intake[8]. Although the intervention did not reduce gestational diabetes (GDM) or large for gestational age delivery, the primary outcomes, there were significant improvements in maternal antenatal diet (maternal glycaemic load/day at 28 weeks' gestation, mean difference -21, SD -26 to -16, p=<0.0001), a reduction in maternal anthropometric measures of body fat assessed by sum of skinfold thicknesses (-3.2mm, -5.6 to -0.8, p=0.008) , lower total gestational weight gain (GWG) (-0.55kg, -1.08 to -0.02, p=0.041), and a modest improvement in physical activity at 28 weeks' gestation (295 min/week, 108 to 485, p=0.0015)[8], all of which have been implicated in childhood obesity.

To examine the hypothesis that the lifestyle intervention might reduce the influence of maternal obesity on offspring adiposity, our principal aim was to assess whether the UPBEAT intervention was associated with a reduction in measures of

childhood adiposity at 6 months of age, a pre-defined hypothesis within the trial protocol[9]. We also examined whether the pregnancy intervention had lasting effects on maternal diet and physical activity, and on known postnatal determinants of infant adiposity, including breastfeeding.

Patients and Methods

Study design and setting

Between July 2010 and May 2015, we conducted a planned follow up at 6 months postpartum of mothers and their offspring who had participated in the UPBEAT RCT in eight inner-city NHS Trust Hospitals in the UK. The study design and protocol[9] were approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 09/H0802/5).

Participants and consent

1555 women were recruited to the UPBEAT trial (≥16 years of age; pre-pregnancy BMI ≥30 kg/m^2). Exclusion criteria included pre-existing disease and multiple pregnancy[9]. Following informed consent for themselves and follow up of their infants at 6 months postpartum, the participants were randomised to the intervention or standard antenatal care at 15^{+0}-18^{+6} weeks' gestation. For the purposes of this follow up study, women (but not their children), were excluded if pregnant at 6 months postpartum. If a participant had withdrawn from the trial but was willing to take part (n=2), written consent was obtained at the 6 month visit. Infants were excluded if aged $\leq$4 months or

≥8 months of age at this visit. Comparison of demographic details at trial entry was made between women who declined to participate and those who took part.

Outcomes

Infant anthropometry

The principal outcome of interest was infant adiposity assessed by measurement of infant skinfold thicknesses (triceps and subscapular, measured in triplicate by trained research staff using infant skinfold callipers). Subsidiary infant outcomes of infant adiposity included sum of skinfold thickness (calculated by addition), estimated total body fat (calculated by applying validated equations specific for infant sex[10]), weight (using a calibrated scale[9]), abdominal and upper mid-arm circumferences. For these measures, when reference World Health Organization population data were available, z-scores were calculated[11], including adjustment for infant age, sex and length. These standards are applicable to infant growth regardless of ethnicity, socioeconomic status and mode of feeding[11]. Z-scores were calculated for infant subscapular, triceps skinfold thickness, weight, BMI and arm circumference but not for sum of skinfold thicknesses. Occipitofrontal circumference, and crown-rump length and

crown-heel length obtained with a calibrated infantometer, were also measured.

Duration of breastfeeding, weaning history, measures of appetite, infant sleeping patterns, physical activity,healthcare resource use and childcare[9] were pre-specified outcomes. These were evaluated using the Infant Feeding and Growth Questionnaire[12], the Child Eating and Behaviour Questionnaire[13], the BISQ (Brief Infant Sleep Questionnaire)[14], the Infant Behaviour Questionnaire (for child physical activity)[15] and questionnaires ascertaining infant health, medical resource use and early care and education, respectively.

Maternal dietary and physical activity analysis

Maternal diet at 6 months postpartum was assessed using the same semi-quantitative food frequency questionnaire (FFQ) and analysed as previously reported for the mothers during their pregnancy[8]. Data was analysed only in questionnaires which were fully completed for both maternal diet and physical activity. Those with incomplete/missing dietary data were excluded (65.8%). There was no missing physical activity

267 data. The main outcomes of interest were maternal dietary
268 glycaemic load, saturated fat intake and energy intake. Other
269 outcomes included glycaemic index (GI), glycaemic load (GL),
270 protein and fibre intake. Physical Activity was assessed, as it
271 had been in pregnancy, using the International Physical
272 Activity Questionnaire (IPAQ) and summarised as metabolic
273 equivalents (METs) of energy expenditure[16].

274

275 *Statistical analyses*

276 A complete-case analysis was undertaken for all participating
277 mothers and infants.Treatment effects for continuous
278 outcomes were expressed as differences in means obtained
279 from multivariable linear regression, and binary endpoints as
280 risk ratios with 95% confidence intervals (95%CI) obtained
281 using binomial regression. For both we adjusted for
282 minimisation variables (maternal BMI at trial enrolment, parity
283 and ethnicity) and infant sex and age at follow up. We
284 evaluated the number of intervention contact sessions during
285 pregnancy on measures of infant adiposity.

286 Although loss to follow-up was similar in both of the trial arms,
287 we assessed the possibility that loss to follow-up resulted in
288 selection bias using three complementary methods (further
289 details in Supplementary Text 1). All sets of analyses were pre-

planned sensitivity analyses. First, we used Little's chi-squared covariate-dependent missing (CDM) test to explore evidence of data being missing not at random (MNAR), i.e. examining the possibility that in those who were lost to follow-up the effect of the intervention on outcomes differed from those who did attend the follow-up[17]. This was done for both offspring and maternal outcomes. Second, for the primary offspring outcomes only (subscapular and triceps skinfold thicknesses), we generated several simulation datasets, over a range of scenarios regarding missing data in both arms of the study that were informed by predictors of loss to follow-up (maternal BMI, parity and ethnicity)[18]. The scenarios selected aimed to cover a range of plausible situations that could result in bias under the assumption of data being missing at random (MAR). Thirdly, for the primary infant outcomes we used multivariate imputation chained equations to impute missing data for infant adiposity. Data were imputed to create 50 datasets using 10 burn-in iterations for live-born infants using the following in the multivariate equations: maternal trial entry BMI, age, ethnicity, parity, early pregnancy smoking status, randomisation allocation, measures of maternal anthropometry including GWG, maternal diet and physical activity at 27-28^{+6}, 34^{+0}-36^{+0} weeks' and 6 months postpartum (glycaemic load, glycaemic index, saturated fat, carbohydrate,

protein, energy intake), gestation at delivery, infant sex, age at follow up, mode and duration of early feeding, sleep, child health and infant inpatient admissions. The multivariate imputations assume MAR and can also increase statistical power and so allow us to explore whether loss to follow-up might have resulted in type-2 statistical errors. Full details of all of these sensitivity analyses are provided in Supplementary Text 1. Analyses were performed using Stata version 14.0.

Results

Participants

Of the 1555 participants randomised to UPBEAT at 15^{+0}-18^{+6} week's gestation between July 2010 and May 2015 and with a live born infant, 1522 were approached at this time. Of these 1522, 720 (47.3%) infants and 707 (46.5%)mothers took part in this study. Thirteen mothers were excluded as they were pregnant at time of study, and 22 infants were excluded because the follow up appointment was held ≤4 months or ≥8 months postpartum (Figure 1). In comparsion to those who did not take part, mothers who attended the 6month visit were on average 1.3 years older, more likely to be Caucasian, nulliparous, to have had GDM in the index pregnancy(28.2% vs. 23.3%; p=0.041), and were less likely to be current smokers (Supplementary Table 1a, Supplementary Text 1). There were no differences in maternal early pregnancy BMI and sum of skinfold thicknesses between women who participated in the 6 month follow-up visit compared to those who did not.

Women in the intervention arm demonstrated reduced GWG as previously reported[8]. The infants who attended the 6 month appointmenthad a longer gestational age at delivery (by 2 days), were 67g heavier, and more likely to have been

breastfed at birth than those that did not attend (Supplementary Table 1b).

There was no difference between mean maternal BMI between the intervention and standard care groups at trial entry (36.17 vs. 36.31 kg/m^2, respectively) or at 6 months postpartum (36.26 vs. 36.45 kg/m^2, respectively). The incidence of maternal smoking at 15^{+0}-18^{+6} weeks' gestation was higher in the standard antenatal care arm in comparison to the intervention arm (5.6% vs. 2.0%)(Table 1). There were no differences in all other demographic and clinical variables between the two study arms (Table 1).

Infant anthropometry

Three hundred and fifty six infants in the standard antenatal care arm and 342 infants in the intervention arm (mean age 5.82 months) had anthropometric measurements at age 6 months. There was no statistical difference in triceps skinfold thickness in the intervention vs. the standard care arm (difference -0.14 SD, 95% CI -0.38 to 0.10), p=0.246), but subscapular skinfold thickness z-score was -0.26 SD (-0.49 to -0.02; p=0.031) lower in the intervention arm (Table 2). Infants

366 in the intervention arm had a 5% lower subscapular skinfold
367 thickness (-0.38mm; -0.70 to -0.06; p=0.021), compared to
368 infants in the standard antenatal care arm (Table 2). The infant
369 sum of skinfold thickness was 0.63mm lower in the
370 intervention arm, but did not reach statistical significance
371 (p=0.058) in comparsion to the standard antenatal care arm
372 (Table 2). There were no differences in BMI z-score and
373 abdominal circumference (Table 2) or in other anthropometric
374 measures between the two arms(Supplementary Table 2).

375 Maternal smoking status at trial entry did not influence the
376 difference in subscapular skinfold thickness between the two
377 arms (Supplementary Table 3). Undertaking sensitivity
378 analyses for deviation from the missing at random assumption,
379 significant differences in infant subscapular skinfold thickness
380 (mm) were found within a range of -0.35 to -0.38mm
381 dependent on the assumption of missinginess taken
382 (Supplementary Text 1 and Supplementary Table 4). Similar
383 results to the complete-case analysis were also observed for
384 infant triceps skinfold thickness (Supplementary Table 5).

385

386 There was no difference in infant feeding between the two
387 trial arms, nor appetite and satiety responsiveness and infant
388 childcare. Infants were exclusively breastfed, on average for

82.7 (SD 65.3) days and total number of hours spent sleeping were similar between arms (Supplementary Table 7). There was an increase in infant inpatient nights in the intervention arm, attributable to 1 infant requiring long-term hospital admission due a ventricular septal defect repair (Supplementary Table 7). We observed no differences in infant use of medications (Supplementary Table 6) or in cause of hospital inpatient admissions, exect for gastrointestinal related disorders, which were lower in the intervention arm (Supplementary Table 8). There was no association between the number of antenatal contact sessions with the health trainer and measures of infant anthropometry (Supplementary Table 9).

No interactions were observed between randomisation allocation and infant sex (Supplementary Table 10), but there was a significant interaction of breast feeding (< 3mths/ ≥3mths) with the intervention; triceps skin fold thickness was lower in infants of mothers in the intervention arm who breastfed ≥3 months *vs* those in the standard care arm -0.90mm (-1.59 to -0.21); p=0.011; Wald interaction test; p=0.016) (Figure 3). Similar patterns of differences of effect by breastfeeding for sum of skinfold thicknesses, estimated total body fat and arm circumference did not achieve statistical

412 significance (p-values for interactions all ≥ 0.05)
413 (Supplementary Table 11).

414

415 *Maternal diet and physical activity*

416 In those women who provided complete dietary data GI, GL,
417 saturated fat and total energy intake were reduced in the
418 mothers in the intervention arm in comparison to standard
419 care, as well as a significant reduction in total fat and protein
420 intakes (Figure 2 & Table 3). When the under-reporters
421 (calorie intake) were included in sensitivity analyses, there
422 were no differences in the effect size estimates of dietary
423 variables. Furthermore we found no difference in maternal
424 characteristics (including maternal age, BMI and
425 socioeconomic deprivation status) between those under-
426 reporting and those not under-reporting calorie intake. There
427 was no effect of the intervention on maternal physical activity
428 (Table 3).

429

430 Causal analysis suggested direct effects of the intervention
431 associated reduction in maternal early GWG (between 15-18^{+6}
432 and 27-28^{+6} weeks' gestation) (p=0.015), late GWG (between
433 27-28^{+6} and 34-36 weeks' gestation) (p=0.009), total GWG

(p=0.014) and maternal dietary saturated fat intake at 27-28^{+6} week's gestation (p=0.016) in relation to infant subscapular skinfold thickness at age 6 months (Supplementary Figure 1). In contrast, there was no suggested effect of postnatal maternal diet on the observed differences in infant subscapular skinfold measurements (Supplementary Figure 2). As there was no effect of the intervention on maternal physical activity, there was no rationale for exploring a causal mediating impact of maternal physical activity on offspring adiposity.

Discussion

This study has addressed the effect of a pregnancy lifestyle behavioural intervention in obese women on offspring adiposity and maternal diet and physical activity at 6 months postpartum. We have found, to our knowledge for the first time, that a dietary and physical activity intervention in pregnant women with obesity was associated with a reduction in a measure of offspring adiposity, and that changes in maternal diet during pregnancy persisted into the postnatal period. Further analyses suggested that the effect of the intervention on offspring adiposity was independently mediated by the observed reduction in maternal gestational weight gain, dietary fat and energy intake in pregnancy and therefore an expectation that lifestyle interventions have the potential to reduce offspring adiposity. Subscapular skinfold thickness, in comparison to the other anthropometric measurements assessed, is recognised as an accurate index of central adiposity, with a generally lower measurement error than triceps skinfold thickness[19,20]. In children and adults, subscapular skinfold thickness has been related to impaired glucose metabolism, and in adolescents to increased serum cholesterol concentration[21, 22]. It is plausible, therefore that the maternal dietary and weight changes resulting from the

intervention may influence infant body composition towards a healthier metabolic profile[22-24].

Although the magnitude of difference in this measure of adiposity (subscapular skinfold thickness) between intervention and controls arms was modest (5%), it reflected a 0.26 reduction in z-score, which incorporated adjustment for infant sex, age and length to allow comparisons to a reference population. Indications from mother-child cohorts, including the USA Project Viva study, suggest that even modest differences in body composition at age 6 months may be amplified as the child grows older, and that this may be apparent as early as 3 years[25]. The Bogalusa Heart Study observed that greater offspring childhood subscapular skinfold thickness related to parental type 2 diabetes was associated with a subsequent adverse metabolic profile in early adulthood[22]. Any persistent influence of the intervention on childhood obesity will only be revealed as the children grow up, but an abundance of evidence suggests that increased adiposity tracks from infancy, through childhood to adulthood[1].

We are aware of only two relevant similar studies. The first, the Lifestyle in Pregnancy study (LIP)[26], assessed body composition in older infants (2.8 years) of obese mothers(n=157) who had been randomised to an antenatal lifestyle intervention with the primary aim of reducing gestational weight gain. No change in infant total fat mass, as assessed by DEXA scan, was observed[27]. However, it was not reported whether this intervention modified specific components of maternal antenatal diet or body composition, although a reduction in median gestational weight gain was observed. Secondly, a recent RCT of a low glycaemic diet, but in women of heterogenous BMI, despite a difference in reduction of thigh circumference found no difference in infant body composition at 6 months of age between intervention and control arms[28, 29]. The difference between these studies and UPBEAT may relate to the greater intensity of the UPBEAT intervention, involving 8 contact sessions with health trainers, at weekly intervals [8].

There remains a paucity of data regarding the long-term efficacy of lifestyle interventions in obese pregnant women[5]. Our study has shown that dietary advice focussing on reduction of maternal insulin resistance, as a component of a

complex intervention, can have a prolonged effect which may have potential to improve long term health as well as familial nutritional environment[12, 30, 31]. We did not, however, find any differences between groups in maternal BMI or measures of adiposity at 6 months postpartum. A sustained effect of any maternal dietary intervention on maternal dietary intake postpartum has to our knowledge not been reported previously. In contrast, in the LIMIT trial, follow up of 50.5% of participants, reported no difference in maternal dietary composition at 4 months postpartum[32], also by self-report. The lower magnitude of intervention effects on maternal dietary variables compared with UPBEAT may explain these differences.

Using the method of causal mediation analysis, we found evidence that the lower dietary saturated fat and energy intake at 28 weeks' gestation induced by the UPBEAT intervention, rather than the change in glycemic load, was associated with the reduction in infant subscapular skinfold thickness at 6 months of age. The reduction in gestational weight gain irrespective of timing and total gestational weight gainwere also directly associated with the observed difference. These observations would concur with several

reports describing associations between maternal gestational weight gain or diet and offspring adiposity[4, 33, 34]. Antenatal interventions shown to improve maternal diet and subsequently reduce GWG may therefore be pragmatic and effective measures to reduce early infant adiposity.

The observation that exclusive breastfeeding for more than 3 months may interact with the maternal intervention to reduce offspring triceps skinfold thickness provides some evidence that breast feeding may compound the benefits of the maternal intervention, although caution should be exercised in over-interpretation as the study was not powered to test interactions such as these. The role of other intrauterine exposures remains to be elucidated; whilst we previously reported no differences in fasting lipids, c-peptide and insulin at 28 weeks' gestation between randomisation arms[8], ongoing biochemical and metabolomic analyses in maternal and cord blood may provide insight into mechanistic pathways.

A limitation of our study was the follow up of only 47.3% of those infants eligible from the original RCT[8], but this was similar to the rate of follow up of recently published RCTs in pregnant women[27, 28, 35]. Due to the stringent inclusion of only

559 complete dietary questionnaires, maternal dietary data was
560 calculated only for 34.2% of the mothers. The dietary data was
561 by self report but compared favourably to a more rigorous
562 method (triple pass 24hr recall) as assessed in the pilot trial[36].
563 Strengths of the study include the prospective collection of in-
564 depth data addressing familial and individual determinants of
565 infant adiposity, and of maternal *in-utero* exposures. The
566 richness of data in the UPBEAT study can be considered both a
567 strength and limitation. Whilst providing comprehensive
568 information relevant to developmental origins of early infant
569 obesity, and assessment of mediation effects, limits are
570 imposed on interpretation of secondary analyses in the
571 context of multiple testing.

572

573 In conclusion, this study provides evidence of the potential for
574 targeted intervention in obese women to improve health for
575 the mother and her offspring. Pregnancy, as demonstrated in
576 this study, appears to be a pragmatic 'teachable' moment for
577 initiating long-term healthier dietary behaviours in the mother
578 and reducing a physiologically relevant measure of adiposity in
579 the offspring.

580

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Conflict of interests

All authors have no financial relationships relevant to this article to disclose.

Supplementary information is available at the International Journal of Obesity's website.

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Figure Legends

Figure 1.Consort diagram of participants enrolled in the UPBEAT trial at 6 months postpartum

Figure 2.Maternal Glycaemic load (a), Saturated fat (b) and Energy intake (c) at 6 months postpartum by randomisation allocation.

Abbreviations: %E- Percentage energy; kcal/day- kilocalorie per day.

Arithmetic mean with standard error plotted at each gestation (weeks), showing nutritional consumption per day.

Figure 3. Relationship between duration of exclusive breast feeding and anthropometry measured at 6 months postpartum in 698 infants from the UPBEAT trial.

Effect estimates/ mean differences plotted with 95% confidence intervals. For triceps skinfold thickness (n=627), sum of skinfold thickness (n=547), total body fat (n=547) and upper mid-arm circumference (n=676).

*Significant Wald test for interaction $p<0.05$