
Peer reviewed version

Link to published version (if available):
10.1038/ijo.2017.44

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via SpringerNature at http://www.nature.com/ijo/journal/vaop/ncurrent/full/ijo201744a.html. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/about/ebr-terms
Infant adiposity following a randomised controlled trial of a behavioural intervention in obese pregnancy.

Nashita Patel MBBS\textsuperscript{1}, Keith M. Godfrey PhD\textsuperscript{2}, Dharmi Pasupathy PhD\textsuperscript{1}, Julia Levin MSc\textsuperscript{3}, Angela C Flynn MSc\textsuperscript{1,4}, Louise Hayes PhD\textsuperscript{5}, Annette L Briley PhD\textsuperscript{1}, , Ruth Bell MD\textsuperscript{5}, Debbie A Lawlor PhD\textsuperscript{6}, Eugene Oteng-Ntim PhD\textsuperscript{7}, Scott M. Nelson PhD\textsuperscript{8}, Stephen C. Robson MD\textsuperscript{9}, Naveed Sattar PhD\textsuperscript{10}, Claire Singh MSc\textsuperscript{7}, Jane Wardle PhD\textsuperscript{*11}, Sara White MSc\textsuperscript{1}, Paul T Seed CStat\textsuperscript{1}, Lucilla Poston PhD\textsuperscript{1}, On behalf of the UPBEAT Consortium.

Affiliations.

1. Division of Women’s Health, Women’s Health Academic Centre, Faculty of Life Sciences and Medicine, King’s College London, St Thomas’ Hospital, London, UK.

2. MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.
3. London School of Hygiene and Tropical Medicine, London, UK.

4. Division of Diabetes and Nutritional Sciences, King’s College London, London, UK.

5. Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK.

6. MRC Integrative Epidemiology Unit at the University of Bristol & School of Social and Community Medicine, Bristol, England, UK.

7. Guys and St Thomas’ NHS Foundation Trust, London, UK.

8. School of Medicine, University of Glasgow, Glasgow, UK.

9. Institute of Cellular Medicine Uterine Cell Signalling Group Newcastle University, Newcastle, UK.

10. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.

11. Health Behaviour Research Centre, Institute of Epidemiology and Health, University College London, London, UK.

*Deceased

**Corresponding author.**
Dr Nashita Patel; Division of Women’s Health, Women’s Health Academic Centre, Faculty of Life Sciences and Medicine, King’s College London, St Thomas’ Hospital, London, UK; Email: Nashita.r.patel@kcl.ac.uk; Telephone: 020 7188 3641

Runningtitle.

Infant adiposity after RCT in obese pregnancy.

Funding source.

This work was supported by the European Union’s 7th Framework Programme (FP7/2007–2013), project EarlyNutrition under grant agreement no. 289346 and the National Institute for Health Research (NIHR) (UK) Programme Grants for Applied Research Programme (RP-0407-10452). The views expressed in this paper are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health or any other listed funders. Support was also provided from the Biomedical Research Centre at Guy’s and St.Thomas’ NHS Foundation Trust and King’s College London, the Chief Scientist Office Scotland, Guy’s and St Thomas’ Charity and Tommy’s Charity (Registered charity no. 1060508). The funders had no role in study design, data collection, data analysis, data interpretation or writing of the final report. The corresponding author had access to all the
data in the study and had final responsibility for the decision
to submit for publication. Professor Godfrey is supported by
the National Institute for Health Research through the NIHR
Southampton Biomedical Research Centre. Professor Lawlor’s
collection to this paper is supported by a grant from the
European Research Council (ObesityDevelop; grant number
669545) the MRC Integrative Epidemiology Unit
and Professor Lawlor and Professor Poston
are National Institute of Health Research Senior Investigators.
Mr Seed is funded by Tommy’s Charity and by CLAHRC South
London (NIHR).

**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’ \textit{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. 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. 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), 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 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/m²). Exclusion criteria included pre-existing disease and multiple pregnancy. 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 15⁴⁻¹⁸⁴⁶ 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 ≤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
The main outcomes of interest were maternal dietary glycaemic load, saturated fat intake and energy intake. Other outcomes included glycaemic index (GI), glycaemic load (GL), protein and fibre intake. Physical Activity was assessed, as it had been in pregnancy, using the International Physical Activity Questionnaire (IPAQ) and summarised as metabolic equivalents (METs) of energy expenditure\(^{16}\).

**Statistical analyses**

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

Although loss to follow-up was similar in both of the trial arms, we assessed the possibility that loss to follow-up resulted in selection bias using three complementary methods (further 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. 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). 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\textsuperscript{th}, 34\textsuperscript{th}-36\textsuperscript{th} 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 comparison to those who did not take part, mothers who attended the 6 month 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. The infants who attended the 6 month appointment had 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
in the intervention arm had a 5% lower subscapular skinfold thickness (-0.38mm; -0.70 to -0.06; p=0.021), compared to infants in the standard antenatal care arm (Table 2). The infant sum of skinfold thickness was 0.63mm lower in the intervention arm, but did not reach statistical significance (p=0.058) in comparison to the standard antenatal care arm (Table 2). There were no differences in BMI z-score and abdominal circumference (Table 2) or in other anthropometric measures between the two arms (Supplementary Table 2).

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

There was no difference in infant feeding between the two trial arms, nor appetite and satiety responsiveness and infant 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, except 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 -0.90 mm (-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
Maternal diet and physical activity

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

Causal analysis suggested direct effects of the intervention associated reduction in maternal early GWG (between 15-18+6 and 27-28+6 weeks’ gestation) (p=0.015), late GWG (between 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\textsuperscript{19,20}. In children and adults, subscapular skinfold thickness has been related to impaired glucose metabolism, and in adolescents to increased serum cholesterol concentration\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{1}.  \textsuperscript{1}
We are aware of only two relevant similar studies. The first, the Lifestyle in Pregnancy study (LIP)\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{8}.

There remains a paucity of data regarding the long-term efficacy of lifestyle interventions in obese pregnant women\textsuperscript{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. 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, 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 gain were 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
complete dietary questionnaires, maternal dietary data was calculated only for 34.2% of the mothers. The dietary data was by self report but compared favourably to a more rigorous method (triple pass 24hr recall) as assessed in the pilot trial. Strengths of the study include the prospective collection of in-depth data addressing familial and individual determinants of infant adiposity, and of maternal in-utero exposures. The richness of data in the UPBEAT study can be considered both a strength and limitation. Whilst providing comprehensive information relevant to developmental origins of early infant obesity, and assessment of mediation effects, limits are imposed on interpretation of secondary analyses in the context of multiple testing.

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

Acknowledgements
We are particularly grateful to the women and children who participated in UPBEAT. We would like to acknowledge Jennie Louise PhD (Senior Statistician at the University of Adelaide) for her statistical advice, and all the UPBEAT staff.

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.
References


16. IPAQ. Guidelines For Data Processing And Analysis Of The International Physical Activity Questionnaire (IPAQ)- Short And Long Forms *International Physical Activity Questionnaire* 2005; [https://sites.google.com/site/theipaq/scoring-protocol](https://sites.google.com/site/theipaq/scoring-protocol) accessed online on 15.11.2015.


19. Mensink M, Feskens EJ, Kruijshoop M, de Bruin TW, Saris WH, Blaak EE. Subscapular Skinfold Thickness Distinguishes Between Transient And Persistent Impaired Glucose


22. Srinivasan SR, Frontini MG, Berenson GS. Longitudinal Changes In Risk Variables Of Insulin Resistance Syndrome From Childhood To Young Adulthood In Offspring Of Parents With Type 2 Diabetes: The Bogalusa Heart Study. *Metabolism* 2003; **52**: 443-50.


27. Tanvig M, Vinter CA, Jorgensen JS, Wehberg S, Ovesen PG, Lamont RF et al. Anthropometrics And Body Composition By Dual Energy X-ray In Children Of Obese Women: A Follow-Up of a randomized controlled trial (the Lifestyle in


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
1555 obese pregnant women randomised

772 (49.6%) allocated to standard antenatal care

757 (98.1%) infants with known birthweight
2 lost to follow up
3 withdrew permission to use data
2 miscarriage
4 fetal death in utero
3 terminations

783 (50.3%) allocated to UPBEAT intervention

765 (97.7%) infants with known birthweight
6 lost to follow up
3 withdrew permission to use data
6 miscarriage
2 fetal death in utero
1 termination

365 (48.2%) infants followed up at 6 months
344 not responded to follow up contact
48 refused follow up

355 (47.0%) principal infant outcomes at 6 months
9 infants excluded as age ≤ 4 months or ≥8 months

356 (47.0%) principal infant outcomes at 6 months
342 (44.7%) infant outcomes at 6 months
13 infants excluded as age ≤ 4 months or ≥8 months

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. *p<0.01.
Figure 3.

Relationship between duration of exclusive breast feeding and anthropometry measured at 6 months postpartum in 698 infants from the UPBEAT trial.
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
## Table 1.

<table>
<thead>
<tr>
<th>Maternal demographics</th>
<th>Intervention (n=342)</th>
<th>Control (n=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)/N(%)</td>
<td>Mean (SD)/N(%)</td>
</tr>
<tr>
<td><strong>Pre-pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>N=342</td>
<td>N=356</td>
</tr>
<tr>
<td>Asian</td>
<td>31.30 (5.04)</td>
<td>31.00 (5.58)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (4.1)</td>
<td>11 (3.1)</td>
</tr>
<tr>
<td>Other</td>
<td>62 (18.1)</td>
<td>72 (20.2)</td>
</tr>
<tr>
<td>White</td>
<td>19 (5.6)</td>
<td>22 (6.2)</td>
</tr>
<tr>
<td>Maternal ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>247 (72.2)</td>
<td>251 (70.5)</td>
</tr>
<tr>
<td>Black</td>
<td>169 (49.4)</td>
<td>174 (48.9)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (4.4)</td>
<td>19 (5.4)</td>
</tr>
<tr>
<td>White</td>
<td>119 (34.9)</td>
<td>136 (38.3)</td>
</tr>
<tr>
<td>Multiparous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td>1 (least deprived)</td>
<td>N=341</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>29 (8.5)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>35 (10.3)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>119 (34.9)</td>
</tr>
<tr>
<td></td>
<td>5 (most deprived)</td>
<td>143 (41.9)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td>N=333</td>
<td>N=344</td>
</tr>
<tr>
<td></td>
<td>10 (3.0)</td>
<td>11 (3.2)</td>
</tr>
<tr>
<td>PET</td>
<td>N=333</td>
<td>N=344</td>
</tr>
<tr>
<td></td>
<td>40 (12.0)</td>
<td>33 (9.6)</td>
</tr>
<tr>
<td>T2DM</td>
<td>N=341</td>
<td>N=356</td>
</tr>
<tr>
<td></td>
<td>86 (25.2)</td>
<td>70 (19.7)</td>
</tr>
<tr>
<td><strong>15-18 weeks’ gestation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker^</td>
<td>N=342</td>
<td>N=356</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>36.17 (4.98)</td>
<td>36.31 (4.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>N=340</td>
<td>117.90 (11.15)</td>
</tr>
<tr>
<td></td>
<td>119.32 (11.00)</td>
<td></td>
</tr>
<tr>
<td>Sum of skin folds (cm)‡</td>
<td>N=337</td>
<td>124.34 (28.46)</td>
</tr>
<tr>
<td></td>
<td>122.18 (25.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal Antenatal and postpartum history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes **</td>
<td>N=336</td>
<td>N=346</td>
</tr>
<tr>
<td></td>
<td>97 (28.9)</td>
<td>93 (26.9)</td>
</tr>
<tr>
<td>Pre-eclampsia∞</td>
<td>N=340</td>
<td>N=353</td>
</tr>
<tr>
<td>Total gestational weight gain from pre-pregnancy weight¶</td>
<td>N=320</td>
<td>6.92 (4.65)</td>
</tr>
<tr>
<td>Maternal 6 month postpartum BMI (kg/m²)</td>
<td>N=345</td>
<td>36.26 (5.14)</td>
</tr>
<tr>
<td>Change in maternal weight from 15-18 weeks to 6 months postpartum (kg)</td>
<td>N=344</td>
<td>-0.37 (7.41)</td>
</tr>
<tr>
<td></td>
<td>0.36 (6.71)</td>
<td></td>
</tr>
<tr>
<td><strong>Infant demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant age at 6 months follow up (months)</td>
<td>N=342</td>
<td>5.80 (0.65)</td>
</tr>
<tr>
<td>Gestation at birth (weeks)</td>
<td>N=342</td>
<td>39.73 (1.54)</td>
</tr>
<tr>
<td>Birthweight (gm)</td>
<td>N=342</td>
<td>N=356</td>
</tr>
<tr>
<td></td>
<td>3479.23 (529.40)</td>
<td>3436.55 (604.09)</td>
</tr>
<tr>
<td>Large for Gestational Age &gt;90th (customised)†</td>
<td>N=342</td>
<td>30 (8.8)</td>
</tr>
<tr>
<td>Artificial feeding</td>
<td>N=341</td>
<td>N=354</td>
</tr>
<tr>
<td></td>
<td>63 (18.5)</td>
<td>78 (22.0)</td>
</tr>
<tr>
<td>Partially breastfeeding</td>
<td>N=341</td>
<td>N=354</td>
</tr>
<tr>
<td></td>
<td>65 (19.1)</td>
<td>132 (37.1)</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>N=341</td>
<td>N=354</td>
</tr>
<tr>
<td></td>
<td>213 (62.5)</td>
<td>216 (61.0)</td>
</tr>
</tbody>
</table>

Maternal and Infant demographics by randomisation allocation at 6 month postpartum visit.

^ Maternal current smoking at 15-18 weeks’ gestation significantly different between intervention and control groups (p=0.02). *IMD quintiles are calculated for the region of residence, by fifths of the population. UK wide-scores were developed by reconciling Scottish data to English norms. ** Gestational diabetes diagnosis by International Association of Diabetes in Pregnancy Study Group criteria at 27th to 28th weeks’ gestation.
† Calculated by the addition of biceps, triceps, suprailiac and subscapular skinfold measurements each measured in triplicate. ∞ Pre-eclampsia defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both, on at least two occasions 4 hours apart, with proteinuria ≥300 mg/24 hours. ¶ Gestational weight gain calculated using estimated weight before pregnancy according to the Institute of Medicine Weight Management in Pregnancy Guidelines. † Customised birthweight centile calculated adjusting for maternal height and weight, ethnic origin, parity and sex of the infant.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Mean Diff/ Risk Ratio* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscapular skinfold thickness z-scores**</td>
<td>N=267 0.08 (1.37)</td>
<td>N=280 0.36 (1.37)</td>
<td>-0.26 (-0.49 to -0.02)</td>
<td>0.031</td>
</tr>
<tr>
<td>Subscapular skinfold thickness (mm)</td>
<td>N=267 7.55 (1.86)</td>
<td>N=281 7.95 (2.03)</td>
<td>-0.38 (-0.70 to -0.06)</td>
<td>0.021</td>
</tr>
<tr>
<td>Triceps skinfold thickness z-scores**</td>
<td>N=296 0.10 (1.56)</td>
<td>N=298 0.24 (1.43)</td>
<td>-0.14 (-0.38 to 0.10)</td>
<td>0.246</td>
</tr>
<tr>
<td>Triceps skinfold thickness (mm)</td>
<td>N=307 9.69 (2.76)</td>
<td>N=320 9.87 (2.69)</td>
<td>-0.22 (-0.64 to 0.20)</td>
<td>0.305</td>
</tr>
<tr>
<td>Sum of skinfolds (mm)</td>
<td>N=267 17.08 (3.93)</td>
<td>N=280 17.71 (3.97)</td>
<td>-0.63 (-1.30 to 0.04)</td>
<td>0.058</td>
</tr>
<tr>
<td>BMI for age z-scores**</td>
<td>N=317 -0.07 (1.86)</td>
<td>N=320 0.04 (1.78)</td>
<td>-0.12 (-0.40 to 0.16)</td>
<td>0.393</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>N=329 43.74 (4.73)</td>
<td>N=347 43.72 (6.27)</td>
<td>0.07 (-0.78 to 0.92)</td>
<td>0.872</td>
</tr>
</tbody>
</table>

Table 2.

Infant anthropometry by randomisation allocation at 6 months postpartum visit
*Treatment effect adjusted for minimisation variables of randomisation (maternal BMI, ethnicity and parity), infant age at 6 month follow up and infant sex. **Z-scores calculated using WHO Anthro; version 3.2.2.
Table 3.

<table>
<thead>
<tr>
<th>Maternal diet**</th>
<th>Intervention</th>
<th>Standard care</th>
<th>Treatment effect*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycaemic Load per day</strong></td>
<td>N=116 98.94 (32.80)</td>
<td>N=126 134.69 (62.68)</td>
<td>-35.34 (-48.00 to -22.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Saturated fat (%E)</td>
<td>N=116 11.89 (2.61)</td>
<td>N=126 13.75 (2.85)</td>
<td>-1.93 (-2.64 to -1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total energy (kcal/day)</strong></td>
<td>N=116 1473.84 (596.60)</td>
<td>N=126 1831.21 (727.65)</td>
<td>-354.52 (-505.95 to -203.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycaemic Index (0-100)</td>
<td>N=116 53.06 (4.06)</td>
<td>N=126 57.04 (3.74)</td>
<td>-3.94 (-4.93 to -2.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbohydrate (%E)</td>
<td>N=116 47.69 (6.71)</td>
<td>N=126 48.03 (6.22)</td>
<td>-0.18 (-1.84 to 1.49)</td>
<td>0.835</td>
</tr>
<tr>
<td><strong>Total fat (%E)</strong></td>
<td>N=116 29.70 (4.94)</td>
<td>N=126 32.26 (4.75)</td>
<td>-2.56 (-3.91 to -1.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein (%E)</td>
<td>N=116 22.57 (4.42)</td>
<td>N=126 19.82 (3.94)</td>
<td>2.70 (1.63 to 3.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibre (g/day)</td>
<td>N=116 12.12 (4.16)</td>
<td>N=126 12.27 (6.81)</td>
<td>-0.12 (-1.57 to 1.33)</td>
<td>0.873</td>
</tr>
<tr>
<td><strong>Maternal physical activity</strong>†</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median regression (95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>MET (min/week)</strong></td>
<td>N=349 2190 (1053, 4158)</td>
<td>N=358 2012 (990, 4088)</td>
<td>93.95 (-264.81 to 452.72)</td>
<td>0.607</td>
</tr>
<tr>
<td><strong>MVPA (min/week)</strong></td>
<td>N=349 120 (0, 360)</td>
<td>N=358 120 (0, 360)</td>
<td>10.43 (-39.31 to 60.18)</td>
<td>0.681</td>
</tr>
<tr>
<td>Walking (min/week)</td>
<td>N=349 420 (180, 840)</td>
<td>N=358 420 (180, 630)</td>
<td>0.00 (-68.88 to 68.88)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Maternal dietary and physical activity data by randomisation allocation at 6 months postpartum

Abbreviations: CI- Confidence Intervals; %E- %Energy; g/day- grams per day; kcal/day- kilocalories per day; MET- Metabolic equivalent of task; MVPA- Moderate and Vigorous physical activity.

*Treatment effect adjusted for maternal trial entry BMI, parity and ethnicity. ** Maternal diet- Women with a reported energy ≤4.5 Mj/day or ≥20Mj/day at 15-18 weeks’ gestation were excluded from the analyses of diet. Dietary intervention estimates were calculated using multiple regression and adjusted for maternal pre-pregnancy current smoking status. ^ Physical activity estimates were calculated using bootstrapped (1000 replications), median regression adjusting for maternal pre-pregnancy current smoking status. † MET is defined as the energy expenditure ratio of activity to rest; one MET is approximately equal to an individual’s resting energy expenditure.