Modifiable early life exposures associated with adiposity and obesity in 3-year old children born to mothers with obesity

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Summary

Background: Children born to mothers with obesity are at increased risk of obesity. Influences underlying this predisposition include in-utero exposures, genetic predisposition and a shared family environment. Effective intervention strategies are needed to prevent obesity in these high-risk children; this requires evaluation of modifiable pregnancy and early-life risk factors.

Objectives: To assess the individual and cumulative contributions of maternal and early-life modifiable exposures on childhood adiposity and obesity outcomes in 3-year-old children born to women with obesity.

Methods: We used adjusted regression to assess the individual and cumulative contributions of six exposures (early pregnancy BMI, excessive gestational weight gain, mode of infant feeding and three measures of childhood eating habits [food responsiveness, slowness in eating and a processed/snacking dietary pattern score]) on body composition in 495 three-year-old children. Outcomes included BMI z-score, arm circumference and overweight/obesity (BMI ≥ 25.0 kg/m²).

Results: While the UPBEAT intervention did not influence adiposity outcomes in 3-year-old children, the six modifiable exposures combined incrementally to increase childhood adiposity and obesity. For each additional exposure, children had a higher BMI z-score (β = 0.35SD [95% confidence interval: 0.23, 0.47]), arm circumference (β = 0.59 cm [0.40, 0.79]) and risk of overweight/obesity (relative risk 1.49 [1.26, 1.77]). Compared to no exposures, children with four or more exposures had a higher BMI z-score (1.11SD [0.65, 1.58]), arm circumference (2.15 cm [1.41, 2.89]) and risk of overweight/obesity (3.01 [1.67, 5.41]) (all P < 0.001).

Conclusion: Our findings suggest that complex interventions targeting preconception, pregnancy, perinatal and early childhood exposures offer a potential strategy for prevention of pre-school obesity.
1 | INTRODUCTION

In parallel with the global obesity epidemic, childhood obesity is increasing worldwide. Between 2000 and 2013 the number of children with overweight and obesity rose from 32 to 42 million, with global prevalence expected to reach 70 million by 2025. The immediate effects of childhood obesity include health complications, such as behavioural disorders, fatty liver disease and asthma. Childhood or early-life obesity is known to track across the lifecourse increasing the risk of cardiovascular disease and type 2 diabetes in the longer term. Prevention of childhood obesity is a worldwide public health priority. In the UK a quarter of children enter primary school with overweight or obesity, the highest prevalence being amongst ethnic minorities and those living in disadvantaged areas.

Environmental and lifestyle factors are widely implicated in the rising prevalence of childhood obesity, including interactions with hereditary predisposition. A substantial body of evidence suggests a key role for the environment in the earliest stages of life. Experimental animal studies, observational cohorts and some randomized controlled trials suggest that adverse in-utero exposures, including maternal obesity or excessive gestational weight gain (GWG), may contribute to offspring obesity, which can persist into later life. Nutritional exposures and behaviours in infancy and early childhood are also increasingly recognized to be influential. These include, short or no breastfeeding duration, and the development of eating habits and behaviours, such as responsiveness to food, high intake of energy dense foods and a higher rate of food consumption. Longitudinal analyses suggest that once established, these eating habits and behaviours persist into adulthood. Therefore, effective strategies implemented during these windows of vulnerability are needed to stem the rising trend of childhood obesity.

Previous studies addressing the early-life determinants of childhood obesity have generally focused on children born to women of heterogeneous BMI in cohorts, which frequently have a small proportion of women with clinical obesity (BMI ≥ 30 kg/m²) yet children of women with obesity are those at greatest risk. In accord with the WHO ECHO report recommending that effective public health strategies to prevent childhood obesity be tailored to high-risk women and their families, we have attempted to identify modifiable risk factors in a cohort confined to children born to women with obesity. Maternal BMI was distributed across the WHO categories (I, II and III) and the women were ethnically diverse and of a predominantly social deprived backgrounds. In a follow-up study of the UK Pregnancies Better Eating and Activity Trial (UPBEAT) we examined the association between six modifiable early-life exposures and their cumulative contribution on nine measures of offspring adiposity and obesity outcomes at 3 years of age. These exposures comprised early pregnancy BMI (WHO obesity categories I, II and III), GWG, mode of infant feeding and childhood eating habits (food responsiveness, slowness in eating and a processed/snacking dietary pattern score) at 3-years of age.

2 | METHODS

2.1 | Setting

UPBEAT, a multi-centre randomized controlled trial, investigated the effect of an intense 8-week diet and physical activity intervention in 1555 pregnant women with obesity (BMI ≥ 30 kg/m²). Participants were randomized to the intervention or to standard antenatal care and were from UK inner-city settings of ethnic diversity and from predominantly socioeconomically deprived backgrounds. Details of the intervention inclusion and exclusion criteria have been published previously. Research Ethics Committee approval was obtained in all participating centres, UK Integrated Research Application System; reference 09/H0802/5 (South East London Research Ethics Committee). All participants provided written informed consent. The intervention had no effect on the primary outcomes, the incidence of maternal gestational diabetes and large-for-gestational-age infants. However, improvements were observed in several secondary maternal outcomes, including a reduction in total GWG.

2.2 | 3-Year post-delivery follow-up

Between August 2014 and October 2017 participants in the UPBEAT study were invited to attend a 3-year post-delivery visit with their children. Of the 1555 women originally recruited, 514 mother-child dyads took part in the 3-year visit (Figure 1). The study design and protocol were approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 13/LO/1108). The children were included in this analysis if they had (1) attended the follow-up visit at 3-years of age and (2) had body composition variables recorded during the 3-year visit. Children were excluded if they were suffering from severe illness (n = 4) or if born before 34 weeks’ gestation (n = 5).

2.3 | Exposures variables

For the purpose of this study we addressed relationships between maternal and early life (nutritional) exposures and measures of childhood adiposity and obesity. Maternal and infant exposures were selected based on previous literature. Maternal exposures...
were defined as: (1) early pregnancy BMI (30.0-34.9 kg/m² vs ≥35.0 kg/m²; WHO classification, I vs II and III,27) measured at trial baseline (15±0-18±6 weeks’ gestation). Height and weight were used to calculate BMI (kg/m²); height was measured to the nearest 0.1 cm with a portable stadiometer (Harpenden; CMS Weighing Equipment Ltd.). Weight was measured to the nearest 0.1 kg with calibrated electronic scales (Seca), after removal of shoes and heavy clothing or jewellery; (2) GWG categorized using the National Academy of Medicine (NAM) guidelines28 (inadequate: <5 kg vs adequate: 5-9 kg vs excessive >9 kg). GWG was calculated using estimated weight before pregnancy by the difference in the mother’s weight measured at baseline minus 1.25 kg and weight recorded at 34±0-36±6 weeks gestation, and (3) mode of infant feeding recorded on hospital discharge as exclusively breastfeeding, exclusively formula feeding or partial breastfeeding (defined as any breast feeding). The nutritional exposures were recorded at 3-years of age and included (1) a “processed/snacking” dietary pattern score, (2) child’s food responsiveness and (3) slowness in eating. The data collection and methodology of these dietary variables have been published previously.29 In brief, dietary patterns were derived using factor analysis of a culturally appropriate 85-item food frequency questionnaire. Eating behaviours were assessed using the validated Childhood Eating Behaviour Questionnaire (CEBQ),30 consisting of 35 items, divided into eight eating behaviours. Slowness in eating and food responsiveness, were selected for analysis; as being most amenable to intervention.31 Furthermore, we reported strong associations between these two eating behaviours and adiposity and obesity in the 3-year old UPBEAT children.29

2.4 | Child Outcomes: Body composition and measures of obesity

Body composition was assessed by sum of skinfold thicknesses using children’s Holtain skinfold callipers (calculated by addition of triceps, biceps, suprailiac, subcapular and abdominal skinfold thicknesses), mid-upper arm and waist circumferences and body fat percentage assessed by ImpediMed Imp SFB7 bioelectrical impedance analysis (BIA). Weight to the nearest 0.1 kg (using calibrated scales) and height (using the Leicester height measurer) to the nearest 0.1 cm was used to derive the WHO z-scores32 and to define childhood overweight by International Obesity Task Force (IOTF) sex-specific centiles (boys overweight = 90.5th centile and girls overweight = 89.3rd centile).33

2.5 | Statistical analysis

We have previously reported that the UPBEAT intervention did not affect any measure of adiposity/obesity in the 3-year old children,34 therefore, the data was treated as a cohort. Demographic results were expressed as mean ± SD (SD), median and interquartile range or percent and number as appropriate. Children’s sum of skinfolds was positively skewed and log-transformed for analysis. Depending on the outcome of interest, adjusted linear or logistic regression was used. Poisson regression with robust variance was used to estimate the relative risk of child overweight. All outcomes were adjusted for maternal age, parity, ethnicity, smoking status at baseline, years spent in full time education, randomization arm and gestational age at delivery. Additional adjustments were made for child age at follow-up (months) and infant sex when indicated. Using regression analyses, the first objective was to assess the relationship between the individual maternal exposures (early pregnancy BMI, excessive GWG and mode of infant feeding on hospital discharge) and measures of childhood adiposity and obesity outcomes. The second objective was to address the incremental impact of the exposure variables on childhood outcomes, using three composite models were created: (i) maternal exposures (BMI, GWG and mode of feeding on hospital discharge), (ii) child nutritional exposures (processed/snacking dietary pattern score, food responsiveness and slowness in eating) and (iii) the combined

FIGURE 1 Consort diagram of participants enrolled in the UPBEAT trial at 3 years after delivery
contribution of all six exposures. To create the composite models, binary variables were derived for each exposure (BMI: 30.0-34.9 kg/m² = 0, ≥35.0 kg/m² = 1; inadequate/adequate GWG = 0, excessive GWG = 1 and exclusively breastfeeding = 0, partial breastfeeding or formula feeding = 1). As the nutritional exposures are continuous variables, with no published reference guidelines to dichotomize the variables, we categorized a high (=1) association as mean ± 1 SD, with the remainder categorized as normal/low (=0); food responsiveness and the dietary pattern scores are positively associated with measures of adiposity, therefore, the high categories were defined as mean ± 1 SD, as slowness in eating in negatively associated with measures of adiposity the high category was defined as mean - 1 SD. Each child was assigned a score for the three models, the maternal model ranged from 0 to 3, the nutritional model ranged from 0 to 2, as categorizes 2 and 3 were combined. For the combined model and overall score was calculated ranging from 0 to 6 (0 was the reference group for all scores). A score, from 0 to 3, based on three maternal exposures was generated, for each child. 23% of the children had no exposures, 41% had one exposure, 30% had two exposures and 6% had three (Table 2). Child BMI z-score, weight-for-height (WH) z-score, arm circumference and overweight/obesity were included in the combined model analyses as these were most frequently associated with maternal risk factors. On a continuous scale, for each additional dietary exposure children had an increase in WH and BMI z-scores of 0.28 SD (0.12-0.36, P < 0.001) and 0.29 SD (0.13-0.55, P < 0.001), respectively. For overweight/obesity, the relative risk increased by 1.24 (1.07-1.44, P = 0.004), and arm circumference by 0.35 cm (0.16-0.55, P < 0.001). Compared to children with no exposures, for those with three exposures WH and BMI z-scores increased by 0.78 (0.33-1.23) and 0.79 (0.31-1.27, P < 0.0001), respectively. Similarly, the risk of overweight/obesity increased by 1.71 (1.04-2.80, P = 0.03) and arm circumference by 1.04 cm (0.25-1.82, P = 0.01) (Table 2).

3.1.2 | GWG

Excessive GWG (>9 kg) was associated with higher child BMI (0.24; 0.002-0.47, P = 0.04), weight-for-age (0.25; 0.17-0.49, P = 0.03) and height-for-age z-scores (0.28; 0.49-0.53, P = 0.01) (Supplementary Table 2).

3.1.3 | Mode of infant feeding

Compared to exclusive breastfeeding, formula feeding on hospital discharge was associated with higher child loged sum of skinfolds (0.29; 0.003-0.57, P = 0.04), arm circumference, (0.51 cm; 0.06-0.96, P = 0.02), BMI z-score (0.35; 0.09-0.62, P = 0.01), weight-for-height z-score (0.31; 0.05-0.57, P = 0.01) and increased risk of overweight/obesity (RR 1.50; 1.11-2.04, P = 0.008). Compared to exclusively breastfeeding at hospital discharge there were no associations between partial breastfeeding and any childhood outcome (Supplementary Table 3).

3.1.4 | Combined contribution of maternal exposures

A score, from 0 to 3, based on three maternal exposures was generated for each child. 23% of the children had no exposures, 41% had one exposure, 30% had two exposures and 6% had three (Table 2). Child BMI z-score, weight-for-height (WH) z-score, arm circumference and overweight/obesity were included in the combined model analyses as these were most frequently associated with maternal risk factors. On a continuous scale, for each additional maternal exposure, child WH and BMI z-scores increased by 0.25 SD (0.13-0.36, P < 0.001) and 0.23 SD (0.12-0.36, P < 0.001), respectively. For overweight/obesity, the relative risk increased by 1.24 (1.07-1.44, P = 0.004), and arm circumference by 0.35 cm (0.16-0.55, P < 0.001). Compared to children with no exposures, for those with three exposures WH and BMI z-scores increased by 0.78 (0.33-1.23) and 0.79 (0.31-1.27, P < 0.0001), respectively. Similarly, the risk of overweight/obesity increased by 1.71 (1.04-2.80, P = 0.03) and arm circumference by 1.04 cm (0.25-1.82, P = 0.01) (Table 2).

3.2 | Childhood Exposures

3.2.1 | Combined contribution of childhood dietary exposures analysis

For the dietary exposures (range 0-3), categorizes 2 and 3 were combined. 58% of children had no exposures, 31% had one exposure, 11% had two or more exposures (Table 3). On a continuous scale, for each additional dietary exposure children had an increase in WH and BMI z-scores of 0.28 SD (0.15-0.341 P < 0.001) and 0.29 SD (0.15-0.43, P < 0.001), respectively. For overweight/obesity, there
TABLE 1 Maternal and offspring demographics of the analysed sample (n = 495)

| Maternal demographics | Mean (SD)/median (IQR)/N (%) |
|------------------------|-----------------------------|
| **Pre-pregnancy**      |                             |
| Age (years)            | 31.2 (5.3)                  |
| Ethnicity              |                             |
| White                  | 337 (68)                    |
| Black                  | 114 (23)                    |
| Asian                  | 20 (4)                      |
| Other                  | 24 (5)                      |
| Years in full time education | 15.1 (2.8)            |
| Maternal BMI (kg/m²)   | 34.7 (32.6-37.9)            |
| Obesity class I (30.0–34.9 kg/m²) | 266 (53.7)        |
| Obesity class II (35.0–39.9 kg/m²) | 143 (28.9)        |
| Obesity class III (>40.0 kg/m²) | 86 (17)             |
| Nulliparous            | 244 (49)                    |
| Index of Multiple Deprivation Quintiles |           |
| 1 (least deprived)    | 28 (6)                      |
| 2                     | 36 (7)                      |
| 3                     | 56 (11)                     |
| 4                     | 176 (35)                    |
| 5 (most deprived)     | 196 (40)                    |
| **Maternal antenatal and neonatal demographics** |   |
| Mother assigned to UPBEAT intervention | 241 (49)            |
| Gestational diabetes mellitus | 120 (26)            |
| Gestational weight gain (kg) | 7.5 (4.3)            |
| Birthweight (g)        | 3499 (497)                  |
| Large for gestational age > 90th centile | 62 (12)             |
| Small for gestational age < 10th centile | 35 (7)             |
| **Child 3-year follow-up demographics** |   |
| Age (years)            | 3.5 (0.28)                  |
| Female                 | 244 (49)                    |
| **Mode of infant feeding at hospital discharge** |           |
| Breastfed              | 312 (63)                    |
| Formula fed            | 96 (19)                     |
| Mixed fed              | 86 (18)                     |
| **World Health Organization z-scores** |   |
| BMI-for-age (n = 485)  | 0.88 (1.0)                  |
| Height-for-age (n = 490) | 0.38 (1.1)             |
| Weight-for-age (n = 490) | 0.83 (1.0)             |
| Weight-for-height (n = 485) | 0.90 (1.0)        |
| **International Obesity Task Force BMI categorizes** |   |
| Underweight            | <18.5 kg/m²                 |
| Healthy                | 18.5-24.9 kg/m²             |
| Overweight             | 25.0-29.9 kg/m²             |
| Obese                  | 30.0-34.9 kg/m²             |
| Morbidly obese         | ≥35.0 kg/m²                 |
| Measures of adiposity  |                             |
| Sum of skinfolds (mm)  | 41.3 (33.9-50.0)            |
| Percentage body fat (%)| 22.4 (6.6)                  |
| Arm circumference (cm) | 17.8 (1.8)                  |
| Waist circumference (cm) | 53.3 (4.2)               |

Abbreviations: BMI, body mass index; IQR, interquartile range.

*WHO BMI categories for adults.

*Customized birthweight centile calculated by adjusting for maternal height, weight, ethnic origin, parity and infant sex.

*z-Scores calculated using WHO Anthro.*

dIOTF International gender specific cut-off as BMI references.
### TABLE 2  Measures of childhood obesity according to number of maternal exposures

| Number of exposures | Number (%) | WH z-score\(^a\) coefficient (95% CI) | P-value\(^b\) | BMI z-score\(^e\) coefficient (95% CI) | P-value\(^b\) | Overweight/obesity (BMI ≥25 kg/m\(^2\))^c relative risk (95% CI) | P-value\(^b\) | Arm circumference (cm) coefficient (95% CI) | P-value\(^b\) |
|---------------------|------------|----------------------------------------|--------------|----------------------------------------|--------------|--------------------------------------------------|--------------|------------------------------------------|-------------|
| 0                   | 101 (23)   | Ref                                    | Ref          | Ref                                    | Ref          | Ref                                              | Ref          | Ref                                      |             |
| 1                   | 181 (41)   | 0.14 (–0.10 to 0.39)                   | 0.25         | 0.14 (–0.12 to 0.40)                   | 0.30         | 1.04 (0.70-1.53)                                 | 0.841        | 0.40 (–0.02 to 0.83)                      | 0.06        |
| 2                   | 135 (30)   | 0.45 (0.18-0.72)                       | 0.001        | 0.41 (0.13-0.69)                       | 0.004        | 1.49 (1.02-2.16)                                 | 0.035        | 0.74 (0.28-1.19)                         | 0.002       |
| 3                   | 26 (6)     | 0.78 (0.33-1.23)                       | 0.001        | 0.79 (0.31-1.27)                       | 0.001        | 1.71 (1.04-2.80)                                 | 0.033        | 1.04 (0.25-1.82)                         | 0.01        |
| Beta                |            | 0.25 (0.13-0.36)                       | <0.0001      | 0.23 (0.12-0.36)                       | <0.0001      | 1.24 (1.07-1.44)                                 | 0.004        | 0.35 (0.16-0.55)                         | <0.0001     |

Abbreviations: BMI, body mass index; CI, confidence intervals.

\(^a\)z-Scores calculated using WHO Anthro.\(^{32}\)

\(^b\)Adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomization arm, gestational age at delivery, child sex, age at follow up, processed/snacking diet score and weekly physical activity. BMI z-score and IOTF category were not adjusted for child sex or age at follow-up.

\(^c\)IOTF International gender specific cut-off as BMI references.

### TABLE 3  Measures of childhood obesity according to number of dietary exposures

| Number of exposures | Number (%) | WH z-score\(^a\) coefficient (95% CI) | P-value\(^b\) | BMI z-score\(^e\) coefficient (95% CI) | P-value\(^b\) | Overweight/obesity (BMI ≥25 kg/m\(^2\))^c relative risk (95% CI) | P-value\(^b\) | Arm circumference (cm) coefficient (95% CI) | P-value\(^b\) |
|---------------------|------------|----------------------------------------|--------------|----------------------------------------|--------------|--------------------------------------------------|--------------|------------------------------------------|-------------|
| 0                   | 283 (58)   | Ref                                    | Ref          | Ref                                    | Ref          | Ref                                              | Ref          | Ref                                      |             |
| 1                   | 149 (31)   | 0.29 (0.09-0.50)                       | 0.004        | 0.27 (0.06-0.50)                       | 0.01         | 1.50 (1.14-1.97)                                 | 0.003        | 0.43 (0.06-0.80)                         | 0.021       |
| 2                   | 53 (11)    | 0.56 (0.27-0.86)                       | <0.001       | 0.60 (0.30-0.90)                       | <0.001       | 1.81 (1.32-2.50)                                 | <0.001       | 0.90 (0.38-1.43)                         | 0.001       |
| Beta                |            | 0.28 (0.15-0.41)                       | <0.001       | 0.29 (0.15-0.43)                       | <0.0001      | 1.37 (1.18-1.60)                                 | <0.0001      | 0.44 (0.21-0.68)                         | <0.0001     |

Abbreviations: BMI, body mass index; CI, confidence intervals.

\(^a\)z-Scores calculated using WHO Anthro.\(^{32}\)

\(^b\)Adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomization arm, gestational age at delivery, child sex and age at follow up. BMI z-score and IOTF category were not adjusted for child sex or age at follow-up.

\(^c\)IOTF International gender specific cut-off as BMI references.
was an increase in relative risk of 1.37 (1.18-1.60, P < 0.001), and for arm circumference an increase of 0.44 cm (0.21-0.68, P < 0.001). Compared to children with no exposures, children with two or more exposures had an increase of 0.56 (0.27-0.86) and 0.60 (0.30-0.90) for WH and BMI z-scores (both P < 0.001), respectively (Table 3). There was a 1.81 (1.32-2.50, P < 0.001) increase in the risk for overweight/obesity and an increase of 0.90 cm (0.38-1.43, P = 0.001) in arm circumference (Table 3).

### 3.3 Combined contribution of maternal and nutritional exposures

For the final model, the maternal and childhood dietary exposures were combined. The total score ranged from 0 to 5 (no child was assigned all six risk factors). The children were subdivided into groups with 0 exposures (15%), 1 exposure (29%) 2-3 exposures (49%) 4-5 exposures (7%), Table 4. Compared to children with no exposures, children with four or more had an increase in WH and BMI z-scores of 1.08 (0.64-1.51) and 1.11 (0.65-1.58) (both P < 0.0001), respectively (Figure 2, Table 4). There was an increase in the relative risk for overweight/obesity of 3.01 (1.67-5.41, P < 0.0001) and in arm circumference of 2.15 cm (1.41-2.89, P = 0.001) (Figure 3, Table 4).

### 3.4 Sensitivity analyses

As the risk factors are associated and may be a result of maternal obesity, we completed an additional analysis to examine the relationship between the offspring outcomes and the combined exposures with maternal BMI as a covariate, rather than an exposure. These results show that the significant incremental increase in childhood adiposity and obesity remained with the five risk factors. Furthermore, our decision to exclude infants born <34 weeks gestation may have resulted in collider bias as prematurity may be a mediator between GWG and childhood obesity. However, inclusion of all infants did not change the final results.

### 4 DISCUSSION

This study reports several important findings that inform the established relationship between maternal obesity and childhood obesity risk. First, we have demonstrated strong associations between maternal early-pregnancy BMI, excessive GWG, mode of infant feeding and measures of adiposity and obesity in 3-year old children born to mothers with obesity. These relationships provide the first demonstration that these maternal exposures, previously implicated in children from weight heterogeneous mothers, also apply to children of mothers with obesity and are likely to contribute to their high risk of obesity. Next, we found that eating behaviours and dietary intake in the children combined incrementally to increase obesity risk. We
also observed positive, additive associations between each of the maternal and nutritional exposures and childhood adiposity and obesity, suggesting that each of these modifiable factors are potential targets for intervention.

In agreement with a meta-analysis of children aged 1-18 years, and our previous study in 6-year old children from the Screening for Pregnancy Endpoints (SCOPE) cohort, we confirmed that maternal early-pregnancy BMI was strongly associated with childhood adiposity and obesity in 3-year olds; 35% of the children studied were overweight or had obesity. Similar relationships have been widely described in animal models of maternal obesity in which maternal metabolic disturbances have been implicated in offspring obesity through persistent developmental changes in the foetus. A recent meta-analysis of 37 cohorts has assessed the separate and combined association of maternal BMI and GWG with the risk of overweight/obesity throughout childhood, and in common with this study, pre-pregnancy BMI was found to be a greater determinant of childhood overweight/obesity than GWG. This meta-analysis also identified the strongest association with maternal BMI and GWG to be in late childhood (10-18 years). Translating this to the UPBEAT children might suggest that the current 35% will be overweight or have obesity in later childhood and adolescence.

Formula feeding on hospital discharge (within 72 hours of delivery) was independently associated with increased rates of obesity and adiposity compared to breastfed children. We have already shown in this cohort that adiposity in 6-month infants was associated with formula feeding and now report that this persists until early childhood. This aligns with previous studies in children of weight heterogeneous women, including the CHOP RCT, which attributed higher adiposity rates in formula-fed children compared to breast fed children to the higher protein content of formula milk. Our data also concord with the recent WHO European Childhood Obesity Surveillance Initiative from 22 European countries, which concluded that formula feeding from birth was associated with the highest rates of obesity in older children (6-9 years) born to women of heterogeneous BMI. While the benefits of any breastfeeding on prevention of childhood obesity remain equivocal our findings support initiation of breastfeeding at birth to reduce obesity in pre-school children born to women with obesity. Importantly, we report for the first time that maternal BMI, GWG and neonatal feeding combine independently to increase the risk of obesity in these children.

Several reports suggest independent relationships between eating behaviours or dietary intake and childhood body composition. To our knowledge no previous study has assessed the combined impact of these nutritional exposures on childhood outcomes. We
recently reported the associations between dietary patterns, eating behaviours and body composition/adiposity in 3-year-old children from the same cohort.29 In the present study, analysing the exposures on a continuous scale, we have found positive independent relationships between the high “processed/snacking” dietary pattern, food responsiveness and overweight/obesity. Conversely, we found a negative relationship between slowness in eating and childhood adiposity and obesity. This added information confirms a robust association between these exposures and childhood adiposity and obesity. While eating behaviours have been repeatedly causally associated with obesity, we are aware of one report, which infers bi-directionality of effect.44 However, in that study the association was stronger between eating behaviours and obesity compared with the reverse.

Finally, evaluating the combined contribution of all maternal and postnatal exposures on childhood outcomes, compared to children with no exposures, the relative risk of overweight/obesity was over three times higher for children with four or more exposures. Three previous mother-child cohorts, The Southampton Women’s Survey (SWS)24 Project Viva23 and Growing Up in Singapore Towards healthy Outcomes (GUSTO)35 have similarly reported that maternal variables summate to increase childhood obesity risk. SWS and Project Viva combined GWG, smoking in pregnancy and short breastfeeding duration in the risk factor model, with SWS also including maternal BMI and vitamin D status, and Project Viva adding reduced infant sleep as additional exposures. GUSTO combined maternal and paternal overweight, GWG, raised fasting plasma glucose during pregnancy, short breastfeeding duration and early introduction of solid foods. Although the exposures in our study differ, altogether these cohorts present strong evidence for a cumulative effect of multiple risk factors on the development of childhood obesity. A limitation of the previous investigations was inclusion of women with a predominantly healthy BMI, recruitment being undertaken prior to the present obesity “pandemic”. Given that children of women with obesity are most at risk of developing obesity, this study adds to the literature by demonstrating for the first-time cumulative risk of early-life exposures in this high-risk group. The importance lies in the translational potential for combined interventions from preconception to postpartum to reduce childhood obesity in children born to mothers with a BMI < 30 kg/m².

**4.1 Strengths and limitations**

Strengths of the study include the rich UPBEAT dataset, which provided comprehensive information including multiple indicators of childhood body composition and adiposity. The mother-child dyads were ethnically diverse and predominantly from low socioeconomic backgrounds, a population with a high-risk of obesity.47 To our knowledge, the UPBEAT cohort is unique in the size of the cohort of women with pre-pregnancy obesity and with detail of in-utero, early postnatal and dietary exposures and multiple health outcomes, with a focus on measures of childhood adiposity, enabling adjustment for recognized confounding factors. Very few previous studies have focused on children of this age, yet pre-school adiposity tracks into adulthood.6 The main limitation is the observational study design, which is subject to residual confounding and potential overestimation of reported effects. The measures of adiposity and obesity, although detailed, have limitations; BMI is an indirect measure of fat mass, and the BIA method has not been validated against dual-energy X-ray absorptiometry, the gold standard for adiposity measurement.48 Attribution of the study population may have resulted in selection bias. However, the UPBEAT population studied at the 3-year visit was a representative sample of the main UPBEAT cohort.34 Furthermore, while the findings are generalizable for clinical practice amongst women with obesity, they are not directly generalizable to the general population.

In conclusion, we identified exposures in pregnancy and early childhood that result in a cumulative increase in the risk of obesity in 3-year-old children born to mothers with obesity. Interventions to reduce childhood obesity have to date predominantly focused on a single age group and have shown little benefit.49,50 Our study suggests that prevention of pre-school obesity is likely to be better achieved through complex interventions beginning pre-conceptually and continuing postpartum. These should encompass pre-conceptual care, weight management in pregnancy, breastfeeding support as well as dietary advice for pre-schoolers. We await with interest the results of the The Healthy Life Trajectories Initiative (HELTI) cohort, which, uniquely, has adopted this approach.51

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CONFLICT OF INTEREST
In relation to the current work, none of the authors report any conflicts of interest. Prof Godfrey has been reimbursed for presenting at Nestlé Nutrition Institute conferences and has received grants from Abbott Nutrition and Nestec, outside the submitted work.

AUTHORS’ CONTRIBUTION
KVD, MOK, KMG and LP conceptualized and designed the study, drafted and carried out the initial analyses, critically reviewed the manuscript and approved the final manuscript as submitted. PTS provided statistical support and advice, critically reviewed the manuscript and approved the final submitted version. ALB and ACF designed the data collection instruments, and coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. KVD wrote the first draft of the paper and coordinated updates following input from co-authors. All other authors critically reviewed the first and subsequent drafts. All authors approved the final version.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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