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Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort

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4 **gestational age birth? Analysis of a UK population-based cohort**
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Abstract

Objective: Maternal obesity during pregnancy increases the risk of large-for-gestational age (LGA) infant and childhood obesity. The aim was to investigate the association between maternal weight change between subsequent pregnancies and risk of having a LGA baby.

Design: Population-based cohort.

Setting: Routinely collected antenatal healthcare data between January 2003 and September 2017 at University Hospital Southampton, England.

Participants: Records of women with their first two consecutive singleton live-birth pregnancies were analysed (n=15940).

Primary outcome measure: Risk of LGA, recurrent LGA and 'new' LGA births in the second pregnancy.

Results: Of the 15940 women included, 16.0% lost and 47.7% gained weight (≥ 1 body mass index (BMI) unit) between pregnancies. A lower proportion of babies born to women who lost ≥ 1 BMI unit (12.4%) and remained weight stable between -1 to 1 BMI unit (11.9%) between pregnancies were LGA compared to 14.5% in women who gained ≥ 1 BMI unit (adjusted odds ratio (aOR) of LGA for weight gain compared to weight stable 1.24, 95% CI 1.11 to 1.39, $P < 0.001$). Normal- and over-weight women who gained weight were at increased risk of LGA after having a non-LGA baby in the first pregnancy (aOR 1.37, 95% CI 1.16 to 1.61, $p < 0.001$ in normal weight and aOR 1.30, 95% CI 1.02 to 1.65, $p = 0.03$ in overweight). Overweight women who had a LGA baby in the first pregnancy were at lower risk of LGA in the second pregnancy if they lost ≥ 1 BMI unit (aOR 0.44, 95% CI 0.23 to 0.85, $p = 0.02$).

Conclusions: Losing weight after an LGA birth in overweight women reduces the risk of subsequent LGA in the next pregnancy, while gaining weight increases its risk in women with no previous history of LGA. Preventing weight gain between pregnancies is an important prevention measure to achieve better maternal and offspring outcomes.

Article summary

Strengths and limitations of this study

- Utilises data from a large population-based cohort including women from all socioeconomic backgrounds
- Data is collected as part of routine care during pregnancy
- Objective measurement of exposure and outcome
- Self-reported data for confounders
- Lack of information on weight gain during pregnancy

Introduction

Maternal obesity has shown a significant increase over time, having more than doubled in England between 1989 to 2007 (7.6% to 15.6%), with the rate of normal weight pregnancies showing a 12% decrease from 65.6% to 53.6%¹. Maternal overweight and obesity is a key risk factor for maternal and foetal outcomes. It also increases the risk of long-term health problems in the child including obesity, cardiovascular disease, diabetes and cognitive and behavioural disorders². Change in maternal body mass index (BMI) between pregnancies could modify the risk in the subsequent pregnancy.

Birthweight is a key early life predictor of long-term health outcomes such as obesity and cardiovascular disease³. The incidence of large-for-gestational age (LGA) birth, defined as >90th percentile weight for gestational age, has increased over time in high-income countries^{4,5}. A key risk factor for LGA birth is gestational diabetes mellitus⁸, the incidence of which has also increased over time^{6,7}. LGA has been found to be associated with childhood obesity prevalence at age 7 years^{9,10} and into adulthood¹¹⁻¹³. Offspring of mothers with gestational diabetes have increased risk of overweight and obesity at age 7 years^{14,15}. Maternal obesity is a known risk factor for both gestational diabetes and LGA birth¹⁶.

Birthweight increases with parity such that the first-born infant on average has the lowest birthweight and the birthweight of subsequent infants increases¹⁷⁻¹⁹ up to the fourth pregnancy²⁰. However, birthweight was found to decrease with parity for women who had short intervals between pregnancies and the increase in birthweight with parity was higher in women with long intervals²⁰. Women who returned to their pre-pregnancy weight before the next conception had subsequent born infants who weighed less than infants of women who retained or gained weight between pregnancies²⁰. Women who lost at least six kilograms by their second pregnancy had a smaller average increase in birthweight compared to women who gained ten kg or more¹⁸.

A large US study showed that women were at an increased risk of having an LGA baby in the second pregnancy if their pre-pregnancy BMI category increased towards overweight or obese from first to second pregnancy regardless of their BMI category in first pregnancy, except in underweight women whose weight increases to become within the normal range. In this study, overweight and obese women who dropped BMI category by their second pregnancy remained at an increased risk of LGA birth, but had a lower risk compared to women whose BMI category increased between pregnancies²¹.

Another US-based study showed that inter-pregnancy weight gain of ≥ 2 BMI units in women who were obese in their first pregnancy was associated with increased risk of LGA. Weight loss of ≥ 2 BMI units was associated with lower risk compared to the reference group of weight maintained between 2 BMI units adjusted for LGA birth in previous pregnancy and other confounders²².

Three studies assessed weight change between first and second pregnancy in relation to 'new' LGA incidence in the second pregnancy, stratified by BMI category ($<$ or ≥ 25)²³⁻²⁵. Two studies found a reduced risk of 'new' LGA with between pregnancy weight loss of >1 BMI unit and an increased risk with modest (1-3 BMI units) and large (≥ 3 BMI units) weight gain. The effect remained in both BMI categories after stratification ($<$ or ≥ 25) but was stronger in women with a healthy first pregnancy BMI ($< 25 \text{ kg/m}^2$). The third study only found an increased risk in normal weight women who gained ≥ 4 BMI units between pregnancies and no association in overweight women²⁵.

Only one published study has examined the risk of recurrent LGA (in both first and second pregnancies) in relation to maternal weight change between pregnancies²⁶. The study, which was conducted in Aberdeen, Scotland, included 24520 women of which 813 women had LGA births in both pregnancies, and found that inter-pregnancy weight gain (≥ 2 BMI

units) was associated with increased risk of recurrent LGA, while weight loss (≥ 2 BMI units) was found to be protective. Women with healthy weight ($\text{BMI} < 25 \text{ kg/m}^2$) were at increased risk of recurrent LGA on gaining weight whereas overweight women ($\text{BMI} \geq 25 \text{ kg/m}^2$) were at reduced risk of recurrent LGA on losing weight²⁶.

We aimed to investigate the association of the incidence of LGA, recurrent LGA and 'new' LGA births in the second pregnancy with maternal change in BMI between the first and second pregnancies in a population-based cohort in the South of England.

Methods

This is a population-based cohort of prospectively collected routine healthcare data for antenatal care between January 2003 and September 2017 at University Hospital Southampton, Hampshire, UK. This included all women delivering at this hospital, which is a regional centre for maternity care in and around Southampton. Records of women with their first two consecutive singleton live birth pregnancies were included. Records with unfeasible weight, height and gestational age values were excluded.

Exposure assessment

Maternal weight in kilograms was measured by a midwife at the first antenatal (booking) appointment of each pregnancy, which is recommended to take place between 8 to 12 weeks gestation in the UK, according to the National Institute for Health and Care Excellence Guidelines²⁷. Any woman who had a booking appointment at or after 24 weeks of pregnancy was excluded. Height was self-reported. BMI was calculated as weight (in kg) divided by height (in metres) squared.

BMI was categorised as underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and obese ($\geq 30 \text{ kg/m}^2$). Change in BMI was calculated as the difference in BMI measured at the booking appointments of the first two consecutive live birth pregnancies for each woman. This change in BMI was then categorised as weight loss (≥ 1 BMI unit), weight stable (-1 to 1 BMI unit) and weight gain (≥ 1 BMI unit).

Outcome assessment

Birthweight (grams) was measured by midwives at birth. Gestational age was based on a dating ultrasound scan which usually takes place by 13 weeks gestation²⁷. Birthweight centiles was calculated using reference values for England and Wales provided in the most recently released data²⁸. Large-for-gestational age was defined as >90 th percentile weight for gestational age. This was only defined for babies born between 24 to 42 weeks gestation as reference values only exist for these gestational ages.

Covariables

Maternal date of birth is recorded at the booking appointment and converted to age on extraction of the dataset to maintain anonymity. Highest maternal educational qualification was self-reported and categorised as primary, secondary, college, undergraduate, postgraduate, graduate and none. For the purposes of this analysis, this was condensed to three categories - secondary (GCSE) and under, college (A levels) and university degree or

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3 above. Self-reported ethnicity was recorded under 16 categories and condensed to White,
4 Mixed, Asian, Black/African/Caribbean, Chinese and Other. Categories of not asked and not
5 stated were coded as missing. Smoking was self-reported as current smoking or non-
6 smoking. Non-smokers were further asked if they had ever smoked or had previously
7 smoked and quit. This was categorised as stopped more than 12 months before conception,
8 stopped less than 12 months before conception or stopped when pregnancy confirmed.
9 Employment was self-reported at booking appointment and categorised as employed,
10 unemployed, in education, and not specified. Infertility treatment was categorised as
11 no/investigations only and yes (hormonal only, in-vitro fertilisation, gamete intrafallopian
12 transfer and other surgical) in either one or both pregnancies. Inter-pregnancy interval was
13 defined as the interval between the first live birth and conception of the second pregnancy.
14 The difference in days between two consecutive live births was calculated and gestational
15 age of the latter birth subtracted from this to derive the inter-pregnancy interval.
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18 *Statistical analysis*

19 All analysis was performed using Stata 15²⁹. Univariable comparisons were carried out using
20 ANOVA for continuous variables and chi square test for categorical variables. Linear
21 regression was used to examine the association of maternal change in BMI between
22 pregnancies in the sub-sample of women who gained ≥ 1 BMI unit weight (assessed as a
23 continuous variable in kg/m^2) with birthweight (assessed as a continuous variable in grams).
24

25 Logistic regression was then used to examine the association between the categorised
26 variable of maternal change in BMI with risk of LGA first in the whole sample and then
27 stratified by maternal BMI category in first pregnancy. Risk of LGA was explored in the full
28 sample adjusting for previous pregnancy outcome of LGA. The risk of LGA in second
29 pregnancy after having a non-LGA baby in the first pregnancy was explored in a sub-sample
30 of women who had non-LGA births in the first pregnancy. The risk of recurrent LGA (LGA in
31 both pregnancies) was explored in a sub-sample of women who had LGA births in the first
32 pregnancy.
33

34 Initial univariable analysis was followed by multivariable models adjusting for potential
35 confounding factors – maternal age, ethnicity, highest educational qualification, whether or
36 not undergone infertility treatment, employment status, smoking behaviour in second
37 pregnancy, gestational diabetes in second pregnancy and inter-pregnancy interval. Linear
38 regression models with birthweight as the outcome were also adjusted for gestational age at
39 birth and birthweight in previous pregnancy.
40

41 A statistical significance level of 0.05 with 95% confidence intervals was used in the
42 regression models.
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45 *Ethical considerations*

46 All data were anonymised to the research team. Ethics approval was granted by the
47 University of Southampton Faculty of Medicine Ethics Committee: study ID 25508.
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50 *Patient and Public Involvement*

51 Patients and public were not involved in setting the research question or the outcome
52 measures, nor were they involved in developing plans for the design or implementation of
53 the study.
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Results

The first and second pregnancies of 15940 women were included. Of these, 16.0% of women lost ≥ 1 BMI unit, 36.3% remained weight stable (-1 to 1 BMI unit) and 47.7% gained ≥ 1 BMI unit between their first and second live birth pregnancies. Weight loss of >2 BMI units was observed in 7.3% of women whereas 10.7% gained >2 BMI units and 19.8% gained three or more BMI units. Mean BMI at second pregnancy booking was 27.9 kg/m^2 (standard deviation (SD) 5.8) in women who gained weight (≥ 1 BMI Unit), 24.1 kg/m^2 (SD 5.1) in women who lost weight, and 23.8 kg/m^2 (SD 4.4) women whose weight remained stable between pregnancies ($p < 0.001$) (Table 1).

Women who gained ≥ 1 BMI unit by the start of their second pregnancy were more likely to be smokers, unemployed, with lower educational attainment and to have a longer inter-pregnancy interval, compared to those who maintained a stable weight between pregnancies. Mean maternal age was lowest in the women who gained weight (28.4 years, standard deviation 5.5) and highest in the women who remained weight stable (29.8 years, standard deviation 5.3).

Within mothers who gained weight, 35.8% were in the normal weight BMI category, 34.3% in the overweight category, and 29.5% in the obese category by the start of their second pregnancy. This compares to 66.8%, 19.7% and 9.2% respectively within those with stable inter-pregnancy weight.

Birthweight (grams) was significantly higher in babies born to women who gained weight between pregnancies (3517g, SD 45) compared to those born to women who lost weight and remained weight stable where the mean birthweight was comparable (3463g, SD 563, 3467g, SD 523 respectively) ($p < 0.001$). A lower proportion of babies born to women who lost weight (12.4%) or remained weight stable (11.9%) between pregnancies were LGA compared to 14.5% in women who gained weight ($p < 0.001$). Compared to normal weight women, overweight and obese women were at increased risk of LGA births in both pregnancies with risk highest in obese women (unadjusted odds ratio 2.2, 95% CI 1.9 to 2.6, $p < 0.001$ and unadjusted odds ratio 2.1, 95% CI 1.8 to 2.3, $p < 0.001$ in first and second pregnancy respectively).

Figure 1 shows the percentage of LGA as recurrent LGA (first and second pregnancy) or LGA in second pregnancy only (after having a non-LGA baby in the first pregnancy) by the inter-pregnancy change in maternal BMI stratified by maternal BMI category in the first pregnancy. The lowest proportion of LGA births in the second pregnancy was in underweight women in the first pregnancy who remained weight stable (5.9%), while the highest was in obese women who gained weight (20.2%). Recurrent LGA was lowest in normal weight and overweight women who lost weight and highest in obese women who lost weight.

There was a significant positive association between birthweight in the second pregnancy with each unit increase in BMI between pregnancies. The largest increase was in normal weight women who gained ≥ 1 BMI unit in weight between pregnancies (adjusted increase in birthweight per unit increase in maternal BMI (13.0g, 95% CI 7.1 to 19.0, $p < 0.001$) (Table 2).

The logistic regression models show an increased risk of LGA in the second pregnancy in the full sample on weight gain compared to remaining weight stable. When stratified by baseline BMI category, there was a significantly increased risk of LGA birth in the second pregnancy in normal weight women who gained ≥ 1 BMI unit weight (adjusted odds ratio (aOR) 1.31, 95% CI 1.13 to 1.52, $p < 0.001$) compared to the reference group of normal-

weight women who remained weight stable (Table 3). No association was observed between the risk of LGA and maternal BMI change in underweight, overweight and obese women.

There was a significantly reduced risk of recurrent LGA birth in the second pregnancy in overweight women who had a LGA infant in the first pregnancy and lost ≥ 1 BMI unit in weight (aOR 0.44, 95% CI 0.23 to 0.85, $p=0.02$) (Table 4). No association was observed between risk of recurrent LGA and maternal BMI change in underweight, normal weight and obese women.

There was a significantly increased risk of 'new' LGA birth in the second pregnancy after having a non-LGA infant in the first pregnancy in normal weight and overweight women who had gained ≥ 1 BMI unit weight (aOR 1.39, 95% CI 1.18 to 1.63, $p>0.001$, aOR 1.31, 95% CI 1.03 to 1.66, $p=0.03$ respectively) (Table 5). No association was observed between the risk of new LGA in the second pregnancy and maternal BMI inter-pregnancy change in underweight and obese women.

Discussion

This study examined the association of change in women's BMI between their first and second live birth pregnancies with LGA risk in their second pregnancy in a population-based cohort of 15940 women in the South of England. A large proportion (48%) of women gained ≥ 1 BMI unit in weight when presenting to antenatal care for their second pregnancy. The proportion of LGA births in women who lost weight was 12.4% and 11.9% in those that remained weight stable compared to 14.5% in women who gained weight. Normal weight women who gained ≥ 1 BMI unit by the start of their second pregnancy had an increased risk of an LGA birth. Overweight women who lost ≥ 1 BMI unit were had a reduced risk of recurrent LGA, whereas both normal and overweight women who gained ≥ 1 BMI unit between pregnancies had an increased risk of LGA birth in their second pregnancy after a non-LGA birth in the first.

Compared to the population-based Swedish cohort which carried out a similar analysis for LGA and other outcomes in 151025 women, a lower proportion of women remained weight stable in this cohort (46% compared to 36%) and a higher proportion lost (11% compared to 16%) or gained (43% compared to 48%) weight. Amongst women who gained weight, a higher proportion gained 3 or more BMI units in this cohort (20%) compared to the Swedish cohort (11%)²³. Similarly, in comparison to a population-based cohort of 24520 women in Aberdeen, Scotland; a larger proportion of women in this study lost (4.8% compared to 7.3%) or gained (25.6% compared to 30.5%) weight (>2 BMI units)²⁶. The Swedish cohort used data from 1992 to 2001 and the Scottish cohort from 1986 to 2013. The differences could reflect the increase in the prevalence of maternal overweight and obesity over time.

We showed an increased risk of LGA in the second pregnancy in the full sample on weight gain compared to weight remaining stable. This effect remained after adjusting for previous outcome of LGA (in first pregnancy). On stratification by BMI, this effect was only observed in normal weight woman. In a population-based cohort in the US, women were found to be at increased risk of LGA in the second pregnancy if their pre-pregnancy BMI category changed towards overweight or obese from first to second pregnancy regardless of their BMI category in first pregnancy except in underweight women who increased to normal weight. This study only examined risk in second pregnancy without adjustment for outcome in first pregnancy and considered weight change as change in BMI category only²¹.

In obese women in the US, inter-pregnancy weight gain of ≥ 2 BMI units was associated with increased risk of LGA and a weight loss of ≥ 2 BMI units was associated with decreased risk

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3 compared to the reference group of weight maintained between 2 BMI units²². We found no
4 association between weight change and risk of second pregnancy LGA in obese women
5 although it may be that as obese women are already at increased risk of LGA births the
6 change in BMI between-pregnancy in this cohort was not large enough to detect a further
7 increase in risk.

8 Risk of recurrent LGA was analysed in one previous study in Scotland which found that inter-
9 pregnancy weight gain (≥ 2 BMI units) was associated with increased risk of recurrent LGA
10 and weight loss (≥ 2 BMI units) was found to be protective. Stratification by BMI showed that
11 women with healthy weight (BMI $< 25\text{kg/m}^2$) were at increased risk of recurrent LGA on
12 gaining weight whereas overweight women (BMI $\geq 25\text{kg/m}^2$) were at reduced risk of recurrent
13 LGA on losing weight²⁶. We showed a similar reduction in risk in overweight women who lost
14 ≥ 1 BMI unit between pregnancies, but found no association in normal weight women.
15

16 We showed an increased risk of 'new' LGA in the second pregnancy (after a non-LGA birth
17 in the first pregnancy) on weight gain compared to remaining weight stable. After
18 stratification by BMI, we found that this association between inter-pregnancy weight gain and
19 new LGA remained only in normal-weight and overweight women. The findings from this
20 study are in line with findings with other studies in Scotland²⁴ and Sweden²³ which found
21 increased risk of 'new' LGA with modest (1-3 BMI units) and large (≥ 3 BMI units) weight
22 gain. Both studies also found a decreased risk with between pregnancy weight loss of > 1
23 BMI unit which was not found in our study. Both studies stratified BMI as $<$ and $\geq 25\text{kg/m}^2$
24 and thus this is not directly comparable with our analysis as we further stratified the
25 $\geq 25\text{kg/m}^2$ category as overweight (BMI 25-29.9 kg/m^2) and obese ($\geq 30\text{kg/m}^2$) and found an
26 increased risk of new LGA in overweight, but not in obese women.
27

28 Women included in this analysis had a range of inter-pregnancy interval of less than 1 to up
29 to 12 years and thus weight change could be due to postpartum weight retention or late
30 postpartum weight gain. A study looking at the effects of pregnancy on long-term weight gain
31 concluded that women who had not lost pregnancy weight at one year postpartum were
32 more likely to retain weight longer term³⁰. We examined the risk of maternal weight gain with
33 length of the inter-pregnancy interval and found that women with an interval of 12-23 months
34 were least likely to start the next pregnancy at a higher weight³¹. We also examined inter-
35 pregnancy interval as a predictor for risk of LGA and found no association but found that an
36 interval of 12-23 months was associated with lower risk of small-for-gestational age (SGA)
37 (data not shown). In this study, we have adjusted for the length of the inter-pregnancy
38 interval in the models.
39

40 Future research that characterises the predictors of postpartum weight change would help
41 design interventions to support postpartum weight loss. Key to this is an understanding of
42 the pattern of weight change during this period as well as identifying the optimal setting and
43 delivery of the intervention. Advice regarding healthy eating and physical activity is more
44 commonly received during pregnancy but when advice is received postpartum, it was found
45 not to be associated with healthy diet or physical activity behaviours³². Most interventions
46 that have been successful in limiting and promoting weight loss were combined diet and
47 physical activity interventions with self-monitoring³³. However, the timing of engaging women
48 and length of intervention or engagement are important with one study showing that an
49 intervention from 16 weeks pregnancy to six months postpartum was more effective than the
50 same intervention from birth to six months postpartum intervention³⁴.

51 As pregnancy and early postpartum is a period of major change for women and their
52 families, interventions need to be carefully designed to be attractive, flexible and feasible for
53 women at this stage with competing priorities and time demands. Contact as part of these
54 interventions also needs to be medium to long term to allow for weight maintenance. The
55 majority of appointments during the postpartum period in the UK are child health and
56 development reviews with the health visitor and one with the general practitioner in the first
57

two years after birth. The feasibility of using these appointments to engage and support maternal weight and health needs to be explored.

Strengths and limitations

This is a relatively large population-based cohort including women from various socioeconomic and ethnic backgrounds delivering at a large maternity centre in Southampton, UK, thus representative of the regional population. One city may not be representative of the national population, and according to the UK Department of Communities and Local Government English indices of deprivation report, Southampton is more deprived than average with the situation having worsened between 2010 and 2015³⁵. However, about half of the women included in this analysis reside in the rest of Hampshire (the region where Southampton is situated), which is less deprived. The sample was 87% White comparable to the 2011 England and Wales population census of 86% White³⁶. The analysis was adjusted for several key confounders that were reasonably complete (96% complete for ethnicity and employment status). Both the exposure and outcome in this study were objectively measured by healthcare professionals as part of routine antenatal and delivery care.

An important limitation was the lack of information on weight gain during pregnancy, which is a key factor influencing risk of LGA births³⁷. Women who had their first booking appointment later into the pregnancy (more than 24 weeks) were excluded from the analysis in order to ensure comparability of weight measurements between pregnancies. Some of the confounding factors which were accounted for in the analysis were self-reported, however the information was collected prospectively, therefore any measurement error is likely to be non-differential. Another limitation is that these findings are based on observational data so inferences about causation cannot be drawn and the risk of residual confounding influencing the results needs to be considered. However, it is not feasible or ethical to conduct a randomised trial to address the aim of this study.

In conclusion, a large proportion of women gained weight between their first and second pregnancy, and a higher proportion of these women had a LGA birth in their second pregnancy compared to their first in this English cohort. Overall, weight gain between pregnancies was associated with an increased risk of LGA in the second pregnancy. Risk of new LGA was higher in normal weight and overweight women who gained weight after a non-LGA birth in their first pregnancy compared who remained weight stable. Overweight women who had a LGA birth in their first pregnancy were at a lower risk of a recurrent LGA birth in their second pregnancy if they lost weight between pregnancies. Supporting efforts to lose weight in overweight and obese women between pregnancies, and stop weight gain in all women planning to have further children (except those who are underweight) are important preventive measures of subsequent adverse maternal and offspring health outcomes.

Author Contributions

Study design (NZ, PJR, NSM, NAA), data analysis (NZ, SW), acquisition and interpretation of the data (NZ, NAA), drafting of the abstract (NZ), revising for content (NZ, SW, PJR, NSM, NAA) and approval of final version before submission (NZ, SW, PJR, NSM, NAA).

Data statement

Anonymised data are only available upon request from the authors conditional on the approval by the appropriate institutional ethics and research governance processes.

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Competing interests

The authors have no competing interests to declare.

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10 11 12 **Figure legend**

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14 Figure 1: The percentage of LGA births in second pregnancy stratified by maternal BMI
15 category and previous outcome of LGA
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17 18 19 20 **Table legends:**

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22 Table 1: Maternal and birth characteristics in second live birth pregnancy categorised by
23 weight loss/no change and weight gain from previous pregnancy for the period of January
24 2003 - September 2017, University Hospital Southampton NHS Foundation Trust,
25 Southampton, Hampshire, England
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27 Table 2: Linear regression estimates for the association between birthweight (in g) in second
28 live birth pregnancy with inter-pregnancy change in maternal BMI in the sub-sample of
29 women who gained ≥ 1 BMI unit stratified by maternal body mass index (BMI) category at
30 the first pregnancy
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32 Table 3: Logistic regression models testing the association between risk of LGA in the
33 second pregnancy and change in maternal body mass index (BMI) measured at the first
34 antenatal visit of each pregnancy stratified by BMI category at the start of first pregnancy
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36 Table 4: Logistic regression models testing the association between risk of recurrent LGA in
37 the second pregnancy and change in maternal body mass index (BMI) measured at the first
38 antenatal visit of each pregnancy stratified by BMI category in first pregnancy
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40 Table 5: Logistic regression models testing the association between the risk of LGA birth in
41 the second pregnancy following a non-LGA birth in the first pregnancy and change in
42 maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy
43 stratified by BMI category in first pregnancy
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Table 1: Maternal and birth characteristics in second live birth pregnancy categorised by weight loss/no change and weight gain from previous pregnancy for the period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, England

	Lost <= -1 BMI units from previous pregnancy	Weight stable (>-1 to <1 BMI unit)	Gained >=1 BMI units from previous pregnancy	p
N	2548	5785	7607	
Maternal age, years (mean ± SD)	28.7 ± 5.4	29.8 ± 5.3	28.4 ± 5.5	<0.001
Timing of first booking appointment, weeks (mean ± SD)	10.8 ± 2.3	11.0 ± 2.3	11.1 ± 2.5	<0.001
Maternal BMI at booking, kg/m ² (mean ± SD)	24.1 ± 5.1	23.8 ± 4.4	27.9 ± 5.8	<0.001
Maternal BMI at booking (%; 95% CI)				<0.001
Underweight (< 18.5)	6.9 (5.9 to 7.9)	4.3 (3.8 to 4.8)	0.4 (0.3 to 0.6)	
Normal weight (18.5 to 24.9)	61.1 (59.2 to 63.0)	66.8 (65.6 to 68.1)	35.8 (34.7 to 36.9)	
Overweight (25.0 to 29.9)	20.1 (18.6 to 21.7)	19.7 (18.7 to 20.7)	34.3 (33.2 to 35.4)	
Obese (≥30.0)	11.9 (10.7 to 13.3)	9.2 (8.5 to 10.0)	29.5 (28.5 to 30.5)	
Maternal smoking status at booking (%; 95% CI)				<0.001
Never smoked/quit	57.2 (55.3 to 59.2)	63.0 (61.8 to 64.3)	56.4 (55.3 to 57.6)	
Stopped >1 year before conceiving	16.1 (14.6 to 17.5)	17.2 (16.3 to 18.2)	16.5 (15.7 to 17.4)	
Stopped <1 year prior to conceiving	4.0 (3.3 to 4.8)	2.8 (2.4 to 3.2)	4.1 (3.7 to 4.6)	
Stopped when pregnancy confirmed	6.8 (5.8 to 7.8)	5.9 (5.3 to 6.6)	8.3 (7.7 to 9.0)	
Continued smoking	15.9 (14.5 to 17.4)	11.0 (10.2 to 11.8)	14.6 (13.8 to 15.4)	
Maternal education (%; 95% CI)				<0.001
Secondary (GCSE) or under	30.7 (28.9 to 32.5)	24.0 (22.9 to 25.2)	32.3 (31.2 to 33.3)	
College (A levels)	40.4 (38.5 to 42.3)	38.8 (37.6 to 40.1)	42.1 (40.1 to 43.2)	
University degree or above	28.9 (27.2 to 30.7)	37.1 (35.9 to 38.4)	25.6 (24.6 to 26.6)	
Maternal employment (%; 95% CI)				<0.001
Employed	66.2 (64.3 to 68.0)	71.7 (70.5 to 72.9)	62.7 (61.6 to 63.8)	
Unemployed	31.8 (30.0 to 33.7)	26.9 (25.8 to 28.1)	35.4 (34.4 to 36.5)	
In education	0.9 (0.6 to 1.4)	0.8 (0.6 to 1.1)	1.2 (0.9 to 1.4)	
Not specified	1.0 (0.7 to 1.5)	0.6 (0.4 to 0.8)	0.7 (0.5 to 0.9)	
Ethnicity (%; 95% CI)				<0.001
White	89.9 (88.7 to 91.1)	88.0 (87.1 to 88.8)	85.0 (84.2 to 85.8)	
Mixed	0.8 (0.5 to 1.3)	0.9 (0.7 to 1.2)	1.5 (1.2 to 1.8)	
Asian	4.2 (3.5 to 5.1)	5.0 (4.4 to 5.6)	6.9 (6.4 to 7.5)	

Black/African/Caribbean	0.6 (0.4 to 1.0)	1.0 (0.8 to 1.3)	1.9 (1.6 to 2.3)	
Chinese	0.5 (0.3 to 0.9)	0.7 (0.5 to 0.9)	0.5 (0.3 to 0.7)	
Other	0.7 (0.4 to 1.1)	1.0 (0.8 to 1.3)	1.1 (0.9 to 1.4)	
Not specified	3.1 (2.5 to 3.9)	3.5 (3.0 to 4.0)	3.0 (2.7 to 3.5)	
Inter-pregnancy interval (median, IQR)	21.7 (14.4 to 32.7)	21.6 (14.1 to 32.0)	25.0 (15.0 to 39.7)	<0.001
Inter-pregnancy interval (% , 95% CI)				
0-11 months	17.4 (15.9 to 18.9)	17.6 (16.6 to 18.6)	17.5 (16.7 to 18.4)	<0.001
12-23 months	39.8 (37.8 to 41.7)	39.9 (38.6 to 41.1)	30.3 (29.3 to 31.3)	
24-35 months	22.6 (21.0 to 24.2)	23.6 (22.5 to 24.7)	22.8 (21.9 to 23.8)	
36 months or more	20.3 (18.7 to 21.9)	18.9 (17.9 to 20.0)	29.4 (28.4 to 30.4)	
Birthweight, grams (mean \pm SD)	3463 \pm 563	3467 \pm 523	3517 \pm 545	<0.001
Previous size at birth (first pregnancy)				
Small-for-gestational age	13.1 (11.8 to 14.4)	12.6 (11.8 to 13.5)	12.0 (11.3 to 12.8)	0.17
Appropriate-for-gestational age	79.6 (77.9 to 81.1)	81.1 (80.0 to 82.1)	80.7 (79.8 to 81.6)	
Large-for-gestational age	7.4 (6.4 to 8.5)	6.3 (5.7 to 7.0)	7.3 (6.7 to 7.9)	
Size at birth (second pregnancy)				
Small-for-gestational age	8.7 (7.6 to 9.8)	7.0 (6.4 to 7.7)	6.4 (5.9 to 7.0)	<0.001
Appropriate-for-gestational age	79.0 (77.3 to 80.5)	81.1 (80.0 to 82.1)	79.1 (78.2 to 80.0)	
Large-for-gestational age	12.4 (11.1 to 13.7)	11.9 (11.1 to 12.8)	14.5 (13.7 to 15.3)	

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Table 2: Linear regression estimates for the association between birthweight (in g) in second live birth pregnancy with inter-pregnancy change in maternal BMI in the sub-sample of women who gained ≥ 1 BMI unit stratified by maternal body mass index (BMI) category at the first pregnancy

	First to second pregnancy														
	Full sample			Underweight at first pregnancy			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
	n	Birthweight (g) per unit increase in maternal BMI change (95% CI)	p	n	Birthweight (g) per unit increase in maternal BMI change (95% CI)	p	n	Birthweight (g) per unit increase in maternal BMI change (95% CI)	p	n	Birthweight (g) per unit increase in maternal BMI change (95% CI)	p	n	Birthweight (g) per unit increase in maternal BMI change (95% CI)	p
Model 1	7607	8.3 3.8 to 12.9	<0.001	353	1.5 -20.4 to 23.3	0.89	4326	10.0 3.6 to 16.5	0.002	1913	-3.8 -12.0 to 4.5	0.37	1015	2.3 -10.0 to 14.6	0.72
Model 2	7607	6.8 2.8 to 10.7	0.001	353	-4.0 -23.0 to 15.0	0.68	4326	9.3 3.7 to 14.9	0.001	1913	-1.6 -8.8 to 5.7	0.67	1015	2.9 -8.0 to 13.7	0.60
Model 3	7324	9.9 5.9 to 14.0	<0.001	338	-2.4 -21.5 to 16.8	0.81	4154	12.0 6.2 to 17.7	<0.001	1839	4.3 -3.3 to 11.8	0.27	993	4.6 -6.7 to 15.8	0.43
Model 4	7324	7.8 3.7 to 11.9	<0.001	338	-3.0 -22.3 to 16.4	0.76	4154	12.1 6.3 to 17.9	<0.001	1839	4.8 -2.7 to 12.4	0.21	993	4.3 -6.9 to 15.6	0.45
Model 5	7324	9.0 4.8 to 13.2	<0.001	338	-2.8 -22.3 to 16.6	0.78	4154	13.0 7.1 to 19.0	<0.001	1839	6.1 -1.7 to 13.8	0.12	993	6.6 -5.0 to 18.1	0.26

Model 1 is adjusted for: gestational age at birth

Model 2 is adjusted for: gestational age at birth, birth weight (previous pregnancy) and gestational age at birth (previous pregnancy)

Model 3 is adjusted for: gestational age at birth, birth weight (previous pregnancy) and gestational age at birth (previous pregnancy), maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status and infant gender

Model 4 is adjusted for: gestational age at birth, birth weight (previous pregnancy) and gestational age at birth (previous pregnancy), maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI and gestational diabetes in current pregnancy

Model 5 is adjusted for: gestational age at birth, birth weight (previous pregnancy) and gestational age at birth (previous pregnancy), maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

Table 3: Logistic regression models testing the association between risk of LGA in the second pregnancy and change in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy stratified by BMI category at the start of first pregnancy

	Maternal BMI change (categorised)	First to second pregnancy														
		Full sample			Underweight at first pregnancy			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p
Unadjusted	Lost <= -1 BMI units from previous pregnancy	15922	1.04 0.90 to 1.20	0.56	599	-	-	9427	0.79 0.63 to 0.99	0.04	3800	0.86 0.67 to 1.12	0.27	2075	1.03 0.75 to 1.40	0.87
	Gained >=1 BMI units from previous pregnancy		1.25 1.13 to 1.39	<0.001		2.19 0.92 to 5.24	0.08		1.23 1.07 to 1.41	0.003		1.11 0.91 to 1.35	0.32		1.11 0.84 to 1.45	0.46
Model 1	Lost <= -1 BMI units from previous pregnancy	15897	1.01 0.87 to 1.17	0.90	599	-	-	9409	0.84 0.67 to 1.06	0.14	3796	0.83 0.63 to 1.09	0.17	2072	0.96 0.69 to 1.32	0.79
	Gained >=1 BMI units from previous pregnancy		1.23 1.11 to 1.37	<0.001		2.09 0.87 to 5.04	0.10		1.22 1.06 to 1.40	0.006		1.11 0.90 to 1.37	0.31		1.07 0.81 to 1.42	0.62
Model 2	Lost <= -1 BMI units from previous pregnancy	15281	1.04 0.89 to 1.21	0.64	553	-	-	9013	0.89 0.70 to 1.13	0.33	3650	0.85 0.64 to 1.12	0.25	2024	0.95 0.68 to 1.32	0.75
	Gained >=1 BMI units from previous		1.29 1.16 to 1.45	<0.001		1.65 0.65 to 4.20	0.29		1.30 1.12 to 1.51	<0.001		1.17 0.94 to 1.44	0.16		1.09 0.82 to 1.45	0.56

Model 3	pregnancy Lost <= -1 BMI units from previous pregnancy Gained >=1 BMI units from previous pregnancy	15281	0.88 0.76 to 1.03	0.13	544	-	-	9013	0.84 0.66 to 1.07	0.16	3650	0.84 0.64 to 1.11	0.23	2024	0.92 0.66 to 1.28	0.61
			1.23 1.10 to 1.37	<0.001		1.67 0.66 to 4.26	0.28		1.29 1.11 to 1.49	0.001		1.16 0.94 to 1.44	0.17		1.08 0.81 to 1.44	0.61
Model 4	Lost <= -1 BMI units from previous pregnancy Gained >=1 BMI units from previous pregnancy	15281	0.89 0.76 to 1.04	0.14	544	-	-	9013	0.84 0.66 to 1.07	0.16	3650	0.84 0.64 to 1.12	0.24	2024	0.95 0.68 to 1.33	0.77
			1.24 1.11 to 1.39	<0.001		1.62 0.63 to 4.20	0.32		1.29 1.11 to 1.50	0.001		1.17 0.94 to 1.45	0.16		1.13 0.84 to 1.51	0.42

* Weight stable (>-1 to <1 BMI unit) was used as the reference group.

Model 1 is adjusted for: previous outcome of LGA

Model 2 is adjusted for: previous outcome of LGA, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status and infant gender

Model 3 is adjusted for: previous outcome of LGA, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI and gestational diabetes in current pregnancy

Model 4 is adjusted for: previous outcome of LGA, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

Table 4: Logistic regression models testing the association between risk of recurrent LGA in the second pregnancy and change in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy stratified by BMI category in first pregnancy

	Maternal BMI change (categorised)	First to second pregnancy											
		Full sample			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	P
Unadjusted	Lost <= -1 BMI units from previous pregnancy	1109	0.80 0.56 to 1.14	0.23	521	0.68 0.35 to 1.32	0.25	338	0.47 0.25 to 0.87	0.02	236	1.33 0.64 to 2.75	0.44
	Gained >=1 BMI units from previous pregnancy		0.93 0.72 to 1.21	0.60		0.89 0.62 to 1.28	0.54		0.67 0.41 to 1.12	0.13		1.45 0.75 to 2.80	0.27
Model 1	Lost <= -1 BMI units from previous pregnancy	1066	0.85 0.59 to 1.23	0.38	500	0.67 0.34 to 1.35	0.26	324	0.45 0.23 to 0.86	0.02	229	1.42 0.66 to 3.05	0.37
	Gained >=1 BMI units from previous pregnancy		1.01 0.77 to 1.34	0.94		0.99 0.67 to 1.46	0.95		0.71 0.42 to 1.21	0.21		1.50 0.75 to 3.00	0.25
Model 2	Lost <= -1 BMI units from previous pregnancy	1066	0.72 0.49 to 1.06	0.09	500	0.63 0.32 to 1.28	0.20	324	0.44 0.23 to 0.85	0.02	229	1.34 0.62 to 2.89	0.46
	Gained >=1 BMI units from previous pregnancy		0.97 0.73 to 1.29	0.84		0.97 0.65 to 1.43	0.86		0.70 0.41 to 1.20	0.20		1.51 0.75 to 3.01	0.25
Model 3	Lost <= -1 BMI units from previous pregnancy	1066	0.72 0.49 to 1.06	0.09	500	0.63 0.31 to 1.27	0.20	324	0.44 0.23 to 0.85	0.02	229	1.39 0.64 to 3.02	0.41
	Gained >=1 BMI units from previous pregnancy		0.97 0.73 to 1.29	0.86		0.96 0.64 to 1.42	0.83		0.70 0.41 to 1.20	0.20		1.59 0.79 to 3.22	0.19

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* Weight stable (>-1 to <1 BMI unit) was used as the reference group.

Model 1 is adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status and infant gender

Model 2 is adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI and gestational diabetes in current pregnancy

Model 3 is adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

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Table 5: Logistic regression models testing the association between the risk of LGA birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy stratified by BMI category in first pregnancy

	Maternal BMI change (categorised)	First to second pregnancy														
		Full sample			Underweight at first pregnancy			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p	n	Odds ratio, OR (95% CI)	p
Unadjusted	Lost <= -1 BMI units from previous pregnancy	14788	1.06 0.90 to 1.24	0.51	585	-	-	8888	0.87 0.68 to 1.12	0.29	3458	0.95 0.70 to 1.28	0.72	1836	0.89 0.62 to 1.27	0.52
	Gained >=1 BMI units from previous pregnancy		1.30 1.16 to 1.46	<0.001		1.78 0.73 to 4.35	0.21		1.29 1.10 to 1.50	0.001		1.24 0.98 to 1.56	0.07		1.01 0.74 to 1.37	0.97
Model 1	Lost <= -1 BMI units from previous pregnancy	14215	1.08 0.92 to 1.28	0.34	540	-	-	8513	0.92 0.71 to 1.19	0.53	3326	0.98 0.72 to 1.33	0.89	1795	0.87 0.60 to 1.25	0.44
	Gained >=1 BMI units from previous pregnancy		1.36 1.21 to 1.54	<0.001		1.41 0.54 to 3.67	0.48		1.38 1.17 to 1.62	<0.001		1.30 1.02 to 1.65	0.03		1.02 0.75 to 1.40	0.89
Model 2	Lost <= -1 BMI units from previous pregnancy	14215	0.93 0.78 to 1.10	0.40	531	-	-	8513	0.87 0.67 to 1.13	0.30	3326	0.97 0.71 to 1.32	0.84	1795	0.84 0.58 to 1.21	0.35
	Gained >=1 BMI units from previous pregnancy		1.29 1.14 to 1.45	<0.001		1.43 0.55 to 3.71	0.47		1.36 1.16 to 1.60	<0.001		1.29 1.02 to 1.64	0.04		1.00 0.73 to 1.38	0.98
Model 3	Lost <= -1 BMI units from previous pregnancy	14215	0.93 0.79 to 1.11	0.43	531	-	-	8513	0.87 0.67 to 1.13	0.30	3326	0.97 0.71 to 1.32	0.86	1795	0.87 0.60 to 1.26	0.47
	Gained >=1 BMI units from previous pregnancy		1.30	<0.001		1.39	0.51		1.37	<0.001		1.30	0.03		1.05	0.77

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	BMI units from previous pregnancy		1.15 to 1.47			0.53 to 3.68			1.16 to 1.61			1.02 to 1.65			0.76 to 1.44	
--	---	--	-----------------	--	--	-----------------	--	--	-----------------	--	--	-----------------	--	--	-----------------	--

* Weight stable (>-1 to <1 BMI unit) was used as the reference group.

Model 1 is adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status and infant gender

Model 2 is adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI and gestational diabetes in current pregnancy

Model 3 is adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, infant gender, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

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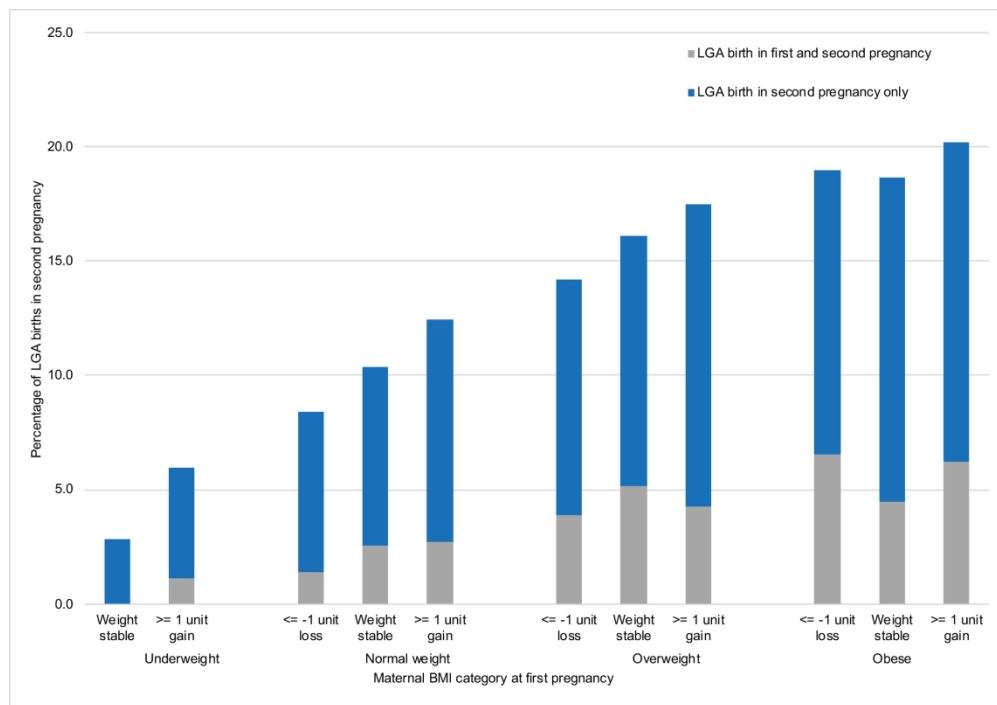


Figure 1: The percentage of LGA births in second pregnancy stratified by maternal BMI category and previous outcome of LGA

203x142mm (300 x 300 DPI)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4

1		#6b	For matched studies, give matching criteria and number of	n/a
2			exposed and unexposed	
3				
4	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	4-5
5			confounders, and effect modifiers. Give diagnostic criteria, if	
6			applicable	
7				
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9				
10	Data sources /	#8	For each variable of interest give sources of data and details of	4-5
11	measurement		methods of assessment (measurement). Describe	
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	n/a
19				
20	Study size	#10	Explain how the study size was arrived at	4
21				
22				
23	Quantitative	#11	Explain how quantitative variables were handled in the	4-5
24	variables		analyses. If applicable, describe which groupings were chosen,	
25			and why	
26				
27				
28	Statistical	#12a	Describe all statistical methods, including those used to control	5
29	methods		for confounding	
30				
31				
32		#12b	Describe any methods used to examine subgroups and	5
33			interactions	
34				
35				
36		#12c	Explain how missing data were addressed	n/a
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	n/a
39				
40				
41		#12e	Describe any sensitivity analyses	n/a
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg	5
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	n/a
52				
53		#13c	Consider use of a flow diagram	n/a
54				
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5-6
57			clinical, social) and information on exposures and potential	
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1		confounders. Give information separately for exposed and	
2		unexposed groups if applicable.	
3			
4		#14b Indicate number of participants with missing data for each	13-14
5		variable of interest	
6			
7		#14c Summarise follow-up time (eg, average and total amount)	n/a
8			
9			
10	Outcome data	#15 Report numbers of outcome events or summary measures	5-6, 13-
11		over time. Give information separately for exposed and	14
12		unexposed groups if applicable.	
13			
14			
15	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	6-7, 15-
16		adjusted estimates and their precision (eg, 95% confidence	21
17		interval). Make clear which confounders were adjusted for and	
18		why they were included	
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22		#16b Report category boundaries when continuous variables were	4-5, 13-
23		categorized	14
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26		#16c If relevant, consider translating estimates of relative risk into	n/a
27		absolute risk for a meaningful time period	
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29			
30	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	n/a
31		interactions, and sensitivity analyses	
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34	Key results	#18 Summarise key results with reference to study objectives	7
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36	Limitations	#19 Discuss limitations of the study, taking into account sources of	8-9
37		potential bias or imprecision. Discuss both direction and	
38		magnitude of any potential bias.	
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41	Interpretation	#20 Give a cautious overall interpretation considering objectives,	9
42		limitations, multiplicity of analyses, results from similar studies,	
43		and other relevant evidence.	
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46	Generalisability	#21 Discuss the generalisability (external validity) of the study	8-9
47		results	
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50	Funding	#22 Give the source of funding and the role of the funders for the	10
51		present study and, if applicable, for the original study on which	
52		the present article is based	
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BMJ Open

Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	obesity, pregnancy, pregnancy outcome, weight gain, large-for-gestational age

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Manuscripts

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3 1 **Is maternal weight gain between pregnancies associated with risk of large-for-**
4 2 **gestational age birth? Analysis of a UK population-based cohort**
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7 4 Nida Ziauddeen¹, Sam Wilding¹, Paul J. Roderick¹, Nicholas S. Macklon^{2,3}, Nisreen A.
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28 **Keywords:** obesity, pregnancy, pregnancy outcome, weight gain, birth weight

29 **Word count:** 4206 words

34 Abstract

35 **Objective:** Maternal overweight and obesity during pregnancy increases the risk of large-for-
36 gestational age (LGA) birth and childhood obesity. We aimed to investigate the association
37 between maternal weight change between subsequent pregnancies and risk of having a
38 LGA birth.

39 **Design:** Population-based cohort.

40 **Setting:** Routinely collected antenatal healthcare data between January 2003 and
41 September 2017 at University Hospital Southampton, England.

42 **Participants:** Health records of women with their first two consecutive singleton live-birth
43 pregnancies were analysed (n=15940).

44 **Primary outcome measure:** Risk of LGA, recurrent LGA and 'new' LGA births in the
45 second pregnancy.

46 **Results:** Of the 15940 women included, 16.0% lost and 47.7% gained weight (≥ 1 kg/m²)
47 between pregnancies. A lower proportion of babies born to women who lost ≥ 1 kg/m²
48 (12.4%) and remained weight stable between -1 to 1 kg/m² (11.9%) between pregnancies
49 were LGA compared to 13.5% and 15.9% in women who gained 1-3 and ≥ 3 kg/m²
50 respectively. Overweight women were at lower risk of recurrent LGA in the second
51 pregnancy if they lost ≥ 1 kg/m² (adjusted risk ratio (aRR) 0.69, 95% CI 0.48 to 0.97)
52 whereas overweight women who gained weight (≥ 3 kg/m²) were at increased risk of 'new'
53 LGA after having a non-LGA birth in their first pregnancy (aRR 1.35, 95% CI 1.05 to 1.75).
54 Normal-weight women who gained weight were also at increased risk of 'new' LGA in the
55 second pregnancy (aRR 1.26, 95% CI 1.06 to 1.50 with weight gain of 1-3 kg/m² and aRR
56 1.34, 95% CI 1.09 to 1.65 with gain of ≥ 3 kg/m²).

57 **Conclusions:** Losing weight after an LGA birth reduced the risk of recurrent LGA in the next
58 pregnancy in overweight women, while gaining weight increased LGA risk in women with no
59 previous history of LGA birth. Preventing weight gain between pregnancies is an important
60 prevention measure to achieve better maternal and offspring outcomes.

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63 Article summary

64 Strengths and limitations of this study

- 65 • Utilises antenatal care and birth data from a large population-based cohort including
66 women from all socioeconomic backgrounds
- 67 • Objective measurement of both exposure (maternal weight) and outcome in two
68 pregnancies per woman
- 69 • Self-reported data for covariables
- 70 • Lack of information on breastfeeding and maternal weight gain during pregnancy

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75 Introduction

76 The prevalence of maternal obesity has been rising over time. It has more than doubled in
77 England between 1989 and 2007 (7.6% to 15.6%), with the proportion of normal weight
78 pregnancies showing a 12% decrease from 65.6% to 53.6%¹. Maternal overweight and
79 obesity is a key risk factor for adverse maternal and birth outcomes. It also increases the risk
80 of long-term health problems in the child including obesity, cardiovascular disease, diabetes
81 and cognitive and behavioural disorders². Birthweight is a key early life predictor of long-term
82 health outcomes such as obesity and cardiovascular disease³ and potentially acts as a
83 mediator on the causal pathway between maternal obesity and long-term offspring
84 outcomes. The incidence of large-for-gestational age (LGA) birth, defined as >90th
85 percentile weight for gestational age, has increased over time in high-income countries^{4,5}.
86 LGA is associated with both childhood^{6,7} and adult obesity⁸⁻¹⁰. A key risk factor for LGA birth
87 is gestational diabetes (GDM)¹¹, the incidence of which has also increased over time^{12,13}.
88 Offspring of mothers with gestational diabetes have increased risk of childhood overweight
89 and obesity^{14,15}. Maternal obesity is an established risk factor for both GDM and LGA birth¹⁶.
90 Change in maternal body mass index (BMI) between pregnancies could modify the risk of
91 LGA birth in the subsequent pregnancy.

92 Birthweight, on average, increases with parity. First-born infants tend to have the lowest
93 birthweight among their younger siblings¹⁷⁻¹⁹ up to the fourth pregnancy²⁰. However,
94 birthweight was found to decrease with parity for women who had short intervals between
95 their pregnancies (<12 months) while the increase in birthweight with parity was more
96 pronounced in women with long intervals (>24 months)²⁰. Also, maternal weight change
97 between pregnancies was found to modify the relationship between parity and birthweight.
98 Women who returned to their pre-pregnancy weight before the next conception had infants
99 who weighed less than infants of women who retained or gained weight between
100 pregnancies²⁰. In a UK-based study, women who lost at least six kilograms between their
101 first and second pregnancy had a smaller average increase in birthweight of the second
102 baby compared to women who gained ten kilograms or more (in a 1.60m tall woman, 6 kg
103 equates to approximately 2.3 kg/m² and 10 kg to approximately 3.8 kg/m²)¹⁸.

104 A large US study showed that women were at an increased risk of having an LGA baby in
105 the second pregnancy if their pre-pregnancy BMI category increased towards overweight or
106 obese between their first and second pregnancies. This applied to all first pregnancy BMI
107 categories, except underweight women who became normal weight by the start of their
108 second pregnancy. Overweight and obese women who dropped BMI category by their
109 second pregnancy remained at an increased risk of LGA birth, but had a lower risk
110 compared to women whose BMI category increased between pregnancies²¹.

111 Another US-based study showed that inter-pregnancy weight gain of ≥ 2 kg/m² in obese
112 women was associated with increased risk of LGA. Weight loss of ≥ 2 kg/m² was associated
113 with a lower adjusted LGA risk compared to the women who maintained their weight within 2
114 kg/m² change between pregnancies²².

115 Two studies found a reduced risk of 'new' LGA in the second pregnancy following a non-
116 LGA birth in the first pregnancy with inter-pregnancy weight loss of >1 kg/m², and an
117 increased risk with modest (1-3 kg/m²) and large (≥ 3 kg/m²) weight gain. In stratified
118 analysis, the association was stronger in women with a first pregnancy BMI of <25 kg/m²
119 ^{23,24}. A third study only found an increased risk of 'new' LGA in normal weight women who
120 gained ≥ 4 kg/m² between pregnancies and no association in overweight women²⁵.

121 To our knowledge, only one study has examined the risk of recurrent LGA (occurring in both
122 first and second pregnancies) in relation to maternal weight change between pregnancies ²⁶.
123 The study, conducted in Aberdeen, Scotland, included 24520 women of which 813 women
124 had LGA births in both pregnancies. Inter-pregnancy weight gain (≥ 2 kg/m²) was associated

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3 125 with increased risk of recurrent LGA, while weight loss (≥ 2 kg/m²) was protective. Women
4 126 with BMI < 25 kg/m² were at increased risk of recurrent LGA on gaining weight whereas
5 127 women with BMI ≥ 25 kg/m² were at reduced risk of recurrent LGA on losing weight²⁶.

7 128 In this study, we aimed to investigate the association between the incidence of LGA,
8 129 recurrent LGA and 'new' LGA births in the second pregnancy and maternal change in BMI
9 130 between the first and second pregnancies, stratifying by maternal BMI category in the first
10 131 pregnancy, in a population-based cohort in the South of England.

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16 134 **Methods**

18 135 This is a population-based cohort of prospectively collected routine healthcare data for
19 136 antenatal care between January 2003 and September 2017 at University Hospital
20 137 Southampton, Hampshire, UK. This included all women delivering at this hospital (n= 82098
21 138 pregnancies), which is a regional centre for maternity care in and around Southampton.
22 139 Records of women with their first two consecutive singleton live birth pregnancies were
23 140 included. Records with unfeasible weight (< 30 kg), height (> 2 m) and gestational age (> 301
24 141 days) values were excluded.

26 142

28 143 *Exposure assessment*

30 144 Maternal weight in kilograms was routinely measured by a midwife at the first antenatal
31 145 (booking) appointment of each pregnancy, which is recommended to take place ideally by 10
32 146 weeks gestation in the UK, according to the National Institute for Health and Care
33 147 Excellence Guidelines²⁷. Any woman who had a booking appointment at or after 24 weeks
34 148 of pregnancy was excluded. Height was self-reported. BMI was calculated as weight (in kg)
35 149 divided by height (in metres) squared.

36 150 BMI at the start of the first pregnancy was categorised as underweight (BMI < 18.5 kg/m²),
37 151 normal weight (18.5 to 24.9 kg/m²), overweight (25.0 to 29.9 kg/m²) and obese (≥ 30 kg/m²).
38 152 Change in BMI was calculated as the difference in BMI measured at the booking
39 153 appointments of the first two consecutive live birth pregnancies for each woman. This
40 154 change in BMI was then categorised as weight loss (≥ 1 kg/m²), weight stable (-1 to 1 kg/m²)
42 155 and two categories of weight gain ($1-3$ kg/m² and ≥ 3 kg/m²).

44 156

46 157 *Outcome assessment*

47 158 Birthweight (grams) was measured by healthcare professionals at birth as part of routine
48 159 care. Gestational age was based on a dating ultrasound scan which routinely takes place
49 160 between 10 and 13 weeks gestation²⁷. Age- and gender- specific birthweight centiles were
50 161 calculated using reference values for England and Wales provided in the most recently
51 162 released national data²⁸. Large-for-gestational age was defined as > 90 th percentile weight
52 163 for gestational age. This was only defined for babies born between 24 to 42 weeks gestation
53 164 as reference values only exist for these gestational ages and with determinate gender.

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57 166 *Covariables*

58 167 Maternal date of birth is recorded at the booking appointment and converted to age (in
59 168 years) on extraction of the dataset to maintain anonymity. Highest maternal educational

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3 169 qualification was self-reported and categorised as primary, secondary, college,
4 170 undergraduate, postgraduate, graduate and none. For the purposes of this analysis, this was
5 171 condensed to three categories - secondary (GCSE) and under, college (A levels) and
6 172 university degree or above. Self-reported ethnicity was recorded under 16 categories and
7 173 condensed to White, Mixed, Asian, Black/African/Caribbean and Other. Categories of not
8 174 asked and not stated were coded as missing. Smoking was self-reported as current smoking
9 175 or non-smoking. Non-smokers were further asked if they had ever smoked or had previously
10 176 smoked and quit. This was categorised as stopped more than 12 months before conception,
11 177 stopped less than 12 months before conception or stopped when pregnancy confirmed.
12 178 Employment status was self-reported at booking appointment and categorised as employed,
13 179 unemployed, in education, and not specified. Infertility treatment was categorised as
14 180 no/investigations only and yes (hormonal only, in-vitro fertilisation, gamete intrafallopian
15 181 transfer and other surgical) in either one or both pregnancies. In this population, an oral
16 182 glucose tolerance test was used for screening for GDM in women with one or more risk
17 183 factors (BMI > 30kg/m²; GDM in previous pregnancy; previous baby weighing ≥4.5kg;
18 184 diabetes in parents or siblings and of Asian, African-Caribbean or Middle Eastern
19 185 ethnicity)²⁹. GDM diagnosis was then reported in the database. Inter-pregnancy interval was
20 186 defined as the interval between the first live birth and conception of the second pregnancy.
21 187 The difference in days between two consecutive live births was calculated and gestational
22 188 age of the latter birth subtracted from this to derive the inter-pregnancy interval.

25 189

27 190 *Statistical analysis*

28
29 191 All analysis was performed using Stata 15³⁰. Univariable comparisons were carried out using
30 192 ANOVA for continuous variables and chi square test for categorical variables. Generalised
31 193 linear regression with log link³¹ was used to examine the association between the
32 194 categorised variable of maternal change in BMI between pregnancies with risk of LGA in the
33 195 second pregnancy. This was analysed first in the whole sample and then stratified by
34 196 'baseline' maternal BMI category as calculated in the first antenatal appointment of the first
35 197 pregnancy.

37 198 Risk of LGA in the second pregnancy was explored in the whole sample adjusting for
38 199 previous pregnancy outcome of LGA. The risk of 'new' LGA in second pregnancy after
39 200 having a non-LGA baby in the first pregnancy was explored in the sub-sample of women
40 201 who had non-LGA births in the first pregnancy. The risk of recurrent LGA (LGA in both
41 202 pregnancies) was explored in a sub-sample of women who had LGA births in the first
42 203 pregnancy.

44
45 204 Initial univariable analysis was followed by multivariable models adjusting for potential
46 205 confounding factors – maternal age, ethnicity, highest educational qualification, whether or
47 206 not undergone infertility treatment, employment status, smoking behaviour in second
48 207 pregnancy, baseline BMI, GDM in second pregnancy and inter-pregnancy interval.
49 208 Sensitivity analysis was conducted adding gestational age at booking in the second
50 209 pregnancy to the models.

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52 210 A statistical significance level of 0.05 with 95% confidence intervals was used in the
53 211 regression models.

54 212

56 213 *Ethical considerations*

57
58 214 All data were fully anonymised by the data holder before being accessed by the research
59 215 team. Ethics approval was granted by the University of Southampton Faculty of Medicine
60 216 Ethics Committee: study ID 25508.

217

218 *Patient and Public Involvement*

219 Patients and public were not involved in setting the research question or the outcome
220 measures, nor were they involved in developing plans for the design or implementation of
221 the study. However, pregnant woman and mothers of young children have been involved in
222 the planning stages of a research project building on this analysis.

223

224

225 **Results**

226 The first and second pregnancies of 15940 women were included. Of these, 16.0% of
227 women lost ≥ 1 kg/m², 36.3% remained weight stable (-1 to 1 kg/m²), 27.9% gained 1-3 kg/m²
228 and 19.8% gained ≥ 3 kg/m² between their first and second live birth pregnancies. Weight
229 loss of >2 kg/m² was observed in 7.3% of women whereas 10.7% gained >2 kg/m². Mean
230 BMI at second pregnancy booking was 30.8 kg/m² (standard deviation (SD) 5.9) in women
231 who gained ≥ 3 kg/m², 25.9 kg/m² (SD 4.7) in women who gained 1-3kg/m², 24.1 kg/m² (SD
232 5.1) in women who lost weight, and 23.8 kg/m² (SD 4.4) women whose weight remained
233 stable between pregnancies ($p < 0.001$) (Table 1).

234 Women who gained ≥ 3 kg/m² by the start of their second pregnancy were more likely to be
235 smokers, unemployed, with lower educational attainment and to have a longer inter-
236 pregnancy interval, compared to those who maintained a stable weight between
237 pregnancies. Mean maternal age was lowest in the women who gained ≥ 3 kg/m² (27.3
238 years, SD 5.5) and highest in the women who remained weight stable (29.8 years, SD 5.3).
239 Mean maternal age in women who lost weight was 28.7 years (SD 5.4).

240 Mothers who gained ≥ 3 kg/m² were more likely to be obese (48.3%) at the start of the
241 second pregnancy compared to 16.1% in women who gained 1-3 kg/m², 9.2% in women
242 who remained weight stable and 11.9% in women who lost ≤ 1 kg/m².

243 A lower proportion of babies born to women who lost weight (12.4%) or remained weight
244 stable (11.9%) between pregnancies were LGA compared to 13.5% in women who gained 1-
245 3 kg/m² and 15.9% in women who gained ≥ 3 kg/m² ($p < 0.001$) (Table 1, Figure 1). Compared
246 to normal weight women, overweight and obese women were at increased risk of LGA births
247 in both pregnancies with risk highest in obese women (unadjusted relative risk (RR) 2.06,
248 95% CI 1.78 to 2.38 and 1.86, 95% CI 1.69 to 2.05 in first and second pregnancy
249 respectively). Figure 2 shows the percentage of all LGA as recurrent LGA or 'new' LGA in
250 second pregnancy by the inter-pregnancy change in maternal BMI stratified by maternal BMI
251 category calculated at the start of the first pregnancy. The lowest proportion of LGA births in
252 the second pregnancy was in underweight women in the first pregnancy who remained
253 weight stable (2.8%), while the highest was in obese women who gained ≥ 3 kg/m² (21.2%).
254 Within BMI categories, recurrent LGA was lowest in normal weight and overweight women
255 who lost weight and highest in obese women who gained 1-3 kg/m².

256 Women who gained ≥ 3 kg/m² were at increased risk of LGA in the second pregnancy in the
257 full sample compared to remaining weight stable (aRR 1.28, 95% CI 1.14 to 1.44) (Figure 1).
258 There was a significantly reduced risk of recurrent LGA birth in the second pregnancy in
259 overweight women who had a LGA infant in the first pregnancy and lost ≥ 1 kg/m² in weight
260 (aRR 0.69, 95% CI 0.48 to 0.97) (Table 2). No association was observed between risk of
261 recurrent LGA and maternal BMI change between pregnancies in underweight, normal
262 weight and obese women.

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3 263 There was an increased risk of 'new' LGA birth in the second pregnancy after having a non-
4 264 LGA infant in the first pregnancy in normal weight women who gained 1-3 kg/m² (aRR 1.26,
5 265 95% CI 1.06 to 1.50) and in normal weight and overweight women who had gained ≥ 3 kg/m²
6 266 weight (aRR 1.34, 95% CI 1.09 to 1.65, aRR 1.35, 95% CI 1.05 to 1.75, respectively) (Table
7 267 3). No association was observed between the risk of 'new' LGA in the second pregnancy
8 268 and maternal BMI inter-pregnancy change in obese women.
9

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14 271 **Discussion**

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16 272 This study examined the association between change in women's BMI between their first
17 273 and second live birth pregnancies and risk of LGA birth in the second pregnancy in a
18 274 population-based cohort of 15940 women in the South of England. Almost half of the sample
19 275 (48%) of women gained ≥ 1 kg/m² in the time between the first antenatal care visits during
20 276 their first and second pregnancies. The proportion of LGA births was significantly higher in
21 277 women with an inter-pregnancy weight gain of ≥ 3 kg/m² (16%) compared to women who lost
22 278 weight (12%) and those who remained weight stable (12%) between pregnancies.
23 279 Overweight women who lost ≥ 1 kg/m² had a reduced risk of recurrent LGA. Normal weight
24 280 women who gained 1–3 kg/m² and both normal weight and overweight women who gained
25 281 ≥ 3 kg/m² between pregnancies had an increased risk of LGA birth in their second pregnancy
26 282 after a non-LGA birth in the first.

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29 283 Compared to the population-based Swedish cohort which carried out a similar analysis for
30 284 LGA and other outcomes in 151025 women using data from 1992 to 2001, a lower
31 285 proportion of women remained weight stable in our cohort (46% compared to 36%) and a
32 286 higher proportion lost (11% compared to 16%) or gained (43% compared to 48%) weight.
33 287 Amongst women who gained weight, a higher proportion gained ≥ 3 kg/m² in this cohort
34 288 (20%) compared to the Swedish cohort (11%)²³. Similarly, in comparison to a population-
35 289 based cohort of 24520 women in Aberdeen, Scotland; for the period 1986 to 2013, a larger
36 290 proportion of women in our study both lost and gained weight²⁶. The differences could reflect
37 291 the increase in the prevalence of maternal overweight and obesity over time since our data
38 292 are more recent.

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41 293 In the adjusted model utilising the full sample, we showed an increased risk of LGA in the
42 294 second pregnancy for inter-pregnancy weight gain compared to weight remaining stable. In a
43 295 population-based cohort in the US, women were found to be at increased risk of LGA in the
44 296 second pregnancy if their pre-pregnancy BMI category changed towards overweight or
45 297 obese from first to second pregnancy regardless of their BMI category in first pregnancy
46 298 except in underweight women who increased to normal weight²¹. This study is different to
47 299 ours in that it only examined risk in second pregnancy without adjustment for LGA outcome
48 300 in first pregnancy. It also considered weight change as change in BMI category only, while
49 301 we studied change in maternal BMI regardless of whether BMI category has changed or not
50 302 in the second pregnancy.

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52 303 In obese women in the US, inter-pregnancy weight gain of ≥ 2 kg/m² was associated
53 304 with increased risk of LGA and a weight loss of ≥ 2 kg/m² was associated with
54 305 decreased risk compared to the reference group of weight maintained (between > -2
55 306 and < 2 kg/m²)²². We found no association between weight change and risk of
56 307 second pregnancy LGA in women who were obese at the start of their first
57 308 pregnancy. This may be because obese women are already at increased risk of LGA
58 309 births, and the average inter-pregnancy BMI change in this subgroup was not large
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310 enough to detect a further increase in risk. Greater efforts are needed for primary
311 prevention of obesity in women of child bearing age and obese women need more effective
312 weight loss strategies in inter-partum period to assess impact on LGA and other outcomes.

313 Risk of recurrent LGA was analysed in one previous study in Scotland which found that inter-
314 pregnancy weight gain (≥ 2 kg/m²) was associated with increased risk of recurrent LGA. In
315 that study, weight loss (≥ 2 kg/m²) was associated with reduced LGA risk. Stratification by
316 first pregnancy BMI showed that women with BMI < 25 kg/m² were at increased risk of
317 recurrent LGA on gaining ≥ 2 kg/m² whereas women with BMI ≥ 25 kg/m² were at reduced risk
318 of recurrent LGA on losing ≥ 2 kg/m² weight²⁶. We showed a similar reduction in risk in
319 overweight women who lost ≥ 1 BMI unit between pregnancies, but found no association in
320 normal weight women. This difference in findings may be because the < 25 kg/m² group in the
321 previous Scottish study included underweight women whereas our stratified analysis
322 examined normal weight women separately to underweight women.

323 We showed an increased risk of 'new' LGA in the second pregnancy (after a non-LGA birth
324 in the first pregnancy) with inter-pregnancy weight gain compared to remaining weight
325 stable. After stratification by BMI, we found that this association between inter-pregnancy
326 weight gain and new LGA remained only in normal-weight and overweight women. The
327 findings from this study are in line with findings with other studies in Scotland²⁴ and
328 Sweden²³ which found increased risk of 'new' LGA with modest (1-3 kg/m²) and large (≥ 3
329 kg/m²) weight gain. Both studies also found a decreased risk with inter-pregnancy weight
330 loss of > 1 kg/m² which was not found in our study. Both studies stratified BMI as $<$ and
331 ≥ 25 kg/m², while we further stratified the ≥ 25 kg/m² category as overweight (BMI 25-
332 29.9kg/m²) and obese (≥ 30 kg/m²) and found an increased risk of 'new' LGA in overweight,
333 but not in obese women. We carried out sensitivity analysis merging overweight and obese
334 categories and found increased risk in this category (data not shown) suggesting that the
335 results are comparable to previous studies.

336 Women included in this analysis had a range of inter-pregnancy interval of less than 1 to up
337 to 12 years and thus weight change could be due to postpartum weight retention or late
338 postpartum weight gain. There is evidence that women who do not lose pregnancy weight at
339 one year postpartum are more likely to retain weight longer term³². We examined the risk of
340 maternal inter-pregnancy weight gain with length of the inter-pregnancy interval and found
341 that women with an interval of 12-23 months were least likely to start the next pregnancy at a
342 higher weight³³. We also examined the length of the inter-pregnancy interval as a predictor
343 for LGA risk adjusting for inter-pregnancy weight change and found no association³⁴.

344 The Development Origins of Health and Disease concept suggests that adverse exposures
345 during development could lead to enhanced susceptibility in the foetus thus increasing the
346 risk of non-communicable diseases in later life. Although the focus has previously been on
347 exposures during pregnancy, the importance of the preconception period is now
348 recognised³⁵⁻³⁷. Efforts to systematically identify women in the preconception period to
349 improve health and lifestyle during conception are underway³⁷. Promoting health of all
350 women of child-bearing age with targeting of women and partners planning a pregnancy has
351 been identified as an effective approach to improving preconception health³⁶. It is difficult to
352 identify all women who are planning a pregnancy but as the inter-conception period is also
353 the preconception period for the next pregnancy, it is important to engage with women
354 during this period to optimise their and their children's health.

355 Future research that characterises the predictors of postpartum weight change would help
356 design interventions to support postpartum weight loss and prevent weight gain. Key to this
357 is an understanding of the pattern of weight change during this period as well as identifying
358 the optimal setting and delivery of the intervention. Support with healthy eating and physical
359 activity is more commonly received during pregnancy than after birth. Even when lifestyle

advice is received postpartum, it was found not to be associated with healthy diet or physical activity behaviours³⁸. Most interventions that have been successful in limiting and promoting postpartum weight loss were combined diet and physical activity interventions with self-monitoring³⁹. However, the timing of engaging women and length of intervention or engagement are important with one study showing that an intervention from 16 weeks pregnancy to six months postpartum was more effective than the same intervention from birth to six months postpartum intervention⁴⁰.

As pregnancy and early postpartum is a period of major change for women and their families, interventions need to be carefully designed to be attractive, flexible, affordable and feasible for women at this stage with competing priorities and time demands. Focus during the postpartum period in the UK healthcare system is mostly on child health and development. The feasibility and effectiveness of better utilising contact time with health professionals during the two years after birth to engage and support maternal health needs to be explored. There may also be a role for mutual support groups for mothers. There is additionally a need to recognise that weight management issues are greater in more disadvantaged mothers so there is also the issue of identifying the most effective weight management strategies for such mothers to reduce social inequity in subsequent birth and maternal outcomes. Weight gain does not occur in isolation and usually combined with other risk factors particularly in socioeconomically disadvantaged groups and hence a holistic approach taking into account priority setting for these families should be considered.

Strengths and limitations

This is a relatively large population-based cohort including women from all socioeconomic and ethnic backgrounds delivering at a large maternity centre in Southampton, UK, thus representative of the regional population. According to the UK Department of Communities and Local Government English indices of deprivation report, Southampton is more deprived than average with the situation having worsened between 2010 and 2015⁴¹. However, about half of the women included in this analysis reside in the rest of Hampshire (the region where Southampton is situated), which is less deprived. Our sample was 87% of White ethnicity, which is comparable to the 2011 England and Wales population census of 86% White⁴². The analysis was adjusted for several key confounders that were reasonably complete (96% complete for ethnicity and employment status). Both the maternal weight (used to calculate exposure) and birthweight in this study were objectively measured by healthcare professionals as part of routine antenatal and delivery care.

An important limitation was the lack of information on gestational weight gain during pregnancy, breastfeeding and paternal characteristics/behaviour, which are potential confounders in the association between maternal inter-pregnancy weight gain and LGA birth⁴³. Women who had their first booking appointment later into the pregnancy (more than 24 weeks) were excluded from the analysis in order to ensure comparability of weight measurements between pregnancies. We also adjusted for gestational age at booking, as this was the point when maternal BMI was measured, in sensitivity analysis and the estimates remained similar. Some of the confounding factors which were accounted for in the analysis were self-reported, however the information was collected prospectively, therefore any measurement error is likely to be non-differential. Another limitation is that these findings are based on observational data so inferences about causation cannot be drawn and the risk of residual confounding influencing the results needs to be considered.

In conclusion, maternal weight gain of 1 or more kg/m² between first and second pregnancy had a prevalence of 48%, and it was associated with risk of LGA in the second pregnancy in this English cohort. Risk of 'new' LGA was higher in normal weight and overweight women who gained weight after a non-LGA birth in their first pregnancy compared to those who remained weight stable. Overweight women were at a lower risk of a recurrent LGA birth in

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3 411 their second pregnancy if they lost weight between pregnancies. Greater efforts are needed
4 412 for primary prevention of overweight and obesity in women of child bearing age. Supporting
5 413 efforts to lose weight in overweight and obese women between pregnancies, and stop
6 414 weight gain in all women planning to have further children (except those who are
7 415 underweight) are important preventive measures of subsequent adverse maternal and
8 416 offspring health outcomes.

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11 418 **Author Contributions**

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14 419 Study design (NZ, PJR, NSM, NAA), data analysis (NZ, SW), acquisition and interpretation
15 420 of the data (NZ, NAA), drafting of the abstract (NZ), revising for content (NZ, SW, PJR, NSM,
16 421 NAA) and approval of final version before submission (NZ, SW, PJR, NSM, NAA).

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18 423 **Data statement**

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21 424 Anonymised data are only available upon request from the authors conditional on approval
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23 426

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40 439

41 440 **Competing interests**

42 441 The authors have no competing interests to declare.

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44 443 **References**

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51 550 **Figure legends**52 551 Figure 1: The percentage and risk of LGA births in second pregnancy stratified by maternal
53 552 inter-pregnancy weight change categories54 553 Figure 2: The absolute percentage of LGA births in second pregnancy by inter-pregnancy
55 554 change in maternal body mass (BMI) stratified by maternal BMI category in the first
56 555 pregnancy and previous outcome of LGA
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559 **Table legends:**

560 Table 1: Maternal and birth characteristics in the second live birth pregnancy categorised by
561 maternal weight change from the first livebirth pregnancy for the period of January 2003 -
562 September 2017, University Hospital Southampton NHS Foundation Trust, Hampshire,
563 England

564 Table 2: Associations between risk of recurrent large-for-gestational age (LGA) birth in the
565 second pregnancy and change in maternal body mass index (BMI) between pregnancies as
566 measured at the first antenatal visit of each pregnancy stratified by BMI category in the first
567 pregnancy

568 Table 3: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the
569 second pregnancy following a non-LGA birth in the first pregnancy and change in maternal
570 body mass index (BMI) between pregnancies measured at the first antenatal visit of each
571 pregnancy stratified by BMI category in the first pregnancy

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Table 1: Maternal and birth characteristics in the second live birth pregnancy categorised by maternal weight change gain from the first live birth pregnancy for the period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust, Hampshire, England

	Lost ≤ -1 kg/m ² from previous pregnancy	Weight stable (>-1 to <1 kg/m ²)	Gained 1-3 kg/m ² from previous pregnancy	Gained ≥ 3 kg/m ² from previous pregnancy	p*
N	2548	5785	4446	3161	
Maternal age, years (mean \pm SD)	28.7 \pm 5.4	29.8 \pm 5.3	29.2 \pm 5.4	27.3 \pm 5.5	<0.001
Timing of first booking appointment, weeks (mean \pm SD)	10.8 \pm 2.3	11.0 \pm 2.3	11.1 \pm 2.4	11.0 \pm 2.6	<0.001
Maternal BMI at booking, kg/m ² (mean \pm SD)	24.1 \pm 5.1	23.8 \pm 4.4	25.9 \pm 4.7	30.8 \pm 5.9	<0.001
Maternal BMI at booking in first pregnancy (%; 95% CI)					<0.001
Underweight (< 18.5)	0.8 (0.5 to 1.2)	4.3 (3.8 to 4.8)	5.3 (4.7 to 6.0)	3.7 (3.1 to 4.4)	
Normal weight (18.5 to 24.9)	47.6 (45.6 to 49.5)	67.4 (66.2 to 68.6)	62.5 (61.0 to 63.9)	49.0 (47.2 to 50.7)	
Overweight (25.0 to 29.9)	30.1 (28.3 to 31.9)	19.4 (18.4 to 20.5)	22.0 (20.8 to 23.3)	29.5 (28.0 to 31.2)	
Obese (≥ 30.0)	21.5 (19.9 to 23.2)	8.9 (8.2 to 9.7)	10.2 (9.3 to 11.1)	17.8 (16.5 to 19.2)	
Maternal BMI at booking in second pregnancy (%; 95% CI)					<0.001
Underweight (< 18.5)	6.9 (5.9 to 7.9)	4.3 (3.8 to 4.8)	0.6 (0.4 to 0.9)	0.0 (0.0 to 0.2)	
Normal weight (18.5 to 24.9)	61.1 (59.2 to 63.0)	66.8 (65.6 to 68.1)	50.7 (49.2 to 52.1)	14.9 (13.7 to 16.2)	
Overweight (25.0 to 29.9)	20.1 (18.6 to 21.7)	19.7 (18.7 to 20.7)	32.6 (31.2 to 34.0)	36.7 (35.0 to 38.4)	
Obese (≥ 30.0)	11.9 (10.7 to 13.3)	9.2 (8.5 to 10.0)	16.1 (15.0 to 17.2)	48.3 (46.6 to 50.1)	
Maternal smoking status at booking (%; 95% CI)					<0.001
Never smoked/quit	57.2 (55.3 to 59.2)	63.0 (61.8 to 64.3)	60.5 (59.0 to 62.0)	50.7 (48.9 to 52.4)	
Stopped >1 year before conceiving	16.1 (14.6 to 17.5)	17.2 (16.3 to 18.2)	17.7 (16.5 to 18.8)	14.9 (13.7 to 16.2)	
Stopped <1 year prior to conceiving	4.0 (3.3 to 4.8)	2.8 (2.4 to 3.2)	3.5 (3.0 to 4.1)	4.9 (4.2 to 5.7)	
Stopped when pregnancy confirmed	6.8 (5.8 to 7.8)	5.9 (5.3 to 6.6)	6.9 (6.2 to 7.7)	10.3 (9.3 to 11.4)	
Continued smoking	15.9 (14.5 to 17.4)	11.0 (10.2 to 11.8)	11.4 (10.5 to 12.4)	19.1 (17.8 to 20.6)	
Maternal education (%; 95% CI)					<0.001
Secondary (GCSE) or under	30.7 (28.9 to 32.5)	24.0 (22.9 to 25.2)	29.4 (28.1 to 30.8)	36.3 (34.6 to 38.0)	
College (A levels)	40.4 (38.5 to 42.3)	38.8 (37.6 to 40.1)	39.5 (38.1 to 41.0)	45.8 (44.0 to 47.5)	

University degree or above	28.9 (27.2 to 30.7)	37.1 (35.9 to 38.4)	31.1 (29.7 to 32.5)	17.9 (16.6 to 19.3)	
Maternal employment (% , 95% CI)					
Employed	66.2 (64.3 to 68.0)	71.7 (70.5 to 72.9)	67.2 (65.8 to 68.5)	56.5 (54.8 to 58.2)	<0.001
Unemployed	31.8 (30.0 to 33.7)	26.9 (25.8 to 28.1)	31.1 (29.7 to 32.5)	41.6 (39.8 to 43.3)	
In education	0.9 (0.6 to 1.4)	0.8 (0.6 to 1.1)	1.1 (0.8 to 1.4)	1.3 (0.9 to 1.8)	
Not specified	1.0 (0.7 to 1.5)	0.6 (0.4 to 0.8)	0.7 (0.5 to 1.0)	0.6 (0.4 to 1.0)	
Ethnicity (% , 95% CI)					
White	89.9 (88.7 to 91.1)	88.0 (87.1 to 88.8)	85.1 (84.0 to 86.1)	84.8 (83.5 to 86.1)	<0.001
Mixed	0.8 (0.5 to 1.3)	0.9 (0.7 to 1.2)	1.4 (1.1 to 1.8)	1.6 (1.1 to 2.0)	
Asian	4.8 (4.0 to 5.7)	5.6 (5.0 to 6.0)	7.2 (6.5 to 8.0)	7.7 (6.8 to 8.7)	
Black/African/Caribbean	0.6 (0.4 to 1.0)	1.0 (0.8 to 1.3)	1.6 (1.3 to 2.1)	2.4 (1.9 to 3.0)	
Other	0.7 (0.4 to 1.1)	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.4)	1.3 (0.9 to 1.7)	
Not specified	3.1 (2.5 to 3.9)	3.5 (3.0 to 4.0)	3.6 (3.1 to 4.2)	2.2 (1.8 to 2.8)	
Inter-pregnancy interval (median, IQR)	21.7 (14.4 to 32.7)	21.6 (14.1 to 32.0)	23.7 (14.4 to 35.6)	27.7 (16.0 to 45.6)	<0.001
Inter-pregnancy interval (% , 95% CI)					
0-11 months	17.4 (15.9 to 18.9)	17.6 (16.6 to 18.6)	18.1 (17.0 to 19.3)	16.6 (15.4 to 17.9)	<0.001
12-23 months	39.8 (37.8 to 41.7)	39.9 (38.6 to 41.1)	33.1 (31.7 to 34.5)	26.3 (24.8 to 27.9)	
24-35 months	22.6 (21.0 to 24.2)	23.6 (22.5 to 24.7)	24.4 (23.2 to 25.7)	20.5 (19.1 to 21.9)	
36 months or more	20.3 (18.7 to 21.9)	18.9 (17.9 to 20.0)	24.3 (23.1 to 25.6)	36.5 (34.9 to 38.2)	
Birthweight, grams (mean ± SD)	3463 ± 563	3467 ± 523	3507 ± 536	3531 ± 558	
Previous size at birth (first pregnancy)					
Small-for-gestational age	13.1 (11.8 to 14.4)	12.6 (11.8 to 13.5)	11.7 (10.8 to 12.7)	12.4 (11.3 to 13.6)	0.11
Appropriate-for-gestational age	79.6 (77.9 to 81.1)	81.1 (80.0 to 82.1)	81.2 (80.1 to 82.4)	79.9 (78.4 to 81.3)	
Large-for-gestational age	7.4 (6.4 to 8.5)	6.3 (5.7 to 7.0)	7.1 (6.3 to 7.8)	7.7 (6.8 to 8.7)	
Size at birth (second pregnancy)					
Small-for-gestational age	8.7 (7.6 to 9.8)	7.0 (6.4 to 7.7)	6.2 (5.5 to 6.9)	6.7 (5.9 to 7.6)	<0.001
Appropriate-for-gestational age	79.0 (77.3 to 80.5)	81.1 (80.0 to 82.1)	80.3 (79.1 to 81.5)	77.4 (75.9 to 78.9)	
Large-for-gestational age	12.4 (11.1 to 13.7)	11.9 (11.1 to 12.8)	13.5 (12.5 to 14.5)	15.9 (14.6 to 17.2)	

*p values calculated using ANOVA for continuous and chi square test for categorical variables

Table 2: Associations between risk of recurrent large-for-gestational age (LGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		n	Relative risk, (RR)*	95% CI	n	RR*	95% CI	n	RR*	95% CI	n	RR*	95% CI
Lost \leq -1 kg/m ² from previous pregnancy	Unadjusted	1109	0.89	0.74 to 1.08	521	0.80	0.54 to 1.20	338	0.68	0.50 to 0.94	236	1.16	0.79 to 1.69
	Adjusted**	1066	0.88	0.72 to 1.07	500	0.79	0.54 to 1.17	324	0.69	0.48 to 0.97	229	1.21	0.79 to 1.83
			Ref			Ref			Ref			Ref	
Weight stable (>-1 to <1 kg/m ²)													
Gained 1-3 kg/m ² from previous pregnancy	Unadjusted		0.97	0.83 to 1.13		0.97	0.78 to 1.21		0.81	0.62 to 1.06		1.25	0.85 to 1.83
	Adjusted**		0.98	0.84 to 1.15		1.02	0.83 to 1.27		0.81	0.61 to 1.08		1.28	0.86 to 1.91
Gained \geq 3 kg/m ² from previous pregnancy	Unadjusted		0.96	0.81 to 1.14		0.89	0.68 to 1.17		0.87	0.66 to 1.14		1.16	0.79 to 1.71
	Adjusted**		1.00	0.83 to 1.20		0.91	0.68 to 1.21		0.91	0.67 to 1.25		1.28	0.84 to 1.94

*Generalised linear model with log link and robust variance estimator used to derive RR

**Adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

Table 3: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Underweight at first pregnancy			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		n	Relative risk, (RR)*	95% CI	n	RR*	95% CI	n	RR*	95% CI	n	RR*	95% CI	n	RR*	95% CI
Lost ≤ -1 kg/m ² from previous pregnancy	Unadjusted	14788	1.05	0.91 to 1.22	606	-	-	8888	0.88	0.68 to 1.14	3458	0.95	0.73 to 1.24	1836	0.90	0.67 to 1.23
	Adjusted**	14215	0.94	0.80 to 1.10		-	-	8513	0.87	0.68 to 1.12	3326	0.96	0.72 to 1.29		0.95	0.67 to 1.34
Weight stable (>-1 to <1 kg/m ²)			Ref			Ref		Ref			Ref			Ref		
Gained 1-3 kg/m ² from previous pregnancy	Unadjusted		1.16	1.03 to 1.31		1.21	0.45 to 3.29		1.20	1.02 to 1.40		1.19	0.94 to 1.50		0.89	0.65 to 1.23
	Adjusted**		1.13	0.99 to 1.28		1.04	0.36 to 3.04		1.26	1.06 to 1.50		1.16	0.89 to 1.50		0.86	0.61 to 1.22
Gained ≥3 kg/m ² from previous pregnancy	Unadjusted		1.40	1.24 to 1.59		2.83	1.08 to 7.40		1.37	1.14 to 1.64		1.22	0.96 to 1.53		1.10	0.82 to 1.46
	Adjusted**		1.34	1.17 to 1.54		2.08	0.67 to 6.51		1.34	1.09 to 1.65		1.35	1.05 to 1.75		1.21	0.89 to 1.65

*Generalised linear model with log link and robust variance estimator used to derive RR

**Adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

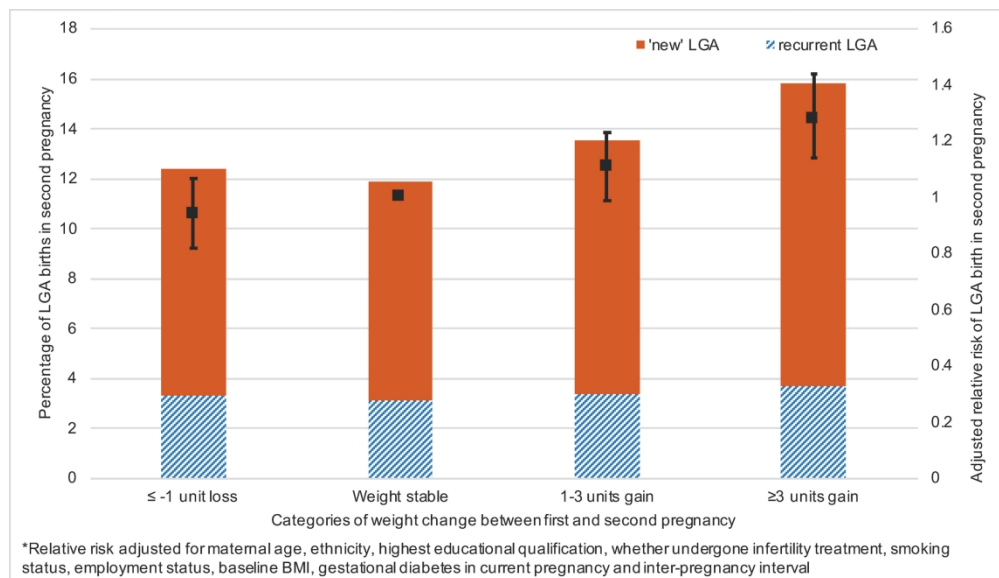


Figure 1: The percentage and risk of LGA births in second pregnancy stratified by maternal inter-pregnancy weight change categories

222x128mm (300 x 300 DPI)

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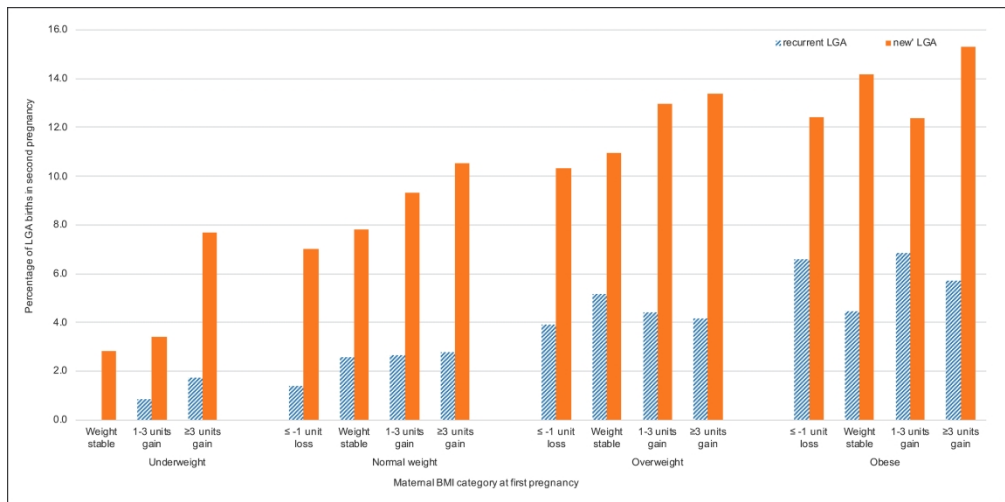


Figure 2: The absolute percentage of LGA births in second pregnancy by inter-pregnancy change in maternal body mass (BMI) stratified by maternal BMI category in the first pregnancy and previous outcome of LGA

346x171mm (300 x 300 DPI)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4

1		#6b	For matched studies, give matching criteria and number of	n/a
2			exposed and unexposed	
3				
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5	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	4-5
6			confounders, and effect modifiers. Give diagnostic criteria, if	
7			applicable	
8				
9				
10	Data sources /	#8	For each variable of interest give sources of data and details of	4-5
11	measurement		methods of assessment (measurement). Describe	
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	n/a
19				
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21	Study size	#10	Explain how the study size was arrived at	4
22				
23	Quantitative	#11	Explain how quantitative variables were handled in the	4-5
24	variables		analyses. If applicable, describe which groupings were chosen,	
25			and why	
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28	Statistical	#12a	Describe all statistical methods, including those used to control	5
29	methods		for confounding	
30				
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32		#12b	Describe any methods used to examine subgroups and	5
33			interactions	
34				
35				
36		#12c	Explain how missing data were addressed	n/a
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	n/a
39				
40				
41		#12e	Describe any sensitivity analyses	n/a
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg	5
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	n/a
52				
53		#13c	Consider use of a flow diagram	n/a
54				
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5-6
57			clinical, social) and information on exposures and potential	
58				
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		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	13-14
	#14c	Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	5-6, 13-14
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7, 15-21
	#16b	Report category boundaries when continuous variables were categorized	4-5, 13-14
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	8-9
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8-9
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

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BMJ Open

Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	obesity, pregnancy, pregnancy outcome, weight gain, large-for-gestational age

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3 1 **Is maternal weight gain between pregnancies associated with risk of large-for-**
4 2 **gestational age birth? Analysis of a UK population-based cohort**
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7 4 Nida Ziauddeen¹, Sam Wilding¹, Paul J. Roderick¹, Nicholas S. Macklon^{2,3}, Nisreen A.
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25 Telephone number: 023 81 206287

28 **Keywords:** obesity, pregnancy, pregnancy outcome, weight gain, birth weight

29 **Word count:** 4287 words

34 Abstract

35 **Objective:** Maternal overweight and obesity during pregnancy increases the risk of large-for-
36 gestational age (LGA) birth and childhood obesity. We aimed to investigate the association
37 between maternal weight change between subsequent pregnancies and risk of having a
38 LGA birth.

39 **Design:** Population-based cohort.

40 **Setting:** Routinely collected antenatal healthcare data between January 2003 and
41 September 2017 at University Hospital Southampton, England.

42 **Participants:** Health records of women with their first two consecutive singleton live-birth
43 pregnancies were analysed (n=15940).

44 **Primary outcome measure:** Risk of LGA, recurrent LGA and 'new' LGA births in the
45 second pregnancy.

46 **Results:** Of the 15940 women, 16.0% lost and 47.7% gained weight (≥ 1 kg/m²) between
47 pregnancies. A lower proportion of babies born to women who lost ≥ 1 kg/m² (12.4%) and
48 remained weight stable between -1 to 1 kg/m² (11.9%) between pregnancies were LGA
49 compared to 13.5% and 15.9% in women who gained 1-3 and ≥ 3 kg/m² respectively. The
50 highest proportion was in obese women who gained ≥ 3 kg/m² (21.2%). Overweight women
51 had a reduced risk of recurrent LGA in the second pregnancy if they lost ≥ 1 kg/m² (adjusted
52 relative risk (aRR) 0.69, 95% CI 0.48-0.97) whereas overweight women who gained ≥ 3
53 kg/m² were at increased risk of 'new' LGA after having a non-LGA birth in their first
54 pregnancy (aRR 1.35, 95% CI 1.05-1.75). Normal-weight women who gained weight were
55 also at increased risk of 'new' LGA in the second pregnancy (aRR 1.26, 95% CI 1.06-1.50
56 with gain of 1-3 kg/m² and aRR 1.34, 95% CI 1.09-1.65 with gain of ≥ 3 kg/m²).

57 **Conclusions:** Losing weight after an LGA birth was associated with a reduced LGA risk in
58 the next pregnancy in overweight women, while inter-pregnancy weight gain was associated
59 with an increased 'new' LGA risk. Preventing weight gain between pregnancies is an
60 important prevention measure to achieve better maternal and offspring outcomes.

61

62

63 Article summary

64 Strengths and limitations of this study

- 65 • Utilises antenatal care and birth data from a large population-based cohort including
66 women from all socioeconomic backgrounds
- 67 • Objective measurement of both exposure (maternal weight) and outcome in two
68 pregnancies per woman
- 69 • Self-reported data for covariates
- 70 • Lack of information on breastfeeding duration and maternal weight gain during
71 pregnancy

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76 Introduction

77 The prevalence of maternal obesity has been rising over time. It has more than doubled in
78 England between 1989 and 2007 (7.6% to 15.6%), with the proportion of normal weight
79 pregnancies showing a 12% decrease from 65.6% to 53.6%¹. Maternal overweight and
80 obesity is a key risk factor for adverse maternal and birth outcomes. It also increases the risk
81 of long-term health problems in the child including obesity, cardiovascular disease, diabetes
82 and cognitive and behavioural disorders². Birthweight is a key early life predictor of long-term
83 health outcomes such as obesity and cardiovascular disease³ and potentially acts as a
84 mediator on the causal pathway between maternal obesity and long-term offspring
85 outcomes. The incidence of large-for-gestational age (LGA) birth, defined as >90th
86 percentile weight for gestational age, has increased over time in high-income countries^{4,5}.
87 LGA is associated with both childhood^{6,7} and adult obesity⁸⁻¹⁰. A key risk factor for LGA birth
88 is gestational diabetes (GDM)¹¹, the incidence of which has also increased over time^{12,13}.
89 Offspring of mothers with gestational diabetes have increased risk of childhood overweight
90 and obesity^{14,15}. Maternal obesity is an established risk factor for both GDM and LGA birth¹⁶.
91 Change in maternal body mass index (BMI) between pregnancies could modify the risk of
92 LGA birth in the subsequent pregnancy.

93 Birthweight, on average, increases with parity. First-born infants tend to have the lowest
94 birthweight among their younger siblings¹⁷⁻¹⁹ up to the fourth pregnancy²⁰. However,
95 birthweight was found to decrease with parity for women who had short intervals between
96 their pregnancies (<12 months) while the increase in birthweight with parity was more
97 pronounced in women with long intervals (>24 months)²⁰. Also, maternal weight change
98 between pregnancies was found to modify the relationship between parity and birthweight.
99 Women who returned to their pre-pregnancy weight before the next conception had infants
100 who weighed less than infants of women who retained or gained weight between
101 pregnancies²⁰. In a UK-based study, women who lost at least six kilograms between their
102 first and second pregnancy had a smaller average increase in birthweight of the second
103 baby compared to women who gained ten kilograms or more (in a 1.60m tall woman, 6 kg
104 equates to approximately 2.3 kg/m² and 10 kg to approximately 3.8 kg/m²)¹⁸.

105 A large US study showed that women were at an increased risk of having an LGA baby in
106 the second pregnancy if their pre-pregnancy BMI category increased towards overweight or
107 obese between their first and second pregnancies. This applied to all first pregnancy BMI
108 categories, except underweight women who became normal weight by the start of their
109 second pregnancy. Overweight and obese women who dropped BMI category by their
110 second pregnancy remained at an increased risk of LGA birth, but had a lower risk
111 compared to women whose BMI category increased between pregnancies²¹.

112 Another US-based study showed that inter-pregnancy weight gain of ≥ 2 kg/m² in obese
113 women was associated with increased risk of LGA. Weight loss of ≥ 2 kg/m² was associated
114 with a lower adjusted LGA risk compared to the women who maintained their weight within 2
115 kg/m² change between pregnancies²².

116 Two studies found a reduced risk of 'new' LGA in the second pregnancy following a non-
117 LGA birth in the first pregnancy with inter-pregnancy weight loss of >1 kg/m², and an
118 increased risk with modest (1-3 kg/m²) and large (≥ 3 kg/m²) weight gain. In stratified
119 analysis, the association was stronger in women with a first pregnancy BMI of <25 kg/m²
120 ^{23,24}. A third study only found an increased risk of 'new' LGA in normal weight women who
121 gained ≥ 4 kg/m² between pregnancies and no association in overweight women²⁵.

122 To our knowledge, only one study has examined the risk of recurrent LGA (occurring in both
123 first and second pregnancies) in relation to maternal weight change between pregnancies ²⁶.
124 The study, conducted in Aberdeen, Scotland, included 24520 women of which 813 women
125 had LGA births in both pregnancies. Inter-pregnancy weight gain (≥ 2 kg/m²) was associated

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3 126 with increased risk of recurrent LGA, while weight loss (≥ 2 kg/m²) was protective. Women
4 127 with BMI < 25 kg/m² were at increased risk of recurrent LGA on gaining weight whereas
5 128 women with BMI ≥ 25 kg/m² were at reduced risk of recurrent LGA on losing weight²⁶.

7 129 In this study, we aimed to investigate the association between the incidence of LGA,
8 130 recurrent LGA and 'new' LGA births in the second pregnancy and maternal change in BMI
9 131 between the first and second pregnancies, stratifying by maternal BMI category in the first
10 132 pregnancy, in a population-based cohort in the South of England.

12 133

14 134

16 135 **Methods**

18 136 This is a population-based cohort of prospectively collected routine healthcare data for
19 137 antenatal care between January 2003 and September 2017 at University Hospital
20 138 Southampton, Hampshire, UK. This included all women delivering at this hospital (n= 82098
21 139 pregnancies), which is a regional centre for maternity care in and around Southampton.
22 140 Records of women with their first two consecutive singleton live birth pregnancies were
23 141 included. Records with unfeasible weight (< 30 kg), height (> 2 m) and gestational age (> 301
24 142 days) values were excluded.

26 143

28 144 *Exposure assessment*

30 145 Maternal weight in kilograms was routinely measured by a midwife at the first antenatal
31 146 (booking) appointment of each pregnancy, which is recommended to take place ideally by 10
32 147 weeks gestation in the UK, according to the National Institute for Health and Care
33 148 Excellence Guidelines²⁷. Any woman who had a booking appointment at or after 24 weeks
34 149 of pregnancy was excluded. Height was self-reported. BMI was calculated as weight (in kg)
35 150 divided by height (in metres) squared.

36 151 BMI at the start of the first pregnancy was categorised as underweight (BMI < 18.5 kg/m²),
37 152 normal weight (18.5 to 24.9 kg/m²), overweight (25.0 to 29.9 kg/m²) and obese (≥ 30 kg/m²).
38 153 Change in BMI was calculated as the difference in BMI measured at the booking
39 154 appointments of the first two consecutive live birth pregnancies for each woman. This
40 155 change in BMI was then categorised as weight loss (≥ 1 kg/m²), weight stable (-1 to 1 kg/m²)
41 156 and two categories of weight gain ($1-3$ kg/m² and ≥ 3 kg/m²).

44 157

46 158 *Outcome assessment*

47 159 Birthweight (grams) was measured by healthcare professionals at birth as part of routine
48 160 care. Gestational age was based on a dating ultrasound scan which routinely takes place
49 161 between 10 and 13 weeks gestation²⁷. Age- and gender- specific birthweight centiles were
50 162 calculated using reference values for England and Wales provided in the most recently
51 163 released national data²⁸. Large-for-gestational age was defined as > 90 th percentile weight
52 164 for gestational age. This was only defined for babies born between 24 to 42 weeks gestation
53 165 as reference values only exist for these gestational ages and with determinate gender.

55 166

57 167 *Covariates*

58 168 Maternal date of birth is recorded at the booking appointment and converted to age (in
59 169 years) on extraction of the dataset to maintain anonymity. Highest maternal educational

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3 170 qualification was self-reported and categorised as primary, secondary, college,
4 171 undergraduate, postgraduate, graduate and none. For the purposes of this analysis, this was
5 172 condensed to three categories - secondary (GCSE) and under, college (A levels) and
6 173 university degree or above. Self-reported ethnicity was recorded under 16 categories and
7 174 condensed to White, Mixed, Asian, Black/African/Caribbean and Other. Categories of not
8 175 asked and not stated were coded as missing. Smoking was self-reported as current smoking
9 176 or non-smoking. Non-smokers were further asked if they had ever smoked or had previously
10 177 smoked and quit. This was categorised as stopped more than 12 months before conception,
11 178 stopped less than 12 months before conception or stopped when pregnancy confirmed.
12 179 Employment status was self-reported at booking appointment and categorised as employed,
13 180 unemployed, in education, and not specified. Infertility treatment was categorised as
14 181 no/investigations only and yes (hormonal only, in-vitro fertilisation, gamete intrafallopian
15 182 transfer and other surgical) in either one or both pregnancies. In this population, an oral
16 183 glucose tolerance test was used for screening for GDM in women with one or more risk
17 184 factors (BMI > 30kg/m²; GDM in previous pregnancy; previous baby weighing ≥4.5kg;
18 185 diabetes in parents or siblings and of Asian, African-Caribbean or Middle Eastern
19 186 ethnicity)²⁹. GDM diagnosis was then reported in the database. Inter-pregnancy interval was
20 187 defined as the interval between the first live birth and conception of the second pregnancy.
21 188 The difference in days between two consecutive live births was calculated and gestational
22 189 age of the latter birth subtracted from this to derive the inter-pregnancy interval.

25 190

27 191 *Statistical analysis*

28
29 192 All analysis was performed using Stata 15³⁰. Univariable comparisons were carried out using
30 193 ANOVA for continuous variables and chi square test for categorical variables. Generalised
31 194 linear regression with log link³¹ was used to examine the association between the
32 195 categorised variable of maternal change in BMI between pregnancies with risk of LGA in the
33 196 second pregnancy. This was analysed first in the whole sample and then stratified by
34 197 'baseline' maternal BMI category as calculated in the first antenatal appointment of the first
35 198 pregnancy.

37 199 Risk of LGA in the second pregnancy was explored in the whole sample adjusting for
38 200 previous pregnancy outcome of LGA. The risk of 'new' LGA in second pregnancy after
39 201 having a non-LGA baby in the first pregnancy was explored in the sub-sample of women
40 202 who had non-LGA births in the first pregnancy. The risk of recurrent LGA (LGA in both
41 203 pregnancies) was explored in a sub-sample of women who had LGA births in the first
42 204 pregnancy.

45 205 Initial univariable analysis was followed by multivariable models adjusting for potential
46 206 confounding factors – maternal age, ethnicity, highest educational qualification, whether or
47 207 not undergone infertility treatment, employment status, smoking behaviour in second
48 208 pregnancy, baseline BMI, GDM in second pregnancy and inter-pregnancy interval.
49 209 Sensitivity analysis was conducted adding gestational age at booking in the second
50 210 pregnancy to the models.

51 211 A statistical significance level of 0.05 with 95% confidence intervals was used in the
52 212 regression models.

54 213

56 214 *Ethical considerations*

58 215 All data were fully anonymised by the data holder before being accessed by the research
59 216 team. Ethics approval was granted by the University of Southampton Faculty of Medicine
60 217 Ethics Committee: study ID 25508.

218

219 *Patient and Public Involvement*

220 Patients and public were not involved in setting the research question or the outcome
221 measures, nor were they involved in developing plans for the design or implementation of
222 the study. However, pregnant woman and mothers of young children have been involved in
223 the planning stages of a research project building on this analysis.

224

225

226 **Results**

227 The first and second pregnancies of 15940 women were included. Of these, 16.0% of
228 women lost ≥ 1 kg/m², 36.3% remained weight stable (-1 to 1 kg/m²), 27.9% gained 1-3 kg/m²
229 and 19.8% gained ≥ 3 kg/m² between their first and second live birth pregnancies. Weight
230 loss of >2 kg/m² was observed in 7.3% of women whereas 30.5% gained >2 kg/m². Mean
231 BMI at second pregnancy booking was 30.8 kg/m² (standard deviation (SD) 5.9) in women
232 who gained ≥ 3 kg/m², 25.9 kg/m² (SD 4.7) in women who gained 1-3kg/m², 24.1 kg/m² (SD
233 5.1) in women who lost weight, and 23.8 kg/m² (SD 4.4) women whose weight remained
234 stable between pregnancies ($p < 0.001$) (Table 1).

235 Women who gained ≥ 3 kg/m² by the start of their second pregnancy were more likely to be
236 smokers, unemployed, with lower educational attainment and to have a longer inter-
237 pregnancy interval, compared to those who maintained a stable weight between
238 pregnancies. Mean maternal age was lowest in the women who gained ≥ 3 kg/m² (27.3
239 years, SD 5.5) and highest in the women who remained weight stable (29.8 years, SD 5.3).
240 Mean maternal age in women who lost weight was 28.7 years (SD 5.4).

241 Mothers who gained ≥ 3 kg/m² were more likely to be obese (48.3%) at the start of the
242 second pregnancy compared to 16.1% in women who gained 1-3 kg/m², 9.2% in women
243 who remained weight stable and 11.9% in women who lost ≤ 1 kg/m².

244 Figure 1 shows the percentage of women in each BMI category in the first and second
245 pregnancy and the weight gain over time. There has been a decline in normal weight women
246 at first pregnancy and a slight increase in overweight and obese women over time. There
247 also was a slight decline in the percentage of women gaining ≥ 3 kg/m² and a slight increase
248 in those gaining 1-3 kg/m².

249 The proportion of LGA births were higher in all BMI categories in the second pregnancy
250 (Figure 2). A lower proportion of babies born to women who lost weight (12.4%) or remained
251 weight stable (11.9%) between pregnancies were LGA compared to 13.5% in women who
252 gained 1-3 kg/m² and 15.9% in women who gained ≥ 3 kg/m² ($p < 0.001$) (Table 1, Figure 3).

253 Compared to normal weight women, overweight and obese women were at increased risk of
254 LGA births in both pregnancies with risk highest in obese women (unadjusted relative risk
255 (RR) 2.06, 95% CI 1.78 to 2.38 and 1.86, 95% CI 1.69 to 2.05 in first and second pregnancy
256 respectively). The lowest proportion of LGA births in the second pregnancy was in
257 underweight women in the first pregnancy who remained weight stable (2.8%), while the
258 highest was in obese women who gained ≥ 3 kg/m² (21.2%). Within BMI categories, recurrent
259 LGA was lowest in normal weight and overweight women who lost weight and highest in
260 obese women who gained 1-3 kg/m².

261 Women who gained ≥ 3 kg/m² were at increased risk of LGA in the second pregnancy in the
262 full sample compared to remaining weight stable (aRR 1.28, 95% CI 1.14 to 1.44) (Figure 3).

263 There was a significantly reduced risk of recurrent LGA birth in the second pregnancy in
264 overweight women who had a LGA infant in the first pregnancy and lost ≥ 1 kg/m² in weight
265 (aRR 0.69, 95% CI 0.48 to 0.97) (Table 2, supplementary Figure 1). No association was
266 observed between risk of recurrent LGA and maternal BMI change between pregnancies in
267 underweight, normal weight and obese women.

268 There was an increased risk of 'new' LGA birth in the second pregnancy after having a non-
269 LGA infant in the first pregnancy in normal weight women who gained 1-3 kg/m² (aRR 1.26,
270 95% CI 1.06 to 1.50) and in normal weight and overweight women who had gained ≥ 3 kg/m²
271 weight (aRR 1.34, 95% CI 1.09 to 1.65, aRR 1.35, 95% CI 1.05 to 1.75, respectively) (Table
272 3, supplementary Figure 2). No association was observed between the risk of 'new' LGA in
273 the second pregnancy and maternal BMI inter-pregnancy change in obese women.

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275

276 Discussion

277 This study examined the association between change in women's BMI between their first
278 and second live birth pregnancies and risk of LGA birth in the second pregnancy in a
279 population-based cohort of 15940 women in the South of England. Almost half of the sample
280 (48%) of women gained ≥ 1 kg/m² in the time between the first antenatal care visits during
281 their first and second pregnancies. The proportion of LGA births was significantly higher in
282 women with an inter-pregnancy weight gain of ≥ 3 kg/m² (16%) compared to women who lost
283 weight (12%) and those who remained weight stable (12%) between pregnancies.
284 Overweight women who lost ≥ 1 kg/m² had a reduced risk of recurrent LGA. Normal weight
285 women who gained 1-3 kg/m² and both normal weight and overweight women who gained
286 ≥ 3 kg/m² between pregnancies had an increased risk of LGA birth in their second pregnancy
287 after a non-LGA birth in the first.

288 Compared to the population-based Swedish cohort which carried out a similar analysis for
289 LGA and other outcomes in 151025 women using data from 1992 to 2001, a lower
290 proportion of women remained weight stable in our cohort (46% compared to 36%) and a
291 higher proportion lost (11% compared to 16%) or gained (43% compared to 48%) weight.
292 Amongst women who gained weight, a higher proportion gained ≥ 3 kg/m² in this cohort
293 (20%) compared to the Swedish cohort (11%)²³. Similarly, in comparison to a population-
294 based cohort of 24520 women in Aberdeen, Scotland; for the period 1986 to 2013, a larger
295 proportion of women in our study both lost and gained weight²⁶. The differences could reflect
296 the increase in the prevalence of maternal overweight and obesity over time since our data
297 are more recent.

298 In the adjusted model utilising the full sample, we showed an increased risk of LGA in the
299 second pregnancy for inter-pregnancy weight gain compared to weight remaining stable. In a
300 population-based cohort in the US, women were found to be at increased risk of LGA in the
301 second pregnancy if their pre-pregnancy BMI category changed towards overweight or
302 obese from first to second pregnancy regardless of their BMI category in first pregnancy
303 except in underweight women who increased to normal weight²¹. This study is different to
304 ours in that it only examined risk in second pregnancy without adjustment for LGA outcome
305 in first pregnancy. It also considered weight change as change in BMI category only, while
306 we studied change in maternal BMI regardless of whether BMI category has changed or not
307 in the second pregnancy.

308 In obese women in the US, inter-pregnancy weight gain of ≥ 2 kg/m² was associated
309 with increased risk of LGA and a weight loss of ≥ 2 kg/m² was associated with

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3 310 decreased risk compared to the reference group of weight maintained (between >-2
4 311 and $<2 \text{ kg/m}^2$)²². We found no association between weight change and risk of
5 312 second pregnancy LGA in women who were obese at the start of their first
6 313 pregnancy. This may be because obese women are already at increased risk of LGA
7 314 births, and the average inter-pregnancy BMI change in this subgroup was not large
8 315 enough to detect a further increase in risk. Greater efforts are needed for primary
9 316 prevention of obesity in women of child bearing age and obese women need more effective
10 317 weight loss strategies in inter-partum period to assess impact on LGA and other outcomes.

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12
13 318 Risk of recurrent LGA was analysed in one previous study in Scotland which found that inter-
14 319 pregnancy weight gain ($\geq 2 \text{ kg/m}^2$) was associated with increased risk of recurrent LGA. In
15 320 that study, weight loss ($\geq 2 \text{ kg/m}^2$) was associated with reduced LGA risk. Stratification by
16 321 first pregnancy BMI showed that women with BMI $<25 \text{ kg/m}^2$ were at increased risk of
17 322 recurrent LGA on gaining $\geq 2 \text{ kg/m}^2$ whereas women with BMI $\geq 25 \text{ kg/m}^2$ were at reduced risk
18 323 of recurrent LGA on losing $\geq 2 \text{ kg/m}^2$ weight²⁶. We showed a similar reduction in risk in
19 324 overweight women who lost ≥ 1 BMI unit between pregnancies, but found no association in
20 325 normal weight women. This difference in findings may be because the $<25 \text{ kg/m}^2$ group in the
21 326 previous Scottish study included underweight women whereas our stratified analysis
22 327 examined normal weight women separately to underweight women.

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24
25 328 We showed an increased risk of 'new' LGA in the second pregnancy (after a non-LGA birth
26 329 in the first pregnancy) with inter-pregnancy weight gain compared to remaining weight
27 330 stable. After stratification by BMI, we found that this association between inter-pregnancy
28 331 weight gain and new LGA remained only in normal-weight and overweight women. The
29 332 findings from this study are in line with findings with other studies in Scotland²⁴ and
30 333 Sweden²³ which found increased risk of 'new' LGA with modest ($1-3 \text{ kg/m}^2$) and large (≥ 3
31 334 kg/m^2) weight gain. Both studies also found a decreased risk with inter-pregnancy weight
32 335 loss of $>1 \text{ kg/m}^2$ which was not found in our study. Both studies stratified BMI as $<$ and
33 336 $\geq 25 \text{ kg/m}^2$, while we further stratified the $\geq 25 \text{ kg/m}^2$ category as overweight (BMI 25-
34 337 29.9 kg/m^2) and obese ($\geq 30 \text{ kg/m}^2$) and found an increased risk of 'new' LGA in overweight,
35 338 but not in obese women. We carried out sensitivity analysis merging overweight and obese
36 339 categories and found increased risk in this category (data not shown) suggesting that the
37 340 results are comparable to previous studies.

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39
40 341 Women included in this analysis had a range of inter-pregnancy interval of less than 1 to up
41 342 to 12 years and thus weight change could be due to postpartum weight retention or late
42 343 postpartum weight gain. There is evidence that women who do not lose pregnancy weight at
43 344 one year postpartum are more likely to retain weight longer term³². We examined the risk of
44 345 maternal inter-pregnancy weight gain with length of the inter-pregnancy interval and found
45 346 that women with an interval of 12-23 months were least likely to start the next pregnancy at a
46 347 higher weight³³. We also examined the length of the inter-pregnancy interval as a predictor
47 348 for LGA risk adjusting for inter-pregnancy weight change and found no association³⁴.

48
49 349 The Development Origins of Health and Disease concept suggests that adverse exposures
50 350 during development could lead to enhanced susceptibility in the foetus thus increasing the
51 351 risk of non-communicable diseases in later life. Although the focus has previously been on
52 352 exposures during pregnancy, the importance of the preconception period is now
53 353 recognised³⁵⁻³⁷. Efforts to systematically identify women in the preconception period to
54 354 improve health and lifestyle during conception are underway³⁷. Promoting health of all
55 355 women of child-bearing age with targeting of women and partners planning a pregnancy has
56 356 been identified as an effective approach to improving preconception health³⁶. It is difficult to
57 357 identify all women who are planning a pregnancy but as the inter-conception period is also
58 358 the preconception period for the next pregnancy, it is important to engage with women
59 359 during this period to optimise their and their children's health.

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3 360 Future research that characterises the predictors of postpartum weight change would help
4 361 design interventions to support postpartum weight loss and prevent weight gain. Key to this
5 362 is an understanding of the pattern of weight change during this period as well as identifying
6 363 the optimal setting and delivery of the intervention. Support with healthy eating and physical
7 364 activity is more commonly received during pregnancy than after birth. Even when lifestyle
8 365 advice is received postpartum, it was found not to be associated with healthy diet or physical
9 366 activity behaviours³⁸. Most interventions that have been successful in limiting and promoting
10 367 postpartum weight loss were combined diet and physical activity interventions with self-
11 368 monitoring³⁹. However, the timing of engaging women and length of intervention or
12 369 engagement are important with one study showing that an intervention from 16 weeks
13 370 pregnancy to six months postpartum was more effective than the same intervention from
14 371 birth to six months postpartum intervention⁴⁰.

16 372 As pregnancy and early postpartum is a period of major change for women and their
17 373 families, interventions need to be carefully designed to be attractive, flexible, affordable and
18 374 feasible for women at this stage with competing priorities and time demands. Focus during
19 375 the postpartum period in the UK healthcare system is mostly on child health and
20 376 development. The feasibility and effectiveness of better utilising contact time with health
21 377 professionals during the two years after birth to engage and support maternal health needs
22 378 to be explored. There may also be a role for mutual support groups for mothers. There is
23 379 additionally a need to recognise that weight management issues are greater in more
24 380 disadvantaged mothers so there is also the issue of identifying the most effective weight
25 381 management strategies for such mothers to reduce social inequity in subsequent birth and
26 382 maternal outcomes. Weight gain does not occur in isolation and usually combined with other
27 383 risk factors particularly in socioeconomically disadvantaged groups and hence a holistic
28 384 approach taking into account priority setting for these families should be considered.

31 385 **Strengths and limitations**

32 386 This is a relatively large population-based cohort including women from all socioeconomic
33 387 and ethnic backgrounds delivering at a large maternity centre in Southampton, UK, thus
34 388 representative of the regional population. According to the UK Department of Communities
35 389 and Local Government English indices of deprivation report, Southampton is more deprived
36 390 than average with the situation having worsened between 2010 and 2015⁴¹. However, about
37 391 half of the women included in this analysis reside in the rest of Hampshire (the region where
38 392 Southampton is situated), which is less deprived. Our sample was 87% of White ethnicity,
39 393 which is comparable to the 2011 England and Wales population census of 86% White⁴². The
40 394 analysis was adjusted for several key confounders that were reasonably complete (96%
41 395 complete for ethnicity and employment status). Both the maternal weight (used to calculate
42 396 exposure) and birthweight in this study were objectively measured by healthcare
43 397 professionals as part of routine antenatal and delivery care.

46 398 An important limitation was the lack of information on gestational weight gain during
47 399 pregnancy, breastfeeding duration/exclusivity and paternal characteristics/behaviour, which
48 400 are potential confounders in the association between maternal inter-pregnancy weight gain
49 401 and LGA birth⁴³. We adjusted for if first feed was breast milk as a proxy for breastfeeding
50 402 initiation in sensitivity analysis and the results remained unchanged (not shown). Women
51 403 who had their first booking appointment later into the pregnancy (more than 24 weeks) were
52 404 excluded from the analysis in order to ensure comparability of weight measurements
53 405 between pregnancies. We also adjusted for gestational age at booking, as this was the point
54 406 when maternal BMI was measured, in sensitivity analysis and the estimates remained
55 407 similar. Some of the confounding factors which were accounted for in the analysis were self-
56 408 reported, however the information was collected prospectively, therefore any measurement
57 409 error is likely to be non-differential. Another limitation is that these findings are based on
58 410 observational data so inferences about causation cannot be drawn and the risk of residual
59 411 confounding influencing the results needs to be considered.

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2
3 412 In conclusion, maternal weight gain of 1 or more kg/m² between first and second pregnancy
4 413 had a prevalence of 48%, and it was associated with risk of LGA in the second pregnancy in
5 414 this English cohort. Risk of 'new' LGA was higher in normal weight and overweight women
6 415 who gained weight after a non-LGA birth in their first pregnancy compared to those who
7 416 remained weight stable. Overweight women were at a lower risk of a recurrent LGA birth in
8 417 their second pregnancy if they lost weight between pregnancies. Greater efforts are needed
9 418 for primary prevention of overweight and obesity in women of child bearing age. Supporting
10 419 efforts to lose weight in overweight and obese women between pregnancies, and stop
11 420 weight gain in all women planning to have further children (except those who are
12 421 underweight) are important preventive measures of subsequent adverse maternal and
13 422 offspring health outcomes.

14 423

15 16 424 **Author Contributions**

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18
19 425 Study design (NZ, PJR, NSM, NAA), data analysis (NZ, SW), acquisition and interpretation
20 426 of the data (NZ, NAA), drafting of the manuscript (NZ), revising for content (NZ, SW, PJR,
21 427 NSM, NAA) and approval of final version before submission (NZ, SW, PJR, NSM, NAA).
22 428 NAA is the project's PI.

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24 25 430 **Data statement**

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27
28 431 The data owner is University Hospital Southampton NHS Trust. Anonymised data are only
29 432 available upon request from the PI (NAA) conditional on approval of the appropriate
30 433 institutional ethics and research governance processes.

31 434

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35
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40 440

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44
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50 447

51 52 448 **Competing interests**

53
54 449 The authors have no competing interests to declare.

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56 57 451 **References**

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57 557

58 **Figure legends**

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3 559 Figure 1: The percentage of women in each body mass index (BMI) category in the first and
4 560 second pregnancy and weight gain over time in the cohort (2003-2017)
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6 561 Figure 2: The percentage of large-for-gestational age (LGA) births in first and second
7 562 pregnancy by maternal body mass index (BMI) category
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9 563 Figure 3: The percentage and risk of large-for-gestational age (LGA) births in second
10 564 pregnancy stratified by maternal inter-pregnancy weight change categories
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12 565 Supplementary Figure 1: Associations between risk of recurrent large-for-gestational age
13 566 (LGA) birth in the second pregnancy and change in maternal body mass index (BMI)
14 567 between pregnancies as measured at the first antenatal visit of each pregnancy stratified by
15 568 BMI category in the first pregnancy
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17 569 Supplementary Figure 2: Associations between the risk of 'new' large-for-gestational age
18 570 (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and
19 571 change in maternal body mass index (BMI) between pregnancies measured at the first
20 572 antenatal visit of each pregnancy stratified by BMI category in the first pregnancy
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25 575 **Table legends:**

26
27 576 Table 1: Maternal and birth characteristics in the second live birth pregnancy categorised by
28 577 maternal weight change from the first livebirth pregnancy for the period of January 2003 -
29 578 September 2017, University Hospital Southampton NHS Foundation Trust, Hampshire,
30 579 England
31

32 580 Table 2: Associations between risk of recurrent large-for-gestational age (LGA) birth in the
33 581 second pregnancy and change in maternal body mass index (BMI) between pregnancies as
34 582 measured at the first antenatal visit of each pregnancy stratified by BMI category in the first
35 583 pregnancy
36

37 584 Table 3: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the
38 585 second pregnancy following a non-LGA birth in the first pregnancy and change in maternal
39 586 body mass index (BMI) between pregnancies measured at the first antenatal visit of each
40 587 pregnancy stratified by BMI category in the first pregnancy
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Table 1: Maternal and birth characteristics in the second live birth pregnancy categorised by maternal weight change gain from the first live birth pregnancy for the period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust, Hampshire, England

	Lost ≤ -1 kg/m ² from previous pregnancy	Weight stable (>-1 to <1 kg/m ²)	Gained 1-3 kg/m ² from previous pregnancy	Gained ≥ 3 kg/m ² from previous pregnancy	p*
N	2548	5785	4446	3161	
Maternal age, years (mean \pm SD)	28.7 \pm 5.4	29.8 \pm 5.3	29.2 \pm 5.4	27.3 \pm 5.5	<0.001
Timing of first booking appointment, weeks (mean \pm SD)	10.8 \pm 2.3	11.0 \pm 2.3	11.1 \pm 2.4	11.0 \pm 2.6	<0.001
Maternal BMI at booking, kg/m ² (mean \pm SD)	24.1 \pm 5.1	23.8 \pm 4.4	25.9 \pm 4.7	30.8 \pm 5.9	<0.001
Maternal BMI at booking in first pregnancy (%; 95% CI)					<0.001
Underweight (< 18.5)	0.8 (0.5 to 1.2)	4.3 (3.8 to 4.8)	5.3 (4.7 to 6.0)	3.7 (3.1 to 4.4)	
Normal weight (18.5 to 24.9)	47.6 (45.6 to 49.5)	67.4 (66.2 to 68.6)	62.5 (61.0 to 63.9)	49.0 (47.2 to 50.7)	
Overweight (25.0 to 29.9)	30.1 (28.3 to 31.9)	19.4 (18.4 to 20.5)	22.0 (20.8 to 23.3)	29.5 (28.0 to 31.2)	
Obese (≥ 30.0)	21.5 (19.9 to 23.2)	8.9 (8.2 to 9.7)	10.2 (9.3 to 11.1)	17.8 (16.5 to 19.2)	
Maternal BMI at booking in second pregnancy (%; 95% CI)					<0.001
Underweight (< 18.5)	6.9 (5.9 to 7.9)	4.3 (3.8 to 4.8)	0.6 (0.4 to 0.9)	0.0 (0.0 to 0.2)	
Normal weight (18.5 to 24.9)	61.1 (59.2 to 63.0)	66.8 (65.6 to 68.1)	50.7 (49.2 to 52.1)	14.9 (13.7 to 16.2)	
Overweight (25.0 to 29.9)	20.1 (18.6 to 21.7)	19.7 (18.7 to 20.7)	32.6 (31.2 to 34.0)	36.7 (35.0 to 38.4)	
Obese (≥ 30.0)	11.9 (10.7 to 13.3)	9.2 (8.5 to 10.0)	16.1 (15.0 to 17.2)	48.3 (46.6 to 50.1)	
Maternal smoking status at booking (%; 95% CI)					<0.001
Never smoked/quit	57.2 (55.3 to 59.2)	63.0 (61.8 to 64.3)	60.5 (59.0 to 62.0)	50.7 (48.9 to 52.4)	
Stopped >1 year before conceiving	16.1 (14.6 to 17.5)	17.2 (16.3 to 18.2)	17.7 (16.5 to 18.8)	14.9 (13.7 to 16.2)	
Stopped <1 year prior to conceiving	4.0 (3.3 to 4.8)	2.8 (2.4 to 3.2)	3.5 (3.0 to 4.1)	4.9 (4.2 to 5.7)	
Stopped when pregnancy confirmed	6.8 (5.8 to 7.8)	5.9 (5.3 to 6.6)	6.9 (6.2 to 7.7)	10.3 (9.3 to 11.4)	
Continued smoking	15.9 (14.5 to 17.4)	11.0 (10.2 to 11.8)	11.4 (10.5 to 12.4)	19.1 (17.8 to 20.6)	
Maternal education (%; 95% CI)					<0.001
Secondary (GCSE) or under	30.7 (28.9 to 32.5)	24.0 (22.9 to 25.2)	29.4 (28.1 to 30.8)	36.3 (34.6 to 38.0)	
College (A levels)	40.4 (38.5 to 42.3)	38.8 (37.6 to 40.1)	39.5 (38.1 to 41.0)	45.8 (44.0 to 47.5)	

University degree or above	28.9 (27.2 to 30.7)	37.1 (35.9 to 38.4)	31.1 (29.7 to 32.5)	17.9 (16.6 to 19.3)	
Maternal employment (% , 95% CI)					
Employed	66.2 (64.3 to 68.0)	71.7 (70.5 to 72.9)	67.2 (65.8 to 68.5)	56.5 (54.8 to 58.2)	<0.001
Unemployed	31.8 (30.0 to 33.7)	26.9 (25.8 to 28.1)	31.1 (29.7 to 32.5)	41.6 (39.8 to 43.3)	
In education	0.9 (0.6 to 1.4)	0.8 (0.6 to 1.1)	1.1 (0.8 to 1.4)	1.3 (0.9 to 1.8)	
Not specified	1.0 (0.7 to 1.5)	0.6 (0.4 to 0.8)	0.7 (0.5 to 1.0)	0.6 (0.4 to 1.0)	
Ethnicity (% , 95% CI)					
White	89.9 (88.7 to 91.1)	88.0 (87.1 to 88.8)	85.1 (84.0 to 86.1)	84.8 (83.5 to 86.1)	<0.001
Mixed	0.8 (0.5 to 1.3)	0.9 (0.7 to 1.2)	1.4 (1.1 to 1.8)	1.6 (1.1 to 2.0)	
Asian	4.8 (4.0 to 5.7)	5.6 (5.0 to 6.0)	7.2 (6.5 to 8.0)	7.7 (6.8 to 8.7)	
Black/African/Caribbean	0.6 (0.4 to 1.0)	1.0 (0.8 to 1.3)	1.6 (1.3 to 2.1)	2.4 (1.9 to 3.0)	
Other	0.7 (0.4 to 1.1)	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.4)	1.3 (0.9 to 1.7)	
Not specified	3.1 (2.5 to 3.9)	3.5 (3.0 to 4.0)	3.6 (3.1 to 4.2)	2.2 (1.8 to 2.8)	
Inter-pregnancy interval (median, IQR)	21.7 (14.4 to 32.7)	21.6 (14.1 to 32.0)	23.7 (14.4 to 35.6)	27.7 (16.0 to 45.6)	<0.001
Inter-pregnancy interval (% , 95% CI)					
0-11 months	17.4 (15.9 to 18.9)	17.6 (16.6 to 18.6)	18.1 (17.0 to 19.3)	16.6 (15.4 to 17.9)	<0.001
12-23 months	39.8 (37.8 to 41.7)	39.9 (38.6 to 41.1)	33.1 (31.7 to 34.5)	26.3 (24.8 to 27.9)	
24-35 months	22.6 (21.0 to 24.2)	23.6 (22.5 to 24.7)	24.4 (23.2 to 25.7)	20.5 (19.1 to 21.9)	
36 months or more	20.3 (18.7 to 21.9)	18.9 (17.9 to 20.0)	24.3 (23.1 to 25.6)	36.5 (34.9 to 38.2)	
Birthweight, grams (mean ± SD)	3463 ± 563	3467 ± 523	3507 ± 536	3531 ± 558	
Previous size at birth (first pregnancy)					
Small-for-gestational age	13.1 (11.8 to 14.4)	12.6 (11.8 to 13.5)	11.7 (10.8 to 12.7)	12.4 (11.3 to 13.6)	0.11
Appropriate-for-gestational age	79.6 (77.9 to 81.1)	81.1 (80.0 to 82.1)	81.2 (80.1 to 82.4)	79.9 (78.4 to 81.3)	
Large-for-gestational age	7.4 (6.4 to 8.5)	6.3 (5.7 to 7.0)	7.1 (6.3 to 7.8)	7.7 (6.8 to 8.7)	
Size at birth (second pregnancy)					
Small-for-gestational age	8.7 (7.6 to 9.8)	7.0 (6.4 to 7.7)	6.2 (5.5 to 6.9)	6.7 (5.9 to 7.6)	<0.001
Appropriate-for-gestational age	79.0 (77.3 to 80.5)	81.1 (80.0 to 82.1)	80.3 (79.1 to 81.5)	77.4 (75.9 to 78.9)	
Large-for-gestational age	12.4 (11.1 to 13.7)	11.9 (11.1 to 12.8)	13.5 (12.5 to 14.5)	15.9 (14.6 to 17.2)	

*p values calculated using ANOVA for continuous and chi square test for categorical variables

Table 2: Associations between risk of recurrent large-for-gestational age (LGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		Total n, n of cases	Relative risk, (RR)*	95% CI	Total n, n of cases	RR*	95% CI	Total n, n of cases	RR*	95% CI	Total n, n of cases	RR*	95% CI
Total unadjusted n, n of cases		1109, 530			521, 234			338, 170			236, 122		
Lost \leq -1 kg/m ² from previous pregnancy	Unadjusted	188, 83	0.89	0.74 to 1.08	45, 17	0.80	0.54 to 1.20	74, 30	0.68	0.50 to 0.94	69, 36	1.16	0.79 to 1.69
	Adjusted**	178, 78	0.88	0.72 to 1.07	44, 16	0.79	0.54 to 1.17	68, 27	0.69	0.48 to 0.97	66, 35	1.21	0.79 to 1.83
Weight stable (>-1 to <1 kg/m ²)	Unadjusted	365, 181	Ref		212, 100	Ref		98, 58	Ref		51, 23	Ref	
	Adjusted**	353, 176	Ref		204, 96	Ref		97, 57	Ref		49, 23	Ref	
Gained 1-3 kg/m ² from previous pregnancy	Unadjusted	313, 150	0.97	0.83 to 1.13	162, 74	0.97	0.78 to 1.21	90, 43	0.81	0.62 to 1.06	55, 31	1.25	0.85 to 1.83
	Adjusted**	301, 142	0.98	0.84 to 1.15	156, 70	1.02	0.83 to 1.27	86, 40	0.81	0.61 to 1.08	53, 30	1.28	0.86 to 1.91
Gained \geq 3 kg/m ² from previous pregnancy	Unadjusted	243, 116	0.96	0.81 to 1.14	102, 43	0.89	0.68 to 1.17	76, 39	0.87	0.66 to 1.14	61, 32	1.16	0.79 to 1.71
	Adjusted**	234, 111	1.00	0.83 to 1.20	96, 39	0.91	0.68 to 1.21	73, 38	0.91	0.67 to 1.25	61, 32	1.28	0.84 to 1.94

*Generalised linear model with log link and robust variance estimator used to derive RR

**Adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

Table 3: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Underweight at first pregnancy			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		Total n, n of cases	Relative risk, (RR)*	95% CI	Total n, n of cases	RR*	95% CI	Total n, n of cases	RR*	95% CI	Total n, n of cases	RR*	95% CI	Total n, n of cases	RR*	95% CI
Total unadjusted n, n of cases		14788, 1573			606, 24			8888, 812			3458, 454			1836, 283		
Lost ≤ -1 kg/m ² from previous pregnancy	Unadjusted	2351, 232	1.05	0.91 to 1.22	-	-	-	1163, 85	0.88	0.68 to 1.14	690, 79	0.95	0.73 to 1.24	477, 68	0.90	0.67 to 1.23
	Adjusted**	2258, 222	0.94	0.80 to 1.10	-	-	-	1108, 81	0.87	0.68 to 1.12	663, 76	0.96	0.72 to 1.29	466, 65	0.95	0.67 to 1.34
Weight stable (>-1 to <1 kg/m ²)	Unadjusted	5411, 508	Ref		244, 7	Ref		3680, 305	Ref		1024, 123	Ref		463, 73	Ref	
	Adjusted**	5191, 489	Ref		234, 7	Ref		3519, 292	Ref		985, 118	Ref		453, 72	Ref	
Gained 1-3 kg/m ² from previous pregnancy	Unadjusted	4122, 450	1.16	1.03 to 1.31	230, 8	1.21	0.45 to 3.29	2606, 259	1.20	1.02 to 1.40	888, 127	1.19	0.94 to 1.50	398, 56	0.89	0.65 to 1.23
	Adjusted**	3944, 427	1.13	0.99 to 1.28	222, 7	1.04	0.36 to 3.04	2497, 251	1.26	1.06 to 1.50	839, 115	1.16	0.89 to 1.50	386, 54	0.86	0.61 to 1.22
Gained ≥3 kg/m ² from previous pregnancy	Unadjusted	2904, 383	1.40	1.24 to 1.59	111, 9	2.83	1.08 to 7.40	1439, 163	1.37	1.14 to 1.64	856, 125	1.22	0.96 to 1.53	498, 86	1.10	0.82 to 1.46
	Adjusted**	2822, 364	1.34	1.17 to 1.54	104, 6	2.08	0.67 to 6.51	1389, 151	1.34	1.09 to 1.65	839, 123	1.35	1.05 to 1.75	490, 84	1.21	0.89 to 1.65

*Generalised linear model with log link and robust variance estimator used to derive RR

**Adjusted for: maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

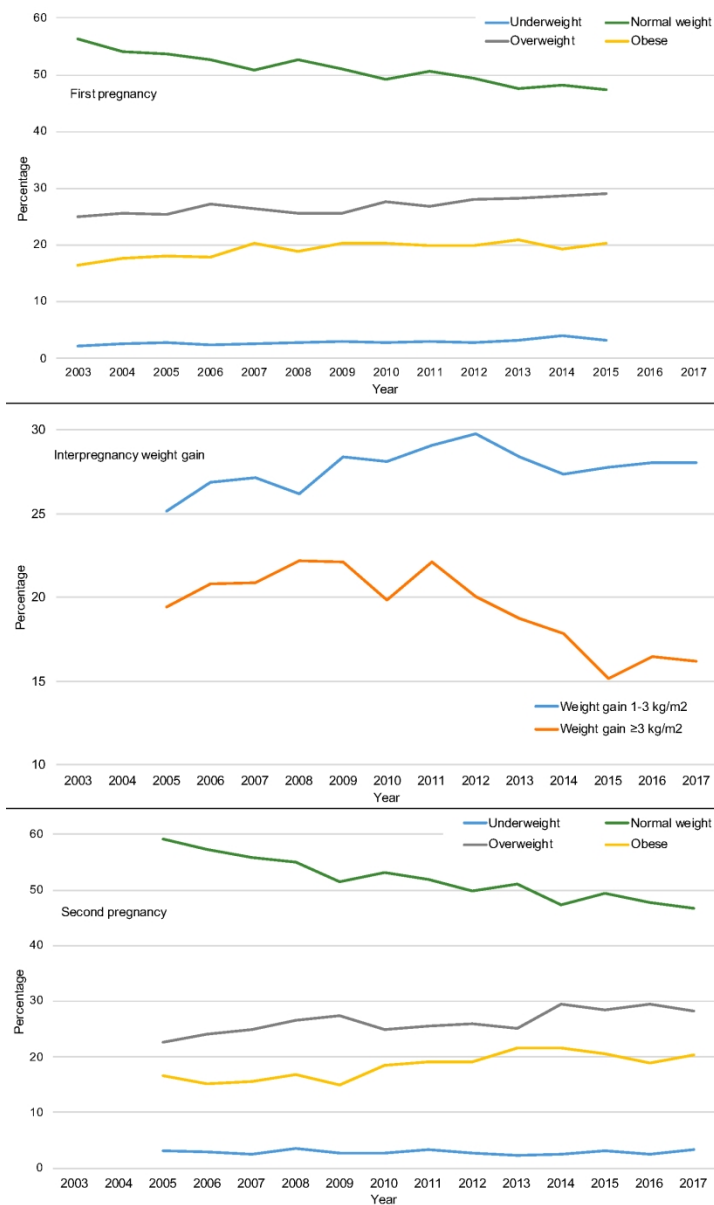


Figure 1: The percentage of women in each body mass index (BMI) category in the first and second pregnancy and weight gain over time in the cohort (2003-2017)

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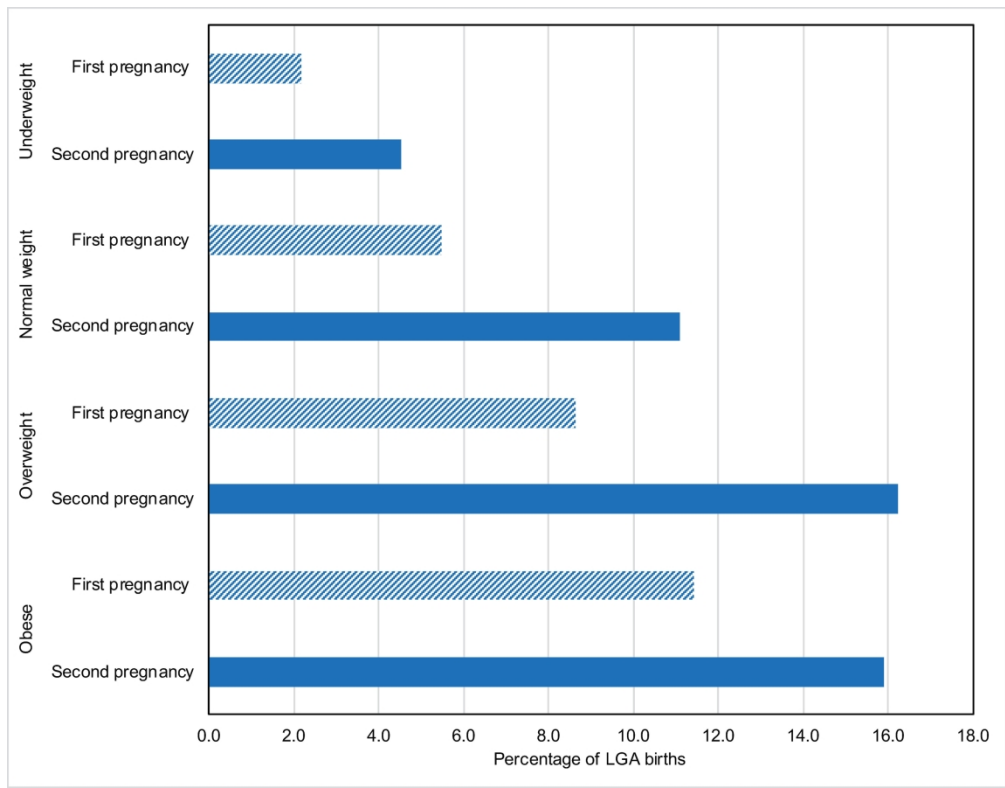


Figure 2: The percentage of large-for-gestational age (LGA) births in first and second pregnancy by maternal body mass index (BMI) category

226x176mm (300 x 300 DPI)

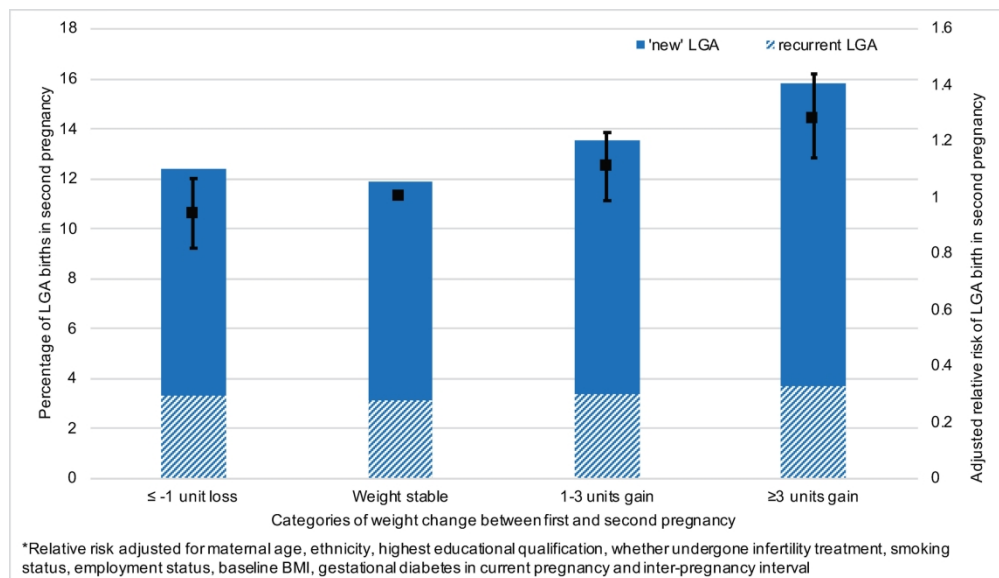
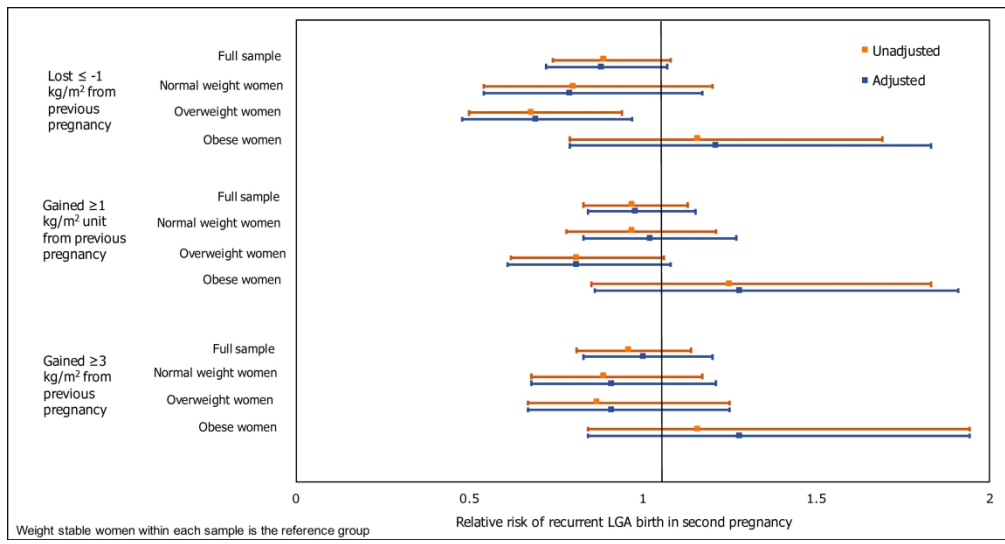


Figure 3: The percentage and risk of large-for-gestational age (LGA) births in second pregnancy stratified by maternal inter-pregnancy weight change categories

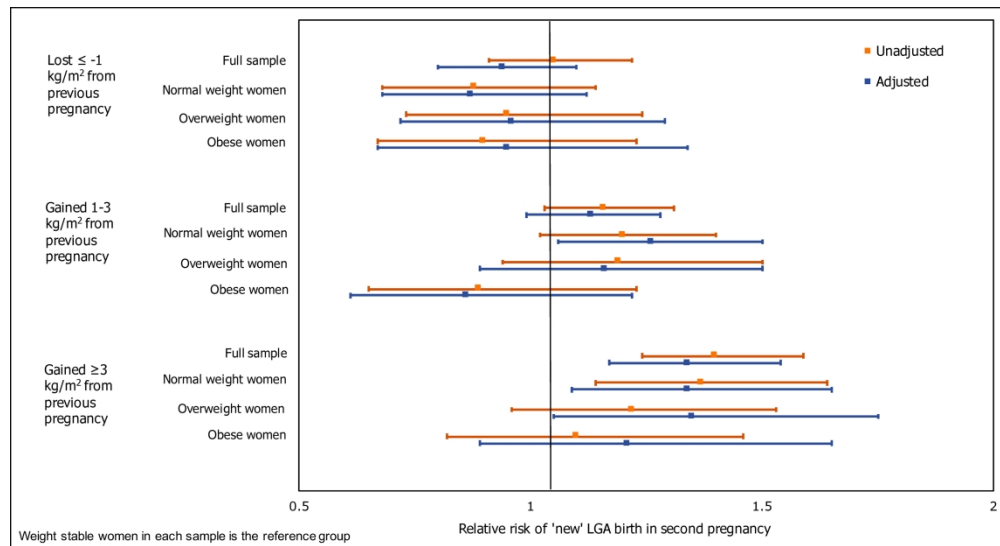
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Supplementary Figure 1: Associations between risk of recurrent large-for-gestational age (LGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

311x165mm (300 x 300 DPI)



Supplementary Figure 2: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

310x168mm (300 x 300 DPI)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4

1		#6b	For matched studies, give matching criteria and number of	n/a
2			exposed and unexposed	
3				
4				
5	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	4-5
6			confounders, and effect modifiers. Give diagnostic criteria, if	
7			applicable	
8				
9				
10	Data sources /	#8	For each variable of interest give sources of data and details of	4-5
11	measurement		methods of assessment (measurement). Describe	
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	n/a
19				
20				
21	Study size	#10	Explain how the study size was arrived at	4
22				
23	Quantitative	#11	Explain how quantitative variables were handled in the	4-5
24	variables		analyses. If applicable, describe which groupings were chosen,	
25			and why	
26				
27				
28	Statistical	#12a	Describe all statistical methods, including those used to control	5
29	methods		for confounding	
30				
31				
32		#12b	Describe any methods used to examine subgroups and	5
33			interactions	
34				
35				
36		#12c	Explain how missing data were addressed	n/a
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	n/a
39				
40				
41		#12e	Describe any sensitivity analyses	n/a
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg	5
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	n/a
52				
53		#13c	Consider use of a flow diagram	n/a
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55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	5-6
57			clinical, social) and information on exposures and potential	
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1		confounders. Give information separately for exposed and	
2		unexposed groups if applicable.	
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4		#14b Indicate number of participants with missing data for each	13-14
5		variable of interest	
6			
7		#14c Summarise follow-up time (eg, average and total amount)	n/a
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10	Outcome data	#15 Report numbers of outcome events or summary measures	5-6, 13-
11		over time. Give information separately for exposed and	14
12		unexposed groups if applicable.	
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14			
15	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	6-7, 15-
16		adjusted estimates and their precision (eg, 95% confidence	21
17		interval). Make clear which confounders were adjusted for and	
18		why they were included	
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22		#16b Report category boundaries when continuous variables were	4-5, 13-
23		categorized	14
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26		#16c If relevant, consider translating estimates of relative risk into	n/a
27		absolute risk for a meaningful time period	
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29			
30	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	n/a
31		interactions, and sensitivity analyses	
32			
33			
34	Key results	#18 Summarise key results with reference to study objectives	7
35			
36	Limitations	#19 Discuss limitations of the study, taking into account sources of	8-9
37		potential bias or imprecision. Discuss both direction and	
38		magnitude of any potential bias.	
39			
40			
41	Interpretation	#20 Give a cautious overall interpretation considering objectives,	9
42		limitations, multiplicity of analyses, results from similar studies,	
43		and other relevant evidence.	
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46	Generalisability	#21 Discuss the generalisability (external validity) of the study	8-9
47		results	
48			
49			
50	Funding	#22 Give the source of funding and the role of the funders for the	10
51		present study and, if applicable, for the original study on which	
52		the present article is based	
53			
54			
55			

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