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Interpregnancy weight changes and impact on pregnancy outcome in a cohort of women with a macrosomic first delivery: A Prospective Longitudinal Study.

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Complete List of Authors:	Crosby, David; National Maternity Hospital, Obstetrics and Gynaecology; University College Dublin, School of Medicine Walsh, Jennifer; University College Dublin, School of Medicine; National Maternity Hospital, Obstetrics and Gynaecology Segurado, Ricardo; University College Dublin, CSTAR, School of Public Health, Physiotherapy and Population Science McAuliffe, Fionnuala; University College Dublin, School of Medicine; National Maternity Hospital, Obstetrics and Gynaecology
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1 **Title:** Interpregnancy weight changes and impact on pregnancy outcome
2 in a cohort of women with a macrosomic first delivery: A
3 Prospective Longitudinal Study.

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5 **Authors:** David A Crosby, Jennifer Walsh, Ricardo Segurado, Fionnuala M
6 McAuliffe

7
8 **Source:** UCD Obstetrics and Gynaecology, School of Medicine and Medical
9 Science, University College Dublin, National Maternity Hospital,
10 Dublin 2, Ireland
11 National Maternity Hospital Dublin, Ireland (FB)
12 CSTAR, UCD (RS)

13
14 **Corresponding author:** Prof Fionnuala M McAuliffe

15
16 **Telephone:** 0035317163216

17
18 **Email:** fionnuala.mcauliffe@ucd.ie

19
20 **Running Title:** Interpregnancy weight gain and impact on pregnancy outcome

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3 26 Abstract:
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5 27 **Objective:**
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7 28 To determine the median interpregnancy maternal weight change between first and
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9 29 second pregnancies, and second and third pregnancies and to assess the impact of this
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11 30 weight change on pregnancy outcome in a cohort of women with a macrosomic first
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13 31 delivery.
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19 33 **Study Design:**

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21 34 Prospective longitudinal study conducted over three pregnancies from 2007 to 2015.
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26 36 **Setting:**

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28 37 Tertiary referral maternity hospital, Dublin, Ireland
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32 39 **Participants:**

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35 40 Women were recruited if their first baby weighed over 4.0kg.
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39 42 **Methods:**

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41 43 The pregnancy outcomes in the second and third pregnancies were analysed separately.
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43 44 Data were also analysed for both interpregnancy intervals comparing outcomes for
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45 45 those who gained any weight, or more weight than the median, with those who did not.
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50 51 **Main Outcome Measures:**
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53 48 Recurrent fetal macrosomia \geq 4.0kg
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3 51 **Results:**
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5 52 There were 280 women who delivered a third baby between 2011 and 2015. There
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7 53 were no difference in pregnancy outcomes for the second pregnancy in women who
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9 54 gained interpregnancy weight compared with those who did not and those who gained
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11 55 more interpregnancy weight than the median compared with those who did not. There
12
13 56 was a statistically significant increase in birthweight $\geq 4.0\text{kg}$ (54.0% vs. 39.6% $p=0.03$)
14
15 57 in those women who gained any weight between the second and third pregnancies. In
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17 58 those women who gained more interpregnancy weight than the median (1.70kg)
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19 59 between a second and third pregnancy, there was a significant increase in the rate of
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21 60 gestational diabetes (6.5% vs 1.4%, $p=0.03$).
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28 62 **Conclusions:**
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30 63 This longitudinal study demonstrates that within this cohort, maternal interpregnancy
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32 64 weight change between a second and third pregnancy is associated with an increase in
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34 65 birthweight $\geq 4.0\text{kg}$. Additionally a gain of more weight than the median (1.70kg) is
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36 66 associated with a higher rate of gestational diabetes.
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41 68 **Key words:** Interpregnancy weight change
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76 **Article Summary**

77 Strengths and Limitations

- 78 • Maternal weight and height were measured at booking visit in each pregnancy <18
79 weeks gestation and BMI calculated accurately, rather than relying on maternal self-
80 reporting.
- 81 • Uniform cohort: they delivered a first baby weight >4.0kg and they did not have GDM or
82 hypertensive disorders in the first pregnancy.
- 83 • Data was prospectively collected by an investigator and accurately recorded into an
84 anonymised computerised database.
- 85 • Longitudinal study, which has advantages over a cross-sectional study.
- 86 • A potential limitation of this study is that we do not have data on women who attended
87 elsewhere for subsequent antenatal care.

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3 111 **Introduction:**
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6 113 Fetal macrosomia is a common obstetric problem, affecting up to 20% of babies born at
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8 114 term (1, 2). The incidence varies according to the birthweight cut-offs employed, as it is
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10 115 varying defined as an absolute birthweight greater than 4000 g, 4500 g, or as a
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12 116 customised birth weight centile of greater than the 90th, 95th or 97th percentile for the
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14 117 infant's gestational age (3). It is associated with adverse obstetric maternal outcomes
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16 118 and neonatal outcomes, such as hypoglycaemia, hypomagnesaemia and
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18 119 hyperbilirubinaemia (4-6). Furthermore, infants with increased weight and body mass
19
20 120 index (BMI) are more likely to be obese in childhood (7), and this is contributing to the
21
22 121 burden of obesity on global health (3). Women with a history of birth of a macrosomic
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24 122 infant are at significantly increased risk of delivering another macrosomic infant in a
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26 123 subsequent pregnancy (8), and the risk increases further with a history of two
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28 124 macrosomic infants (9). Maternal weight gain during pregnancy influences fetal
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30 125 birthweight (10), and excessive gestational weight gain is strongly associated with fetal
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32 126 macrosomia (11). Interventions to limit gestational weight gain are, however, limited at
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34 127 best, perhaps due to perceived concerns regarding dietary and lifestyle changes during
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36 128 the prenatal period (12).
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45 130 Less attention has been traditionally focused on weight changes, and weight gain in
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47 131 particular, during the interval between pregnancies. Interpregnancy weight gain has,
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49 132 however, been associated with gestational hypertensive disease, gestational diabetes
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51 133 (GDM), caesarean section (CS), fetal macrosomia and even stillbirth (13-16). The
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53 134 postpartum and interval pregnancy time period therefore may represent a specific
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55 135 opportunity for targeted public health education, in women from every BMI category to
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3 136 prevent movement into a higher BMI category (17). To date, there are paucity of
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5 137 published longitudinal data on interpregnancy weight changes and the impact on both
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7 138 maternal and neonatal outcomes.
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12 140 The objective of this longitudinal study was to determine the median interpregnancy
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14 141 maternal weight change between first and second pregnancies, and second and third
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16 142 pregnancies and to assess the impact of this weight change on pregnancy outcome in a
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18 143 cohort of women with a macrosomic first delivery.
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23 145 **Methods:**

24
25 146 This is a prospective longitudinal study over three pregnancies. Women were initially
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27 147 recruited to the ROLO study (Randomised cOntrol trial of LOw glycaemic index diet
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29 148 versus no dietary intervention to prevent recurrence of fetal macrosomia) if their first
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31 149 baby weighed over 4.0kg (8). Recruitment to the randomised trial, with institutional
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33 150 ethical approval and maternal written consent, commenced in January 2007 and
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35 151 completed in January 2011. 800 secundigravida women without diabetes, who had
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37 152 previously given birth to a macrosomic baby (> 4.0kg) and were therefore at increased
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39 153 risk of delivering another macrosomic infant (9), were randomised to receive either low
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41 154 glycaemic index (GI) dietary advice or usual antenatal care. Detailed methodology and
42
43 155 results of the ROLO study have previously been published (8, 18). In brief; the low GI
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45 156 diet did not impact on birthweight, but maternal benefits were noted in terms of less
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47 157 gestational weight gain (12.2 Kg vs. 13.7Kg, $p < 0.05$) and less glucose intolerance (21%
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49 158 vs. 28%, $p < 0.05$). Low GI dietary advice was given at week 14 of pregnancy and the
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51 159 women in the intervention group were found to have a significantly reduced glycaemic
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53 160 index and glycaemic load following the intervention (8).
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3 161 Mothers were then followed prospectively and data collated and anonymised on 280
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5 162 women who delivered two further babies up to 2015. Weight and height were
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7 163 measured accurately at first presentation prior to 18 weeks gestation in each pregnancy
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9 164 and BMI calculated. Relevant descriptive statistics were obtained for the study
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11 165 population.

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14 166 The pregnancy outcomes in the second and third pregnancies were analysed separately
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16 167 with respect to the previous interpregnancy period, using absolute weight change. Data
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18 168 were also analysed for both interpregnancy intervals comparing outcomes for those
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20 169 who gained any weight, or those who gained more weight than the median with those
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22 170 who did not, which may be a more convenient definition for clinical practice. The
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24 171 pregnancy outcomes analysed were CS, GDM, recurrent fetal macrosomia, gestational
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26 172 hypertensive disease, neonatal intensive care unit (NICU) admission and stillbirth. We
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28 173 used the Mann-Whitney-U test to evaluate differences in continuous variables between
29
30 174 the groups or over time and χ^2 tests to compare categorical variables between groups.
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32 175 We set statistical significance at $P < 0.05$ and used SPSS version 23.0 for statistical
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34 176 analysis.

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40 41 178 **Results:**

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43 179 Of the initial 800 women recruited to the ROLO study, 280 (35.0%) women delivered a
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45 180 third baby between 2011 and 2015. Of these, the median maternal weight in the first
46
47 181 pregnancy was 68.8kg (IQR 16.5) and the median BMI was 24.9kg/m² (IQR 4.7). In total,
48
49 182 11.4% (n=32) of the cohort were obese in the first trimester of the first pregnancy.
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51 183 Table 1 details the demographic data for the cohort in the first trimester of the first,
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53 184 second and third pregnancies respectively.

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3 186 Overall, 72.9% (n=204) gained weight between the first and second pregnancy within a
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5 187 median interpregnancy interval of 24 months (IQR 12.0) and the overall median weight
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7 188 change was 2.60kg (IQR 3.5). 67.5% (n=189) gained weight between the second and
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9 189 third pregnancy within a median interpregnancy interval of 36.0 months (IQR 24.0),
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11 190 and the overall median weight change was 1.70kg (IQR 5.3). This resulted in a median
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13 191 weight gain from first to third pregnancy of 4.30kg (IQR 7.5). Overall the rate of obesity
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15 192 rose from 11.4% in first pregnancy to 22.1% by the beginning of the third pregnancy.
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21 194 There were no difference in pregnancy outcomes for the second pregnancy (gestational
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23 195 hypertensive disease, GDM, CS, recurrent fetal macrosomia \geq 4kg, NICU admission and
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25 196 stillbirth) in women who gained interpregnancy weight compared with those who did
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27 197 not and those who gained more interpregnancy weight than the median compared with
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29 198 those who did not.
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35 200 There was a statistically significant increase in birthweights \geq 4.0kg (54.0% vs. 39.6%
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37 201 $p=0.03$) in those women who gained weight between the second and third pregnancies.

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39 202 In those women who gained more interpregnancy weight than the median (1.70kg)
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41 203 between a second and third pregnancy, there was a significant increase in the rate of
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43 204 gestational diabetes (6.5% vs. 1.4%, $p=0.03$). There were no differences in gestational
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45 205 hypertensive disease, CS, NICU admission and stillbirth (Table 3).
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50 207 To examine the effect of cumulative weight gain over both interpregnancy intervals, and
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52 208 to control for the effect of maternal age and BMI less than 18 weeks gestation in the
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54 209 index pregnancy on the above results, logistic regression models to predict a
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56 210 birthweight \geq 4.0kg were run. Weight gain between the first and second, second and
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3 211 third and overall between first and third pregnancies had broadly similar effects, with a
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5 212 2-3% higher odds of a high birthweight per kilogram gain, which increased to 3-5%
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7 213 when adjusting for maternal age and BMI. Statistical significance was marginal, but
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9 214 present for weight gain in the earlier interval and between first and third pregnancies.
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216 **Discussion:**

217 218 Main Findings

219 This longitudinal study found that women who delivered a macrosomic infant ≥ 4.0 kg in
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21 220 their first pregnancy without gestational diabetes gained a median of 2.60kg between a
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23 221 first and second pregnancy and a median of 1.70kg between a second and third
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25 222 pregnancy resulting in a median 4.30kg weight gain from first to third pregnancy. This
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27 223 resulted in increase in obesity rates from 11.4% in first pregnancy to 22.1% in third
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29 224 pregnancy, highlighting the central role pregnancy has in weight gain across the life
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31 225 course. The interpregnancy weight gain between first and second pregnancies did not
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33 226 appear to impact on pregnancy outcome, however interpregnancy weight gain between
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35 227 second and third pregnancies was associated with an increased rate of recurrent fetal
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37 228 macrosomia ≥ 4.0 kg. Additionally those with a weight gain of more than the median
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39 229 (≥ 1.70 kg) between second and third pregnancies was associated with increased
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41 230 incidence of GDM.
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231 232 Interpretation

233 One possible explanation for the lack of associations in second pregnancy may arise due
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235 234 to the Hawthorne effect of trial participation in both the intervention and control arms.
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235 235 Another more likely hypothesis could be that weight gain may be cumulative. The
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236 236 median weights at booking visit in the first, second and third pregnancies were 68.8kg,
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3 237 71.3kg and 73.1kg respectively. Is weight gain cumulative so that it is only over a
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5 238 certain level that effects on birthweight and GDM are noted? There are a paucity of
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7 239 longitudinal studies on postpartum weight changes, because these studies are
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9 240 challenging to conduct (19). This longitudinal study adds to the evidence that
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11 241 interpregnancy weight gain causes GDM and macrosomic babies. Many studies relating
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13 242 to interpregnancy weight changes are cross sectional and retrospective in nature.
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15 243 Furthermore, many of these studies use self-reported maternal weight, which can be
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17 244 unreliable and leads to BMI miscategorization (20). High postpartum weight retention
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19 245 is an important contributor to long-term maternal obesity, which has detrimental
20
21 246 effects on long-term maternal health (21).

247 Strengths and Limitations in relation to other studies

248 Bogaerts et al. found that in a population of 7,897 women in Belgium, there was an
249 increase rate of GDM (aOR 2.25, 95% CI 1.33-3.78; P=0.002) in those who had
250 interpregnancy weight retention of 2 or more BMI units. However, this study used self-
251 reported prepregnancy weight and no prior information on hypertension and GDM
252 available (15). A large Swedish retrospective epidemiological study of 151,025 women
253 who had their first two consecutive births between 1992 and 2001 found that those
254 who gained 3 or more BMI units between pregnancies compared with those women
255 whose BMI changed between -1.0 and 0.9 units had an adjusted odds ratio of GDM of
256 2.09 (1.68-2.61) (13). Wallace et al. (22) conducted a retrospective cohort study of
257 12,740 women in Aberdeen, Scotland who delivered their first and second children
258 between 1986 and 2007. Weight gain of greater than three BMI units was associated
259 with an increase in large for gestational age infants. Jain et al. (23) analysed a
260 population based historical cohort of 10,444 obese women in Missouri who delivered
261 their first infant between 1998-2005. Interpregnancy weight gain was associated with

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3 262 an increased risk of a LGA infant (aOR 1.37; 95% CI, 1.21-1.54). These studies are
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5 263 retrospective. Our study is a prospective longitudinal illustrating that interpregnancy
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7 264 weight gain is associated with recurrent fetal macrosomia in a unique population of
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9 265 women who delivered a macrosomic baby ≥ 4.0 kg in their index pregnancy, and that
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11 266 interpregnancy weight gain of greater than the median is associated with an increased
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14 267 rate of GDM.
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19 269 The interpregnancy interval is an important time for diet and lifestyle intervention in
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21 270 women who have delivered a macrosomic infant in their first pregnancy in the
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23 271 prevention of recurrent macrosomia and the development of GDM.
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25 272 Strengths and Limitations

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28 273 This longitudinal study has strengths. Maternal weight and height were measured at
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30 274 booking visit in each pregnancy <18 weeks gestation and BMI calculated accurately,
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32 275 rather than relying on maternal self-reporting. Furthermore, this cohort of women was
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34 276 uniform in that they delivered a first baby weight >4.0 kg and they did not have GDM or
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36 277 hypertensive disorders in the first pregnancy. Data was prospectively collected by an
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38 278 investigator and accurately recorded into an anonymised computerised database.
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41 279 Finally, this longitudinal study has advantages over a cross-sectional study.
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46 281 A potential limitation of this study is that we do not have data on women who attended
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48 282 elsewhere for subsequent antenatal care. Another potential limitation is that the
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50 283 interpregnancy interval varied between subjects within this study. Finally, this study
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52 284 applies to women who delivered a first baby >4 kg, which applies to approximately 15%
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55 285 of our overall primiparous population.
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3 287 **Conclusions:**
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5 288 This longitudinal study demonstrates that within this cohort maternal interpregnancy
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7 289 weight change between a second and third pregnancy is associated with an increase in
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9 290 birthweight ≥ 4.0 kg. Additionally a gain of more weight than the median (1.70kg) is
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11 291 associated with a higher rate of gestational diabetes. It is important to identify ways for
12
13 292 women to maintain a normal weight and BMI throughout her life, particularly between
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15 293 pregnancies. Obstetricians should consider postnatal advice on interval pregnancy
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17 294 weight gain in order to reduce rates of macrosomia and gestational diabetes in future
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19 295 pregnancy in at risk women.
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25 297 **Acknowledgments**
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28 298 Nil of note
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32 300 **Contribution to Authorship**
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35 301 FMMcA conceived and designed the study. JW contributed to the study design and
36
37 302 manuscript preparation. DAC performed the analysis and wrote the manuscript. RS
38
39 303 performed analysis. All of the authors reviewed and revised the final version of the
40
41 304 manuscript. FMMcA is the guarantor.
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46 306 **Ethical Approval**
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48 307 Not applicable
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312 **Competing Interests**

313 We have read and understood BMJ policy on declaration of interests and declare that
314 we have no competing interests.

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39 401 *Gynecol*. 2013 Mar;208(3):205
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3 410 **Table 1:** Demographics of the cohort at in the first trimester of the first, second and
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5 411 third pregnancies respectively (n=280)
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	Pregnancy 1	Pregnancy 2	Pregnancy 3
Maternal Age (years)	29.0 (8.1)	31.8 (5.5)	34.8 (5.8)
Maternal Weight (kg)	68.8 (16.5)	71.4 (17.5)	73.1 (19.4)
BMI (kg/m ²)	24.9 (4.7)	25.7 (5.4)	26.0 (5.7)
Birthweight (kg)	4.2 (0.26)	4.1 (0.61)	4.0 (0.69)
Gestational Age (Days)	288 (10.0)	283 (11.0)	280 (13.8)
Obese (≥ 30kg/m ²)	11.4% (n=32)	20.0% (n=56)	22.1% (n=62)

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All values are median with interquartile ranges in hypotheses, except for obesity (demonstrated in absolute numbers and percentages). Maternal weight and body mass index (BMI) were calculated at ≤ 18 weeks gestation.

441 **Table 2. Effect of weight gain on odds of birthweight ≥ 4 kg unadjusted and**
 442 **adjusted for maternal age and BMI calculated at less than 18 weeks gestation in**
 443 **the index pregnancy**

	Unadjusted			Adjusted for maternal age and BMI		
	OR	95% CI	p-value	OR	95% CI	p-value
Weight gain from pregnancy 1 to 2	1.03	0.99, 1.07	0.169	1.05	1.01, 1.10	0.024
Weight gain from pregnancy 2 to 3	1.02	0.98, 1.06	0.243	1.03	0.99, 1.08	0.107
Weight gain from pregnancy 1 to 3	1.03	1.00, 1.06	0.093	1.04	1.01, 1.08	0.013

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3 457 Table 3:
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5 458 Pregnancy outcomes for the third pregnancy based on those who gained inter-
6 pregnancy weight compared with those who did not and those who gained more inter-
7 pregnancy weight than the median compared with those who did not.
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9 461
10 462

	Gained interpregnancy weight n=189	Did not gain interpregnancy weight n=91	P value
CS overall	41 (21.7%)	21 (23.1%)	NS
GDM	9 (4.8%)	2 (2.2%)	NS
BW ≥4kg	102 (54.0%)	36 (39.6%)	P=0.03
Hypertensive Disease	5 (2.6%)	2 (2.2%)	NS
NICU	4 (2.1%)	2 (2.2%)	NS
Stillbirth	1 (0.5%)	1 (1.1%)	NS
	Gained > 1.70kg inter-pregnancy weight (n=139)	Gained ≤ 1.70kg inter-pregnancy weight (n=141)	P value
CS overall	28 (20.1%)	34 (24.1%)	NS
GDM	9 (6.5%)	2 (1.4%)	0.03
BW ≥4kg	75 (54.0%)	63 (44.7%)	NS
Hypertensive Disease	4 (2.9%)	3 (2.1%)	NS
NICU	4 (2.9%)	2 (1.4%)	NS
Stillbirth	0 (0%)	2 (1.4%)	NS

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(a) 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	
		(b) Report category boundaries when continuous variables were categorized	8-9
		(c) 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—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
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	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Interpregnancy weight changes and impact on pregnancy outcome in a cohort of women with a macrosomic first delivery: A Prospective Longitudinal Study.

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Obstetrics and gynaecology
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Keywords:	Interpregnancy weight change, Body mass index, Fetal macrosomia, tional diabetes mellitus

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1 **Title:** Interpregnancy weight changes and impact on pregnancy outcome
2 in a cohort of women with a macrosomic first delivery: A
3 Prospective Longitudinal Study.

4
5 **Authors:** David A Crosby, Jennifer Walsh, Ricardo Segurado, Fionnuala M
6 McAuliffe

7
8 **Source:** UCD Obstetrics and Gynaecology, School of Medicine and Medical
9 Science, University College Dublin, National Maternity Hospital,
10 Dublin 2, Ireland
11 National Maternity Hospital Dublin, Ireland (FB)
12 CSTAR, UCD (RS)

13
14 **Corresponding author:** Prof Fionnuala M McAuliffe

15
16 **Telephone:** 0035317163216

17
18 **Email:** fionnuala.mcauliffe@ucd.ie

19
20 **Running Title:** Interpregnancy weight gain and impact on pregnancy outcome

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2
3 26 Abstract:
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5 27 **Objective:**
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7 28 To determine the median interpregnancy maternal weight change between first and
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9 29 second pregnancies, and second and third pregnancies and to assess the impact of this
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11 30 weight change on pregnancy outcome in a cohort of women with a macrosomic first
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13 31 delivery.
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19 33 **Study Design:**

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21 34 Prospective longitudinal study conducted over three pregnancies from 2007 to 2015.
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26 36 **Setting:**

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28 37 Tertiary referral maternity hospital, Dublin, Ireland
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32 39 **Participants:**

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35 40 Women were recruited if their first baby weighed over 4.0kg.
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39 42 **Methods:**

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41 43 The pregnancy outcomes in the second and third pregnancies were analysed separately.
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43 44 Data were also analysed for both interpregnancy intervals comparing outcomes for
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45 45 those who gained any weight, or more weight than the median, with those who did not.
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50 51 **Main Outcome Measures:**
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53 48 Recurrent fetal macrosomia \geq 4.0kg
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55 49 Gestational diabetes mellitus
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3 51 **Results:**
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5 52 There were 280 women who delivered a third baby between 2011 and 2015. There
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7 53 were no difference in pregnancy outcomes for the second pregnancy in women who
8
9 54 gained interpregnancy weight compared with those who did not and those who gained
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11 55 more interpregnancy weight than the median compared with those who did not. There
12
13 56 was a statistically significant increase in birthweight $\geq 4.0\text{kg}$ (54.0% vs. 39.6% $p=0.03$)
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15 57 in those women who gained any weight between the second and third pregnancies. In
16
17 58 those women who gained more interpregnancy weight than the median (1.70kg)
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19 59 between a second and third pregnancy, there was a significant increase in the rate of
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21 60 gestational diabetes (6.5% vs 1.4%, $p=0.03$).
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28 62 **Conclusions:**
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30 63 This longitudinal study demonstrates that within this cohort, maternal interpregnancy
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32 64 weight change between a second and third pregnancy is associated with an increase in
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34 65 birthweight $\geq 4.0\text{kg}$. Additionally a gain of more weight than the median (1.70kg) is
35
36 66 associated with a higher rate of gestational diabetes.
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41 68 **Key words:** Interpregnancy weight change
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43 69 Body mass index
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45 70 Fetal macrosomia
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48 71 Gestational diabetes mellitus
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3 76 **Article Summary**
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5 77 Strengths and Limitations
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- 7
8 • Maternal weight and height were measured at booking visit in each pregnancy <18
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10 weeks gestation and BMI calculated accurately, rather than relying on maternal self-
11
12 reporting.
13
14 • Uniform cohort: they delivered a first baby weight >4.0kg and they did not have GDM or
15
16 hypertensive disorders in the first pregnancy.
17
18 • Data was prospectively collected by an investigator and accurately recorded into an
19
20 anonymised computerised database.
21
22 • Longitudinal study, which has advantages over a cross-sectional study.
23
24 • A potential limitation of this study is that we do not have data on women who attended
25
26 elsewhere for subsequent antenatal care.
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29 88 **Data Sharing Statement**
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31 89 There is no additional unpublished data from this study. All co-authors can access this data.
32 90 Anonymous data can be obtained by contacting the corresponding author.
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60**112 Introduction:**

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114 Fetal macrosomia is a common obstetric problem, affecting up to 20% of babies born at
115 term (1, 2). The incidence varies according to the birthweight cut-offs employed, as it is
116 varyingly defined as an absolute birthweight greater than 4000 g, 4500 g, or as a
117 customised birth weight centile of greater than the 90th, 95th or 97th percentile for the
118 infant's gestational age (3). It is associated with adverse obstetric maternal outcomes
119 and neonatal outcomes, such as hypoglycaemia, hypomagnesaemia and
120 hyperbilirubinaemia (4-6). Furthermore, infants with increased weight and body mass
121 index (BMI) are more likely to be obese in childhood (7), and this is contributing to the
122 burden of obesity on global health (3). Women with a history of birth of a macrosomic
123 infant are at significantly increased risk of delivering another macrosomic infant in a
124 subsequent pregnancy (8), and the risk increases further with a history of two
125 macrosomic infants (9). Maternal weight gain during pregnancy influences fetal
126 birthweight (10), and excessive gestational weight gain is strongly associated with fetal
127 macrosomia (11). Interventions to limit gestational weight gain are, however, limited at
128 best, perhaps due to perceived concerns regarding dietary and lifestyle changes during
129 the prenatal period (12).

130

131 Less attention has been traditionally focused on weight changes, and weight gain in
132 particular, during the interval between pregnancies. Interpregnancy weight gain has,
133 however, been associated with gestational hypertensive disease, gestational diabetes
134 (GDM), caesarean section (CS), fetal macrosomia and even stillbirth (13-16). The
135 postpartum and interval pregnancy time period therefore may represent a specific
136 opportunity for targeted public health education, in women from every BMI category to

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3 137 prevent movement into a higher BMI category (17). To date, there are paucity of
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5 138 published longitudinal data on interpregnancy weight changes and the impact on both
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7 139 maternal and neonatal outcomes.
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11 141 The objective of this longitudinal study was to determine the median interpregnancy
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13 142 maternal weight change between first and second pregnancies, and second and third
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15 143 pregnancies and to assess the impact of this weight change on pregnancy outcome in a
16
17 144 cohort of women with a macrosomic first delivery.
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23 146 **Methods:**

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25 147 This is a prospective longitudinal study over three pregnancies. Women were initially
26
27 148 recruited to the ROLO study (Randomised cOntrol trial of LOw glycaemic index diet
28
29 149 versus no dietary intervention to prevent recurrence of fetal macrosomia) if their first
30
31 150 baby weighed over 4.0kg (8). Recruitment to the randomised trial, with institutional
32
33 151 ethical approval and maternal written consent, commenced in January 2007 and
34
35 152 completed in January 2011. 800 secundigravida women without diabetes, who had
36
37 153 previously given birth to a macrosomic baby (> 4.0kg) and were therefore at increased
38
39 154 risk of delivering another macrosomic infant (9), were randomised to receive either low
40
41 155 glycaemic index (GI) dietary advice or usual antenatal care. Detailed methodology and
42
43 156 results of the ROLO study have previously been published (8, 18). In brief; the low GI
44
45 157 diet did not impact on birthweight, but maternal benefits were noted in terms of less
46
47 158 gestational weight gain (12.2 Kg vs. 13.7Kg, $p < 0.05$) and less glucose intolerance (21%
48
49 159 vs. 28%, $p < 0.05$). Low GI dietary advice was given at week 14 of pregnancy and the
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51 160 women in the intervention group were found to have a significantly reduced glycaemic
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53 161 index and glycaemic load following the intervention (8).
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3 162 Mothers were then followed prospectively and data collated and anonymised on 280
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5 163 women who delivered two further babies up to 2015. Weight and height were
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7 164 measured accurately at first presentation prior to 18 weeks gestation in each pregnancy
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9 165 and BMI calculated. Relevant descriptive statistics were obtained for the study
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11 166 population.

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14 167 The pregnancy outcomes in the second and third pregnancies were analysed separately
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16 168 with respect to the previous interpregnancy period, using absolute weight change. Data
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18 169 were also analysed for both interpregnancy intervals comparing outcomes for those
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20 170 who gained any weight, or those who gained more weight than the median with those
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22 171 who did not, which may be a more convenient definition for clinical practice. The
23
24 172 pregnancy outcomes analysed were CS, GDM, recurrent fetal macrosomia, gestational
25
26 173 hypertensive disease, neonatal intensive care unit (NICU) admission and stillbirth. We
27
28 174 used the Mann-Whitney-U test to evaluate differences in continuous variables between
29
30 175 the groups or over time and χ^2 tests to compare categorical variables between groups.
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32 176 We set statistical significance at $P < 0.05$ and used SPSS version 23.0 for statistical
33
34 177 analysis.

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40 41 179 **Results:**

42
43 180 Of the initial 800 women recruited to the ROLO study, 280 (35.0%) women delivered a
44
45 181 third baby between 2011 and 2015. Of these, the median maternal weight in the first
46
47 182 pregnancy was 68.8kg (IQR 62.0,78.5) and the median BMI was 24.9kg/m² (IQR
48
49 183 22.7,27.3). In total, 11.4% (n=32) of the cohort were obese in the first trimester of the
50
51 184 first pregnancy. Table 1 details the demographic data for the cohort in the first
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53 185 trimester of the first, second and third pregnancies respectively.
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3 187 Overall, 72.9% (n=204) gained weight between the first and second pregnancy within a
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5 188 median interpregnancy interval of 24 months (IQR 23,35) and the overall median
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7 189 weight change was 2.60kg (IQR -0.28,3.28). 67.5% (n=189) gained weight between the
8
9 190 second and third pregnancy within a median interpregnancy interval of 36.0 months
10
11 191 (IQR 24,48), and the overall median weight change was 1.70kg (IQR -0.68,4.58). This
12
13 192 resulted in a median weight gain from first to third pregnancy of 4.30kg (IQR 0.3,7.8).
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15 193 Overall the rate of obesity rose from 11.4% in first pregnancy to 22.1% by the beginning
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17 194 of the third pregnancy.
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23 196 There were no difference in pregnancy outcomes for the second pregnancy (gestational
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25 197 hypertensive disease, GDM, CS , recurrent fetal macrosomia \geq 4kg, NICU admission and
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27 198 stillbirth) in women who gained interpregnancy weight compared with those who did
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29 199 not and those who gained more interpregnancy weight than the median compared with
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31 200 those who did not.
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37 202 There was a statistically significant increase in birthweights \geq 4.0kg (54.0% vs. 39.6%
38
39 203 $p=0.03$) in those women who gained weight between the second and third pregnancies.
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41 204 In those women who gained more interpregnancy weight than the median (1.70kg)
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43 205 between a second and third pregnancy, there was a significant increase in the rate of
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45 206 gestational diabetes (6.5% vs. 1.4%, $p=0.03$). There were no differences in gestational
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47 207 hypertensive disease, CS, NICU admission and stillbirth (Table 2).
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53 209 To examine the effect of cumulative weight gain over both interpregnancy intervals, and
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55 210 to control for the effect of maternal age and BMI less than 18 weeks gestation in the
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57 211 index pregnancy on the above results, logistic regression models to predict a
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3 212 birthweight ≥ 4.0 kg were run. Weight gain between the first and second, second and
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5 213 third and overall between first and third pregnancies had broadly similar effects, with a
6
7 214 2-3% higher odds of a high birthweight per kilogram gain, which increased to 3-5%
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9 215 when adjusting for maternal age and BMI. Statistical significance was marginal, but
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11 216 present for weight gain in the earlier interval and between first and third pregnancies
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14 217 (Table 3).
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19 **Discussion:**

20 Main Findings

21 221 This longitudinal study found that women who delivered a macrosomic infant ≥ 4.0 kg in
22
23 222 their first pregnancy without gestational diabetes gained a median of 2.60kg between a
24
25 223 first and second pregnancy and a median of 1.70kg between a second and third
26
27 224 pregnancy resulting in a median 4.30kg weight gain from first to third pregnancy. This
28
29 225 resulted in increase in obesity rates from 11.4% in first pregnancy to 22.1% in third
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31 226 pregnancy, highlighting the central role pregnancy has in weight gain across the life
32
33 227 course. The interpregnancy weight gain between first and second pregnancies did not
34
35 228 appear to impact on pregnancy outcome, however interpregnancy weight gain between
36
37 229 second and third pregnancies was associated with an increased rate of recurrent fetal
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39 230 macrosomia ≥ 4.0 kg. For each kilogram increase in interpregnancy weight, the odds of
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41 231 giving birth to an infant of ≥ 4.0 kg increased. Additionally those with a weight gain of
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43 232 more than the median (≥ 1.70 kg) between second and third pregnancies was associated
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45 233 with increased incidence of GDM.
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53 236 Interpretation

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3 237 One possible explanation for the lack of associations in second pregnancy may arise due
4
5 238 to the Hawthorne effect of trial participation in both the intervention and control arms.
6
7 239 Another more likely hypothesis could be that weight gain may be cumulative. The
8
9 240 median weights at booking visit in the first, second and third pregnancies were 68.8kg,
10
11 241 71.3kg and 73.1kg respectively. Is weight gain cumulative so that it is only over a
12
13 242 certain level that effects on birthweight and GDM are noted? There are a paucity of
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15 243 longitudinal studies on postpartum weight changes, because these studies are
16
17 244 challenging to conduct (19). This longitudinal study adds to the evidence that
18
19 245 interpregnancy weight gain causes GDM and macrosomic babies. Many studies relating
20
21 246 to interpregnancy weight changes are cross sectional and retrospective in nature.
22
23 247 Furthermore, many of these studies use self-reported maternal weight, which can be
24
25 248 unreliable and leads to BMI miscategorization (20). High postpartum weight retention
26
27 249 is an important contributor to long-term maternal obesity, which has detrimental
28
29 250 effects on long-term maternal health (21).

251 Strengths and Limitations in relation to other studies

252 Bogaerts et al. found that in a population of 7,897 women in Belgium, there was an
253 increase rate of GDM (aOR 2.25, 95% CI 1.33-3.78; P=0.002) in those who had
254 interpregnancy weight retention of 2 or more BMI units. However, this study used self-
255 reported prepregnancy weight and no prior information on hypertension and GDM
256 available (15). A large Swedish retrospective epidemiological study of 151,025 women
257 who had their first two consecutive births between 1992 and 2001 found that those
258 who gained 3 or more BMI units between pregnancies compared with those women
259 whose BMI changed between -1.0 and 0.9 units had an adjusted odds ratio of GDM of
260 2.09 (1.68-2.61) (13). Wallace et al. (22) conducted a retrospective cohort study of
261 12,740 women in Aberdeen, Scotland who delivered their first and second children

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3 262 between 1986 and 2007. Weight gain of greater than three BMI units was associated
4
5 263 with an increase in large for gestational age infants. Jain et al. (23) analysed a
6
7 264 population based historical cohort of 10,444 obese women in Missouri who delivered
8
9 265 their first infant between 1998-2005. Interpregnancy weight gain was associated with
10
11 266 an increased risk of a LGA infant (aOR 1.37; 95% CI, 1.21-1.54).
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15
16 268 Our study is a prospective longitudinal illustrating that interpregnancy weight gain is
17
18 269 associated with recurrent fetal macrosomia in a unique population of women who
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20 270 delivered a macrosomic baby ≥ 4.0 kg in their index pregnancy, and that interpregnancy
21
22 271 weight gain of greater than the median is associated with an increased rate of GDM.
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28 273 The interpregnancy interval is an important time for diet and lifestyle intervention in
29
30 274 women who have delivered a macrosomic infant in their first pregnancy in the
31
32 275 prevention of recurrent macrosomia and the development of GDM.
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35 276 Strengths and Limitations

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37 277 This longitudinal study has strengths. Maternal weight and height were measured at
38
39 278 booking visit in each pregnancy <18 weeks gestation and BMI calculated accurately,
40
41 279 rather than relying on maternal self-reporting. Furthermore, this cohort of women was
42
43 280 uniform in that they delivered a first baby weight >4.0 kg and they did not have GDM or
44
45 281 hypertensive disorders in the first pregnancy. Data was prospectively collected by an
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47 282 investigator and accurately recorded into an anonymised computerised database.
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53 284 A potential limitation of this study is that we do not have data on women who attended
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55 285 elsewhere for subsequent antenatal care. Another potential limitation is that the
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57 286 interpregnancy interval varied between subjects within this study. Finally, this study
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3 287 applies to women who delivered a first baby >4kg, which applies to approximately 15%
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5 288 of our overall primiparous population.
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10 **290 Conclusions:**

11 291 This longitudinal study demonstrates that within this cohort maternal interpregnancy
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13 292 weight change between a second and third pregnancy is associated with an increase in
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15 293 birthweight ≥ 4.0 kg. Additionally a gain of more weight than the median (1.70kg) is
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17 294 associated with a higher rate of gestational diabetes. It is important to identify ways for
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19 295 women to maintain a normal weight and BMI throughout her life, particularly between
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21 296 pregnancies. Obstetricians should consider postnatal advice on interval pregnancy
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23 297 weight gain in order to reduce rates of macrosomia and gestational diabetes in future
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25 298 pregnancy in at risk women.
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32 **300 Acknowledgments**

33 301 Nil of note
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40 **303 Contribution to Authorship**

41 304 FMMcA conceived and designed the study. JW contributed to the study design and
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43 305 manuscript preparation. DAC performed the analysis and wrote the manuscript. RS
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45 306 performed analysis. All of the authors reviewed and revised the final version of the
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47 307 manuscript. FMMcA is the guarantor.
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52 **309 Ethical Approval**

53 310 Not applicable
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314 commercial or not-for-profit sectors.

315 **Competing Interests**

316 We have read and understood BMJ policy on declaration of interests and declare that
317 we have no competing interests.

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3 410 **Table 1:** Demographics of the cohort at in the first trimester of the first, second and
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5 411 third pregnancies respectively (n=280)
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	Pregnancy 1	Pregnancy 2	Pregnancy 3
Maternal Age (years)	29.0 (23.9,32.0)	31.8 (29.0,34.5)	34.8 (31.6,37.4)
Maternal Weight (kg)	68.8 (62.0,78.5)	71.4 (63.6,81.1)	73.1 (65.1,84.5)
BMI (kg/m ²)	24.9 (22.7,27.3)	25.7 (23.4,28.8)	26.0 (23.6,29.3)
Birthweight (kg)	4.2 (4.07,4.33)	4.1 (3.74,4.35)	4.0 (3.68,4.36)
Gestational Age (Days)	288 (282,292)	283 (277,288)	280 (273,287)
Obese (≥ 30kg/m ²)	11.4% (n=32)	20.0% (n=56)	22.1% (n=62)

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All values are median with interquartile ranges (25th and 75th) in hypotheses, except for obesity (demonstrated in absolute numbers and percentages). Maternal weight and body mass index (BMI) were calculated at ≤ 18 weeks gestation.

441 **Table 2:**

442 Pregnancy outcomes for the third pregnancy based on those who gained inter-
 443 pregnancy weight compared with those who did not and those who gained more inter-
 444 pregnancy weight than the median compared with those who did not.
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	Gained interpregnancy weight n=189	Did not gain interpregnancy weight n=91	P value
CS overall	41 (21.7%)	21 (23.1%)	NS
GDM	9 (4.8%)	2 (2.2%)	NS
BW ≥4kg	102 (54.0%)	36 (39.6%)	P=0.03
Hypertensive Disease	5 (2.6%)	2 (2.2%)	NS
NICU	4 (2.1%)	2 (2.2%)	NS
Stillbirth	1 (0.5%)	1 (1.1%)	NS
	Gained > 1.70kg inter-pregnancy weight (n=139)	Gained ≤ 1.70kg inter-pregnancy weight (n=141)	P value
CS overall	28 (20.1%)	34 (24.1%)	NS
GDM	9 (6.5%)	2 (1.4%)	0.03
BW ≥4kg	75 (54.0%)	63 (44.7%)	NS
Hypertensive Disease	4 (2.9%)	3 (2.1%)	NS
NICU	4 (2.9%)	2 (1.4%)	NS
Stillbirth	0 (0%)	2 (1.4%)	NS

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3 458 **Table 3. Effect of weight gain on odds of birthweight ≥ 4 kg unadjusted and**
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5 459 **adjusted for maternal age and BMI calculated at less than 18 weeks gestation in**
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8 460 **the index pregnancy**

	Unadjusted			Adjusted for maternal age and BMI		
	OR	95% CI	p-value	OR	95% CI	p-value
Weight gain from pregnancy 1 to 2	1.03	0.99, 1.07	0.169	1.05	1.01, 1.10	0.024
Weight gain from pregnancy 2 to 3	1.02	0.98, 1.06	0.243	1.03	0.99, 1.08	0.107
Weight gain from pregnancy 1 to 3	1.03	1.00, 1.06	0.093	1.04	1.01, 1.08	0.013

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(a) 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	
		(b) Report category boundaries when continuous variables were categorized	8-9
		(c) 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—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
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	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.