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1 **Is dietary macronutrient composition during pregnancy associated with offspring birthweight?**
2 **An observational study.**

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12 **Short version of the title:-**

13 Macronutrients in pregnancy and birthweight

14 **Keywords:** Macronutrients: Protein: Carbohydrate: Fat: Birthweight: Birth Centile: Pregnancy: Diet

15 **Abstract**

16 There is lack of evidence on the differential impact of maternal macronutrient consumption:
17 carbohydrates (CHO), fats and protein on birthweight. We investigated the association between
18 maternal dietary macronutrient intakes and their sub-components such as saccharides and fatty acids
19 and birthweight. This analyses included 1,196 women with singleton pregnancies who were part of
20 the CARE (CAffeine and REproductive health) study in Leeds, UK between 2003 and 2006. Women
21 were interviewed in each trimester. Dietary information was collected twice using a 24 hour dietary
22 recall around 8-12 weeks and 13-27 weeks of gestation. Multiple linear regression models adjusted
23 for alcohol and smoking in trimester 1, showed that each additional 10g/day CHO consumption was
24 associated with an increase of 4g (95% CI 1g to 7g; P=0.003) in birthweight. Conversely, an
25 additional 10g/day fat intake was associated with a lower birthweight of 8g (95% CI 0g to 16g;
26 P=0.04) when we accounted for energy contributing macronutrients in each model, and maternal
27 height, weight, parity, ethnicity, gestational age at delivery and sex of the baby. There was no
28 evidence of an association between protein intake and birthweight. Maternal diet in trimester 2
29 suggested that higher intakes of glucose (10g/day) and lactose (1g/day) were both associated with
30 higher birthweight of 52g (95% CI 4g to 100g; P=0.03) and 5g (95% CI 2g to 7g; P<0.001)
31 respectively. These results show that dietary macronutrient composition during pregnancy is
32 associated with birthweight outcomes. An appropriately balanced intake of dietary CHO and fat
33 during pregnancy could support optimum birthweight.

34 **Introduction**

35 There is increasing evidence elucidating the role of diet during pregnancy on the growing fetus^(1,2)
36 and subsequently, in the offspring metabolic health in adulthood⁽³⁾. Maternal diet in pregnancy is
37 suggested to contribute in the alteration of fetal outcomes⁽⁴⁾, including birthweight⁽⁵⁾, preterm
38 delivery⁽⁶⁾, low birthweight infants(<2500 g)⁽⁷⁾ and small for gestational age (SGA) births⁽⁸⁾. Meta-
39 analyses⁽⁹⁻¹¹⁾ have examined the role of micronutrients in the maternal diet, including vitamin C⁽⁹⁾,
40 iron⁽¹²⁾ and folate^(13,14) in the development of adverse birth outcomes. Amongst dietary
41 macronutrients, evidence has been restricted to exploring the use of protein-energy supplementation
42 in pregnancy for improving offspring birthweight amongst low-income countries ⁽¹⁵⁻¹⁷⁾. However,
43 amongst high-income countries the prevalence of maternal and infant protein-energy under nutrition
44 is low due to sufficient macronutrient consumption during pregnancy.

45 Although during pregnancy, in well-nourished women, the recommended dietary allowances of
46 protein, CHO and fat are largely met^(5,18,19), the influence of the source of energy intake:
47 macronutrients during pregnancy on birth outcomes including birthweight remains unclear. The
48 specific source of energy (dietary protein, fat and CHO) consumed may also have a differential impact
49 on birth outcomes^(2,20-23). Evidence remains inadequate and conflicting from previous observational
50 studies^(2,20-23) that investigated the potential association between energy composition of food
51 consumed during pregnancy and birthweight. Studies have also explored the effect of
52 macronutrient/energy-dense dietary patterns in pregnancy^(6,8,24) on birth outcomes. These “western”
53 or “junk” dietary patterns in the studies, included energy-dense food items, for instance, sweet snacks,
54 desserts, bakery products and processed foods, were suggested to have negative implications on the
55 quality of birth outcome. Amongst macronutrient sub-components, results remain conflicting in
56 studies which explored the effect of fatty acids, including long chained polyunsaturated fatty acids
57 (LC-PUFA) on birth outcomes⁽²⁵⁻²⁹⁾. In addition, no studies, to our knowledge, have explored the
58 effect of dietary saccharides (mono-saccharides, di-sachcharides, dietary fibres) during pregnancy on
59 birth outcomes including birth weight or “customised” birthweight centiles– computer generated
60 antenatal growth charts for individual pregnancies that allow variation in the maternal characteristics,
61 taking birthweights from previous pregnancies into consideration⁽³⁰⁾. Customized birthweight centiles
62 are used in this study as they set individual standards for fetal growth that allow better differentiation
63 between optimal and abnormal growth *in utero*⁽³¹⁾. This method adjusts for a number of variables
64 including maternal height, weight, parity, sex of the baby, ethnicity, and across all gestational ages.
65 Using this external adjustment is particularly useful for some categories, such as minor ethnic groups
66 which require large numbers from which to derive precise model coefficients.

67 We aimed to investigate the association between intakes of specific dietary macronutrients
68 (carbohydrate [CHO], fat and protein, and their sub-components such as saccharides and fatty acids)
69 during pregnancy in a well-nourished population and birth outcomes: birthweight, birth centile, small-
70 for-gestational-age (SGA) infants and large-for-gestational-age (LGA) infants.

71 **Methods**

72 *Study design and population*

73 The CARE (CAffeine and REproductive health) study prospectively recruited low risk pregnant
74 women from two large teaching hospital maternity units in Leeds, UK from September 2003 to June
75 2006^(32,33). This study was designed to explore diet with a focus on maternal caffeine intake in relation
76 to fetal growth. The inclusion criteria were pregnant women aged between 18-45 years and carrying
77 singleton pregnancies accurately dated by ultrasound. Women with concurrent medical disorders,
78 psychiatric illness, HIV infection, or hepatitis B infection were excluded. Participants completed a
79 consent form indicating their willingness to participate in the study. They were interviewed by
80 research midwives during their booking appointment in the antenatal clinic. Questionnaires for
81 trimester 1 (8-12 weeks of gestation) and 3 (from 28 weeks of gestation) were interviewer-
82 administered, and the questionnaire for trimester 2 (13-27 weeks of gestation) was self-
83 administered⁽³⁴⁾. Their demographic details (age, parity, maternal height, weight, socioeconomic
84 status, and gestational age) were self-reported by means of an interviewer-administered questionnaire.
85 Ethical approval was obtained from Leeds West Local Research Ethics Committee (LREC) Ref 7260.

86 *Dietary data*

87 Out of 1,289 participants in the original study, dietary information was available for 1,196 women in
88 the first trimester and 575 women in the second trimester. The dietary intake was collected at home
89 twice in a 24 hour dietary recall⁽³³⁻³⁵⁾ administered by a trained research midwife; once during
90 trimester 1 (8-12 weeks of gestation) and again during trimester 2 (13-27 weeks of gestation). Trained

91 personnel entered the 24 hour dietary recalls by using nutrient analysis package– ‘DANTE’ (Diet and
92 Nutrition Tool for Evaluation). The nutrient analysis computed by this software package was based
93 on the standard UK food composition tables by the Royal Society of Chemistry⁽³⁶⁾.

94 Primary exposures were macronutrients: protein, fat and CHO and their sub-components including
95 fatty acids and saccharides. The carbohydrate sub-components included mono-saccharides (glucose,
96 fructose), di-saccharides (sucrose, maltose and lactose), and complex sugars (starch, soluble fibre).
97 The dietary fat sub-components included saturated fatty acids (SFA), monounsaturated fatty acids
98 (MUFA) and polyunsaturated fatty acids (PUFA). However, total protein was considered for sub-
99 component analyses as the data for animal and vegetable protein, and amino acid contents were
100 unavailable.

101 *Other data*

102 Questionnaires administered by trained midwives included information on confounders such as
103 smoking habits, alcohol consumption, and other information such as episodes of nausea. The multiple
104 linear regression models were adjusted for smoking status⁽³⁷⁾ and alcohol intake⁽³⁸⁾ due to their
105 adverse effects on infant and prenatal nutrition. Smoking status for trimesters 1 and 2 listed the
106 frequency of smoking and was categorised into three: ‘non-smoker’, ‘current smoker’ and ‘occasional
107 smoker – previously smoked everyday but do not smoke now’. The participant’s average alcohol
108 consumption (unit/day) (continuous variable) was measured during trimester one and two. Physical
109 activity was self-reported and was recorded into 3 categories: ‘no weekly physical activity’,
110 ‘light/moderate physical activity’ and ‘vigorous physical activity (up to <20 minutes 1-2/week).’
111 Three questionnaires were administered to determine lifestyle behaviours with a focus on caffeine
112 intake in pregnancy from four weeks before pregnancy until recruitment into the study—at 8-12 weeks
113 of pregnancy; the second covered the period 13-27 weeks; and the third included the period from 28-
114 40 weeks of pregnancy⁽³⁴⁾.

115 *Outcome: Birthweight, Birth centile, SGA and LGA births*

116 The information on antenatal pregnancy complications and delivery details (gestational age at
117 delivery, birth weight, and sex of the baby) were obtained from the electronic maternity databases.
118 The primary outcomes in our study were birthweight and birth centile. Birthweight was recorded in
119 grams (g) in the electronic maternity database. The customized birth centiles were computed by using
120 customized centile charts^(31,39) which accounted for the following factors: maternal weight, height,
121 ethnicity, parity, gestational age at delivery and sex of the baby. Other outcomes additionally explored
122 were small-for-gestational-age (SGA) births and large-for-gestational-age (LGA) births (refer
123 supplementary material). These particular definitions were chosen as they are clinically relevant
124 amongst at-risk infant groups. On the customized centile chart, SGA birth was defined as birth weight
125 <10th centile^(30,31,40), and LGA birth was defined as birthweight >90th centile^(30,41). Both of these
126 outcomes accounted for the following variables: maternal height, weight, ethnicity, parity, gestational
127 age at delivery and sex of the baby⁽³¹⁾.

128 *Statistical analysis*

129 We calculated the mean and standard deviation (SD), and absolute frequency distributions with
130 percentages [n (%)] for demographic characteristics of interest (Table 1 in results). To examine
131 associations between macronutrients or their sub-components, and birthweight/centile; multiple
132 linear regression models (model 1 and 2) were designed for first and second trimesters separately.
133 Each macronutrient and its sub-component model were adjusted for other energy contributing
134 macronutrients and sub-components within the model. In order to help with the interpretation of birth
135 centiles, we have additionally presented these results in actual birthweight in grams. In the centile
136 model (model 1) we made use of customised centile charts^(31,39) which automatically accounted for

137 these variables: maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the
138 baby. The birthweight model (model 1) was adjusted for maternal height, weight, parity, ethnicity,
139 gestational age at delivery and sex of the baby. All regression models (birthweight/centile models)
140 under model 2 were additionally adjusted for participants' alcohol consumption and smoking habits
141 in pregnancy.

142 We carried out logistic regression analyses to explore the odds ratio (OR) for delivering an SGA/LGA
143 infant. In the logistic regression models, SGA and LGA births were binary outcomes. Model 2
144 additionally adjusted for alcohol intake and smoking habits.

145 The results of the macronutrient consumption (CHO, fat and protein) were presented for 10g/day
146 increments, and sub-components of dietary fat and CHO were presented for 1g/day increments.
147 However, couple of sub-components consumed in higher amounts: starch and glucose intakes were
148 presented for 10g/day increments. The statistical significance level for the results was set at 5%. All
149 analyses were performed using Stata SE, version 13.1 (StataCorp 1985-2013, TX USA).

150 **Results**

151 *Baseline characteristics*

152 The CARE study analyses included 1196 women in the first trimester, amongst which trimester 2
153 included 575 women (45% lost to follow-up). The descriptive characteristics of 1196 participants in
154 our analyses are similar to the remaining non-participants in the original cohort.

155 The mean age of the women in this cohort was 30 (SD 5) years, with (42%, n=540) being primiparous
156 (Table 1). A majority of the cohort were of European origin (93%, n=1202). The mean body mass
157 index (BMI) (kg/m²) of the participants measured at baseline was 25 (SD 5). A majority of women
158 (98%, n=1171) were employed; one third (39%, n= 472) of the participants completed university
159 degree as the highest level of education. Approximately half of the cohort (52%, n=585) were non-
160 smokers during pregnancy, and approximately 68% (n=753) and 78% (n=610) did light/moderate
161 physical activity in trimester 1 and 2 respectively. Amongst the neonates, the mean birthweight was
162 3434 g (SD 559), and the mean gestational age at delivery was 40 weeks (SD 2). Around 4%, (n=51)
163 infants were termed low birthweight (<2500 g) and preterm births respectively, and approximately
164 14% (n=165) were large for gestational age (>90th centile) infants.

165 Mean total energy intake per day of the participants in trimester 1 and 2 was 2120 kcal (SD 692) and
166 2279 kcal (SD 634) respectively (Table 2). During trimester 1, the mean total carbohydrate, protein
167 and fat intakes per day were 274g (SD 99), 77g (SD 29) and 86g (SD 39) respectively. However,
168 during trimester 2 the mean total carbohydrate, protein and fat intakes per day slightly increased to
169 300g (SD 92), 81g (SD 28) and 91g (SD 36) respectively. There was a slight increase in mean added
170 sugar intake per day from 127g (SD 73) in trimester 1 to 149g (SD 69) in trimester 2.

171 *Relationship between macronutrients, and birth centile/birthweight*

172 We observed associations between first trimester macronutrient intake and both birth centile and
173 birthweight (Table 3). In the first trimester, there was a positive association between CHO
174 consumption and birth centile/birthweight. The fully adjusted models (model 2) indicated that a
175 higher intake of CHO (10g/day increment) was associated with a higher birth centile (0.2; 95% CI
176 0.1 to 0.4; P=0.002) and a higher birthweight (4g; 95% CI 1g to 7g; P=0.003). Conversely, a higher
177 total fat intake (10 g/day increment) at this stage of pregnancy was negatively associated with birth
178 centile (-0.7; 95% CI -1.2 to -0.1; P=0.008) on the customized centile chart. However, on further
179 adjusting the model for alcohol intake and smoking habits (model 2), higher fat intake (10g/day
180 increment) was not associated with birth centile (-0.5; 95% CI -1.0 to 0.0; P=0.06) in spite of narrow
181 confidence intervals. When we explored its relation with birthweight, fat consumption (10g/day

182 increment) was negatively associated with birthweight (-8g; 95% CI -16g to -0.3; P=0.04) in the fully
183 adjusted model (model 2). Amongst other macronutrients, protein intake was not associated with birth
184 centile or birthweight after adjusting for smoking status and alcohol intake, but it had wide confidence
185 intervals.

186 The odds of delivering a SGA infant were positively associated with a high fat consumption (10g/day
187 increment), unadjusted OR 1.05 (95% CI 1.00 to 1.10; P=0.03). However, after adjusting the model
188 (model 2) the odds of delivering a SGA infant (adjusted OR 1.03, 95% CI 0.98 to 1.09; P=0.14) were
189 not associated with a high fat intake (10g/day increment). Our analyses showed no evidence of an
190 association between macronutrient intake, and the risk of giving birth to LGA infants.

191 *Relationship between macronutrient sub-components, and birth centile/birthweight*

192 In trimester 1 (model 2) (Table 4 and 5), among the complex CHO sub-components, higher starch
193 intake (10g/day increment) was positively associated with birth centile (0.3; 95% CI 0.0 to 0.7;
194 P=0.05) but not with birthweight (5g; 95% CI -0.6g to 10g; P=0.08). Amongst saccharides, higher
195 lactose intake (1g/day increment) was associated with a higher birth centile (0.1; 95% CI 0.0 to 0.2;
196 P=0.03) and not with higher birthweight (2g; 95% CI -0.1g to 4g; P=0.06). In the second trimester
197 (model 2), higher glucose (10g/day increment) consumption was positively associated with a higher
198 birthweight (52g; 95% CI 4g to 100g; P=0.03). Lactose intake (1 g/day increment) was positively
199 associated with a higher birth centile (0.2; 95% CI 0.0 to 0.4; P=0.01) and birthweight (5g; 95% CI
200 2g to 7g; P<0.001). Amongst fat sub-components in the first trimester (model 2), a higher PUFA
201 intake (1 g/day increment) was negatively associated with birthweight (-4g; 95% CI -8g to 0.1g;
202 P=0.05) but not with birth centile.

203 **Discussion**

204 This analysis has shown that dietary macronutrient composition and its sub-components could be
205 associated with birth outcomes. To our knowledge, this is the first observational study to explore
206 relationships between dietary macronutrient sub-components in pregnancy and birth outcomes,
207 including birthweight and birth centile. These associations were mostly observed in the first trimester.
208 A possible explanation for this might be that placentation is established and the fetal growth
209 programmed in the first trimester⁽⁴²⁻⁴⁴⁾. Up to 11 weeks of gestation, the embryo develops in a stable
210 nutritional environment. This may explain why the associations seem to weaken or disappear in the
211 second trimester. Early pregnancy reflects infant organ developmental stages, where the overall
212 energy intake may be less important than the quality of diet. So it might be that the diets high in
213 carbohydrate and fat might just reflect poorer quality diets. Additionally, 45% women in trimester 2
214 (n=575) were lost to follow-up as fewer women responded to the request for a second 24 hour dietary
215 recall, since communication at this point with the women was by post rather than a study visit. Despite
216 this, the size of the estimates and confidence intervals were similar between trimesters 1 and 2. In
217 trimester 2, glucose and lactose were associated with increasing birthweight, this might be attributed
218 to the increased availability of free maternal glucose ready to be utilised as a primary source of
219 energy to meet fetal demands required for organ growth during this period⁽⁴⁵⁻⁴⁹⁾.

220 Higher intakes of total CHO during the first trimester was associated with higher birthweight and an
221 increase in birth centile. This finding in our study is in agreement with literature. A study reported
222 similar associations between low contribution of CHO to total energy during pregnancy and thinness
223 at birth⁽⁵⁰⁾. Another study reported that high percentage (%) of energy from CHO in the diet could be
224 associated with high offspring birthweight⁽²⁰⁾.

225 Interestingly, amongst mono-saccharides, we observed that in trimester 2 additional consumption of
226 dietary glucose was associated with heavier birthweight. A similar association was observed in a
227 study⁽⁵¹⁾ amongst pregnant women with type 1 diabetes mellitus. They reported an association

228 between increased maternal glucose levels amongst diabetic pregnant women and LGA offspring. In
229 our study, we observed that high intake of starch was associated with increased odds of delivering
230 LGA infants. According to a study⁽⁵²⁾ which compared normal versus pregnant women with
231 gestational diabetes mellitus (GDM), participants who consumed a CHO-rich diet were likely to have
232 high blood glucose levels, and an increased risk of delivering LGA offspring. Randomised controlled
233 trials (RCTs) have reported possible effects of a high CHO intake vs a low CHO intake amongst
234 women with GDM and increased risk of macrosomia^(53,54). A possible explanation for these results
235 could be that high CHO intakes could lower maternal insulin sensitivity, making higher levels of free
236 glucose available for placental circulation, subsequently activating fetal glycogenesis⁽⁵⁵⁾. Pedersen⁽⁵⁶⁾
237 attributed the role of maternal hyperglycaemia to this birth outcome which reportedly caused increase
238 in fetal insulin levels and led to fetal hyperglycaemia.

239 A high lactose intake might be attributed to high milk and dairy product intake by the women. The
240 Danish National Birth Cohort (DNBC) study⁽⁵⁷⁾ explored the association between maternal milk and
241 dairy products consumption with birthweight among 50,117 mother-infant pairs and found that higher
242 dairy consumption promoted higher birthweight. Another study came to a similar conclusion
243 suggesting a decreased risk of SGA⁽⁵⁸⁾. Additional lactose consumption (in the form of dairy products)
244 leading to a higher birthweight could also be related to higher iodine levels found in milk and dairy
245 sources in the UK^(59,60). Iodine levels could influence birthweight^(61,62) through a role in controlling
246 metabolic rate and development of body structures⁽⁶³⁾. The lactose association observed may also be
247 indirectly attributed to the level of placental calcium transferred to the fetus⁽⁶⁴⁾, increasing bone
248 calcification during skeletal development, and overall birthweight⁽⁶⁵⁾.

249 Unlike previous studies^(1,20,22) which reported an association with protein, our study did not find any
250 evidence of an association between protein and birthweight/centile, and LGA/SGA. Although we
251 found a positive association between protein intake and birthweight under model 1 during the first
252 trimester, no association was observed after adjusting for alcohol and smoking habits, but the
253 confidence intervals were wide. Our study participants were adequately nourished, hence this might
254 be the reason we did not notice any effects. A study⁽²⁰⁾ suggested that the energy contribution from
255 protein in the diet is associated with increased birthweight and placental weight. They considered the
256 type of protein such as animal/ vegetable protein but their results were of low statistical power, and
257 did not adjust for mother's alcohol consumption. However, in support of our finding, a study⁽²¹⁾ in
258 Asia found no evidence of an association between protein intake in pregnancy and offspring weight.

259 Our analyses suggest that total fat intake and its sub-components such as PUFA were associated with
260 lower birthweight and birth centile. However, our result conflicts with a South-Asian study⁽²⁹⁾ which
261 reported a positive association between dietary fat intake in pregnancy and increased birthweight.
262 Contradicting results from other studies^(20,21,23) reported no association between them; an
263 observational study⁽²⁰⁾ explored the relation between energy percentage (%) from total dietary fat and
264 birthweight, and suggested no evidence of an association after adjusting for other energy contributing
265 nutrients. Our analysis adjusted for alcohol, as it is associated with increased risk of lower
266 birthweight⁽⁶⁶⁻⁶⁸⁾ and fat-rich foods are often consumed with alcohol. Conversely, the study by Moore
267 et al.⁽²⁰⁾ did not adjust for alcohol consumption during pregnancy. However, amongst randomised
268 controlled trials (RCTs) on animal models, there is no evidence suggesting an association between a
269 high fat diet in pregnancy and changes in birthweight. Previous studies^(69,70) based on animal models
270 explored the effect of a high-fat diet in pregnancy on the development of offspring metabolic
271 disorders including hyperinsulinemia, blood pressure, and changes in serum leptin levels. An RCT⁽⁷⁰⁾
272 amongst pups, explored the effects of high-fat diet on offspring and suggested that maternal adiposity
273 and not dietary fat per se, was associated with increased offspring weight, and metabolic disorders
274 such as hyperinsulinemia which could further persist through adulthood. During the first trimester,

275 higher PUFA intake was associated with lower birthweight of infants. Three studies^(1,71,72) discussed
276 the “anti-obesogenic” property of PUFA during pregnancy which reportedly prevented extra fat mass
277 deposits in the fetus. Ethical issues make studies of this nature challenging in humans such as acidosis
278 and ketosis in response to low CHO-high fat diets, alterations in cholesterol and free fatty acid
279 metabolism in pregnancy. Further studies are needed to validate our result.

280 The CARE cohort was a well-nourished group; the participants’ average dietary macronutrient
281 intake/day during trimesters 1 and 2 largely met the estimated average requirements of energy (EAR)
282 recommended during pregnancy in the Committee on Medical Aspects of Food Policy (COMA)
283 report by the Department of Health, UK⁽⁷³⁾, and the intakes were similar to those found in other studies
284 involving pregnant women^(20,50,74). Our previous publication of results made use of the specially
285 designed questionnaire to capture caffeine intake, which demonstrated that maternal caffeine intake
286 was inversely associated with birthweight⁽³²⁾. We chose to use the 24 hour dietary recall which was
287 also collected, to measure the whole dietary intake of our participants in detail on a specific day.
288 Alternative approaches such as a food frequency questionnaire were not available for the whole diet
289 in this sample and require participants to subjectively average out a potentially varied diet over a
290 longer period of time. A number of validation studies⁽⁷⁵⁻⁷⁸⁾ have shown that 24 hour dietary recall is
291 a well-established method which correlates well with true usual intake, and are adequate and suitable
292 to large populations rather than individuals. Though this method is less suited to episodically
293 consumed foods, it has been shown to work well for commonly consumed foods and nutrients,
294 particularly macronutrients, present in most food items that are the subject of this current
295 research^(75,76).

296 The estimates of change in birthweight by macronutrient intake are small because we have chosen a
297 small macronutrient increment/day (10g is 1/10th of a standard deviation). Using a larger increment
298 for all macronutrients, such as 100g/day, equivalent to 1 SD, would be associated with an increase in
299 birthweight of around 40 g. Such a change in birthweight might have a modest impact on preterm
300 infants or those already having low birthweight, but need not be of great concern to infants with a
301 better starting point. Furthermore, it is essential to consider that small effects on a population level
302 could be important⁽⁷⁹⁾, through shifting the whole distribution of birthweights, higher or lower
303 depending on the type of macronutrient consumed.

304 *Strengths and weaknesses*

305 Our study had some strengths to be considered. This is a large cohort comprising of 1196 pregnant
306 women, from whom dietary data was collected on two occasions during their pregnancy i.e. in
307 trimester 1 and 2. Diet was assessed using an interviewer led 24h recall; allowing detail of food types
308 and amounts to be recorded. The regression models were carefully adjusted for potential confounders:
309 alcohol intake, smoking habits, maternal height, weight, parity, ethnicity and sex of the baby. We had
310 detailed dietary information, including values of macronutrient sub-components including
311 saccharides and fatty acids.

312 There are few limitations to any study which explores nutritional intake. For sub-components, the
313 nutrient values computed in the software using the food composition database⁽³⁶⁾ may not be accurate
314 or complete. A couple of studies^(80,81) reported issues of missing values for nutrients in databases,
315 including McCance and Widdowson’s food composition database⁽⁸¹⁾. Energy intake estimations from
316 food items and beverages of the participants were based on memory recall and are subjected to
317 mis/under-reporting and bias⁽⁸²⁻⁸⁴⁾. Some studies suggest use of a combination of dietary assessments
318 to cross check the dietary information for correct quantity estimation, measurement uniformity and
319 frequency of consumption^(85,86), however, this is more common where food frequency questionnaires
320 are the main dietary measure. Dietary data in our study was recorded only for trimesters 1 and 2. Data

321 was unavailable for type of protein (animal/vegetable) and amino acid content, which led us to include
322 total protein in the regression models.

323 ***Conclusion***

324 These results show that dietary macronutrient composition during pregnancy is associated with
325 birthweight outcomes. Carbohydrate and its sub-components such as lactose, glucose and starch were
326 associated with increasing offspring birthweight. Conversely dietary fat and its sub-component–
327 PUFA were associated with decreasing birthweight. Offspring birthweight could be supported
328 through carefully balanced fat and carbohydrate intakes during pregnancy.

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340 Obtained from the local ethics committee (Leeds West Local Research Ethics Committee),
341 Directorate of Research and Development, Leeds, LREC Ref 7260. Participants gave signed informed
342 consent before enrolment into the study.

343 ***Conflict of Interest***

344 None.

345 ***Authorship***

346 S.S. Sharma undertook the project, formulated the research question, performed the statistical
347 analyses of the data, and wrote all the drafts of the manuscript. D.C. Greenwood helped formulate the
348 research question and designing the study, supervised the analyses and commented on all the drafts.
349 N.A.B. Simpson helped formulate the research question and study design, and commented on all the
350 drafts. J.E. Cade was the PI on the original CARE Study, formulated the study design and the research
351 question, supervised the analyses and commented on all the drafts.

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570 **Table 1: Characteristics of the participants and their infants in the CARE study**

Characteristic¹	
Maternal characteristics	n=1196
Age (years), mean (SD)	30 (5)
Pre-pregnancy weight (kg), mean (SD)	67 (14)
Body mass index (BMI) (kg/m ²), mean (SD)	25 (5)
Primiparous [n (%)]	497 (42)
Ethnicity, European origin [n (%)]	1115 (93)
Dietary supplement users [n (%)]	988 (83)
Smoking status [n (%)]	
Trimester 1 (n=1118)	
Non-smoker	585 (52)
Occasional smoker	342 (31)
Current smoker	191 (17)
Trimester 2 (n=821)	
Non-smoker	470 (57)
Occasional smoker	252 (31)
Current smoker	99 (12)
Alcohol consumption (unit/day), mean (SD)	
First trimester	0.5 (0.9)
Second trimester	0.2 (0.4)
Physical activity [n (%)]	
Trimester 1 (n=1102)	
No weekly physical activity	170 (15)
Light/moderate physical activity	753 (68)
Vigorous physical activity (up to <20 minutes 1-2/week)	109 (10)
Trimester 2 (n=781)	
No weekly physical activity	59 (8)
Light/moderate physical activity	610 (78)
Vigorous physical activity (up to <20 minutes 1-2/week)	73 (9)
Infant characteristics	n=1196
Birthweight (g), mean (SD)	3434 (559)
Preterm births [n (%)]	51 (4)
Low birthweight (<2500 g) [n (%)]	51 (4)
Birthweight (>4000 g) [n (%)]	165 (14)
Gestational age at delivery (weeks), mean (SD)	40 (2)
Pregnancy outcomes	
Live births [n (%)]	1189 (99)
Still births [n (%)]	3 (0.3)
Fetal deaths [n (%)]	4 (0.3)
Infants by sex [n (%)]	
Male	602 (50)
Female	594 (50)

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¹ Results of the descriptive statistics have been restricted to participants included in the later analyses

572 **Table 2: Mean dietary macronutrient intakes of the CARE study participants in trimesters 1 and 2**

Mean macronutrient intake (per/day)	Trimester 1 (n= 1196)	Trimester 2 (n= 575)
	Mean (SD)	Mean (SD)
Total energy (kcal/day)	2120 (692)	2279 (634)
Total carbohydrate (g/day)	274 (99)	300 (92)
Total protein (g/day)	77 (29)	81 (28)
Total fat (g/day)	86 (39)	91 (36)
Mono-unsaturated fatty acids (MUFA) (g/day)	26 (15)	27 (12)
Poly-unsaturated fatty acids (PUFA) (g/day)	14 (10)	14 (9)
Saturated fatty acids (SFA) (g/day)	31 (16)	34 (17)
Cholesterol (mg/day)	243 (169)	239 (152)
Added sugar (g/day)	127 (73)	149 (69)
Starch (g/day)	141 (55)	146 (52)
Mono-saccharides (g/day)		
Glucose	25 (19)	27 (17)
Fructose	27 (28)	30 (24)
Di-saccharides (g/day)		
Sucrose	54 (36)	64 (36)
Maltose	2 (7)	2 (3)
Lactose	16 (13)	19 (15)
Total dietary fibre (g/day) (Englyst method)	14 (7)	16 (7)

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Table 3: Association between macronutrients (g) in trimester 1 and 2, and birth centile/birthweight.

Macronutrient*intake ² 10 g/day increment	Birth centile, Model 1			Birth centile, Model 2		
	Centile ^a	95% CI	<i>P</i> value	Centile ^{a,c}	95% CI	<i>P</i> value
Trimester 1 n=1196						
Total carbohydrate	0.3	0.1 to 0.5	0.001	0.2	0.1 to 0.4	0.002
Total fat	-0.7	-1.2 to -0.1	0.008	-0.5	-1.0 to 0	0.06
Protein	0.6	0 to 1.3	0.07	0.4	-0.2 to 1.2	0.22
Trimester 2 n=575						
Total carbohydrate	0.2	0 to 0.5	0.06	0.2	0 to 0.5	0.07
Total fat	-0.3	-1.1 to 0.4	0.37	-0.3	-1.1 to 0.5	0.43
Protein	-0.2	-1.2 to 0.8	0.70	-0.3	-1.4 to 0.6	0.48
	Birthweight (g), Model 1			Birthweight (g), Model 2		
Trimester 1 n=1196	Birthweight ^b	95% CI	<i>P</i> value	Birthweight ^{b,c}	95% CI	<i>P</i> value
Total carbohydrate	4.0	1.6 to 7.0	0.002	4.0	1.0 to 7.0	0.003
Total fat	-10.0	-18.0 to -3.0	0.006	-8.0	-16.0 to -0.3	0.04
Protein	10.0	0.4 to 20.0	0.04	8.0	-2.0 to 19.0	0.12
Trimester 2 n=575						
Total carbohydrate	4.0	-0.3 to 8.0	0.07	3.0	-0.6 to 7.0	0.09
Total fat	-2.0	-14.0 to 9.0	0.64	-1.0	-13.0 to 10.0	0.76
Protein	-6.0	-20.0 to 8.0	0.40	-6.0	-22.0 to 8.0	0.38

^{2a}Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby ^b Adjusted for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby ^cAdditional adjustment for average alcohol intake and smoking status *Mutually adjusted for other energy contributing macronutrients

Table 4: Association between macronutrient sub-components during trimester 1 and 2, and birthweight.

Macronutrient sub-components ³ g/day increment	Birthweight (g), Model 1			Birthweight (g), Model 2		
	Birthweight ^a	95% CI	<i>P</i> value	Birthweight ^{a,b}	95% CI	<i>P</i> value
Trimester 1 n=1196						
Sources of total carbohydrate ^{†‡}						
Starch (10g)	4.0	-1.0 to 9.0	0.13	5.0	-0.6 to 10.0	0.08
Glucose (10g)	13.0	-20.0 to 45.0	0.43	13.0	-20.0 to 47.0	0.43
Fructose (1g)	0.4	-1.0 to 2.0	0.62	0.2	-2.0 to 2.0	0.83
Sucrose (1g)	-0.6	-1.0 to 0.1	0.11	-0.3	-1.0 to 0.4	0.40
Lactose (1g)	2.0	-0.1 to 4.0	0.07	2.0	-0.1 to 4.0	0.06
Maltose (1g)	5.0	-4.0 to 15.0	0.28	2.0	-8.0 to 13.0	0.66
Soluble fibre (1g)	6.0	-4.0 to 15.0	0.23	2.0	-8.0 to 12.0	0.67
Sources of total fat ^{†*}						
Saturated fatty acid (1g)	-2.0	-4.0 to 1.0	0.21	-1.0	-4.0 to 2.0	0.46
Monounsaturated fatty acid (1g)	2.0	-2.0 to 6.0	0.28	1.0	-2.0 to 5.0	0.44
Polyunsaturated fatty acid (1g)	-4.0	-8.0 to -0.4	0.02	-4.0	-8.0 to 0.09	0.05
Protein ^{*‡} (10g)	10.0	0.5 to 20.0	0.04	8.0	-2.0 to 19.0	0.12

³ ^aAdjusted for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby ^bAdditional adjustment for average alcohol intake and smoking status ^{*}Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Macronutrient sub-components ⁴ g/day increment	Birthweight (g), Model 1			Birthweight (g), Model 2		
	Birthweight ^a	95% CI	<i>P</i> value	Birthweight ^{a,b}	95% CI	<i>P</i> value
Sources of total carbohydrate ^{†‡}						
Starch (10g)	4.0	-4.0 to 12.0	0.34	4.0	-4.0 to 12.0	0.32
Glucose (10g)	42.0	-6.0 to 90.0	0.09	52.0	4.0 to 100.0	0.03
Fructose (1g)	-1.0	-4.0 to 2.0	0.40	-2.0	-5.0 to 1.0	0.20
Sucrose (1g)	-1.0	-2.0 to 0.3	0.14	-1.0	-2.0 to 0.1	0.08
Lactose (1g)	3.0	1.0 to 6.0	0.005	5.0	2.0 to 7.0	<0.001
Maltose (1g)	-0.5	-15.0 to 14.0	0.94	-0.01	-14.0 to 14.0	0.99
Soluble fibre (1g)	2.0	-12.0 to 16.0	0.78	-0.5	-14.0 to 13.0	0.94
Sources of total fat ^{†*}						
Saturated fatty acid (1g)	2.0	-2.0 to 6.0	0.35	3.0	-1.0 to 7.0	0.14
Monounsaturated fatty acid (1g)	-2.0	9.0 to 4.0	0.46	-4.0	-11.0 to 2.0	0.19
Polyunsaturated fatty acid (1g)	-2.0	-7.0 to 3.0	0.51	0.2	-0.5 to 0.05	0.12
Protein ^{*‡} (10g)	-6.0	-21.0 to 8.0	0.40	0.2	-5.0 to 6.0	0.93

⁴ ^aAdjusted for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby ^bAdditional adjustment for average alcohol intake and smoking status ^{*} Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Table 5: Associations between macronutrient sub-components in trimester 1 and 2, and birth centile.

Macronutrient sub-components ⁵ g/day increment	Birth centile, Model 1			Birth centile, Model 2		
	Centile ^a	95% CI	<i>P</i> value	Centile ^{a,b}	95% CI	<i>P</i> value
Trimester 1 n=1196						
Sources of total carbohydrate ^{†‡}						
Starch (10g)	0.4	0.02 to 0.75	0.03	0.36	-0.01 to 1.0	0.05
Glucose (10g)	2.0	-0.18 to 4.44	0.07	2.0	-0.37 to 4.0	0.09
Fructose (1g)	-0.03	-0.17 to 0.10	0.60	-0.04	-0.18 to 0.09	0.52
Sucrose (1g)	-0.04	-0.09 to 0.01	0.15	-0.02	-0.07 to 0.03	0.48
Lactose (1g)	0.13	0.0 to 0.27	0.04	0.15	0.01 to 0.29	0.03
Maltose (1g)	0.07	-0.62 to 1.0	0.82	-0.01	-1.0 to 1.0	0.96
Soluble fibre (1g)	0.31	-0.32 to 1.0	0.33	0.14	-0.53 to 1.0	0.67
Sources of total fat ^{†*}						
Saturated fatty acid (1g)	-0.10	-0.28 to 0.06	0.22	-0.05	-0.23 to 0.12	0.56
Monounsaturated fatty acid (1g)	0.06	-0.19 to 0.32	0.60	0.04	-0.22 to 0.31	0.74
Polyunsaturated fatty acid (1g)	-0.20	-0.46 to 0.04	0.11	-0.21	-0.5 to 0.05	0.12
Protein ^{*‡} (10g)	0.64	-0.06 to 1.0	0.07	0.45	-0.28 to 1.19	0.22

⁵ ^aAdjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby ^bAdditional adjustment for average alcohol intake and smoking status

*Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes

Macronutrient sub-components ⁶ g/day increment	Birth centile, Model 1			Birth centile, Model 2		
	Centile ^a	95% CI	<i>P</i> value	Centile ^{a,b}	95% CI	<i>P</i> value
Trimester 2 n=575						
Sources of total carbohydrate ^{†‡}						
Starch (10g)	0.35	-0.14 to 1.0	0.16	0.34	-0.16 to 1.0	0.18
Glucose (10g)	2.0	-0.1 to 6.0	0.16	3.0	-0.5 to 6.0	0.09
Fructose (1g)	-0.08	-0.30 to 0.13	0.45	-0.11	-0.33 to 0.10	0.29
Sucrose (1g)	-0.04	-0.12 to 0.03	0.30	-0.04	-0.12 to 0.03	0.23
Lactose (1g)	0.17	0.0 to 0.34	0.05	0.23	0.04 to 0.41	0.01
Maltose (1g)	-0.16	-1.0 to 1.0	0.75	-0.03	-1.05 to 1.0	0.94
Soluble fibre (1g)	0.19	-1.0 to 1.0	0.68	0.01	-1.0 to 1.0	0.97
Sources of total fat ^{†*}						
Saturated fatty acid (1g)	0.07	-0.20 to 0.36	0.57	0.11	-0.17 to 0.39	0.44
Monounsaturated fatty acid (1g)	-0.22	-0.67 to 0.21	0.31	-0.26	-1.0 to 0.19	0.25
Polyunsaturated fatty acid (1g)	0.03	-0.32 to 0.39	0.84	0.07	-0.29 to 0.45	0.67
Protein ^{*‡} (10g)	-0.19	-1.0 to 1.0	0.70	-0.38	-1.0 to 0.68	0.48

⁶ ^aAdjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby ^bAdditional adjustment for average alcohol intake and smoking status

*Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes