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

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Short version of the title:-

Macronutrients in pregnancy and birthweight

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

Abstract

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

Introduction

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

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

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

Methods

Study design and population

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

Dietary data

Out of 1,289 participants in the original study, dietary information was available for 1,196 women in the first trimester and 575 women in the second trimester. The dietary intake was collected at home twice in a 24 hour dietary recall[33-35] administered by a trained research midwife; once during trimester 1 (8-12 weeks of gestation) and again during trimester 2 (13-27 weeks of gestation). Trained personnel entered the 24 hour dietary recalls by using nutrient analysis package– 'DANTE' (Diet and Nutrition Tool for Evaluation). The nutrient analysis computed by this software package was based on the standard UK food composition tables by the Royal Society of Chemistry[36].

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

Other data

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

Outcome: Birthweight, Birth centile, SGA and LGA births

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

Statistical analysis

We calculated the mean and standard deviation (SD), and absolute frequency distributions with percentages [n (%)] for demographic characteristics of interest (Table 1 in results). To examine associations between macronutrients or their sub-components, and birthweight/centile; multiple linear regression models (model 1 and 2) were designed for first and second trimesters separately. Each macronutrient and its sub-component model were adjusted for other energy contributing macronutrients and sub-components within the model. In order to help with the interpretation of birth centiles, we have additionally presented these results in actual birthweight in grams. In the centile model (model 1) we made use of customised centile charts[31,39] which automatically accounted for these variables: maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby. The birthweight model (model 1) was adjusted for maternal height, weight, parity, ethnicity, gestational age at delivery and sex of the baby. All regression models (birthweight/centile models) under model 2 were additionally adjusted for participants' alcohol consumption and smoking habits in pregnancy.

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

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

Results

Baseline characteristics

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

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

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

Relationship between macronutrients, and birth centile/birthweight

We observed associations between first trimester macronutrient intake and both birth centile and birthweight (Table 3). In the first trimester, there was a positive association between CHO consumption and birth centile/birthweight. The fully adjusted models (model 2) indicated that a higher intake of CHO (10g/day increment) was associated with a higher birth centile (0.2; 95% CI 0.1 to 0.4; P=0.002) and a higher birthweight (4g; 95% CI 1g to 7g; P=0.003). Conversely, a higher total fat intake (10 g/day increment) at this stage of pregnancy was negatively associated with birth centile (-0.7; 95% CI -1.2 to -0.1; P=0.008) on the customized centile chart. However, on further adjusting the model for alcohol intake and smoking habits (model 2), higher fat intake (10g/day increment) was not associated with birth centile (-0.5; 95% CI -1.0 to 0.0; P=0.06) in spite of narrow confidence intervals. When we explored its relation with birthweight, fat consumption (10g/day increment) was negatively associated with birthweight (-8g; 95% CI -16g to -0.3; P=0.04) in the fully adjusted model (model 2). Amongst other macronutrients, protein intake was not associated with birth centile or birthweight after adjusting for smoking status and alcohol intake, but it had wide confidence intervals.

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

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

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

Discussion

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

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

Interestingly, amongst mono-saccharides, we observed that in trimester 2 additional consumption of dietary glucose was associated with heavier birthweight. A similar association was observed in a study[51] amongst pregnant women with type 1 diabetes mellitus. They reported an association between increased maternal glucose levels amongst diabetic pregnant women and LGA offspring. In our study, we observed that high intake of starch was associated with increased odds of delivering LGA infants. According to a study[52] which compared normal versus pregnant women with gestational diabetes mellitus (GDM), participants who consumed a CHO-rich diet were likely to have high blood glucose levels, and an increased risk of delivering LGA offspring. Randomised controlled trials (RCTs) have reported possible effects of a high CHO intake vs a low CHO intake amongst women with GDM and increased risk of macrosomia[53,54]. A possible explanation for these results could be that high CHO intakes could lower maternal insulin sensitivity, making higher levels of free glucose available for placental circulation, subsequently activating fetal glycogenesis[55]. Pedersen[56] attributed the role of maternal hyperglycaemia to this birth outcome which reportedly caused increase in fetal insulin levels and led to fetal hyperglycaemia.

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

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

Our analyses suggest that total fat intake and its sub-components such as PUFA were associated with lower birthweight and birth centile. However, our result conflicts with a South-Asian study[29] which reported a positive association between dietary fat intake in pregnancy and increased birthweight. Contradicting results from other studies[20,21,23] reported no association between them; an observational study[20] explored the relation between energy percentage (%) from total dietary fat and birthweight, and suggested no evidence of an association after adjusting for other energy contributing nutrients. Our analysis adjusted for alcohol, as it is associated with increased risk of lower birthweight[66-68] and fat-rich foods are often consumed with alcohol. Conversely, the study by Moore et al.[20] did not adjust for alcohol consumption during pregnancy. However, amongst randomised controlled trials (RCTs) on animal models, there is no evidence suggesting an association between a high fat diet in pregnancy and changes in birthweight. Previous studies[69,70] based on animal models explored the effect of a high-fat diet in pregnancy on the development of offspring metabolic disorders including hyperinsulinemia, blood pressure, and changes in serum leptin levels. An RCT[70] amongst pups, explored the effects of high-fat diet on offspring and suggested that maternal adiposity and not dietary fat per se, was associated with increased offspring weight, and metabolic disorders such as hyperinsulinemia which could further persist through adulthood. During the first trimester, higher PUFA intake was associated with lower birthweight of infants. Three studies[1,71,72] discussed the "anti-obesogenic" property of PUFA during pregnancy which reportedly prevented extra fat mass deposits in the fetus. Ethical issues make studies of this nature challenging in humans such as acidosis and ketosis in response to low CHO-high fat diets, alterations in cholesterol and free fatty acid metabolism in pregnancy. Further studies are needed to validate our result.

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

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

Strengths and weaknesses

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

There are few limitations to any study which explores nutritional intake. For sub-components, the nutrient values computed in the software using the food composition database[36] may not be accurate or complete. A couple of studies[80,81] reported issues of missing values for nutrients in databases, including McCance and Widdowson's food composition database[81]. Energy intake estimations from food items and beverages of the participants were based on memory recall and are subjected to mis/under-reporting and bias[82-84]. Some studies suggest use of a combination of dietary assessments to cross check the dietary information for correct quantity estimation, measurement uniformity and frequency of consumption[85,86], however, this is more common where food frequency questionnaires are the main dietary measure. Dietary data in our study was recorded only for trimesters 1 and 2. Data was unavailable for type of protein (animal/vegetable) and amino acid content, which led us to include total protein in the regression models.

Conclusion

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

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Ethical approval

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

Conflict of Interest

None.

Authorship

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

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

Characteristic[1]	
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)

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

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)

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**		
Trimester 1 n=1196	Centile[a]	95% CI	P value	Centile[a,c]	95% CI	P value
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	P value	Birthweight[b,c]	95% CI	P 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

[2] [a]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 [c]Additional 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		
Trimester 1 n=1196	**Birthweight[a]**	**95% CI**	**P value**	**Birthweight[a,b]**	**95% CI**	**P value**
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 [a]Adjusted for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby [b]Additional 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**		
Trimester 2 n=575	**Birthweight[a]**	**95% CI**	**P value**	**Birthweight[a,b]**	**95% CI**	**P 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 [a]Adjusted for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby [b]Additional 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		
Trimester 1 n=1196	**Centile[a]**	**95% CI**	**P value**	**Centile[a,b]**	**95% CI**	**P value**
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 [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby [b]Additional 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**		
Trimester 2 n=575	**Centile**[a]	**95% CI**	**P value**	**Centile**[a,b]	**95% CI**	**P value**
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 [a]Adjusted using customised growth charts for maternal weight, height, ethnicity, parity, gestational age at delivery, sex of baby [b]Additional adjustment for average alcohol intake and smoking status [*]Adjusted for carbohydrate intakes [†]Adjusted for dietary protein intakes [‡]Adjusted for dietary fats intakes