Key messages

- Reduced weight for length (ponderal index) at birth was associated with a threefold increased risk of non-insulin dependent diabetes in Swedish men at age 60 years
- There is no evidence that reduced fetal growth is associated with impaired β cell function at age 50 years (as measured by the insulin response to intravenous glucose)
- The combination of thinness at birth and overweight in adult life is associated with higher insulin concentration at 1 hour after intravenous glucose, suggesting an effect on insulin resistance
- Control of obesity in adult life is likely to be especially effective in reducing the risk of non-insulin dependent diabetes in those who were thin at birth

be especially effective in reducing the risk of diabetes in people who were thin at birth.

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Maternal nutrition in early and late pregnancy in relation to placental and fetal growth

K Godfrey, S Robinson, DJP Barker, C Osmond, V Cox

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Medical Research Council Environmental Epidemiology Unit (University of Southampton), Southampton General Hospital, Southampton SO16 6YD
K Godfrey, *epidemiologist*
S Robinson, *nutritionist*
D J P Barker, *director*
C Osmond, *statistician*
V Cox, *computer analyst*

Correspondence to:
Dr Godfrey.

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Abstract

***Objective*—To assess how nutrient intakes of mothers in early and late pregnancy influence placental and fetal growth.**

***Design*—Prospective observational study.**

***Setting*—Princess Anne Maternity Hospital, Southampton.**

***Subjects*—538 mothers who delivered at term.**

***Main outcome measures*—Placental and birth weights adjusted for the infant's sex and duration of gestation.**

***Results*—Mothers who had high carbohydrate intakes in early pregnancy had babies with lower placental and birth weights. Low maternal intakes of dairy and meat protein in late pregnancy were also associated with lower placental and birth weights. Placental weight fell by 49 g (95% confidence interval 16 g to 81 g; P=0·002) for each log g increase in intake of carbohydrate in early pregnancy and by 1·4 g (0·4 g to 2·4 g; P=0·005) for each g decrease in intake of dairy protein in late pregnancy. Birth weight fell by 165 g (49 g to 282 g; P=0·005) for each log g increase in carbohydrate intake in early pregnancy and by 3·1 g (0·3 g to 6·0 g; P=0·03) for each g decrease in meat protein intake in late pregnancy. These associations were independent of the mother's height and body mass index and of strong relations between the mother's birth weight and the placental and birth weights of her offspring.**

***Conclusion*—These findings suggest that a high carbohydrate intake in early pregnancy suppresses placental growth, especially if combined with a low dairy protein intake in late pregnancy. Such an effect could have long term consequences for the offspring's risk of cardiovascular disease.**

Introduction

Most low birthweight babies have a small placenta.[1 2] The growth of the placenta precedes that of the fetus, and surgical restriction of placental growth in sheep causes retardation of fetal growth.[3] Recent experimental studies in sheep have shown that high nutrient intakes in early pregnancy may also suppress placental growth, resulting in reduced placental and fetal size.[4] In humans we know little about how nutrient intakes in early pregnancy relate to placental and fetal size. Whereas nutrient intakes in late pregnancy have been reported to have inconsistent effects on fetal size,[5 6] their relation to placental size is largely unknown. Any such effects may be of long term importance in view of the associations between placental and birth size and adult cardiovascular disease.[2 7] In a prospective study we have assessed the relations between the mother's

nutrient intakes in early and late pregnancy and placental and fetal weight.

Subjects and methods

We approached all 655 white women aged 16 years or older with singleton pregnancies who registered under two consultants over one year and who attended the midwives' antenatal booking clinic at the Princess Anne Maternity Hospital in Southampton at less than 17 weeks' gestation. Twelve miscarried or had a termination of pregnancy, and seven delivered outside the district. Of the 636 remaining women, 596 (94%) agreed to participate.

The mothers were visited at home by a trained research nurse shortly after recruitment and again around 32 weeks' gestation (median duration of gestation 15·3 and 32·7 weeks, respectively). Mothers were asked about their menstrual and obstetric history, weight before pregnancy, and smoking habits and were requested to contact their parents and ascertain their own birth weight. Height was measured with a stadiometer. Social class was allocated according to the mother's current or last occupation.[8,9] Social class could not be allocated for 15 mothers.

In early and late pregnancy a food frequency questionnaire was administered that assessed the average frequency of consumption of 100 foods or food groups in the three months preceding the visit. The nutrient content[10–13] of a standard portion of each food[14] was multiplied by its reported frequency of use to calculate average daily nutrient intake. The early pregnancy estimates have been validated against those determined from food diaries kept over four days.[15]

At birth the baby was weighed to the nearest 5 g with digital scales. The placenta was weighed on digital scales after trimming by stripping the amnion to the cord, cutting the chorion at the edge of the placenta, and removing the cord flush with the placenta. Duration of gestation was estimated from menstrual history and ultrasound scan data by using a standard algorithm.[16]

The study was approved by the local ethics committee. Of the 596 mothers recruited, 39 delivered before 259 days' (37 weeks') gestation and were excluded from this analysis in view of the strong dependence of birth weight on gestation. Three mothers were not visited in late pregnancy and placental weight was not recorded for 16, leaving 538 term pregnancies with complete data on nutrition and delivery (85% of the sample of 636).

Statistical analysis was by tabulation of means and paired *t* tests. Multiple linear regression was used to take account of the independent effects of separate variables. Levels of significance refer to regression analysis of continuous variables. Nutrient intakes were log transformed when necessary to satisfy assumptions of normality.

Results

Table 1 shows the characteristics of the 538 mothers and babies. Placental and birth weights rose with increasing gestational age at birth by 1·6 g/day and 21 g/day, respectively, and were higher in boys than girls. We adjusted both weights for the baby's sex and duration of gestation, and subsequent analyses use the adjusted values.

Table 2 shows the mothers' median daily nutrient intakes. Between early and late pregnancy a small fall in carbohydrate and rise in fat intakes resulted in a fall in the proportion of energy derived from carbohydrate (from 49·4% to 49·0%) and a corresponding rise in that derived from fat (from 35·7% to 36·4%). While intakes of dairy protein rose (from 20·5 g to 22·3 g/day) those of meat protein remained constant and those of cereal protein fell (from 34·7 g to 33·7 g/day). Intakes of iron and folate rose during pregnancy (table 2) because of higher intakes from supplements in late pregnancy.

NUTRIENT INTAKES IN EARLY PREGNANCY AND PLACENTAL AND BIRTH WEIGHTS

Table 3 shows mean placental and birth weights according to the mother's intakes of energy and macronutrients. Placental and birth weights were inversely related to energy intake in early pregnancy, falling by 38 g (95% confidence interval 5 g to 72 g; P=0·03) and 134 g (11 g to 256 g; P=0·03), respectively, for each log kcal increase in intake. These relations were largely dependent on an association with carbohydrate intake, placental weight falling by 41 g (10 g to 73 g; P=0·01) and birth weight by 143 g (28 g to 258 g; P=0·01) for each log g increase in carbohydrate. Division of carbohydrate into total sugars and starch showed that the relations with intakes of sugars (P=0·01 and P=0·02, respectively) were stronger than those with intakes of starch (P=0·09 and P=0·1).

Placental weight fell by 27 g (−2 g to 56 g; P=0·07) and birth weight by 101 g (−4 g to 207 g; P=0·06) for each log g increase in fat. Both were unrelated to the mother's intakes of protein, iron, or folate in early pregnancy. After carbohydrate intakes in early pregnancy were taken into account no more variance in placental and birth weights was explained when we also considered fat, protein, iron, or folate intakes in early pregnancy.

Table 1—*Characteristics of 538 mothers and babies*

Mothers	
No (%) primiparous	285 (53·0)
No (%) of smokers	139 (25·8)
Social class:	
No (%) I, II	144 (26·8)
No (%) IIIN, IIIM	283 (52·6)
No (%) IV, V	111 (20·7)
Mean (SD) height (m)*	1·63 (0·06)
Mean (SD) body mass index (kg/m²) before pregnancy*	23·1 (4·4)
Mean (SD) age (years)	26·4 (4·9)
Mean (SD) birth weight of mother (g)†	3312 (534)
Babies (boys; girls)	
Mean (SD) placental weight (g)	544 (125); 522 (115)
Mean (SD) birth weight (g)	3527 (496); 3344 (463)
Mean (SD) placental ratio (%)	15·4 (2·8); 15·7 (2·9)
Mean (SD) gestation (days)	281·4 (9·3); 281·2 (9·3)

*Body mass index unknown for 10 mothers and height for two mothers.
†Mother's own birth weight unknown for 47 mothers.

Table 2—*Median daily intakes (lower and upper quartile) of the 538 mothers*

Intake	Early pregnancy	Late pregnancy
Energy (kcal)	2329 (1882, 2789)	2314 (1970, 2729)
Carbohydrate (g)	302·7 (245·7, 372·9)	301·9 (254·3, 360·6)
Fat (g)	91·2 (74·2, 112·6)	93·2 (75·8, 111·9)
Protein (g)	87·2 (69·8, 101·3)	85·7 (72·4, 99·8)
Proportion (%) kcal carbohydrate	49·4 (46·2, 53·4)	49·0 (46·1, 52·2)
Proportion (%) kcal fat	35·7 (32·5, 38·7)	36·4 (33·3, 39·1)
Proportion (%) kcal protein	14·7 (13·3, 16·5)	14·7 (13·3, 16·0)
Total sugars (g)	141·7 (109·9, 185·0)	151·5 (115·9, 189·1)
Starch (g)	150·3 (123·2, 190·0)	144·3 (116·9, 176·9)
Cereal protein (g)	34·7 (27·7, 42·0)	33·7 (27·2, 40·2)
Meat protein (g)	28·1 (19·0, 38·3)	28·3 (20·5, 37·3)
Dairy protein (g)	20·5 (15·2, 28·2)	22·3 (16·4, 28·9)
Iron (mg)	15·5 (12·7, 21·2)	16·8 (13·2, 29·6)
Folate (μg)	315 (252, 397)	327 (260, 449)

Table 3—*Mean placental weight and birth weight adjusted for baby's sex and duration of gestation according to mother's daily intakes in early and late pregnancy*

Intake	Placental weight (g)	Birth weight (g)	No of subjects
Early pregnancy			
Energy (kcal):			
≤2080	547	3468	180
-2560	535	3446	173
>2560	520	3412	185
Carbohydrate (g):			
≤265	554	3501	181
-340	531	3444	172
>340	517	3381	185
Fat (g):			
≤80	542	3456	191
-105	543	3461	165
>105	517	3409	182
Protein (g):			
≤76	537	3462	175
-95	536	3427	175
>95	528	3437	188
Late pregnancy			
Energy (kcal):			
≤2080	537	3452	175
-2560	531	3438	182
>2560	534	3436	181
Carbohydrate (g):			
≤265	544	3492	170
-340	529	3427	190
>340	530	3409	178
Fat (g):			
≤80	538	3443	165
-105	530	3432	187
>105	534	3450	186
Protein (g):			
≤76	530	3419	173
-95	534	3453	189
>95	537	3452	176

NUTRIENT INTAKES IN LATE PREGNANCY AND PLACENTAL AND BIRTH WEIGHTS

There were no significant univariate relations between the mother's nutrient intakes in late pregnancy and placental and birth weights (table 3). After the mother's carbohydrate intake in early pregnancy was taken into account, however, a low protein intake in late pregnancy was associated with decreased placental weight (P=0·02) and birth weight (P=0·01). Though the relation with placental weight reflected an association with dairy protein, there being no associations with either cereal (P=0·2) or meat protein (P=0·5), birth weight was more closely related to intakes of meat protein than those of dairy (P=0·2) or cereal protein (P=0·2). Thus placental weight fell by 49 g (16 g to 81 g; P=0·002) for each log g increase in carbohydrate intake in early pregnancy and by 1·4 g (0·4 g to 2·4 g; P=0·005) for each g decrease in dairy protein intake in late pregnancy (table 4). Birth weight fell by 165 g (49 g to 282 g; P=0·005) for each log g increase in carbohydrate intake in early pregnancy and by 3·1 g (0·3 g to 6·0 g; P=0·03) for each g decrease in meat protein intake in late pregnancy (table 5).

Placental and birth weights fell by 15 g (1 g to 28 g; P=0·03) and 63 g (14 g to 112 g; P=0·01), respectively, for each log mg decrease in iron intake in late pregnancy and by 34 g (11 g to 57 g; P=0·004) and 98 g (15 g to 181 g; P=0·02) for each log μg decrease in folate. These relations largely reflected associations with iron and folate intakes from supplements and were independent of those with dietary carbohydrate and protein intakes.

MOTHER'S CHARACTERISTICS AND PLACENTAL AND BIRTH WEIGHTS

Primiparous mothers had placentas that were 29 g (8 g to 49 g; P=0·006) lighter and babies that were 121 g (48 g to 195 g; P=0·001) lighter than those of multiparous mothers. Placental and birth weights fell with decreasing maternal height (by 336 g/m (180 g/m to 492 g/m; P<0·0001) and 1541 g/m (977 g/m to 2105 g/m; P<0·0001), respectively) and, weakly, with decreasing maternal body mass index (g/weight(kg)/height(m)^2) before pregnancy (by 1·6 g (−0·7 g to 3·9 g; P=0·2) and 8·1 g (−0·5 g to 16·6 g; P=0·06)). Though placental weight was similar in mothers who smoked and did not smoke (difference 1 g (−24 g to 22 g; P=0·9)), birth weight was 146 g (62 g to 229 g; P=0·0007) lower in mothers who smoked. After maternal height and smoking were taken into account, placental and birth weights were unrelated to maternal age and social class.

Multiple regression analyses showed that the relations between placental and birth weights and intakes of carbohydrate and dairy and meat protein were independent of the mother's height and body mass index and were similar in primiparous and multiparous mothers and in mothers who did or did not smoke.

MOTHER'S BIRTH WEIGHT

Of the 538 mothers, 491 (91%) ascertained their own birth weight. Placental and birth weights were strongly related to the mother's weight at birth (table 6), falling by 0·041 g (0·021 g to 0·061 g; P=0·0001) and 0·204 g (0·133 g to 0·276 g; P<0·0001), respectively, for each g decrease in the mother's birth weight. These

Table 4—*Mean placental weight (g) adjusted for baby's sex and duration of gestation according to mother's daily intakes of carbohydrate in early pregnancy and dairy protein in late pregnancy. Figures in parentheses are numbers of subjects*

Dairy protein intake in late pregnancy (g/day)	Carbohydrate intake in early pregnancy (g/day)			
	≤265	-340	>340	All
≤18·5	539 (72)	507 (49)	494 (54)	516 (175)
-26·5	556 (73)	546 (63)	509 (48)	540 (184)
>26·5	582 (36)	533 (60)	536 (83)	544 (179)
All	554 (181)	531 (172)	517 (185)	534 (538)

Table 5—*Mean birth weight (g) adjusted for baby's sex and duration of gestation according to the mother's daily intakes of carbohydrate in early pregnancy and meat protein in late pregnancy. Figures in parentheses are numbers of subjects*

Meat protein intake in late pregnancy (g/day)	Carbohydrate intake in early pregnancy (g/day)			
	≤265	-340	>340	All
≤23·5	3450 (71)	3419 (61)	3312 (43)	3405 (175)
-34·0	3539 (58)	3472 (56)	3359 (69)	3451 (183)
>34·0	3529 (52)	3443 (55)	3443 (73)	3468 (180)
All	3501 (181)	3444 (172)	3381 (185)	3442 (538)

Table 6—*Mean placental weight and birth weight adjusted for baby's sex and duration of gestation according to mother's own birth weight*

Mother's own birth weight (g)	Placental weight (g)	Birth weight (g)	No of subjects
≤2500	503	3309	28
-3000	510	3359	111
-3500	533	3394	180
-4000	550	3553	132
>4000	586	3705	40

relations were both little changed when we simultaneously took account of the mother's adult height (adjusted regression coefficients 0·033 for placental weight and 0·162 for birth weight) and were similar in primiparous and multiparous mothers and in mothers who smoked and did not smoke. Multiple regression analyses showed that the relations between placental and birth weights and the mother's dietary intakes were independent of her own weight at birth.

Comparison of recalled birth weight with the actual weight recorded in the original obstetric records was possible for 136 mothers born in local hospitals. Actual birth weight averaged 32 g heavier than recalled birth weight (SD of difference 264 g); 84% differed by 250 g or less. Among the 136 mothers the relations between actual maternal birth weight and the offspring's placental and birth weights were similar to those with recalled birth weight.

PLACENTAL RATIO

The ratio of placental weight to birth weight (placental ratio) fell by 0·05% for each day increase in gestational age at birth and was 0·3% lower in boys than girls (table 1). The ratio, adjusted for gestation and sex, fell by 0·77% (0·01% to 1·53%; P=0·05) for each log g increase in early pregnancy carbohydrate intakes and by 0·025% (0·001% to 0·049%; P=0·04) for each g decrease in late pregnancy dairy protein intakes and was 0·66% (0·11% to 1·21%; P=0·02) higher in mothers who smoked than in those who did not smoke. The ratio also fell with decreasing folate intake in late pregnancy (P=0·05) but was unrelated to meat protein or iron intakes or to parity, height, body mass index, or the mother's birth weight.

Discussion

We have examined how the nutrient intakes in pregnancy of an unselected group of mothers delivering at term are related to placental and fetal size at birth. The 538 mothers represent 85% of the original sample approached. Their social class distribution (table 1) was similar to that of mothers in England and Wales.[9]

We administered a food frequency questionnaire to assess nutrient intakes over the first trimester and repeated this in late pregnancy. The estimates of energy intake given by the questionnaire were consistent with predicted requirements based on calculations of basal metabolic rate.[15 17] Among those who did not have nausea in early pregnancy the questionnaire to assess intakes over the first trimester ranked mothers similarly to a four day food diary in the second trimester (rank correlation coefficient for energy 0·41),[15] and nutrient intakes estimated by the two methods were similarly related to placental weight (unpublished observations). Though food frequency questionnaires give an assessment of diet useful in ranking the nutrient intakes of individual subjects,[18–20] they can, however, be subject to bias[21 22] and allow only cautious conclusions.

We have found that placental and fetal size at birth are associated with the mother's intakes of carbohydrate and protein. These relations could reflect an effect of total food intakes as it is difficult to disentangle the effects of highly correlated nutrients whose error of measurement may differ. Our analyses suggest, however, that carbohydrate and protein in early and late pregnancy may have specific and differing effects. High carbohydrate intakes in early pregnancy were associated with low placental and birth weights (table 3). Although this seems paradoxical, in sheep farming it is common practice for ewes to be put on rich pasture before they are mated and then on poor pasture for a period in early pregnancy.[23] Experimental studies in farm animals suggest that the scientific basis of this practice may lie partly in stimulation of placental growth by undernutrition in early pregnancy.[4 24 25] Our data provide the first evidence that similar effects may occur in humans.

Key messages

- The babies of mothers who had high carbohydrate intakes in early pregnancy had smaller placentas and lower birth weights
- Low intakes of animal protein in late pregnancy were also associated with lower placental and birth weights
- These associations were independent of strong relations between the mother's birth weight and the placental and birth weights of her offspring
- In sheep high nutrient intakes in early pregnancy can suppress placental and fetal growth
- Though these effects could be of long term importance for the development of cardiovascular disease, they are not currently a basis for changing dietary recommendations to pregnant women

In late pregnancy low intakes of dairy protein in relation to carbohydrate were also associated with low placental weight (table 4). A recent reanalysis of a survey of diet in late pregnancy, carried out in Aberdeen, similarly showed that low intakes of animal protein in relation to carbohydrate were associated with low placental weight.[26] This survey, however, did not differentiate meat and dairy protein. Interestingly, follow up of the babies in this survey, now 40 years old, showed that low maternal intakes of animal protein in relation to carbohydrate not only led to decreased placental size but were also associated with raised blood pressure in adult life.[26] This parallels experimental studies in rats.[27]

We found that low intakes of meat protein in late pregnancy were associated with lower birth weight (table 5). High protein intakes in late pregnancy have been associated with both positive and negative effects on birth weight.[5 6 28] Supplements in which protein contributed less than 21% of energy have had beneficial effects on birth weight, whereas adverse effects have resulted from supplements with a higher protein density.[6] Our results raise the possibility that both the source and density of the protein may be important.

High intakes of iron and folate from supplements late in pregnancy were associated with both higher placental and birth weights. While this could reflect a beneficial effect of supplementation the results of randomised trials of iron and folate supplementation suggest this is unlikely.[29 30] One possibility is that the higher iron requirement of large babies leads to greater falls in maternal haemoglobin,[31] making their mothers more likely to be supplemented.

Consistent with the results of other studies[32] mothers who had low birth weights had babies with lower birth weights (table 6). Although our analyses were dependent on recalled birth weights, validation against labour ward records showed a high degree of agreement between recalled and actual weights. The effects of the mother's birth weight were largely independent of her adult height and at least as strong. We showed for the first time that the babies of low birthweight mothers had lower placental weights. This strong relation supports the hypothesis that maternal constraint of fetal growth may operate largely through constraint of placental growth,[33] perhaps as a conse-

quence of impaired uterine or ovarian development during the mother's own fetal life.[34]

One observational study cannot form the basis for changing dietary recommendations to pregnant women. The differing relations of nutrient intakes in early and late pregnancy to placental and fetal growth need replication in other studies. Our findings, however, do parallel those of experimental studies in sheep in which high nutrient intakes in early pregnancy have been shown to suppress placental and fetal growth.

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Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study

Keith R Neal, Helen M Scott, Richard C B Slack, Richard F A Logan

Department of Public Health Medicine, University of Nottingham, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH
Keith R Neal, *lecturer in communicable disease control*
Helen M Scott, *medical student*
Richard F A Logan, *reader in clinical epidemiology*

Nottingham Health Authority, Nottingham NG1 6GN
Richard C B Slack, *consultant in communicable disease control*

Correspondence to:
Dr Neal.

keith.neal@nottingham.ac.uk

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Gastric acid protects against enteric infections,[1] and patients who have had gastric surgery or are taking H_2 antagonists are more susceptible to salmonella infection.[2,3] Antibiotic treatment also increases the risk of infection.[3] It is not known whether these factors are also associated with campylobacter infection, for which statutory notifications now exceed those for salmonella.[4] We conducted a case-control study to assess whether gastric antisecretory drugs, antibiotics, and abdominal surgery are associated with campylobacter infection.

Patients, methods, and results

Between January 1992 and August 1994, 243 notified cases of campylobacter infection, confirmed by faecal culture, were identified in people aged 45 and over in two of the local district councils within Nottingham Health Authority. Thirty two cases were excluded (non-resident (four), general practitioner declined (19), patient died and notes unobtainable (six), and notes unobtainable at general practice (three)), leaving 211 (123 women). The minimum age was 45 because people over this age have higher rates of prescribing by general practitioners. Controls were identified as the next two patients matched for sex and age within two years in the practice computerised records. No controls were excluded.

Data on previous surgical operations; prescriptions for H_2 antagonists, proton pump inhibitors, antibiotics, hydroxocobalamin, and corticosteroids; and regular precriptions and other drugs used before infection were extracted from the general practice records. Data were analysed by conditional logistic regression using the EGRET package with the magnitude of associations measured by odds ratios. The study had 80% power to detect a 2·5-fold risk, given that 4% of the general population was exposed.

Omeprazole treatment in the month before infection was associated with a 10-fold increased risk of campylobacter infection (table 1). This was independently significant only for current use. The association with H_2 antagonists was not significant after omeprazole use was controlled for. Antibiotic treatment in the two to