but our data suggest a mediating role for disturbances in insulin mediated uptake of glucose, which is already implicated in the association between ponderal index and risk of non-insulin dependent diabetes.[14] Further work needs to be done to elaborate the nature of this mechanism and to refine the nature of the fetal growth impairment that is likely to underlie the association of birth weight with blood pressure.

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Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years

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Abstract

***Objective*—To establish whether the relation between size at birth and non-insulin dependent diabetes is mediated through impaired β cell function or insulin resistance.**

***Design*—Cohort study.**

***Setting*—Uppsala, Sweden.**

***Subjects*—1333 men whose birth records were traced from a cohort of 2322 men born during 1920-4 and resident in Uppsala in 1970.**

***Main outcome measures*—Intravenous glucose tolerance test at age 50 years and non-insulin dependent diabetes at age 60 years.**

***Results*—There was a weak inverse correlation ($r=-0{\cdot}07$, P=0·03) between ponderal index at birth and 60 minute insulin concentrations in the intravenous glucose tolerance test at age 50 years. This association was stronger ($r=-0{\cdot}19$, P=0·001) in the highest third of the distribution of body mass index than in the other two thirds (P=0·01 for the interaction between ponderal index and body mass index). Prevalence of diabetes at age 60 years was 8% in men whose birth weight was less than 3250 g compared with 5% in men with birth weight 3250 g or more (P=0·08; 95% confidence interval for difference −0·3% to 6·8%). There was a stronger association between diabetes and ponderal index: prevalence of diabetes was 12% in the lowest fifth of ponderal index compared with 4% in the other four fifths (P=0·001; 3·0% to12·6%).**

***Conclusion*—These results confirm that reduced fetal growth is associated with increased risk of diabetes and suggest a specific association with thinness at birth. This relation seems to be mediated through insulin resistance rather than through impaired β cell function and to depend on an interaction with obesity in adult life.**

Introduction

Long term follow up studies in England have shown that the prevalence of impaired glucose tolerance and non-insulin dependent diabetes in middle age is inversely related to birth weight.[1,2] Initially it was suggested that the relation between reduced fetal growth and glucose intolerance was mediated through impairment of β cell function.[1,3] More recent work has led the same investigators to suggest instead that the association is mediated through insulin resistance.[4,5] The objective of our study was to distinguish between these two possible mechanisms. We traced birth records of a cohort of men in Uppsala, Sweden, who

had been examined at age 50 years and tested for diabetes at age 60 years. This allowed us to study the relation of fetal growth to measurements of insulin response to glucose challenge recorded before the development of glucose intolerance.

Methods

The longitudinal study of Uppsala men has been described previously.[6-8] In 1970-3 all 2841 men living in the municipality of Uppsala who were born between 1920 and 1924 were invited to take part in a health survey. The participation rate was 82% (2322 of 2841). Participants were examined in the morning after an overnight fast. An intravenous glucose tolerance test was performed on the last 1692 participants. A 50% solution of glucose at a dose of 0·5 g/kg body weight was injected into an antecubital vein over about 2·5 minutes. Glucose concentrations were measured at 0, 20, 30, 40, 50, and 60 minutes after the start of the glucose injection and insulin concentrations at 0, 4, 6, 8, and 60 minutes.[7] Serum insulin concentration was measured in the specimens obtained in 1970-3 by radioimmunoassay based on a double antibody solid phase technique (Pharmacia, Uppsala). Whole blood glucose concentration was measured by the glucose oxidase method. High density lipoprotein was separated by heparin-manganese chloride precipitation. Serum triglyceride and cholesterol concentrations were measured by enzymatic methods as described previously.[8]

In 1980 the 2139 participants who were still resident in Uppsala were invited for re-examination. The participation rate was 87% (1860 of 2139). Concentration of fasting whole blood glucose was measured in all participants, and in those whose fasting glucose was 5·7 mmol/l or higher an oral glucose tolerance test was performed by measuring glucose concentrations at 0, 30, 60, 90, and 120 minutes after challenge with 75 g anhydrous dextrose.

Of the initial cohort of 2322 men examined in 1970-3, 615 were born in the Uppsala Academic Hospital, 1585 were born elsewhere in Sweden, and 122 were born outside Sweden. The birth records of the men born in the Academic Hospital included information on weight, length, placental weight, gestational age, head circumference, maternal age, and maternal parity. By searching records in other Swedish hospitals and county archives we were able to trace records of birth weight on 718 of the 1585 men who had been born elsewhere in Sweden. For 575 of these 718 men birth length had also been recorded. Records of birth weight were thus traced for 61% (1333 of 2200) of the men born in Sweden who were examined in 1970-3. Of these 1333 men, 1187 had records of length at birth, 1038 had intravenous glucose tolerance test results from 1970-3, and 1093 attended for examination in 1980-4. When the 615 participants in the cohort study who were born in the Uppsala Academic Hospital were compared with the 1877 other men who had been discharged alive after birth in the Academic Hospital during 1920-4 but had not been examined in 1970-3 there were no significant differences between the two groups in birth weight, birth length, or ponderal index.

Intervals for grouping birth weight values were chosen to take account of the frequent rounding to the nearest 500 g in the original birth records. Ponderal index was calculated as birth weight divided by the cube of birth length. The acute insulin response in the intravenous glucose tolerance test was defined as the sum of 4, 6, and 8 minute insulin concentrations. Participants were classified as diabetic if one of the following criteria was fulfilled when they were examined in 1980-4: two fasting blood glucose values $>6·7$ mmol/l (one in 1970-3 and one in 1980-4); 2 hour blood glucose value and one other blood glucose value during the oral glucose tolerance test $>10·0$ mmol/l; or drug treatment for diabetes.[9] To facilitate comparison with an earlier study[10] which used fasting insulin and glucose concentrations to calculate "homeostasis model assessment" (HOMA) indices, HOMA β cell function was calculated as (insulin/(glucose-3·5)), and HOMA insulin resistance was calculated as the product of insulin and glucose values (equivalent to the original formulas without multiplying by constants).[11]

The statistical software used was SAS for Windows 6.08 (SAS Inc, North Carolina). Insulin, triglyceride, and glucose values were log transformed before computation of means, correlations, or regression models, and the values given in the tables are geometric means. Correlations were adjusted for body mass index (weight (kg)/height (m)^2) by calculating partial correlation coefficients.[12] Tests for trend in means across categories of birth weight or ponderal index were based on Spearman correlation coefficients. Associations of diabetes with birth weight or ponderal index were tested for significance by the Mantel-Haenszel test, by stratifying by third of body mass index at age 50 years. As the associations of diabetes with size at birth were clearly non-linear, in logistic regression models birth weight was dichotomised at 3250 g and ponderal index was dichotomised at the 20th centile.

Table 1—*Uppsala men at age 50 years: correlations of birth weight and ponderal index with anthropometric and metabolic variables*

	Birth weight (n=1333)		Ponderal index (n=1187)	
Variable	Unadjusted	Adjusted for body mass index aged 50	Unadjusted	Adjusted for body mass index aged 50
Body mass index	0·100 (P<0·001)		0·026	
Acute insulin response	−0·006	−0·029	0·026	0·021
Fasting insulin	−0·037	−0·095 (P=0·002)	−0·032	−0·047
60 Minute insulin	−0·052	−0·101 (P=0·001)	−0·070 (P=0·03)	−0·087 (P=0·008)
Fasting glucose	−0·052	−0·068 (P=0·01)	−0·062 (P=0·03)	−0·066 (P=0·02)
60 Minute glucose	−0·073 (P=0·02)	−0·100 (P=0·001)	−0·058	−0·066 (P=0·05)
Fasting triglyceride	−0·012	−0·056 (P=0·04)	−0·003	−0·015
Fasting high density lipoprotein cholesterol	−0·020	0·005	0·027	0·033
Homeostasis model assessment[11] β cell function	−0·003	−0·032	0·017	0·011
Homeostasis model assessment[11] insulin resistance	−0·043	−0·101 (P=0·001)	−0·046	−0·063

Results

MEASUREMENTS AT AGE 50 YEARS

Body mass index at age 50 was correlated with fasting insulin ($r=0·43$, $P<0·001$) and 60 minute insulin ($r=0·38$, $P<0·001$) and also with birth weight (table 1). After adjustment for body mass index there were significant inverse correlations of fasting and 60 minute insulin concentrations with birth weight. Ponderal index was inversely correlated with 60 minute insulin, but the correlation with fasting insulin was not significant. Because ponderal index was uncorrelated with body mass index, adjustment for body mass index did not alter the strength of the associations between ponderal index and insulin concentrations. When we excluded subjects with fasting hyperglycaemia or abnormal intravenous glucose tolerance, the inverse correlations between 60 minute insulin concentrations and size at birth persisted: after adjustment for body mass index, the correlation coefficients were −0·11 for birth weight ($P<0·001$) and −0·10 for ponderal index ($P=0·003$).

The acute insulin response in the intravenous glucose tolerance test was uncorrelated with birth weight or ponderal index.

When the relations between size at birth and insulin concentrations were examined separately in each third of the distribution of body mass index there was no evidence that the strength of the associations between birth weight and insulin concentrations varied with body mass index (table 2). The relation of ponderal index to insulin concentrations seemed to depend on body mass index (table 3): the correlation coefficient between ponderal index and 60 minute insulin concentrations was −0·05 (NS) in the lowest third of body mass index, −0·03 (NS) in the middle third, and −0·19 (P=0·001) in the highest third. This interaction between the effects of ponderal index and body mass index was tested in a least squares regression model with 60 minute insulin as dependent variable and the independent variables of age, body mass index, ponderal index, and an interaction term (ponderal index × body mass index). The interaction was significant at P=0·01. In a similar analysis with fasting insulin as the dependent variable the interaction was not significant. Concentrations of triglyceride and high density lipoprotein cholesterol were uncorrelated with birth weight or ponderal index, before and after adjustment for body mass index (table 1). There was no evidence of any interactions between the effects of body mass index and size at birth on triglyceride and high density lipoprotein cholesterol concentrations (tables 2 and 3).

Table 2—*Uppsala men at age 50 years: geometric mean concentrations of insulin, high density lipoprotein cholesterol, and triglycerides by thirds of body mass index at age 50 years and categories of weight at birth*

Detail	Geometric mean fasting insulin (n=1038)	Geometric mean 60 min insulin (n=1032)	Geometric mean high density lipoprotein cholesterol (n=1091)	Geometric mean triglyceride (n=1333)
First third of body mass index (<23·55)				
Birthweight range (g):				
<3250	9·4	17·8	1·45	1·44
≥3250-<3750	9·6	20·0	1·43	1·53
≥3750-<4250	9·1	16·1	1·44	1·45
≥4250	8·7 (P=0·39*)	16·4 (P=0·15*)	1·48 (P=0·78*)	1·41 (P=0·65*)
Second third of body mass index (23·55-25·99)				
Birthweight range (g):				
<3250	10·7	24·7	1·30	1·70
≥3250-<3750	11·5	26·3	1·32	1·71
≥3750-<4250	10·7	21·6	1·31	1·63
≥4250	9·9 (P=0·28*)	23·3 (P=0·07*)	1·33 (P=0·96*)	1·62 (P=0·62*)
Third third of body mass index (≥26)				
Birthweight range (g):				
<3250	15·5	34·8	1·21	2·09
≥3250-<3750	14·3	30·2	1·22	2·18
≥3750-<4250	13·9	29·6	1·20	2·12
≥4250	13·5 (P=0·12*)	30·0 (P=0·11*)	1·23 (P=0·84*)	2·16 (P=0·64*)

*P value is for Spearman rank correlation between variables and birthweight group.

Table 3—*Uppsala men at age 50 years: geometric mean concentrations of insulin, high density lipoprotein cholesterol, and triglycerides by thirds of body mass index at age 50 years and fifths of ponderal index at birth*

Detail	Geometric mean fasting insulin (n=932)	Geometric mean 60 min insulin (n=927)	Geometric mean high density lipoprotein cholesterol (n=977)	Geometric mean triglyceride (n=1187)
First third of body mass index (<23·55)				
Fifths of ponderal index:				
1	10·2	18·5	1·46	1·44
2	9·1	18·9	1·45	1·53
3	9·4	17·9	1·46	1·43
4	10·2	17·9	1·31	1·52
5	8·3 (P=0·06*)	16·8 (P=0·23*)	1·53 (P=0·68*)	1·44 (P=0·78*)
Second third of body mass index (23·55-25·99)				
Fifths of ponderal index:				
1	10·9	23·9	1·26	1·71
2	10·2	23·6	1·36	1·59
3	11·0	26·1	1·24	1·73
4	11·5	24·1	1·38	1·69
5	11·0 (P=0·64*)	23·7 (P=0·96*)	1·38 (P=0·12*)	1·66 (P=0·89*)
Third third of body mass index (≥26)				
Fifths of ponderal index:				
1	16·6	36·0	1·23	2·28
2	14·4	34·2	1·26	2·03
3	14·6	33·3	1·23	2·19
4	13·7	28·1	1·18	2·10
5	13·7 (P=0·03*)	27·0 (P=0·002*)	1·16 (P=0·12*)	2·25 (P=0·56*)

*P value is for Spearman rank correlation between variables and fifths of ponderal index.

GLUCOSE TOLERANCE AT AGE 60 YEARS

When prevalence of diabetes at age 60 years was compared across the four birthweight groups there was an inverse relation between birth weight and diabetes which was significant at P=0·05 after standardisation for body mass index (table 4). There was a stronger but non-linear association between ponderal index and diabetes, with prevalence of diabetes three times higher in the lowest fifth of ponderal index than in the other four fifths (table 5).

To examine the effects of adjustment for insulin concentrations the logistic regression analyses with birth weight or ponderal index as independent variables were restricted to the men on whom complete data were available for insulin concentrations in the intravenous glucose tolerance test at age 50 and for prevalence of diabetes at age 60 years (1030 men with birth weight and 920 men with ponderal index). In a model that adjusted only for age the association of diabetes with low birth weight was not significant (table 6). The relative risk was increased from 1·9 to 2·3 with adjustment for body mass index and increased further to 2·8 with adjustment for acute insulin response at age 50 years. When fasting and 60 minute insulin concentrations were included in the model with body mass index, the association of diabetes with low birth weight was no longer significant. With ponderal index instead of birth weight in these analyses the associations with diabetes were much stronger (table 7). Although the relative risk of diabetes was reduced by including fasting and 60 minute insulin concentrations in the model, the association with low ponderal index was still significant. When the logistic regression analyses were repeated with the exclusion of men who were already diabetic at age 50 years the results were similar. When product terms (birth weight×body mass index, or ponderal index×body mass index) were included in the models to test for interaction between the effects of size at birth and body mass index on diabetes prevalence, the interaction effects were not significant.

Discussion

These results confirm that reduced fetal growth is associated with increased risk of non-insulin dependent diabetes and suggest a specific association with thinness at birth. Although the relation between size at birth and risk of diabetes is clearly non-linear, there is no evidence of the U shaped relation between diabetes and birth weight reported in Pima Americans, in whom non-insulin dependent diabetes is common even in women of childbearing age.[13] McCance and colleagues suggested that the inverse association between fetal growth and diabetes could be accounted for by an inverse association between genetic susceptibility to diabetes and mortality among low birthweight infants.[13] Our results are not consistent with this explanation: when the men in this cohort were born in 1920-4 the infant mortality in Uppsala County was around 60 per 1000 live births, similar to the

Table 4—*Uppsala men at age 60 years: prevalence of diabetes by birth weight*

Detail	Range of birth weight (g)				Test for trend
	<3250	≥3250-<3750	≥3750-<4250	≥4250	
No of men	261	407	326	99	
No with diabetes	21	19	17	4	
Prevalence (%):					
Crude	8·1	4·7	5·2	4·0	NS
Standardised for body mass index at 50 years	8·7	4·6	5·2	3·3	P=0·05

Table 5—*Uppsala men at age 60 years: prevalence of diabetes by ponderal index*

Detail	Fifth of ponderal index (kg m⁻³)					Test for trend
	<24·2	≥24·2-<25·9	≥25·9-<27·4	≥27·4-<29·4	≥29·4	
No of men	193	193	196	188	201	
No with diabetes	23	10	7	8	7	
Prevalence (%):						
Crude	11·9	5·2	3·6	4·3	3·5	P=0·001
Standardised for body mass index at 50 years	12·2	5·4	3·4	4·0	3·6	P<0·001

Table 6—*Uppsala men at age 60 years (n=1030): logistic regression analyses of prevalence of diabetes in relation to birth weight, adjusted for body mass index and insulin response to intravenous glucose challenge at age 50 years*

Independent variables in model (other than age)	Relative odds (95% confidence interval) of diabetes	P value
Birth weight <3250 g	1·9 (1·0 to 3·8)	
Birth weight <3250 g	2·3 (1·1 to 4·6)	0·02
Body mass index at age 50 (1 SD increase)	2·3 (1·7 to 3·1)	<0·001
Birth weight <3250 g	2·8 (1·3 to 5·8)	0·007
Body mass index at age 50 (1 SD increase)	3·0 (2·1 to 4·1)	<0·001
Acute insulin response at age 50 (1 SD decrease)	4·4 (2·2 to 8·7)	<0·001
Birth weight <3250 g	1·6 (0·8 to 3·5)	
Body mass index at age 50 (1 SD increase)	1·6 (1·2 to 2·3)	0·004
Fasting insulin at age 50 (1 SD increase)	1·2 (0·9 to 1·6)	
60 Minute insulin at age 50 (1 SD increase)	1·7 (1·3 to 2·4)	<0·001

Table 7—*Uppsala men at age 60 years (n=925): logistic regression analyses of prevalence of diabetes in relation to ponderal index, adjusted for body mass index and insulin response to intravenous glucose challenge at age 50 years*

Independent variables in model (other than age)	Relative odds (95% confidence interval) of diabetes	P value
Ponderal index at birth (lowest fifth)	4·4 (2·2 to 8·6)	<0·001
Ponderal index at birth (lowest fifth)	4·6 (2·2 to 9·2)	<0·001
Body mass index at age 50 (1 SD increase)	2·3 (1·7 to 3·1)	<0·001
Ponderal index at birth (lowest fifth)	5·0 (2·4 to 10·5)	<0·001
Body mass index at age 50 (1 SD increase)	2·9 (2·1 to 4·0)	<0·001
Acute insulin response at age 50 (1 SD decrease)	3·5 (1·8 to 6·6)	<0·001
Ponderal index at birth (lowest fifth)	3·5 (1·7 to 7·3)	<0·001
Body mass index at age 50 (1 SD increase)	1·7 (1·2 to 2·4)	0·005
Fasting insulin at age 50 (1 SD increase)	1·2 (0·9 to 1·6)	0·22
60 Minute insulin at age 50 (1 SD increase)	1·7 (1·2 to 2·3)	0·002

national rate for Sweden.[14] Even if all these deaths had occurred in the lowest fifth of the ponderal index among infants who were not susceptible to diabetes, such selection at birth could account only for a prevalence ratio for diabetes in adults of 1·3 in the lowest fifth compared with the other four fifths. This contrasts with the prevalence ratio of 3·0 observed in this cohort. To explain the association between reduced fetal growth and glucose intolerance the Cambridge-Southampton group initially suggested that inadequate fetal nutrition might impair the development of the endocrine pancreas.[1-3] This is not consistent with the lack of association between birth weight and acute insulin response to intravenous glucose challenge in Uppsala and in an earlier study of men and women born in Preston.[4] In the Preston study insulin resistance was inversely related to ponderal index but not to birth weight[5]; this led the investigators to suggest that the association between reduced fetal growth and glucose intolerance is mediated through insulin resistance. This hypothesis is consistent with the associations of low ponderal index with raised insulin concentrations and subsequent diabetes observed in this study. Because the inverse association between ponderal index and insulin resistance is strongest in overweight people, who account for most new cases of diabetes, a weak overall association between low ponderal index and insulin resistance is compatible with a strong association between low ponderal index and diabetes.

A criticism of the fetal origins hypothesis has been that the associations of diabetes and insulin concentrations with birth weight depend on adjustment for adult body mass index, which may be inappropriate if low body mass index is a consequence of reduced fetal growth.[15] This argument does not apply to the associations with ponderal index shown in this study, which do not depend on adjustment for body mass index. Low ponderal index may be a more specific indicator of fetal malnutrition than is low birth weight.[16]

One possible explanation for the association between insulin resistance and reduced fetal growth is that inadequate nutrition programmes the fetus to develop resistance to insulin-stimulated uptake of glucose in later life: a "thrifty phenotype." Alternatively, a genetically determined defect in insulin action could manifest itself in utero as reduced growth and in later life as impairment of insulin-stimulated uptake of glucose: a "thrifty genotype." This is consistent with observations that human infants with genetic defects that cause severe insulin resistance are small at birth[17] and with observations on mice in which the gene for insulin receptor substrate-1 has been destroyed: in comparison with their normal litter mates these mice are lighter at birth and resistant to insulin-stimulated uptake of glucose as adults.[18]

In the general population insulin resistance and hyperinsulinaemia are associated with glucose intolerance, hypertension, higher concentrations of plasma triglyceride, and lower concentrations of high density lipoprotein cholesterol.[19,20] It has been suggested that impaired fetal growth may account for the clustering of these disturbances in the population, and the insulin resistance syndrome should therefore be renamed the "small baby syndrome."[21] In Uppsala men, however, as in Mexicans and Europeans in the United States[22] reduced fetal growth predicts hyperinsulinaemia and glucose intolerance but does not predict the lipid abnormalities characteristic of the insulin resistance syndrome: higher concentrations of triglycerides and lower concentrations of high density lipoprotein cholesterol. Thus the "small baby syndrome" is not identical with the syndrome of hyperinsulinaemia and lipid disturbances described by others.

In summary, our results support the hypothesis that thinness at birth is associated with insulin resistance and consequently with increased risk of non-insulin dependent diabetes. It remains to be established whether this relation is mediated by genetic or environmental influences. Our results suggest that the association may depend on an interaction with obesity in adult life; if this is correct, control of obesity is likely to

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

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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