PAPERS

Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men

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Abstract

Objectives—**To clarify the type of fetal growth impairment associated with increased blood pressure in adult life, and to establish whether this association is influenced by obesity and is mediated through impairment of insulin action.**

Design—**Cross sectional survey with retrospective ascertainment of size at birth from obstetric archives.**

Subjects—**1333 men resident in Uppsala, Sweden, who took part in a 1970 study of coronary risk factors at age 50 and for whom birth weight was traced.**

Main outcome measures—**Systolic and diastolic blood pressure at age 50.**

Results—**In the full study population for a 1000 g increase in birth weight there was a small change in systolic blood pressure of −2·2 mm Hg (95% confidence interval −4·2 to −0·3 mm Hg) and in diastolic blood pressure of −1·0 mm Hg (−2·2 to 0·1 mm Hg). Much stronger effects were observed among men who were born at term and were in the top third of body mass index at age 50, for whom a 1000 g increase in birth weight was associated with a change of −9·1 mm Hg (−16·4 to −1·9 mm Hg) systolic and −4·2 mm Hg (−8·3 to −0·1 mm Hg) diastolic blood pressure. Men who were light at birth (<3250 g) but were of above median adult height had particularly high blood pressure. Adjustment for insulin concentrations reduced the associations of birth weight with systolic and diastolic blood pressure.**

Conclusions—**A failure to realise growth potential in utero (as indicated by being light at birth but tall as an adult) is associated with raised adult blood pressure. Impaired fetal growth may lead to substantial increases in adult blood pressure among only those who become obese. Metabolic disturbances, possibly related to insulin resistance, may provide a pathway through which fetal growth affects blood pressure.**

Introduction

Studies of blood pressure in adults over the age of 20 years have consistently found a negative association with birth weight. These include investigations of blood pressure in 28 year old Swedish conscripts,[1] 36 year old men and women from the 1946 British birth cohort,[2-4] men and women aged 46-54 years born at the Sharoe Green Hospital, Preston,[5-7] those aged 50 born at the Jessop Hospital for Women, Sheffield,[8 9] and those aged between 64 and 71 born in Hertfordshire.[7 8 10]

It has been proposed that "retarded intrauterine growth" leads to adult hypertension.[11] It is implied that the important factor is being small at birth in relation to one's growth potential. In the studies so far conducted, however, growth retardation has been defined simply in terms of dimensions at birth (for example, birth weight, crown-heel length). Even when gestational age is taken into account[5 9] this does not provide a measure of actual growth relative to growth potential. A novel alternative is to suggest that a failure to achieve one's growth potential in utero could be indicated by being relatively small at birth but tall as an adult.

It has been assumed that birth weight and body mass index act independently on blood pressure.[5] If impaired fetal growth is associated with a susceptibility to increased blood pressure, however, this may be apparent only in the presence of adult risk factors such as raised body mass index. This possibility has received scant attention.

The biological mechanisms that have been proposed to explain the association between birth weight and blood pressure have tended to focus on long term structural consequences of the in utero environment. These include effects of impaired fetal growth on blood vessel structure or compliance[9 11 12] or on the number of nephrons.[13] Despite the growing evidence of an association between size at birth and insulin resistance[14 15] and the possible involvement of insulin resistance in the aetiology of hypertension[16] the possibility of a mediating role for insulin resistance has been largely overlooked.

We investigated the association between size at birth and blood pressure in a large group of 50 year old Swedish men for whom we have information on birth length and birth weight, placental weight, and gestational age.

Subjects and methods

In 1970-3 all 2841 men living in the municipality of Uppsala, Sweden, who were born between 1920 and 1924 were invited to take part in a health survey.[17] The participation rate was 82% (2322/2841). Participants were examined in the morning after an overnight fast. Height (without shoes) was measured to the nearest centimetre and weight (in undershorts) to the nearest kilogram. Blood pressure was measured once on the right arm to the nearest 5mm Hg in the supine position after 10 minutes' rest. Diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (phase V). A self administered questionnaire was used to gather information on various factors including education and alcohol consumption. As described in more detail elsewhere[14] an intravenous glucose tolerance test was performed on the last 1692 participants.

Of the initial cohort of 2322 men examined, 615 were born in the Uppsala Academic Hospital, 1585 were born elsewhere in Uppsala or in other parts of Sweden, and 122 were born outside Sweden. The birth records from the Academic Hospital comprise a complete and

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comprehensive record of all deliveries in the hospital since the 1870s. The obstetric information was recorded on detailed pro formas, and the measurements taken were almost certainly done in a systematic fashion, the obstetric department having a training function for midwives as well as medical staff. For over 95% of the subjects born in the hospital, information was found on birth weight, length, placental weight, and date of mother's last menstrual period, and hence gestational age. By searching midwives' and other obstetric archives in Uppsala and other parts of Sweden we were able to trace the birth weights of 718 of the other 1585 men who had been born in Sweden either at home or in other hospitals. For 576 of these 718 men we also obtained birth length. Birth weight was thus available for 60% (1333) and birth weight and length for 54% (1187) of the 2200 men born in Sweden. Of the 1692 men given an intravenous glucose tolerance test, birth weight was known for 1018 and birth weight and length for 896. For men with known birth weight mean (range) age at examination was 49·6 (48·6-51·1) years.

Four birthweight categories were defined (<3250, 3250-<3750, 3750-<4250, ≥4250 g) so as to minimise misclassification due to the tendency for birth weight to be recorded to the nearest whole or half kilo. Gestational age was calculated as the difference in days between the reported date of the last menstrual period and the date of delivery. Ponderal index was defined as birth weight divided by the cube of birth length. Thirds of body mass index (weight (kg)/height (m)^2) were defined based on the distribution for all 2322 men examined at age 50, with category means of 21·8 (range 15·1-23·4), 24·7 (23·5-25·9), and 28·5 (26·0-42·1). Educational level was categorised as primary only (67%), primary and secondary education (22%), or university (11%). Information on education was missing for 511 (22%).

When appropriate, linear regression was used to quantify the strength of the association between size at birth and blood pressure adjusted for potential confounders. All regression estimates were adjusted for exact age at examination. Analyses were carried out with the STATA statistical package.[18]

Results

The systolic blood pressure of those with known birth weight was 133·4 compared with 132·8 for those for whom birth weight could not be traced (P=0·40), there being virtually no difference in diastolic blood pressure. Those born in the Academic Hospital had a lower mean birth weight than those born elsewhere (3501 g *v* 3680 g, P<0·001). Men with known birth weight born in the Academic Hospital had a mean systolic blood pressure of 135·2 compared with 131·9 for men born elsewhere (P<0·001), the equivalent diastolic blood pressures being 84·5 and 83·1 (P=0·02). Mean body mass indices were very similar (25·1 *v* 25·0). Men born in the Academic Hospital were of a lower educational level, only 3% having been to university compared with 13% of those born elsewhere.

Table 1 shows blood pressure according to birth weight and body mass index at age 50. Men in the two lowest birthweight categories had higher systolic blood pressure than those in the two highest birthweight categories. Expressed as a change in blood pressure per 1000 g increase in birth weight these effects were −2·2 mm Hg systolic blood pressure (95% confidence interval −4·2 to −0·3 mm Hg) and −1·0 mm Hg diastolic blood pressure (−2·2 to 0·1 mm Hg).The strength of these associations was similar in men born in the Uppsala Academic Hospital and elsewhere.

GESTATIONAL AGE

Gestational age was known for 577 men born as singletons in the Uppsala Academic Hospital. Table 2 shows mean blood pressures in this group by birth weight and gestational age defined as preterm, term, and post-term.[19] A clear decline in blood pressure with increasing birth weight was apparent among men who were born at term. For a 1000 g increase in birth weight there was a change in systolic blood pressure of −4·9 mm Hg (−8·7 to −1·0 mm Hg) and in diastolic blood pressure of −1·9 mm Hg (−4·1 to 0·4 mm Hg). These effects were larger and more consistent than among all men with known gestational age. In those who were preterm there was evidence of a significant positive trend of blood pressure with birth weight that was significantly different from the trend observed for term births (P<0·001), whereas those born after term showed no clear pattern.

ADULT HEIGHT AND GROWTH POTENTIAL

Adult height and birth weight were significantly correlated in our data (*r*=0·22; P<0·001). Table 3 shows mean blood pressure by birth weight and adult height dichotomised around the median of 176 cm. Those men who were above the median height at age 50 but weighed less than 3250 g at birth had the highest blood pressures of all, even when compared with men of the same birth weight who were shorter. The difference in blood pressure by height within the lowest birthweight category was significant for diastolic blood pressure (P=0·02). Men in the other discordant cell of the table (those in the top birth weight but the bottom height group) had higher blood pressure than men in the same birth weight group who were taller. The change in systolic blood pressure per 1000 g increase in birth weight was −4·2 mm Hg (−7·2 to −1·3 mm Hg) for men of above median adult height

Table 1—*Mean systolic and diastolic blood pressure (mm Hg) at age 50 by birth weight and body mass index at age 50 among men resident in Uppsala, Sweden, in 1970. Figures in parentheses are numbers of men*

Body mass index (kg/m^2)	Birth weight (g) <3250	3250-<3750	3750-<4250	≥4250	Total	P value for trend
<23·5:						
Systolic blood pressure	128·5 (115)	131·3 (171)	127·7 (108)	125·4 (36)	129·2 (430)	0·51
Diastolic blood pressure	78·8	81·7	79·2	78·2	80·0	0·92
23·5-25·9:						
Systolic blood pressure	134·5 (99)	132·7 (176)	130·0 (148)	129·1 (32)	131·9 (455)	0·02
Diastolic blood pressure	84·3	83·5	82·2	82·5	83·2	0·05
≥26·0:						
Systolic blood pressure	141·7 (92)	140·3 (170)	136·2 (135)	137·8 (51)	139·1 (448)	0·02
Diastolic blood pressure	89·5	88·9	86·5	85·8	87·9	0·01
Total:						
Systolic blood pressure	134·4 (306)	134·7 (517)	131·5 (391)	131·7 (119)	133·4 (1333)	0·02
Diastolic blood pressure	83·8	84·7	82·9	82·6	83·7	0·08

Table 2—*Mean systolic and diastolic blood pressure (mm Hg) at age 50 by birth weight and gestational age among singleton men resident in Uppsala, Sweden, in 1970. Figures in parentheses are numbers of men*

Gestational age	Birth weight (g) <3250	3250-<3750	3750-<4250	≥4250	Total	P value for trend
Preterm (≤37 weeks):						
Systolic blood pressure	132·5 (40)	141·2 (13)	158·3 (6)	162·5 (2)	137·9 (61)	<0·01
Diastolic blood pressure	82·8	86·2	97·5	97·5	85·4	0·05
Term (38-41 weeks):						
Systolic blood pressure	136·7 (97)	135·8 (204)	132·9 (113)	128·6 (28)	134·8 (442)	0·02
Diastolic blood pressure	84·4	85·2	83·3	81·6	84·3	0·18
Post-term (≥42 weeks):						
Systolic blood pressure	125·5 (11)	137·4 (38)	133·4 (19)	142·5 (6)	135·2 (74)	0·23
Diastolic blood pressure	78·2	86·6	83·9	90·0	84·9	0·16
All with gestational age:						
Systolic blood pressure	134·7 (148)	136·3 (255)	134·1 (138)	132·8 (36)	135·1 (577)	0·47
Diastolic blood pressure	83·5	85·4	84·0	83·9	84·5	0·98

Table 3—*Mean systolic and diastolic blood pressure (mm Hg) at age 50 by birth weight and height at examination among men resident in Uppsala, Sweden, in 1970. Figures in parentheses are numbers of men*

Height* at age 50 (cm)	Birth weight (g) <3250	3250-<3750	3750-<4250	≥4250	Total	P value for trend
≤176:						
Systolic blood pressure	133·2 (196)	134·6 (284)	130·2 (179)	136·5 (43)	133·2 (702)	0·46
Diastolic blood pressure	82·5	85·4	82·7	85·1	83·9	0·62
>176:						
Systolic blood pressure	136·6 (110)	134·9 (233)	132·6 (212)	129·0 (76)	133·7 (631)	<0·01
Diastolic blood pressure	86·0	83·7	83·0	81·2	83·6	<0·01

*In full data set of 2322 men median height was 176 cm.

Table 4—*Mean systolic and diastolic blood pressure (mm Hg) at age 50 by birth weight and height among men in top third of distribution of body mass index at age 50 resident in Uppsala, Sweden, in 1970. Figures in parentheses are numbers of men*

Height* at age 50 (cm)	Birth weight (g) <3250	3250-<3750	3750-<4250	≥4250	Total	P value for trend
≤176:						
Systolic blood pressure	135·5 (54)	139·9 (103)	135·6 (66)	141·5 (23)	137·9 (246)	0·90
Diastolic blood pressure	86·0	89·1	86·8	87·4	87·7	0·65
>176:						
Systolic blood pressure	150·5 (38)	140·9 (67)	136·7 (69)	134·8 (28)	140·4 (202)	<0·001
Diastolic blood pressure	94·5	88·4	86·2	84·5	88·3	<0·001

*In full data set of 2322 men median height was 176 cm.

and −1·0 mm Hg (−3·6 to 1·6 mm Hg) for those who were shorter. The equivalent estimates for diastolic blood pressure are −2·7 mm Hg (−4·5 to −0·9 mm Hg) and 0·4 mm Hg (−1·2 to 2·0 mm Hg) for the taller and shorter, respectively, this difference in the diastolic blood pressure slopes between height groups being significant (P=0·01). The body mass index for men who were below and above median height was 25·1 and 25·0, respectively.

Men of above median height who weighed less than 3250 g at birth were delivered with the lightest placentas of any group in table 3, including those in the same birthweight group who were shorter at age 50. Men who were singleton, term births weighing less than 3250 g at birth and who were of above median height at age 50 had a mean placental weight of 534 g compared with 573 g for those in the same birthweight group who were shorter. This is despite the fact that they had a somewhat higher birth weight (3061 *v* 2935 g). When this difference in birth weight is accounted for, the difference in placental weights by height in the lowest birthweight group is more pronounced and becomes significant (P=0·045).

BODY MASS INDEX

In our data, birth weight was positively correlated with body mass index at age 50 (r=0·09; P<0·01). On adjustment for body mass index the crude effects of birth weight were strengthened: a 1000 g increase in birth weight being associated with a change of −3·1 mm Hg systolic blood pressure (−5·0 to −1·2 mm Hg) and −1·7 mm Hg diastolic blood pressure (−2·9 to −0·6 mm Hg). It is a consistent feature of our data, however, that the effect of birth weight on blood pressure was most pronounced among men in the top part of the distribution of body mass index. This is apparent from inspection of table 1, in which only weak associations between birth weight and blood pressure are seen among men in the bottom third of body mass index, stronger and more consistent effects being seen in the middle and top thirds.

The enhancement of the association of birth weight with blood pressure in men in the upper part of the distribution of body mass index is well illustrated in table 4. This shows the same contrasts in blood pressure by adult height and birth weight as presented in table 3 but restricted to men in the top third of body

Table 5—*Slope of relation of systolic and diastolic blood pressure (mm Hg)* at age 50 per 1 kg increase in birth weight by thirds of distribution of body mass index at age 50 for subgroups of study population of men resident in Uppsala, Sweden, in 1970. Figures in parentheses are numbers of men*

	Third of body mass index (kg/m²) at age 50						
	<23·5		23·5-25·9		≥26·0		
Study subgroup	Difference	95% Confidence interval	Difference	95% Confidence interval	Difference	95% Confidence interval	P value for interaction†
All subjects (1333):							
Systolic blood pressure	−1·3 (430)	−4·3 to 1·7	−3·9 (455)	−7·1 to −0·6	−4·1 (448)	−7·6 to −0·5	0·40
Diastolic blood pressure	0·2	−1·9 to 1·6	−2·1	−4·2 to −0·1	−2·8	−5·0 to −0·8	0·10
Singletons, gestation 38-41 weeks (term) (442):							
Systolic blood pressure	−1·4 (136)	−7·6 to 4·7	−3·5 (154)	−10·1 to 3·1	−9·1 (152)	−16·4 to −1·9	0·06
Diastolic blood pressure	1·2	−2·8 to 5·1	−2·7	−6·6 to 1·3	−4·2	−8·3 to −0·1	<0·01
Adult height > median of 176 cm (631):							
Systolic blood pressure	−2·1 (211)	−6·8 to 2·5	−2·3 (218)	−7·1 to 2·5	−9·3 (202)	−14·8 to −3·8	<0·01
Diastolic blood pressure	−1·5	−4·1 to 1·0	−1·8	−5·1 to 1·5	−5·5	−8·6 to −2·3	0·03

*Adjusted for exact age and body mass index at examination as continuous variables.
†Interaction between birth weight and body mass index assessed by fitting model based on body mass index and birth weight as continuous variables with term equal to product of birth weight and body mass index.

mass index. Compared with the effects seen in table 3 for the total study population, in table 4 the trends with birth weight among the taller men are steeper, and the blood pressure differences by height in the lowest birth weight group are larger and are significant for both systolic blood pressure ($P<0{\cdot}001$) and diastolic blood pressure ($P=0{\cdot}001$).

Table 5 provides a more systematic examination of this interaction of body mass index with birth weight. As body mass index increased the association of birth weight with blood pressure became stronger. This is apparent for the total study population, the subset of singleton term births, and the subset of men who were of above median adult height. The interaction was significant for diastolic blood pressure among men who were term singleton births and for systolic blood pressure and diastolic blood pressure among men of above median height. The largest effects of birth weight on blood pressure were in the group of 66 men born at term, who at age 50 were of above median height and in the top third of body mass index, among whom a 1000 g increase in birth weight was associated with a change of −15·9 mm Hg (−26·5 to −5·2 mm Hg) systolic and −7·4 mm Hg (−14·4 to −0·4 mm Hg) diastolic blood pressure.

INSULIN RESISTANCE

In this study population blood pressure and 60 minute insulin concentrations were positively correlated.[20] As shown in table 6, adjustment for the log transformed value of 60 minute insulin consistently reduced the size of the associations between blood pressure and birth weight, although the effects of adjustment were modest in size.

EDUCATION AND ALCOHOL

Adjustment for educational level at age 50 and alcohol consumption in the day before examination had no consistent effect on the associations. The maximum change in the estimates due to adjustment was 0·2 mm Hg for a 1000 g difference in birth weight.

OTHER BIRTH DIMENSIONS

In our data there were no significant effects of ponderal index on systolic or diastolic blood pressure. Contrary to previous reports[5] there was little evidence of increased blood pressure among men who were light at birth but had large placentas.

Discussion

Our total study population showed a weak negative association between birth weight and blood pressure at age 50 consistent with the results of other studies.[1 2 5 7 9] These associations, however, were much stronger and more consistent in men born at term and in those in the top third of body mass index at age 50. Moreover, men who failed to express their full growth potential in utero, in that they were light at birth but grew to be tall adults, had particularly high blood pressure.

Earlier studies of birth weight in relation to adult blood pressure have tended to concentrate on systolic blood pressure; our data show clearly that diastolic blood pressure has similar patterns of association. In line with other studies, we have found that socioeconomic confounding[2 4 5] and alcohol consumption[9] do not explain the association of birth weight with blood pressure. Consistent with a recent study of blood pressure in 50 year old men and women born in Sheffield[9] we found no evidence that high placental weight or a high placental to birth weight ratio was associated with increased blood pressure[5] nor of a negative association between ponderal index at birth and blood pressure.[6] This latter observation contrasts with our finding that, in this group of Swedish men, ponderal index rather than birth weight is most strongly associated with the risk of non-insulin dependent diabetes.[14]

It is well known that adult height is correlated with birth weight even after adjustment for socioeconomic circumstances.[21 22] The notion of measuring growth potential in utero by reference to attained adult height, however, is a novel one. In doing this we are making the reasonable assumption that in well nourished

Table 6—*Slope of relation of systolic and diastolic blood pressure (mm Hg)* at age 50 per 1000 g increase in birth weight among men in top third of distribution of body mass index at age 50 who were resident in Uppsala, Sweden, in 1970*

	Difference (95% confidence interval)	
Study group	Not adjusted	Adjusted†
All subjects (n=347):		
Systolic blood pressure	−2·8 (−6·8 to 1·0)	−2·1 (−6·1 to 1·9)
Diastolic blood pressure	−2·6 (−5·0 to −0·3)	−2·3 (−4·6 to 0·0)
Adult height > median of 176 cm (n=157):		
Systolic blood pressure	−7·8 (−14·1 to −1·6)	−7·1 (−13·3 to −0·8)
Diastolic blood pressure	−5·8 (−9·4 to −2·3)	−5·3 (−8·8 to −1·8)

*Adjusted for exact age and body mass index at examination as continuous variables and restricted to men in top third of distribution of body mass index for whom 60 minute insulin concentration was measured and recorded.
†Adjusted for log 60 minute insulin concentration.

populations, such as found in Sweden this century, adults who are tall are going to tend to be those who genetically have higher growth potential than those who are short adults. The validity of our approach is supported by the intriguing fact that, in clear contrast with birth weight, adult height among men born during or after the Dutch hunger winter of 1944-5 was not related to whether their mothers were exposed to famine conditions during their time in utero.[23] We propose that men who were light at birth (< 3250 g) but grew to be of above median height (> 176 cm) include a disproportionate number of those whose fetal growth was impaired, in that they failed to realise their growth potential in utero. The plausibility of this is enhanced by the fact that these men had particularly light placentas, suggesting that their reduced birth weight reflected placental insufficiency. The raised blood pressure of this group may thus be due to disturbances in fetal growth in part mediated by placental insufficiency rather than growth in the postnatal period.[24]

Men heavy at birth but of median height or less at age 50 also had somewhat raised blood pressure. This group may include a disproportionate number of macrosomic babies, born to mothers who had impaired glucose tolerance during pregnancy, who are thought to have abnormal metabolism in later life.[25]

GESTATIONAL AGE

Only two other studies of the association of birth weight with blood pressure in adult life have included data on gestational age.[5,9] Adjustment for length of gestation had little if any effect on the association, strongly suggesting that variation in fetal growth rate is important, rather than gestational age per se. What is intriguing about gestational age in our data is that men born at term (38 to 41 weeks) show a stronger negative association between birth weight and blood pressure than in the study population as a whole. This has been observed previously,[9] although little attention was given to it. We suggest that it is among term deliveries that birth weight most directly reflects underlying processes of fetal growth impairment. In preterm births this correlation will be weaker, as variations in birth weight are principally accounted for by differences in gestational age rather than by differences in fetal growth rate. The fact that babies born after term often have birth weights higher than those born at term does not preclude fetal growth impairment. Babies born after term have raised infant mortality,[19] and large babies who endure a particularly extended gestation might be subject to fetal growth impairment precisely because their demands for nutrients outstrip the reserve capacity of the mother and placenta.[26]

ADULT BODY MASS INDEX

Birth weight is positively correlated with adult body mass index, which in turn is one of the strongest influences on blood pressure. Not surprisingly, therefore, it has been found repeatedly that the association of birth weight with blood pressure is strengthened on adjustment for this factor. It has been suggested, however, that to adjust for body mass index is to ignore the advantage of being small at birth that follows from the association with lower body mass index in adulthood.[27] Simply to adjust for adult body mass index may not be appropriate for another reason. Parallel to the interaction we have already reported between body mass index and ponderal index with respect to insulin concentrations in this cohort of Uppsala men[14] we found evidence of an interaction of body mass index and birth weight with respect to blood pressure. Such an interaction has not been reported previously, possibly because in comparison with our Uppsala men the other adult populations examined have body mass index distributions that are shifted to the right and have smaller proportions of people with low body mass index. The interactions we observed in Uppsala question the logic of attempting to partition the variation in blood pressure or impaired glucose tolerance between factors in fetal and adult life as the impact of each is dependent on the level of the other.

An interaction between body mass index and size at birth with respect to adverse health outcomes in adult life, such as raised blood pressure and impaired glucose tolerance, might be a manifestation of the same underlying process that leads to increased prevalence of these conditions among migrant groups, who originate in populations that have a low plane of nutrition and move to westernised societies with diets of much higher energy density (more fats and refined carbohydrates). The relevance of the high prevalence of diabetes among Ethiopian Jews who migrated to Israel in the 1980s[28] has already been discussed in the context of the fetal origins of diabetes hypothesis.[29] These ideas, however, have not been extended to suggest that in any population it is those who are obese in adult life who will show the strongest effects of variations in fetal growth on their adult metabolism and disease status.

The mechanisms that underlie the association between impaired fetal growth at term and blood pressure in adult life are unclear. The 60 minute insulin concentrations after an intravenous glucose tolerance test administered to the 50 year old men in our study may be regarded as a rough measure of insulin resistance.[14] Adjustment for it led to a moderate reduction in the strength of the birth weight-blood pressure association, and larger reductions may have been evident if a better measure of insulin resistance had been available. This suggests that disturbances in insulin mediated carbohydrate metabolism[16] may be one of the factors mediating the association between impaired fetal growth and adult blood pressure.

Key messages

- In adult life diastolic and systolic blood pressure decline as birth weight increases among those born at term (38-41 weeks)
- These associations are strongest among those who are obese and seem to be almost absent among those who are thin
- Men who were light at birth but grew to be tall adults seem to have particularly high blood pressure, suggesting that it is a failure to realise growth potential in utero that is important
- Impairment of insulin action may mediate at least part of the association between fetal growth impairment and blood pressure

CONCLUSION

Our evidence clearly shows that diastolic and systolic blood pressures are inversely associated with birth weight among those born at term. We suggest that it is a failure to express one's full growth potential in utero, rather than small size at birth per se, that is related to raised adult blood pressure. In part, this failure may be due to placental insufficiency. The pronounced interactions with body mass index that we observe in our data suggest that impaired fetal growth may be associated with a propensity to develop high blood pressure that is only fully expressed among those who become obese in adult life. The mechanisms underlying this phenomenon are as yet unresolved, 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=−0·07, 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=−0·19, 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