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Testing the fetal origins hypothesis in twins: the Birmingham twin study

J. Baird[1], C. Osmond[1], A. MacGregor[2], H. Snieder[2], C. N. Hales[3], D. I. W. Phillips[1]

[1] MRC Environmental Epidemiology Unit, Southampton General Hospital, Tremona Road, Southampton, UK
[2] The Twin Research & Genetic Epidemiology Unit, St Thomas' Hospital, Lambeth Palace Road, London, UK
[3] The Dept of Clinical Biochemistry, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge, UK

Abstract

Aims/hypothesis. To test whether the link between birthsize and raised blood pressure or glucose tolerance is due to genetic or intrauterine factors, we studied whether differences in birthweight between pairs of monozygous and dizygous twins are associated with adult differences in blood pressure and glucose tolerance.
Methods. A sample of 58 monozygous and 140 dizygous twins were identified from a register of births in Birmingham, United Kingdom, between 1950 and 1954. The twins had their blood pressure measured and underwent an oral glucose tolerance test.
Results. There were no statistically significant associations between birthweight, length or ponderal index, and either blood pressure or glucose tolerance in the twins. Although there were substantial within-pair differences in birthweight between monozygous and dizygous twin pairs, these differences did not correlate with the adult outcomes. Monozygous correlations, however, for both blood pressure and glucose tolerance were statistically significantly higher than dizygous correlations and a quantitative genetic model suggested statistically significant heritability for these traits. In contrast correlations of birthsize were similar in monozygous and dizygous pairs suggesting only a small genetic component in determining fetal size.
Conclusion/interpretation. Our results show that birthsize in twins does not predict adult blood pressure or glucose tolerance. We also suggest that shared genetic determinants for fetal growth and adult outcomes are not likely to be prevalent or powerful. [Diabetologia (2001) 44: 33–39]

Keywords Fetal growth, birthweight, twins, programming, blood pressure, glucose tolerance, the "fetal origins" hypothesis.

A series of studies from Europe, the United States and developing countries, has shown that low birthweight, or other indices of suboptimal fetal growth including thinness or stunting at birth, are linked with raised blood pressure, glucose intolerance and an increased risk of coronary heart disease in adult life [1]. Although the mechanisms are not understood, two possible explanations account for these associations. The first is that they arise as a result of programming. This term is used to describe persistent changes in structure and function caused by fetal undernutrition or exposure to other adverse influences during critical periods of development. It was suggested that the undernourished fetus makes metabolic and endocrine adaptations which benefit it in the short term but are detrimental in the long term [2, 3]. The second explanation is that the associations represent the influence of one or more genes which influence fetal growth and predispose infants to raised blood pressure or metabolic disease in adult life. As insulin has a central role in controlling fetal growth, genetic factors which increase insulin resistance or impair insulin secretion would reduce fetal growth [4]. This has been shown experimentally in transgenic mice lacking key intermediates in the insu-

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Corresponding author: Prof. D. I. W. Phillips PhD FRCP, MRC Unit, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
Abbreviations: WHR, Waist-to-hip ratio

lin signalling pathway [5], in human infants with inherited insulin receptor mutations [6], or as a result of genetic polymorphisms which influence insulin secretion [7, 8].

Studies of twins provide an opportunity to distinguish between these two hypotheses. The birthweights of monozygous twins are frequently dissimilar as a result of the unequal partitioning of nutrients or placental blood supply between them. Because of their genetic identity, associations between within-pair differences in birthsize and adult outcomes cannot have a genetic basis and must depend on environmental differences between the twins. In addition, by investigating within-pair differences in twins parental confounding factors (such as smoking and socioeconomic class) are controlled. Few studies, however, have examined the long-term effects of discordant prenatal twin growth. A study on extreme differences in birthweight in monozygous pairs has shown that the smaller twin at birth remained the smaller in height, weight and head circumference in adult life [9]. An analysis based on the Danish twin register identified 14 monozygous twin pairs who were discordant for Type II (non-insulin-dependent) diabetes mellitus and showed that the diabetic twins had statistically significanlty lower birthweight than the non-diabetic co-twins [10]. Two recent studies found that the lighter twin at birth in monozygous and dizygous pairs had higher blood pressure [11, 12]. One of these studies, however, was based on 8-year-old children and the other depended on self-reported birthweight in a volunteer cohort of adult twins. We have therefore examined the relation between birthsize and adult obesity, glucose tolerance or blood pressure in a population-based sample of adult twins born in Birmingham, United Kingdom, from 1950 to 1954 where birthweight and other obstetric details were recorded as part of a longitudinal study of births. First, we tested the hypothesis that within-pair differences in birthsize are linked with within-pair differences in obesity, glucose tolerance or blood pressure in adult life. Second, by making use of the classical twin design we estimated to what extent genetic factors influence birthweight and adult-outcome variables.

Subjects and methods

Subjects. From 1950 onwards details of all births in the City of Birmingham, including those delivered at home, were recorded [13]. The records included birthweight (pounds), length at birth from crown to heel (inches) and gestational age (estimated from the date of the mothers' last menstrual period). Between 1950 and 1954 there were 94474 births in Birmingham. Twin births were ascertained by a search for pairs of subjects with matching dates of birth, surname, maiden name of the mother and address at birth. When the twin status was not certain, copies of the birth certificates were obtained to check that the address, date and time of birth were consistent with those recorded in the birth register. Using this technique, 2560 twins (1280 pairs) born from 1950 to 1954 were identified, of which 796 (400 men, 396 woman) were of the same and 484 of the opposite sex to the other. We used the National Health Service (NHS) central register to trace the 477 twin pairs, now in middle-age, who were still residing in Birmingham or the surrounding health authority areas of Solihull, Sandwell, Dudley, Staffordshire, Coventry, Warwickshire and Hereford and Worcester. A total of 508 twins (53% of the original sample) with complete birthweight information agreed to take part. This sample included 198 complete twin pairs. Each twin was visited at home by one of three trained field workers who did not know the twin's birth details. Zygosity was ascertained by a standard questionnaire [14]. Subjects were asked about their smoking habits, alcohol consumption, current and past medical history, current medication and family history. A standard series of questions was asked to assess the past and current level of physical activity . Current social class was based on the subject's or husband's occupation. During the interview the twins' height was measured using a portable stadiometer (CMS weighing Equipment, Camden, London, UK) and weight by a SECA scale (SECA, Birmingham, UK). Body mass index (BMI) was calculated as the weight (kg) divided by the height (m^2). The waist and hip circumferences were measured with a steel tape measure and the waist-to-hip ratio (WHR) calculated. Before starting the study the measurement procedures were standardised and no important inter-observer differences were found during checks throughout the survey. Ethics approval was obtained from each of the health authority areas in which subjects resided and each participating subject gave their informed consent.

The twins were invited to attend a local clinic after an overnight fast. Excluding two male twins (both monozygous) who were known to suffer from diabetes, the remainder had a standard 75 g oral glucose tolerance test. Plasma glucose and insulin concentrations were measured at 0, 30 and 120 min using standard assays [15]. Of the twins seen at home, 372 (73%) had full glucose tolerance tests comprising 44 monozygous pairs, 91 dizygous pairs and 102 twins with a co-twin who was not studied. We used the revised World Health Organisation (WHO) criteria for diagnosing Type II Diabetes (fasting plasma glucose ≥ 7.0 mmol/l or 2-h plasma glucose ≥ 11.1 mmol/l), impaired glucose tolerance (fasting plasma glucose < 7.0 mmol/l and 2-h plasma glucose ≥ 7.8 but < 11.1 mmol/l) and impaired fasting glycaemia (fasting plasma glucose ≥ 6.1 but < 7.0 mmol/l) [16]. We calculated the glucose and insulin areas under the curve with the trapezoidal rule.

Statistical analysis. Regression was used to estimate the extent to which within-pair differences in birth size account for within-pair differences in adult outcome variables. The measurements of glucose and insulin were log-transformed to normality before analysis. We used multiple linear regression to analyse the relation of between-twin differences in birthweight, length and ponderal index (defined as weight/length^3) with the between-twin differences in blood pressure and glucose tolerance in adult life. The regression line was constrained to pass through the origin so that the results were independent of whether the twin was labelled as the first or second. Significant differences were defined as a p value of less than 0.05 using two-tailed tests.

Quantitative genetic model fitting. In our second analysis we used the twin design to assess the extent to which differences in birthweight and adult outcome variables is explained by genetic variation using maximum likelihood model fitting. The technique is based on comparing the covariances (or correla-

Table 1. Means (SD) of birthsize, gestational age, current BMI, WHR, blood pressure and glucose tolerance according to zygosity

	Monozygous twins	Dizygous twins	Twin with co-twin not studied
No. of twins	116	280	112
Age (years)	43.7 (1.4)	43.7 (1.4)	43.4 (1.4)
Birthweight (Kg)	2.43 (0.46)	2.51 (0.47)	2.53 (0.51)
Length at birth (cm)	46.9 (2.7)	47.0 (2.7)	47.8 (3.0)
Gestational age (weeks)	37.7 (2.3)	37.8 (2.4)	37.9 (2.7)
BMI (kg/m^2)	25.5 (3.9)	26.1 (4.4)	26.7 (5.0)
Waist-to-hip ratio(%)	83.9 (9.7)	84.8 (9.2)	83.9 (8.6)
Systolic blood pressure (mmHg)	130.5 (12.5)	131.2 (16.9)	130.8 (15.9)
Glucose tolerance			
No. of twins	88	182	102
Fasting glucose (mmol)[a]	5.1 (1.1)	5.1 (1.1)	5.3 (1.1)
Fasting insulin (pmol)[a]	34.7 (1.8)	35.6 (1.6)	45.1 (1.7)
30-min glucose (mmol)[a]	7.5 (1.2)	7.9 (1.2)	7.8 (1.2)
30-min insulin (pmol)[a]	300 (1.8)	294 (1.7)	301 (1.8)
2-h glucose (mmol)[a]	5.3 (1.3)	5.4 (1.3)	5.5 (1.3)
2-h insulin (pmol)[a]	161 (2.3)	159 (2.1)	168 (2.3)
Glucose area (h · mmol/l)[a]	12.8 (1.1)	13.3 (1.2)	13.4 (1.2)
Insulin area (h · pmol/l)[a]	462 (1.7)	450 (1.6)	472 (1.7)
No. with diabetes (%)	0 (0)	2 (1)	3 (3)
No. with impaired glucose tolerance (%)	3 (3)	11 (6)	5 (5)
No. with impaired fasting glycaemia (%)	0 (0)	2 (1)	2 (2)

[a] geometric

tions) in monozygous and dizygous twin pairs and allows separating the observed phenotypic variance into additive (A) or dominant (D) genetic components and shared (C) or unique (E) environmental components. The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, for example the heritability (h^2) which can be defined as the proportion of the total variance attributable to genetic variation. A weakness of this model is that the estimated heritability includes both genetic effects and early environmental influences resulting from the more similar prenatal environment of monozygous compared with dizygous twins [17].

For analysis, we categorised twin pairs into five groups according to their sex and zygosity (male and female, monozygous and dizygous pairs, and dizygous pairs of the opposite sex).We did a univariate analysis calculating intra-class correlation coefficients to assess the heritability of birthsize and adult outcome variables. Sex differences in variance component estimates were examined by comparing the full model in which variable estimates were allowed to differ between men and women with a reduced model in which variable estimates were constrained to be equal across the sexes. The significance of variance components A, C, D was assessed by testing the deterioration in model fit after each component was dropped from the full model. We used standard methods to select the models which reflected the best balance between goodness of fit and parsimony [18].

Results

The characteristics of the twin pairs where both twins had blood pressure measured and oral glucose tolerance tests performed compared with twins where only one member of the pair had these measurements are shown in Table 1. There were no statistically significant differences in age, birthweight, birthlength or gestational age between the monozygous and dizygous twins. The levels of obesity, systolic blood pressure, fasting, 30-min, and 2-h glucose and insulin concentrations and glucose and insulin areas were also similar. The unpaired twins who had a co-twin who was not studied were slightly more obese and had higher fasting insulin concentrations ($p < 0.001$) than the paired monozygous and dizygous twins. Their 30-min and 2-h glucose and insulin concentrations, however, were similar. In the overall sample of twins a total of five subjects (1.3%) had Type II Diabetes, 19 (5.1%) had impaired glucose tolerance and 4 (1.1%) impaired fasting glycaemia (IFG). There were, however, no statistcally significant differences in the prevalence of glucose intolerance or diabetes between monozygous and dizygous twins or between the paired and unpaired twins.

Among the monozygous pairs 12 (21%) had a 1-pound (0.45 kg) or greater difference in birthweight between the members of the pair, whereas in 4 (7%) the difference in birthweight was 1.5 pounds (0.68 kg) or more. Within-pair differences between dizygous twins were similar, 43 (31%) having a 1 pound (0.45 kg) or greater difference and 15 (11%) having a 1.5-pound (0.68 kg) or greater difference. The results of an analysis relating within-pair differences in height, weight, BMI, blood pressure and glucose tolerance to these within-pair differences in birthweight are shown in Table 2. Our analysis showed that monozygous and dizygous twins have a positive correlation between differences in birthweight and adult

Table 2. Difference in outcome variable for every kilogram difference in birthweight in monozygous and dizygous twins and all twins combined

Outcome variable	Monozygous twins (95 % CI)	Dizygous twins[a] (95 % CI)	All twins[a] (95 % CI)
Height (cm)	3.3 (1.6 to 5.0)[c]	4.1 (1.6 to 6.7)[c]	4.0 (2.0 to 5.9)[c]
Weight (kg)	2.4 (–3.9 to 8.6)	6.0 (–0.4 to 12.4)	5.2 (0.2 to 10.2)[c]
BMI (kg/m^2)	–0.1 (–2.2 to 1.9)	0.9 (–1.3 to 3.1)	0.7 (–1.1 to 2.4)
Waist-to-hip ratio(%)	1.6 (–4.9 to 8.0)	4.5 (–1.0 to 9.9)	3.8 (–0.5 to 8.2)
Systolic blood pressure[b](mmHg)	5.8 (–3.5 to 15.2)	2.6 (–5.5 to 10.7)	3.3 (–3.1 to 9.7)
Fasting glucose[b](log mmol)	0.04 (–0.02 to 0.10)	0.06 (–0.01 to 0.12)	0.05 (0.01 to 0.10)[c]
Fasting insulin[b](log pmol)	0.12 (–0.36 to 0.59)	0.07 (–0.24 to 0.38)	0.08 (–0.18 to 0.33)
30-min glucose$^+$(log mmol)	0.04 (–0.14 to 0.22)	–0.02 (–0.13 to 0.10)	0.00 (–0.10 to 0.09)
30-min insulin$^+$(log pmol)	–0.19 (–0.63 to 0.25)	–0.03 (–0.39 to 0.33)	–0.05 (–0.34 to 0.23)
2-h glucose$^+$(log mmol)	0.13 (–0.10 to 0.35)	–0.10 (–0.27 to 0.06)	–0.04 (–0.18 to 0.09)
2-h insulin$^+$(log pmol)	0.12 (–0.64 to 0.88)	–0.35 (–0.82 to 0.12)	–0.23 (–0.62 to 0.16)

[a] Adjusted for gender differences [b] adjusted for BMI [c] $p < 0.05$

Table 3. Twin correlations according to zygosity and sex

	Monozygous twins		Dizygous twins		
	Men	Women	Men	Women	Unlike-sexed
No. of pairs	30	28	35	45	60
Birthweight (kg)	0.78	0.65	0.62	0.56	0.67
Birthweight[a](kg)	0.70	0.52	0.37	0.23	0.53
Height (m)	0.90	0.92	0.46	0.42	0.43
Weight (kg)	0.66	0.82	0.18	0.36	0.18
BMI (kg/m^2)	0.64	0.81	0.17	0.28	0.11
Waist-to-hip ratio (%)	0.34	0.73	0.19	0.15	0.06
Systolic blood pressure (mmHg)	0.33	0.64	0.15	0.32	0.24
Fasting glucose (mmol)	0.20	0.54	0.06	0.18	0.16
Fasting insulin (pmol)	0.51	0.72	–0.35	0.12	0.00
2-h glucose (mmol)	0.39	0.42	–0.2	0.33	0.01
2-h Insulin(pmol)	0.49	0.34	–0.54	0.26	–0.04

[a] Adjusted for gestational age

height indicating that the smaller twin at birth became the shorter adult. There were, however, no correlations between within-pair differences in birthweight and adult obesity, blood pressure or the measurements of insulin or glucose. These findings were not affected by adjustment for current social class, alcohol intake, hypertensive medication, smoking or the level of physical activity. The results were similar when the monozygous and dizygous twins were combined into one group, although in this combined analysis adult weight and fasting plasma glucose (after adjustment for BMI) were somewhat lower in the smaller twin at birth. A further analysis showed no relation between adult obesity, blood pressure or glucose tolerance and within-pair differences in length or ponderal index.

In the combined group of 508 subjects (including both twin pairs and twins with a co-twin who was not studied) there were no statistically significant associations between birthweight and systolic blood pressure [systolic pressure rose by 1.1 mmHg (95 % CI –2.1 to 4.3 mmHg) per kg increase in birthweight]. Likewise, there were no statistically significant associations between birthweight and glucose tolerance [2-h plasma glucose fell by 1.5 % (95 % CI –3.8 to 6.6 %) per kg increase in birthweight]. Similar results were obtained after adjustment for gestational age.

The twin intra-class correlation coefficients for birthweight, birthweight adjusted for gestational age, height, weight, BMI, WHR, blood pressure, fasting insulin and the 2-h glucose and insulin concentrations are shown in Table 3. Twin correlations for birthweight were high in both monozygous and dizygous twin pairs, indicating shared environmental influences. Adjusting for gestational age (which explained 32 % of the variance in birthweight) reduced the twin correlation especially in the same-sexed dizygous pairs. In general monozygous correlations were higher than dizygous correlations for all other traits which is consistent with a statistically significant genetic influence although the effect of intrauterine factors cannot be excluded. Probably because of small numbers some dizygous correlations for glucose and insulin measurements were negative. Overall dizygous correlations were not different considerably from zero for these variables.

Variance components and 95 % CIs of the best fitting models are shown in Table 4. Most variance in birthweight could be explained by shared environment. The contribution of genetic factors appeared

Table 4. Variance component estimates and 95 % CI: results of best fitting models

	Heritability		Shared environment		Unique environment	
	h^2	95 % CI	c^2	95 % CI	e^2	95 % CI
Birthweight (kg)	0.19	0.00 to 0.40	0.53	0.39 to 0.69	0.28	0.20 to 0.39
Birthweight (kg)[3]	0.33	0.00 to 0.65	0.26	0.001 to 0.51	0.41	0.30 to 0.57
Height (m)	0.92	0.88 to 0.95	–		0.08	0.05 to 0.12
Weight (kg)	0.78	0.67 to 0.85	–		0.22	0.15 to 0.33
BMI (kg/m^2)	0.77	0.67 to 0.85	–		0.23	0.15 to 0.34
Waist-to-hip ratio(%)	0.51	0.31 to 0.67	–		0.49	0.33 to 0.69
Systolic blood pressure (mmHg)	0.48	0.25 to 0.65	–		0.52	0.35 to 0.75
Fasting glucose (mmol)	0.58	0.25 to 0.74	–		0.42	0.26 to 0.75
Fasting insulin (pmol)	0.48	0.25 to 0.65	–		0.52	0.35 to 0.75
2-h glucose (mmol)	0.36	0.11 to 0.57	–		0.64	0.43 to 0.89
2-h insulin (pmol)	0.28	0.04 to 0.49	–		0.72	0.51 to 0.96

[a] Birthweight adjusted for gestational age
Note: h^2 is broad sense heritability, i. e. includes dominance (for weight and BMI)

relatively small (19 %), and was not statistically significant. Adjusting for gestational age increased the influence of genetic factors (33 %), although still not reaching statistical significance. Differences between subjects in height (92 %) and measures of obesity (78 % for weight and 77 % for BMI) could mostly be explained by genetic factors. Blood pressure (48 %) and variables related to glucose tolerance showed a somewhat smaller heritability, ranging from 28 to 48 %. For all variables, variance component estimates were not statistically significantly different between men and women. None of the variables showed a statistically significant association with age which could be related to the small age range of our sample (40–46.5 years). Age was therefore not included in the model fitting.

Discussion

Substantial evidence from studies of singleton births shows that reduced fetal growth is associated with raised blood pressure and impaired carbohydrate tolerance in adult life. There have been few studies in twins. Our population sample of twins was born in the same area of Britain and had not been selected for metabolic or other diseases. It comprised subjects who were traced and are still living in or around Birmingham and who were willing to take part in the study. We believe our group is representative as there were no differences in birthweight between the twins who were traced or not and those who agreed to take part or those who did not. We used a standard questionnaire to ascertain zygosity which is known to identify monozygous twins with a high degree of accuracy [14]. Nevertheless, it is possible that a small number of monozygous twins with extreme differences in size could have been incorrectly classified as dizygous, which would tend to reduce the power of our study. Although the twins where only one member of the pair agreed to be interviewed or to come to the clinic were somewhat heavier and had higher fasting insulin concentrations, there were no differences in birthweight, systolic blood pressure or glucose tolerance between these twins and the complete twin pairs that we studied. We found monozygous twins showed much greater similarity for obesity, systolic blood pressure and glucose tolerance than dizygous twins which accords with data from several other twin studies. For example, our data for BMI concur with published data[19, 20] whereas heritability estimates of fasting insulin concentrations range from 0.25 to 0.54 [21, 22].

In our study although the mean birthweight of the twins (2.5 kg) and their gestational age (37.6 weeks) were similar to those recorded in another study of twins in Birmingham [23], their weight was 0.6 kg lighter than that recorded for singleton pregnancies in the same study with a similar duration of gestation. Despite their lower weight at birth, there was no evidence of greater adult morbidity. Although there is no comparison data available for the prevalence of diabetes in Birmingham, the frequency of diabetes and glucose intolerance is similar to that observed for this age group in the NHANES study [24]. Moreover, we found no relation between birthweight, length or ponderal index and blood pressure or glucose tolerance in the entire group of twins. Although there is substantial evidence that monozygous twins and in particular the subgroup of monozygous twins who are monochorionic (sharing a placenta) have a more adverse prenatal environment and higher perinatal mortality than dizygous twins [17], we found, contrary to a recent study, no evidence that blood pressure or glucose tolerance was worse in monozygous twins compared with dizygous twins [25]. We had hypothesised that within-pair differences in birthweight would correlate with within-pair differences in adult outcomes and in the case of monozygous twins would test the importance of environmental factors compared with genetic factors in explaining the link between birth size and glucose tolerance.

Although there were substantial within-pair differences in birthweight in both monozygous and dizygous twins, these differences did not correlate with adult blood pressure or glucose tolerance. Our results therefore, do not confirm recently published data [11, 12].

It is possible that the failure to show correlations between size at birth and adult outcomes is due to the fairly small size of our study. The analysis of the relation between birthweight and adult blood pressure or glucose tolerance in the combined group of all 508 twins suggests, however, that birthsize in twins cannot be a major predictor of these outcomes. A possible explanation of our findings is that low birthweight in twins does not have the same implication as low birthweight in singletons. Because of the complex fetal development of twins, a variety of factors influence size at birth, only some which result in fetal programming. The fetal origins hypothesis suggests that the links between reduced fetal growth and adult disease result from the persistence of metabolic and endocrine adaptations to growth retardation in late gestation [26]. Ultrasound evidence suggests that twins down-regulate their growth rate as early as the 16^{th} week of gestation [27]. Studies in fetal lambs suggest that early down-regulation of fetal growth protects against growth retardation induced by undernutrition in later gestation [28]. Finally, the metabolic and endocrine changes associated with growth retardation in singletons, including hypoinsulinaemia, are not observed in twins [29]. This suggests that small size at birth in twins is less likely to indicate maternal constraint of growth or growth retardation and could explain the absence of relation between size at birth and adult blood pressure or glucose tolerance in our study and other studies showing unexceptional cardiovascular mortality in twins [30, 31]. Similar arguments could explain why the data on within-pair differences in birthsize were also not informative (Table 2).

The absence of correlations between birthsize and adult outcomes does not exclude the operation of fetal programming. In a study of survivors of the Dutch "hunger winter", the effects of the famine on adult glucose tolerance were observed in the presence of only minor changes in birthweight [32]. Fetal programming in the absence of changes in body size at birth could only be detected if greater detail concerning the prenatal environment of the twins were available. This data should include the type of placentation of the twins, as it is possible that the more similar fetal environment of monozygous twins, resulting from their closer placental relation, could lead to greater phenotypic similarity of adult monozygous twins compared with dizygous twins. This could not be distinguished from heritable traits unless the form of placentation of the twins were known [17].

Although we found that twin correlations for blood pressure and glucose tolerance were much higher in monozygous than in dizygous twins, the correlations for birthweight were very similar in both monozygous and dizygous twins suggesting a low degree of heritability of birthweight. This is supported by our model fitting analyses which indicated that environmental factors (in particular shared environment) are largely responsible for population variation in birthweight. This finding is also confirmed by a recent study of 2930 twin pairs from the Netherlands twin registry [33]. The contrast between the low heritability of birthweight and the high heritability of blood pressure and glucose tolerance suggests that common genetic determinants for fetal growth and adult blood pressure or glucose tolerance are not likely to be prevalent or powerful.

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