

# Genetic and Non-Genetic Factors Affecting Birth-Weight and Adult Body Mass Index

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Birthweight affects neonatal mortality and morbidity and has been used as a marker of foetal undernutrition in studies of prenatal effects on adult characteristics. It is potentially influenced by genetic and environmental influences on the mother, and effects of foetal genotype, which is partially derived from the maternal genotype. Interpretations of variation in birthweight and associated characteristics as being due to prenatal environment ignore other possible modes of materno-foetal transmission. Subjects were adult twins recruited through the Australian Twin Registry, aged 17 to 87 years, and the sample comprised 1820 men and 4048 women. Twins reported their own birthweight as part of a health questionnaire. Body Mass Index (BMI) was calculated from self-reports of height and weight. Correlations between co-twins' birthweights were high for both monozygotic ( $r = 0.77$ ) and dizygotic ( $r = 0.67$ ) pairs, leading to substantial estimates of shared environmental effects (56% of variance) with significant additive genetic (23%) and non-shared environmental (21%) components. Adult BMI was mainly influenced by genetic factors, both additive (36% of variance) and nonadditive (35%). The correlation between birthweight and BMI was positive, in that heavier babies became on average more obese adults. A bivariate model of birthweight and adult BMI showed significant positive genetic ( $r_g = 0.16$ ,  $p = 0.005$ ) and environmental ( $r_e = 0.08$ ,  $p = 0.000011$ ) correlations. Intra-uterine environmental or perinatal influences shared by cotwins exercise a strong influence on birthweight, but the factors which affect both birthweight and adult BMI are partly genetic and partly non-shared environmental.

Study of the factors influencing human birthweight is of value for several reasons. It has multiple implications for perinatal health; small babies are more likely to experience perinatal morbidity, require more healthcare resources, and are less likely to survive. The relationship between birthweight and mortality has been of longstanding interest to geneticists, because the higher mortality at both extremes leads to selection for an optimum birthweight (Mather, 1973). Foetal weight and size at the time of birth also represent an interesting trade-off between the offspring's interest in fuller development *in utero* and the maternal interest in a producing smaller baby to avoid death in childbirth. Birthweight has also been used as a marker of foetal nutrition in many studies relating intrauterine environment to health in adult life, specifically in the 'foetal origins hypothesis' of the insulin resistance syndrome, cardiovascular disease and susceptibility to diabetes in adulthood. The evidence for the foetal origins hypothesis has been summarised by Barker (1995, 1998) and is alluded to in other papers in

this issue. Arguments against the hypothesis include the fact that twins, who might be expected to be susceptible to under-nutrition during pregnancy, do not show high rates of adult ischaemic heart disease (Vågerö & Leon, 1994) or increased mortality (Christensen et al., 1995), and that studies following famines in Finland (Kannisto et al., 1997) and Russia (Stanner et al., 1997) did not support long-term effects of prenatal exposure to under-nutrition. Looking specifically at obesity as measured by the body mass index, the Dutch famine of 1944-45 produced a significant decrease in adult obesity if foetal exposure was in the last trimester of pregnancy, but an increase in adult obesity if exposure was during the first half of pregnancy (Ravelli et al., 1976).

Studies which have compared data on weight at the time of birth and BMI in adult life (Curhan, Chertow, et al., 1996; Curhan, Willet, et al., 1996; Lithell et al., 1996; Philips & Young, 2000; Rasmussen & Johansson 1998; Seidman et al., 1991; Sorenson et al., 1997) have found positive associations between them. This is paradoxical, because high birthweight is associated with obesity and obesity is associated with insulin resistance, but low birthweight is also associated with insulin resistance. Some of the discrepancies may be resolved by considering adult obesity (as BMI) and insulin resistance syndrome as potentially separable and subject to differing effects of birthweight.

It is also possible that low birthweight, adult obesity, insulin resistance, and susceptibility to diabetes and cardiovascular disease, are manifestations of the same genotype rather than the same environmental influence. This has been suggested as the 'foetal insulin resistance hypothesis' (Hattersley & Tooke, 1999). Such hypotheses, which involve pleiotropic actions of genes, are best tested by studies on genetically related subjects such as twin pairs.

Assessments of the sources of variation in birthweight using twin data have been conducted by a number of groups; the results are discussed below. Comparisons may be made between the birthweights of twins, or the offspring of twins, or even in one paper between the grandchildren of twins (Magnus, 1984b), or between parents and offspring,

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or cousins. Whatever the design, the objective is to ascertain the relative importance of shared prenatal environment (whether the environment is shared simultaneously, as with twin pregnancies, or sequentially as occurs with singleton siblings), foetal genotype, and non-shared environmental factors. Because the shared environment is the uterine environment, and this is potentially a consequence of maternal genotype, the relationships between environment and genotype may be complex.

In this paper, we describe the sources of covariation in self-reported birthweight and in adult BMI in a sample of Australian twins.

## Materials and Method

### Sample

Participants were members of a cohort of 3,808 twin pairs who completed and returned a mailed health and lifestyle questionnaire (HLQ) in 1980-82 from the Australian National Health and Medical Research Council Twin Register (Eaves et al., 1989; Jardine et al., 1984; Martin & Jardine, 1986). Ages of respondents at the time of the survey ranged from 17 to 87 years, with mean age of 35.7 years in 1232 monozygotic female pairs (MZ<sub>F</sub>), 34.4 years in 567 monozygotic male pairs (MZ<sub>M</sub>), 35.4 years in 747 dizygotic female pairs (DZ<sub>F</sub>), 32.3 in 352 dizygotic male pairs (DZ<sub>M</sub>), and 32.9 in 910 opposite-sex (DZ<sub>OS</sub>) pairs.

The 1980-82 mailed self-report questionnaire contained items on general health, personality, symptoms of anxiety and depression, drinking and smoking habits. Two items concerning similarity in appearance and being mistaken by others were used to determine zygosity (Jardine et al., 1984). Such questionnaires have been shown to give at least 95 % agreement with diagnosis based on extensive blood-typing (Martin & Martin, 1975; Ooki et al., 1990). More recently, members of a subsample of 198 same-sex pairs from this group, who reported themselves to be monozygotic (MZ), were typed for 11 independent highly polymorphic markers in the course of an asthma study; no errors in our previous zygosity diagnosis were detected (Duffy, 1994).

### Items

As part of the HLQ, twins reported their birthweight and that of their co-twin, and also their own current weight and height, from which Body Mass Index (BMI) was calculated. Complete responses for these items were obtained from 1820 individual men and 4048 women. In a subsequent 1989-91 survey, twins' mothers also provided information on the twins' birthweights. Birthweights were normally distributed and no transformation was used. However, some reported results were unrealistic and the data set was reduced to include only subjects whose birthweight was within 3 SDs of the mean.

Reliability of reported birthweights was assessed by correlations between self-reports and co-twins' reports, and between self-reports and maternal reports. To test the validity of BMI, self-report of height and weight for calculation of body mass index was compared against measured height and weight in a subsample of 140 female and 112 individual twins who participated in a laboratory-based study

around the same time (Grant et al., 1999). Coefficients for height were 0.95 for men and 0.92 for women, for weight were 0.92 and 0.93, and for BMI were 0.95 and 0.85 respectively. Eight-year repeatability coefficients for questionnaire self-reported height, weight and BMI were available from a subsequent survey of the same twins conducted from 1988-1990 (Baker et al., 1996). Coefficients for men and women were 0.94 for height, 0.84 and 0.83 for weight, and 0.79 and 0.81 for BMI.

### Data Analysis

SPSS 9 for Windows (SPSS Inc., 1997) was used for phenotypic analysis, twin pair correlations and data handling. Models of sources of variation and covariation in birthweight and BMI were fitted to the data using Mx 1.50 (Neale, 1999), which is designed for analysis of twin and family data and allows simultaneous modeling of both fixed effects (e.g. age, sex) on means as well as sources of covariation between members of a twin pair. In univariate and bivariate genetic model-fitting we estimated the contributions to phenotypic variation of additive genetic (A) and nonadditive genetic (D), shared (C) and non-shared (E) environmental effects. With data on MZ and DZ twins reared together, the effects of C and D are confounded and in univariate analysis only one can be estimated at a time.

We used a general bivariate model, with parameterisation of a bivariate Cholesky or triangular decomposition for A and E, with common factor effects on both birthweight and BMI, and specific factor effects for BMI. A bivariate model containing all four sources of variation (ACDE) is possible if one variable is affected by C and not D, while the other is affected by D and not C. We estimated C for birthweight and D for BMI in the model. Although evidence suggested some influence of D on BMI in twins aged < 30 years, particularly in women, but not in those > 30 years (Neale & Cardon, 1992), we decided not to stratify our sample on age, in order to maximize power for bivariate analyses. We finally estimated genetic and specific environmental correlations between birthweight and BMI and tested their significance by dropping cross loadings from the model.

We fitted models to raw data, including data from incomplete pairs, and tested significance of parameters by dropping them in turn from the model, and calculating the likelihood ratio chi-square (LR; Neale et al., 1989). On the grounds of parsimony the model with the least number of parameters which offered a fit not significantly worse than that of the full model was chosen. Data analysis methods are described more fully elsewhere (Kendler et al., 1992; Neale & Cardon, 1992).

## Results

Birthweights were significantly ( $p < 0.001$ ) greater in males than in females (mean 2600 grams vs 2440 grams). These birthweights indicate 36 weeks mean gestation. Consistency of reported birthweights was assessed by calculating correlations across twins (e.g. twin1's self-report vs. twin2's report of twin1's weight, and vice versa). This gave Pearson correlation coefficients of 0.95 and 0.96. Consistency of birthweight reporting did not differ between male and female

twins, although a higher percentage of female (83%) than male (66%) twins reported their own birthweight, i.e. had no missing data. Correlations between reports from the mother and each twin were very similar ( $r = 0.96, 0.96$ ). These correlations suggest a high degree of consistency in reported birthweights, although they do not address their validity.

Within-pair birthweight correlations by zygosity were calculated for both self-report and co-twin report with very similar results (Table 1). The twin pair correlations for calculated BMI are also shown in Table 1. There were only marginally significant phenotypic correlations between

reported birthweight and reported BMI, whether taken as a single group or broken down into two age groups (Table 2).

Univariate results under alternative models are shown in Table 3. It is clear from the correlations by zygosity and from the univariate model-fitting results ( $LR\chi^2$ ) that shared environment, the uterine environment shared by members of a twin pair up to the time of birth (C), should be included in the univariate model for birthweight, and nonadditive genetic effects such as dominance or epistasis (D) for BMI.

In bivariate model-fitting we included two definition variables: sex for both birthweight and BMI, and age for BMI only. Bivariate model-fitting results are shown in Table 4. Path coefficients are shown in Figure 1. In Figure 1 the path from A1 to BMI represents a small but significant positive genetic correlation ( $r_g = 0.16, p = 0.005$ ) between birthweight and adult BMI and a specific environmental correlation of 0.08. Dropping these two correlation paths gave significant deterioration of fit in each case,  $LR\chi^2 = 7.75 (p = 0.0054)$  for the additive genetic correlation and  $LR\chi^2 = 19.3 (p = 0.000011)$  for the non-shared environmental correlation.

**Table 1**  
Twin Pair Correlations for Self-reported and Co-twin Reported Birthweight and Adult BMI, by Zygosity

|                               | MZF   | MZM   | DZF   | DZM   | DZOS  |
|-------------------------------|-------|-------|-------|-------|-------|
| Birthweight (self-report)     | 0.768 | 0.767 | 0.687 | 0.672 | 0.665 |
| Birthweight (cotwin's report) | 0.758 | 0.802 | 0.695 | 0.678 | 0.706 |
| Adult BMI (self-report)       | 0.741 | 0.753 | 0.318 | 0.431 | 0.309 |

Note: MZF = monozygotic female pairs; MZM = monozygotic male pairs; DZF = dizygotic female pairs; DZM = dizygotic male pairs; DZOS = dizygotic male-female pairs.

**Table 2**  
Phenotypic Correlations Between Self-reported Birthweight and Self-reported Adult BMI, by Sex and Age Group

| Ages | Males    |                 |          | Females  |                 |          |
|------|----------|-----------------|----------|----------|-----------------|----------|
|      | <i>r</i> | <i>p</i> -value | <i>N</i> | <i>r</i> | <i>p</i> -value | <i>N</i> |
| < 40 | 0.049    | 0.061           | 1431     | 0.037    | 0.047           | 2874     |
| > 40 | 0.111    | 0.049           | 314      | 0.033    | 0.293           | 1027     |
| All  | 0.050    | 0.035           | 1745     | 0.026    | 0.101           | 3901     |

**Table 4**  
The Bivariate ACDE Model for Birthweight and BMI: Percentages of Variation and Covariation

|             | Percentages of variance |       |       |       |       |       |
|-------------|-------------------------|-------|-------|-------|-------|-------|
|             | A1                      | A2    | C     | D     | E1    | E2    |
|             | %                       | %     | %     | %     | %     | %     |
| Birthweight | 22.84                   | —     | 55.75 | —     | 21.41 | —     |
| BMI         | 0.83                    | 33.42 | —     | 37.50 | 0.17  | 28.08 |

Note:  $r_g = 0.16 (P = 0.005)$ ,  $r_e = 0.08 (P = 0.000011)$

Two definition variables were included: sex for both birthweight and BMI, and age for BMI only.

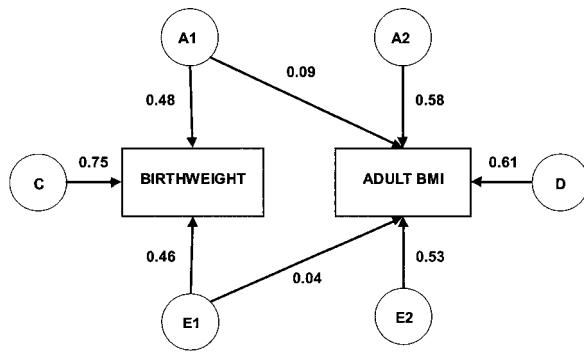
**Table 3**  
Univariate Model-fitting for Birthweight and Adult BMI, with Birthweight Corrected for Sex, and BMI Corrected for Age and Sex

|                     | Model           | Model fit |           |                  | Standardised parameter estimate |      |      |      |
|---------------------|-----------------|-----------|-----------|------------------|---------------------------------|------|------|------|
|                     |                 | -2LL      | <i>df</i> | $\Delta\chi^2_i$ | A%                              | C%   | E%   | D%   |
| <b>Birth weight</b> |                 |           |           |                  |                                 |      |      |      |
|                     | ACE             | 35655.3   | 5827      | —                | 22.82                           | 55.7 | 21.4 | —    |
|                     | AE              | 35864.6   | 5828      | 209.3            | 79.50                           | —    | 20.5 | —    |
|                     | CE              | 35713.9   | 5828      | 58.6             | —                               | 72.8 | 21.2 | —    |
| <b>BMI</b>          |                 |           |           |                  |                                 |      |      |      |
|                     | ADE             | 35596.2   | 7356      | —                | 36.18                           | —    | 28.4 | 35.4 |
|                     | ACE             | 35615.4   | 7356      | —                | 70.73                           | 0.0  | 29.3 | —    |
|                     | AE <sup>a</sup> | 35615.4   | 7357      | 19.2             | 70.73                           | —    | 29.3 | —    |
|                     | CE <sup>b</sup> | 36016.2   | 7357      | 400.8            | —                               | 47.8 | 52.2 | —    |

Note: Two definition variables were included: sex for both birthweight and BMI, and age for BMI only.

<sup>a</sup> fit compared with ADE model

<sup>b</sup> fit compared with ACE model



**Figure 1.**

Genetic (additive A and dominance D) and environmental (shared C and non-shared E) factors influencing birthweight of twins and their body mass index (BMI) as adults. Path coefficients are standardised and can be squared to obtain proportions of variance due to each factor.

## Discussion

Data on both birthweight and BMI were derived from self-reports. However, in each case they are consistent. The birthweight data are potentially subject to incorrect information from the mothers, who were presumably the only source of information for the twins. A validity of 0.97 was obtained from maternal questionnaire response (Nance et al., 1983). Our correlation between maternal and twin reports was very strong. Obtaining birth weights from hospital records for this Australia-wide sample of adult twins was not feasible. Validity testing for even a subsample would be complicated by ethical issues such as obtaining maternal consent to access hospital records relating to confinement even if records were available, and logistic issues regarding delivery of twins, such as correctly identifying unnamed twins in same-sex pairs. Mean birthweights, however, were close to the Australian means for twins recorded in national perinatal statistics of 2485 grams for male twins and 2382 grams for female twins (Roberts & Lancaster, 1999).

The twin sample was representative of the Australian population on a number of variables, such as personality factors, and anxiety and depression (Jardine et al., 1984; Kendler, 1983). A follow-up sub-sample of female twins has been shown to be representative of the Australian population on indicators including age, general level of education and marital status (Baker et al., 1996). Twins had volunteered to participate in medical research in general, and cooperativeness in the 1980–82 HLQ study was unlikely to be correlated with our variables of interest. It is possible, however, that twin pairs, where one or both twins were at the extremes of BMI or birthweight distributions, might not have been represented either on the Twin Register or among the questionnaire respondents.

The major source of variation for birthweight was C, the effect of environment shared by both members of a twin pair. This presumably reflects variation in gestational age at delivery, as well as aspects of the uterine environment provided by the mother, particularly nutrition and metabolism.

However, significant A and E contributions to variation were also detected and the heritability estimate was 23%. A caveat about our findings is that, unlike the East Flanders Prospective Twin Survey (Loos et al., 1998), we have no data on chorionicity and placentation of these twins, and it is possible that these factors might account for some proportion of non-shared as well as shared environmental influence. A small but significant effect of chorionicity was found in the Belgian survey, with dichorionic cotwins showing greater similarity in birthweight than monozygotic cotwins (Vlietinck et al., 1989). Previous studies of factors influencing birthweight have varied considerably, with some (Magnus, 1984a, 1984b, Magnus et al., 1984) finding evidence of substantial genetic effects (heritability ~ 50%) but others (Langhoff-Roos et al., 1987; Little, 1987; Mi et al., 1986; van Baal & Boomsma, 1998) obtaining lower estimates. The magnitude of the estimated genetic contributions does not seem to depend on the specific family relationships studied. Birth order effects on birthweight of offspring of MZ twins have been identified, suggesting that later pregnancies are exposed to additional sources of variation, including the previous reproductive experience of the mother and the birthweight of the previous child (Nance et al., 1983).

For BMI, additive and non-additive genetic effects, and non-shared environmental effects, contributed about equally. The final bivariate model contained all four sources of variation but, to maintain identification of the model, C only for birthweight and D only for BMI. The significant genetic and environmental correlations provided evidence for additive genetic effects that influenced both birthweight and BMI, and also for nonshared environmental effects acting on both variables. Many previous studies have found weak but significant phenotypic associations between birthweight and subsequent obesity (Curhan et al., 1996a, 1996b; Lithell et al., 1996; Philips & Young, 2000; Rasmussen & Johansson 1998; Seidman et al., 1991; Sorenson et al., 1997). These have also tended to be in a positive direction.

With respect to the implications for adult disease, the relationships between birthweight, adult BMI, and manifestations of the insulin resistance syndrome are complex. High BMI is a risk factor for insulin resistance and associated conditions but the effects of birthweight on these two characteristics (BMI and insulin resistance syndrome) seem to be in the opposite direction. Larger babies tend to be more obese in adult life, whereas smaller babies tend (at least in the majority of published studies) to be more prone to insulin resistance, hypertension and dyslipidaemias. Resolution of this paradox through definition of genetic, shared environmental and non-shared environmental paths between these variables will require multivariate data on large numbers of twin pairs, including a distinction between overall obesity (BMI) and abdominal obesity.

Phenotypic correlations between BMI and birthweight in our study were very small but uniformly positive. The positive correlation between birthweight and BMI, although suggesting that heavier babies became on average more obese adults, could also possibly indicate that heavier adults report having been bigger babies. In the full model there was

a significant positive genetic correlation between them, showing that some genes have effects on both. There was also a significant (positive) non-shared environmental correlation, which can be interpreted as meaning that random events occurring between conception and birth are able to affect both pre-natal growth (from one cell to about 2.5 kg) and post-natal growth (from about 2.5 kg to about 70 kg). In some ways this is even more intriguing than the existence of genes which affect both characteristics.

An earlier study of birthweight in offspring of MZ twins analysed full-sib and maternal and paternal half-sib correlation matrices, identifying the relative contributions to variance of prenatal maternal influences shared by MZ cotwins (72%) or unique to individual mothers (28%; Nance et al., 1983). Offspring of MZ and DZ twin pairs, both same-sex male and female and opposite-sex pairs, might in the future provide data to distinguish maternal genetic, foetal environmental and paternal genetic effects on both birthweight and BMI. In the meantime, despite a small effect size, their environmental correlation suggests that the general concept that pre-natal events can have life-long consequences should not be dismissed, even though the view that foetal under-nutrition (which should be shared by co-twins) is an important determinant of adult obesity is not supported by our results.

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