Exploring the Etiology of the Association Between Birthweight and IQ in an Adolescent Twin Sample

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The negative effects of very low birthweight on intellectual development have been well documented, and more recently this effect has been shown to generalise to birthweights within the normal range. In this study we investigate the etiology of this relationship by using a classical twin design to disentangle the contributions of genes and environment. A previous Dutch study (Boomsma et al., 2001) examining these effects indicated that genes were important in mediating the association of birthweight to full IQ measured at ages 7 and 10, but not at ages 5 and 12. Here the association between birthweight and IQ at age 16 is considered (N = 523 twin pairs). Using variance components modeling we found that the genetic variance in birthweight (4%) completely overlapped with that in verbal IQ but not performance or full IQ. Results further showed the importance of shared environmental effects on birthweight (~ 60%) but not on IQ (with genes explaining up to 72% of IQ variance). Models incorporating a direction of causation parameter between birthweight and IQ provided adequate fit to the data in either causal direction for performance and full IQ, but the model with verbal IQ causing birthweight was preferred to one in which birthweight influenced verbal IQ. As the measurement of birthweight precedes the measurement of twins' IQ at age 16, the influence of verbal IQ might be better considered as a proxy for parents' IQ or education, and it is possible that brighter mothers provide better prenatal environments for their children.

While much early research has focused on the consequences of very low birthweight for physical and psychological development (Barker, 1994; Issley & Mitchell, 1984), more recent investigations have also confirmed that birthweight within the normal range can affect cognitive development (Martyn et al., 1996; Richards et al., 2001; Shenkin et al., 2001; Sorensen et al., 1997). A number of population-based studies find support for this association when adjusting for confounding factors like maternal age, race, education, socioeconomic status and birth order. The association between birthweight and cognitive ability can be influenced by (maternal and fetal) genes and/or the environment and this has been investigated in a single study only (Boomsma et al., 2001). In this paper, we use a classical twin design to establish the proportions in which fetal genes and environment contribute to the relationship between birthweight and IQ in adolescents.

In two longitudinal studies (Jefferis et al., 2002; Richards et al., 2001) examining the effects of birthweight within the normal range, cognitive ability was measured at several time points spanning childhood, adolescence and adulthood. One study involved 3900 English, Scottish and Welsh individuals born in 1946 (Richards et al., 2001). The positive association between birthweight (> 2500g) and cognitive performance was significant at age 8 and persisted at ages 11, 15 and 26 indirectly through the relationship with intelligence quotients (IQ) at age 8; at age 43 verbal memory and perceptual speed were unrelated to birthweight. In the other study (Jefferis et al., 2002), 10,845 individuals born in 1958 were given cognitive tests at ages 7, 11 and 16 years. The combined effects of socioeconomic status and birthweight on cognitive ability were considered, with the finding that each independently contributed to the variability in cognition although the effect of birthweight was weaker explaining between 0.5 and 1.5% of variation in the cognitive measures. These results agreed with a prior study (Shenkin et al., 2001) which also found no relationship between birthweight and social class, with birthweight explaining 3.8% of variance in IQ at age 11. Hence, there was no indication that birthweight was a marker for social deprivation or that social background altered the effect of birthweight on intellectual ability.

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In a more rigorous test of this hypothesis Matte and colleagues (2001) sampled two siblings within the same family and examined the association of the birthweight difference and IQ difference between siblings. This study design removed any effects from maternal or socioeconomic factors since sibpairs acted as controls for each other, notwithstanding their different age. A significant positive association between differences in IQ measured at age 7 and birthweight was found for boys but not girls. Effects of birth order and maternal smoking were not significant.

The twin design provides an even better control for common environmental effects than the singleton sibling pair design since twins are perfectly matched for age and maternal effects in addition to family environment. Furthermore, this design can unravel the genetic and environmental contributions to the association between birthweight and IQ. Differences within monozygotic (MZ) twin pairs (who share 100% of their genes) implicate environmental influence only, while differences within dizygotic (DZ) twin pairs (who share ~ 50% of their segregating genes) reflect both genetic and environmental influences. Assuming that genes were the only source of variance contributing to the relationship of birthweight to IQ, Boomsma et al. (2001) obtained the correlation between intrapair difference scores in birthweight and IQ separately for MZ and DZ twins in a longitudinal study of 170 same-sex twins. Genetic mediation of the birthweight–IQ relationship would be implied if the intrapair difference scores showed a positive association in DZ twins but no association in MZ twins since a genetic model predicted some trait difference between DZ twins but no trait difference between MZ twins. This effect was confirmed for IQ measured at ages 7 and 10 (where DZ r = 0.29 and r = 0.27, respectively, and MZ r = –0.02 and r = 0.01, respectively), but not at ages 5 nor 12 years (Boomsma et al., 2001). Furthermore, the effect was reproduced when twin pairs with a gestational age of less than 37 weeks were excluded. The absence of gene effects at age 5 may be because IQ is less reliably measured in young children (Schuerger & Witt, 1989), while at age 12 it may be that some aspect of the common environment is interacting with genes to modify the effects of birthweight on IQ.

Birthweights of twins are generally lower than singletons, and within MZ twins, monochorionic twins (i.e., those that share a chorion) are lighter at birth than dichorionic (i.e., separate chorions) or DZ twins (Phillips, 1993). A recent Australian study has shown, although, that the risk factors for low birthweight are similar in singleton and multiple births (Mohsin et al., 2003). Moreover, birthweight effects on IQ follow the same trend in twins as they do in singletons and they do not differ according to zygosity (Akerman & Thomassen, 1991; Fraser & Nylander, 1988; Willerman & Churchill, 1967). Further evidence for the generalisability of twin findings to the singleton population is that the difference between twins and singletons in IQ dissipates by the first few years of schooling. For example, in a study conducted by Wilson (1983) the IQ (particularly verbal) of twins was lower than singletons at 4 years of age, but by age 6 their IQ was equal to that of singletons. Additionally, in a more recent Dutch sample (mean age of ~ 37 years) of 260 twin pairs and 98 non-twin siblings, no differences in IQ were found between twins and their matched siblings (Posthuma et al., 2000).

This paper examines the genetic and environmental sources of covariation between birthweight and intellectual ability in an adolescent twin sample. In their non-genetic study Matte and colleagues (2001) found sex differences for the correlations between the sibling pair difference in birthweight and IQ, so males and females will be considered separately. A genetic influence on the relationship between birthweight and IQ at ages 7 and 10 has been supported (Boomsma et al., 2001) but has not yet been confirmed in an adolescent sample such as ours. Our analyses will build on the previous tests of MZ and DZ correlations of intrapair differences in birthweight and IQ by introducing variance components modeling which allows partitioning of the genetic and environmental proportions of variance contributing to a trait and to the relationship between traits. The effects of infant prematurity (i.e., gestational age < 37 weeks) and MZ twin pair chorionicity on estimates of genetic and environmental influence will be taken into account. Furthermore, direction of causation models between birthweight and IQ will be tested to establish whether the combined sources of variance influencing one measure determine the other, or whether pleiotropic effects (same genetic factor influences both traits) are present.

Subjects and Methods

This is an ongoing Australian twin study of cognition in adolescence (Wright et al., 2001). Birthweight was recorded and IQ examined in the first 523 twin pairs (128 MZ female, 110 MZ male, 69 DZ female, 68 DZ male, 148 DZ opposite-sex). Zygosity was determined by ABO, MN and Rh blood groups and by nine independent polymorphic DNA markers (ABI Profiler system) with a probability of error < 10^{-4}. Twin pairs were excluded if either one had a history of significant head injury, neurological or psychiatric illness, substance dependence or if they were currently taking long-term medications with central nervous system effects. The twins were mostly in their penultimate year of secondary school and aged between 15 and 18 years (16.2 years; SD = 0.3), although 91% of the sample were aged 16 years. Written informed consent was obtained from the participant, as well as their parent/guardian, prior to testing.

The IQ test was part of a psychometric battery, which also included two reading tests (see Wainwright et al., 2003) and two elementary cognitive tasks (see Luciano et al., 2003); it approximated

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1.5 hours in length. A shortened version of the Multidimensional Aptitude Battery (Jackson, 1984, 1998) was used which included three verbal subtests (Information, Arithmetic, Vocabulary) and two performance subtests (Spatial and Object Assembly). Each subtest had a multiple-choice format and was timed at 7 minutes; administration and scoring were computerized. Birthweight was obtained by a questionnaire completed by the twins' mother in 95% of cases and by the father or close relative in the remaining cases when the twins were aged 12 years (in a study investigating mole development, see Aitken et al., 1994) or at the time of cognitive testing (for twins not recruited through the mole study). The validity of mother's reporting of child's birthweight has been demonstrated by a study in which the mother's report and birthweight reported on the birth certificate was correlated at 0.84 (Sanderson et al., 1998). Information about infant prematurity and chorionicity (or placentation) of twins was similarly obtained by questionnaire. Twins were considered monochorionic if the parent (usually mother) indicated the presence of a single placenta (or afterbirth) and dichorionic if a fused placenta or two separate placentas were reported. Placentation was not known in 18.5% of cases. While the validity of the questionnaire method to retrospectively establish chorion type has been recently questioned (Derom et al., 2003), the frequency at which monochorionicity based on placentation occurs in our MZ sample (63%) is not dissimilar to the estimate of 75% commonly reported (Duffy, 1993).

Statistical Analyses

Means Analysis

Following the method adopted by Boomsma et al. (2001) a comparison of mean IQ between co-twins with the lighter and heavier birthweight was performed using paired *t* tests in the MZ and DZ same-sex samples. Genetic influence is indicated if a significant mean difference in IQ is found between the lighter and heavier co-twin for DZs but not MZs. In the DZ pairs, the prediction is that the IQ of lighter twins will be lower than heavier twins. This means analysis was repeated excluding twins with a gestational age less than 37 weeks, and for exploratory purposes, was also performed separately for males and females. While multiple comparisons were made, the dependence of the measures (full IQ is an average of verbal and performance scales, while verbal and performance scales are correlated around .50) meant that a Bonferroni adjustment based on the comparisons for verbal, performance and full IQ would be too conservative. However, *p*-values were adjusted to a significance level of .025 to account for the repeated analysis in twins with a gestational age less than 37 weeks. As we had no a priori hypotheses for the sex analyses a familywise error correction was not applied to these analyses.

Genetic Model Fitting

The purpose of the genetic model fitting, or variance components analysis, was to quantify the influence of genes and environment on the variation and covariation between birthweight and IQ. Hence, simultaneous equations, established by the relationships predicted from genetic theory among MZ and DZ co-twins, were applied to the raw data, and solved by a maximum likelihood estimation procedure using the statistical program Mx 1.51 (Neale et al., 1999). Models were fitted in which the total variances and covariances between variables were parameterized in terms of additive genes (A), common environment (C) and unique environment (E). The expected covariance for MZ twin pairs is Variance (A) + Variance (C), while for DZ twin pairs it is 0.5 × Variance (A) + Variance (C).

To boost the power of the analysis, DZ opposite-sex twins were also included. As males and females differed in mean birthweight and IQ (see Results), a correction for sex was included in the means model of the analysis (without this correction sex differences in the means can inflate twin resemblance for same-sex twins). A deviation for mean birthweight was also parameterized for births with a gestational age less than 37 weeks. Separate putative monochorionic and dichorionic MZ groups were specified to allow differences between groups in means and variances of birthweight, although the expected twin covariance did not differ between monochorionic and dichorionic groups. The structure of covariation between birthweight and IQ was specified as a bivariate triangular (Cholesky) decomposition for each source of variance (A, C & E). In the initial variance components model, genetic and environmental parameters were free to vary for females and males, but the correlation of the genetic effect in opposite-sex pairs was fixed to the same as within sexes.

In the model of causation, a unidirectional phenotypic pathway was included between the two correlated variables (Duffy & Martin, 1994; Neale et al., 1994). If the major source of variation (A, C or E) influencing two correlated variables (in this case birthweight and IQ) is very different, then there will be different expectations for the cross-twin inter-trait correlations in the competing direction of causation models (Heath et al., 1993). This allows comparisons of the two models, with each being nested within the Cholesky decomposition. Like the bivariate factor model, measurement error in the directional causation model will increase estimates of unique environment, but unlike the bifactor model, all other parameter estimates will also be biased since the expectation for the phenotypic covariance between traits includes the multiplication of the causal parameter by the nonshared environmental variance in the causal variable (Heath et al., 1993). By ignoring measurement error when it exists will bias parameter estimates and may lead to acceptance of a false causal model. Hence, in our

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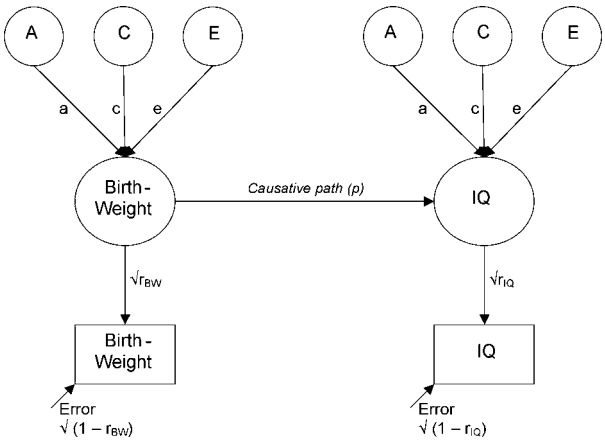

Figure 1

A standardized direction of causation model in which the relationship between the observed variables, birthweight and IQ is modeled in terms of each measure's reliable variance. The latent birthweight and IQ factors are constrained to unit variance, while the pathways leading from the latent factors to the observed variables are fixed to the square root of the test–retest correlation (rBW & rIQ) of each respective measure.

direction of causation models, birthweight and IQ were modeled as latent variables with the standardized pathway leading to the observed variable fixed to the square root of the test–retest correlation of each respective measure (estimated from our own data); the causative pathway was included between the latent birthweight and IQ factors, which are free of measurement error (see Figure 1). Additive genetic, common environmental and unique environmental effects were parameterized to load on the latent birthweight and IQ factors. The goodness-of-fit of the direction of causation models was judged using the likelihood ratio Chi-square test relative to the full Cholesky decomposition in which A, C, and E parameters were estimated separately for females and males.

Results

Mean Comparisons

Results from the mean comparison tests of IQ between co-twins with the lower and higher birthweights for same-sex twins are shown in Table 1. In the full sample, *p*-values indicated that mean effects between DZ co-twins were significant for verbal, performance and full IQ, but not significant for verbal and full IQ, and marginally significant for performance IQ between MZ co-twins. The direction of these effects was supported in males and females for verbal IQ and in males for full IQ. In the subsample (i.e., excluding twins with gestational age < 37 weeks), this pattern was supported for verbal IQ, but not for performance or full IQ which showed non-significant mean effects for DZs.

Table 1

Means (Standard Deviations) for Full, Verbal and Performance IQ of Co-twins with the Lower and Higher Birthweights Separately for Dizygotic (DZ) and Monozygotic (MZ) Twins

	DZ Pairs				MZ Pairs			
	N pairs	Lower birthweight co-twin	Higher birthweight co-twin	*p**	*N* pairs	Lower birthweight co-twin	Higher birthweight co-twin	*p**
Full Sample (all twins)								
Birth Weight (g)		2475.6 (529.9)	2771.4 (544.5)			2356.6 (517.0)	2655.0 (527.2)	
Verbal IQ	136	109.5 (11.8)	112.6 (11.7)	**.001**	235	109.1 (11.4)	109.2 (11.3)	.400
Males	*67*	*110.8 (13.2)*	*114.4 (11.9)*	***.009***	*108*	*110.4 (12.4)*	*110.3 (11.9)*	*.449*
Females	*69*	*108.1 (10.1)*	*110.8 (11.4)*	***.019***	*127*	*108.1 (10.4)*	*108.4 (10.7)*	*.307*
Performance IQ	137	110.1 (17.0)	113.2 (16.0)	**.016**	238	111.0 (16.3)	112.5 (16.4)	**.023**
Males	*68*	*114.1 (17.3)*	*116.8 (15.6)*	*.090*	*110*	*114.2 (14.9)*	*114.8 (16.1)*	*.295*
Females	*69*	*106.2 (15.8)*	*109.7 (15.8)*	*.050*	*128*	*108.1 (16.9)*	*110.5 (16.4)*	***.011***
Full IQ	137	110.6 (13.3)	113.9 (13.0)	**.001**	235	110.9 (12.5)	111.8 (13.0)	.046
Males	*67*	*113.4 (14.25)*	*116.7 (12.8)*	***.021***	*108*	*113.3 (12.1)*	*113.6 (13.1)*	*.370*
Females	*69*	*107.8 (11.9)*	*111.2 (12.8)*	***.012***	*127*	*108.9 (12.6)*	*110.3 (12.7)*	***.021***
Subsample excluding twins with gestational age < 37 wks								
Birth Weight (g)		2748.5 (402.9)	3046.9 (384.2)			2629.9 (383.3)	2941.3 (340.6)	
Verbal IQ	73	109.2 (11.6)	112.2 (11.8)	**.008**	125	109.5 (10.6)	110.1 (10.7)	.163
Performance IQ	74	111.5 (15.8)	113.6 (15.9)	.155	126	111.3 (15.6)	113.5 (16.0)	**.023**
Full IQ	73	111.1 (12.6)	113.8 (12.9)	.032	125	111.3 (11.8)	112.9 (12.4)	**.011**

* *p* = probability that heavier birth weight predicts higher IQ.

Note: the one-tailed *t* tests are judged significant at a corrected *p*-value < .025, except for the exploratory analyses for females and males where a criterion of .05 is retained. Significant *p*-values are indicated in bold, and the results for females and males are shown in italics.

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Table 2

Twin Correlations for Birthweight (BW) and IQ by Zygosity and Sex, and (for MZ Twins) Reported Chorionicity, Adjusted for Gestational Age < 37 Weeks (Upper Section of Table). Across Variable Co-twin Correlations Are Displayed for BW–IQ Relationships (Lower Section of Table). The Phenotypic Correlation (r_p) Between BW and IQ Was Constrained Equal Across Birth Order and Zygosity

	MZ MC		MZ DC		Dizygotic		
	F	M	F	M	F	M	OS
Birthweight (BW)	0.62	0.54	0.73	0.49	0.62	0.67	0.63
Verbal IQ (VIQ)	0.83	0.83	0.88	0.75	0.54	0.45	0.57
Performance IQ (PIQ)	0.72	0.70	0.82	0.70	0.39	0.49	0.31
Full IQ (FIQ)	0.81	0.82	0.91	0.83	0.50	0.49	0.48
BW–VIQ (r_p = .09)	0.07	0.06	0.11	0.19	–0.05	0.04	0.00
BW–PIQ (r_p = .09)	0.00	-0.02	0.07	0.15	–0.09	0.03	0.07
BW–FIQ (r_p = .11)	0.03	0.02	0.10	0.19	–0.10	0.05	0.05

Note: MZ monochorionic (MC) and dichorionic (DC) co-twin correlations within sex were not significantly different for all variables except FIQ, where the female estimates differed significantly from each other. Across variable co-twin correlations differed between male MC and DC groups for the BW–FIQ correlation.

Variance Components Analysis

Variance components modeling was used to determine the proportion in which genes influenced the association between birthweight and IQ, and to specifically test whether these gene effects differed across sex. Co-twin correlations for each variable are shown in Table 2 according to zygosity, with MZ groups further separated into monochorionic and dichorionic. Correlations were estimated by maximum likelihood from a model in which means and variances were set equal across birth order and zygosity (but means differed between chorionicity groups); means were adjusted for the effects of sex and a gestational age less than 37 weeks. Co-twin correlations indicated the presence of large common environmental effects for birthweight (as MZ and DZ correlations were similar) and substantial additive genetic influences on IQ (MZ correlations were greater than DZ correlations).

Comparisons of nested models using the Chi-square likelihood ratio test indicated that the genetic and environmental parameters were equivalent in females and males (see Table 3). By equating male and female A, C and E parameters the Chi-square change for a difference of 9 degrees of freedom was 7.97 (p = .54) in the verbal IQ analysis, 10.7 (p = .30) for performance IQ and 5.50 (p = .79) for full IQ. The standardized parameter estimates of the genetic and environmental factor loadings in the bivariate Cholesky decompositions are displayed in Table 4. Also included in this table are the genetic and environmental proportions of variance contributing to each trait, and the genetic (r_g) and environmental (r_c & r_e) correlation between birthweight and IQ, including their 95% confidence intervals.

The relationship between birthweight and verbal IQ was the only one to show significantly greater genetic than environmental covariation. Genetic influences were substantial for IQ, explaining 59% and 72% of variance for respective verbal and performance IQs. In the bivariate analysis with verbal IQ, 4% of variance in birthweight was explained by common genetic effects, while the other bivariate analyses detected slight genetic influence on birthweight. As the second genetic factor in each analysis showed a zero (or close to zero) factor loading on IQ, the genetic correlation between birthweight and IQ

Table 3

Goodness of Fit Statistics for the Bivariate Models of Birthweight (BW) and IQ (Verbal, Performance, Full). The Chi-square (χ^2) and Degrees of Freedom (df) Change Are Calculated from the Initial Model in which Additive Genes (A), Common Environment (C), and Unique Environment (E) Are Parameterized Separately for Females ($_f$) and Males ($_m$)

Model	Verbal IQ			Performance IQ			Full IQ		
	$\Delta\chi^2$	*df*	*p*	$\Delta\chi^2$	*df*	*p*	$\Delta\chi^2$	*df*	*p*
1. Base — $A_f C_f E_f A_m C_m E_m$	—	—	—	—	—	—	—	—	—
2. A C E (no sex limitation) [a]	7.97	9	**.540**	10.70	9	**.300**	5.50	9	**.790**
3. BW → IQ [b]	16.36	8	.037	14.14	9	.120	13.65	9	.135
4. IQ → BW	11.30	8	.185	13.91	9	.126	12.13	9	.206

Note: [a] Parameter estimates are shown in Table 4.

[b] See Figure 1 for model with path BW → IQ; model with IQ → BW was the same except path was reversed. C & E components are parameterized for BW, whereas A and E components are parameterized for IQ (C is additionally specified for verbal IQ).

p-value of best fitting model highlighted in bold.

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Table 4

Standardized Additive Genetic (A), Common Environmental (C), and Unique Environmental (E) Path Coefficients in the Bivariate Cholesky Decompositions of Birthweight and IQ (Verbal, Performance, Full). Proportions of Genetic (h^2) and Environmental (e^2, c^2) Variance and the Genetic and Environmental Correlation (*r*) Between Variables Are Presented with 95% Confidence Intervals

	BW	VIQ	*r*	BW	PIQ	*r*	BW	FIQ	*r*
A_1	.21	.77	*1 (.42, 1)*	.01 ^{ns}	.84	.99 *(–1, 1)*	.11 ^{ns}	.83	1 *(–1, 1)*
A_2	—	.00 ^{ns}		—	.10 ^{ns}		—	.01 ^{ns}	
h^2	.04 *(0, .14)*	.59 *(.44, .77)*		.00 *(0, .12)*	.72 *(.51, .78)*		.01*(0, .12)*	.69 *(.53, .85)*	
C_1	–.77	.10 ^{ns}	–.21 *(–.70, .08)*	.79	.03 ^{ns}	.21 *(–1, 1)*	.78	–.04 ^{ns}	–.09 *(–1, 1)*
C_2	—	.47		—	.12 ^{ns}		—	.38 ^{ns}	
c^2	.59 *(.50, .66)*	.23 (*.06, .38)*		.62 *(.52, .67)*	.01 *(0, .20)*		.61 *(.52, .67)*	.14 *(0, .30)*	
E_1	.60	.01 ^{ns}	.03 *(–.10, .16)*	.61	.10	.19 *(.06, .31)*	.61	.07	.16 *(.03, .29)*
E_2	—	.41		—	.51		—	.40	
e^2	.36*(.31, .42)*	.17 *(.14, .22)*		.38 *(.32, .44)*	.27 *(.22, .33)*		.37 *(.32, .43)*	.17 *(.13, .21)*	

Note: ^{ns} = not significant

(verbal, performance, full) was equal to one. However, for performance and full IQ analyses the confidence interval for the genetic correlation with birthweight spanned zero, indicating that genetic mediation of this relationship was not significant. Common environmental effects accounted for roughly 60% of variance in birthweight and 23% of variance in verbal IQ, but were not significant for performance and full IQ.

The major sources of variance influencing birthweight and IQ were different, with common environment showing a much larger influence on birthweight and additive genes influencing IQ to a greater extent. This pattern of effects thus allowed the modeling of the direction of causation between birthweight and IQ (verbal, performance, full). In the direction of causation models we parameterized a C influence on the latent birthweight factor, an A effect on the latent IQ factor, E influences on latent birthweight and IQ factors, and a causal parameter from either birthweight to IQ or from IQ to birthweight latent factors. For verbal IQ, which showed influences from the common environment, a C factor was additionally specified to load on the latent verbal IQ factor. The test–retest correlation (r = 0.82) for birthweight was estimated from mother's reports of birthweight when the twins were aged 12 and then again at age 14 in 608 twin pairs (342 of these pairs were included in the present study). Test–retest correlations for verbal, performance and full IQ were 0.88, 0.84 and 0.89, respectively, and were estimated from a retest sample of 49 twin pairs over a 3-month interval (all of whom were included in the present study). While these test–retest estimates were lower than those reported in the Multidimensional Aptitude Battery manual (Jackson, 1998), it must be noted that our IQ scales comprised fewer subtests and our retest interval was longer.

The goodness-of-fit of the direction of causation models is shown in Table 3. For both performance and full IQ either direction of causation model showed acceptable fit to the data. However, for verbal IQ, the model in which verbal IQ influenced birthweight provided a significantly better fit than the reverse direction of causation model ($p < .05$). Causal parameters ranged from 0.11 for the model in which birthweight influenced verbal IQ to 0.15 for the model in which full IQ influenced birthweight. Although the direction of causation models fitted the data, the Cholesky decomposition with equal female and male parameters showed the smallest $\Delta\chi^2$ in each analysis indicating superior model fit.

Discussion

In a large sample of twin pairs we have shown that the relationship between birthweight and verbal IQ, measured at 16 years of age, is primarily mediated by genes. In contrast, the relationships with performance and full IQ were influenced to a greater extent by common aspects of the unique environment. One may interpret the latter results in terms of nonshared prenatal influences that differentially affect the birthweights of twin pairs and also have lasting effects on IQ. While either direction of causation model showed acceptable fit to the data for performance and full IQ, the model in which verbal IQ caused birthweight provided better fit than the reverse direction of causation. As birthweight temporally precedes IQ measurement, it may be that the influences from IQ (being correlated with parent's IQ; Alarcon et al., 1998; Plomin et al., 1997) on birthweight represent the health behaviours of mothers during pregnancy (e.g., diet, smoking) which may be related to their IQ. Although this notion is in contrast to findings showing that socioeconomic status (also related to mother's IQ) does not alter the effects of birthweight on cognitive ability (Jefferis et al., 2002; Shenkin et al., 2001), a study in which mother's IQ is recorded in addition to the child's IQ and birthweight is required to explicitly test this hypothesis.

With a sample size of 523 twin pairs the direction of causation models examined in the present study were likely to be underpowered; in fact, we could not

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discriminate between the competing direction of causation models for performance and full IQ. Power calculations by Heath et al. (1993) showed that for two traits free of measurement error with different causes of major variation (e.g., 0.75 heritability for one versus 0.75 shared environment for the other) and a causal parameter equal to .15 (similar to the estimates obtained in this study), no fewer than 1000 twin pairs are needed to falsify the competing model of causation with 80% power. So while the direction of causation models we tested showed acceptable fit to the data (with the exception of birthweight influencing verbal IQ), the saturated bivariate factor model was the slightly better fitting model in each IQ analysis, and hence these results will be discussed.

It has been documented that the relationship between birthweight and IQ is strongest in childhood then tends to diminish with age (Jefferis et al., 2002; Richards et al., 2001). In our adolescent sample the variance in verbal IQ accounted for by birthweight was low (.08%) but significant. The bivariate analysis with verbal IQ showed birthweight heritability to be modest, accounting for 4% of variance, while the analyses with performance and full IQ showed, at most, genetic effects amounting to 1% of variance, although they were not significant. This indicates that birthweight heritability is minimal and only detectable when analyzed in combination with a genetically related phenotype.

As we studied the birthweight of twin pairs rather than the birthweight of the offspring of twins, the genes implicated in our study relate to fetal rather than maternal effects. Our heritability estimate of birthweight was particularly low which agrees with some previous estimates (Morton, 1955; Nance et al., 1983) but not others (Langhoff-Roos et al., 1987; Magnus et al., 1984). In a study by van Baal and Boomsma (1998) in which a heritability of 0.10 for birthweight was reported, they proffered an explanation based on chorionicity of MZ twins to explain the low influence from fetal genes. As monochorionic MZ twins compete against each other for nutrients arising from the single chorion they may exhibit differences in birthweight not predicted by a genetic model (Machin, 1996). Similarly, monochorionic twins with the twin–twin transfusion syndrome (incidence of 5–15%) will be particularly discordant for birthweight, and hence inconsistent with the predictions of a genetic model (Seng & Rajadurai, 2000). As we factored chorionicity (based on placentation) into our variance components modeling these effects cannot explain the low (virtually nonexistent) heritability we obtain for birthweight. However, it must be recognized that our chorionicity information is likely to contain some error due to the inaccuracy of self-report, especially considering the lapse in time (at least 12 years) from childbirth to reported placentation by the mother.

In the only other study (Boomsma et al., 2001) of the genetic influence on the birthweight–IQ relationship, full IQ was analyzed rather than verbal and performance scales. Our study showed that genes mediated the relationship between birthweight and verbal IQ but not performance IQ. This finding may explain why Boomsma et al. (2001) did not detect any genetic mediation effect in their sample at age 12, since full IQ is a conglomerate measure of verbal and performance abilities. While our finding is consistent with literature that shows the presence of some non-overlapping genetic influences on verbal and performance IQs, one might expect genetic mediation of the relationship between birthweight and performance IQ rather than verbal IQ since verbal abilities are influenced to a greater extent by common environment than are performance (or fluid) abilities. However, as verbal abilities tap acculturalised learning and thus depend substantially on processes such as long-term memory, the gene/s influencing birthweight might have an effect on a specific information process that is strongly related to verbal IQ but not to performance IQ.

Common environmental effects on birthweight in our study were large (~ 60% of variance) agreeing with previous estimates (e.g., Whitfield et al., 2002) and they may involve many diverse environmental factors. Of these, gestational age has been confirmed by others to be a major predictor of birthweight, accounting for 27 to 44% of variance (van Baal & Boomsma, 1998; Vlietinck et al., 1989). Additional common environmental factors shown to influence birthweight include maternal influences such as age, smoking and nutrition (Goldstein, 1981; Kramer, 1987), though we have suggested that some of these influences may be correlated with mother's IQ, which is largely heritable. The effects of maternal genes in our classical twin design will be distributed as common environmental variance since these effects will differ between twin families and not within them. The variance accounted for by maternal gene effects on birthweight have been estimated in the range of 12% to 40% (Magnus, 1984; Nance et al., 1983; Penrose, 1954). There was negligible overlapping common environmental influence on birthweight and IQ, and similarly, specific common environmental effects on performance and full IQ were minor. It is reasonable that verbal IQ, which allegedly taps acculturalised learning, should be affected by aspects of the shared environmental while performance IQ, a measure of novel learning, should not.

Unique environmental effects were moderate for birthweight and less so for IQ. Similar proportions of nonshared environmental effects have been reported for birthweight (e.g., Ijzerman et al., 2002; Vlietinck et al., 1989; Whitfield et al., 2002) and IQ (Dunn & Plomin, 1990; Plomin et al., 1994). Prenatal nonshared environmental effects on birthweight may relate to co-twin competition for nourishment, especially in monochorionic MZ pairs. As evidenced by

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the unique environmental covariation between birthweight and IQ (particularly performance IQ), this differential nourishment in utero might affect fetal brain development which is reflected in resulting IQs, but it is possible that the negative effects of nourishment on verbal abilities can be alleviated by positive influences from the common environment, which were shown to have a greater effect on verbal than performance abilities. Independent unique environmental factors influencing IQ might relate to differences in extracurricular reading or other activities that foster intellectual growth.

In summary, we have confirmed genetic mediation of the relation between birthweight and verbal IQ in an adolescent sample and we have furthermore estimated the proportion in which genes influence this relationship. The variation in birthweight was predominantly influenced by common environmental effects, while the variation in IQ was primarily affected by additive genes. The overlapping variance between birthweight and verbal IQ was primarily genetic in origin, while for performance and full IQ the covariance with birthweight stemmed mainly from unique environmental influences. Models including a phenotypic causal pathway between birthweight and IQ (in each direction) fitted the data for performance and full IQ but not for verbal IQ, where the model with verbal IQ influencing birthweight showed better fit to the data than the reverse. A two-fold increase in sample size is needed for sufficient power to resolve the direction of causation between birthweight and IQ, although based on the smaller Chi-square change our results suggest that the causal direction is from IQ to birthweight. A fuller investigation of the birthweight and IQ relationship requires collection of IQ data for mother's of twins and of mother's lifestyle/health behaviour during pregnancy, although for such a minor association continued analysis may not be justified.

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