No Evidence of Genetic Mediation in the Association Between Birthweight and Academic Performance in 2,413 Danish Adolescent Twin Pairs

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Evidence of a positive association between birthweight and IQ has been established in several studies. Analyses of within twin pair differences in birthweight and IQ have been used to shed light on the basis of the association. The strength of this approach is the possibility of controlling for both unmeasured common childhood–environmental factors as well as genetic factors shared by the co-twins. Two twin studies suggest the existence of genetic mediation between birthweight and IQ, that is, common genetic factors influence both fetal growth and IQ in childhood, while two other twin studies find no evidence of such mediation. In the present study we use a large population-based national register study of 2,413 Danish twin-pairs from birth cohorts 1986–1990, of which we have zygosity information on 74%. We perform individual level as well as intra-pair analyses of birthweight and school achievements at age 16. For both sexes we observed a monotonic increase in academic performance with increasing percentiles of birthweight. However, we did not find that this association is due to genetic mediation.

Keywords: twins, academic performance, genetic mediation, birthweight

Many studies have examined, and established, a positive relationship between birthweight and intelligence in later life, and the association has been demonstrated to continue from low birthweights well into the normal range of birthweight (Breslau et al., 1996; Matte et al., 2001; Richards et al., 2001; Sorensen et al., 1997). The same trend was observed in a study of school achievements among Danish twins and singletons from birth cohorts 1986–1988 (Christensen et al., 2006). It has been hypothesized that the association between birthweight and IQ is causal; either directly or mediated through an early postnatal catch-up growth of low birthweight children (Estourgie-van Burk et al., 2009). Early postnatal catch-up growth may require more energy thereby draining resources from neural development and consequently have a negative influence on the cognitive development. Other studies of twins propose that part of the positive association between birthweight and IQ may be mediated through genetic effects and consequently noncausal (Boomsma et al., 2001; Tsou et al., 2008).

Twins deliver an almost perfect counterfactual set-up. They have the same parents, the same childhood socio-economic status, are the same age, and usually grow up in the same family environment. Moreover, dizygotic (DZ) twins, like ordinary siblings, share on average, 50% of their segregating genes, while monozygotic (MZ) twins have 100% of their genes in common. In nearly all twin pregnancies, the twins have the same gestational age at birth but, due to differences in genes and the intrauterine milieu, they do not necessarily have the same birthweight. Hereby, studies of within twin-pair differences in IQ and birthweight provide an opportunity to control for important measured and unmeasured confounders common for the twins.

Various studies have analyzed the association between within twin-pair differences in IQ and birthweight both in epidemiology (Boomsma et al., 2001; Newcombe et al., 2007; Tsou et al., 2008) as well as in economics (Behrman & Rosenzweig, 2006; Black et al., 2007; Royer, 2009). Studies of non-twin sibling-pair differences (Lawlor et al., 2005; Lawlor et al., 2006; Matte et al., 2001) have likewise been performed in an attempt to shed light on the physiological

Received 13 May, 2009; accepted 1 August, 2009.

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mechanism behind the birthweight–IQ association. The results of these studies give an ambiguous picture of the connection between birthweight and IQ.

In a study of sibships collected from 1,683 US families (Matte et al., 2001) the authors found a significant positive within-pair association between birthweight and measured IQ at the age of 7 for children born 1959–1966, but only for males, not for females. Lawlor et al. found no association between differences in birthweight for gestational age and IQ at age 7 for either males or females in a study of 1,635 sibling pairs in the Aberdeen 1950–1956 birth cohorts (Lawlor et al., 2006). In a study of 235 sibling pairs from Brisbane born in the first half of the 1980s, Lawlor et al. (Lawlor et al., 2005) found that within pair differences in intrauterine growth were positively associated with differences in verbal comprehension at age 5 and general intelligence at age 14, but not with reading ability at age 14. A Dutch study of 170 twin pairs tested 4 times in the age range 5–12 found a significant positive association between differences in birthweight and differences in IQ at age 7 and at age 10 within DZ pairs, but no similar associations within MZ pairs (Boomsma et al., 2001). In a recent study of 316 same-sex and 61 opposite-sex Taiwanese twin pairs (Tsou et al., 2008), the authors found a positive within-pair association birthweight and both mathematics and English test scores in opposite-sex twin pairs but not in same-sex twin pairs; the authors did not have access to zygosity information. Failure to observe within pair associations between measures of cognitive functioning and birthweight in MZ pairs in the Dutch study (Boomsma et al., 2001) and same-sex pairs in the Taiwanese study (Tsou et al., 2008) led the researchers to conclude that their results imply that the birthweight–IQ association is partly due to genetic confounding, that is, that common genetic factors are influencing both fetal growth and IQ. Contrary to the Taiwanese and Dutch studies, Newcombe et al. demonstrated a positive within-pair association in birthweight and IQ at age 5 in 563 MZ twin pairs born in 1994–1995 (Newcombe et al., 2007). These authors did not include analyses of DZ twin-pairs, but they repeated the analyses on a pooled sample consisting of the 563 MZ pairs and 553 same-sex DZ pairs. The results showed a slightly lower regression coefficient in the pooled sample compared with MZ twins. These results suggest that the IQ–birthweight association among DZ twins is weaker than the association among MZ twins. The same approach was used by Black et al. (2007) to examine the association between the logarithm of birthweight and IQ-test scores from military records of 2,538 Norwegian same-sex males (of whom MZ twins) from birth cohorts 1967–1979 (aged 18–20 years). The results showed no difference of the regression coefficients for the pooled sample compared with that for the sample consisting of MZ twins. Behrman and Rosenzweig studied the association between birthweight and length of education in a sample of 1,418 female US twins, of whom 804 were MZ twins. In a regression analysis of the pooled sample they found that a 450g increase in birthweight corresponded to one-third of a year longer education; the effect was observed to be doubled when conducting an intra-pair analysis on the MZ twin pairs (Behrman & Rosenzweig, 2006). In a recently published paper on the association between birthweight and education in a sample of US female twins (N = 3,396 pairs), the within-pair effect was estimated to be 0.15 years longer education per kg increase of birthweight (Royer, 2009). The investigators did not have access to information on zygosity.

There is currently mixed evidence for a genetic mediation between birthweight and childhood IQ. The studies of twins indicating genetic mediation were conducted on 170 same-sex pairs in a Dutch study (Boomsma et al., 2001) and 316 same-sex and 61 opposite-sex pairs in a Taiwanese study (Tsou et al., 2008), whereas two large studies (Black et al., 2007; Newcombe et al., 2007) found no difference between MZ within pair estimates and within pair estimates from a pooled sample of same-sex twins for the association between birthweight and IQ-test scores at age 5 and age 18–20, respectively. These results indicate but, as pointed out by Boomsma et al. (2005), they do not prove the nonexistence of a genetic mediation between birthweight and IQ. In the present national register-based study we are able to perform within pair analyses on a population (2,413 twin pairs) of unselected Danish twins from birth cohorts 1986–1990, for which we have zygosity information on 1,780 (74%) pairs.

Methods

Material

In this study we linked twins identified through the Danish Twin Registry (Skytthe et al., 2002) from birth cohorts 1986–1990 to their 9th-grade test scores and teacher assessments obtained from the Danish Ministry of Education (Danish Ministry of Education, 2004), along with birthweight from the Fertility Database (Statistics Denmark, 2007). The linkage between the population-based registries is enabled by means of the unique civil personal registration number (CPR-number) assigned to all Danish residents at birth.

The Danish Twin Registry comprises more than 73,000 twin pairs born in Denmark since 1870, including all twins born since 1973 as identified through the Medical Birth Registry (Skytthe et al., 2002). Zygosity of same-sex pairs has been classified by means of four standard questions, a method with 3% misclassification for the birth cohorts 1953–1982 (Christiansen et al., 2003).

Danish 9th-grade students (average age 16) are required to complete a general test of academic achievement, which is scored on a scale of 0–13, with average performance rated as 8 and a standard deviation of approximately 1.0 (Christensen et al., 2006).

The tests cover major domains of academic achievement, including Danish, foreign languages, mathematics, and science; both oral and written performances are graded. Teacher ratings of student performance are also given. Reporting of all 9th-grade test scores and teacher assessments to the ministry of education is a legal requirement for all public schools except special schools for those with learning difficulties. Very few private schools do not test, and a small proportion of students choose not to take all tests. Teacher scores are subjective evaluations of the pupils' academic performance over an extended time period, while the test scores are the actual performance of the pupil rated by the teacher and an external examiner at a specific time point. By analyzing the average of all marks (both tests and teacher ratings) given in 9th grade we attempted to rule out the subjectivity of the teacher ratings, as well as the effect of a high stress level at the pupils' performance at the examination. In a study of 9th-grade Swedish children, it was shown that different aptitude factors are important in different domains of school achievements as well as in the overall average (Gustafsson & Balke, 1993). Hence, we supplemented the analyses of the overall average of school achievements with analyses of subject specific averages of the achievements in Danish, mathematics, and English. The school achievements were available for the years 2002–2006 corresponding to the 1986–1990 birth cohorts.

A total of 2,994 complete twin pairs (396 MZ, 833 same-sex DZ, 932 opposite-sex, and 833 pairs with unknown zygosity) with reported birthweight were identified but, due to missing gestational age (*N* = 38 individuals, excluding 19 twin pairs) or 9th-grade marks (*N* = 854 individuals, excluding 562 twin pairs) on one or both twins in a pair, a total of 2,413 pairs (81%) (348 MZ, 696 same-sex DZ, 736 opposite-sex, and 633 pairs with unknown zygosity) were included in the analyses.

Confounders

Parental education and age at birth of the twins, along with the children's age at the 1st of June the year of the test (exact age in years), and gestational age (weeks) were chosen as potential confounders. Parental education was chosen as an indicator of socio-economic status, while parental age was expected to be associated with school achievements due to age-dependence in parental commitment to the schooling of their children. Age of the twin at test as well as gestational age are expected to be proxies for perinatal complications; having perinatal difficulties may imply that the children are enrolled in school later than expected and therefore finish primary school at an older age as compared with other children of the same year of birth.

Statistical Methods

Ordinary least squares (OLS) linear regression was used to assess the association between birthweight and school achievement on an individual level. The analyses were performed on the raw data as well as controlling for potential known confounders (sex, parental age and education along with the twins' gestational age and age at test time) in a multiple linear regression approach. Regression analyses were repeated separately for each zygosity, as well as the group consisting of unknown zygosity twins. Stata's cluster-option (option cluster (twin pair id)) was used to account for possible intra-pair correlations when estimating the standard errors. The cluster-option automatically induces the use of robust standard error estimation in the analyses, thereby relaxing the assumption of identical distribution across the ranges of exposures.

To identify whether there is any association between birthweight and school achievement within twin pairs we used the twin linear fixed effect (FE) approach; thereby regressing within-pair school achievement differences on within-pair birthweight differences. Using this method, the measured association between birthweight and school achievements controls for any observed and unobserved parental, environmental, and genetic factors shared by the two siblings of a twin pair. The FE analyses were performed for the pooled sample of same-sex twin pairs and stratified by zygosity and sex groups.

Comparison of the regression coefficients obtained from the within twin pair analyses with those obtained from the OLS approach gives an indication of the combined effect of all unobserved shared environmental and genetic factors. Stronger intra-pair birthweight school achievement association among DZ twins compared with MZ twins indicates the possible presence of common genetic factors for both fetal growth and IQ in childhood.

An alternative way to assess the impact of genetic factors on the correlation between birthweight and school performance is to estimate the genetic correlation through bivariate structural equation modeling (SEM; Neale & Cardon, 1992). The method is based on the assumption of a linear decomposition of the total variance of the observed traits into four uncorrelated components: additive genetic effects (V_A), genetic dominance (V_D), shared environmental effects (V_C), and nonshared environmental effects (V_E); that is, $V_P = V_A + V_D + V_C + V_E$. While MZ twins share all their genes, DZ twins share on average half of the additive factors and a quarter of the dominant genetic factors. Hence: $\text{Cov(twin1,twin 2)}_{MZ} = V_A + V_D + V_C$ and $\text{Cov(twin1,twin 2)}_{DZ} = ½V_A + ¼V_D + V_C$. Only three of these components can simultaneously be estimated from these three equations; thus ACE and ADE models along with submodels of these can be fitted. Best-fitting model was chosen as the one with the lowest Akaike's Information Criterion (ΔAIC = Δ[–2*Loglikelihood) – Δ(2*degrees of freedom]) in order to accommodate the best balance between goodness of fit and parsimony. The extent to which the same genes contribute to the observed correlation between two traits can be estimated from the bivariate modeling, that is, the correlation of a bivariate phenotype (traits X and Y) can be decomposed as: $r(x,y) = h_x h_y r_g + c_x c_y r_c + e_x e_y r_e$, where r_g, r_c, and r_e represent the genetic, shared environment, and nonshared environment correlations, respectively, while h_i, c_i, and e_i represent the decomposition into genetic, shared and nonshared environmental components of the variance of trait *i*. The SEM analyses were all carried out on variance–covariance matrices of residuals from regression of birthweight and test scores on gestational age, age at test, and parental age and education of 455 male (149 MZ and 306 same-sex DZ) and 528 female twin pairs (179 MZ and 349 same-sex DZ) with full information on all covariates.

The Stata 10.0 software was used for all analyses except the SEM analyses for which we used the standard Mx software (Neale et al., 2003).

Results

Descriptive statistics of sex, birthweight, gestational age, parental age and education, and school achievement scores for the pooled samples and stratified by zygosity are shown in Table 1. The unknown zygosity twins have lower school achievement scores compared with the other zygosity groups; their parents are also slightly younger and have a shorter education. The age of parents at birth of DZ twins is approximately 1.6 years higher than that of MZ twins. Otherwise no systematic differences between zygosity groups are observed.

Table 2 gives the overall average of school achievements as a function of birthweight percentile, both for males and females separately as well as for the total

Table 1

Summary Statistics (Mean and Standard Deviation) of Age, Parental Age and Education, Birthweight, and School Achievement Scores for Danish Twins Born 1986–1990

	Opposite-sex dizygotic	Monozygotic	Same-sex dizygotic	Unknown zygosity	All
Number of individuals	1,472	696	1,392	1,266	4,826
Male (%)	50.0	47.4	47.1	49.0	48.5
Birth weight (g) (mean (SD) N) [b]	2,630 (518) 1,472	2,536 (520) 696	2,585 (506) 1,392	2,555 (526) 1,266	2,584 (518) 4,826
Gestational age (weeks) (mean [*SD*] N)	37.1 (2.2) 1,472	36.9 (2.4) 696	37.1 (2.2) 1,392	37.0 (2.4) 1,266	37.0 (2.3) 4,826
Father's age at birth (mean [*SD*] N) [b]	32.8 (5.6) 735	31.0 (5.3) 347	32.5 (5.7) 694	31.1 (5.7) 629	32.0 (5.6) 2,405
Mother's age at birth (mean [*SD*] N)[b]	30.1 (4.4) 736	28.3 (4.2) 348	29.7 (4.4) 696	28.6 (4.7) 633	29.3 (4.5) 2,413
Father's education N[b]	705	331	664	586	2,286
Basic school 8th–10th grade (N, %)	145 (20.6)	65 (19.6)	153 (23.0)	143 (24.4)	506 (22.1)
Vocational main course (N, %)	307 (43.6)	161 (48.6)	286 (43.1)	279 (47.6)	1,033 (45.2)
Upper secondary education (N, %)	38 (5.4)	14 (4.2)	32 (4.8)	28 (4.8)	112 (5.0)
Short-cycle higher education (N, %)	35 (5.0)	13 (3.9)	34 (5.1)	29 (5.0)	111 (4.9)
Medium-cycle higher education (N, %)	96 (13.6)	45 (13.6)	81 (12.2)	59 (10.1)	281 (12.3)
Bachelor's degree (N, %)	5 (0.7)	2 (0.3)	2 (0.3)	4 (0.7)	12 (0.5)
Master's degree and PhD (N, %)	79 (11.2)	32 (9.7)	76 (11.5)	44 (7.5)	231 (10.1)
Mother's education N[b]	710	345	684	612	2,351
Basic school 8th–10th grade (N, %)	154 (21.7)	80 (23.2)	148 (21.6)	190 (31.1)	572 (24.3)
Vocational main course (N, %)	251 (35.4)	132 (38.3)	261 (38.2)	229 (37.4)	873 (37.1)
Upper secondary education (N, %)	25 (3.5)	18 (5.2)	26 (3.8)	29 (4.7)	98 (4.2)
Short-cycle higher education (N, %)	32 (4.5)	18 (5.2)	40 (5.9)	21 (3.4)	111 (4.7)
Medium-cycle higher education (N, %)	190 (26.8)	79 (22.9)	177 (25.9)	112 (18.3)	558 (23.7)
Bachelor's degree (N, %)	5 (0.7)	3 (0.9)	3 (0.4)	1 (0.2)	12 (0.5)
Master's degree and PhD (N, %)	53 (7.5)	15 (4.4)	29 (4.2)	30 (4.9)	127 (5.4)
Age at test[a] (mean [*SD*])[b]	16.0 (0.4)	16.0 (0.3)	16.0 (0.3)	16.1 (0.4)	16.0 (0.4)
Overall average of tests (mean [*SD*] N)[b]	8.1 (1.1) 1,472	8.3 (1.0) 696	8.2 (1.0) 1,392	7.8 (1.1) 1,266	8.1 (1.1) 4,826
Average of achievement in Danish[b] (mean [*SD*] N)	8.2 (1.1) 1,464	8.3 (1.0) 688	8.2 (1.0) 1,382	7.9 (1.0) 1,256	8.1 (1.1) 4,790
Average of achievements in mathematics [b] (mean [*SD*] N)	8.0 (1.2) 1,464	8.3 (1.1) 688	8.2 (1.1) 1,382	7.8 (1.2) 1,248	8.1 (1.2) 4,782
Average of achievements in English [b] (mean [*SD*] N)	8.3 (1.5) 1,430	8.4 (1.5) 686	8.3 (1.5) 1,364	7.9 (1.5) 1,224	8.2 (1.5) 4,704

Note: [a] Age at 1st of June in 9th-grade (years with 2 decimal places)
[b] Significant differences between MZ, same-sex DZ, opposite-sex DZ and unknown zygosity (5% significance level)

sample of twins. The results show a monotonic increase in average school achievement for increasing birthweight percentile for each sex as well as for the pooled sample. The results also reveal a substantial sex-difference in school achievement: females in the lowest birthweight percentile (0–10%) have approximately the same overall average school achievement as males in the highest percentile (91–100%).

Ordinary Least Squares Regression

Coefficients obtained from raw and confounder adjusted linear regression of overall average school achievements on birthweight for the pooled sample of same-sex twins and stratified by sex are shown in the lower part of Table 2. The effect of birthweight is higher for males compared with females (0.20 vs. 0.10 standard deviation per kg in the raw analyses, $p = .13$) but when controlling for potential known confounders (age, parental age and education, and gestational age) only males demonstrated a positive, but nonsignificant ($p = .08$), association. The same pattern was seen for averages of school achievements in Danish, mathematics, and English (results not shown). Confounder adjusted OLS estimates in separate zygosity groups revealed significant positive associations between overall average school achievements and birthweight for same-sex DZ male twins, 0.31 (95%CI = 0.14–0.49, $p < .01$, per kg for males and for opposite-sex females, 0.20 (95%CI = 0.02–0.39, $p = .03$) per kg. Estimates for MZ twins, both males and females, were approximately zero, while the estimates for opposite-sex DZ and unknown zygosity males were positive (0.17 respectively 0.15 per kg) but nonsignificant ($p = .10$ respectively $p = .25$). The association between birthweight and school achievements in female same-sex DZ twins and twins with unknown zygosity were very weak (0.06 ($p = .59$) respectively 0.05 ($p = .68$) per kg).

Within Twin Pair Comparison

Table 3 presents the results of the FE regressions of the overall average of 9th-grade school achievements as well as results for subject specific analyses. No difference between the group of opposite-sex and the pooled sample of same-sex twins were observed and, when stratifying by zygosity, no statistically significant differences were observed between the three groups of known zygosity along with the group consisting of same-sex unknown zygosity. Separate analyses for males and females showed that the tendency toward an association between within pair birthweight differences and differences in school achievement vanishes completely among females ($p = .59$). Among males the association between within-pair differences of birthweight and school achievements persists when indirectly controlling for unmeasured confounders using the FE approach ($p < .01$). The general picture is unchanged when repeating the analyses for averages of subject specific achievements as well as analyzing the averages of teachers assessments and test scores separately: there is a tendency toward a stronger association between birthweight differences and school

Table 2

Mean of Average of School Achievements for Birthweight Percentiles for Twins Born 1986–90 (Raw and Confounder Adjusted OLS Regression Results in Second Part of the Table)

	Males			Females			All twins		
Birthweight percentiles	N[a]	Mean (*SD*) birthweight (g)	Mean (SD) average achievement score		Mean (SD) birthweight (g)	Mean (SD) average achievement score	N[a]	Mean (SD) birthweight (g)	Mean (*SD*) average achievement score
0–10	239	1612 (249)	7.63 (1.06)	251	1604 (259)	8.12 (1.02)	495	1611 (254)	7.91 (1.08)
11–25	354	2142 (109)	7.78 (1.07)	379	2090 (91)	8.18 (1.02)	724	2113 (97)	8.01 (1.06)
26–50	628	2536 (114)	7.86 (1.06)	659	2407 (95)	8.22 (1.03)	1208	2451 (100)	8.08 (1.05)
51–75	550	2865 (89)	7.94 (1.07)	593	2711 (87)	8.26 (0.99)	1255	2780 (97)	8.07 (1.07)
76–90	356	3149 (83)	8.04 (1.07)	376	3002 (85)	8.32 (1.04)	671	3079 (75)	8.15 (1.03)
91–100	215	3523 (171)	8.14 (0.99)	226	3371 (200)	8.41 (1.04)	473	3440 (192)	8.24 (1.05)
OLS regression	*N*[a]	Regression-coefficients[b]	*P*	*N*[a]	Regression-coefficients[b]	*P*	*N*[a]	Regression-coefficients[b]	*P*
Raw[c]	1482	**0.20 (0.10;0.30)**	**< .01**	1632	0.10 (-0.01;0.20)	0.06	3114	**0.11 (0.04;0.18)**	**< .01**
Adjusted[c,d]		0.13 (-0.01;0.27)	.08		-0.02 (-0.17;0.13)	0.78		0.06 (-0.04;0.16)	.28

Note: Significant results at 5% level are shown in bold face.

[a] Number of individuals

[b] The regression coefficient is the increase in achievement score per 1.0 kg increase in birthweight.

[c] Regression analyses restricted to same-sex twin pairs with information on parental education. (Missing information on parental education in 346 same-sex pairs)

[d] Controlled for exact age (years with 2 decimal places) at 1st of June at year of test, gestational age (weeks), parental age at birth of the twin pair (exact) and education (in 7 categories: basic school [8th–10th grade], vocational main course, upper secondary education, short-cycle higher education, medium-cycle higher education, bachelor's degree, master's degree and PhD). The pooled sample is additionally controlled for sex.

achievement differences among males compared with females, and also, for males, the associations seem to be stronger for same-sex DZ than for MZ twin pairs. Still the differences between results for MZ and same-sex DZ male twins are not statistically different.

Structural Equation Modeling

For males the AE-model gave the best fit for the bivariate genetic analyses of birthweight and school achievements, and we found an estimated genetic correlation of $r_g = -0.02$ ($p = .81$), nonshared environmental correlation of $r_e = 0.04$ ($p = .56$). For females, however, the best fitting model was the ACE-model giving a genetic correlation of $r_g = -0.69$ ($p = .08$), a shared environmental correlation of $r_c = 0.76$ ($p = .07$), and a nonshared environmental correlation of $r_e = .03$ (0.69).

Discussion

In this study we found a positive association between birthweight and average of school achievement scores at 9th-grade (around age 16) in a sample of 2,413 Danish twin pairs. But, when controlling for measured and unmeasured confounders in a fixed effect approach, we did not observe any difference between MZ- and same-sex DZ- twin estimates of the association between birthweight differences and differences of school achievement scores. Hence, our study indicates that genetic mediation does not explain the association between birthweight and school achievements at age 16. Applying SEM analysis to the data confirms this conclusion.

A previous study of all Danish twins and randomly selected singletons from birth cohorts 1986–1988 (Christensen et al., 2006) includes the average test scores stratified for birthweight percentiles. The average test scores demonstrated a monotonic increase with increasing birthweight percentiles; we observe the same pattern in the present study that represents an extension of the previous study to include birth

Table 3

Regression Coefficients of the Fixed-Effect Approach for Within Pair Differences of Subject Specific Averages of 9th-grade School Achievement Scores on Within Pair Differences of Birthweight

	Opposite-sex dizygotic		All same-sex		Monozygotic		Same-sex dizygotic		Unknown zygosity	
	N[a]	Regression coefficient[b] (95% CI) *p* value	*N*[a]	Regression coefficient[b] (95% CI) *p* value	*N*[a]	Regression coefficient[b] (95% CI) *p* value	*N*[a]	Regression coefficient[b] (95% CI) *p* value	*N*[a]	Regression coefficient[b] (95% CI) *p* value
Overall average	736	0.12 (–0.07;0.31)	1677	**0.10 (0.01;0.19)**	348	0.07 (–0.08;0.22)	696	0.09 (–0.05;0.24)	633	0.13 (–0.02;0.27)
		p = .21		***p* = .02**		*p* = .37		*p* = .21		*p* = .08
Males			803	**0.22 (0.10;0.35)**	165	0.18 (–0.08;0.44)	328	**0.27 (0.07;0.48)**	310	0.17 (–0.02;0.37)
				***p* < .01**		*p* = .18		***p* < .01**		*p* = .08
Females			874	–0.03 (–0.16;0.09)	183	–0.03 (–0.20;0.14)	368	–0.12 (–0.33;0.09)	323	0.07 (–0.14;0.28)
				p = .59		*p* = .75		*p* = .27		*p* = .50
Danish	732	–0.03 (–0.24;0.17)	1663	0.08 (–0.01;0.17)	344	0.00 (–0.17;0.18)	691	0.11 (–0.04;0.26)	628	0.07 (–0.08;0.22)
		p = .77		*p* = .09		*p* = .97		*p* = .17		*p* = .34
Males			793	**0.22 (0.08;0.35)**	163	0.08 (–0.22;0.38)	324	**0.31 (0.09;0.52)**	306	0.15 (–0.07;0.36)
				***p* < .01**		*p* = .61		***p* < .01**		*p* = .18
Females			870	–0.07 (–0.20;0.06)	181	–0.06 (–0.26;0.13)	367	–0.12 (–0.34;0.10)	322	–0.01 (–0.22;0.19)
				p = .27		*p* = .53		*p* = .29		*p* = .89
Mathematics	732	**0.33 (0.12;0.53)**	1659	0.11 (0.00;0.22)	344	0.03 (–0.16;0.21)	691	0.09 (–0.09;0.27)	624	0.17 (–0.02;0.35)
		***p* < .01**		*p* = .06		*p* = .79		*p* = .34		*p* = .08
Males			798	**0.17 (0.02;0.32)**	164	0.05 (–0.25;0.36)	326	0.22 (-0.03;0.47)	308	0.15 (–0.08;0.38)
				***p* = .02**		*p* = .72		*p* = .08		*p* = .20
Females			861	0.03 (–0.13;0.20)	180	0.00 (–0.22;0.22)	365	–0.07 (–0.34;0.19)	316	0.18 (–0.10;0.47)
				p = .69		*p* > .99		*p* = .60		*p* = .21
English	715	0.10 (–0.19;0.38)	1637	0.13 (–0.01;0.28)	343	0.16 (–0.13;0.44)	682	0.17 (–0.07;0.40)	612	0.08 (–0.16;0.32)
		p = .50		*p* = .07		*p* = .28		*p* = .16		*p* = .51
Males			782	**0.33 (0.12;0.53)**	163	0.32 (–0.15;0.80)	321	**0.47 (0.14;0.79)**	298	0.14 (–0.17;0.45)
				***p* < .01**		*p* = .18		***p* < .01**		*p* = .36
Females			855	–0.08 (–0.30;0.13)	180	0.01 (–0.33;0.35)	361	–0.19 (–0.53;0.15)	314	0.01 (–0.36;0.38)
				P = .43		*p* = .95		*p* = .27		*p* = .97

Note: Number of pairs varies due to missing values of school achievement scores. Significant results at 5% level are shown in bold face.
[a] Number of twin pairs
[b] The regression coefficient is the difference in achievement score per 1.0 kg difference in birthweight within twin pair.

cohorts 1989–1990. Repeating this analysis for each sex separately reveals that the birthweight–school achievement association is stronger for males than for females. Hence the sex-difference in overall average of school achievements diminishes with increasing percentiles; the difference is approximately 49% of a standard deviation in the lowest birthweight percentile (0–10%) but only about half this size (27%) in the highest percentile (91–100%). These results suggest that females may be better able to compensate for lower birthweight than males with respect to school achievements. This result is supported by previous findings of a sex-difference in the association between very low birthweight and lower IQ, need for special education, and lower school achievements as summarized in a review article (Aylward, 2002) and a cohort study of 241 preterm children (median age at test was 6 year and 4 months) born in the United Kingdom (Wolke et al., 2008). Both articles report substantially lower cognitive scores among very low birthweight males compared with their female counterparts while no sex-differences were found in the comparison group consisting of classmates in Wolke et al.

Using the FE approach to compare the association between within-pair differences of birthweight and differences of school achievement scores we did not observe statistically significant differences between opposite-sex and same-sex twin pairs, neither for the overall average of the school achievement scores nor for subject specific averages. This result contradicts the findings in the study of 377 Taiwanese same-sex twin pairs born in 1983–1985 (Tsou et al., 2008). When stratifying for sex we found a tendency in line with a US study of 1,683 US sibling pairs born in 1959–66 (Matte et al., 2001) of IQ at age 7 that sib differences in birthweight were directly associated with sib differences in school achievements, but only for males.

In the zygosity specific confounder adjusted OLS analyses we observed nonsignificant associations between birthweight and overall average of school achievements for same-sex DZ, MZ, and unknown zygosity males and females. It is therefore not surprising that we did not find strong associations using the FE approach to estimate the association of within-pair differences of birthweight and school achievements stratified for sex and zygosity. We found a tendency among all four school average achievement measures toward a stronger association between birthweight differences and school achievement differences in the group consisting of same-sex DZ twins compared with MZ twins, but this result is entirely due to male twins. The analyses were repeated restricting the twin sample to twins with gestational age > 36 weeks, and for various compositions of school achievements (averages of test scores, teacher assessments as well as subject specific test, and teacher assessments). All approaches resulted in the same pattern (results not shown). Nevertheless, as can be inferred from the large overlap of 95% confidence intervals, the differences between the regression coefficients for MZ and same-sex DZ male twin pairs are not statistically significant in our study of the association between school achievement differences and birthweight differences, and the results were confirmed in the bivariate SEM analyses where we found nonsignificant genetic correlations for both sexes. We therefore conclude that our data do not substantiate the findings in the Dutch study (Boomsma et al., 2001) and recently restated in a Taiwanese study (Tsou et al., 2008) regarding genetic mediation of the relation between birthweight and childhood IQ. Our results, however, point in direction of shared environment explaining the association between birthweight and school achievements. This result was confirmed in the SEM approach, where we found a borderline significant shared environment component when decomposing the cross-trait correlation into environmental and genetic components, but only for females.

Contrary to the study of IQ in 563 MZ 5-year-old twin pairs (Newcombe et al., 2007), as well as the study of educational length of 1,418 twins from the Minnesota Twin Registry (Behrman & Rosenzweig, 2006), we did not find evidence of a significant positive association between birthweight differences and school achievement differences for MZ twin pairs.

The twins in our data are on average 16 years of age. The Dutch study's (Boomsma et al., 2001) findings with children (5–12 years of age) led the authors to conclude that genetic factors mediate part of the association between birthweight and IQ, at least until age 10, as they did not find any association at age 12. Hence it may be that genetic mediation between birthweight and IQ is present at younger ages but vanishes at older ages. On the other hand the study by Tsou et al. suggested a genetic mediation between birthweight and college examinations of Taiwanese twins at age 18 (Tsou et al., 2008). Hence, the literature gives mixed evidence of the existence of an age-dependent genetic mediation between birthweight and IQ.

The strengths of the present study are the sample size (2,413 twin pairs), along with the register-based data, thereby being subject to minimal selection and recall bias. The rather large group of twins (26%) not responding to the zygosity questionnaire is a weakness of the study. According to Weinberg's rule (Fellman & Eriksson, 2006), the group of same-sex DZ twins is expected to be approximately the same size as the group of opposite-sex twins. Since the Danish Twin Registry (Skytthe et al., 2002) holds all twins born in the period of interest in the present study, and opposite-sex twins are easily identified through the birth registry, Weinberg's rule implies that most of the unknown zygosity twins are indeed MZ. Pooling the twins of unknown zygosity with monozygotic twins in our study does not change the main conclusions concerning no statistically significant support of genetic mediation of the relation between birthweight and school achievement (results not shown). Some misclassification regarding zygosity is to be expected. It has previously been shown that the misclassification of the youngest Danish twins (birth cohorts 1953–1982) was 3% and that there were more MZ twins classified as DZ than vice versa (Christiansen et al., 2003). We therefore expect that this misclassification does not significantly bias the results of the present study.

A second concern about this study is missing school achievement scores. The school achievement scores are absent for one or both twins for 12% of the MZ pairs, 16% of the same-sex DZ pairs, 21% of the opposite-sex pair, and 24% of pairs with unknown zygosity. It is likely to be the case that the group of unknown zygosity twins contains a larger proportion of twin pairs, for whom one or both have health problems or low socio-economic status, as zygosity classification depends on parental response to a questionnaire. Combined with the fact, as mentioned above, that there seems to be an overrepresentation of MZ twins in the group with unknown zygosity, it can be argued that the parents of MZ twins where one or both do not manage well are less inclined to respond to the mailed questionnaire on physical similarities than DZ twins. However, pooling twins with unknown zygosity with MZ twins does not change the conclusions of this study.

Our results are based upon 9th-grade school achievements, while earlier research results are based on formalized IQ tests. In a review by Naglieri & Bornstein (2003) the authors found a high correlation between IQ and standardized achievement tests (average 0.70 to 0.74), and the correlation between national achievement tests and IQ seems to be almost as high (Bartels et al., 2002). Hence, we can reasonably expect that 9th-grade school achievements produce results similar to IQ measurements.

Conclusion

In line with previous studies we found an association between birthweight and 9th-grade school achievements for Danish twins. The association vanished when controlling for known confounders, but was reinstated for males using an intra-pair approach to estimate the association between within-pair birthweight differences and within-pair differences of school achievement scores at age 16. However, we did not observe significant differences between the results for MZ and same-sex DZ twin pairs, and SEM analyses showed no positive genetic correlation. We therefore conclude that, in spite of a large sample of twins with minimal selection bias, we were not able to find evidence of genetic mediation between school performance of adolescent Danish twins and birthweight.

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