Birthweight Predicts IQ: Fact or Artefact?

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It has been shown that lower birthweight is associated with lower IQ, but it remains unclear whether this association is causal or spurious. We examined the relationship between birthweight and IQ in two prospective longitudinal birth cohorts: a UK cohort of 1116 twin pairs (563 monozygotic [MZ] pairs), born in 1994–95, and a New Zealand cohort of 1037 singletons born in 1972–73. IQ was tested with the Wechsler Intelligence Scales for Children. Birthweight differences within MZ twin pairs predicted IQ differences within pairs, ruling out genetic and shared environmental explanations for the association. Birthweight predicted IQ similarly in the twin and nontwin cohorts after controlling for social disadvantage, attesting that the association generalized beyond twins. An increase of 1000 g in birthweight was associated with a 3 IQ point increase. Results from two cohorts add to evidence that low birthweight is a risk factor for compromised neurological health. Our finding that birthweight differences predict IQ differences within MZ twin pairs provides new evidence that the mechanism can be narrowed to an environmental effect during pregnancy, rather than any familial environmental influence shared by siblings, or genes. With the increasing numbers of low-birthweight infants, our results support the contention that birthweight could be a target for early preventive intervention to reduce the number of children with compromised IQ.

Low birthweight is a risk factor for children's poor intellectual development. Differences between children with low birthweight and control children have been documented using a wide range of tests measuring cognitive functions and the intelligence quotient (IQ; Anderson et al., 2003; Breslau et al., 1994; Hack et al., 2002). These differences have been observed early in childhood and appear to persist into adulthood.

Most of this research has focused on children with very low birthweight: < 1500 g, 1.2% of UK live births (Office of National Statistics, 2004; Hack et al., 2002; Rickards et al., 2001); or on children with low birthweight: < 2500 g, 7.6% of live UK births (Office of National Statistics, 2004; Breslau et al., 1994). However, even within the normal range of birthweight, lower birthweight is linked to lower cognitive functioning and IQ scores (Jefferis et al., 2002; Matte et al., 2001; Richards et al., 2001; Shenkin et al., 2001). Although the link between low birthweight and low IQ is well documented, it remains an open question whether this is a causal link or a spurious association.

The majority of studies of birthweight and IQ have compared children born to different mothers, in different families. Such comparisons are controversial because children may differ from each other not only in their birthweight, but also in their rearing environments. An especially important confound is social class. Social class is related to IQ, (Bradley & Corwyn, 2002) and to the extent that poorer women more often deliver low birthweight children, the association between low birthweight and children's IQ may be an artefact of social class differences between families. When studies have introduced statistical controls for social class differences between families, the strength of the association between birthweight and IQ is attenuated, but remains significant in many (Shenkin et al., 2004), but not all studies (Richards et al., 2001; Shenkin et al., 2001). However, unless studies are able to control for all relevant differences between families, the interpretation of a causal association between low birthweight and low IQ is unwarranted.

A more powerful observational design compares siblings growing up within the same family, preferably siblings close in age who have experienced similar postnatal environments. Most (Bergvall et al., 2006; Lawlor et al., 2005; Matte et al., 2001), but not all (Lawlor et al., 2006), sibling studies report that sib-pair differences in birthweight are related to sib-pair differences in IQ. However, comparisons of ordinary siblings may be incomplete for two reasons (Boomsma et al., 2001; Leon, 2001; Luciano et al., 2004). First, comparisons of closely aged siblings do not control for prenatal environmental differences between siblings that may be linked to later IQ

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differences (e.g., differential exposure to maternal smoking during pregnancy; Weitzman et al., 2002). In contrast, studies of twins (who share the womb) are able to rule out potential pregnancy differences between siblings. Second, studies using ordinary siblings, and even those using dizygotic (DZ) twins, are not able to resolve whether the association between low birthweight and low IQ is due to common genetic factors. In contrast, if differences in birthweight within genetically identical monozygotic (MZ) twin pairs predict differences between the twins' IQ, this would provide evidence that the association between birthweight and IQ cannot be explained by genetic factors (and would also rule out other pre- and postnatal factors shared by twins).

In the present article, we use comparisons within MZ twin pairs to document that birthweight differences between genetically identical siblings sharing the same environment are related to later IQ differences between these siblings. To our knowledge, our MZ twin difference design, with 563 MZ twin pairs, is the largest twin difference study to examine the association between birthweight and IQ. Moreover, we complement these analyses by using a traditional singleton birth cohort to document that the association between birthweight and IQ generalizes to nontwins.

Study 1: Methods
Participants
Participants in the first cohort are twins who are members of the Environmental Risk (E-risk) Longitudinal Twin Study (Moffitt et al., 2002). The E-risk sampling frame was two consecutive birth cohorts (1994 and 1995) from a birth register of twins born in England and Wales. The E-risk Study was constructed in 1999–2000, when 1116 families with same-sex 5-year-old twins (93% of those eligible) participated in a home-visit assessment, forming the base cohort. Findings from the twin cohort can be generalized to the population of British families with children born in the 1990's, based on maternal age at twins' birth (Bennett et al., 1996). Zygosity was determined by a questionnaire administered to the parent about physical similarities, differences, and confusion between the twins. This questionnaire has been found to accurately classify the zygosity of 95% of twins (Price et al., 2000). Unclear zygosity was resolved by DNA testing. The cohort includes 55% MZ and 45% DZ twin pairs. Sex is evenly distributed within zygosity (49% male). The E-risk study received ethical approval from the Maudsley Hospital Ethics Committee for each phase of this longitudinal study. Parents gave informed consent.

Measures
Each twin's birthweight was obtained by parental recall when the twins were 1 year old. Parental recall has been shown to be an accurate proxy for recorded birthweight (Tate et al., 2005; Walton et al., 2000). Birth information was obtained for 2076 children (93% of the cohort). Mean birthweight was 2436 grams (SD = 544 g; range = 454 g–4114 g). The present study used a continuous measure of birthweight in grams rather than a dichotomous classification of low birthweight (LBW) versus normal birthweight (NBW), given that these cut-offs have been predominantly used for singletons rather than twins. Mean gestational age was 36.2 weeks (SD = 2.7 weeks; range = 24–43 weeks).

Children's IQ was assessed at age 5 using a short form of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI; Wechsler, 1990), following procedures outlined by Sattler (Sattler, 1992, pp. 998–1004). The short form is correlated with the full version of the WPPSI (r = .76). Psychometrists were blind to children's birthweight. The WPPSI prorated scores ranged from 52 to 145 (M = 97.8, SD = 14.4).

The socioeconomic disadvantage of the children's families was measured at age 5 by summing the following disadvantages: 1) head of household has no educational qualifications; 2) head of household is employed in an unskilled occupation or is not in the labour force; 3) total household gross annual income is less than £10,000; 4) family receives at least one government benefit, excluding disability benefit; 5) family housing is government subsidized; 6) family has no access to a vehicle, and 7) family lives in the poorest of six neighbourhood categories, in an area dominated by government subsidized housing, low incomes, high unemployment, and single parent families (Kim-Cohen et al., 2004). Summing across these seven items yielded a composite index of socioeconomic disadvantage, ranging from 0 to 7 (M = 1.2, SD = 1.7).

Study 2: Methods
Participants
Participants in the second cohort are singletons who are members of the Dunedin Multidisciplinary Health and Development Study (Moffitt et al., 2001). Study members were born in Dunedin, New Zealand between April 1972 and March 1973. 1037 children (91% of eligible births; 52% male) participated in the first follow-up assessment at age 3, constituting the base sample for the remainder of the study. Study members have been followed up regularly to age 32 (96% retention). This article reports on IQ, last assessed at age 13 years. The Otago Ethics Committee approved each phase of this longitudinal study. Study members' parents gave informed consent before participating.

Measures
Hospital records were the source of children's birthweight (M = 3375 grams; SD = 524 g; range 1420 g–5400 g) and gestational age (M = 40 weeks; SD = 1.6 weeks; range 29–44 weeks).

Children's IQ was assessed using the Wechsler Intelligence Scale for Children (WISC-R; Wechsler, 1974), administered at ages 7, 9, 11, and 13 years.
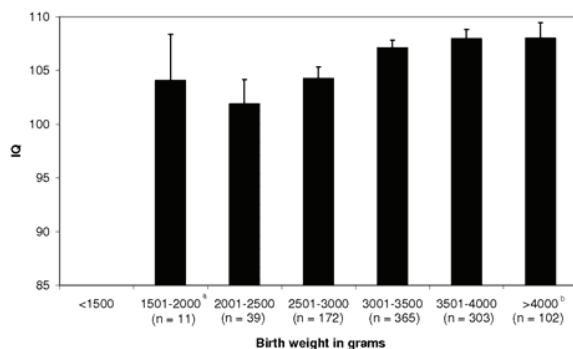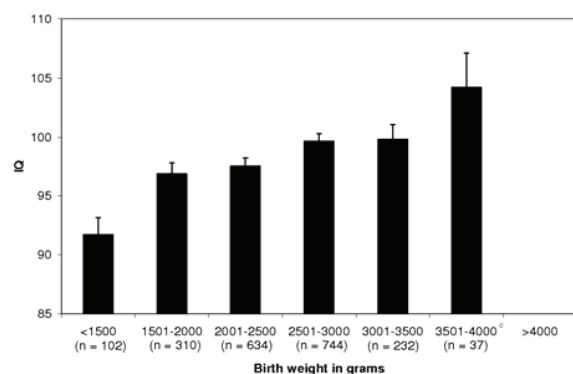
Figure 1A. Singleton cohort

Figure 1B. Twin cohort.

Figure 1

IQ by birthweight in (A) the singleton cohort, and (B) the twin cohort.

Note: [a] Includes $n = 3$ cases where birth weight < 1500 g.

[b] There was no decrease in IQ for babies with birthweight > 4000 g.

[c] Includes $n = 2$ cases where birth weight > 4000 g.

Psychometrists were blind to children's birthweight. The WISC-R scores from the four age periods were averaged to form an overall score ($M = 106.7$; $SD = 14.3$; range = 40–147).

The *socioeconomic status* of the children's families was measured with a 6-point scale assessing parents' self-reported occupational status. The scale places each occupation into one of 6 categories (1 = professional, 6 = unskilled labourer) based upon the educational levels and income associated with that occupation in data from the New Zealand census ($M = 3.2$, $SD = 1.1$; range = 1–6).

Statistical Methods

In both cohorts, multiple regression analysis was used to test the association between birthweight and IQ. First, we tested the association between birthweight and IQ, controlling for sex. Second, we tested the association between birthweight and IQ with statistical controls added for socioeconomic differences between families. In the twin cohort, results are based on the sandwich or Huber/White variance estimator (Rogers, 1993; Williams, 2000), which adjusts

estimated standard errors to account for the dependence in the data due to analyzing two children per family and provides results that are robust to model assumptions (Lumley et al., 2002). Gestational age was controlled in these analyses. Third, we tested whether the association between birthweight and IQ could be explained by shared genes and environments by using MZ twins from the twin cohort. We created difference scores for MZ twin pairs (twin 1–twin 2) for birthweight and IQ, and tested the association between birthweight difference within MZ pairs, and later IQ difference within these same pairs, controlling for sex. No control for gestational age was needed for this comparison, as twins in a pair have the same gestational age.

Results

Is birthweight associated with IQ? In both cohorts, birthweight was positively associated with IQ (twin: $n = 2059$ children, $\beta = .11$, $p < .001$; singleton: $n = 992$ children, $\beta = .11$, $p < .01$). An increase of 1000 g in birthweight was associated with a 3.6 IQ point increase in the twin cohort, and a 3.0 IQ point increase in the singleton cohort. There was no sex interaction in either cohort (both p's > .10), indicating that the birthweight-IQ association held for both males and females. Figures 1a and 1b show children's mean IQ scores as a function of birthweight interval. Overall, there was a dose-response relation in both cohorts; as birthweight increased, so too did IQ, and this held among those with birthweights in the normal range (> 2500 g).

Is the association between birthweight and IQ explained by socioeconomic differences between families? Socioeconomic disadvantage was not associated with birthweight ($\beta = -.03$, $p > .10$), but was associated with IQ in the singleton cohort ($\beta = -.42$, $p < .001$). Socioeconomic disadvantage was associated with both birthweight ($\beta = -.06$, $p < .05$) and IQ in the twin cohort ($\beta = -.33$, $p < .001$). However, controlling for socioeconomic disadvantage did not substantially reduce the association between birthweight and IQ in either cohort (twin: $\beta = .12$, $p < .001$; singleton: $\beta = .09$, $p < .01$).

Does the association between birthweight and IQ survive controls for confounding by all genetic and any environmental factors shared by the twin pair? Differences within MZ twin pairs in birthweight were significantly and positively associated with differences within pairs in IQ ($n = 563$ pairs, $\beta = .17$, $p < .001$). Continuous data were used for statistical analyses, but for ease of presentation Figure 2 displays this association graphically for twins very discordant in birthweight (± 500g). Within pairs, heavier twins had significantly higher IQ scores on average than lighter twins. We evaluated two potential confounds: birth order within a twin delivery and cerebral palsy. Birth order within a twin delivery was

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not related to birthweight ($\beta = -.04$, $p > .10$) or IQ ($\beta = -.02$, $p > .10$), and so was not considered further. Cerebral palsy affected one twin in seven MZ pairs. Excluding the seven pairs where one twin had cerebral palsy did not affect the significance of the relationship between birthweight differences and IQ differences ($\beta = .16$, $p < .01$).

Discussion

These findings from two birth cohort studies add to growing evidence that low birthweight (or its causes) compromises neurological health. Three main implications stand out from the reported research. First, the findings confirm the usefulness of genetically sensitive research designs in studying the effects of prenatal environments on later health outcomes. Epidemiologists have previously used twin studies to study the fetal origins of adult disease, including diabetes (Beck-Nielsen et al., 2003) and hypertension (Dwyer et al., 1999), and the present study documents that the MZ twin difference design offers a powerful observational method for identifying potential causal effects. Second, although individual differences in IQ are known to be influenced by genetic factors (Plomin et al., 2001), the findings from this study contribute to growing evidence that the prenatal environment influences cognitive development, independent of direct additive genetic influences (Devlin et al., 1997). Third, the positive association between birthweight and IQ is not simply an artefact of an association at the low end of the birthweight range. As such, despite the fact that the change in IQ as a function of each 1000 grams of birthweight is small on an individual basis, the association is important at the population level (Matte et al., 2001; Shenkin et al., 2004).

The reported research has several limitations. First, although our twin cohort afforded a powerful test of the association between birthweight and IQ, twins may not represent singletons. On the one hand, newborn twins are growth retarded, and it is not clear that the growth retardation of twins is the same as that of singletons (Phillips et al., 2001). On the other hand, in both our twin and singleton cohorts, a 1000g increase in birthweight was associated with an increase in about 3 IQ points, which is similar to previous published estimates (Matte et al., 2001). A Danish comparison between 3500 twins and 8000 singletons also found significant association between birthweight and IQ in both samples (Christensen et al., 2006). Second, we do not have data on chorionicity and therefore cannot take into account the potential effect of chorion type on twin discordance. However, it is not clear this invalidates the MZ twin difference design; the limited empirical evidence available has not shown any differences in MZ concordance on IQ according to chorion type (Sokol et al., 1995). Third, our research focused on the intelligence quotient (IQ), as assessed by standardized
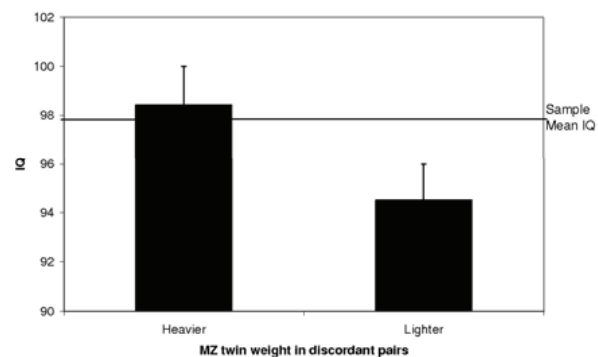

Figure 2

IQ for monozygotic twin pairs very discordant in birth weight (+/− 500 g) in the twin cohort. Means for the heavier and lighter twin of each pair are displayed.

tests, because it is a nonspecific, yet reliable and valid, index of the overall integrity of the brain's intellectual functions (Gray et al., 2004). However, future research must go further, to apply neuropsychological assessments and neuroimaging methods to reveal the specific brain functions involved.

The findings appear to meet several criteria suggestive of a causal association between low birthweight and low IQ (Grimes & Schulz, 2002): low birthweight preceded the outcome; the association between low birthweight and low IQ appeared to be independent of correlated risk factors (in particular, as documented by the MZ twin difference design); and there was evidence of a dose-response relation between birthweight and low IQ. These findings support the contention that birthweight could be a target for early preventive intervention to prevent the number of children with compromised IQ, especially in light of emerging evidence from longitudinal studies that low childhood IQ predicts poor adult health and early mortality (Deary et al., 2004). The increased survival rate of premature infants (Martin et al., 2003), the long-term costs of prematurity (Petrou et al., 2001), and the increase of multiple births (Martin et al., 2003), underscores the importance of identifying the mechanisms involved in the association between low birthweight and compromised IQ. We do not know whether birthweight itself is the causal agent, or whether it is a proxy for some other prenatal factor. However, our data suggest that the mechanism can be narrowed to one involving an environmental experience during pregnancy and/or delivery that affects an individual infant, rather than any genetic influence or any environmental factor shared by siblings.

Acknowledgments

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