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Title: The effect of intra-uterine growth on Verbal IQ scores in childhood: a monozygotic twin study

Year of publication: 2010

Citation: Edmonds, C.J. et al. (2010) 'The effect of intra-uterine growth on Verbal IQ scores in childhood: a monozygotic twin study' *Pediatrics* 126 (5) pp. e1095-e1101

Link to published version: <http://dx.doi.org/10.1542/peds.2008-3684>

DOI: 10.1542/peds.2008-3684

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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Pediatrics published online Oct 11, 2010;

DOI: 10.1542/peds.2008-3684

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<http://www.pediatrics.org>

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American Academy of Pediatrics

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The Effect of Intrauterine Growth on Verbal IQ Scores in Childhood: A Study of Monozygotic Twins

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KEY WORDS

cognitive function, intellectual functioning, intrauterine growth retardation, twins

ABBREVIATIONS

VIQ—verbal IQ

PIQ—performance IQ

TTS—twin-to-twin transfusion syndrome

WISC—Wechsler Intelligence Scale for Children

IQdiff—difference in IQ scores within twin pairs

VIQdiff—difference in VIQ scores within twin pairs

PIQdiff—difference in PIQ scores within twin pairs

BWdiff—difference in birth weight within twin pairs

CI—confidence interval

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www.pediatrics.org/cgi/doi/10.1542/peds.2008-3684

doi:10.1542/peds.2008-3684

Accepted for publication Jul 28, 2010

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*



WHAT'S KNOWN ON THIS SUBJECT: Undernutrition during the fetal period affects future cognition, and nutritional interventions affect brain structure. Birth weight is correlated with later cognitive ability, but a number of variables can confound this link, including parental IQ and education, social background, genes, and gestational age.



WHAT THIS STUDY ADDS: We used a study design with monozygotic twins to reduce the effect of confounding variables. Our results suggest that suboptimal intrauterine growth is related to impaired cognitive outcome in both children born small and those with birth weights across the spectrum.

abstract

OBJECTIVE: Given the adverse neurobiological effects of suboptimal nutrition on the developing brain, it is of social and medical importance to determine if the global prevalence of poor intrauterine growth causes lasting cognitive deficits. We examined whether suboptimal intrauterine growth relates to impaired cognitive outcome by comparing birth weight and cognition in monozygotic twins and considered whether children within-pair differences in birth weight were related to within-pair differences in IQ scores.

METHODS: A total of 71 monozygotic twin pairs (aged 7 years 11 months to 17 years 3 months) participated. The Wechsler Intelligence Scale for Children, Third Edition, was administered, and verbal IQ (VIQ) and performance IQ (PIQ) scores were calculated. Regression was used to relate within-pair differences in birth weight to within-pair differences in IQ scores.

RESULTS: VIQ but not PIQ score was affected by prenatal growth restriction. The results suggest that the mean advantage for heavier twins relative to their lighter co-twins can be as much as half an SD in VIQ points. In pairs with minimal discordance, heavier twins had lower VIQ scores than their lighter co-twins.

CONCLUSIONS: Our study results suggest that lower birth weight in monozygotic twins can also have a negative long-term impact on cognition both in infants who are small at birth and also those with birth weights across the spectrum. Studying monozygotic twins enabled us to examine the effect of reduced intrauterine growth on cognition independently of confounding factors, including parental IQ and education and infant gender, age, genetic characteristics, and gestation. *Pediatrics* 2010;126:e1095–e1101

Numerous experimental studies in animals have shown that early undernutrition influences future cognition.¹ Twenty years ago, Smart² reviewed 165 animal studies and reported that in the majority of studies early undernutrition was found to negatively affect later learning. In humans, numerous observational studies and more recent experimental studies have shown that postnatal nutrition has long-term effects on cognition.^{3,4} In animals, documented effects of early undernutrition on brain structure include changes in cell number, growth of the cerebral cortex, and dendritic arborization.^{5,6}

Much research into the cognitive effects of nutrition in humans has focused on the postnatal period. However, the prenatal period is a time of rapid brain development, which includes marked changes in cortical folding,⁷ myelination,⁸ and gray-matter distribution.⁹ Consistent with these findings, we have demonstrated that nutritional interventions that lasted only a few weeks had large, long-term, and likely permanent effects on cognitive function in infants who were born preterm and in whom interventions took place *ex utero* but before the equivalence of term.¹⁰ We have shown that nutritional interventions affect brain macrostructure.¹⁰

These findings raise the hypothesis that infants who suffer growth restriction during the prenatal period, and hence are likely to be deprived of an optimal supply of nutritional substrates, are at risk of impaired neural and cognitive development. Elucidation of such effects is of global medical and social importance given the high prevalence of infants who fail to reach optimal birth weight, which we hypothesize to result from lower placental perfusion or, in developing countries, maternal malnutrition. Birth weight *per se* correlates with later cognitive ability,^{11,12} but these studies are com-

plicated by a number of variables that can confound, mediate, or modify the link between prenatal growth restriction and subsequent cognitive skills. These include parental IQ, education, and social background^{13–15}; infant gender¹⁶; genetic effects on both birth weight and cognition^{17,18}; and gestational age.^{19–21} Previous work, potentially confounded by these factors, has focused on infants born small for gestational age,^{14,15,19} and did not address whether loss of cognitive potential can occur in the presumably larger numbers infants who suffer suboptimal nourishment during the fetal period but do not fall into the low birth weight category (for example with intrauterine weight that is in the normal centile range but has dropped from the 75th to the 25th centile). The magnitude and biological importance of cognitive effects related to the degree of fetal growth retardation across the birth weight spectrum has not been evaluated.

To address these issues we used a study design in which the study participants were monozygotic twins. An experimental model that involves monozygotic twins can eliminate or markedly reduce the effect of confounders; monozygotic twins share gestation length, family background, parental IQ, gender, and genetic influences on growth and cognition. Studies of monozygotic twins can be used to test whether differences in birth weight within twin pairs are related to within-pair differences in IQ. Although other twin studies have considered the differential effects of genes and birth weight on IQ,²² we used monozygotic twins in our study to control for genetic characteristics and examine environmental effects of poor prenatal growth. Thus, we conducted a dose-response analysis of cognitive impact in relation to loss of growth potential. Birth weight has generally been taken

as an index of prenatal nutrition and was the key parameter used in this study. Twins typically have IQ scores that are in the normal range and do not differ from those of unrelated singletons²³ or singleton siblings,²⁴ which suggests that data from twins can be generalized to singletons.

We examined the effect of intrauterine growth restriction on childhood IQ scores by relating intrapair differences in birth weight with intrapair differences in verbal IQ (VIQ) and performance IQ (PIQ) scores. Subsequent subgroup analyses explored the effect of preterm birth and twin-to-twin transfusion syndrome (TTTS).

METHODS

Participants

We recruited 71 monozygotic twin pairs (41 male twin pairs) through the Multiple Births Foundation (MBF), Queen Charlotte's and Chelsea Hospital, and via various twin support groups. The twins were aged between 7 years 11 months and 17 years 3 months (mean 11 years 6 months). Three additional pairs of twins were excluded because 1 or both children had autism spectrum disorder. Zygosity was assessed by using molecular genetic methods; the following genetic markers were used (approximate chromosomal position shown in parentheses): PLA2A (12q-23-qter), FRP2 (6), D3S1300 (3), D14S74 (14), D22S264 (22), TH (11), CYAR (15q21.1), FABP (4q28), DI7S798 (17), DIS255 (1), D16S519 (16), and D18S51 (18q21.3).

Recruitment was initially performed by using registers made available from the Multiple Births Foundation, and same-gender twins born between 1982 and 1996 were contacted. After this initial recruitment drive, advertisements were placed in newsletters and sent to support groups. Information on birth weight and gestational age were obtained from parents and

were verified by comparison with notes for twins born at Queen Charlotte's and Chelsea Hospital. There were no losses to follow-up; this was a cross-sectional study.

The following exclusion criteria were applied: severe chronic disease (eg, cerebral palsy); received treatment at birth for acute TTTS (although 6 twin pairs with reported evidence of TTTS were included in the study); born at <32 weeks' gestation; and unwell on the study day.

Written informed consent was obtained from parents/guardians, and assent from children. The study was approved by local ethics committees.

Psychometric Tests

Each child was tested individually. Observers were, as far as possible, blinded to whether children were the heavier or lighter twin. We administered a short form of the Wechsler Intelligence Scale for Children (WISC), Third Edition.²⁵ VIQ was calculated by using information, similarities, vocabulary, and digit-span subtests, and PIQ was calculated by using picture completion, coding, picture arrangement, and block design. IQ scores were prorated. If subtests were omitted, IQ scores were prorated from the administered subtests. IQ scores have a general population mean of 100 and SD of 15.

Statistical Methods

The analyses focused on differences in IQ (IQdiff), VIQ (VIQdiff), PIQ (PIQdiff), and birth weight (BWdiff) between the heavier and lighter infants in each monozygotic twin pair. Differences were calculated as score for heavier twin — score for lighter twin, so BWdiff was always a positive value. Linear regression analysis was used to relate IQdiff to BWdiff with the possible confounder of birth order, or interactions with mean birth weight, gestation, or gender, which were tested by the inclu-

TABLE 1 Educational Level of the Parents of the Monozygotic Twins

Level of Education	Mother	Father
No educational qualifications, %	2.8	8.6
Certificate or general certificate of secondary education, %	22.5	15.8
A level or equivalent, %	15.5	12.9
Degree or equivalent, %	59.2	62.9

Data are expressed as percentages of total.

TABLE 2 Occupation of the Parents of the Monozygotic Twins

Occupation Type	%
Professional	42.3
Managerial	40.8
Skilled nonmanual	5.6
Skilled manual	9.9
Partly skilled	1.4

Data are expressed as percentages of total.

sion of suitable main effects and interactions. The linearity of association was tested by inclusion of a quadratic term in BWdiff. Sensitivity of results to outlying data or the most preterm infants was tested by omitting these data. To test whether proportional rather than absolute difference in birth weight was a better predictor of IQdiff, the natural logarithm of the ratio of birth weights was derived and related to IQdiff by using linear regression. Data were analyzed by using Data Desk 6.2.1 (Data Description, Ithaca, NY) and R 2.5.1 (Available at: www.r-project.org).

RESULTS

Socioeconomic status was determined by using data on parental occupations.²⁶ Data presented in Tables 1 and 2 show that parents were predominantly educated to a college-degree level and that

the majority reported professional or managerial occupations.

Mean birth weight was just below 2500 g (see Table 3). Seven pairs of twins (10%) were born before 34 weeks' gestation, the cutoff used to define severe prematurity. We measured PIQ and VIQ scores rather than full-scale IQ scores because evidence increasingly suggests that VIQ scores are selectively vulnerable to nutrition.^{27,28}

Figure 1 shows a plot of birth weight for the heavier twin versus the lighter twin. The line of equality is shown, and the perpendicular distance from the line to each point reflects the BWdiff. These data show the spectrum of birth weights from 1070 to 3500 g and differences from 30 to 1480 g. The gender and birth order of twins showed no pattern with respect to which member of each twin pair was heaviest.

Figure 2 shows a plot of VIQdiff in relation to BWdiff with the fitted linear regression line superimposed, which shows a clear positive trend. The slope of the regression line was 13.0 (95% confidence interval [CI]: 7.1–18.9) units of VIQ per kg difference in birth weight, and the intercept was –4.4 (95% CI:

TABLE 3 Summary Statistics for 71 Monozygotic Twin Pairs

	All	Heavier Twin	Lighter Twin	Difference (Heavier — Lighter)
Gender, male/female, <i>n</i>	41/30	—	—	—
Gestation, <i>n</i>				
<34 wk	7	—	—	—
34–36 wk	22	—	—	—
37–41 wk	42	—	—	—
Gestation length, mean (SD), wk	36.5 (2.2)	—	—	—
First born, <i>n</i>	—	33	38	—
Birth weight, mean (SD), g	2435 (498)	2641 (427)	2229 (479)	412 (322)
VIQ, mean (SD)	108.0 (16.4)	108.5 (15.7)	107.5 (17.1)	0.9 (8.9)
PIQ, mean (SD)	105.2 (16.7)	106.0 (17.0)	104.3 (16.4)	1.7 (11.4)

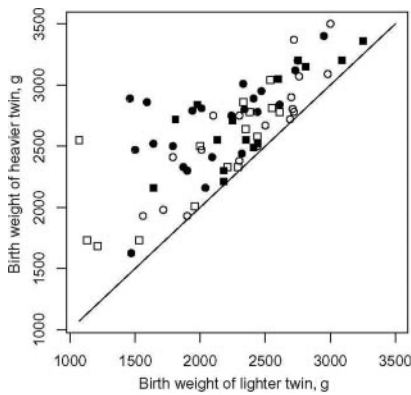


FIGURE 1

Plot of birth weights in the twin pairs, with the heavier twins' data on the y-axis and the lighter twins' data on the x-axis. Male infants are indicated by circles, and female infants are indicated by squares; the symbol is filled if the heavier twin was born first.

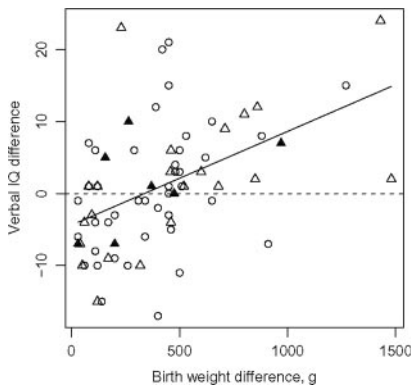


FIGURE 2

Plot of the VIQdiff between twin pairs versus the corresponding BWdiff, with the fitted linear regression line superimposed. Term infants are indicated by circles, and preterm infants are indicated by triangles; the symbols are filled for if gestation was <34 weeks. Both the slope and intercept of the regression line are highly significantly different from 0.

−7.4 to −1.4) units. Thus, the slope and intercept were highly significantly different from 0 ($P < .0001$ and $P = .006$, respectively).

Omitting data for the twin pairs with the 7 most preterm births from our analysis did not substantially alter the findings. The symbols in Fig 2 identify term and preterm births, and highlight the 7 most preterm (gestation < 34 weeks) pairs. Omission of data from these twins changed the regression slope to 13.2 ($P < .0001$), and omission

of the 3 outlying pairs to the right in Fig 2 changed the slope to 13.0 ($P < .001$). Adding to the regression-equation interactions of BWdiff with mean birth weight, gestation, gender, or birth order makes no difference to the findings. The quadratic term in BWdiff was not significant ($P = .5$). The regression of VIQdiff on the log of the birth weight ratio was appreciably weaker than the same regression on BWdiff (regression slope t : 3.8 vs 4.4), which confirmed that the absolute difference in birth weight was a better predictor than the ratio of birth weights.

Six twin pairs had reported evidence of TTS, which may have affected cognitive outcome.²⁹ However, removing these 6 pairs from our data analyses did not substantially alter the findings (slope = 12.3; slope $t = -3.8$; $P = .0004$).

The association we observed was not based on twin pairs with the most discordant birth weights. Exclusion of the twin pairs in whom the weight difference exceeded 0.5 kg reduced the n to 46, but the association remained significant (slope = 21.1; slope $t = 2.6$; $P = .01$). Thus, the findings are robust.

The regression line in Fig 2 crosses the x-axis at a BWdiff of 340 g. This significantly negative intercept indicated that for twin pairs with a BWdiff of <340 g, VIQ is predicted to be lower in the heavier twin, in contrast to the higher VIQ predicted when birth weights are more discordant. Mean VIQdiff was calculated in the 25 most concordant pairs (BWdiff ≤ 200 g). In this group the mean VIQdiff was −4.4

(95% CI: −6.8 to −2.0) units, highly significantly negative. Thus, in pairs concordant for birth weight, the heavier twin tended to have a lower VIQ, whereas in discordant pairs the reverse was true such that the heavier twin's estimated IQ advantage was 8.6 (95% CI: 13.0−4.4) units for a 1-kg-greater birth weight and 15.1 units (95% CI: 19.5−4.4) for a 1.5-kg-greater birth weight, the largest degree of difference in our cohort.

We conducted subgroup analyses to examine the trend in increases in VIQdiff as a function of increases in BWdiff. Table 4 shows mean VIQdiff in twin pairs grouped according to BWdiff. For pairs closest in birth weight, VIQ was significantly less in the heavier twin (ie, the difference was significantly less than 0), whereas the reverse was true for pairs in whom the weight difference exceeded 750 g. Throughout the groups there was a clear linear trend to increasing VIQdiff with BWdiff, as confirmed by the linear regression analysis.

It is important to note that had we not performed linear regression analysis to assess IQdiff relative to BWdiff, we would have missed the principal effect; with a mean BWdiff of 412 g (close to the intercept), overall paired comparisons were not significant (see Table 2). A similar analysis was conducted for PIQdiff, which showed a nonsignificant relation to BWdiff. The slope of the regression line was −0.4 (95% CI: −9.0 to 8.2) units of PIQ per kg difference in birth weight, and the intercept was 1.8 (95% CI: −2.6 to 6.3) units. Thus, the

TABLE 4 Paired Comparisons of Heavier and Lighter Twins

BWdiff, g	<i>n</i>	VIQdiff, Mean (SD)	Birth Weight, Mean (SD), g
0 to <250	26	−3.4 (7.9) ^a	2453 (418)
250 to <500	24	1.8 (9.1)	2506 (432)
500 to <750	12	2.9 (5.6)	2425 (502)
≥750	9	8.2 (8.9) ^b	2192 (204)

VIQ scores were grouped according to birth weight data.

^a $P < .05$.

^b $P < .01$.

slope and intercept were not significantly different from 0 ($P = .922$ and $.412$, respectively).

DISCUSSION

These results show that in the monozygotic twin pairs in our study there was a relationship between a within-pair difference in birth weight and a subsequent within pair-difference in VIQ scores. This relationship differed according to the degree of discrepancy in birth weight. However, the mean advantage for the heavier twin can be as large as half an SD in VIQ score (7–8 IQ points). Because an monozygotic twin study controls for key confounders, our results strongly suggest that suboptimal intrauterine nutrition results in impaired cognition in childhood, even in children with normal birth weights. We cannot exclude the possibility that growth restriction, and hence reduced cognition, occurred in larger twins, but this would not be expected to influence the results of our study, which focused only on the cognitive impact of any given difference in birth weight within twin pairs. We recognize that a more extreme decline in birth weight of twin pairs may reflect factors other than nutrition, such as TTTS. We found the same effect, however, both when we excluded twin pairs with indicators of TTTS and when we examined twin pairs in which the weight discordancy was ≤ 500 g (large discordancies could indicate TTTS).

Results of similar analyses of PIQ data showed no significant associations with BWdiff. Different VIQ and PIQ effects may explain differences between our study findings and those of a recent study in which investigators found no relation between intrapair differences in birth weight and IQ³⁰; that study reported data for full-scale IQ, a composite of VIQ and PIQ. Increasingly, evidence suggests that nutrition

selectively impacts VIQ.^{27,28} Although results of another twin study suggested that PIQ scores were more affected,²² investigators in this study compared heavier and lighter co-twins, an analysis we found to lack statistical sensitivity. The selective vulnerability of VIQ is commonly attributable to differences in parental education, IQ, and social class, but in twin studies these factors are controlled. VIQ score may be susceptible because neural areas that underlie verbal performance are more vulnerable to suboptimal nutrition than those that underlie PIQ subtest performance. Ultrasound estimates of prenatal growth could help identify the timing of the effect of early growth on cognitive outcome.

The finding of a negative intercept, which indicated that the heavier twin tended to have a lower VIQ in pairs with concordant birth weight and a higher VIQ in pairs with discordant birth weight, deserves additional comment. Although our data suggest that, across the range of BWdiffs from 340 to 1480 g, there is a progressive VIQ advantage for the heavier twin, this effect was offset against a disadvantage for the heavier twin in pairs with a smaller degree of birth weight discordance. Larger differences in birth weight may indicate greater competition for resources and lead to a VIQ score advantage in heavier twins. Our data suggest that, up to a difference of 340 g, there may be a biological advantage for VIQ score in being born the lighter twin. However, there is no clear biological mechanism that might explain this advantage for the lighter twin. It is possible that this finding results from an unknown confounding variable or chance, and additional research is necessary.

In studies of singleton siblings in which study participants were matched for family but not genetic factors, results have been inconclusive

concerning the relation between weight at birth relative to gestation, or birth weight, and childhood cognition. Results of such studies have shown positive relationships,³¹ effects only in boys,¹⁶ no relationship,^{32,33} or a weak relationship.³⁴ Caution has been urged in interpreting twin studies, and we accept that the majority of the population are singletons.³¹ However, twin studies do provide the best control for genetic factors. The striking relation we report between prenatal growth restriction and childhood IQ could reflect an influence of genetic factors linked to twinning, but there is no sound basis for this interpretation. Even if this proposition were entertained, our data would apply to ~ 150 million individuals within the global population who were born as a twin. The PIQ and VIQ scores of our study participants exceeded the population norm of 100 (105.2 and 108.0, respectively). This finding may be attributable to the high socioeconomic status of our sample, because children's IQ scores are associated with parental education and socioeconomic status.³⁵ In that case, the generalizability of these results could be questioned. However, it is likely that this finding is an artifact related to the restandardization of the WISC from the third to the fourth edition³⁶, which was published in 2003, shortly after the completion of this study. IQ scores are subject to the Flynn effect and increase across populations.³⁷ If we had used the fourth edition of the WISC, our mean IQ scores may have been more similar to population means.

If, as we suggest, lowered birth weight is a risk factor for cognitive outcome across the birth weight spectrum, this finding may have a strong impact on medical and educational resources. Within the population of infants who are 1 kg lighter than their potential weight,

this shift implies that the proportion of children who score <70 for VIQ (ie, 2SDs below the mean) would more than treble, increasing from 2.3% to 7.7%. Overall, the impact of intrauterine growth restriction on the number of children with special educational needs could be putting a hitherto unidentified and unquantified demand on health and educational resources.

CONCLUSIONS

Our findings have implications for the primary prevention of reduced cognitive function. Results of our randomized trial of nutritional intervention in

term infants who were small for gestational age showed no effect of nutritional rescue on the brain,³⁸ whereas a corresponding trial in preterm infants showed a large impact on VIQ.²⁸ These findings suggest that during the period before term, a time of rapid brain growth, the fetus is most vulnerable to the impact of suboptimal nutrition. A clear approach for the amelioration of the IQ deficit in those infants who do not fulfill their intrauterine growth potential has not been established, and the development of strategies for tackling intrauterine growth restriction remains an important area for future focus.

ACKNOWLEDGMENTS

This work was funded by the Medical Research Council, which had no role in the study design, collection, analysis, or interpretation of the data, writing of this report, or the decision to submit the article for publication.

We thank John Buckler for providing access to a subsample. We thank the children and parents who took part in the study and the staff at the Multiple Births Foundation. Atul Singhal set up the “Programming in Twins” study, which allowed this research to be conducted.

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Pediatrics published online Oct 11, 2010;

DOI: 10.1542/peds.2008-3684

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