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The role of genetic and environmental factors in the association between birthweight and blood pressure: evidence from meta-analysis of twin studies

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Background An inverse association between birthweight and later blood pressure has been found in many studies in singletons. Twin studies have been used to examine whether genetic factors or family environment could account for this association.

Methods A systematic review identified 10 studies covering 3901 twin pairs. Meta-analysis of regression coefficients for the association between birthweight and systolic blood pressure was carried out for unpaired versus paired associations and for paired associations in dizygotic versus monozygotic pairs.

Results After adjustment for current weight or body mass index (BMI), the difference in systolic blood pressure per kg birthweight was −2.0 (95% CI: −3.2, −0.8) mmHg in the unpaired analysis and −0.4 (95% CI: −1.5, 0.7) mmHg in the paired analysis in the same subjects. In the paired analysis by zygosity, in all twins the coefficients were −0.7 (95% CI: −2.3, 0.8) mmHg in dizygotic pairs and −0.8 (95% CI: −2.1, 0.4) mmHg in monozygotic pairs, but in studies which included zygosity tests the coefficients were −1.0 (95% CI: −3.3, 1.6) mmHg in dizygotic pairs and −0.4 (95% CI: −1.9, 1.3) mmHg in monozygotic pairs.

Conclusions The attenuation of the regression coefficient in the paired analysis provides support for the possibility that factors shared by twins contribute to the association between birthweight and blood pressure in singletons. Comparison of paired analysis in monozygotic and dizygotic pairs could not provide conclusive evidence for a role for genetic as opposed to shared environmental factors.

Keywords Twins, blood pressure, birthweight, meta-analysis

The 'fetal origins' hypothesis proposed by Barker and colleagues suggests that birthweight is inversely associated with risk of cardiovascular and other metabolic disease in adult life through a long-term effect of sub-optimal intra-uterine nutrition on later metabolism.[1] Others have suggested that the observed association may result from unmeasured socio-economic confounding[2] or genetic or other inter-generational factors influencing both birthweight and adult disease risk.[3,4] Twin studies provide an opportunity to test these alternative possibilities, since twins share their maternal and early family environment and some or all of their genes but often differ considerably in birthweight. If the association between birthweight and disease risk seen in singletons can be reproduced in twins when treated as a population of individuals, or 'unpaired twins' and is also seen in analyses within twin pairs, the influence of genetic or family environment on the association is likely to be small. If however the association is seen in unpaired twins but is attenuated in paired analyses, genetic factors and/or family environment are likely to play a role in the association. Furthermore, since dizygotic (DZ) pairs share half of their genes but monozygotic (MZ) pairs share all their genes, partial attenuation in DZ pairs and total attenuation in MZ pairs would provide evidence for a role of genetic factors as opposed to other shared family environment influences.

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Early studies of the association between birthweight and systolic blood pressure in singletons suggested an effect of the order of 5 mmHg per kg birthweight,[5,6] but more recent systematic reviews have suggested that the effect size is considerably smaller.[7–9] One of these reviews included a meta-analysis of data from MZ pairs from nine twin studies and found a similar effect size to that found in larger studies of singletons,[9] which would be consistent with a lack of effect of genetic factors and socio-economic environment in childhood on the observed association in singletons. However, these authors did not explore the unpaired data or data from DZ pairs in the twin studies. We therefore carried out meta-analyses of published twin studies to permit the comparison of unpaired versus paired results and the comparison of MZ versus DZ twins. We also analysed the data before and after exclusion of studies which used self-reported rather than obstetric or midwives' records of birthweight and studies which did not include zygosity tests to investigate the possible impact of errors in birthweight and zygosity in these studies.

Materials and Methods

A *Medline* search for articles published from 1960 to January 2004 using the terms 'twin$' and 'birth weight' and 'blood pressure' yielded 40 articles of which 10 were original studies with information on within-pair differences in blood pressure and birthweight.[10–19] In five of the studies the methods used to assess zygosity were not given in detail and in one study the direction of the regression coefficient was not clearly stated: authors of these studies were contacted to obtain more detailed information. The regression coefficients were extracted from the articles by two authors (GMcN, CT) independently. Values were used in meta-analysis with the number of decimal places provided in the original articles, though for consistency in the Tables all values for regression coefficients were rounded to the nearest 0.1 mmHg. Meta-analysis of the regression coefficients was carried out using Stata version 7.0 (Stata Corporation, College Station, Texas, USA) using a random effects model with weighting according to the inverse of the variance of the coefficients for each study. Analyses were carried out before and after exclusion of studies which used self-reported birthweight and studies which did not include zygosity tests.

Results

Table 1 gives details of the studies reporting within-pair differences in birthweight and blood pressure, listed in ascending order of age. The studies varied widely in size and in age of the subjects: two studies reported data from two separate groups of different ages so are listed twice in the Table. Only four studies provided data on diastolic blood pressure so this was not analysed further. In eight studies birthweight was based on obstetric or midwives' records and in six studies records of tests of zygosity based on blood group and/or DNA fingerprinting had been carried out either in all pairs or in those in whom there was doubt from questionnaire-based assessments.

The regression coefficients for systolic blood pressure per kg birthweight difference in paired analyses in DZ and MZ twins are given in Table 2. There was no evidence for higher coefficients in studies with older subjects. All studies reported coefficients adjusted for body weight, fatness or BMI: four studies also reported the unadjusted coefficients which tended to be less negative than the corresponding adjusted coefficients, i.e. the negative association between birthweight and blood pressure was strengthened by adjustment for current body size and other factors. In one study there was a significant negative association in DZ pairs, but the associations for MZ pairs were not significantly different from zero in any of the studies.

Table 3 shows the unpaired versus paired analyses for the five studies which reported these results. In four of these studies the unpaired coefficients were attenuated in the paired analyses. The pooled value for the unpaired coefficients of −2.0 mmHg/kg was significantly different from zero ($P < 0.001$) but the pooled value for the paired analysis was not significantly different from zero (Figure 1). Restricting the analyses to studies which used birthweight from obstetric or midwives' records (studies 2, 3, 8 and 10) gave similar results: −2.0 (95% CI: −3.8, −0.3) mmHg per kg birthweight in the unpaired analysis and −0.3 (95% CI: −1.5, 0.9) mm Hg per kg birthweight in the paired analysis.

Figure 2 shows the regression coefficients for systolic blood pressure for DZ and MZ twins in paired analyses for all studies, and Table 4 shows the results for all studies and for the subsets of studies with birthweight based on obstetric or midwives' records and measurement of zygosity. When all studies were included there was little difference in the regression coefficients between DZ and MZ pairs. In the studies which used birthweight based on obstetric or midwives' records the coefficients were closer to zero, particularly in the MZ pairs. This pattern was also seen in studies which included zygosity tests. However, in all cases the pooled regression coefficients in DZ and MZ pairs were not significantly different either from zero or from each other.

Discussion

To assess the validity of using twins to explore the mechanisms for the association between birthweight and blood pressure in singletons it is useful to compare the unpaired regression coefficients in twins with those seen in singletons. Unfortunately there is no clear reference value from singleton studies: one meta-analysis of 45 studies in singletons suggested a value of −2 mmHg/kg[7] while a more recent analysis of 55 studies reported a value of −1.38 (95% CI: −1.66, −1.10),[8] and authors of both studies highlighted the possibility of publication bias with larger studies showing smaller effects: one group suggested that the true effect could be as small as −0.6 mmHg per kg.[9] The pooled value of −2.0 mmHg per kg in the unpaired analysis in twins in this analysis is of the same order of magnitude and direction as these values, suggesting that twins provide a reasonable model for the singleton effect.

The attenuation of the regression coefficients between unpaired and paired analyses in the twins suggests that factors which are common to twins in a pair contribute to the observed association in singletons. The degree of attenuation in DZ versus MZ pairs is more difficult to interpret, as in the paired analyses of all studies there was no difference in the regression coefficients between DZ and MZ pairs, suggesting that shared environmental factors such as maternal physiology or socio-economic conditions in early childhood are more likely to explain the attenuation, but restricting the analysis to studies with zygosity tests gave lower coefficients in MZ than DZ pairs,

Table 1 Studies of birthweight differences and blood pressure differences in twins

Study no	Author and year	Country	Age (years)	Gender	DZ[a] pairs	MZ[b] pairs	XZ[c] pairs	Birthweight	Zygosity test[d]
1	Zhang *et al.*, 2001[13]	USA	7	M + F	86	119	—	Obstetric records	Yes
2	Dwyer *et al.*, 1999[10]	Australia	7–8	M + F	39[e,f]	16[e]	—	Obstetric records	No[g]
3a	Christensen *et al.*, 2001[14]	USA	11–12	M + F	250	467	—	Obstetric records	Yes
3b	Christensen *et al.*, 2001[14]	USA	17–18	M + F	199	394	—	Obstetric records	Yes
4	Ijzerman *et al.*, 2000[12]	Netherlands	17 SD 2	M + F	53	61	—	Birth certificate	Yes
5	Johannson-Kark *et al.*,	Sweden	17–19	M	269	384	233	Obstetric records	No
6	Loos *et al.*, 2001[15]	Belgium	18–34	M + F	86	225	—	Obstetric records	Yes
7a	Nowson *et al.*, 2001[16]	New Zealand	12 SD 2	F	53[e]	65[e]	—	Self-reported	No
7b	Nowson *et al.*, 2001[16]	New Zealand	35 SD 13	F	112[e]	66[e]	—	Self-reported	No
8	McNeill *et al.*, 2003[19]	UK	19–50	M + F	65	57	—	Obstetric records	Yes
9	Baird *et al.*, 2001[17]	UK	42–46	M + F	140	58	—	Obstetric records	No
10	Poulter *et al.*, 1999[11]	UK	54 SD 8	F	237	167	—	Self-reported	Yes
	Total	—	—	—	1589	2079	233	—	—

[a] Dizygotic.
[b] Monozygotic.
[c] Uncertain zygosity.
[d] Blood group and/or DNA fingerprinting carried out in all pairs or in those of uncertain zygosity from questionnaire.
[e] Includes triplets treated as pairs.
[f] Includes opposite sex DZ pairs.
[g] Test result reported by parents where available but not carried out by authors.

Table 2 Regression coefficients for difference in blood pressure (mmHg) per kg difference in birthweight in paired analyses, both unadjusted and adjusted for factors listed

		Unadjusted coefficients[a] (95% CI)			Adjusted coefficients (95% CI)	
Study	**Exclusion**	DZ[b]	MZ[c]	**Adjustment**	DZ	MZ
1	None reported	—	—	Body weight	2.9 (−2.6, 8.4)	−1.7 (−7.0, 3.3)
2	None reported	—	—	Fat by skinfolds	−4.9 (−15.8, 6.0)	−6.5 (−22.5, 9.4)
3a	None reported	0.5 (−3.1, 4.1)	1.2 (−2.1, 4.5)	BMI[d]	−0.1 (−3.7, 3.5)	0.0 (−3.6, 3.6)
3b	None reported	0.8 (−3.5, 5.1)	0.0 (−2.7, 2.6)	BMI	0.6 (−3.6, 4.8)	-0.7 (−3.3, 1.9)
4	Oral contraceptives	−3.7 (−8.1, 0.8)	0.4 (−4.7, 5.6)	Weight	−5.7 (−10.4, −1.0)	−0.1 (−5.4, 5.2)
5	Wt <45 kg or >120 kg; SBP[e] <100 or >180 mm Hg; possible cross-over[f]	1.5 (−2.1, 5.1)	0.0 (−2.9, 2.8)	Height and weight, age, year, centre, gestational age	0.1 (−3.5, 3.8)	−1.3 (−4.2, 1.5)
6	Wt ≥100 kg; BP treatment	—	—	BMI	−2.7 (−8.7, 3.2)	1.6 (−1.9, 5.5)
7a and 7b[g]	None reported	—	—	BMI	−1.3 (−5.6, 3.0)	−2.7 (−6.3, 0.9)
8	BP treatment; BMI difference >15	−0.3 (-8.8, 8.2)	−1.1 (−7.7, 5.4)	BMI, age, gender, gestational age, smoking, alcohol	0.1 (−9.6, 9.9)	−3.5 (−10.4, 3.5)
9	None reported	—	—	BMI	2.6 (−5.5, 10.7)	5.8 (−3.5, 15.2)
10	None reported	—	—	Height and weight, smoking,alcohol	−3.2 (−11.0, 4.6)	−4.9 (−13.9, 4.1)

[a] Blank denotes none reported.
[b] Dizygotic.
[c] Monozygotic.
[d] Body mass index.
[e] Systolic blood pressure.
[f] See text for explanation.
[g] Results given for both age groups combined.

Table 3 Regression coefficients for systolic blood pressure (mmHg/kg birthweight) in unpaired versus paired analysis, adjusted for the factors listed in Table 2

			Regression coefficient (95% CI)	
Study	**No. of individuals**	**No. of pairs**	Unpaired	Paired
2[a]	104[a]	55	−7.0 (−10.1, −3.9)	−5.3 (−13.8, 3.21)
3	1434	717	−1.6 (−3.1, −0.1)	−0.1 (−2.5, 2.4)
3	1186	593	−0.4 (−2.4, 1.6)	−0.2 (−2.4, 2.0)
5	1772	886	−1.7 (−3.15, −0.2)	−0.2 (−2.1, 1.7)
7a[b,c]	244	118	−2.1 (−4.4, 0.1)	−1.2 (−5.3, 2.9)
7b[b,c]	467	178	−2.2 (−4.4, −0.1)	−1.1 (−5.4, 3.3)
8	244	122	−0.1 (−4.0, 3.8)	−0.9 (−6.4, 4.6)
All studies	5,451	2,669	−2.0 (−3.2, −0.8)	−0.4 (−1.5, 0.7)

[a] Two sets of triplets included as six pairs.
[b] Unpaired twins included in unpaired ananlysis.
[c] Four sets of triplets included as eight pairs.

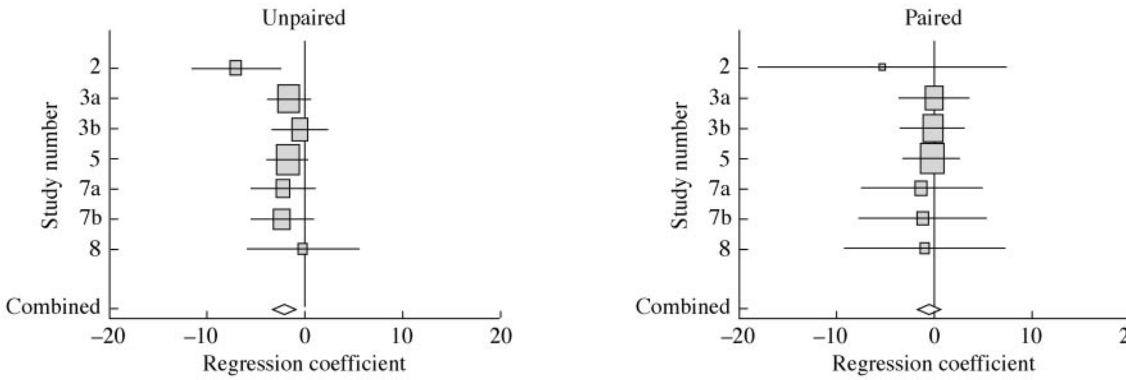

Figure 1 Meta-analysis of the unpaired regression coefficients (mmHg per kg birthweight) and paired regression coefficients (mm Hg difference per kg birthweight difference) for systolic pressure in twins (monozygotic and dizygotic combined).

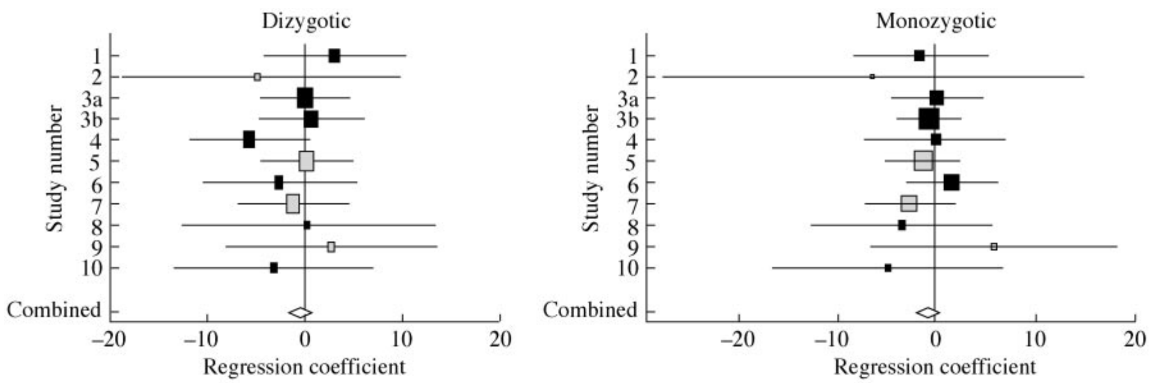

Figure 2 Meta-analysis of regression coefficients for systolic blood pressure (mmHg difference per kg birthweight difference) in dizygotic and monozygotic twins in all studies. Studies with zygosity tests are shown as solid fill boxes.

Table 4 Pooled regression coefficients for systolic blood pressure (mmHg difference/kg birthweight difference) in paired analyses, adjusted for the factors listed in Table 2

Inclusion criteria	Studies included	No. of pairs		Regression coefficient (95% CI)	
		DZ[a]	MZ[b]	DZ	MZ
All studies	1–10	1589	2079	−0.7 (−2.3, 0.8)	−0.8 (−2.1, 0.4)
Studies with independent measures of birthweight	1–6, 8, 9	1187	1781	−0.6 (−2.2, 1.2)	−0.4 (−1.8, 0.9)
Studies with zygosity tests	1, 3, 4, 6, 8, 10	976	1490	−1.0 (−3.2, 1.2)	−0.4 (−2.0, 1.1)
Studies with independent measures of birthweight and zygosity tests	1, 3, 4, 6, 8	739	1323	−0.8 (−3.3, 1.6)	−0.3 (−1.9, 1.3)

[a]Dizygotic.
[b]Monozygotic.

as would be expected if genetic factors contributed to the association. Lower coefficients in MZ than DZ pairs were also observed when the analysis was restricted to studies which used obstetric or midwives' records of birthweight. The importance of these possible sources of error is difficult to assess as it is likely to differ between study populations and probably differs between singletons and twins. One study of the accuracy of self-reported birthweight in 302 adult twins found that the mean agreement between self-reported weight and birth records was 6.2 g but the 95% CI ranged from −660 to +672 g, and for the 139 pairs in the survey the mean agreement for birthweight difference was −24 g but the 95% CI ranged from −863 to +815 g.[20] For zygosity the possibility of errors due to incorrectly assignation of zygosity is highlighted by a recent US study of adolescent same-sex twins which found that 26% of mothers who received DNA results by mail changed their opinions of the twins' zygosity, while 22% of those who did not receive DNA result also altered their opinions on a second questionnaire.[21] In our own study population most mothers had been sent information on zygosity after birth, based on either blood groups or DNA fingerprinting, but at age 19–50 years 5% of twins said they were not sure of their zygosity and a further 8% reported zygosity which did not agree with the results of DNA fingerprinting.

Another factor which could attenuate the association between birthweight differences and adult risk factors in twins compared to singletons is 'cross over' of birthweights due to errors in recall of birth order and hence birthweight, which is usually recorded by birth order, within a twin pair. This would lead to attenuation of the associations in both unpaired and paired analyses, though the effect would be possibly be greater in the paired analyses due to reversal of the direction of within-pair differences in birthweight. One study attempted to address this issue by using discrepancies between self-reported birth order and that recorded on a birth register to exclude pairs in which this effect was considered likely.[18] Although the regression coefficients in this study were not obviously different from other studies, this is a potential source of error which should be borne in mind in all twin studies of birthweight.

One possible criticism of the use of MZ pairs is that two-thirds of MZ pregnancies are monochorionic and in these pregnancies twin-twin transfusion syndrome may result in birthweight discordance and blood pressure differences through mechanisms not experienced by singletons.[22] Although a recent study found no difference in within-pair differences in birthweight between monochorionic and dichorionic twins,[23] the results from the DZ pairs may be considered more reliable as they cannot be influenced by twin-twin transfusion syndrome. An alternative approach would be to present results separately for monochorionic and dichorionic MZ pairs: we tried to do this in our own study by examining obstetric case notes but diagrams of the membranes were only found for 29 of the 60 MZ pairs.

Although the present analysis covers almost 4000 twin pairs, several limitations of the data are apparent. Unadjusted and unpaired coefficients were not given by all studies, though they were available for the two largest studies[14,18] and the trends were consistent among the studies for which these results were given. Of the five studies which presented unpaired data only two reported using methods to account for the pairing within this data.[14,17] As pointed out by the authors of one of these studies,[14] failure to do so will lead to underestimation of the standard errors of the coefficients, which in their study was of the order of 20%, so the CI for unpaired analyses in Table 3 and Figure 1 should be viewed in this light.

In summary, the evidence from published twin studies lends support to the possibility that factors shared by twins contribute to the association between birthweight and blood pressure in singletons. While the comparison of DZ versus MZ pairs in twins of confirmed zygosity in the current analysis is consistent with a role for genetic as opposed to environmental factors, the small effect size in the paired analysis means that much larger studies would be needed to provide a definitive test of the difference between the two values. For other variables associated with the metabolic syndrome such as glucose intolerance and lipid levels, the twin approach could be of greater value in assessing the relative contribution of genetic and environmental factors to the associations seen in singletons.

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KEY MESSAGES

- Twin studies provide an opportunity to test whether genetic factors can account for the association between birthweight and later blood pressure observed in singletons.
- A systematic review of the literature identified 10 published studies covering 3901 twin pairs.
- In unpaired analysis there was a significant negative association between birthweight and systolic blood pressure similar to that seen in singletons.
- In paired analysis the association was attenuated and was not significantly different from zero in either monozygotic or dizygotic pairs.
- The results support the possibility that factors shared by twins contribute to the association between birthweight and blood pressure seen in singletons.
- Due to the small effect size it was not possible to differentiate between genetic and environmental influences.

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