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Original Article

Relationship of birth weight with congenital cardiovascular malformations in a population-based study

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Abstract *Introduction:* A known comorbidity of congenital cardiovascular malformations is low birth weight, but the reasons for this association remain obscure. This retrospective study examines the relationship between congenital cardiovascular malformations and the birth weight of singletons, taking into account differences in gestational age and other factors. *Methods:* Using data from the retrospective, population-based Baltimore–Washington Infant Study, six types of congenital cardiovascular malformations were investigated in comparison with controls (n = 3519) through linear regression: d-transposition of the great arteries (n = 187), other conotruncal heart defects (n = 361), endocardial cushion defects (n = 281), left heart obstructive lesions (n = 507), atrial septal defects (n = 281), and membranous ventricular septal defects (n = 622). *Results:* Infants with conotruncal heart defects (−218 g), endocardial cushion defects with Down syndrome (−265 g), endocardial cushion defects without Down syndrome (−194 g), left heart obstructive lesions (−143 g), atrial septal defects (−150 g), and membranous ventricular septal defects (−127 g) showed significant birth weight deficits, adjusting for gestational age, and other covariates. Infants with d-transposition of the great arteries (−67 g) did not show significant birth weight deficits compared with the control group. *Discussion:* The degree of birth weight decrement appears to be highly related to the specific type of congenital cardiovascular malformation. As a whole, these infants do not exhibit low birth weights solely because of being premature, and thus other mechanisms must underlie these associations.

Keywords: Congenital heart malformations; cardiovascular disease; infants; birth weight

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Despite decades of progress in diagnosis and treatment, congenital heart disease still accounts for 3% of all infant deaths, and 46% of deaths from congenital malformations.[1] It has been well documented that low birth weight infants with congenital malformations are particularly vulnerable to adverse outcomes.[2–5] Whether low birth weight is a consequence of the heart defect itself or the co-outcome of a common underlying cause is not known at this time.

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The clinical and public health issue raised by this association is the prevention or mitigation of the complications endured by affected infants. Although broad-based efforts have been made to promote increased birth weights through timely and increased access to prenatal care, their impacts remain unclear.[6,7] By discerning the underlying morphological reasons behind low birth weight and heart defects, it might be possible to design, implement, and evaluate more effective prenatal and postnatal prevention and intervention programmes.

Several authors have previously reported observations of low birth weight among infants with congenital cardiovascular malformation.[8–10] Many have classified

diverse cardiac diagnostic groups into one category, often to address the problem of small sample sizes, yet obscuring potentially differential effects. In contrast, our data are from the Baltimore–Washington Infant Study – one of the largest case-control studies of congenital cardiovascular malformation to date, with over 7000 subjects – allowed us to address the question of the potential heterogeneity of low birth weight associations.

Materials and methods

Cases: The 4390 cases enrolled in the Baltimore–Washington Infant Study were liveborn infants with congenital cardiovascular malformation ascertained through multiple sources from 1981 to 1989 in the defined geographic area of Maryland, the District of Columbia, and Virginia. Diagnosis was confirmed before the infant's first birthday by echocardiography, cardiac catheterisation, surgical inspection, or autopsy, in collaboration with all six paediatric cardiology centres of the region. The study methods have been reported in detail.[11] A clinical update report from the paediatric cardiologist was obtained at each infant's first birthday.

All components of the anatomic cardiac diagnosis were coded using the International Society of Cardiology's classification system.[12] The paediatric cardiologists assigned a primary diagnosis using a hierarchical order that prioritised the structural malformations of the earliest embryonic origin. This coding system formed 30 mutually exclusive cardiac diagnostic groups, of which the largest six were investigated in this study: d-transposition of the great arteries, conotruncal heart defects, endocardial cushion defects, left heart obstructive lesions, atrial septal defects (secundum only), and membranous ventricular septal defects. Conotruncal heart defects were defined by grouping tetralogy of Fallot, truncus arteriosus, and double outlet right ventricle. Left heart obstructive lesions were defined by grouping hypoplastic left heart, aortic stenosis, aortic coarctation, and bicuspid aortic valve. Owing to the known association of endocardial cushion defects with Down syndrome, endocardial cushion defects were analysed by the presence or absence of Down syndrome – endocardial cushion defects-Down and endocardial cushion defects-other, respectively. Of the eligible case families, 90% participated in a parental interview.

Controls: The 3572 control infants were selected to be representative of the regional live birth cohort of 906,626 live births of the same period.[11] The infants were selected by a computer algorithm as a random sample of the birth cohort, stratified by year and hospital of birth. If the family of the infant chose not to participate, the selection was passed to the infant with the next nearest birth date in the same hospital. Of the participating controls, 95% were first or second choices from the birth listings.[11]

Data collection: Trained interviewers administered a questionnaire to the parents to ascertain medical, reproductive, genetic, sociodemographic, lifestyle, and environmental factors. About 75% of the interviews for both cases and controls were carried out before the infant was 7 months old, more than 90% before the infant's first birthday, and nearly 100% within 18 months of age.[11] Mothers of cases and controls reported the birth weight of the infant in pounds and ounces, converted to grams for our analysis, and we calculated the gestational age, completed weeks of gestation, from the reported dates of the infant's birth and the expected date of delivery, as previously described.[8,13]

Statistical methods: The data used in this study were restricted to liveborn singletons. Of the 3572 controls in the Baltimore–Washington Infant Study, 3519 met this criterion. A total of 2239 cases were analysed, subdivided into the six cardiac diagnostic groups: d-transposition of the great arteries ($n = 187$), conotruncal heart defects ($n = 361$), endocardial cushion defects ($n = 281$), left heart obstructive lesions ($n = 507$), atrial septal defects ($n = 281$), and membranous ventricular septal defects ($n = 622$). In descriptive analysis, we determined the mean, median, standard deviation, and 95% confidence interval of birth weight and gestational age for each of these groups; we also determined the percent of infants who were classified as low birth weight, very low birth weight, and extremely low birth weight, using standard definitions, that is, <2500, 1500, and 1000 g, respectively.[14]

Linear regression analysis was used to model an equation for the birth weight of infants born between 30 and 40 weeks of gestation. This range was chosen to maximise the statistical power of the analysis, as relatively few babies in the study were born at earlier or older gestational ages. The models included case-control status and the infant's gestational age, sex, race, and non-cardiac malformations – chromosome anomalies, syndromes, and single-organ malformations – and maternal smoking, overt diabetes, and gestational diabetes. We defined sex (male/female), race (white/other), smoking (yes/no) and the presence or absence of self-reported diabetes as binary variables. An interaction variable defined as (gestational age) × (case status) was evaluated for statistical significance ($p < 0.05$) in each model, where gestational age was coded in weeks and case status was binary (control = 0, case = 1). We checked for non-linearity by including quadratic terms in the model and checking for their statistical significance ($p < 0.05$).

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From the large number of variables available from the Baltimore–Washington Infant Study questionnaire, we selected those previously reported to be associated either with increased risk of congenital cardiovascular malformation or low birth weight.[8,11] We considered several other variables in the data from the Baltimore–Washington Infant Study, but ultimately decided to exclude them from our final regression model as they were not significantly associated with birth weight in this study: birth order, previous premature births, previous miscarriages, mother's age at conception, maternal home, and occupation exposures – for example, dry cleaning solvents, degreasing solvents, and miscellaneous solvents, previously shown to be associated with increased congenital cardiovascular malformation risk in this population – maternal alcohol use, and maternal frequency of alcohol drinking. From the final regression equation, we derived the 95% confidence interval for the slope of each independent variable.

Results

Study population and its characteristics: Table 1 shows the distributions of infant and maternal characteristics in the cases and controls. It is evident that the mean gestational age varied little between controls and the case groups – that is <1 week for most case groups and a maximum of 1.5 weeks – whereas the proportion of preterm births was markedly greater in conotruncal heart defects (16.3%) and atrial septal defects (20.3%), relative to controls (5.5%). Of the infants with d-transposition of the great arteries, the majority were male (69.0%), whereas the majority of cases with atrial septal defects were female (62.6%). A large proportion of the cases with endocardial cushion defects (71.9%) were found to have chromosome anomalies, mainly Down syndrome. The greatest proportion of mothers with overt diabetes was found in conotruncal heart defects (3.9%). Mothers of infants with conotruncal heart defects (5.5%) or atrial septal defects (5.7%) were most likely to report gestational diabetes. Mothers of controls were much less likely to report either overt (0.7%) or gestational diabetes (3.2%). Rates of maternal smoking varied little across case groups and controls.

Birth weight and associated factors: Before linear regression analyses, we examined birth weight distributions across the six groups of congenital cardiovascular malformation (data not shown). The average birth weight among infants with d-transposition of the great arteries (3382 g) was found to be comparable to that of controls (3365 g). Conversely, infants with conotruncal heart defects, endocardial cushion defects, and atrial septal defects exhibited average birth weights of under 3000 g. In addition, we looked at percentages of infants in each subgroup that were low birth weight, very low birth weight, and extremely low birth weight. The greatest proportion of low birth weight infants was found in conotruncal heart defects (24.7%) and atrial septal defects (22.8%). Moreover, in atrial septal defects and conotruncal heart defects, we observed particularly high proportions of very low birth weight infants (7.1 and 3.9%, respectively) and extremely low birth weight infants (3.9 and 1.4%, respectively).

Multivariate analysis: There was no evidence of non-linearity nor of a statistically significant interaction between any of the heart defects groups and gestational age. As shown in Table 2, the average birth weight deficit was –67 g in d-transposition of the great arteries; however, statistically, d-transposition of the great arteries and control infants cannot be

Table 1. Descriptive statistics for cardiac malformation groups in the BWIS.

	Controls (n = 3519)	DTGA (n = 187)	CONO (n = 361)	ECD (n = 281)	LH (n = 507)	ASD (n = 281)	VSD (n = 622)
Mean gestational age (SD)	39.6 (2.2)	39.7 (2.0)	38.8 (2.9)	38.9 (2.1)	39.2 (2.2)	38.1 (3.9)	39.1 (2.5)
Preterm birth (<37 weeks) (%)	5.5	4.3	16.3	8.9	9.7	20.3	8.5
Sex (% male)	50.8	69.0	56.2	42.0	59.4	37.4	51.6
Race (% white versus non-white)	66.3	71.7	62.3	70.5	75.4	58.0	58.8
Maternal smoking (% smoker)	35.4	30.5	33.5	35.2	35.5	40.2	37.3
Overt diabetes	0.7	1.6	3.9	2.1	1.2	1.4	1.8
Gestational diabetes	3.2	3.2	5.5	3.2	4.7	5.7	3.9
Non-cardiac malformations							
Chromosome anomaly (%)	0.1	0.5	11.1	71.9	7.7	15.0	9.8
Syndrome (%)	0.6	4.8	11.9	5.0	6.3	6.1	5.3
Single-organ malformation (%)	1.0	3.2	10.0	1.4	3.8	6.1	6.9
None (%)	98.3	98.4	67.0	21.7	82.3	73.0	78.0

ASD = atrial septal defect; BWIS = Baltimore–Washington Infant Study; CONO = conotruncal heart defects; DTGA = d-transposition of the great arteries; ECD = endocardial cushion defect; LH = left heart obstructive lesions; VSD = membranous ventricular septal defect

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Table 2. Regression results: average birth weight deficits of cases compared with controls.

CCVM	Average birth weight deficit (g)	95% CI	p-value
DTGA	−67	−147.4 to 13.4	0.1062
CONO	−218	−282.7 to −153.3	<0.0001
ECD-Down	−265	−335.6 to −194.4	<0.0001
ECD-other	−194	−307.7 to −80.3	0.0009
LH	−143	−194.0 to −92.0	<0.0001
ASD	−150	−220.6 to −79.4	<0.0001
VSD	−127	−176.0 to −78.0	<0.0001

ASD = atrial septal defect; CCVM = congenital cardiovascular malformation; CONO = conotruncal heart defects; DTGA = d-transposition of the great arteries; ECD = endocardial cushion defect; LH = left heart obstructive lesions; VSD = membranous ventricular septal defect

distinguished on the basis of birth weight, that is, the 95% confidence interval included zero.

In contrast, we found an adjusted mean birth weight deficit of −218 g for conotruncal heart defects. The mean birth weight deficit for endocardial cushion defect-Down was −265 g, and for endocardial cushion defects-other it was −194 g. Somewhat lesser magnitudes of birth weight deficits were observed for left heart obstructive lesions (−143 g), atrial septal defects (−150 g), and membranous ventricular septal defects (−127 g) (Table 2), each of which was statistically significant. In addition (data not shown), we evaluated tetralogy of Fallot separately from all other conotruncal malformations (2939 versus 2956 g in all conotruncal heart defects, not statistically significant) and found a large birth weight deficit for infants with tetralogy of Fallot (−263 g [±74.3] relative to controls, $p < 0.01$). Although the number of infants with other subtypes of contruncal malformations was too small to permit regression modelling, we checked to observe whether the unadjusted mean birth weights of the 41 infants with truncus arteriosus (3095 g) or 15 with double outlet right ventricle (2968 g) were significantly smaller than those of controls (3365 g): both groups had significantly smaller mean birth weights ($p = 0.0365$ and 0.0364, respectively). We also analyzsd coarctation of the aorta, hypoplastic left heart syndrome, and aortic valve stenosis separately from all left heart obstructive lesions phenotypes combined: they had lower mean birth weights – 3119, 3091, and 3212 g for coarctation of the aorta, hypoplastic left heart syndrome, and aortic valve stenosis, respectively ($p < 0.01$ for each comparison with controls).

Discussion

As compared with a representative sample of controls from the general population, infants with d-transposition of the great arteries in this population-based study of congenital cardiovascular malformation were not born with significantly reduced birth weight, whereas those with conotruncal heart defects, endocardial cushion defects-Down, endocardial cushion defects-other, left heart obstructive lesions, atrial septal defects, and membranous ventricular septal defects showed statistically and clinically significant birth weight deficits. As a whole, these infants did not exhibit low birth weights solely because of being premature, and thus other mechanisms must underlie these associations. Altogether, these results show that the degree of birth weight decrement appears to be related to the specific type of congenital cardiovascular malformation. In previous studies, however, distinct cardiac lesions have been grouped together into one category,[4,5] a common practice to address smaller sample sizes that, unfortunately, obscures potentially important and mechanistic differences. Furthermore, very few of the prior studies adjusted for covariates such as sex and race.

Statistically, d-transposition of the great arteries and control infants cannot be distinguished on the basis of birth weight in our data set, as noted in previous studies.[8–10] Consistent with our results, Jacobs and Kramer observed a striking difference in the birth weight distributions of infants with d-transposition of the great arteries in comparison with those with conotruncal heart defects.[9,10] Lindinger's population study on German infants showed similar low birth weight percentages for d-transposition of the great arteries (6.5 versus 5.9%) and conotruncal heart defects (24.9 versus 24.7%); the latter group of congenital cardiovascular malformation are typically smaller and growth retarded compared with controls in most studies. Lindinger also reported significantly high proportions of male infants with d-transposition of the great arteries and preterm infants with conotruncal heart defects,[15] consistent with our results. Furthermore, Gelson's study of tetralogy of Fallot found similar mean birth weights to our conotruncal subset (2980 versus 2956 g).[16] Because of this large birth weight deficit, infants with conotruncal malformations may be at higher mortality risk from surgical interventions.[2–5]

In light of the well-known association of endocardial cushion defects with chromosome anomalies, we divided the endocardial cushion defects group into two subsets: those with Down syndrome (endocardial cushion defects-Down, $n = 201$) and those without (endocardial cushion defects-other, $n = 80$). This was done to isolate the impact of the heart defects from the chromosomal aberration, that is, to determine whether we observed the same results as in the full group of endocardial cushion defects. Both subsets revealed an association with low birth

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weight, somewhat more pronounced in the endocardial cushion defects-Down group. Very little comparable research on endocardial cushion defects has been reported elsewhere.

Infants with left heart obstructive lesions also showed significant birth weight deficits, relative to controls. However, the deficit was not as substantial as most of the other cardiac diagnostic groups. Lindinger's German population study found similar low birth weight percentages to our results (17.6 versus 14.4%).[15] Similarly, Hirsch's United States population study of hypoplastic left heart syndrome revealed similar low birth weight percentages (16 versus 14.4%).[17] Left heart malformations have typically been studied and reported in their separate components: hypoplastic left heart, aortic stenosis, aortic coarctation, and bicuspid aortic valve. Rosenthal cited a likely cause for aortic coarctation's birth weight deficit as "embryonic flow abnormalities into, within, and from the developing heart".[8] Similarly, both Donofrio and Limperopoulos have proposed that circulatory abnormalities, such as those in left heart obstructive lesions and d-transposition of the great arteries, may contribute to systemic disease, including impaired brain development.[18,19]

Infants with atrial septal defects and membranous ventricular septal defects showed birth weight deficits of −150 and −127 g, respectively, in our study. Moreover, infants with septal defects have consistently reported to have even larger average birth weight deficits in other studies.[9,10,15] Consistent with our results, Kramer observed similar birth weight deficits for infants with membranous ventricular septal defects (−155 g),[10] but a far greater birth weight deficit for atrial septal defects. It should be noted that Kramer used non-parametric kernel estimates, whereas we used regression analysis, in which we found no evidence of non-linearity. Furthermore, our study population showed greater percentages of low birth weight infants relative to Kramer's study in both atrial septal defects (13.5 versus 22.8%) and membranous ventricular septal defects (10 versus 16.7%), as well as greater mean birth weights in both groups, by ~200 g.[10] Another possible explanation for the differences in results is a selection factor in the Kramer study that may have attenuated the birth weight distribution, relative to our population-based study with complete ascertainment: Kramer's study relied solely on echocardiography findings and did not include cases discovered at autopsy.

Conversely, and in agreement with our findings, Jacobs' study on a southern Chinese population found a significantly high proportion of low birth weight babies with atrial septal defects.[9] Lindinger's German population study also found low birth weight percentages similar to ours for atrial septal defects (26 versus 22.8%) and membranous ventricular septal defects (14 versus 16.7%), as well as a significantly high proportion of both female and preterm births for infants with atrial septal defects.[15] Finally, it should be acknowledged that an alternative explanation for the association of atrial septal defect and low birth weight is ascertainment bias wherein the heart defect was discovered incidentally to the clinical evaluation of an infant born prematurely, growth retarded, or with other illness.

Several limitations of this study should be noted. The reported birth weights were those which the mothers recalled in pounds and ounces, instead of the babies being measured on a gram scale. In addition, there could have been some recall error from the mothers concerning their baby's birth weight and expected date of delivery, which were not independently confirmed. Similarly, maternal covariates were self-reported and may have been subject to some degree of recall error or bias. On the other hand, a key strength of this study is the accuracy of diagnosis: all case diagnoses were confirmed by paediatric cardiologists using echocardiography, cardiac catheterisation, surgical observation, or autopsy findings. The Baltimore–Washington Infant Study achieved complete regional ascertainment of cases (>99%) and is therefore free from selection bias.[11] Random control selection was performed annually at 52 birth hospitals in the region and was independent of the enrolment of cases, resulting in a control group that closely mirrored the underlying birth cohort, as reported previously; indeed, the proportion of controls with preterm births (5.5%) mirrored that of the regional birth cohort for this period (7%).[13] High participation rates of parents of both cases and controls further limited bias, and large sample sizes allowed us to look at several different types of subsets of cardiovascular heart defects. In addition, a large number of covariates were available for inclusion in the analyses. However, the Baltimore–Washington Infant Study was not designed to look at birth weight, and therefore we did not collect data on all the factors that might have been influential (e.g. maternal nutrition), nor did the study measure other somatic growth parameters that might have shed light on specific developmental pathways. In the absence of follow-up studies on these infants, we do not know whether these growth deficits persist into childhood or adulthood; however, others have reported persistent growth trajectory impairments throughout childhood.[20,21] It is also possible that the birth of a low birth weight infant may have prompted a cardiac examination, leading in some instances to the diagnosis of a mild case of congenital cardiovascular malformation that might not have otherwise been detected. Finally, this study was

conducted in the 1980s, and hence its relevance to the current era may not be completely applicable: for example, increased awareness of the detrimental effects of smoking and alcohol may have influenced contemporary birth weight distributions in the population. Nonetheless, our population statistics closely resemble those reported in several more recent congenital cardiovascular malformation studies.[9,15–17]

In conclusion, our study is one of the largest to examine the association of low birth weight and congenital cardiovascular malformation. We have confirmed previous evidence that identifies d-transposition of the great arteries as distinct from other types of outflow tract defects: the former group is characterised by a birth weight distribution that is highly similar to unaffected infants, whereas the latter group suffers from both prematurity and foetal growth retardation. All other groups of congenital cardiovascular malformation in this study, including endocardial cushion defects, left heart obstructive lesions, atrial septal defects, and membranous ventricular septal defects, were observed to have birth weight deficits compared with controls. The specific mechanisms that underlie these patterns are unknown at the present; however, previous authors[8,18,19,22] have speculated about two opposing hypotheses, either: (a) foetal growth retardation is the result of hemodynamic and other disturbances resulting from the heart malformation in utero, or (b) impaired embryonic growth predisposes to congenital cardiovascular malformation. Rosenthal,[8] examining detailed patterns of neonatal anthropometry of affected infants, found that the underlying mechanisms of hypoplasia and cell migration errors, while leading to the related phenotypes of d-transposition of the great arteries or tetralogy of Fallot, resulted in very different foetal growth patterns, that is, profound growth retardation in the latter group and little evidence for it in d-transposition of the great arteries, thereby calling into question the validity of hypothesis (a). On the other hand, under hypothesis (b), if embryonic growth impairment leads to congenital cardiovascular malformation, particularly those types that are sensitive to altered hemodynamic flow such as hypoplastic left heart, coarctation of the aorta, and d-transposition of the great arteries, then one might expect to observe similarities of neonatal anthropometry among those groups, when in fact they display quite different patterns. Epidemiological studies alone are therefore unlikely to resolve these paradoxes. Experimental models, simulation studies, and prospective foetal imaging studies[22] with repeated measurements of cardiovascular function and growth have potentially important roles to play in elucidating the mechanisms. Although we do not have follow-up data on these infants, future studies could be designed to examine the consequences of congenital cardiovascular malformation and low birth weight, including persistent growth deficits in childhood and other late effects such as myocardial dysfunction. Such studies would be invaluable to testing the hypothesis that the birth weight decrements described here are associated with more systemic abnormalities than have been previously recognised.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the United States Department of Health and Human Services (Federal regulation 45 CFR 46.102(f)) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Institutional Review Board of the University of Maryland School of Medicine.

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