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Increased Prevalence of Cardiovascular Defects among 56,709 California Twin Pairs

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Abstract

This study compared the prevalence of cardiovascular defects in twin and singleton births and explored the influences of zygosity (monozygotic and dizygotic) and maternal age (<35 and ≥35 years of age) on concordance.

Data on twin and singleton infants with (n=628 twin pairs and n=14,078 singletons) and without (n=53,974 twin pairs and n=4,858,255 singletons) cardiovascular defects were obtained from the California Birth Defects Monitoring Program and the California vital statistics birth and fetal death records during the period 1983-2003. Prevalence ratios (PR) (prevalence of twin/singleton) and approximate 95% confidence intervals were calculated for sixteen congenital cardiovascular categories. Poisson regression techniques using log-linear models were employed to assess whether the probability of concordance of defects within each cardiovascular category varied by zygosity or maternal age.

An increased prevalence was observed in twins compared to singletons in all 16 cardiovascular categories. Seven of the cardiovascular categories had at least double the prevalence in twins compared to singletons. Like-sex twins, as a proxy of monozygosity, had an increased prevalence of cardiovascular defects compared to unlike sex twins. Probabilities of concordance for flow lesions were higher among monozygotic than dizygotic twins.

Our study provides evidence that twinning is associated with more cardiovascular defects than singletons. Increased concordance for flow lesions in monozygotic twins was observed, an observation that is in agreement with findings from familial recurrence studies of cardiovascular defects.

Keywords

cardiovascular diseases; congenital heart defect; twins; twins; monozygotic; twins; dizygotic; prevalence

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INTRODUCTION

Cardiovascular defects occur in approximately one per 100 live births [Pradat, 1992; Reamon-Buettner et al, 2006; Reller et al, 2008] and represent one-tenth of all infant deaths worldwide [Reamon-Buettner et al, 2006] yet relatively little is known regarding their causes [Jenkins et al, 2007]. The various phenotypes that comprise all cardiovascular defects are likely to be etiologically heterogeneous, resulting from cytogenetic, Mendelian, and environmental contributions. For example, conotruncal defects appear to have a higher recurrence risk than other cardiovascular defects, suggesting the importance of monogenic inheritance [Becker et al, 1996; Digilio et al, 1997; Digilio et al, 2001]. This group of defects may also be associated with chromosomal abnormalities [Ferencz et al, 1989; Giglio et al, 2000; Johnson et al, 1997; Schuffenhauer et al, 1998], especially microdeletion 22q11 [Goldmuntz et al, 1998], and Mendelian disorders [Debrus et al, 1996; Lammer et al, 2001; Pacileo et al, 1992]. However, individually, each suspected genetic contribution to etiology thus far appears to be rare.

Twin studies are a means of elucidating the contributions of genetic and environmental factors to the development of a given condition. The underlying assumption in twin studies of congenital malformations is that all twins share similar prenatal environments and that monozygotic (MZ) twins share identical genotypes whereas dizygotic (DZ) twins are no more similar genetically than are other siblings [Anderson, 1977; Layde et al, 1980; Luke et al, 1990; Myrianthopoulos, 1978; Windham et al, 1984]. The study of twins may be a powerful approach for identifying clues about cardiovascular defects. For example, elevated risks of cardiovascular defects in MZ relative to DZ twins may suggest increased heritability [Motulsky, 1996].

Cardiovascular defects have been reported as more common among twins compared to singletons [Doyle et al, 1991; Glinianaia et al, 2008; Layde et al, 1980; Little et al, 1989; Mastroiacovo et al, 1999; Myrianthopoulos, 1975; Myrianthopoulos, 1978; Pradat, 1992; Windham et al, 1984] in most studies, but not all [Anderson, 1977; Berg et al, 1989]. However, some investigations of specific cardiovascular phenotype groups have reported that twins have lower frequencies of conotruncal defects [Berg et al, 1989], other anomalies of the aorta [Mastroiacovo et al, 1999], transposition of the great vessels [Doyle et al, 1991; Little et al, 1989], atrial and ventricular septal defects [Layde et al, 1980; Little et al, 1989]. Increased frequency of cardiovascular defects in MZ and in like sex twins compared to singletons have been reported in some [Berg et al, 1989; Burn et al, 1984; Little et al, 1989; Schinzel et al, 1979] but not all investigations [Layde et al, 1980; Windham et al, 1984]. Concordance of cardiovascular defects within twin pairs has been reported to be higher among MZ than DZ twins [Anderson, 1977; Berg et al, 1989].

Inconsistencies in previous results may be due to differences in methods of subject ascertainment, differences in diagnostic inclusion criteria, and limited sample sizes. Given the limited and inconsistent findings on this topic, we investigated cardiovascular defects among twins and singletons in a large, population-based, actively ascertained birth defects registry. We compared the prevalence of specific phenotypes of cardiovascular defects among twins and singletons overall and separately among like sex and unlike sex twins. We also estimated probabilities of concordance for specific phenotypes of cardiovascular defects among twin pairs and whether they varied based on zygosity or maternal age.

MATERIALS AND METHODS

Study Population

Data on twin and singleton newborn infants with major defects were obtained from the California Birth Defects Monitoring Program (CBDMP), a population-based registry that

actively collects information on births with structural and chromosomal malformations from medical records of non-military hospitals in California. Analyses included singleton and twin offspring born during 1983 2003. Medical records at hospitals and genetic centers in selected California counties were reviewed to identify all structural malformations diagnosed within one year of age. The overall ascertainment has been estimated to be 97% complete [Schulman et al, 1993].

A modified version of the British Pediatric Association (BPA) codes was used. The codes were developed by Birth Defect & Genetic Disease Branch, Centers for Disease Control based on BPA classification of disease (1979) and WHO ICD 9 CM (1977). Malformations were grouped according to BPA classification codes. A clinical geneticist (EJL) created classifications that consisted of one or more cardiovascular defects to create phenotype groups that reflected an underlying similarity in pathogenesis within each group. These cardiovascular phenotype groups were guided by the timing and shared structures in embryogenesis. Each phenotype grouping contained a unique set of subjects; that is no subject appears in more than one category.

Births with chromosomal aneusomy (BPA code 758), identifiable single gene disorders (BPA code 759.8), acardia (BPA codes 746.805, 746.888, and 746.890), and conjoined (BPA code 759.4) twins were excluded (n=56 twin pairs concordant for any birth defect, n=226 twin pairs discordant for any birth defect, and n=81,423 singleton subjects). Births with one or more cardiovascular defects were included, specifically n=44 twin pairs concordant for any cardiovascular defect, n=584 twin pairs discordant for any birth defect, and n=14,078 singletons with any cardiovascular defect.

Twin pairs (n=53,974) and singleton subjects (n=4,858,255) without congenital malformations were extracted from California vital statistics birth and fetal death records (fetal deaths at more than 20 weeks gestation) for the years 1983–2003. Members of each twin pair were linked using mother's last name, mother's maiden name, maternity hospital, and child's date of birth.

Twin pairs (n=2,107) and singleton subjects (n=79,164) with malformations other than cardiovascular defects were included in some analyses. Therefore, the total population at risk of a cardiovascular defect consisted of 56,709 twin pairs and 4,951,497 singleton subjects.

Twin zygosity (MZ, DZ, or missing) was abstracted from malformed twins' medical records. Zygosity was determined where there was agreement between two variables abstracted from medical records; specifically results from placental examination and "reported" type of twin. Where zygosity information from medical record review was incomplete or in disagreement, twins of unlike sex pair were declared DZ, while designation of MZ twins was not inferred. Zygosity information was available for only 49% of twins with cardiovascular defects. Zygosity information was not available for non-malformed twins. Twin sex pairing (male-male, male-female, female-female pair, or missing), maternal race-ethnicity, and maternal age variables were obtained from either California birth or fetal death certificates.

ANALYSIS

Prevalence Ratios

Prevalence of each cardiovascular phenotype group was calculated separately for twins and singletons among all births in the population at risk. The expression for prevalence in twin subjects denoted $\hat{p_t}$, is given by:

$$\widehat{p}_t = \frac{2n_c + n_d}{2n_t}$$

where n_c = number of twin pairs concordant for a given malformation, n_d = number of twin pairs discordant for a given malformation, and n_t = number of twin pairs at risk of a malformation. The expression for prevalence in singletons $\hat{p}_s$, is given by:

$$\widehat{p}_s = \frac{n_{ms}}{n_s}$$

where n_{ms} = number of malformed singletons, and n_s = number of singletons at risk of a malformation. These prevalence measures were compared using prevalence ratios ($\hat{p}_t / \hat{p}_s$). The variance distribution of the logarithm of the prevalence ratio is estimated by:

$$\widehat{\sigma}^2 = \left(\frac{1 - \widehat{p}_t}{\widehat{p}_t n_t}\right) + \left(\frac{1 - \widehat{p}_s}{\widehat{p}_s n_s}\right)$$

The bounds of an approximate 95% confidence intervals for the prevalence ratios are given by:

$$e^{\log\left(\widehat{p}_t / \widehat{p}_s\right) \pm 1.96\widehat{\sigma}}$$

Log-linear Models

Poisson regression applied to log-linear models was used to compare the probability of concordance of cardiovascular defects within twin pairs by zygosity (MZ, DZ) or maternal age (< 35, ≥ 35 years of age). Zygosity was investigated because MZ twins would illustrate an increased probability of concordance compared to DZ twins if a given cardiovascular defect illustrated stronger heritability. Some congenital defects are more prevalent with increasing maternal age and we sought to investigate the effects of older maternal age on cardiovascular defects.

The dependent variable is the logarithm of the counts of twin pairs with specific cardiovascular phenotypes in each category while the independent variables are the categorical variables concordance, zygosity, twin sex pairing, and maternal age. In log-linear analyses, two independent variables were investigated by combining categories of specific phenotypes of cardiovascular defects to create two broader pathogenetic groups: 1) flow lesions (hypoplastic left heart syndrome, congenital stenosis of aortic valve, coarctation of aorta, and ostium secundum type atrial septal defects); and 2) conotruncal defects (truncus arteriosus communis, transposition of the great vessels, tetralogy of Fallot, and ventricular septal defects) groups so that sufficient numbers of twin subjects provided stable estimates. These pathogenetic groups were created as the phenotypes have shared structures in embryogenesis and because cell sizes were too limited for more refined phenotype groups.

In these analyses, additive and non-additive log-linear models were constructed to evaluate the association between the independent variables and cardiovascular defects. Specifically, these two models are:

Model 1: log (cell frequency) = a + b1*concordance + b2*male-female pairing + b3*female-female pairing + b4*zygosity + b5*concordance*zygosity

Model 2: log (cell frequency) = a + b1*concordance + b2*male-female pairing + b3*female-female pairing + b4*maternal age + b5*concordance*maternal age

Additive models allow for estimation of a single probability of concordance for cardiovascular defects adjusted for the influences of twin sex pairing and zygosity and twin sex pairing and maternal age, respectively. The non-additive models produce estimated probabilities of concordance for both MZ and DZ twins. Likelihood ratio chi-square statistics were used to select the appropriate additive or non-additive model. Details of log linear models are contained in Supplemental Data and in Tables VI, VII, and VIII.

RESULTS

Table I presents the distribution of maternal age, maternal race-ethnicity, and twin sex pairing among twins and singletons with and without malformations. Using a criterion of at least a five percent difference among twins, mothers of concordant malformed twins were more likely to be 25-29 years of age (32.6%) and less likely to be older than or equal to 35 years of age (15.1%) than mothers of discordant malformed twins or non-malformed twins. Twins concordant for malformations are more likely to be non-Hispanic White (51.7%) or male-male (50.8%) and less likely to be Hispanic (30.2%) or male-female (33.2%) than the other groups of twins.

Prevalence Ratios

Table II presents prevalence ratios and approximate 95% confidence intervals for 16 cardiovascular phenotypic groups. For each group, we observed increased risk among twins compared to singletons. Seven of the 16 groups show at least double the prevalence in twins compared to singletons. The largest prevalence ratio was observed for pulmonary artery atresia and stenosis (PR=4.01, 95% CI: 3.44, 4.68).

Prevalence ratios tended to be larger for like sex twins than for unlike sex twins (Table III). Eight of the 16 phenotypic groups had at least double the prevalences among like sex twins compared to singletons, whereas only four phenotype groups showed at least a doubling of the prevalences among unlike sex twins. Results suggested substantially reduced prevalence of congenital stenosis of aortic valve and coarctation of aorta among unlike sex twins compared to singletons (PR=0.63, 95% CI: 0.46, 0.88).

We also compared prevalences between the two most common race-ethnicity groups. Results indicated that prevalence ratios of cardiovascular defects among non-Hispanic Whites and Whites were not substantially different (data not shown).

Log-linear Models

We explored whether the concordance of flow lesions and conotruncal defects varied between zygosities (MZ and DZ) and maternal age groups (>35 and ≤ 35 years of age). Table IV presents the observed number of twin pairs among zygosity and maternal age categories for each of the pathogenetic groups investigated and is presented as reference to Table V.

Table V shows the probability of concordance of cardiovascular defects by zygosity. The concordance of flow lesions differed by zygosity (p=0.02) and was higher among MZ compared to DZ twins. In contrast, the concordance of conotruncal defects did not vary by zygosity (p=0.30). Concordance of flow lesions also did not vary by maternal age groups (p=0.18) (data

not shown). Concordance of conotruncal defects could not be examined by maternal age group due to insufficient numbers of twin subjects.

DISCUSSION

Our analyses examined the prevalence of cardiovascular defects in twins compared to singletons and then stratified the twin population by like and unlike sex and compared each of these groups to singletons.

We identified an increased prevalence of cardiovascular defects in twins compared to singletons for 16 congenital cardiovascular phenotype groups, with a doubling or more in prevalence for seven of the 16 phenotype groups. We analyzed cardiovascular defects by specific phenotype groups because of evidence of etiologic and pathogenetic heterogeneity among the cardiovascular phenotype groups in singletons [Clark, 1986; Clark, 1996].

Several studies [Glinianaia et al, 2008; Myrianthopoulos, 1978; Taffel, 1978; Windham et al, 1984] have combined cardiovascular phenotype groups into a single analytical group; therefore, we cannot compare our results for the 16 cardiovascular phenotype groups that we investigated. Five studies [Doyle et al, 1991; Layde et al, 1980; Little et al, 1989; Mastroiacovo et al, 1999; Myrianthopoulos, 1975] have examined the prevalence of seven of the 16 cardiovascular phenotype groups we investigated. The studies' findings [Doyle et al, 1991; Layde et al, 1980; Little et al, 1989; Mastroiacovo et al, 1999; Myrianthopoulos, 1975] for six of the seven cardiovascular phenotype groups are similar to our findings. In contrast, for ostium secundum type atrial septal defects, only one [Layde et al, 1980] of two [Layde et al, 1980; Little et al, 1989] studies showed increased prevalence in twins compared to singletons. The variation in results may be due to differences in subject ascertainment methods or diagnostic criteria or due to random variation due to few numbers of twin subjects for study. Our analyses examines a substantially larger population of twin pairs (n=56,709) in comparison to the other two studies [Layde et al, 1980; Little et al, 1989] (n=4,490 and n=2,636 respectively) that examined ostium secundum type atrial septal defects.

As an attempt to assess the contribution of genetics to the increased prevalence of the 16 cardiovascular phenotype groups in twins compared to singletons, we investigated prevalence in like sex and unlike sex twins and whether concordance varied by zygosity in two pathogenetic groups. We were unable to examine prevalence in MZ and DZ twins as zygosity information was unavailable for unaffected twins and therefore we used like and unlike sex as a proxy.

Our study showed that eight of the 16 phenotype groups had at least double the prevalence in like sex twins compared to singletons whereas we showed at least double the prevalence for only four phenotype groups in unlike sex twins compared to singletons. Differences in prevalence of specific cardiovascular groupings among like sex and unlike sex twins has only been investigated in one other study [Layde et al, 1980]. The authors [Layde et al, 1980] reported increased prevalence of ventricular septal defects in like sex twins compared to unlike sex twins in African-Americans, but they found the reverse association among Whites. The study had fewer pairs of African-American twins than White twins and did not enumerate the twins in each race-ethnicity category with a ventricular septal defect.

Why MZ twins show higher rates of cardiac malformations compared to DZ twins is unknown. Burn [Burn, 1991] has suggested heart malformations are two to three times more likely among MZ twins compared to DZ twins or singletons. He suggests two explanations for the higher likelihood. The first involves a two-hit hypothesis where one twin, weakened by the twinning event is damaged by an external agent. The second explanation occurs as a result of altered

laterality, i.e., Burn hypothesizes that MZ twinning disturbs laterality to a sufficient degree to cause a variety of abnormalities of heart septation and development.

Our study found that the probability of concordance for flow lesions was approximately three times higher in MZ compared to DZ twins (0.179 versus 0.048 respectively; p-value=0.02). This suggests greater heritability within this pathogenetic group assuming the cardiovascular defects of a concordant twin pair are likely due to the same single gene disorder. A study [Gill et al, 2003] of recurrences of congenital cardiovascular defects among first-degree relatives of index cases, reported a family history of 38% for aortic valve stenosis, 33% for hypoplastic left heart syndrome, and 13% for coarctation of the aorta, but 0% for atrial septal defects. A positive family history was defined as a first-degree relative and index case having an identical type of congenital cardiovascular defect. A recent review of the literature [Calcagni et al, 2007] regarding familial recurrence of congenital cardiovascular defects noted that the different types of flow lesions (hypoplastic left heart syndrome, aortic coarctation, aortic valve stenosis and bicuspid aortic valve) segregate in some families, indicating these cardiovascular defects may share a common genetic basis. These reports [Calcagni et al, 2007; Gill et al, 2003] in combination with our observations for the flow lesion pathogenetic group suggest greater heritability for these defects.

Probabilities of concordance for conotruncal defects were similar for MZ and DZ twins, suggesting lesser heritability of this phenotypic group. No increased familial recurrence of conotruncal defects was reported in one study [Gill et al, 2003], which in conjunction with our results suggests that there is not a common genetic basis for these defects. However, increased familial recurrence for conotruncal defects was reported in another study but it was conducted before cytogenetic testing for the 22q11 deletion syndrome was available [Corone et al, 1983]. We excluded those subjects with identifiable syndromes, which would eliminate some subjects with 22q11 microdeletions and may explain the lack of agreement with Corone et al [Corone et al, 1983].

Two smaller studies [Anderson, 1977; Berg et al, 1989] compared the probability of concordance of cardiovascular defects among MZ and DZ twin pairs and reported higher concordance among MZ twins. However, these studies [Anderson, 1977; Berg et al, 1989] did not investigate specific cardiovascular phenotype groups due to limited sample sizes and therefore our flow lesion results are not directly comparable. The estimation of the probability of concordance for other specific pathogenetic groups was not possible due to insufficient numbers of twins.

Limitations of our study include the possibility for systematic diagnostic bias in that twin subjects may be given more detailed physical examinations than singleton subjects. If this had occurred, we would expect to see higher prevalence ratios among twins for cardiovascular defects that are of lesser severity and therefore more likely to be observed as a result of greater diagnostic scrutiny. In fact, our results indicate higher prevalence ratios for nearly all groupings of cardiovascular defects. Zygosity information was available for only 49% of twins with cardiovascular defects, which limited our ability to investigate differences in prevalence in MZ and DZ twins. Therefore, we instead used like and unlike sex twins to investigate prevalence differences and the role of inheritance in these cardiovascular defects.

Strengths of our study include the large population, the use of an active, population-based, ascertainment method and inclusion of fetal deaths at more than 20 weeks gestation, which improves the accuracy of the observed results. These data from California reflect approximately 12% of the United States population [2006] and include a racially and ethnically diverse population. Our study investigates prevalence of specific cardiovascular defects in like

and unlike sex twins and adds to the results from just one other study [Layde et al, 1980] that used this approach.

Our results show that twins have a higher prevalence of a variety of cardiovascular defect phenotypes compared to singletons. Increased concordance for the flow lesions pathogenetic group in MZ twins was observed, which in conjunction with findings from familial recurrence studies [Calcagni et al, 2007; Gill et al, 2003] provides further evidence of a genetic component for these defects. Future work may benefit from high throughput genetic investigations to identify specific genetic regions associated with these cardiac malformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table I

Distribution of maternal race-ethnicity, maternal age, and twin sex pairing among malformed and non-malformed twin pairs and singletons in selected California counties, 1983-2003

	Twin Pairs				Singletons		
	Malformed[1]		Non- malformed N[2](%)	Total N[2](%)	Malformed[1] N[2](%)	Non- malformed N[2](%)	Total N[2](%)
	Concordant N[2](%)	Discordant N[2](%)					
Maternal age (years)							
13-19	28 (8.5)	168 (7.0)	3548 (6.6)	**3744 (6.6)**	11079 (11.9)	563679 (11.6)	**574758 (11.6)**
20-24	65 (19.6)	480 (20.0)	10395 (19.3)	**10940 (19.3)**	22939 (24.6)	1215182 (25.0)	**1238121 (25.0)**
25-29	108 (32.6)	638 (26.5)	14722 (27.3)	**15468 (27.3)**	25451 (27.3)	1377256 (28.4)	**1402707 (28.3)**
30-34	79 (23.9)	634 (26.4)	14613 (27.1)	**15326 (27.0)**	20242 (21.7)	1088977 (22.4)	**1109219 (22.4)**
35-55	50 (15.1)	484 (20.1)	10666 (19.8)	**11200 (19.8)**	13420 (14.4)	610815 (12.6)	**624235 (12.6)**
Missing	1 (0.3)	--	30 (0.1)	**31 (0.1)**	111 (0.1)	2346 (0.1)	**2457 (0.1)**
Total	**331**	**2404**	**53974**	**56709**	**93242**	**4858255**	**4951497**
Maternal race- ethnicity							
Non-Hispanic White	171 (51.7)	1142 (47.5)	22186 (41.1)	**23499 (41.4)**	37006 (39.7)	1627933 (33.5)	**1664939 (33.6)**
Hispanic	100 (30.2)	769 (32.0)	20199 (37.4)	**21068 (37.2)**	38148 (40.9)	2234885 (46.0)	**2273033 (45.9)**
African- American	32 (9.7)	249 (10.4)	5510 (10.2)	**5791 (10.2)**	7807 (8.4)	358877 (7.4)	**366684 (7.4)**
Asian	15 (4.5)	136 (5.7)	3299 (6.1)	**3450 (6.1)**	5624 (6.0)	374249 (7.7)	**379873 (7.7)**
Other	10 (3.0)	93 (3.9)	2309 (4.3)	**2412 (4.3)**	4061 (4.4)	235387 (4.9)	**239448 (4.8)**
Unknown	3 (0.9)	15 (0.6)	471 (0.9)	**489 (0.9)**	596 (0.6)	26924 (0.6)	**27520 (0.6)**
Total	**331**	**2404**	**53974**	**56709**	**93242**	**4858255**	**4951497**
Sex pairing							
Male-male	168 (50.8)	1021 (42.5)	18687 (34.6)	**19876 (35.1)**			
Female- female	110 (33.2)	729 (30.3)	19188 (35.6)	**20027 (35.3)**			
Male-female	53 (16.0)	650 (27.0)	16093 (29.8)	**16796 (29.6)**			
Missing	--	4 (0.2)	6 (0.01)	**10 (0.02)**			
Total	**331**	**2404**	**53974**	**56709**			

[1]Includes all malformations.

[2]Percentages are calculated using column totals.

Table II

Prevalence Ratios of cardiovascular defects (twin / singleton)

Phenotype Group	BPA Code(s)	Defect Description[1]	Singleton Cases[2]	Concordant twin pairs[3]	Discordant twin pairs[3]	Prevalence Ratios[4]	approximate 95% CI
1	745.6	Endocardial cushion defects	766	2	20	1.37	1.26, 1.49
2	745.0	Truncus arteriosus communis	298	1	9	1.61	1.34, 1.94
3	745.1	Transposition of great vessels	1756	2	49	1.32	1.27, 1.37
4	745.2	Tetralogy of fallot	1167	3	57	2.35	2.28, 2.44
5	745.3	Single ventricle	89	0	3	1.47	0.75, 2.89
6	746.7	Hypoplastic left heart syndrome	662	2	19	1.51	1.39, 1.65
7	746.3 747.1	Congenital stenosis of aortic valve; Coarctation of aorta	1400	3	70	2.37	2.31, 2.43
8	746.010	Stenosis valve, pulmonary	913	2	42	2.20	2.10, 2.30
9	746.11 746.19	Anomaly valve, tricuspid other; Anomaly valve, tricuspid, unspecified	96	0	3	1.36	0.69, 2.67
10	746.13	Atresia valve, tricuspid	60	0	5	3.63	2.38, 5.55
11	747.200 747.210 747.215 747.230 747.250 747.290	Atresia aorta; Hypoplasia aorta, any part; Interrupted arch, aortic; Persistent right aortic arch; Ring vascular, aorta; Anomaly aorta, unspecified	481	0	20	1.81	1.64, 2.01
12	747.300 747.320	Atresia artery pulmonary; Stenosis artery, pulmonary, main	152	1	12	4.01	3.44, 4.68
13	745.4	Ventricular septal defect	2722	4	110	1.86	1.82, 1.89
14	745.5	Ostium secundum type atrial septal defect	3194	24	151	2.72	2.69, 2.74
15	746.200	Ebstein Anomaly	71	0	3	1.84	0.93, 3.64
16	745.700 746.000 746.881 746.882 747.410 747.420	Cor biloculare; Atresia valve, pulmonary; Hypoplasia ventricle, right; Hypoplasia ventricle, left; Persistent left superior vena cava; Anomalous pulmonary venous return, total	201	0	11	2.39	1.98, 2.88

[1] as defined by the British Pediatric Association Reporting system.

[2] total number of singletons = 4951497.

[3] total number of twin pairs = 56709.

[4] Sample calculation of prevalence ratio for phenotype group #1: prevalence ratio (twins/singletons) = [((2*2) + 20) / (2*56709)] / [766/4951497] = 0.000211607/0.000154701 =1.37

Table III

Prevalence Ratios of cardiovascular defects (twin / singleton) stratified by like and unlike sex twins

Phenotype Group	Defect Description[1]	Singleton Cases[2]	Like Sex Twins			Unlike Sex Twins		
			Concordant twin pairs[3]	Discordant twin pairs[3]	Prevalence Ratios[4] & approximate 95% CIs	Concordant twin pairs[5]	Discordant twin pairs[5]	Prevalence Ratios & approximate 95% CIs
1	Endocardial cushion defects	766	2	14	1.46 (1.30, 1.63)	0	6	1.16 (0.83, 1.61)
2	Truncus arteriosus communis	298	0	7	1.46 (1.09, 1.94)	1	2	1.98 (1.20, 3.25)
3	Transposition of great vessels	1756	2	34	1.34 (1.27, 1.42)	0	15	1.26 (1.10, 1.44)
4	Tetralogy of Fallot	1167	3	41	2.50 (2.39, 2.61)	0	15	1.90 (1.66, 2.16)
5	Single ventricle	89	0	2	1.39 (0.51, 3.80)	0	1	1.66 (0.23, 12.02)
6	Hypoplastic left heart syndrome	662	2	15	1.78 (1.60, 1.98)	0	4	0.89 (0.54, 1.46)
7	Congenital stenosis of aortic valve; Coarctation of aorta	1400	3	64	3.10 (3.01, 3.20)	0	6	0.63 (0.46, 0.88)
8	Stenosis valve, pulmonary	913	1	33	2.38 (2.24, 2.52)	1	9	1.78 (1.48, 2.13)
9	Anomaly valve, tricuspid other; Anomaly valve, tricuspid, unspecified	96	0	3	1.94 (0.99, 3.80)	0	0	--
10	Atresia valve, tricuspid	60	0	4	4.14 (2.45, 6.98)	0	1	2.46 (0.34, 18.02)
11	Atresia aorta; Hypoplasia aorta, any part; Interrupted arch, aortic; Persistent right aortic arch; Ring vascular, aorta; Anomaly aorta, unspecified	481	0	13	1.68 (1.44, 1.96)	0	7	2.15 (1.62, 2.85)
12	Atresia artery pulmonary; Stenosis artery, pulmonary, main	152	0	10	4.08 (3.31, 5.03)	1	2	3.88 (2.35, 6.41)
13	Ventricular septal defect	2772	4	87	2.13 (2.08, 2.17)	0	23	1.22 (1.12, 1.33)
14	Ostium secundum type atrial septal defect	3194	22	122	3.23 (3.19, 3.27)	2	29	1.52 (1.43, 1.62)
15	Ebstein Anomaly	71	0	2	1.75 (0.64, 4.79)	0	1	2.08 (0.29, 15.15)
16	Cor biloculare; Atresia valve, pulmonary; Hypoplasia ventricle, right; Hypoplasia ventricle, left; Persistent left superior vena cava; Anomalous pulmonary venous return, total	201	0	9	2.78 (2.21, 3.49)	0	2	1.47 (0.55, 3.95)

[1] as defined by the British Pediatric Association Reporting system.

[2] total number of singletons = 4951497.

[3] total number of like sex twin pairs =39903.

[4] Sample calculation of prevalence ratio for like sex phenotype group #1: prevalence ratio (twins/singletons) = [((2*2) + 14) / (2*39903)] / [766/49514497] = 0.000225547/0.000154701 =1.46

[5] total number of unlike sex twin pairs = 16796.

Table IV

Observed number of twin pairs concordant and discordant for cardiovascular defects among zygosity and maternal age categories

Pathogenetic Group	Maternal age < 35 years		Maternal age ≥35 years		Monozygotic		Dizygotic	
	Concordant twin pairs	Discordant twin pairs	Concordant twin pairs	Discordant twin pairs	Concordant twin pairs	Discordant twin pairs	Concordant twin pairs	Discordant twin pairs
[1]Flow lesions	22	206	7	34	12	55	3	59
[2]Conotruncal defects	10	175	0	49	3	40	2	70

[1]Hypoplastic left heart syndrome, Congenital stenosis of aortic valve, Coarctation of aorta, and Ostium secundum type atrial septal defect.

[2]Truncus arteriosus communis, Transposition of great vessels, Tetralogy of Fallot, Ventricular septal defect.

Table V

Additive and non-additive log-linear model results, for zygosity and concordance of cardiovascular defects

Pathogenetic Group	Additive estimates	Non-additive estimates		-2*log likelihood	P- value
	Probability of concordance among twins (approximate 95% CI)	Probability of concordance among MZ twins (approximate 95% CI)	Probability of concordance among DZ twins (approximate 95% CI)		
[1]Flow lesions	0.116 (0.071, 0.184)	0.179 (0.105, 0.290)	0.048 (0.016, 0.140)	5.73	0.02
[2]Conotruncal defects	0.044 (0.018, 0.100)	0.070 (0.023, 0.195)	0.028 (0.007, 0.104)	1.10	0.30

[1]Hypoplastic left heart syndrome, Congenital stenosis of aortic valve, Coarctation of aorta, and Ostium secundum type atrial septal defect.

[2]Truncus arteriosus communis, Transposition of great vessels, Tetralogy of Fallot, Ventricular septal defect.

Table VI

Additive log-linear model components for zygosity and concordance

	Model		
	Male-male	**Male-female**	**Female-female**
monozygotic - discordant	$\log(n_{11})=a$	--	$\log(n_{13})=a+c_2$
monozygotic - concordant	$\log(n_{21})=a+b$	--	$\log(n_{23})=a+b+c_2$
dizygotic - discordant	$\log(n_{31})=a+d$	$\log(n_{32})=a+c_1+d$	$\log(n_{33})=a+c_2+d$
dizygotic - concordant	$\log(n_{41})=a+b+d$	$\log(n_{42})=a+b+c_1+d$	$\log(n_{43})=a+b+c_2+d$

The numeric subscripts represent the row, column designations.

Where a=defect; b=concordant; c_1=male-female sex pair; c_2=female-female sex pair; d=dizygotic

Table VII

Additive log-linear model components for maternal age and concordance

	Model		
	Male-male	**Male-female**	**Female-female**
age < 35, discordant	$\log(n_{11})=a$	$\log(n_{12})=a+c_1$	$\log(n_{13})=a+c_2$
age < 35, concordant	$\log(n_{21})=a+b$	$\log(n_{22})=a+b+c_1$	$\log(n_{23})=a+b+c_2$
age >= 35, discordant	$\log(n_{31})=a+d$	$\log(n_{32})=a+c_1+d$	$\log(n_{33})=a+c_2+d$
age >= 35, concordant	$\log(n_{41})=a+b+d$	$\log(n_{42})=a+b+c_1+d$	$\log(n_{43})=a+b+c_2+d$

The numeric subscripts represent the row, column designations.

Where a=defect; b=concordant; c_1 =male-female sex pair; c_2=female-female sex pair; d=age>=35

Table VIII

Observed number of twin pairs concordant and discordant for cardiovascular defects among zygosity and maternal age categories

Pathogenetic Group	Maternal age < 35 years		Maternal age ≥35 years		Monozygotic		Dizygotic	
	Concordant twin pairs	Discordant twin pairs	Concordant twin pairs	Discordant twin pairs	Concordant twin pairs	Discordant twin pairs	Concordant twin pairs	Discordant twin pairs
[1]Flow lesions	22	206	7	34	12	55	3	59
[2]Conotruncal defects	10	175	0	49	3	40	2	70

[1]Hypoplastic left heart syndrome, Congenital stenosis of aortic valve, Coarctation of aorta, and Ostium secundum type atrial septal defect.

[2]Truncus arteriosus communis, Transposition of great vessels, Tetralogy of Fallot , Ventricular septal defect