

# Prevalence of congenital anomalies in newborns with congenital heart disease diagnosis

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## ABSTRACT

- Background** : There is a known association between congenital heart disease (CHD) and other congenital anomalies (CA). These associations have been altered by changes in prenatal factors in recent time. We reviewed the largest database of inpatient hospitalization information and analyzed the current association between common CHD diagnoses and other congenital anomalies.
- Materials and Methods** : Case-control study design. We reviewed the Nationwide Inpatient Sample (NIS) database from 1998 to 2008 and identified all live births with CHD diagnosis (case) and live births without CHD diagnosis (control). We compared prevalence of associated congenital anomalies between the case and control groups.
- Results** : Our cohort consisted of 97,154 and 12,078,482 subjects in the case and control groups, respectively. In the CHD population, prevalence of non-syndromic congenital anomaly (NSCA), genetic syndrome (GS), and overall extra-cardiac congenital anomaly (CA) were 11.4, 2.2, and 13.6%, respectively. In the control group, prevalence of NSCA, GS, and CA were 6.7, 0.3, and 7.0%, respectively. NSCA (odds ratio (OR): 1.88, confidence interval (CI): 1.73-1.94), GS (OR 2.52, CI 2.44-2.61), and overall CA (OR: 2.01, CI: 1.97-2.14) were strongly associated with CHD. Prevalence of GS and multiple organ-system CA decreased significantly over the study period.
- Conclusions** : This is the largest and most comprehensive population-based study evaluating association between CHD and extra-cardiac malformation (ECM) in newborns. There was significant decrease in prevalence of GS and multiple CA over the study period.
- Keywords** : Congenital anomalies, epidemiology, extra cardiac, newborn, prevalence

## INTRODUCTION

Previous studies have shown association between congenital heart disease (CHD) and other congenital anomalies (CAs) and genetic syndromes (GSs).<sup>[1-7]</sup> Depending on the severity of CHD diagnosis, the clinical course may range from spontaneous closure of defect as seen with small septal defects to a lifelong need for

medical and surgical interventions.<sup>[8,9]</sup> The presence of non-cardiac CAs also significantly impacts the natural history and clinical course of CHD as these patients may require medical and/or surgical interventions independent of their cardiac pathology.

Epidemiology of CHD is well-described.<sup>[2,10-12]</sup> However, we believe that changes with certain prenatal factors have altered the epidemiology of this patient population. First, there has been a tremendous progress in fetal diagnosis of congenital malformations with concordant increase in the rate of termination of pregnancy for fetal anomaly (TOPFA) in the last 2 decades.<sup>[13,14]</sup> Second, some studies have shown that prenatal folic acid and other multivitamin supplementation significantly decreased the birth prevalence of some congenital malformations.<sup>[15,16]</sup> We hypothesized that the above factors have altered prevalence of CA in the CHD population. The purpose of

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our study was therefore to provide up-to-date estimates of the current association between CHD and CA.

## MATERIALS AND METHODS

All data was derived from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality.<sup>[17]</sup> NIS is an all-payer administrative database reporting clinical and resource use hospitalization information. We chose the NIS database instead of other databases such as the Kids' Inpatient Database (KID) because NIS is the largest inpatient care database in the United States; containing approximately 8 million hospital stays each year from about 1,000 hospitals sampled to approximate a 20% stratified sample of the United States community hospitals. NIS large sample size makes it ideal for analysis of rare conditions such as specific congenital malformations. Approval for this study was obtained from both HCUP and institutional review board.

We reviewed all birth entries in the NIS database from January 1998 to December 2008 and identified all live births with CHD during birth hospitalization (case group) using CHD International Classification of Diseases (ICD)-9 codes. We also identified all live-births without CHD during the same period (control group). Twenty-three CA diagnoses and 10 CHD diagnoses were selected for analysis. We compared the prevalence of these 23 selected CA diagnoses in the case and control group. Longitudinal analysis was performed to determine temporal variation of CA prevalence in the CHD population during the study period.

We only included diagnoses made either clinically during birth hospitalization or by autopsy for live births that died during birth hospitalization. In order to avoid double counting, we restricted our inclusion criteria to diagnoses made during birth hospitalization. We ensured this by including only hospitalizations with ICD-9 code for normal and complicated delivery (650.0-669.0); hence, excluding diagnoses made during inter-hospital transfer or readmission hospitalization. In patients with multiple congenital malformations, each malformation was counted separately. We grouped all CA into different organ-systems. Based on the classification system used by Christensen *et al.*,<sup>[18]</sup> we defined multiple organ system involvement as live births with non-cardiac CA involving two or more organ-systems.

Data weighting was performed with Statistical Analytical Software (SAS) in accordance with HCUP recommendations.<sup>[19]</sup> The NIS has undergone some changes over time in terms of sampling strategy, weighting strategy, and data element available. We adjusted for these changes in accordance with the

recommendations in NIS Trend Supplemental files.<sup>[19]</sup> As per HCUP data use agreement prohibiting reporting of cell size  $\leq 10$ , CHD diagnoses with cell size  $\leq 10$  were either grouped together or excluded from analysis. We used MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium) to estimate odds ratio (OR) and 95% confidence interval (CI) in order to assess strength of association of CA diagnosed in the case group relative to the control group. Time trend analysis was performed using chi-square test based on a 12-month moving average of CA prevalence calculated by dividing the number of entries of CA diagnoses in the CHD population (case group) by the total number of subjects in the case group for each 12-month period. The moving average gives a rate for all 12-month periods, thereby removing the restriction of calendar years. *P*-value of  $<0.05$  was set as the cutoff for statistical significance.

## RESULTS

Our cohort consisted of 97,154 and 12,078,482 subjects in the case and control groups, respectively. In the CHD population (case), prevalence of non-syndromic congenital anomaly (NSCA), GS, and overall extra-cardiac congenital anomaly (CA) were 11.4, 2.2, and 13.6%, respectively. In the control group, prevalence of NSCA, GS, and CA were 6.7, 0.3, and 7.0%, respectively. NSCA (OR: 1.88, CI: 1.73-1.94), GS (OR 2.52, CI 2.44-2.61), and overall CA (OR: 2.01, CI: 1.97-2.14) were strongly associated with CHD [Table 1].

When we analyzed specific CA diagnosis, our study showed that laryngo-tracheal anomaly was associated with ventricular septal defect (VSD;OR 1.9; CI 1.2-2.7), endocardial cushion defect(ECD;OR 1.9, CI 1.5-2.4), double outlet right ventricle/tetralogy of fallot (DORV/TOF; OR 2.9, CI 1.9-3.7), and pulmonary atresia (OR 1.4, CI 1.1-2.9). Hypospadias/epispadias was associated with VSD (OR 2.1, CI 1.8-2.3) and pulmonic stenosis (OR 2.6; CI 1.8-3.3). Renal dysplasia was associated

**Table 1: Prevalence of congenital anomalies in CHD population**

Congenital anomaly groups	Case	Control	OR (CI)
Total non-cardiac CA	13,213 (13.6%)	845,494 (7.0%)	2.01 (1.97-2.14)
Genetic syndromes	2,137 (2.2%)	36,235 (0.3%)	2.52 (2.44-2.61)
NSCA	11,075 (11.4%)	809,258 (6.7%)	1.88 (1.73-1.94)
Multiple organ-system CA	2,332 (2.4%)	48,314 (0.4%)	1.39 (1.14-1.60)

OR (CI): Odds ratio (95% confidence interval), CA: Congenital anomaly, multiple organ-systems, CA: Extra-cardiac anomalies involving  $\geq 2$  organ-systems, NSCA: Non-syndromic CA, GS: Genetic syndrome, MCA: Multiple congenital anomalies (extra-cardiac anomalies involving  $\geq 2$  organ systems)

with DORV/TOF (OR 1.9, CI 1.7-2.1) and pulmonic stenosis (OR 1.6, CI 1.1-2.0). Heterotaxy/situs inversus is associated with ECD (OR 1.9, CI 1.7-2.1), truncus arteriosus (OR 2.1, CI 1.8-2.3), and DORV/TOF (OR 2.1, CI 1.8-2.3). GSs were strongly associated with most CHD diagnoses [Tables 2 and 3].

Figure 1 shows relative distribution of syndromic and NSCA in our CHD population. Figure 2 shows time trend analysis of CA prevalence in the case group over the 11-year study period. Prevalence of GSs ( $P = 0.01$ ) and multiple congenital anomalies ( $P = 0.01$ ) decreased significantly over the study period.

## DISCUSSION

Published studies suggest association between CHD and certain extra-cardiac congenital anomalies.<sup>[4,5,11,12,20-25]</sup> Evidence in support of such association is stronger for syndromic malformations compared to non-syndromic malformations.<sup>[2,11,20,25]</sup> Although there are several studies that have looked at association between certain CHD diagnoses and selected extra-cardiac CA, there is paucity of population-based studies focusing on comprehensive evaluation of association between all major CHD and all major extra-cardiac CAs. Part of the reason for this is because of the low prevalence of some CAs making

**Table 2: Prevalence of anomalies in CHD population**

Congenital anomalies	ASD	VSD	ECD	Ebstein anomaly	Tricuspid atresia	TAPVR/PAPVR	d-TGA	Truncus arteriosus
Anencephaly	31	38	11	#	13	#	11	13
Encephalocele	1.2 (0.9-1.3)	1.4 (0.9-1.5)			1.1 (0.9-1.3)		1.4 (0.7-1.6)	1.1 (0.8-1.3)
Microcephaly	22	29	15	13	#	11	16	12
	1.1 (0.9-1.3)	1.1 (0.8-1.3)	0.9 (0.7-1.1)	1.1 (0.8-1.3)		1.1 (0.8-1.3)	1.1 (0.8-1.3)	0.9 (0.7-1.1)
Spinal bifida/NTD	26	41	12	14	13	#	11	14
	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	1.1 (0.9-1.3)	0.9 (0.7-1.1)		1.2 (0.9-1.3)	1.0 (0.8-1.3)
Cleft lip	36	71	38	14	19	12	19	12
+/-cleft palate	1.1 (0.8-1.4)	0.9 (0.6-1.5)	1.4 (0.9-1.5)	1.3 (0.9-1.8)	1.1 (0.9-1.3)	0.9 (0.7-1.1)	1.5 (0.6-2.1)	1.0 (0.8-1.3)
Ear anomaly NOS	18	17	14	13	11	#	#	#
	1.1 (0.9-1.3)	1.1 (0.8-2.3)	1.1 (0.8-1.3)	1.1 (0.8-1.3)	1.1 (0.8-1.3)			
Choanal atresia	28	32	#	#	#	#	#	12
	0.9 (0.8-1.1)	0.7 (0.6-1.9)						1.0 (0.8-1.3)
Laryngotracheal	26	97	23	18	#	#	13	12
	1.1 (0.9-1.3)	1.9 (1.2-2.7)*	1.9 (1.5-2.4)	1.1 (0.8-1.3)			1.1 (0.8-1.3)	1.2 (0.9-1.3)
TEF/esophageal anomaly	16	24	18	16	13	#	#	16
	1.5 (0.6-2.2)	1.1 (0.9-1.3)	1.1 (0.8-1.3)	1.2 (0.9-1.5)	1.1 (0.9-1.3)			1.1 (0.9-1.3)
Meckel's diverticulum	18	27	#	#	#	#	#	#
	1.1 (0.9-1.3)	1.1 (0.8-1.3)						
Intestinal atresia	11	22	15	#	13	#	#	11
	1.7 (0.5-4.9)	1.1 (0.9-1.3)	3.1 (0.8-5.3)		1.1 (0.9-1.3)			2.1 (0.9-3.3)
Hirschsprung's dx	12	18	11	#	#	#	#	11
	0.8 (0.6-0.9)	1.1 (0.8-1.3)	1.1 (0.9-1.3)					1.1 (0.8-1.3)
Hepatobiliary dx	13	26	16	#	13	#	11	#
	1.0 (0.8-1.1)	1.1 (0.9-1.3)	1.1 (0.9-1.3)		1.1 (0.8-1.3)		1.1 (0.8-1.3)	
Polycystic kidney	13	18	11	#	13	#	#	13
	1.2 (0.9-1.3)	1.4 (0.9-1.5)			1.1 (0.9-1.3)			1.1 (0.8-1.3)
Renal dysplasia	16	29	18	11	#	12	13	12
	1.1 (0.8-1.4)	0.9 (0.6-1.5)	1.4 (0.9-1.5)	1.3 (0.9-1.8)		0.9 (0.7-1.1)	1.8 (0.6-2.1)	2.0 (1.8-2.3)*
Hypospadias/Epispadias	14	17	12	#	#	#	#	#
	1.1 (0.9-1.3)	2.1 (1.8-2.3)*	1.1 (0.8-1.3)					
Hip dislocation	31	38	11	#	13	#	11	13
	1.2 (0.9-1.3)	1.4 (0.9-1.5)			1.1 (0.9-1.3)		1.4 (0.7-1.6)	1.1 (0.8-1.3)
Heterotaxy/Situs inversus	22	29	15	13	#	11	11	14
	1.1 (0.9-1.3)	1.1 (0.8-1.3)	1.9 (1.7-2.1)	1.1 (0.8-1.3)		1.1 (0.8-1.3)	1.1 (0.8-1.3)	1.9 (1.7-2.1)
Down	46	141	62	34	31	#	33	24
	0.9 (0.8-1.1)	1.5 (1.1-1.9)*	2.9 (2.7-1.1)	1.1 (0.9-1.3)	0.9 (0.7-1.1)		1.2 (0.9-1.3)	2.0 (1.8-2.3)*
Patau	16	31	38	14	29	12	19	12
	1.1 (0.8-1.4)	1.7 (1.6-1.9)*	1.4 (1.3-1.5)*	1.5 (1.1-1.8)	1.1 (0.9-1.3)	0.9 (0.7-1.1)	1.8 (1.6-2.1)	2.0 (1.8-2.3)*
Edward	13	17	14	#	11	#	#	#
	1.4 (1.1-1.7)*	2.1 (1.8-2.3)*	6.1 (5.8-6.3)		1.1 (0.8-1.3)			
DGS/VCF	18	22	11	#	13	#	#	12
	1.6 (0.8-1.9)	1.7 (1.6-1.9)	2.4 (1.7-2.6)		0.7 (0.6-1.9)			2.0 (1.8-2.3)
Turner	11	27	13	12	24	18	19	12
	1.1 (0.9-1.3)	1.9 (1.2-2.7)*	0.9 (0.5-1.4)	1.1 (0.8-1.3)	1.6 (1.2-2.3)*	1.1 (0.8-1.3)	1.1 (0.8-1.3)	1.2 (0.9-1.3)
Noonan	16	29	18	#	#	12	13	#
	1.7 (1.3-2.4)	0.9 (0.6-1.5)	1.4 (0.9-1.5)			0.9 (0.7-1.1)	1.8 (0.6-2.1)	

NTD: Neural tube defect, DGS/VCF: DiGeorge syndrome/velocardiofacial syndrome, VSD: Ventricular septal defect, ASD: Atrial septal defect, TAPVR: Total anomalous pulmonary venous return, PAPVR: Partial anomalous pulmonary venous return, d-TGA: Complete transposition of great arteries, TEF: Tracheoesophageal fistula, NOS: Not otherwise specified, ECD: Endocardial cushion defect

**Table 3: Prevalence of anomalies in CHD population**

<b>Congenital anomalies</b>	<b>DORV/TOF</b>	<b>Pulmonic stenosis</b>	<b>Pulmonic atresia</b>	<b>COA/IAA</b>	<b>Aortic stenosis</b>	<b>HLHS</b>	<b>Others</b>
Anencephaly	19	27	#	#	13	#	11
Encephalocele	1.3 (0.8-1.3)	1.2 (0.9-1.3)			1.1 (0.9-1.3)		
Microcephaly	15	19	#	13	#	11	16
Spinal bifida/NTD	1.2 (0.7-1.8)	1.1 (0.8-1.3)		1.1 (0.8-1.3)		1.1 (0.8-1.3)	
	16	38	12	14	13	#	21
Cleft lip	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	1.1 (0.9-1.3)	0.9 (0.7-1.1)		
+/-Cleft palate	36	71	38	14	19	12	19
Ear anomaly	1.1 (0.8-1.4)	0.9 (0.6-1.5)	1.4 (0.9-1.5)	1.3 (0.9-1.8)	1.1 (0.9-1.3)	0.9 (0.7-1.1)	
	14	21	11	13	11	#	#
Choanal atresia	1.1 (0.9-1.3)	1.1 (0.8-2.3)	1.4 (0.8-1.9)	1.1 (0.8-1.3)	1.1 (0.8-1.3)		
	28	32	#	#	#	#	12
Laryngotracheal	0.9 (0.8-1.1)	0.7 (0.6-1.9)					
	36	66	18	18	#	#	27
TEF/esophageal anomaly	2.9 (1.9-3.7)*	1.9 (1.5-2.3)*	1.4 (1.1-2.0)*	1.1 (0.8-1.3)			
	13	21	12	14	13	#	#
Meckel's diverticulum	0.9 (0.5-1.3)	1.1 (0.9-1.3)	1.1 (0.8-1.3)	1.2 (0.9-1.5)	1.1 (0.9-1.3)		
	18	27	#	#	#	#	#
Intestinal atresia	1.1 (0.9-1.3)	1.1 (0.8-1.3)					
	15	19	#	11	13	#	#
Hirschsprung's dx	1.2 (0.7-1.8)	1.1 (0.8-1.3)		1.1 (0.8-1.3)	1.1 (0.9-1.3)		
	16	14	11	#	#	#	#
Hepatobiliary dx	0.8 (0.6-0.9)	1.1 (0.8-1.3)	1.1 (0.9-1.3)				
	11	22	16	#	13	#	11
Polycystic kidney	1.0 (0.8-1.1)	1.1 (0.9-1.3)	1.1 (0.9-1.3)		1.1 (0.8-1.3)		
	13	18	11	#	13	#	#
Renal dysplasia	1.2 (0.9-1.3)	1.4 (0.9-1.5)	1.1 (0.8-1.3)		1.1 (0.9-1.3)		
	15	26	14	11	#	12	34
Hypospadias/epispadias	1.9 (1.7-2.1)	1.6 (1.1-2.0)	1.4 (0.9-1.5)	1.3 (0.9-1.8)		0.9 (0.7-1.1)	
	14	17	12	#	#	#	#
Hip dislocation	1.1 (0.9-1.3)	2.1 (1.8-2.3)*	1.1 (0.8-1.3)				
	31	38	11	#	13	#	11
Heterotaxy/situs inversus	1.2 (0.9-1.3)	1.4 (0.9-1.5)	1.1 (0.8-1.3)		1.1 (0.9-1.3)		
	18	22	#	#	#	#	#
Down	2.1 (1.9-2.3)*	1.1 (0.8-1.3)					
	33	43	22	14	23	#	13
Patau	2.9 (1.7-4.1)*	1.5 (1.1-1.9)*	2.9 (2.7-1.1)	1.1 (0.9-1.3)	0.9 (0.7-1.1)		
	12	21	#	#	#	#	#
Edward	1.9 (1.2-2.4)*	1.7 (1.6-1.9)*					
	17	17	11	#	#	#	#
DGS/VCF	1.4 (1.1-1.7)*	2.1 (1.8-2.3)*	2.1 (1.8-2.3)				
	15	22	13	#	13	#	#
Turner	1.6 (0.8-1.9)	1.1 (0.8-1.3)	2.4 (1.7-2.6)		0.7 (0.6-1.9)		
	11	27	13	12	24	18	#
Noonan	1.1 (0.9-1.3)	1.9 (1.2-2.7)*	0.9 (0.5-1.4)	1.8 (1.1-1.9)	1.6 (1.2-2.3)*	1.1 (0.8-1.3)	
	16	24	18	#	12	#	#
	1.7 (1.3-2.4)	1.4 (1.1-1.8)	1.4 (0.9-1.5)		0.9 (0.7-1.1)		

NTD: Neural tube defect, DGS/VCF: DiGeorge syndrome/velocardiofacial syndrome, DORV: Double outlet right ventricle, TOF: Tetralogy of fallot, IAA: Interrupted aortic arch, COA: Coarctation of aorta, HLHS: Hypoplastic left heart syndrome, others: Cor triatriatum, L-TGA, mitral stenosis, TEF: Tracheoesophageal fistula

it very difficult to obtain sample population powered enough to analyze such associations. The purpose of our study was therefore to perform a comprehensive analysis of association of all major CA based on a large representative sample population powered to detect any significant difference.

Our data showed that newborns with CHD frequently have associated extra-cardiac CA. This association is true for both syndromic malformation (OR 2.52, CI 2.44-2.61) and NSCA (OR: 1.88, CI: 1.73-1.98). Craniofacial, respiratory, and genitourinary malformations were associated with CHD in our cohort. Situs inversus was also associated with CHD diagnosis specifically

with endocardial cushion defect and pulmonary valve disease. Our results were consistent with prior studies,<sup>[4,5,12,25,26]</sup> which showed similar associations. However, contrary to some published data,<sup>[22-24]</sup> we did not find any association between CHD diagnosis and gastrointestinal and limb anomalies. The reason for this discrepant finding is not apparent. It is possible that certain gastrointestinal abnormalities like malrotation and biliary atresia may be diagnosed later and not at the birth admission. However, we believe that our result is more applicable to the general population because our estimates were based on large representative population.

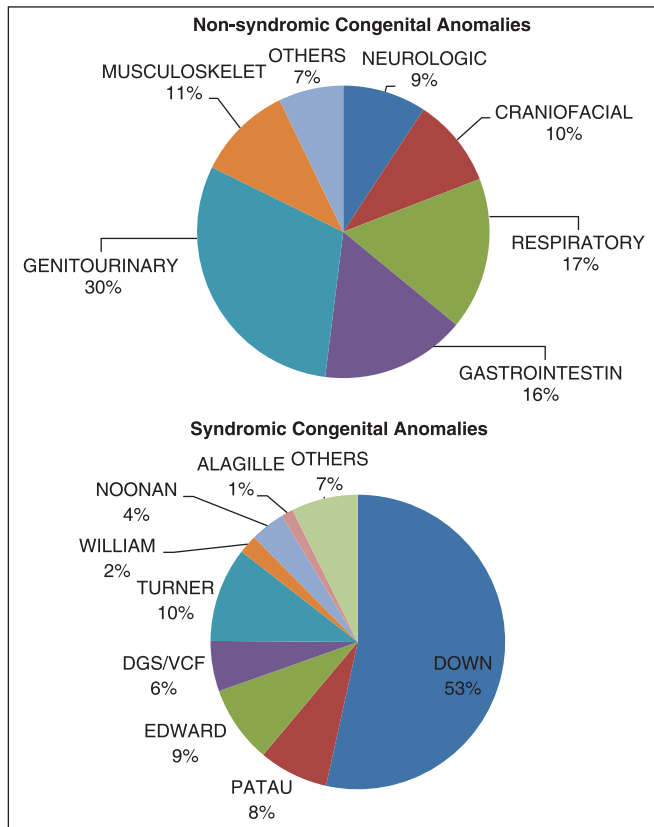


Figure 1: Distribution of congenital anomalies

Consistent with prior studies,<sup>[4,5,11]</sup> GSs were strongly associated with CHD diagnoses and this association was most significant with septal defects, endocardial cushion defect, pulmonary valve disease, tricuspid valve disease, aortic valve disease, truncus arteriosus, and aortic arch anomalies. This finding may be as a result of common underlying etiology because CHD is a known phenotypic manifestation of most of the GSs included in our study.

Although prevalence of extra-cardiac CA did not change in the CHD population, prevalence of GSs and multiple organ-system CA decreased significantly during the study period. We believe that this change could be as a result of modification of prenatal factors such as TOPFA and prenatal vitamin supplementation. However, our study was not designed to establish direct causality.

This study has some limitations. It is a retrospective review of entries from a de-identified administrative database. Second, there is always the risk of ‘double counting’ when using data from a de-identified database. We circumvented this problem by including only cases of diagnosed made during the birth hospitalization. Our study population comprised of neonates only, and as a result we could have missed diagnoses that presented after birth hospitalization. However, since we used the same inclusion criteria (diagnosis during birth hospitalization) for our case and control group and as a result; any underestimation caused by our restrictive

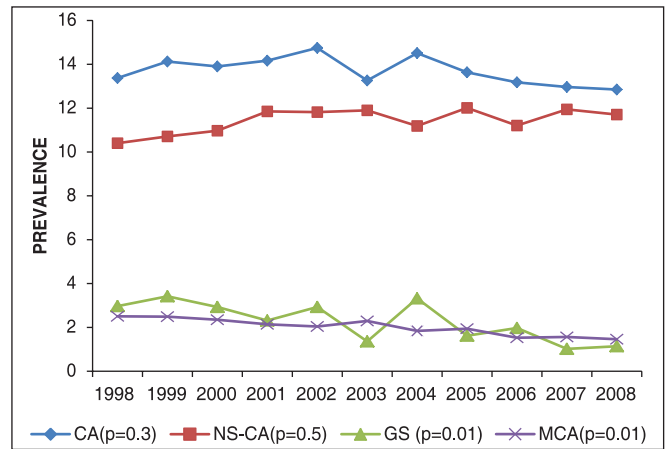


Figure 2: Time trend analysis of congenital anomalies prevalence

inclusion criteria should not affect our measure of association.

## CONCLUSION

This is the largest and most comprehensive population-based study evaluating association between CHD and CA in newborns. Our data also showed significant decrease in prevalence of syndromic malformations and multiple organ-system CA in the CHD population, while prevalence of overall extra-cardiac CA remained unchanged.

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