

# Descriptive Study of the Different Phenotypes of Congenital Heart Disease in a Cohort of Egyptian Patients Diagnosed with Down Syndrome

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## Abstract

**Background:** Approximately half of all Down syndrome (DS) infants have a congenital heart defect (CHD), including atrioventricular septal defects (AVSD), atrial septal defect (ASD), ventricular septal defect (VSD) and tetralogy of Fallot (ToF).

**Aim of Study:** The study aimed to determine the prevalence, cardiovascular phenotypes, and gender differences in CHD associated with DS in Alexandria, Egypt.

**Patients and Methods:** The present study is a retrospective descriptive single-centre study included 722 DS patients attending the Human Genetics clinic, Medical Research Institute, Alexandria University. Data were retrieved from the medical files of DS patients.

**Results:** CHD was present in 59% of DS patients. The most common were ASD (42.3%) and AVSD (25.1%). CHDs were more frequent in females, including total CHDs ( $p=0.03$ , OR: 1.393), ASD ( $p=0.043$ , OR: 1.417), AVSD ( $p=0.034$ , OR: 1.56), and severe CHDs ( $p=0.024$ , OR: 1.544).

**Conclusion:** CHDs are more prevalent in female DS patients. Gender differences may imply a role of sex in the association between CHD and DS.

**Key Words:** Congenital heart defects – Down syndrome – Prevalence – Gender.

## Introduction

DOWN syndrome (DS) is the most common autosomal anomaly in live born infants with a worldwide incidence ranging from 1-1.6 per 1000 live births [1,2]. In Egypt, the incidence is 1 in 600 live births [3]. About 60% of DS patients have congenital anomalies, the most prevalent being cardiac defects and digestive system malformations [4]. In the Arab

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region, the frequency of CHDs is high and ranges from 36% to 86.8% [5,6]. This contributes significantly to mortality and morbidity, increasing health care cost and neurodevelopmental delay [7]. In a study on predictors of survival in children with DS, the presence of CHDs was found to significantly increase the risk of mortality [8]. Echocardiography is an integral part of the evaluation of DS infants to allow for proper management with the ultimate goal of reducing mortality. The most common CHDs observed in DS patients include AVSD, ASD and VSD [4,5]. Due to the paucity of data regarding CHDs in DS patients in Egypt, the study was conducted with the aim of identifying the prevalence, cardiovascular phenotypes and gender differences in CHD associated with DS in Alexandria, Egypt.

## Patients and Methods

### Studied group:

Seven hundred and twenty-two DS patients attending the Human Genetics clinic, Medical Research Institute, Alexandria University, from January 2016 to December 2022 were included in

### Abbreviations:

ASD : Atrial septal defect.  
AVSD : Atrioventricular septal defect.  
CHD : Congenital heart defects.  
DORV : Double outlet right ventricle.  
DS : Down syndrome.  
OR : Odds ratio.  
PDA : Patent ductus arteriosus.  
PFO : Patent foramen ovale.  
PS : Pulmonary stenosis.  
ToF : Tetralogy of Fallot.  
VSD : Ventricular septal defect.

the study. We are the main referral center for diagnosing DS patients living in Alexandria and El Beheira Governorates (approximately 1/10 of the Egyptian population).

*Study design:*

This is a retrospective descriptive single-centre study. We retrieved data from the medical files of DS patients including age and sex of the DS patients, parental ages, consanguinity, karyotypes, and echocardiographic findings (The type of congenital heart disease whether simple or complex one). In the group of DS patients with CHDs, we recorded specific heart defects, including AVSD, ASD, patent ductus arteriosus (PDA), patent foramen ovale (PFO), VSD, tetralogy of Fallot (ToF), and others (valve anomalies, Ebstein anomaly, dextrocardia, and double outlet right ventricle). We used the EUROCAT classification to identify patients with severe CHDs [9].

*Statistical analysis:*

This study analyzed data using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution of variables. The number of cases with CHD among DS patients was calculated for males and females. Comparisons between groups for categorical variables were assessed using the Chi-square test. Odds ratio between males and females with *p*-values and 95% confidence interval were calculated.

**Results**

The study included 722 DS; 93.6% were standard trisomy, 4.7% carried a Robertsonian translocation, and 1.7% were mosaics (Table 1). The age ranged from 2 days to 18 years. The male/female ratio was 1.2. A CHD was present in 426 cases representing 59% of the total. A single heart defect was present in 71.4% of patients with a CHD. The characteristics of the studied group are presented in Table (2).

Table (1): Distribution of the DS patients according to Karyotype (n=722).

	No. (%)
<i>Karyotype:</i>	
ROB	34 (4.7%)
<i>Non ROB:</i>	688 (95.3%)
Standard trisomy	676 (93.6%)
Mosaics	12 (1.7%)

ROB = Robertsonian translocation/Non.  
ROB = Non Robertsonian translocation.

Table (2): Demographic data of Down syndrome.

	No. (%)
<i>Age/months:</i>	
<12	608 (84.2%)
≥ 12	114 (15.8%)
Median (Min. - Max.)	2.5 (0.07-216.0)
Mean ± SD	8.94±19.61
<i>Sex:</i>	
Male	392(54.3%)
Female	330 (45.7%)
<i>Maternal Age:</i>	
<20	28 (3.9%)
20 < 25	123 (17.0%)
25 < 30	135 (18.7%)
30 < 35	139 (19.3%)
35 < 40	161 (22.3%)
≥40	136 (18.8%)
<i>Consanguinity:</i>	
Non-consanguineous	573 (79.4%)
1st Cousins and distant	149 (20.6%)

A total of 573 CHDs were present in 426 DS patients; ASD (42.3%), AVSD (25.1%), PDA (18.8%), PFO (16.7%), and VSD (11.3%). ToF was present in 11 DS patients (2.6%). Table (3).

Table (3): Congenital heart defects in Down syndrome patients.

CHD	No. (%)
ASD	180 (42.3%)
AVSD	107 (25.1%)
PDA	80 (18.8%)
PFO	71 (16.7%)
VSD	48 (11.3%)
Mitral valve anomalies	34 (8%)
Tricuspid valve anomalies	29 (6.8%)
ToF	11 (2.6%)
PS	7 (1.6%)
Aortic valve anomalies	3 (0.7%)
Ebstein Anomaly	1 (0.2%)
DORV	1 (0.2%)
Dextrocardia	1 (0.2%)
<b>Total</b>	<b>573</b>

ASD : Atrial septal defect.  
AVSD : Atrioventricular septal defect.  
PDA : Patent ductus arteriosus.  
PFO : Patent foramen ovale.  
VSD : Ventricular septal defect.  
ToF : Tetralogy of Fallot.  
PS : Pulmonary stenosis.  
DORV : Double outlet right ventricle.

Pulmonary hypertension was present in 30 DS (7.3%); 18 had AVSD, and 12 had an ASD or VSD.

We observed a higher frequency of CHDs in female DS. The gender difference was significant

for total CHDs ( $p=0.03$ , OR: 1.393), ASD ( $p=0.043$ , OR: 1.417), AVSD ( $p=0.034$ , OR: 1.56), and severe

CHDs ( $p=0.024$ , OR: 1.544). We found no gender difference for VSD or ToF. Table (4).

Table (4): Congenital heart defects in Down syndrome according to sex.

	Total (n=722)	Sex		$\xi^2$	$p$	OR	95% CI	
		Male (n=392)	Female (n=330)				LL	UL
Total CHD	426 (59.0%)	217 (55.4%)	209 (63.3%)	4.712*	0.030*	1.393	1.032	1.880
ASD	180 (24.9%)	86 (21.9%)	94 (28.5%)	4.102*	0.043*	1.417	1.011	1.988
AVSD	107 (14.8%)	48 (12.2%)	59 (17.9%)	4.505*	0.034*	1.560	1.032	2.358
VSD	48 (6.6%)	25 (6.4%)	23 (7.0%)	0.101	0.750	1.100	0.612	1.977
ToF	11 (1.5%)	7 (1.8%)	4 (1.2%)	0.393	0.531	0.675	0.196	2.326
Severe CHD	132 (18.3%)	60 (15.3%)	72 (21.8%)	5.086*	0.024*	1.544	1.057	2.256

$\xi^2$  : Chi square test.

LL: Lower limit.

$p$ :  $p$ -value for comparing between the studied groups.

OR: Odds ratio.

UL: Upper Limit.

\*: Statistically significant at  $p!0.05$ .

CI : Confidence interval.

There was no evidence of maternal age effect nor consanguinity in the association of CHD and DS ( $p>0.1$ ,  $p>0.7$  respectively). (Table 5).

Table (5): Relation between CHD with consanguinity and maternal age.

	CHD		$\xi^2$	$p$
	Normal (n=296)	Abnormal (n=426)		
<b>Consanguinity:</b>				
Negative	233 (78.7%)	340 (79.8%)	0.128	0.720
Positive (1st C and distant)	63 (21.3%)	86 (20.2%)		
<b>Maternal age:</b>				
<35	183 (61.8%)	242 (56.8%)	1.815	0.178
>35	113 (38.2%)	184 (43.2%)		

$\xi^2$  : Chi square test.

$p$  :  $p$ -value for comparing between the studied groups.

### Discussion

CHD is the leading cause of morbidity and early mortality in patients diagnosed with DS. In the present study, 59% of DS had a CHD. Previous Egyptian studies have reported lower values ranging from 36.9% to 40% [4,5,10]. Seasonal variation in the occurrence of birth defects in DS patients has been reported [11]. However, due to lack of data, this could not be evaluated in the present study. Although the frequency of CHDs in DS is higher in the current study compared to previous Egyptian studies, yet it is in agreement with studies from Lebanon (54.2%), Saudi Arabia (58.6%), Iraq (53%), Norway (58%), and Mexico (58%) [12-16].

We observed isolated CHDs in 71.4% of DS patients with a CHD, in agreement with studies from Algeria (68%) and Libya (65%) [17,18].

Geographical differences in the pattern of CHDs in DS have been reported; AVSD is more common in Western countries [14,19]. VSD is prevalent in Asia [20,21]. Whereas, ASD is more common in Latin America [22]. In the present study, ASD was the most common anomaly encountered. In Egypt, ASD, VSD, and AVSD were reported to be the most prevalent CHD in 3 different studies [4,5,10]. In the Arab region, in agreement with the present study, ASD was reported to be the most prevalent CHD in studies from Libya and Oman [18,23]. Our observation disagrees with studies from Saudi Arabia, Algeria, and Morocco, reporting AVSD was the most prevalent CHD in their DS patients, [16,17,24] and a research from Iraq where VSD was the most common CHD among Iraqi DS patients [13]. The variability in the prevalence of specific cardiac phenotypes in DS has been attributed to differences in population characteristics, time period, availability of prenatal care, and pregnancy termination [25].

As trisomy 21 is insufficient to cause CHD, factors contributing to the association of CHD and DS are currently being investigated. One proposed contributing factor recently addressed is gender [26,27]. In agreement with studies from Libya, we observed a higher frequency of CHD in the female gender ( $p=0.03$ , OR: 1.393, IC: 1.032 to 1.880), implying that this gender is more susceptible to CHD in DS patients. In the present study, AVSD and ASD were more prevalent in females. These results are in accordance with previous studies [26-28]. We did not observe a sex difference in the prevalence of VSD in agreement with a meta-analysis including 12 publications [26]. Severe CHD was significantly higher in female DS in accordance with previous studies [27,29]. The mechanism by which gender contributes to the associa-

tion of CHD and DS remains to be elucidated. One proposed explanation is that gender differences may reflect a different susceptibility of gender to different CHD pathogenetic pathways; AVSD and ASD prevalent in females are an extracellular matrix anomaly whereas ToF more common in males is an ecto-mesenchymal tissue migration anomaly [26].

The effect of maternal age on the association of CHD and DS is unclear; some studies reported a greater risk for CHDs in young mothers, [12,30] whereas others observed no maternal age effect [27,28]. We did not find any association between maternal age and the CHDs in our cohort of DS patients.

We observed no effect of consanguineous mating on the occurrence of CHDs in DS in disagreement with the previous Egyptian Studies [4,5]. The low frequency of consanguineous mating in urban compared to rural areas, and the decline of consanguineous mating during the past decades may be possible explanations.

A clear limitation is the retrospective nature of the study. However the study provides data on a large cohort of DS patients with CHDs.

#### Conclusion:

In conclusion, the study revealed that 59% of our DS cohort had a CHD. In DS patients with CHDs, females are approximately 1.5 times more at risk for ASD, AVSD, and severe CHDs. Gender differences may imply a role of sex in the association between DS and CHD. No relation between maternal age and CHDs in this cohort.

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## عيوب القلب الخلقية لدى مرضى متلازمة داون في الإسكندرية، مصر الانتشار والأنماط الظاهرية والاختلافات بين الجنسين

يعانى ما يقرب من نصف الأطفال من متلازمة داون من عيب خلقى فى القلب، بما فى ذلك عيوب الحاجز الأذينى البطينى، وعيوب الحاجز الأذينى، وعيوب الحاجز البطينى ورباعية فالوت وكان الهدف من الدراسة تحديد مدى انتشار الأنماط الظاهرية للقلب والأوعية الدموية والاختلافات بين الجنسين فى أمراض الشرايين التاجية المرتبطة بالمتلازمة داون فى الإسكندرية، مصر.

المرضى والأساليب: وشملت الدراسة ٧٢٢ مريضاً فى عيادة الطب الوراثى، معهد البحوث الطبية، جامعة الإسكندرية، فى الفترة من يناير ٢٠١٦ إلى ديسمبر ٢٠٢٢. وتم استرجاع البيانات من الملفات الطبية لمرضى متلازمة داون وذلك لتحديد المرضى الذين يعانون من عيوب القلب الخلقية.

النتائج: تواجدت عيوب القلب الخلقية فى ٥٩٪ من مرضى متلازمة داون كان أكثرها شيوعاً هو عيب الحاجز الأذينى حيث تواجد فى ٤٢.٣٪ من الحالات يليها عيب الحاجز البطينى فى ٢٥.١٪ من الحالات. كما لوحظ أن عيوب القلب الخلقية أكثر شيوعاً عند الإناث.

الاستنتاجات: أمراض الشرايين التاجية أكثر انتشاراً فى النساء المصابات بالمتلازمة داون. قد تشير الفروق بين الجنسين إلى دور الجنس فى الارتباط بين عيوب القلب الخلقية ومتلازمة داون.