Review Article on Pediatric Heart

Gender differences in congenital heart defects: a narrative review

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Background and Objective: Congenital heart defects (CHD) represent the most frequent human birth defects, occurring in almost 1% of all live newborns. Understanding the effects of gender in the prevalence of CHD has a key role in defining personalized prevention, disease identification, prognosis definition and individualized therapeutic strategies. Recently, the attempt to achieve a holistic approach to patients with CHD cannot be separated from accounting for existing gender differences. The main aim of this narrative review is to provide an overview of gender differences in the epidemiology of CHD.

Methods: A standardized research through three electronic databases (PubMed/Scopus/Embase) was performed using a combination of keywords and Medical Subject Headings (MeSH) terms to include congenital heart diseases, gender difference(s), prevalence. Observational, prospective, population based and retrospective studies reporting gender differences in the prevalence of CHD were included. Conference abstracts were excluded as well as studies not written in English language and non-human studies. Further relevant papers were selected by hand-searching of the references list of selected articles.

Key Content and Findings: Search results returned 1,904 papers. Screening articles by title and abstracts resulted in 17 articles for full text review. Of these, 10 were included for analysis and additional 11 articles were included after hand searching review of reference lists. A total of 21 articles were included.

Conclusions: Our narrative review confirms that there is a significant gender variation in specific CHD subgroups. In particular, we summarized the evidence that there is a significantly greater risk for males to be born with severe CHD and for females with milder CHD subtypes. The etiology of the different distribution of CHD among genders is still under investigation and a deeper understanding of how gender influences the risk for CHD is warranted. In the future, a gender-based management of CHD should become an established medical approach.

Keywords: Congenital heart defect (CHD); gender; prevalence

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Introduction

Background

Congenital heart defects (CHD) represent the most frequent human birth defects, occurring in almost 1% of all live newborns and up to 10% of stillbirths globally (1). Moreover, if mild cardiac structural anomalies are included [i.e., bicuspid aortic valve (BAV) and septal defects] the cumulative prevalence of CHD in liveborn infants may be as high as ~5% (2).

In the last decades, the outstanding progress in the diagnostic tools and surgical strategies for CHD determined a substantial improvement of short-term and long-term survival, allowing a growing proportion of newborns with critical CHD reaching adulthood.

Moreover, the global improvement of personalized care and clinical research on CHD diagnosis and management has changed the landscape of adult patients with CHD.

Despite that, the morbidity burden of CHD is still high since the presence of these defects often leads to altered quality of life in terms of health-related complications, reduced exercise tolerance, higher risk of arrhythmias and endocarditis, neurodevelopmental impairment, pulmonary arterial hypertension and suboptimal kidney function (3).

The concept of "gender medicine" has first emerged in the late 1990s (4) and it refers to the study of how gender influences the complex interaction among biological, genetic, epigenetic, cultural, and environmental factors in defining several pathological entities (5).

Biological gender, also known as sex, refers to the classification of individuals as male or female based on their reproductive anatomy and physiology. It is determined by a combination of genetic, hormonal, and anatomical factors. The term "gender" in the following text refers to biological gender.

Currently, gender medicine has to be considered as a crucial step to achieve a personalized medicine and patient-centered care (6).

Understanding the effects of gender in pathophysiological processes has a key role in defining personalized prevention, disease identification, prognosis definition and individualized therapeutic strategies and, nowadays, the attempt to achieve a holistic approach to patients and diseases cannot be separated from applying gender difference.

Rationale and knowledge gap

Despite the growing evidence regarding gender differences for acquired heart diseases (coronary artery diseases and arrhythmias), the contribution of gender to pathophysiology and epidemiology of CHD to our knowledge has been poorly investigated.

Objective

The main objective of this narrative review is to provide the reader with an overview of gender differences in the epidemiology of CHD in order to improve the entire management of people born with CHD. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-260/rc).

Methods

This narrative review was performed through a standardized search of three electronic databases (Medline via PubMed; Scopus and Embase via Elsevier) using the following Medical Subject Headings (MeSH) terms: gender, difference(s), male, female, congenital heart defects, epidemiology, prevalence and their variable combinations.

Two researchers (Pugnaloni F, Felici A) in consensus assessed each investigation.

We decided to include observational, prospective, population based and retrospective studies reporting gender differences in the prevalence of isolated or syndromic CHD. We screened all available articles with at least an abstract.

Exclusion criteria were the following: no English language, conference abstracts or study setting different from included studies, non-human studies, no full text available.

Further relevant papers were later selected by hand-searching of the references list of chosen articles.

Two reviewers (Pugnaloni F, Felici A) independently analyzed the search results and developed a dedicated online data extraction sheet (Excel 16: Microsoft Corporation, Redmond, WA, USA).

Studies included in data extraction sheet were marked for inclusion or exclusion with exclusion reason based on the predefined criteria. Any disagreement about data extraction was resolved by discussion with a third review author (Putotto C) in order to resolve any disputes. The last update

Table 1 The search strategy summary

Items	Specification
Date of search	March 15th, 2023
Databases and other sources searched	Medline via PubMed, Embase via Elsevier, and Scopus via Elsevier
Search terms used	Gender, difference(s), male, female, congenital heart defects, epidemiology, prevalence and their variable combinations
Timeframe	Inception to March 15th, 2023
Inclusion and exclusion criteria	Inclusion criteria: observational, prospective, population based and retrospective studies reporting gender differences in CHD
	Exclusion criteria: no English language, conference abstracts, no human studies, no full text available on request
Selection process	Prior to initialize the search, a detailed protocol was agreed in order to determine search modalities, eligibility criteria, and methodological details. For reliability two reviewers (F Pugnaloni and A Felici) independently analyzed the search results. Studies were analyzed and marked for inclusion and exclusion criteria. Data from eligible studies were independently extracted by two authors (F Pugnaloni and A Felici) who developed a dedicated online data extraction sheet (Excel 16: Microsoft Corporation, Redmond, WA, USA)

CHD, congenital heart defects.

was performed on March 15th, 2023. The search strategies are available in *Table 1*.

Results

The initial search identified 1,904 potentially relevant papers: 945 papers were found via PubMed, 594 studies via Embase and 365 studies via Scopus. After removing duplicates, 1,885 papers were screened by title or abstract. Excluding papers not written in English, wrong study design/conference abstracts and irrelevant papers for the topic, 17 full-text studies were considered potentially eligible for inclusion.

After exclusion of seven studies, additional 11 papers were included by hand-searching review of references lists. The final number of articles included is 21.

The flow diagram of the study selection process is provided in *Figure 1*.

Changing incidence and prevalence of CHD

The incidence of CHD has been demonstrated to progressively rise over years, reaching current values of 10–14/1,000 live births (7-12).

A recent meta-analysis reported that worldwide birth prevalence in children <5 years of age increased from 0.6/1,000 live births in 1930 to 9.1/1,000 live births after 1995 (13) and that mild CHD, such as not hemodynamically significant atrial septal defects (ASDs) and patent ductus arteriosus (PDA), have substantially increased, while severe and critical CHD have shown a trend of decreasing incidence in recent decades.

This effect is the result of two parallel phenomena. On one hand, the great improvement in diagnostic and screening tools (i.e., color-Doppler echocardiography) enabled a significant increase in case detection, on the other hand the greater availability of prenatal diagnosis tests and voluntary abortion determined a significant reduction in the incidence of complex and critical CHD (8,13).

In the changing background of epidemiology of CHD, gender differences in worldwide prevalence have been previously recognized. From the literature reports, the cumulative prevalence of CHD is considerably higher in females both in adulthood and childhood (7,14,15).

This observation may be related to the fact that the relevant proportions of mild forms of CHD, which are growing over the years, are more preponderant in females (16).

Prevalence of specific CHD among genders

Biological differences between females and males include genetic and hormonal status differences that may contribute to different anatomical subtypes of CHD.

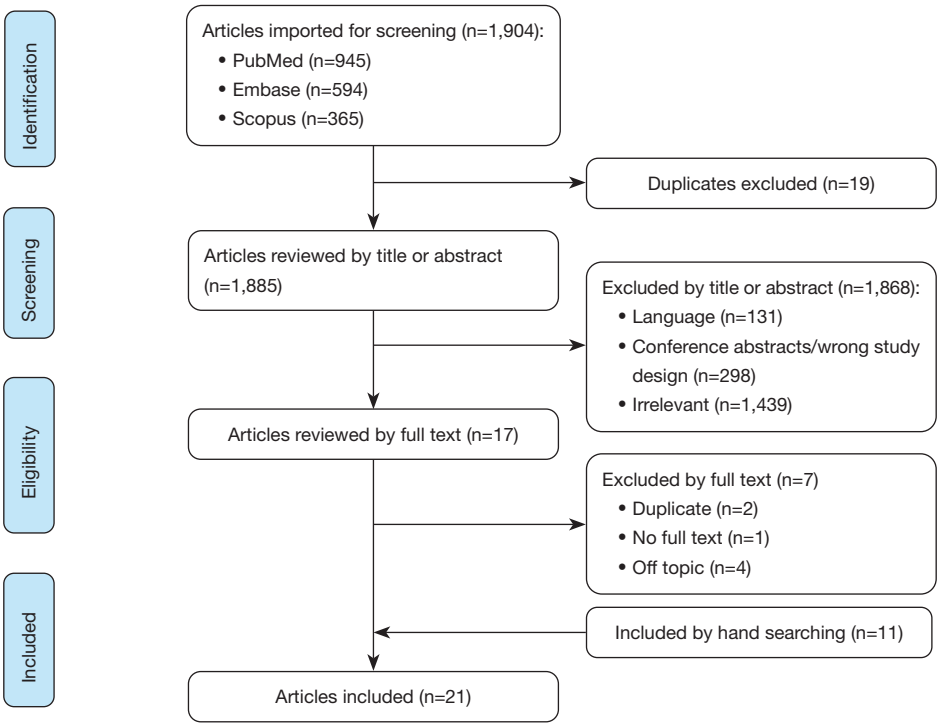

Figure 1 Flow diagram of study selection process.

Gender differences in specific CHD have been documented since 1970s, and these observations have been consistent over time. The first description of a gender-specific distribution of different CHD dates back to the late 1970s when national registries of congenital diseases, including CHD, became widespread. We included in our review epidemiologic studies based on data extracted from international, national, and regional registries. Those large healthcare databases provide precise CHD prevalence information, that can be generalizable to the entire population under analysis. The additional studies incorporated within the review primarily investigate the epidemiology of CHD with a specific emphasis on factors such as gender distribution and demographics of cohorts. Despite the limitations in sample size, these studies yield valuable data that contribute to our understanding of gender-related distribution of CHD and a summary of all the studies is shown in *Table 2*.

Left ventricular outflow tract obstruction (LVOTO)

A consistent association is observed between the presence of LVOTO and male sex. In a multicenter study by García *et al.* (22) involving 5,000 Colombian children with CHD, it was found that only 33.5% of patients with LVOTO were female. Similar findings were reported by Hoang *et al.* (26) in their analysis of data from the Pediatric Cardiac Genomics Consortium (PCGC) cohort, which included 8,693 patients. Among cases with LVOTO, approximately 65.8% were male. McBride *et al.* (29) conducted a study specifically focused on patients with non-complex LVOTO and demonstrated a male sex predisposition with respect to aortic valvular stenosis (AVS), coarctation of the aorta (CoAo), and hypoplastic left heart syndrome (HLHS).

Additionally, all included studies consistently establish a correlation between aortic stenosis (AS) and male sex. Egbe *et al.* (8) utilized data from the National Institutes of Health (NIH) (USA) national registry in 2008, focusing on live birth hospitalizations, and reported a fourfold higher prevalence of AS in males compared to females. Pradat *et al.* (27) conducted a study using a substantial case series derived from medical records in three countries (Sweden, France, and the USA) between 1981 and 1992, revealing an M:F ratio of 2.41 among AS patients. Similarly, Sokal *et al.* (24) observed nearly double the prevalence in males based on a sample of 794,169 infants, while Tennant *et al.* (20), analyzing healthcare records from the Northern Congenital Abnormality Survey (NorCAS) registry between

Table 2 Summary of included studies

Authors; study setting; population under analysis	CHD with male predominance	CHD with female predominance
Marelli *et al.*, 2007, (7); population with CHD, data extracted from Quebec administrative healthcare databases, 1985–2000, Quebec, Canada; n=45,960 (male to female PR)	Adults: TGA complex (1.67); CoAo (1.60)	Adults: shunt lesions ASD, VSD, PDA, and AVSD (0.69); all CHD (0.79); severe CHD (0.85)
	Childrens: CoAo (1.58); TGA complex (1.40)	Childrens: shunt lesions (0.80)
Egbe *et al.*, 2014, (8); live birth hospitalizations, data extracted from NIS database, January to December 2008, USA; n=1,204,887 (13,249 with CHD) (M:F ratio)	AS (4:1); TGA (4:1); left-sided lesions, combined (3:1); CoAo (2.3:1); HLHS (1.8:1); PA + VSD (1.5:1)	PS (0.6:1); ASD (0.7:1)
Yeh *et al.*, 2013, (15); CHD patients (age 0–18 y), data extracted from Taiwan NHI database, 2000–2010, Taiwan; n=45,119 (male to female PR)	TGA (1.8); AS (1.6); ToF (1.2); severe CHD (1.1)	PDA (0.6); ECD (0.7); ASD OS (0.8); simple CHD (0.8); total CHD (0.8); VSD (0.9)
Pfitzer *et al.*, 2017, (16); CHD patients requiring hospital care, data extracted from NRCHD registry, 1996–2015, Germany; n=15,703 (male to female PR)	AoV (2.3); TGA IVS (2.1); CoAo (1.5); common ventricle (1.4); ToF (1.2)	ASD (0.5); PDA (0.5); AVSD (0.8); Ebstein's anomaly (0.6)
Ferencz *et al.*, 1997, (17); infants with CHD (age <1 y), regional CHD screening program (Baltimore-Washington infants study), 1981–1989, USA; n=4,390 cases (3,572 controls) (% males)	AS (71.6%); TGA (66.1%)	PS (28.2%); ASD (34.7%); muscular VSD (42.7%)
Rothman *et al.*,1976, (18); children with CHD (age <1 y), July 1968–June 1974, multicenter CHD screening program (NERICP), New England, USA; n=2,336 (male %)	AS (78%); TGA (66%); HLHS (65%); CoAo (59%)	PDA (36%); AVSD (40%); complex VSD (40%)
Šamánek *et al.*, 1994, (19); live birth with CHD, January 1977–January 1984 regional CHD screening program, Bohemia, Czech Republic; n=4,409 (M:F ratio)	DORV (2.68:1); HLHS (2.25:1); TGA (2.11:1); AS (1.95:1); PA (1.55:1); TA (1.45:1); CoAo (1.30:1); functionally corrected TGA (1.25:1)	PDA (0.61:1); Ebstein's anomaly (0.64:1); truncus arteriosus (0.82:1); AVSD (0.85:1); ToF (0.89:1)
Tennant *et al.*, 2011, (20); foetus, stillbirth, and live birth, data extracted from NorCAS registry, 1985–2003, North of England; n=646,174 (12,795 with congenital anomalies) (male to female PR)	Single ventricle (2.84); aortic stenosis and atresia (2.50); TAPVR (2.13); other aortic/mitral valve anomalies (2.07); TGA (2.01); CoAo (1.68); ToF (1.28)	ASD (0.61); PS (0.80)
Lary *et al.*, 2001, (21); live birth, data extracted from MACDP registry, 1968–1995, Atlanta, USA; n=853,456 totals (28,965 with at least one major defect) (male to female PR)	AS (1.51); TGA (1.38); HLHS (1.34); TA and TS (1.16); other specified anomalies of aorta (2.76); total cardiovascular defects (1.07)	ASD OP (0.33); ASD OS (0.68)
García *et al.*, 2016, (22); children with CHD, multicenter CHD screening program, 2008–2013, Colombia; n=5,900 (female %)	LVOTO (33.5%)	PDA (63.6%)
Shaw *et al.*, 2003, (23); stillbirths and live birth, data extracted from CBDMP database, 1989–1997, California, USA; n=2,537,001 (50,962 with congenital malformations) (male to female PR)	TGA (1.6); common ventricle (1.4); CoAo (1.3); aortic valve insufficiency (1.3); HLHS (1.3)	ECD (0.7)
Sokal *et al.*, 2014, (24); infants (age <1 y), THIN database, 1990–2009, UK; n=794,169 (21,931 with congenital anomalies) (male to female PR)	HLHS (2.76); TGA (2.14); AS (2.12); CoAo (1.49); severe CHD (1.40)	ASD (0.73)

Table 2 (*continued*)

Table 2 (*continued*)

Authors; study setting; population under analysis	CHD with male predominance	CHD with female predominance
Verheugt *et al.*, 2008, (25); patients with CHD (age ≥16 y), data extracted from CONCOR registry, 2002–2008, Netherlands; n=7,414 (female %)	AS (35%); BAV (34%); TGA (34%)	PDA (84%); ASD (62%); PA (60%)
Hoang *et al.*, 2018, (26); patients with specific CHD, multicentric prospective study (PCGC cohort), 2010–2014, USA; n=8,693 (2,656 aged <1 y) (male %)	LVOT (65.8%); LAT (57.1%); CTD (56.3%)	ASD (37.3%); AVSD (38.9%)
Pradat *et al.*, 2003, (27); infants with CHD (age <1 y), data extracted from various national databases, France [1983–1992]; Sweden [1981–1992]; USA [1985–1992]; n=12,932 (M:F ratio)	AS (2.41:1); TGA (2.25:1); HLHS (1.74:1); CoAo (1.72:1); DORV (1.64:1); TAPVR (1.56:1); PA (1.47:1); ToF (1.44:1); VSD + CoAo (1.35:1)	IAA + other CHD (0.57:1); ECD (0.70:1); VSD + PS (0.72:1); ASD (0.86:1)
Li *et al.*, 2022 (28); patients with echocardiographic diagnosis of BAV, multicentric retrospective study, 2008–2017, China; n=992 (prevalence, male% *vs.* female%)	Aortic diffuse dilation (25.3% *vs.* 4.3%) Aortic valve regurgitation (39.0% *vs.* 12.8%) All aortopathies (75.3% *vs.* 67.4%)	Moderate to severe AS (21.3% *vs.* 45.7%) Isolated AoA dilation (46.2% *vs.* 61.2%)
McBride *et al.*, 2005, (29); children with non-complex LVOTO (age <1 y), data extracted from Texas Birth Defects Registry, 1999–2001, Texas, USA; n=499 (male to female PR)	AVS (2.71); CoAo (1.51); HLHS (1.95)	–
Calzolari *et al.*, 2003, (30); stillbirth and live birth, data extracted from IMER database, 1980–1994, Emilia Romagna, Italy; n=330,017 (1,542 with CHD) (M:F ratio)	TGA (2.23:1)	ASD OS (0.71:1); VSD (0.87:1); CAT (0.90:1)
Favilli *et al.*, 2012, (31); patient with CHD (age >16 y), data extracted from Tuscan GUCH registry, November 2008–June 2010, Tuscany, Italy; n=1,641 (male %)	Severe CHD (55,6%)	–

CHD, congenital heart defects; PR, prevalence ratio; TGA, transposition of great arteries; CoAo, aortic coarctation; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; AVSD, atrioventricular septal defects; NIS, Nationwide Inpatient Sample; AS, aortic stenosis; HLHS, hypoplastic left heart syndrome; PA, pulmonary atresia; PS, pulmonary stenosis; M, male; F, female; y, years; NHI, National Health Insurance; ToF, tetralogy of Fallot; ECD, endocardial cushion defect; OS, ostium secundum; NRCHD, National Register for Congenital Heart Defects; AoV, aortic valve disease; TGA IVS, transposition of great arteries with intact ventricular septum; NERICP, New England Regional Infant Cardiac Program; TA, tricuspid atresia; DORV, double outlet right ventricle; NorCAS, Northern Congenital Abnormality Survey; TAPVR, total anomalous pulmonary venous return; MACDP, Metropolitan Atlanta Congenital Defects Program; TS, tricuspid stenosis; ASD OP, ostium primum ASD; LVOTO, left ventricular outflow tract obstruction; CBDMP, California Birth Defects Monitoring Program; THIN, The Health Improvement Network; CONCOR, CONgenital CORvitia; BAV, bicuspid aortic valve; PCGC, Pediatric Cardiac Genomics Consortium; LVOT, left ventricular outflow tract; LAT, laterality defects; CTD, conotruncal defects; IAA, interrupted aortic arch; AoA, aortic arch; ASD, aortic valve stenosis; IMER, Emilia-Romagna Congenital Malformation Registry; CAT, common arterial trunk; GUCH, Grown-Up Congenital Heart Disease.

1985 and 2003 encompassing fetuses, stillbirths, and live births, reported a male to female relative risk of 2.50 for AS/aortic atresia. Other studies also support a higher prevalence of AS in males, albeit with less pronounced results (15,19,21,26). Among studies focused on cohorts of cardiac patients, Rothman's study (18), drawing from CHD infants data in the New England Regional Infant Cardiac Program (NERICP) registry, and Ferencz *et al.* (17), examining the Baltimore-Washington infants study, disclosed a male percentage of 78% and 71.6%, respectively, among infants with AS.

In the context of aortic coarctation (CoAo), numerous studies have indicated a correlation with male sex, although the association is not as pronounced as that observed for AS. Egbe *et al.* (8) reported a male-to-female (M:F) ratio of 2.3:1, which aligns with the M:F ratio of 1.72 reported by Pradat

et al. (27). Other population-based studies have found a slightly higher prevalence of males compared to females, with male-to-female prevalence ratios ranging from 1.3 to 1.68 (7,20,22,24).

In the case of HLHS, a distinct preference for male sex is evident. Sokal *et al.* (24), supported by a large sample, revealed an even stronger correlation with male sex compared to AS. Other studies included in the review consistently associate HLHS with a higher incidence in males, although the results may vary (8,18,19,21,23,27).

Right ventricular outflow tract obstruction

In contrast to the findings discussed earlier regarding LVOTO, there is evidence suggesting a preference for the female sex in cases of right outflow tract obstruction caused by pulmonary stenosis (PS). Tennant *et al.* (20), in a population-based study, report a slightly higher prevalence of this condition in females. Egbe *et al.* (8) describe a higher representation of females with PS and among infants in the Baltimore-Washington study, Ferencz (17) reports a significant female majority (77.8%).

Notably, the study by Pradat *et al.* (27) highlights a statistically significant association between pulmonary atresia and male sex, a finding supported by Šamánek's study (19). Additionally, in the pediatric patient cohort presented by Egbe (8), there appears to be a statistically significant correlation between pulmonary atresia and male sex when associated with ventricular septal defects (VSDs), but not in cases of isolated pulmonary atresia.

Some studies also report a slight male predominance among patients with right-sided obstructions due to tricuspid valve stenosis and tricuspid valve atresia (19).

The findings from various studies suggest a slight association with male sex for the tetralogy of Fallot (ToF) as shown by population studies by Shu-Jen Yeh (15), Tennant (20), and Pradat (27). A predilection for male sex in ToF is also observed in the study by Pfitzter *et al.* (16), based on hospital records. Conversely, Šamánek (19) reports a slightly higher proportion of females in patients with ToF, although the study's impact is limited due to a relatively small sample size.

Cardiac septation defects

In relation to cardiac septation defects, the studies analyzed reveal notable sex-related differences. Population-based studies demonstrate an association between female sex and the presence of these defects, although the strength of the association varies depending on the specific defect examined. These studies consistently indicate a higher prevalence of ASDs among females, with male-to-female prevalence ratios ranging from 0.61 to 0.73 (8,15,17,20,21,24,27,30).

The results of Ferencz's study (17) on infants and Verheugt's study (25) on CHD patients older than 16 exhibit similar patterns in terms of the sex-specific distribution of ASD, suggesting that the sex distribution of this condition is independent of patient age. Moreover, in the study by Pfitzter *et al.* (16), based on medical records of CHD patients who received hospital care, the prevalence of ASD was almost twice as high in females as in males.

In regard to VSDs, few studies observe statistically significant differences and report a slight association with female sex. Yeh *et al.* (15), using data from Taiwanese health-care registries, report a male-to-female prevalence ratio of 0.9. Similarly, among Italian patients presented by Calzolari *et al.* (30), a slight male predominance was observed among VSD patients. The study conducted by Ferencz (17) also reports a higher proportion of females in patients with muscular VSD.

Similarly, atrioventricular septal defects (AVSD) also appear to have a higher prevalence in the female sex, as evidenced by several population-based studies or large cohorts (7,16,18,19,21,26).

Patent ductus arteriosus

Marelli *et al.* (7), through their analysis of population health records in Quebec, observed a higher frequency of shunt lesions (including ASD, VSD, AVSD, and PDA) among female individuals in both childhood and the adult population (8). Additionally, apart from the aforementioned cardiac shunt lesions, a predisposition of the female sex for PDA has been observed across different age groups, including the first year of life (18), childhood (15,22), and in patients older than 16 years (25).

Conotruncal defects

Collectively, conotruncal heart defects demonstrate a subtle yet statistically significant association with male sex, as observed by Hoang *et al.* (26) among pediatric patients enrolled in the PCGC program.

In the case of transposition of the great arteries (TGA), Egbe *et al.* (8) report a fourfold higher representation of males compared to females. Similarly, Ferencz (17),

Rothman (18), Šamánek (19), and Pradat (27) report that more than two-thirds of TGA cases were males. Similar findings are reported by additional population-based studies (15,19-21,23,24). The gender-specific disparities in prevalence of TGA do not exhibit significant differences between pediatric and adult populations, as reported by Marelli *et al.* (7). Verheugt's study (25) of CHD patients older than 16 years aligns with other pediatric patient cohorts, highlighting a higher representation of males among patients with TGA. Conversely, data on functionally corrected TGA are limited, with only the results of Šamánek (19) indicating a male predilection.

Among other truncal congenital heart diseases, the limited available data suggest a greater distribution in the male sex regarding double outlet right ventricle (DORV) (19,27) and a predilection for the female sex regarding truncus arteriosus (19).

Other congenital heart defects

Among various subtypes of CHD that exhibit gender-specific distribution differences, there is evidence indicating a male predilection for total anomalous pulmonary venous return (TAPVR). Pradat *et al.* (27) report a clear majority of males among individuals with TAPVR, while Tennant *et al.* (20) describe a more than twofold higher prevalence of this defect among male fetuses, stillbirths, and infants in northern England. Additionally, the latter study (20) highlights a significant difference in the prevalence of univentricular heart disease between genders, with nearly three times higher prevalence in males compared to females. This association between male sex and univentricular heart is also described in Pfitzer *et al.* (16). Lastly, in the studies conducted by Šamánek *et al.* (19) and Pfitzer *et al.* (16), Ebstein's anomaly is observed more frequently in female patients.

BAV is more prevalent in males, with a three to fourfold higher prevalence compared to females (28). Sievers and Schmidtke proposed a surgical classification system for BAV based on the number of cusps, location of raphe, and commissure orientation (32) and a study by Roman *et al.* (33) found that men more frequently presented with type 1 BAV, characterized by fusion between the left and right coronary cusps, while women more frequently had type 2 BAV, which involved fusion between the right and non-coronary cusps. However, other studies did not find a significant association between BAV phenotypes and gender (28).

In summary, BAV is more common in males, and there are different BAV phenotypes based on cuspal fusion patterns, which may exhibit some gender-specific differences. However, the association between BAV phenotypes and gender is not consistently observed in all studies.

In patients with BAV, Li *et al.* (28) observed different distribution in BAV related complications; In particular, aortic valve regurgitation and aortic dilatation are more common in men, while moderate to severe AS are more commonly observed in women.

Taken together, these studies support the evidence that heart defects involving the outflow tract predominate in males, while inflow tract defects and shunt lesions prevail in females.

Moreover, severe CHD, defined as all cyanotic CHD or hemodynamically significant not cyanotic lesions requiring surgical and/or percutaneous correction, seem to be significantly associated with male sex in addition to younger age, higher New York Heart Association (NYHA) class, absence of systemic hypertension and hematocrit >50% (31).

Discussion

Despite the consistency of findings among studies on CHD gender prevalence ratio, there is still little evidence on the explanation of these differences.

However, the variation in CHD prevalence by gender may provide valuable clues to their etiology, and a complex interplay between hormonal, genetic, epigenetic and environmental factors affecting heart development may be involved.

The interaction between different sex hormones and system development has been hypothesized as a possible cause of gender differences in some congenital anomalies for example cleft palate and cleft lip (34) as well as in utero exposure to environmental toxins or exogenous exposures (i.e., maternal smoking) (34).

The theory proposed by James in 1999 (35) is that some congenital gender anomalies may be associated with different concentrations of parental sex hormones near conception.

Specifically, James argued that a male preponderance of TGA may be secondary to a hormonal balance favoring androgen in pregnant women. However, there is still no validated evidence for this hypothesis.

Furthermore, there have been studies assessing differences in how males and females respond to stressors during fetal life.

Some authors have suggested that fetal stress factors (maternal illness, drugs during pregnancy, exposure to environmental toxins) may increase the risk of CHD and that the different response of males and females to these stressors may contribute to gender differences in CHD prevalence (36-38).

The differences in CHD prevalence observed between males and females at birth may be suggestive of the theory that one gender is more susceptible to certain endogenous or exogenous factors during the critical early stages of embryonic development.

Consistent with the previous hypothesis, X- and Y-linked genes might contribute differently to the normal development of structures during early stages of development.

For example, the male preponderance of aortopathies (i.e., AS, CoAo) and BAV are thought to be related to genes located on chromosome X.

A significantly high prevalence of aortic defects is also found in one of the most common sex aneuploidies, Turner syndrome, which is caused by the complete or partial absence of X chromosome.

Comparing Turner syndrome patients with the general population, aortic valve anomalies occur 146 times more commonly and women with pure 45, X monosomy show a significantly higher prevalence of aortic diseases than women with Xq isochromosome (39,40).

In light of the above, it is reasonable to hypothesize that a genetic factor located on the X chromosome modulates the development of the aorta itself and the aortic valve.

There are several putative genes expressed from sex chromosomes that play a role in cardiovascular development. Among the X-linked genes, genes encoding vascular endothelial growth factor (VEGF)-D and the angiotensin type 2 receptor have been extensively studied for their implication in cardiogenesis (41).

As well as for other aortopathies, BAV is thought to be related to a reduced dosage of X-linked genes that escape X inactivation (42).

Gender differences in CHD may also extend to clinical presentation, short- and long-term outcomes and comorbidities, and several efforts have been made over time to summarize these aspects (25,43,44).

It is important to acknowledge that biological gender is a complex concept with a degree of variability. While most individuals can be classified as male or female based on typical biological characteristics, there are instances where intersex variations or other medical conditions can result in atypical presentations.

It is also crucial to recognize that biological gender is distinct from gender identity, which is a deeply-held sense of being male, female, or non-binary, and may not necessarily align with an individual's biological characteristics. Gender identity is a personal and subjective experience that goes beyond biological factors.

Societal understanding and recognition of gender have evolved, and it is important to respect and acknowledge individuals' self-identified gender identities and experiences.

Strengths and limitations

Although there is still little information to date, our review has the potential to focus on the importance of gender differences in the prevalence of CHD.

One of the strengths of our study is to summarize the current evidence on gender differences in CHD epidemiology in order to guide gender-specific management and therapy based on the individual characteristics of CHD.

The main limitation of this narrative review derives from the lack of a large sample of population-based data from well-defined geographical areas and well-structured national or international registries. Additionally, epidemiological differences in CHD should also account for the differences in race and ethnicity. Our narrative review also highlights the need for standardized reporting from multiple and uniform sources and a consistent approach to data collection and recording.

Most of the studies presented are, indeed, limited to specific geographic areas and therefore may not be representative of the general population.

Furthermore, most of the reviewed studies showed data not adjusted for socio-economic factors or maternal information that may play a role in the association between gender and the risk for CHD.

An additional issue to consider is that most reports are unable to include CHD diagnosed in pregnancies ending in voluntary termination or spontaneous abortion and the exclusion of these cases may result in a different gender distribution of CHD.

Moreover, to date knowledge of epidemiological data on prevalence does not result in changes in management or therapy. This is evident from the fact that existing guidelines still recommend treatments primarily derived from data obtained from men, which are then extrapolated to women. Unfortunately, women remain underrepresented in clinical

trials involving cardiovascular issues and thus, further studies are needed to deeply examine these differences and translate them in gender-specific clinical approaches.

Conclusions

The present review article summarizes the differences between males and females in terms of prevalence of CHD. Our review confirms that there is a greater risk for males to be born with severe CHD mostly involving the outflow tract and for females with milder CHD subtypes occurring in the inflow tract of the heart.

The causative mechanisms of CHD gender distribution are still under investigation, but the widespread use of large population-based resources, such as national or international registries, offers great potential to examine gender differences across the whole spectrum of CHD, as isolated or in the context of genetic syndromes.

Furthermore, healthcare providers should receive education and training on the importance of considering sex and gender in the diagnosis, treatment, and management of CHD.

Developing updated guidelines and clinical protocols that explicitly incorporate gender-specific considerations is crucial. These guidelines should adapt diagnostic criteria, treatment algorithms, and follow-up strategies tailored to the unique needs of both males and females based on collaboration among multidisciplinary teams (cardiologists, geneticists, psychologists, and other specialists) for a holistic approach to care.

Consequently, personalized healthcare should be based on evidence from research studies aimed at understanding how gender influences the risk for CHD and gender medicine should become an established medical approach.

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References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation 2022;145:e153-639. Erratum in: Circulation 2022;146:e141.
2. Martin LJ, Benson DW. Focused Strategies for Defining the Genetic Architecture of Congenital Heart Defects. Genes (Basel) 2021;12:827.
3. Sable C, Foster E, Uzark K, et al. Best practices in managing transition to adulthood for adolescents with congenital heart disease: the transition process and medical and psychosocial issues: a scientific statement from the American Heart Association. Circulation 2011;123:1454-85.
4. Legato MJ. Gender-specific physiology: how real is it? How important is it? Int J Fertil Womens Med 1997;42:19-29.
5. Baggio G, Corsini A, Floreani A, et al. Gender medicine: a task for the third millennium. Clin Chem Lab Med

2013;51:713-27.
6. Arain FA, Kuniyoshi FH, Abdalrhim AD, et al. Sex/gender medicine. The biological basis for personalized care in cardiovascular medicine. Circ J 2009;73:1774-82.
7. Marelli AJ, Mackie AS, Ionescu-Ittu R, et al. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007;115:163-72.
8. Egbe A, Uppu S, Stroustrup A, et al. Incidences and sociodemographics of specific congenital heart diseases in the United States of America: an evaluation of hospital discharge diagnoses. Pediatr Cardiol 2014;35:975-82.
9. Qu Y, Liu X, Zhuang J, et al. Incidence of Congenital Heart Disease: The 9-Year Experience of the Guangdong Registry of Congenital Heart Disease, China. PLoS One 2016;11:e0159257.
10. Wren C, Richmond S, Donaldson L. Temporal variability in birth prevalence of cardiovascular malformations. Heart 2000;83:414-9.
11. Oyen N, Poulsen G, Boyd HA, et al. National time trends in congenital heart defects, Denmark, 1977-2005. Am Heart J 2009;157:467-473.e1.
12. Fixler DE, Pastor P, Chamberlin M, et al. Trends in congenital heart disease in Dallas County births. 1971-1984. Circulation 1990;81:137-42.
13. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241-7.
14. Moons P, Sluysmans T, De Wolf D, et al. Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st century. Acta Paediatr 2009;98:472-7.
15. Yeh SJ, Chen HC, Lu CW, et al. Prevalence, mortality, and the disease burden of pediatric congenital heart disease in Taiwan. Pediatr Neonatol 2013;54:113-8.
16. Pfitzer C, Helm PC, Ferentzi H, et al. Changing prevalence of severe congenital heart disease: Results from the National Register for Congenital Heart Defects in Germany. Congenit Heart Dis 2017;12:787-93.
17. Gillette PC. Genetic and environmental risk factors of major cardiovascular malformations: The baltimore–washington infant study: 1981–1989 edited by Charlotte Ferencz, Adolfo Correa–Villasenor, Christopher A. Loffredo, P. David Wilson, Futura Publishing Company, Inc., Armonk, N.Y. (1998) 463 pages, illustrated, $95.00 ISBN: 1044–4157. Clin Cardiol 2009;21:867-8.
18. Rothman KJ, Fyler DC. Sex, birth order, and maternal age characteristics of infants with congenital heart defects. Am J Epidemiol 1976;104:527-34.
19. Samánek M. Boy:girl ratio in children born with different forms of cardiac malformation: a population-based study. Pediatr Cardiol 1994;15:53-7.
20. Tennant PW, Samarasekera SD, Pless-Mulloli T, et al. Sex differences in the prevalence of congenital anomalies: a population-based study. Birth Defects Res A Clin Mol Teratol 2011;91:894-901.
21. Lary JM, Paulozzi LJ. Sex differences in the prevalence of human birth defects: a population-based study. Teratology 2001;64:237-51.
22. García A, Moreno K, Ronderos M, et al. Differences by Altitude in the Frequency of Congenital Heart Defects in Colombia. Pediatr Cardiol 2016;37:1507-15.
23. Shaw GM, Carmichael SL, Kaidarova Z, et al. Differential risks to males and females for congenital malformations among 2.5 million California births, 1989-1997. Birth Defects Res A Clin Mol Teratol 2003;67:953-8.
24. Sokal R, Tata LJ, Fleming KM. Sex prevalence of major congenital anomalies in the United Kingdom: a national population-based study and international comparison meta-analysis. Birth Defects Res A Clin Mol Teratol 2014;100:79-91.
25. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. Gender and outcome in adult congenital heart disease. Circulation 2008;118:26-32.
26. Hoang TT, Goldmuntz E, Roberts AE, et al. The Congenital Heart Disease Genetic Network Study: Cohort description. PLoS One 2018;13:e0191319.
27. Pradat P, Francannet C, Harris JA, et al. The epidemiology of cardiovascular defects, part I: a study based on data from three large registries of congenital malformations. Pediatr Cardiol 2003;24:195-221.
28. Li Y, Chen X, Qi Y, et al. Gender differences in bicuspid aortic valve Sievers types, valvulopathy, aortopathy, and outcome of aortic valve replacement. Echocardiography 2022;39:1064-73.
29. McBride KL, Marengo L, Canfield M, et al. Epidemiology of noncomplex left ventricular outflow tract obstruction malformations (aortic valve stenosis, coarctation of the aorta, hypoplastic left heart syndrome) in Texas, 1999-2001. Birth Defects Res A Clin Mol Teratol 2005;73:555-61.
30. Calzolari E, Garani G, Cocchi G, et al. Congenital heart defects: 15 years of experience of the Emilia-Romagna Registry (Italy). Eur J Epidemiol 2003;18:773-80.
31. Favilli S, Santoro G, Ballo P, et al. Prevalence and clinical

characteristics of adult patients with congenital heart disease in Tuscany. J Cardiovasc Med (Hagerstown) 2012;13:805-9.
32. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226-33.
33. Roman MJ, Pugh NL, Devereux RB, et al. Aortic Dilatation Associated With Bicuspid Aortic Valve: Relation to Sex, Hemodynamics, and Valve Morphology (the National Heart Lung and Blood Institute-Sponsored National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions). Am J Cardiol 2017;120:1171-5.
34. Nagase Y, Natsume N, Kato T, et al. Epidemiological Analysis of Cleft Lip and/or Palate by Cleft Pattern. J Maxillofac Oral Surg 2010;9:389-95.
35. James WH. Is transposition of the great arteries a consequence of maternal hormone imbalance? Evidence from the sex ratios of relatives of probands. J Theor Biol 1999;198:301-3.
36. Austin MP, Leader LR, Reilly N. Prenatal stress, the hypothalamic-pituitary-adrenal axis, and fetal and infant neurobehaviour. Early Hum Dev 2005;81:917-26.
37. Gu J, Guan HB. Maternal psychological stress during pregnancy and risk of congenital heart disease in offspring: A systematic review and meta-analysis. J Affect Disord 2021;291:32-8.
38. Zhu JL, Olsen J, Sørensen HT, et al. Prenatal maternal bereavement and congenital heart defects in offspring: a registry-based study. Pediatrics 2013;131:e1225-30.
39. Prandstraller D, Mazzanti L, Picchio FM, et al. Turner's syndrome: cardiologic profile according to the different chromosomal patterns and long-term clinical follow-Up of 136 nonpreselected patients. Pediatr Cardiol 1999;20:108-12.
40. Elsheikh M, Dunger DB, Conway GS, et al. Turner's syndrome in adulthood. Endocr Rev 2002;23:120-40.
41. Sachdev V, Matura LA, Sidenko S, et al. Aortic valve disease in Turner syndrome. J Am Coll Cardiol 2008;51:1904-9.
42. Prakash SK, Bondy CA, Maslen CL, et al. Autosomal and X chromosome structural variants are associated with congenital heart defects in Turner syndrome: The NHLBI GenTAC registry. Am J Med Genet A 2016;170:3157-64.
43. Warnes CA. Sex differences in congenital heart disease: should a woman be more like a man? Circulation 2008;118:3-5.
44. Putotto C, Unolt M, Caiaro A, et al. Congenital heart diseases in women. G Ital Cardiol (Rome) 2013;14:120-5.

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