Congenital Heart Disease prevalence. What does the future hold?

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In the current issue of the European Journal of Preventive Cardiology Giang et al (1) present the changes in birth prevalence of congenital heart disease (CHD) in Sweden between 1970 and 2017. The authors report an increase in prevalence which may be attributed to improvements in the diagnostic accuracy of echocardiogram that became widely available after the mid-eighties. Prior to this era mild or even moderate CHD could go undetected. By contrast the diagnosis of a severe cyanotic congenital cardiac lesion CHD, would be difficult to miss due to its potential life threatening nature and its clinical presentation. Through the period of the study there was a statistically significant, but small, increase in the complex CHD prevalence, in the Swedish cohort (1). The authors report a decline in cardiac interventions from 40.7% of the CHD population in 1970 to less than 17% during the period 2014-2016 while the absolute number of
cardiac interventions increased. Cardiac interventions also increased for patients with
the most complex lesions. Unfortunately, the authors were unable to report on the
specific types of interventions, and the differences in performance over the study period
were not available in the registries. It would have been informative to discover the
changing nature of interventional procedures from 1970 to 2017. In figure, a timeline of
CHD transcatheter and surgical interventions underlines the tremendous progress in the
interventional management of CHD (2).

As fetal echocardiogram became widely available, prenatal diagnosis of critical CHD
became possible (3). This resulted in the ability to individualize care and to improve
outcomes. Despite these advances not all CHD are diagnosed before birth.

In a recent study, prevalence of CHD determined by echocardiography screening at
birth, was higher and more accurate that obtained from birth defect registries (4).
There is no doubt that CHD diagnosis is the first step in medical and interventional
management, thus improving significantly the survival of young patients.

A recent metanalysis of 260 studies that incorporated global data, concluded that the
reported prevalence of CHD continued to increase (5). The prevalence of mild lesions
increased at the same period as in the Swedish study (1). There were significant regional
discrepancies, with prevalence reported from Africa being the lowest (overall and mild
lesions) and Asia the highest (mild lesions).

Geographical and socioeconomic factors have been shown to influence the birth
prevalence in China, underlying the importance of environment and health resources in
diagnosis and adequate management of CHD (6).

Congenital anomalies like CHD, cleft lip and palate are associated with environmental
risk factors (maternal exposure to air pollution, toxic chemicals etc), parental smoking,
maternal health (infectious diseases during pregnancy, pregestational and gestational
diabetes mellitus, maternal obesity, maternal drug intake), artificial reproductive
technologies as well as socioeconomic factors (7).

In this light, identification of risk factors leading to congenital anomalies is fundamental
for future preventative strategies.

Genetics play a central role in CHD pathogenesis, a discovery that has benefited from
considerable technical advances in examining the human genome. In earlier studies
karyotyping patients with syndromic CHD uncovered aneuploidies, most commonly
trisomy 13, 18 or 21 (Down syndrome) and monosomy X (Turner syndrome). These
occur in ~12% of patients with CHD.

Genes linked to CHD provide new insights into the crucial molecules and pathways
involved in cardiogenesis. They complement and extend the considerable information
derived from experimental models exploring heart development. Studies of
spontaneous (de novo) gene variants in sporadic CHD can identify new genes involved in
cardiogenesis. At the same time, detailed clinical evaluations allow the definition of a broader spectrum of cardiac and extracardiac phenotypes compared to studies based on experimental models. Given that most human variants are heterozygous, studies based on experimental models often explore homozygous variants. For this reason human CHD data had the potential to be more informative about subtler influences on heart formation (8).

Why is CHD the most common congenital anomaly? One hypothesis is that complex developmental processes of heart formation are exquisitely sensitive to changes in gene dosage among many essential genes and pathways. When gene dosage is altered, developmental errors can occur - many of which are readily detected by contemporary screening fetal echocardiogram during the second trimester of pregnancy. Genes linked to CHD are increasingly identified through analyses of CHD cohorts, carried out in single centers or by national and international collaborations. Most studies have enrolled patients with severe or critical CHD, while they under-represent patients with simple lesions and exclude patients with clinically established genetic syndromes.

The discovery of genes and variants with a potential causal link to CHD combined with analyses of gene expression during development and functional studies in model systems, provide crucial evidence for assigning causality in the clinical setting. The identification of definitive causal CHD variants influences patient care. Both the family of a newborn baby with CHD and adults with repaired or palliated CHD, benefit when genotyping can accurately inform the risk of recurrence thus giving increased opportunity for prenatal genetic counselling and pre-implantation genotyping. The genotype may lead to identifying associated extracardiac anomalies or comorbidities such as neurodevelopmental delay and underlines the need for surveillance for unfavorable postoperative outcomes and future cancer development. Variants are typically discovered by whole-exome sequencing (WES) and analyses of case–control comparisons. These studies show that patients with CHD have the same rates of total de novo variants but significantly more rare damaging variants compared with the general population, including 9% excess of de novo damaging variants, 7% excess of dominant inherited variants and 1% recessive inherited variants.

In conclusion, as the CHD birth prevalence is increasing, there is need for maternal risk factor modification in the general population, as well as genetic assessment in selected cohorts. These components emphasize the multifactorial etiology of CHD and highlight it as part of a genetic-based disruption of human cardiac morphogenesis. Even if improvements in CHD diagnosis and management (including catheter-based intervention, cardiac surgery, medical management and psychological support), have secured a longer life of higher quality for even the most complex cases it is clear that the prevalence of CHD could be modified by lifestyle and further advances in genetic counseling.
No conflicts of Interest

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References


Figure Legend

Developments over the years in cardiac surgery and interventional cardiology. MRI magnetic resonance imaging, TAVI transcatheter aortic valve implantation, PDA patent ductus arteriosus, PA pulmonary artery, AV aortic valve, PV pulmonary valve, VSD ventricular septal defect, ASD atrial septal defect, Pears Personalized External Aortic Root Support, Tx cardiac transplantation, HLTx heart-lung transplantation, AVSD atrioventricular septal defect, TAPVD Total anomalous pulmonary venous drainage, CPB cardiac pulmonary bypass, TOF tetralogy of Fallot, BT Blalock-Taussig. From Reference 2

![Figure 1](252x142 mm (8.1 x DPI))