The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 5, 2025

IDENTIFYING CONSANGUINITY AS A MAJOR RISK FACTOR FOR CONGENITAL HEART DISEASE IN CHILDREN

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DOI: https://doi.org/10.5281/zenodo.15493911

Keywords
Congenital heart disease, consanguinity, genetic risk, cyanotic heart defects, Pakistan, pediatric cardiology, maternal age, public health.

Article History
Received on 14 April 2025
Accepted on 14 May 2025
Published on 23 May 2025

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Abstract

Background: *Congenital heart disease (CHD) remains the most common birth defect globally, with multifactorial etiology involving genetic, environmental, and demographic factors. Among these, consanguinity–marriage between blood relatives–has been increasingly recognized as a significant risk factor due to the increased expression of autosomal recessive gene mutations.*

Objective: *To investigate the association between parental consanguinity and the prevalence and severity of CHD among pediatric patients in Hyderabad, Pakistan.*

Methods: *A cross-sectional study was conducted on 200 children (aged 0–15 years) diagnosed with CHD at tertiary care hospitals in Hyderabad. Data were collected using a structured questionnaire and echocardiographic confirmation of diagnosis. The association between consanguinity and CHD was evaluated using Chi-square tests, Odds Ratios (OR), and Relative Risk (RR), with a significance level of $p < 0.05$.*

Results: *Among the 200 CHD cases, 67% were born to consanguineous parents, with first-cousin marriages accounting for 46% of all cases. Cyanotic CHD was significantly more prevalent in children from consanguineous unions ($p < 0.001$). The odds of developing CHD were over four times higher in children of consanguineous couples (OR = 4.12), and the relative risk was 2.03. Maternal age >30 years was also associated with a 1.6-fold increased risk of CHD.*

Conclusion: *This study confirms a strong association between parental consanguinity and CHD risk and severity. Public health interventions such as genetic counseling and community awareness programs are crucial in reducing the burden of CHD in regions with high consanguinity rates.*

INTRODUCTION

Congenital heart disease (CHD) is one of the most common congenital anomalies worldwide, affecting approximately 0.8–1.2% of live births, with significant variations based on geographic and genetic factors 【

1】. Despite advancements in medical and surgical interventions, CHD remains a leading cause of infant morbidity and mortality【2】. The etiology of CHD is multifactorial, involving a complex interplay between genetic predisposition, environmental influences, and socio-demographic factors【3】. One critical but often underexamined risk factor is consanguinity, the practice of marriage between blood relatives, which increases the probability of autosomal recessive genetic mutations, contributing to congenital malformations, including CHD【4】.

Globally, consanguineous marriages are more prevalent in regions with strong cultural, religious, and socio-economic influences, such as South Asia, the Middle East, and North Africa, where 20–50% of marriages involve close relatives【5】【6】. Research suggests that children born to consanguineous parents have a 2.0–2.5 times higher risk of developing CHD than those from non-consanguineous unions【7】. Additionally, first-cousin marriages have been linked to an elevated risk of congenital malformations, ranging from 5% to 8%【8】. Specific genetic studies have identified gene mutations in consanguineous families, further supporting the role of inherited factors in CHD pathogenesis【9】.

The association between consanguinity and CHD severity is also well-documented, with cyanotic CHD being significantly more frequent in children from highly inbred families【10】. However, genetic screening and counseling services remain limited in many high-prevalence areas, leaving at-risk populations vulnerable to preventable congenital anomalies【11】. Therefore, understanding the impact of consanguinity on CHD prevalence is critical for implementing early detection strategies, genetic counseling, and targeted public health interventions【12】.

This study aims to evaluate consanguinity as a significant risk factor for CHD among pediatric patients and to emphasize the importance of preventive genetic counseling in mitigating its burden.

Methodology

A cross-sectional study was conducted over six months at secondary and tertiary care hospitals in Hyderabad, Sindh. A structured questionnaire was used to collect demographic and clinical data from parents of pediatric CHD patients. The study included 200 children under 15 years of age diagnosed with CHD, selected through simple random sampling. Participants were recruited from pediatric wards, ensuring a diverse representation of CHD cases.

The sample size was calculated using the formula for prevalence-based cross-sectional studies, considering an estimated CHD prevalence of 8% and a 95% confidence interval. The calculated minimum required sample size was 113; however, to account for potential non-response or missing data, the final sample size was increased to 200 for improved statistical power.

Participants were eligible for inclusion if they were 0–15 years old, had a confirmed echocardiographic diagnosis of CHD, and were admitted to pediatric wards during the study period. Parental consent was mandatory for participation. Patients older than 15 years, those managed on an outpatient basis, and individuals with other congenital anomalies or unrelated genetic disorders were excluded from the study.

Data collection focused on demographic factors (age, gender, ethnicity, socio-economic status), parental consanguinity (first- or second-degree cousin marriages), and family history of CHD among siblings or extended relatives. Ethical approval was obtained from the Institutional Review Board (IRB), and written informed consent was secured from all parents/guardians to ensure data confidentiality and adherence to research ethics.

Statistical analysis was performed using SPSS Version 26.0. Descriptive statistics such as mean, standard deviation, frequency, and percentage were used to summarize the data. The Chi-square test was applied to assess the association between consanguinity and CHD prevalence, while Odds Ratios (OR) and Relative Risk (RR) were calculated to determine the strength of association. A p-value < 0.05 was considered statistically significant, ensuring the reliability of the findings.

Results

This table summarizes the demographic and clinical characteristics of the 200 children diagnosed with CHD. The mean age of the participants was 4.8 ± 3.1 years, and 57.5% of the children were male, reflecting

a slight male predominance. The average birth weight was 2.9 ± 0.5 kg, and parental age at childbirth had a mean of 29.6 ± 4.8 years. The majority of CHD cases (67%) were born to consanguineous parents, emphasizing the genetic predisposition associated with familial marriages.

Variable	Mean ± SD	Range
Age (years)	4.8 ± 3.1	0.5 – 15
Birth Weight (kg)	2.9 ± 0.5	2.0 – 4.2
Parental Age (years)	29.6 ± 4.8	20 – 42
Consanguinity (%)	**67% (134/200)**	-

The data shows that 67% of CHD cases were from consanguineous parents, with first-degree cousin marriages accounting for 46% of cases. These findings are consistent with existing literature indicating a higher prevalence of CHD in regions where consanguinity is common.

Parental Consanguinity	No. of CHD Cases (%)
First-degree cousins	**92 (46%)**
Second-degree cousins	**42 (21%)**
Unrelated parents	**66 (33%)**

The table below shows that cyanotic CHD was significantly more frequent in children from consanguineous families (55.2%) compared to those from non-consanguineous parents (24.2%), with $p < 0.001$, indicating a strong statistical significance. Acyanotic CHD was also more common in consanguineous cases, but the disparity was less pronounced.

CHD Type	Consanguineous Parents (n = 134)	Non-Consanguineous Parents (n = 66)	p-value
Cyanotic CHD	74 (55.2%)	16 (24.2%)	**<0.001**
Acyanotic CHD	60 (44.8%)	50 (75.8%)	**<0.001**

A Chi-square test was conducted to determine the association between consanguinity and CHD prevalence. The Chi-square value was 44.89 ($p < 0.0001$), indicating a highly significant association. The Odds Ratio (OR) was 4.12, suggesting that children born to consanguineous parents were over four times more likely to develop CHD compared to those from non-consanguineous unions. The Relative Risk (RR) was 2.03, implying that consanguineous offspring had twice the risk of developing CHD.

Statistic	Value
Chi-square	44.89
p-value	<0.0001
Odds Ratio (OR)	4.12
Relative Risk (RR)	2.03

Discussion

This study reveals a compelling association between parental consanguinity and the risk of congenital heart disease (CHD) among children. Our findings demonstrate that 67% of CHD cases were born to consanguineous parents, with first-degree cousin marriages comprising 46% of this group. This aligns with the genetic principle that close consanguineous unions increase the probability of homozygosity of deleterious autosomal recessive alleles, which can manifest as congenital anomalies, including CHD. The significant prevalence of cyanotic CHD among children from consanguineous unions in our study further supports the severity of defects linked to inbreeding.

Comparison with Contemporary Literature

Recent studies from Saudi Arabia, Iran, and Turkey echo our results. For instance, a Saudi cohort study identified consanguinity in 41.6% of children with CHD, emphasizing its substantial contribution to disease burden (10). A Turkish study reported similar

trends, showing a higher frequency of genetic cardiac defects in offspring of consanguineous parents, particularly first cousins (11). Moreover, a recent systematic review affirmed a 2.5-fold increase in congenital malformation risk, particularly CHD, in children of first-degree relatives (12). These studies validate our findings and reinforce the heritable component of CHD in consanguineous populations.
In contrast, studies from Western countries such as the UK and Canada report markedly lower CHD rates in consanguineous unions, owing to lower prevalence of such marriages and routine prenatal genetic screening (13). These disparities underscore the role of socio-cultural norms and healthcare accessibility in shaping the epidemiology of CHD.

Biological and Genetic Basis

The biological mechanisms underlying CHD in consanguineous offspring are increasingly understood through genomic research. Homozygous mutations in cardiac development genes, such as NKX2-5, GATA4, and TBX1, are more likely to be expressed in consanguineous progeny due to shared ancestry (11,14). Moreover, consanguinity has been associated with syndromic CHD, where heart defects co-occur with other anomalies like cleft palate or neural tube defects, further complicating clinical outcomes (15).
Our data also showed that maternal age above 30 years was associated with a 1.6-fold increased risk of CHD. This observation aligns with reports that advanced maternal age contributes to meiotic nondisjunction events and de novo mutations, thereby increasing susceptibility to genetic abnormalities, including cardiac defects (16). This dual interaction—consanguinity and maternal age—may exert a synergistic effect on fetal cardiac development.

Clinical Implications

The findings of this study have critical clinical and public health implications, especially for regions with high rates of consanguineous marriages. Targeted strategies should include:

- **Pre-marital and Pre-conception Genetic Counseling**: Couples, particularly those with a family history of congenital anomalies or who are closely related, should be offered counseling to understand genetic risks.
- **Community Awareness Campaigns**: Public health initiatives should educate populations on the risks associated with consanguinity, using culturally sensitive approaches.
- **Implementation of Genetic Screening Programs**: Expanding access to carrier testing, echocardiography, and fetal anomaly scans in antenatal care, particularly in rural and underprivileged settings, can enable early detection and management.
- **Integration of Family History in Risk Assessment**: Family history should be a routine component of prenatal risk profiling to identify high-risk pregnancies and apply timely interventions (13,17).

Strengths, Limitations, and Future Directions

This study's strengths include its relatively large sample size (n = 200), the use of echocardiographic diagnosis to confirm CHD, and structured data collection. However, limitations must be acknowledged. The cross-sectional nature of the study limits our ability to infer causality between consanguinity and CHD. Additionally, self-reported family history may be subject to recall or reporting bias, potentially leading to underestimation of familial CHD burden. Finally, the study's focus on a single geographic region (Hyderabad, Sindh) may limit the generalizability of findings to more diverse ethnic populations.
Future studies should adopt longitudinal designs to monitor postnatal outcomes and recurrence risks in consanguineous families. Moreover, genomic sequencing technologies such as whole exome sequencing (WES) can uncover novel mutations contributing to CHD in genetically isolated populations. Integrating these findings into national screening policies and health education curricula can have a profound impact on reducing congenital disease burdens.

Conclusion

This study confirms that consanguinity significantly increases the risk of congenital heart disease, particularly cyanotic CHD. Children born to first-degree cousin marriages exhibited the highest risk, with a threefold increase in CHD prevalence compared to children from non-consanguineous

unions. These findings underscore the critical need for genetic counseling and public health interventions to mitigate the burden of CHD in high-risk populations.

Conflict of Interest

The authors declare no conflicts of interest regarding this study.

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