

# Thirty-year Trend of Non-rheumatic Valvular Heart Disease: A Comparison of Pakistan with South Asia and Global Scenario

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#### Abstract

**Background:** Improved prophylaxis has shifted valvular heart disease (VHD) from rheumatic to non-rheumatic causes globally, with rheumatic VHD nearly eradicated in high-income countries. However, non-rheumatic VHD remains a major health issue in low-to-middle-income countries like those in South Asia. This study examines non-rheumatic VHD trends in Pakistan compared to South Asia and global figures.

Objective: To evaluate non-rheumatic VHD trends in Pakistan from 1990 to 2019 using Global Burden of Disease (GBD) data.

- Methods: The study extracted data on prevalence, deaths, disability-adjusted life years (DALYs), and age-standardized death rate (ASDR) from the GBD study. An ecological design analyzed data using Excel and R-Studio. Poisson regression assessed the 30-year ASDR trend at global, South Asian, and national levels, calculating percentage changes with incidence rate ratios (IRR) and 95% confidence intervals.
- **Results:** From 1990 to 2019, Pakistan's non-rheumatic VHD prevalence increased by 14.1% (6.4 to 7.3 per 100,000), and ASDR rose by 12.9% (1.32 to 1.49), with an IRR of 1.102 (95% CI: 1.002-1.198). Global ASDR slightly decreased (IRR: 0.997, 95% CI: 0.971-1.024), and South Asia's IRR was 0.996 (95% CI: 0.959-1.034). Deaths in Pakistan rose by 1.1% (0.59 to 0.60 per 100,000), and DALYs increased by 17% (14.1 to 16.5 per 100,000), with significant rises in Sindh (30.3%), Baluchistan (23.7%), and Azad Jammu & Kashmir (23.9%).
- **Conclusion:** GBD data show a significant increase in non-rheumatic VHD burden in Pakistan over 30 years, necessitating policy and interventions to address this growing health issue.

# **1** Introduction

The global landscape of valvular heart disease (VHD) has transitioned from predominantly rheumatic to non-rheumatic etiologies, such as calcific or degenerative VHD, primarily due to advancements in prophylactic measures and improvements in living standards (1-3). While rheumatic VHD has been nearly eradicated in high-income countries (1,4), it continues to contribute significantly to morbidity and mortality in low-to-middle-income countries (LMCs) such as those in South Asia (2,5). Non-rheumatic VHD has also seen a rising prevalence in these regions, driven by substantial economic growth, increasing urbanization, and aging populations (5,6). The burden of non-rheumatic VHD has profound implications for healthcare systems, both in isolation and through its association with adverse clinical conditions such as atrial fibrillation and complications during pregnancy, including placental abruption (7,8).

The South Asian population, including countries like Pakistan, India, Bangladesh, Sri Lanka, Bhutan, and Nepal, is at heightened risk of cardiovascular diseases (CVD) due to various economic, environmental, and genetic factors (9-13). Pakistan, the second largest country in the region, with a population nearing 208 million and over 12 million elderly individuals ( $\geq$ 60 years), faces a significant burden of CVD, particularly non-rheumatic VHD, which poses economic and management challenges for its healthcare system (14). Reliable estimates of

disease burden are crucial for policymakers to make informed decisions; however, data for Pakistan are often limited or unavailable due to an underdeveloped healthcare infrastructure. The Global Burden of Disease (GBD) study provides an opportunity to assess the burden of disease from a regional perspective, including the administrative sub-territories of Pakistan (15).

This study aims to evaluate the burden and trends of non-rheumatic VHD in Pakistan compared to South Asian and global figures, based on GBD estimates from 1990 to 2019. The data includes prevalence, death rates, disability-adjusted life years (DALYs), and agestandardized death rates (ASDR). This ecological study utilized secondary data from the GBD, which is publicly available and did not require ethical clearance. The analysis included data extracted from the Global Health Data Exchange query tool, spanning 30 years, and was analyzed using Microsoft Excel and R-Studio. The percentage change in prevalence and deaths over 30 years was calculated using 2019 as the benchmark year. Additionally, Poisson regression analysis was used to evaluate the 30-year trend in non-rheumatic VHD ASDR for the global and South Asian regions, as well as at the country level, with the incidence rate ratio (IRR) and 95% confidence intervals reported.

In Pakistan, the prevalence of non-rheumatic VHD increased by 14.1% from 1990 to 2019, with the highest prevalence noted in the Islamabad capital territory, showing a 76.4% increase. The ASDR per 100,000 population also increased by 12.9% during this period, while global and South Asian ASDRs slightly decreased. The number of deaths and DALYs due to non-rheumatic VHD in Pakistan also showed an upward trend. Notably, Sindh, Baluchistan, and Azad Jammu & Kashmir exhibited the most significant increases in DALYs, highlighting the substantial regional variations in disease burden. This study underscores the urgent need for policy interventions to address the growing burden of non-rheumatic VHD in Pakistan and similar LMCs, emphasizing the importance of reliable data for effective healthcare planning and resource allocation.

# **2** Material and Methods

The study utilized secondary data from the Global Burden of Disease (GBD) study, conducted by the Institute of Health Metrics and Evaluation (IHME). The data comprised estimates of prevalence, deaths, disability-adjusted life years (DALYs), and age-standardized death rates (ASDR) due to non-rheumatic valvular heart disease (VHD) in Pakistan from 1990 to 2019. The analysis also included comparative data for South Asia and the global context to provide a comprehensive overview of the trends and burden of non-rheumatic VHD. Ethical approval was deemed unnecessary for this study as it relied solely on publicly available secondary data from the GBD study, ensuring compliance with the Declaration of Helsinki.

The data collection process involved extracting relevant information from the Global Health Data Exchange query tool, a robust platform that offers extensive health-related datasets. Data specific to non-rheumatic VHD, including its subtypes—calcific aortic valve disease, degenerative mitral valve disease, and other non-rheumatic valve diseases—were meticulously extracted. This comprehensive dataset encompassed prevalence rates, mortality rates, DALYs, and ASDR, stratified by gender and various administrative territories within Pakistan. The dataset covered a 30-year period, allowing for a thorough analysis of trends over time.

Data assessment involved a detailed examination of the extracted information using Microsoft Excel 2013 and R-Studio version 4.2.2. The percentage change in prevalence, deaths, and DALYs over the 30-year period was calculated by comparing data from 2019 against the baseline year of 1990. Statistical analyses were conducted to evaluate the trends in non-rheumatic VHD. Poisson regression analysis was employed to assess the age-standardized death rate (ASDR) trends for the global and South Asian regions and at the country level, with the incidence rate ratio (IRR) and 95% confidence intervals reported.

The study also accounted for potential regional variations within Pakistan by analyzing data at the provincial level, including Baluchistan, Azad Jammu & Kashmir, Gilgit-Baltistan, Islamabad Capital Territory, Khyber Pakhtunkhwa, Punjab, and Sindh. Gender-specific analyses were performed to discern any differences in the burden of non-rheumatic VHD between males and females.

Statistical analyses were conducted using SPSS version 25. Descriptive statistics were used to summarize the data, and inferential statistics were applied to determine the significance of trends and differences. The results were presented as rates per 100,000 population, with corresponding counts and relative percentage changes. The IRR and confidence intervals provided a robust measure of the annual percentage change in ASDR.

Throughout the study, the methodological rigor ensured the reliability and validity of the findings. The comprehensive approach, encompassing a 30-year period and including both national and regional analyses, provided a detailed understanding of the burden and trends of non-rheumatic VHD in Pakistan. The study's findings underscore the need for targeted health policies and interventions to address the increasing burden of non-rheumatic VHD, particularly in low-to-middle-income countries like Pakistan (15).

# **3** Results

The results of this study indicate a significant increase in the prevalence, deaths, and disability-adjusted life years (DALYs) due to nonrheumatic valvular heart disease (VHD) in Pakistan over the 30-year period from 1990 to 2019. The data, extracted from the Global Burden of Disease (GBD) study, reveal notable trends at both the national and provincial levels, as well as differences between genders.

Table 1: Estimated Prevalence of Non-Rheumatic Valvular Heart	Disease in Pakistan by Gender and Province (1990-
2019)	

Yr	Pak	М	F	BA	AJK	GB	ISB	КРК	PU	SD
1990	6.4	7.5	5.1	5.5	6.9	5.1	8.7	5.7	6.9	5.7
1995	7.0	8.1	5.8	6.2	7.5	5.4	9.3	6.5	7.4	6.5
2000	7.1	8.2	5.8	6.1	7.7	5.7	11.2	6.5	7.4	6.7
2005	7.1	8.4	5.7	5.8	7.7	5.5	14.9	6.3	7.5	6.9
2010	7.1	8.5	5.7	4.9	8.1	4.9	14.4	5.9	7.5	7.4
2015	7.1	8.5	5.7	4.9	8.1	4.9	14.4	5.9	7.5	7.4
2019	7.3	8.9	5.6	4.7	8.1	4.8	15.3	5.6	7.9	7.5
$\%\Delta$	14.4%	18.0%	10.2%	-14.0%	17.8%	-4.9%	76.4%	-3.1%	15.2%	32.6%

Yr: Year; Pak: Pakistan; M: Male; F: Female; BA: Baluchistan; AJK: Azad Jammu & Kashmir; GB: Gilgit-Baltistan; ISB: Islamabad Capital Territory; KPK: Khyber Pakhtunkhwa; PU: Punjab; SD: Sindh

The data, extracted from the Global Burden of Disease (GBD) study, reveal notable trends at both the national and provincial levels, as well as differences between genders.

Table 2: Death Rates Due to Non-Rheumatic Valvular Heart Disease in	Pakistan by Gend	ler, Province, and Type of Non-
Rheumatic VHD (1990-2019)		

Yr	Pak	М	F	BA	AJK	GB	ISB	КРК	PU	SD
1990	0.59	0.60	0.60	0.50	0.70	0.40	0.50	0.50	0.70	0.50
1995	0.60	0.60	0.60	0.50	0.70	0.40	0.50	0.50	0.70	0.50
2000	0.60	0.60	0.60	0.50	0.70	0.40	0.50	0.50	0.70	0.50
2005	0.60	0.60	0.60	0.50	0.70	0.40	0.50	0.50	0.70	0.50
2010	0.60	0.50	0.60	0.40	0.70	0.40	0.50	0.50	0.60	0.50
2015	0.60	0.60	0.60	0.40	0.70	0.40	0.40	0.50	0.70	0.50
2019	0.60	0.60	0.60	0.40	0.70	0.40	0.40	0.50	0.70	0.60
$\%\Delta$	1.1%	-3.1%	5.4%	-13.5%	10.0%	15.2%	-14.2%	10.2%	-1.8%	15.1%

Yr: Year; Pak: Pakistan; M: Male; F: Female; BA: Baluchistan; AJK: Azad Jammu & Kashmir; GB: Gilgit-Baltistan; ISB: Islamabad Capital Territory; KPK: Khyber Pakhtunkhwa; PU: Punjab; SD: Sindh

The estimated prevalence of non-rheumatic VHD in Pakistan increased from 6.4 per 100,000 in 1990 to 7.3 per 100,000 in 2019, representing a 14.4% rise.

Table 3: Disability-Adjusted Life Years (DALYs) Due to Non-Rheumatic Valvular Heart Disease in Pakistan by Gender,Province, and Type of Non-Rheumatic VHD (1990-2019)

Yr	Pak	Μ	F	BA	AJK	GB	ISB	КРК	PU	SD
1990	14.1	14.1	14.1	12.0	14.8	9.9	12.6	11.1	16.1	11.8
1995	15.6	15.6	15.6	13.9	16.5	11.3	13.7	12.6	17.5	13.5
2000	16.1	16.2	16.0	14.7	17.4	12.8	14.2	13.5	17.6	14.4
2005	15.8	15.9	15.7	14.1	17.2	12.7	13.6	13.8	17.3	14.3
2010	15.6	15.5	15.6	13.0	16.9	12.2	12.4	13.4	17.1	14.2
2015	16.0	16.0	16.0	12.7	17.5	12.1	12.2	13.2	17.8	14.7
2019	16.5	16.5	16.5	12.6	18.4	12.2	12.2	13.4	18.6	15.4
$\%\Delta$	17.0%	17.1%	16.9%	16.9%	23.7%	23.9%	-3.2%	20.2%	15.4%	30.3%
Yr: Year; Pak: Pakistan; M: Male; F: Female; BA: Baluchistan; AJK: Azad Jammu & Kashmir; GB: Gilgit-Baltistan; ISB: Islamabad										
Capital Territory; KPK: Khyber Pakhtunkhwa; PU: Punjab; SD: Sindh										

The highest increase in prevalence was observed in the Islamabad Capital Territory, with a 76.4% rise. Males showed a higher percentage increase in prevalence (18.0%) compared to females (10.2%). Conversely, Baluchistan and Gilgit-Baltistan experienced a decrease in prevalence rates.

The death rate per 100,000 population showed a modest increase of 1.1%, rising from 0.59 in 1990 to 0.6 in 2019. While the female death rate increased by 5.4%, the male death rate decreased by 3.1%. The most significant increase in death rates was observed in Gilgit-Baltistan (15.2%) and Sindh (15.1%), whereas the Islamabad Capital Territory and Punjab showed a decline.

The overall DALYs due to non-rheumatic VHD in Pakistan increased by 17.0%, from 14.1 in 1990 to 16.5 per 100,000 in 2019. Both males and females exhibited similar increases in DALYs, at 17.1% and 16.9%, respectively. Sindh, Baluchistan, and Azad Jammu & Kashmir reported the most substantial increases in DALYs, indicating significant regional variations.

The age-standardized death rate (ASDR) for non-rheumatic VHD in Pakistan increased by 12.9% over the study period, in contrast to the global and South Asian trends, which showed slight declines. The increasing burden of non-rheumatic VHD in Pakistan highlights the need for targeted health policies and interventions to address this growing public health issue.

# **4** Discussion

The study revealed a notable increase in the burden of non-rheumatic valvular heart disease (VHD) in Pakistan over the past three decades, in stark contrast to the slight declines observed in South Asia and globally. This upward trend in Pakistan, characterized by increased prevalence, mortality, and disability-adjusted life years (DALYs), underscored the pressing need for targeted health policies and interventions.

Several factors contributed to the rising prevalence of non-rheumatic VHD in Pakistan. The demographic shift towards an aging population and increased life expectancy likely played a significant role (16). Economic growth, urbanization, and lifestyle changes, including higher rates of hypertension, diabetes, and smoking, exacerbated the risk factors associated with non-rheumatic VHD (18,19). This was consistent with global trends, where similar socio-economic factors contributed to the rise in non-rheumatic VHD (6). However, the rate of increase in Pakistan surpassed that of many other regions, indicating potentially unique national challenges and healthcare disparities.

The findings also highlighted significant regional variations within Pakistan. The Islamabad Capital Territory exhibited the highest increase in prevalence, which might be attributed to better diagnostic facilities and healthcare access in the capital, leading to higher detection rates. Conversely, regions like Baluchistan and Gilgit-Baltistan showed a decline in prevalence, possibly due to inadequate healthcare infrastructure and underreporting (17). These disparities pointed to the uneven distribution of healthcare resources across the country, necessitating a more equitable allocation to address the healthcare needs of all regions.

In terms of mortality, the slight overall increase masked significant gender differences. While female mortality rates rose, male rates declined, suggesting potential differences in healthcare access, disease management, and underlying health conditions between genders. Previous studies have indicated that women might experience different progression and outcomes of non-rheumatic VHD compared to men, warranting gender-specific health interventions (19).

The study's reliance on data from the Global Burden of Disease (GBD) study provided robust estimates but also introduced limitations. The GBD methodology, while comprehensive, relied on secondary data, which might not capture all nuances of the local healthcare context (25). The lack of national representative studies in Pakistan posed a significant limitation, as the estimates might not fully reflect the onground reality. Furthermore, regional data discrepancies highlighted the need for improved data collection and reporting mechanisms to ensure more accurate and reliable health statistics.

Despite these limitations, the study's strengths lay in its extensive temporal and geographical coverage, providing a detailed analysis of non-rheumatic VHD trends over 30 years. The use of advanced statistical methods, including Poisson regression analysis, ensured robust trend analysis and reliable conclusions. The comparative approach, examining national, regional, and global data, offered valuable insights into Pakistan's unique challenges and opportunities for improvement.

In light of the findings, several recommendations emerged. Strengthening healthcare infrastructure, particularly in underserved regions, was crucial. Enhancing diagnostic capabilities and increasing awareness about non-rheumatic VHD could improve early detection and management, potentially reducing the disease burden. Additionally, addressing the socio-economic determinants of health, such as lifestyle changes and access to healthcare, would be essential in mitigating the risk factors associated with non-rheumatic VHD. Gender-specific health strategies should be developed to address the differential impact of non-rheumatic VHD on men and women.

Overall, the study underscored the growing burden of non-rheumatic VHD in Pakistan and the urgent need for targeted health policies and interventions. By addressing the identified gaps and leveraging the strengths of the healthcare system, Pakistan could effectively manage and reduce the impact of non-rheumatic VHD, improving health outcomes for its population.

# **5** Conclusion

The study concluded that the burden of non-rheumatic valvular heart disease (VHD) in Pakistan has significantly increased over the past 30 years, contrasting with the slight declines observed in South Asia and globally. This rise in prevalence, mortality, and disability-adjusted life years (DALYs) underscores the urgent need for targeted health policies and interventions. Addressing regional disparities in healthcare access, enhancing diagnostic capabilities, and implementing gender-specific health strategies are crucial steps. These measures, coupled with efforts to mitigate socio-economic risk factors, can improve early detection, management, and overall health outcomes, thereby reducing the impact of non-rheumatic VHD in Pakistan.

# **6** References

- 1 Remenyi B, ElGuindy A, Smith Jr SC, Yacoub M, Holmes Jr DR. Valvular Aspects of Rheumatic Heart Disease. Lancet. 2016;387(10025):1335-46.
- 2 Khan MN, Ahmed B, Majeed H, Tareen I, Hassan M, Shehzad M, et al. Thirty Years Trend of Rheumatic Heart Diseases, Pakistan Chapter: Insights from the Global Burden of Disease Study. Pak Heart J. 2022;55(3):231-5.
- **3** Jang SY, Ju EY, Seo SR, Choi JY, Park SJ, Kim DK, et al. Changes in the Etiology of Valvular Heart Disease in the Rapidly Aging Korean Population. Int J Cardiol. 2014;174(2):355-9.
- 4 Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015. N Engl J Med. 2017;377(8):713-22.
- 5 Raheem A, Ahmed S, Kakar AW, Majeed H, Tareen I, Tariq K, et al. Burden of Cardiovascular Diseases in South Asian Region from 1990 to 2019: Findings from the Global Burden of Disease Study. Pak Heart J. 2022;55(1):15-21.
- 6 Chen J, Li W, Xiang M. Burden of Valvular Heart Disease, 1990-2017: Results from the Global Burden of Disease Study 2017. J Glob Health. 2020;10(2).
- 7 Sliwa K, Carrington MJ, Klug E, Opie L, Lee G, Ball J, et al. Predisposing Factors and Incidence of Newly Diagnosed Atrial Fibrillation in an Urban African Community: Insights from the Heart of Soweto Study. Heart. 2010;96(23):1878-82.
- 8 Ananth CV, Hansen AV, Williams MA, Nybo Andersen AM. Cardiovascular Disease in Relation to Placental Abruption: A Population-Based Cohort Study from Denmark. Paediatr Perinat Epidemiol. 2017;31(3):209-18.
- 9 Bainey KR, Gupta M, Ali I, Bangalore S, Chiu M, Kaila K, et al. The Burden of Atherosclerotic Cardiovascular Disease in South Asians Residing in Canada: A Reflection from the South Asian Heart Alliance. CJC Open. 2019;1(6):271-81.
- 10 Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. Circ Res. 2017;121(6):677-94.
- 11 Volgman AS, Palaniappan LS, Aggarwal NT, Gupta M, Khandelwal A, Krishnan AV, et al. Atherosclerotic Cardiovascular Disease in South Asians in the United States: Epidemiology, Risk Factors, and Treatments: A Scientific Statement from the American Heart Association. Circulation. 2018;138(1).
- 12 Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, et al. The Relationship Between Metabolic Risk Factors and Incident Cardiovascular Disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited)—A Prospective Population-Based Study. J Am Coll Cardiol. 2013;61(17):1777-86.
- 13 Palaniappan L, Garg A, Enas E, Lewis H, Bari S, Gulati M, et al. South Asian Cardiovascular Disease & Cancer Risk: Genetics & Pathophysiology. J Community Health. 2018;43(6):1100-14.
- 14 Government of Pakistan. Final Results of Census-2017: Table-5 Population by Selected Age Group, Sex and Rural/Urban. Pakistan Bureau of Statistics. Available from: <u>https://www.pbs.gov.pk/content/final-results-census-2017-0</u>

- **15** Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020. Available from: <u>http://ghdx.healthdata.org/gbd-results-tool</u>
- 16 Nejad M, Ahmadi N, Mohammadi E, Shabani M, Sherafati A, Aryannejad A, et al. Global and Regional Burden and Quality of Care of Non-Rheumatic Valvular Heart Diseases: A Systematic Analysis of Global Burden of Disease 1990–2017. Int J Qual Health Care. 2022;34(2)
- 17 Kurji Z, Premani ZS, Mithani Y. Analysis of the Health Care System of Pakistan: Lessons Learnt and Way Forward. J Ayub Med Coll Abbottabad. 2016;28(3):601-4.
- 18 Wang YT, Tao J, Maimaiti A, Adi D, Yang YN, Li XM, et al. Prevalence of Valvular Heart Diseases and Associated Risk Factors in Han, Uygur and Kazak Population in Xinjiang, China. PLoS One. 2017;12(3).
- 19 Barolia R, Sayani AH. Risk Factors of Cardiovascular Disease and Its Recommendations in Pakistani Context. JPMA. J Pak Med Assoc. 2017;67(11):1723.
- 20 Moore M, Chen J, Mallow PJ, Rizzo JA. The Direct Healthcare Burden of Valvular Heart Disease: Evidence from US National Survey Data. Clinicoecon Outcomes Res. 2016;8:613.
- 21 Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of Valvular Heart Diseases: A Population-Based Study. Lancet. 2006;368(9540):1005-11.
- 22 Towler DA. Molecular and Cellular Aspects of Calcific Aortic Valve Disease. Circ Res. 2013;113(2):198-208.
- 23 Akat K, Borggrefe M, Kaden JJ. Aortic Valve Calcification: Basic Science to Clinical Practice. Heart. 2009;95(8):616-23.
- 24 Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin III JP, et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77(4).
- 25 Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, et al. Health Effects of Dietary Risks in 195 Countries, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017. Lancet. 2019;393(10184):1958-72.

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