Global, Regional, and National Burden of Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990–2017

Running Title: *Yadgir et al.; Global Burden of Aortic and Mitral Valve Disease*

Simon Yadgir MPH et al.

The full author list is available on page 17

Address for Correspondence
Gregory Roth MD MPH, FACC FAHA
Division of Cardiology, University of Washington
Institute for Health Metrics and Evaluation
2301 5th Avenue, Suite 600, Seattle, WA 98121
Tel: (206) 897-2897
Fax: (206) 897-2899
Email: rothg@uw.edu

1

Abstract

Background: Non-rheumatic valvular heart diseases (NRVDs) are common; however, no studies have estimated their global or national burden. As part of the Global Burden of Disease (GBD) 2017 study, mortality, prevalence, and disability-adjusted life years (DALYs) for calcific aortic valve disease (CAVD), degenerative mitral valve disease (DMVD), and other NRVD were estimated for 195 countries and territories from 1990 to 2017.

Methods: Vital registration data, epidemiological survey data, and administrative hospital data were used to estimate disease burden using the GBD modeling framework, which ensures comparability across locations. Geospatial statistical methods were used to estimates disease for all countries, as data on NRVD are extremely limited for some regions of the world, such as sub-Saharan Africa and South Asia. Results accounted for estimated level of disease severity as well as the estimated availability of valve repair or replacement procedures. DALYs and other measures of health-related burden were generated for each sex, five-year age group, location, and year from 1990 to 2017.

Results: Globally, CAVD and DMVD caused 102,700 (95% uncertainty interval [UI] 82,700 to 107,900) and 35,700 (95% UI 30,500 to 42,500) deaths, and had 12.6 million (95% UI 11.4 million to 13.8 million) and 18.1 million (95% UI 17.6 million to 18.6 million) prevalent cases in 2017, respectively. 1.5 million (95% UI 1.4 million to 1.6 million) DALYs were estimated as due to NRVD, globally, representing 0.26% (95% UI 0.22% to 0.27%) of total lost health from all diseases in 2017. The number of DALYs increased for CAVD and DMVD between 1990 and 2017, by 123% (95% UI 101% to 137%) and 64% (95% UI 50% to 75%), respectively. There is significant geographic variation in the prevalence, mortality rate, and overall burden of these diseases, with highest age-standardized DALY rates of CAVD estimated for high-income countries.

Conclusion: These global and national estimates demonstrate that CAVD and DMVD are important causes of disease burden among older adults. Efforts to better understand modifiable risk factors and improve access to valve interventions are necessary if progress is to be made toward reducing, and eventually eliminating, the burden of these highly treatable diseases.

Non-standard Abbreviations and Acronyms:

NRVD	non-rheumatic valve disease
GBD	Global Burden of Disease
DALY	disability-adjusted life year
CAVD	calcific aortic valve disease
DMVD	degenerative mitral valve disease
UI	uncertainty interval
RHD	rheumatic heart disease
SR	sample registration
CODEm	Cause of Death Ensemble model
YLL	years of life lost
YLD	years lived with disability.

Clinical Perspective

What is new?

- In 2017, there were an estimated 12.6 million (95% UI 11.4 million to 13.8 million) cases of CAVD and 18.1 million (95% UI 17.6 million to 18.6 million) cases of DMVD globally, with higher rates of the former among men and higher rates of the latter among women.

- In 2017, there were an estimated 102,700 (95% UI 82,700 to 107,900) CAVD deaths and 35,700 (95% UI 30,500 to 42,500) DMVD deaths, globally.

- Aging and population growth led to a 112% (95% UI 83% to 123%) increase in the number of deaths due to NRVD since 1990.

What are the clinical implications?

- The burden of disease due to CAVD and DMVD is increasing.

- Health systems should anticipate having to care for an increasing number of patients with non-rheumatic valve disease as populations age.

Introduction

Non-rheumatic, non-congenital causes of valvular heart disease are common, treatable, result in substantial morbidity and mortality, and require a substantial allocation of health resources.[1] Despite this public health significance, consistent and comparable estimates of death and disability due to calcific aortic valve disease (CAVD) and degenerative mitral valve disease (DMVD), the two most common types of non-rheumatic valve disease (NRVD),[2] do not exist, as previous efforts to quantify the global burden of valvular heart disease have focused on rheumatic heart disease (RHD).[3] Clinicians and policymakers need evidence on NRVD burden to inform decisions on health system spending and guide trade-off decisions related to investment in the specialized diagnostic and treatment services required to identify and care for patients with these diseases.

The sparsity of comprehensive estimates of valvular heart disease burden is due in part to a limited number of population-based studies of prevalence as well as underdiagnosis of asymptomatic disease.[4,5] An underutilized data source is vital registration, where CAVD and DMVD are routinely reported as an underlying cause of death.

The Global Burden of Disease (GBD) study is a long-term global effort to quantify health-related burden for over 350 specific diseases. GBD methods are well-suited to estimating burden of NRVD as they are designed to integrate all available information, including observed prevalence, case fatality, and mortality, even when data sources are limited. The GBD 2017 study provides for the first time the estimated number of deaths, prevalent cases, and disability-adjusted life years (DALYs) for all NRVD combined, CAVD, DMVD, and other NRVD (non-congenital diseases of the pulmonic and tricuspid valves) for 195 countries and territories from 1990 to 2017, by age and sex.

Methods

The GBD study incorporates information on both fatal and non-fatal disease burden for over 350

causes of disease; NRVD were included for the first time in GBD 2017. To allow estimation of

burden due to each cause of NRVD in data-sparse locations, location-specific covariates were

incorporated into geospatial epidemiologic models. Estimates were produced separately by sex

and for five-year age strata. Uncertainty for all estimates was produced with 1000 draws at each

modeling step, and propagated to each subsequent estimate, with upper and lower bounds

reported at the 97.5% and 2.5% of the distribution of draws.[6] Detailed methods have been

reported previously and are summarized below and in the supplemental appendix.[7,8] The GBD

2017 study complied with the Guidelines for Accurate and Transparent Health Estimates

Reporting (GATHER) statement and the Transparency and Openness Promotion Guidelines.[9]

Results, data sources and detailed analytic methods and code is available via the Global Health

Data Exchange and can be accessed at http://ghdx.healthdata.org/gbd-2017.

Case definitions

Case definitions were based on American Heart Association/American Medical Association

definitions for valvular heart disease and are described in detail in the supplemental appendix.

CAVD was defined as clinical diagnosis of aortic valve stenosis or regurgitation due to

progressive calcification of the aortic valve or annulus leading to hemodynamically moderate or

severe aortic stenosis or regurgitation.[10] Cases of hemodynamically significant CAVD due to

progressive calcification of bicuspid aortic valve were included. DMVD was defined as

myxomatous degeneration of the mitral valve leading to hemodynamically moderate or severe

regurgitation. Other NRVD is a residual category that captures non-rheumatic, non-congenital

valve disorders of the tricuspid and pulmonary valves. A category of total NRVD was defined as

the aggregate of these three categories. Detailed case definitions and inclusion/exclusion criteria

for data sources are provided in the supplemental appendix.

Estimation of deaths

Data on deaths due to total NRVD, CAVD, DMVD, and other NRVD were identified from vital

registration (VR) systems and sample registration (SR) systems using the International

Classification of Diseases (ICD) codes as reported in supplemental table 1. VR systems provide

all available death certificates in a population, whereas SR systems provide an incomplete but

representative sample of death certificates. Verbal autopsy is a method to discern cause of death

based on post-mortem interviews with family members of the deceased, but these reports were

not used for this analysis due to the presumed difficulty of diagnosing NRVD in this manner. VR

and SR data were split into five-year age and sex bins as necessary. Non-specific or implausible

cause of death codes were redistributed to true underlying causes of death as previously

described. This method has been shown to improve data in locations and years where mortality

data systems are incomplete or low-quality.[7] Figure 1 shows the number of location-years of data

available for total NRVD deaths, stratified by 21 global regions. 17,073 country-years of data

were used to estimate mortality for all locations, including those without available data. Counts

for CAVD, DMVD, and other NRVD are shown in the supplemental tables 2 and 3.

Estimates of mortality rates were generated using CODEm, (Cause of Death Ensemble

model) a spatiotemporal modeling tool.[11] This approach allowed estimation of mortality rates

with uncertainty in years and locations where few or no data were available by using information

in surrounding years and locations alongside information from covariates that were found to

successfully predict mortality of these diseases. CODEm weights and combines a large variety of

distinct models based on out-of-sample predictive validity. Candidate covariates tested in models

6

are reported in supplemental tables 4-7. To ensure consistency, cause-specific results of CAVD, DMVD, and other NRVD were adjusted by scaling them within the estimates for total NRVD, all cardiovascular diseases, and all-cause mortality.

Estimation of prevalence and disability-adjusted life years

DisMod-MR was used to produce estimates of prevalence for hemodynamically moderate or worse CAVD and DMVD, by age, sex, location, and year. DisMod-MR is a geospatial compartmental mixed-effects meta-regression tool developed for the GBD study that integrates data on incidence, remission, and mortality to estimate disease prevalence for all locations, including those without available data.[12] This analysis included published literature and administrative health facility data reporting population-level disease rates from 46 countries to estimate disease prevalence. It was assumed that inpatient admissions with primary diagnosis codes for these conditions represented hemodynamically severe valve lesions.

This study estimated the proportion of these cases that remained asymptomatic due to only moderate-severity valve lesions to ensure that, when calculating YLDs, disability would only be attributed to symptomatic cases. Using all available data reporting the proportion of all cases with moderate disease, a logistic regression with a fixed effect over age and a random effect by study was run. This model yielded age-, but not sex- or location-specific estimates of the proportion of asymptomatic cases. Due to a low availability of data, a single pooled model of the asymptomatic proportion of cases was run and applied to estimates of both CAVD and DMVD.

Next, the proportion of cases with severe valve lesions that received treatment with valve replacement or repair was estimated using studies reporting this proportion and a logistic

7

regression model with terms for age and the Healthcare Access and Quality (HAQ) Index. The details on the estimation of the HAQ Index, a measure of health care access and quality for every country, have been previously published.[13] This model informed estimates of the proportion of asymptomatic cases. Due to a low availability of data, a single pooled model of the treated proportion of cases was run and applied to estimates of both CAVD and DMVD.

Due to much more limited data and relatively low levels of population prevalence of non-congenital, non-endocarditis diseases of the tricuspid and pulmonary valves, an alternate strategy was adopted for their estimation, as described in the supplemental appendix.

Disability weights are a standardized measure of disease-specific disability. Years lived with disability (YLDs) were estimated by multiplying the number of cases by heart-failure-specific disability weights developed for the GBD study, and applied separately for proportions of cases estimated to have heart failure that is either medically managed, mild, moderate, or severe, using results from an analysis of the US Medical Expenditure Panel Survey.[8] Supplemental appendix table 8 reports each disease state and its corresponding disability weight. An adjustment for comorbidity was applied following methods developed for the GBD 2017 study, in order to account for co-occurrence of diseases which could lead to overestimation of total YLDs.[8] Years of life lost (YLLs) were estimated by multiplying the difference between standard life expectancy and age at death for each age group by the number of deaths in each age, sex, location, and year.[7] DALYs were calculated as the sum of YLDs and YLLs.

Results were examined by relevant strata, including age, sex, time, location, and levels of socioeconomic development, as represented by quintiles of the Socio-demographic Index (SDI), a measure of average country-level socioeconomic status. The method for estimation of SDI has been previously published.[14] RHD burden from the GBD study has been previously reported,[3]

with GBD 2017 RHD estimates shown here for comparison with NRVD.[8] All country-level results for prevalence, mortality, and DALYs in 2017 are reported in the supplemental appendix and available online (http://ghdx.healthdata.org/gbd-results-tool). The study was approved by the University of Washington Institutional Review Board, IRB application number 46665-EJ.

Results

Disease Prevalence

In 2017, there were an estimated 12.6 million (95% UI 11.4 million to 13.8 million) cases of CAVD, 18.1 million (95% UI 17.6 million to 18.6 million) cases of DMVD, and 26,900 (95% UI 22,100 to 32,100) cases of other NRVD. Between 1990 and 2017, the global number of prevalent cases increased by 124% (95% UI 117% to 131%) and 58% (95% UI 53% to 63%) for CAVD and DMVD, respectively, while the age-standardized prevalence did not change significantly. Prevalence varied widely across levels of SDI (Figure 2) and geography (Figure 3).

The prevalence rate of CAVD was similar in men and women (163 cases per 100,000 in men [95% UI 148 to 179] versus 166 cases per 100,000 in women [95% UI 150 to 184]), while the prevalence rate of DMVD was higher in women than men (265 cases per 100,000 in women [95% UI 259 to 272] versus 209 cases per 100,000 in men [95% UI 204 to 215]).

Among individuals 70 or older, the age group in which disease burden is largest, there was a global prevalence in 2017 of 1,841 per 100,000 persons (95% UI 1,634 to 2,066) for CAVD and 1,827 per 100,000 persons (95% UI 1,773 to 1,888) for DMVD.

Mortality

In 2017, there were 102,700 (95% UI 82,700 to 107,900) CAVD deaths, 35,700 (95% UI 30,500 to 42,500) DMVD deaths, and 6,400 (95% UI 4,800 to 8,600) other NRVD deaths globally. Figure 4 shows the age-standardized mortality rates of CAVD, DMVD, and other NRVD for all regions of the world. The highest rates of CAVD mortality were in high SDI regions such as Western Europe, USA, Canada, Chile, Argentina, Australia, and New Zealand, whereas the highest rates of DMVD mortality were in low SDI regions such as Central sub-Saharan Africa and Oceania.

Between 1990 and 2017, the number of deaths due to all NRVD increased by 112% (95% UI 83% to 123%). In contrast, the age-standardized mortality rates of CAVD and other NRVD have not changed significantly, and the age-standardized mortality rate of DMVD has decreased (-33% since 1990 [95% UI -38% to -27%]). For CAVD, age-standardized death rates peaked in 2012 before slowly declining, though this trend was not significant, while DMVD did show a small but significant decline.

DALYs

CAVD, DMVD, and other NRVD caused 1.5 million (95% UI 1.4 million to 1.6 million) DALYs, 0.87 million (95% UI 0.75 million to 1.0 million) DALYs, and 0.14 million (95% UI 0.12 million to 0.19 million) DALYs, respectively, in 2017. Figure 5 shows the change in number of DALYs between 1990 and 2017, by SDI quintile. Men and women had a similar number of DALYs due to CAVD, DMVD, and other NRVD. The age-standardized DALY rate, however, was higher among men for CAVD (22.9 per 100,000 [95% UI 19.55 to 25.1], compared to 16.83 per 100,000 [95% UI 13.96 to 19.14]), and comparable between men and women for DMVD (11.2 [95% UI 9.4 to 13.2] versus 11.1 [95% UI 9.1 to 13.7] DALYs per 100,000).

NRVD in comparison to RHD

Together, CAVD, DMVD, and other NRVD accounted for 0.26% (95% UI 0.22% to 0.27%) of all global deaths and 0.41% (95% UI 0.33% to 0.41%) of all deaths among those age 70 and older. RHD accounted for 0.51% (95% UI 0.48% to 0.54%) of global deaths. Figure 6 shows the deaths due to RHD compared with deaths due to each type of NRVD, as proportions of all cardiovascular deaths. CAVD accounts for an increasing proportion of acquired valvular heart disease. NRVD contributed a total of 0.1% (95% UI 0.09% to 0.11%) of all DALYs for all ages, and 0.31% (95% UI 0.27% to 0.35%) among those aged 70 and older in 2017. In comparison, RHD caused 0.38% (95% UI 0.34% to 0.41%) of all DALYs for all ages in that year.

Discussion

This study provides the first global and national estimates of disease burden due to NRVD. Globally, the burden of NRVD is increasing, driven by population growth and aging. For 2017, there were an estimated 29.7 million cases of NRVD and 145,000 deaths due to NRVD globally, with 12.6 million of these cases and 103,000 of these deaths due to CAVD. Regular assessment of the burden of NRVD as part of the GBD study will allow countries to benchmark progress in the prevention and treatment of these diseases.

This study estimated large geographic differences in the prevalence of CAVD and DMVD, with the highest rates of disease in high-SDI locations. Levels of atherosclerotic risk factors such as high serum cholesterol, smoking, high body mass index, and high systolic blood pressure are known to vary widely across global populations[15,16] and are causally associated with CAVD.[17,18] Unlike other atherosclerotic diseases, antihypertensive medication and statins have not been found to reverse or slow the progression of CAVD.[19,20] There was much less geographic

11

variation in the mortality rate of DMVD than CAVD, which is consistent with literature

suggesting that DMVD may be independent of traditional atherosclerotic risk and may have

fewer modifiable risk factors.[21,22]

It is possible that rates of CAVD and DMVD are higher in high-SDI locations due to a

lack of competing mortality from other conditions, in particular when those conditions lead to

death at younger ages. Low access to health care services also likely leads to lower survivorship

among individuals with NRVD, which could explain the lower prevalence of CAVD and DMVD

in low-SDI locations. This phenomenon could have also driven the higher rates of DMVD

mortality in some low-SDI locations, which, unlike CAVD, is less likely to be driven by

geographic differences in risk factors. Investments in improved population-level surveillance of

valvular heart diseases would be an important step in further investigating these hypotheses,

especially for low- and middle-income countries.

Access to health care may influence the probability of detecting, accurately diagnosing,

or effectively treating these conditions. This likely contributes to the low burden estimated in

low-SDI locations. Differentiating between low estimated burden of NRVD due to competing

mortality or low survivorship and low estimated burden of NRVD due to low detection is not

possible in this study. Future population-based echocardiographic studies in low- and middle-

SDI locations would be necessary to verify the results of this study.

There is significant variation in the burden of NRVD even among high-income locations.

Variation in genetic factors in a population could explain these geographic differences; for

example, bicuspid aortic valve is a relatively common genetic condition that predisposes an

individual to developing CAVD, and is known to be more common in some populations.[23]

The burden of NRVD varied by both age and sex. Greater age-standardized burden of CAVD among men but comparable burden of DMVD between men and women may be due to increased prevalence of atherosclerotic risk factors among men.[24] The comparable all-age prevalence rates of both diseases for both men and women appears to be due to women developing increasing rates of NRVD as they survive to the oldest age groups. In addition to the marked increase in prevalence and mortality with age, older individuals with prevalent NRVD were more likely to have symptomatic disease and less likely to have had a valve replacement or repair. Population aging has increased the number of older, higher-risk individuals requiring treatment for NRVD, highlighting the potential role of transcatheter aortic valve replacement (TAVR) and transcatheter mitral valve repair (TMVR).[25-27]

Limitations

This study is limited primarily by the availability and quality of echocardiographic data on NRVD at the population level. Though many locations reported NRVD deaths through vital registration or health facility administrative data systems, there are only a small number of population-based studies, now identified by this study's review of the scientific literature, that quantify the prevalence of NRVD using diagnostic imaging. Data on mortality help to inform data on prevalence; however, in sub-Saharan Africa and South Asia, there are few mortality data. Although standardized case definitions were used, it is possible that unmeasured heterogeneity in measurement practices across these studies contributed to geographic variation in the results. The prevalence of bicuspid aortic valve could not be estimated due to limited data. This study also did not differentiate between surgical and catheter-based valve interventions. No data sources reported repeated testing of hemodynamic severity for the same individual, and thus these measures were not adjusted for measurement error or temporal variation. Similarly, assessment

of whether individuals with hemodynamically moderate valvular heart disease are truly symptomatic can be challenging, complicating the limited data available on this subject.

This study used vital registration and administrative hospital data to inform disease trends across geography and time; these data were adjusted to account for differences in reporting of disease across health systems. Varying practices, resources, patient populations, and quality of care across hospitals, however, likely cause differences in the diagnosis of NRVD, which is difficult to distinguish from true differences in the prevalence of NRVD. It is also possible that diagnosis and correct ICD code classification of NRVD increases as procedures to treat these diseases become more available, which could contribute to the estimated increasing rate of NRVD burden over time. The estimation methods used for this study aim to adjust for these biases to create population-representative estimates; however, it is difficult to validate these methods in developing parts of the world given the sparse amount of data on these diseases, and uncertainty intervals in some locations are therefore relatively wide.

Additionally, it may be difficult to distinguish between cases of valve disease that meet this study's criteria for NRVD from cases that arise from other etiologies. Death records used in this study may have misclassified mitral regurgitation due to DMVD as secondary mitral regurgitation, or vice versa. In locations with high prevalence of RHD, NRVD may be misclassified as RHD, or RHD may be misclassified as NRVD. This issue is likely more prominent for DMVD, as RHD most commonly affects the mitral valve.[28] This may explain the higher rates of death due to DMVD reported in parts of sub-Saharan Africa. Determining if these trends are due to true variation in disease burden, differences in excess mortality, or diagnostic misclassification would require improved surveillance for valvular diseases, including more population-based studies using echocardiography. Quantifying the proportion of individuals with

asymptomatic NRVD and treated NRVD is similarly limited by a small number of population-based studies. The increasing availability of less expensive, more portable ultrasound devices may improve feasibility for such studies.

The GBD framework allows us to create standardized estimates with uncertainty for all countries and years despite gaps in data. However, this framework has several limitations. It is not possible to validate estimates in countries with no data, and for this reason estimates of uncertainty are a crucial component of the presented results. Additionally, disability weights represent an average estimate of disease burden for a given disease state. Different disability weights were applied depending on the hemodynamic severity of NRVD, though this does not account for variation in symptoms or disability within the same severity classification.

This study assumed that all valve replacements and repairs were done among symptomatic individuals. Though this is not always the case,[29] it is likely that the number of individuals with hemodynamically moderate disease undergoing surgery remains relatively small. Although operative mortality would have been captured by the mortality models, procedure complications and repeat procedures were not estimated.[30]

Conclusion

CAVD and DMVD are important causes of disease burden among older adults. Increasing burden due to these diseases, primarily driven by population aging, is likely to pose a significant challenge to health systems that are only now investing in the diagnostic and treatment technologies needed to care for affected individuals. Countries will need to reduce the modifiable risk factors driving CAVD as well as improve access to valve repair and replacement if progress

15

is to be made toward reducing, and eventually eliminating, the burden of these highly treatable diseases.

Authors

GBD 2017 NRVD Collaborators

Simon Yadgir[1], MPH; Catherine Owens Johnson[1], PhD; Victor Aboyans[2,3], MD; Oladimeji M Adebayo[4], MD; Rufus Adesoji Adedoyin[5], PhD; Mohsen Afarideh[6], MD; Fares Alahdab[7], MD; Alaa Alashi[8], MD; Vahid Alipour[9,10], PhD; Jalal Arabloo[9], PhD; Samad Azari[9], PhD; Celine M. Barthelemy[1], MPH; Catherine P Benziger[11], MD; Adam E. Berman[12], MD; Ali Bijani[13], PhD; Juan J Carrero[14], PhD; Félix Carvalho[15,16], PhD; Ahmad Daryani[17], PhD; Andre R Durães[18,19], PhD; Alireza Esteghamati[6], MD; Talha A Farid[20], MD; Farshad Farzadfar[21], MD; Eduarda Fernandes[22], PhD; Irina Filip[23,24], MD; Mohamed M Gad[25,26], MD; Samer Hamidi[27], DrPH; Simon I Hay[1,28], FMedSci; Olayinka Stephen Ilesanmi[29], PhD; Seyed Sina Naghibi Irvani[30], MD; Mikk Jürisson[31], PhD; Amir Kasaeian[32,33], PhD; Andre Pascal Kengne[34,35], PhD; Abdur Rahman Khan[20], MD; Adnan Kisa[36,37], PhD; Sezer Kisa[38], PhD; Dhaval Kolte[39], MD; Navid Manafi[40,41], MD; Amir Manafi[42], MD; George A Mensah[35,43], MD; Erkin M Mirrakhimov[44,45], MD; Yousef Mohammad[46], MD: Ali H Mokdad[1,28], PhD; Ruxandra Irina Negoi[47,48], PhD; Huong Lan Thi Nguyen[49], MPH, Trang Huyen Nguyen[50], BMedSci; Molly R Nixon[1], PhD; Catherine M Otto[51], MD; Shanti Patel[52], MD; Thomas Pilgrim[53], MD; Amir Radfar[54,55], MD; David Laith Rawaf[56,57], MD; Salman Rawaf[58,59], MD; Wasiq Faraz Rawasia[60], MD; Aziz Rezapour[9], PhD; Leonardo Roever[61], PhD; Anas M Saad[62], MBBCh; Seyedmohammad Saadatagah[63], MD; Subramanian Senthilkumaran[64], MD; Karen Sliwa[35], MD; Berhe Etsay Tesfay[65], MPH; Bach Xuan Tran[66], PhD; Irfan Ullah[67,68], PhD; Muthiah Vaduganathan[69], MD; Tommi Juhani Vasankari[70], MD; Charles D A Wolfe[71,72], MD; Naohiro Yonemoto[73], MPH; and Gregory A Roth[1,28,51]†, MD.

†Corresponding author

Dr. Gregory A. Roth
Division of Cardiology, University of Washington
Institute for Health Metrics and Evaluation
2301 5th Avenue, Suite 600 | Seattle, WA 98121 | USA
Tel: +1-206-897-2897
rothg@uw.edu

Affiliations

1   Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA
2   Department of Cardiology, Dupuytren University Hospital, Limoges, France
3   Institute of Epidemiology, University of Limoges, Limoges, France
4   College of Medicine, University College Hospital, Ibadan, Ibadan, Oyo, Nigeria
5   Department of Medical Rehabilitation, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria
6   Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Tehran, Iran
7   Evidence Based Practice Center, Mayo Clinic Foundation for Medical Education and Research, Rochester, MN
8   Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH

9   Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Tehran, Iran

10   Health Economics Department, Iran University of Medical Sciences, Tehran, Tehran, Iran

11   Heart and Vascular Center, Essentia Health, Duluth, MN

12   Department of Medicine, Medical College of Georgia at Augusta University, Augusta, GA

13   Social Determinants of Health Research Center, Babol University of Medical Sciences, Babol, Mazandaran, Iran

14   Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

15   Applied Molecular Biosciences Unit, University of Porto, Porto, Portugal

16   Institute of Public Health, University of Porto, Porto, Portugal

17   Toxoplasmosis Research Center, Mazandaran University of Medical Sciences, Sari, Mazandaran, Iran

18   School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil

19   Medical Board, Roberto Santos General Hospital, Salvador, Bahia, Brazil

20   Division of Cardiovascular Medicine, University of Louisville, Louisville, KY

21   Non-communicable Diseases Research Center, Tehran University of Medical Sciences, Tehran, Tehran, Iran

22   REQUIMTE/LAQV, University of Porto, Porto, Portugal

23   Psychiatry Department, Kaiser Permanente, Fontana, CA

24   Department of Health Sciences, A.T. Still University, Mesa, AZ

25   Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH

26   Gillings School of Global Public Health, University of North Carolina Chapel Hill, Chapel Hill, NC

27   School of Health and Environmental Studies, Hamdan Bin Mohammed Smart University, Dubai, United Arab Emirates

28   Department of Health Metrics Sciences, School of Medicine, University of Washington, Seattle, WA

29   Department of Community Medicine, University of Ibadan, Ibadan, Nigeria

30   Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Tehran, Iran

31   Institute of Family Medicine and Public Health, University of Tartu, Tartu, Tartumaa, Estonia

32   Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Tehran, Iran

33   Hematologic Malignancies Research Center, Tehran University of Medical Sciences, Tehran, Tehran, Iran

34   Non-communicable Diseases Research Unit, Medical Research Council South Africa, Cape Town, South Africa

35   Department of Medicine, University of Cape Town, Cape Town, South Africa

36   Department of Health Management and Health Economics, Kristiania University College, Oslo, Norway

37   Department of Health Services Policy and Management, University of South Carolina, Columbia, SC

38   Department of Nursing and Health Promotion, Oslo Metropolitan University, Oslo, Norway

39   Department of Medicine, Brown University, Providence, RI

40   Ophthalmology Department, Iran University of Medical Sciences, Tehran, Tehran, Iran

41 Ophthalmology Department, University of Manitoba, Winnipeg, Manitoba, Canada
42 Department of Surgery, University of Virginia, Charlottesville, VA
43 Center for Translation Research and Implementation Science, National Institutes of Health, Bethesda, MD
44 Faculty of General Medicine, Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan
45 Department of Atherosclerosis and Coronary Heart Disease, National Center of Cardiology and Internal Disease, Bishkek, Kyrgyzstan
46 Internal Medicine Department, King Saud University, Riyadh, Riyadh, Saudi Arabia
47 Anatomy and Embryology Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Bucharest, Romania
48 Department of Cardiology, Cardio-Aid, Bucharest, Bucharest, Romania
49 Institute for Global Health Innovations, Duy Tan University, Hanoi, Hanoi, Vietnam
50 Center of Excellence in Behavioral Health, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam
51 Division of Cardiology, University of Washington, Seattle, WA
52 Department of Medicine, Maimonides Medical Center, Brooklyn, NY
53 Department of Cardiology, University of Bern, Bern, Switzerland
54 College of Graduate Health Sciences, A.T. Still University, Mesa, AZ
55 Medichem, Barcelona, Spain.
56 WHO Collaborating Centre for Public Health Education and Training, Imperial College London, London, United Kingdom
57 University College London Hospitals, London, United Kingdom
58 Department of Primary Care and Public Health, Imperial College London, London, United Kingdom
59 Public Health England, London, United Kingdom
60 Cardiovascular Medicine, West Virginia University, Morgantown, WV
61 Department of Clinical Research, Federal University of Uberlândia, Uberlândia, Brazil
62 Faculty of Medicine, Ain Shams University, Cairo, Egypt
63 Department of Cardiology, Tehran University of Medical Sciences, Tehran, Tehran, Iran
64 Emergency Department, Manian Medical Centre, ERODE, Tamil Nadu, India
65 Department of Public Health, Adigrat University, Adigrat, Tigray, Ethiopia
66 Department of Health Economics, Hanoi Medical University, Hanoi, Vietnam
67 Gomal Center of Biochemistry and Biotechnology, Gomal University, Faisalabad, Punjab, Pakistan
68 TB Culture Laboratory, Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan
69 Heart and Vascular Center, Harvard University, Boston, MA
70 UKK Institute, Tampere, Finland
71 School of Population Health & Environmental Sciences, King's College London, London, United Kingdom
72 Biomedical Research Council, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom
73 Department of Psychopharmacology, National Center of Neurology and Psychiatry, Tokyo, Japan

References

1. Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA, Galper BZ, Meduri CU, Arnold SV, Baron SJ, Reardon MJ, et al. Cost-Effectiveness of Transcatheter Aortic Valve Replacement With a Self-Expanding Prosthesis Versus Surgical Aortic Valve Replacement. *Journal of the American College of Cardiology.* 2016;67: 29–38.

2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *The Lancet*. 2006;368: 1005–1011.

3. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, Nascimento BR, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015. *New England Journal of Medicine.* 2017;377: 713–722.

4. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, Frangou E, Farmer AJ, Mant D, Wilson J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *European Heart Journal.* 2016;37: 3515–3522.

5. Vavalle JP, Phillips HR, Holleran SA, Wang A, O'Connor CM, Smith PK, Hughes GC, Harrison JK, Patel MR. Analysis of Geographic Variations in the Diagnosis and Treatment of Patients With Aortic Stenosis in North Carolina. *American Journal of Cardiology.* 2014;113: 1874–1878.

6. King G, Tomz M, Wittenberg J. Making the Most of Statistical Analyses: Improving Interpretation and Presentation. *American Journal of Political Science.* 2000;44: 341–355.

7. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392: 1736–1788.

8. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392: 1789–1858.

9. Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, Grove JT, Hogan DR, Hogan MC, Horton R, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *The Lancet.* 2016; e19–e23.

10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129: 2440–2492.

11. Foreman KJ, Lozano R, Lopez AD, Murray CJ. Modeling causes of death: an integrated approach using CODEm. *Population Health Metrics*. 2012; 1.

12. Flaxman AD, Vos T, Murray CJL eds. An integrative metaregression framework for descriptive epidemiology. 1 edition. Seattle: University of Washington Press; 2015.

13. Barber RM, Fullman N, Sorensen RJD, Bollyky T, McKee M, Nolte E, Abajobir AA, Abate KH, Abbafati C, Abbas KM, et al. Healthcare Access and Quality Index based on mortality from

causes amenable to personal health care in 195 countries and territories, 1990–2015: a novel analysis from the Global Burden of Disease Study 2015. *The Lancet.* 2017; 231–266.

14. Murray CJL, Callender CSKH, Kulikoff XR, Srinivasan V, Abate D, Abate KH, Abay SM, Abbasi N, Abbastabar H, Abdela J, et al. Population and fertility by age and sex for 195 countries and territories, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392: 1995–2051.

15. Ezzati M, Hoorn SV, Lawes CMM, Leach R, James WPT, Lopez AD, Rodgers A, Murray CJL. Rethinking the "Diseases of Affluence" Paradigm: Global Patterns of Nutritional Risks in Relation to Economic Development. *PLOS Medicine*. 2005;2: e133.

16. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392: 1923–1994.

17. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD. Incidence and Progression of Aortic Valve Calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). *American Journal of Cardiology*. 2010;105: 701–708.

18. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical Factors Associated With Calcific Aortic Valve Disease fn1fn1This study was supported in part by Contracts NO1-HC85079 through HC-850086 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. *Journal of the American College of Cardiology*. 1997;29: 630–634.

19. Chan Kwan Leung, Teo Koon, Dumesnil Jean G., Ni Andy, Tam James. Effect of Lipid Lowering With Rosuvastatin on Progression of Aortic Stenosis. *Circulation*. 2010;121: 306–314.

20. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of Outcome in Severe, Asymptomatic Aortic Stenosis. New England Journal of Medicine. 2000;343: 611–617.

21. Aikawa E, Schoen FJ. Chapter 9 - Calcific and Degenerative Heart Valve Disease. In: Willis MS, Homeister JW, Stone JR, eds. Cellular and Molecular Pathobiology of Cardiovascular Disease. *San Diego: Academic Press*; 2014: 161–180.

22. Delling FN, Vasan RS. Epidemiology and Pathophysiology of Mitral Valve Prolapse: New Insights Into Disease Progression, Genetics, and Molecular Basis. *Circulation*. 2014;129: 2158–2170.

23. Otto CM. Calcification of bicuspid aortic valves. *Heart*. 2002;88: 321–322.

24. Braverman AC, Güven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. *Current Problems in Cardiology*. 2005;30: 470–522.

25. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, Apruzzese P, Fail P, Rinaldi MJ, Smalling RW, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *Journal of the American College of Cardiology*. 2015;66: 2844–2854.

26. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *New England Journal of Medicine*. 2011;364: 2187–2198.

27. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis. *New England Journal of Medicine*. 2014;45: 1790–1798.

28. Zühlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, Mauff K, Islam S, Joachim A, Daniels R, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *European Heart Journal*. 2015;36: 1115–1122.
29. Vaishnava P, Fuster V, Goldman M, Bonow RO. Surgery for asymptomatic degenerative aortic and mitral valve disease. *Nature Reviews Cardiology*. 2011;8: 173–177.
30. Anyanwu AC, Itagaki S, Varghese R, Castillo J, Chikwe J, Adams DH. Re-repair of the mitral valve as a primary strategy for early and late failures of mitral valve repair. *European Journal of Cardio-Thoracic Surgery.* 2014;45: 352–358.
31. Burstein, R, Fleming, T, Haagsma, J et al. Estimating distributions of health state severity for the global burden of disease study. *Population Health Metrics*. 2015:13

Figure Legends

Figure 1: Availability of total non-rheumatic valvular heart disease mortality data by year and geography. The size of each circle represents the number of country-years of data in a given region. Country-years represent the number of countries with at least one data point for a given year. Results are shown colored by super-region as defined by the Global Burden of Disease project. There are fewer data points in high-income North America as compared to Western European and the Caribbean regions because there are fewer countries in the North American region.

Figure 2: Distribution of country-level age-standardized prevalences of CAVD and DMVD by SDI in 2017 (cases per 100,000 persons). The prevalence of both calcific aortic valve disease (CAVD) and degenerative mitral valve disease (DMVD) decreased with socio-demographic index (SDI). The variation in prevalence of CAVD decreased with SDI, whereas the variation in the prevalence of DMVD varied relatively little in Middle to Low SDI countries. Median estimate and 95% uncertainty intervals are shown. Individual dots represent countries outside of the Interquartile Range for a given SDI category.

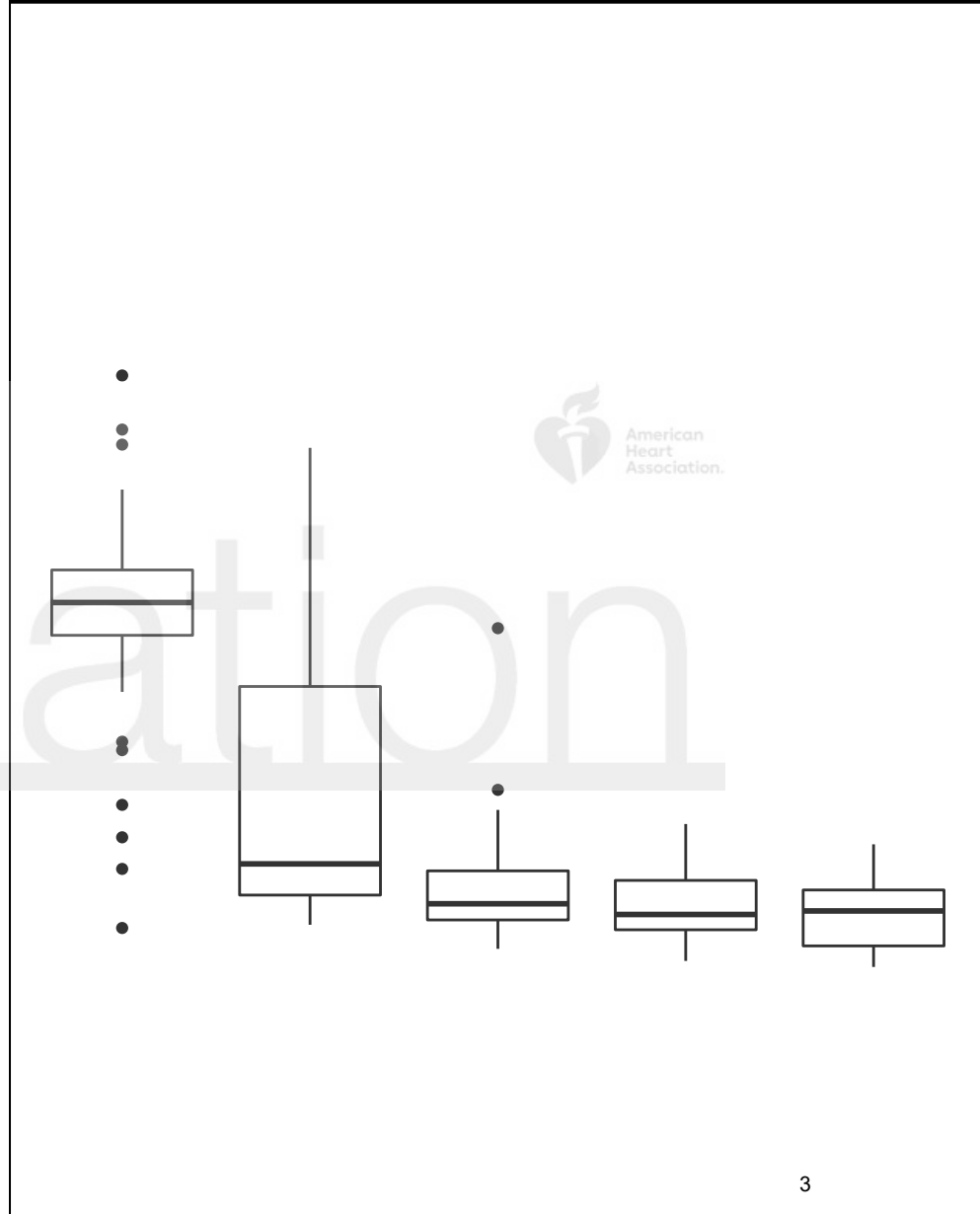**Figure 3:** Age-standardized prevalences of CAVD and DMVD in 2017 (cases per 100,000 persons). CAVD – Calcific aortic valve disease. DMVD – Degenerative mitral valve disease.

Figure 4: Age-standardized mortality rate of CAVD, DMVD, and Other NRVD by region in 2017 (deaths per 100,000 persons).

23

CAVD – Calcific aortic valve disease. DMVD – Degenerative mitral valve disease. NRVD –

Non-rheumatic valvular heart diseases.

Mean estimate and 95% uncertainty intervals are shown.

Figure 5: Number of DALYs due to CAVD, DMVD, and Other NRVD from 1990 to 2017 by

SDI. DALYs – Disability adjusted life-years. CAVD – Calcific aortic valve disease. DMVD –

Degenerative mitral valve disease. NRVD – Non-rheumatic valvular heart diseases. SDI – Socio-

demographic index. Mean estimate (line) and 95% uncertainty intervals (shaded) are shown.

Figure 6: Proportion of all CVD deaths due to RHD, CAVD, DMVD, and Other NRVD from

1990 to 2017. The colored area represents the proportion of all cardiovascular disease (CVD)

deaths due to each respective disease. Rheumatic heart disease (RHD) contributes the largest

proportion of deaths due to these diseases and has declined over time. The proportion of CVD

deaths due to calcific aortic valve disease (CAVD) has increased slightly over time, and the

proportions due to degenerative mitral valve disease (DMVD) and other non-rheumatic valve

diseases (Other NRVD) have remained comparatively small.

Supplemental Materials
- Online-Only Figures I-XIII
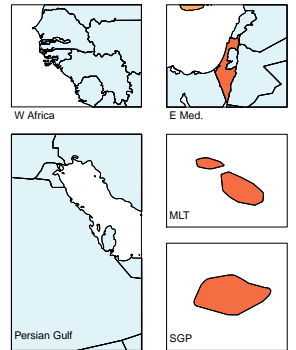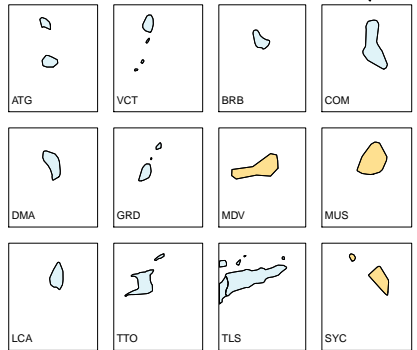- Online-Only Tables I-XXI
- Reference 31

2

Legend:
- <50
- 50 to 100
- 100 to 150
- 150 to 200
- 200 to 250
- 250 to 300
- 300 to 350
- >350

Caribbean

ATG · VCT · BRB · COM
DMA · GRD · MDV · MUS
LCA · TTO · TLS · SYC

W Africa · E Med.
Persian Gulf · MLT · SGP

Balkan Peninsula

MHL · KIR
SLB · FSM
VUT · WSM
FJI · TON

4

Legend:

- <50
- 50 to 100
- 100 to 150
- 150 to 200
- 200 to 250
- 250 to 300
- 300 to 350
- \>350

Inset labels: ATG, VCT, BRB, COM, DMA, GRD, MDV, MUS, LCA, TTO, TLS, SYC, Caribbean, W Africa, E Med., Persian Gulf, MLT, SGP, Balkan Peninsula, MHL, KIR, SLB, FSM, VUT, WSM, FJI, TON

5

7

8