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

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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 estimate 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.

**Key Words:** valve; epidemiology

**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. Detailed methods have been reported previously and are summarized below and in the supplemental appendix. The GBD 2017 study complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement and the Transparency and Openness Promotion Guidelines. 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. 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...
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
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14} RHD burden from the GBD study has been previously reported.\textsuperscript{3}
with GBD 2017 RHD estimates shown here for comparison with NRVD. 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 and are causally associated with CAVD. Unlike other atherosclerotic diseases, antihypertensive medication and statins have not been found to reverse or slow the progression of CAVD. There was much less geographic
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.\textsuperscript{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.\textsuperscript{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. 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).

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, 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.

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

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A full author list follows the references in this manuscript.

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References


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.


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).

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
Calcific aortic valve disease

Degenerative mitral valve disease

Prevalence (cases per 100,000 persons)