Burden of valvular heart diseases: a population-based study

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Background Valvular heart diseases are not usually regarded as a major public-health problem. Our aim was to assess their prevalence and effect on overall survival in the general population.

Methods We pooled population-based studies to obtain data for 11 911 randomly selected adults from the general population who had been assessed prospectively with echocardiography. We also analysed data from a community study of 16 501 adults who had been assessed by clinically indicated echocardiography.

Findings In the general population group, moderate or severe valve disease was identified in 615 adults. There was no difference in the frequency of such diseases between men and women (p=0·90). Prevalence increased with age, from 0·7% (95% CI 0·5–1·0) in 18–44 year olds to 13·3% (11·7–15·0) in the 75 years and older group (p<0·0001). The national prevalence of valve disease, corrected for age and sex distribution from the US 2000 population, is 2·5% (2·2–2·7). In the community group, valve disease was diagnosed in 1505 (1·8% adjusted) adults and frequency increased considerably with age, from 0·3% (0·2–0·3) of the 18–44 year olds to 11·7% (11·0–12·5) of those aged 75 years and older, but was diagnosed less often in women than in men (odds ratio 0·90, 0·81–1·01; p=0·07). The adjusted mortality risk ratio associated with valve disease was 1·36 (1·15–1·62; p=0·0005) in the population and 1·75 (1·61–1·90; p<0·0001) in the community.

Interpretation Moderate or severe valvular diseases are notably common in this population and increase with age. In the community, women are less often diagnosed than are men, which could indicate an important imbalance in view of the associated lower survival. Valve diseases thus represent an important public-health problem.

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Introduction

In the past, valvular heart diseases were typically caused by rheumatic heart disease, which remains a major burden in developing countries.[1] However, in industrialised countries, rheumatic disease has fallen substantially,[1,2] and residual valvular diseases are now mostly degenerative[3–8] and are not regarded as a major public-health problem. The low number of valve replacements, by comparison with coronary bypass surgery,[9] and the low mortality attributed to valve diseases in the USA lend support to this view.[10]

However, several facts suggest that the role of valve disease as a public-health problem should be reconsidered. Valve diseases are poorly represented in the international classification of diseases, and their contribution to mortality and morbidity might have been ignored without echocardiography. Also, the results of the EuroHeart Survey[11] suggest that a substantial burden of such disease exists, at least in Europe, a situation that is lent support by the link between degenerative valve disease, older age,[3–8] and increasing life expectancy.[12]

Nevertheless, the burden of valve diseases is unknown because previous studies have focused mostly on hospital patients[11] and because assessment of valve diseases is clinically imprecise[13] and requires large samples with echocardiography. Seminal echocardiographic studies reported some data for valve disease prevalence.[6,14–16] Although these and observational[17] studies suggest a link to ageing, the absolute prevalence in specific age groups and comprehensive burden of valve diseases are unknown. Furthermore, in the community—a population that can inform us about diseases that are of potential concern—the rates of diagnosed valve diseases are unknown.

We postulated that valvular diseases are highly prevalent and are a public-health problem. Thus, our aim was to assess the prevalence, distribution patterns, and consequences of noteworthy (moderate or severe) left-sided valve disease in the general population and in the community.

Methods

Study population

The National Heart, Lung, and Blood Institute (NHLBI) organises the gathering of data from large epidemiological studies with well-characterised population samples. From this database, we selected studies with prospectively defined echocardiographic valvular analysis. Echocardiography with comprehensive, specific valvular analysis was done prospectively in three large national population-based epidemiological studies—the Coronary Artery Risk Development in Young Adults (CARDIA) Study,[18] the Atherosclerosis Risk in Communities (ARIC) Study,[19] and the Cardiovascular Health Study (CHS).[20] All these studies had strictly defined criteria; technical approaches, design, rationale, and selection criteria were much the same, and all participants were randomly selected from the population.

The NHLBI included 5115 participants aged 18–30 years who had been recruited in 1985–86 from the CARDIA Study (46% black, 54% white), 15 792 participants aged 45–64 years recruited between 1987 and 1989 in the ARIC Study (26% black, 72% white), and 5888 participants aged 65 years and older recruited between 1989 and 1992 (16% black, 84% white) in CHS. Echocardiographs were

obtained in 1989–92 from 4351 CARDIA and 5125 CHS participants, and in 1994–96 from 2435 ARIC participants. We assessed these 11 911 individuals from the NHLBI studies as our sample of the general US population. We reviewed the original prospectively defined echocardiographic criteria for valve diseases and data sets were merged. The participant population was diverse for age, sex, and race (40% black, 59% white, and 1% other) and by design oversampled the elderly population compared with the general population. The study was approved by the Mayo Clinic Institutional Review Board.

Community studies, by contrast with systematic samples of the general population, analyse diseases as they are diagnosed in the population. The Mayo Clinic (Rochester, MN, USA) is the sole provider of echocardiographic services in Olmsted County. The Rochester epidemiology project allows information about all clinical cases of valve disease in Olmsted County to be obtained through a medical-records linkage system that encompasses care delivered to residents of Rochester and Olmsted County by the Mayo Clinic and other providers in the community.[21] More than 90% of the population of Olmsted County has at least one medical contact in every 3-year period with these providers.[21] The demographic characteristic of Olmsted County from the 2000 census was 2·7% black and 90·3% white. Echocardiographs done in 1990–2000 of adult Olmsted County residents 18 years or older were obtained, unless they had previously denied research authorisation in accordance with Minnesota law or if they were incarcerated in the federal medical centre. To estimate the prevalence of valve diseases in the community, residents with moderate or more severe valve disease who were alive in January, 2000, were retained. The echocardiograph closest to January, 2000, was used when more than one was available. We examined the outcome in residents diagnosed with valve disease between 1990 and 1995 to determine the effect of the presence of such conditions on survival.

Procedures

Prospectively defined diagnostic criteria, which formed part of the study protocols, were much the same in the three population-based studies. Judicious, comprehensive assessment was applied to ensure that all clinically significant valve diseases were noted. Specifically, valvular stenosis of moderate or high severity was judged present if valve leaflet motion was obviously limited or if increased flow velocity across the valve suggested such a degree of stenosis.[22,23] Detection and gradation of valvular regurgitation was made on the basis of standard colour doppler criteria for aortic regurgitation (width of regurgitant colour jet area half or more of the width of the left ventricular outflow tract)[24] and mitral regurgitation (maximum displacement of atrial area by regurgitant colour flow jet equal or greater than a third in any view),[25] in agreement with current guidelines.[26]

In the Olmsted County community, valvular stenosis assessment was made on the basis of quantitative criteria. Moderate or more severe valve stenosis (aortic and mitral) was diagnosed if valve area was smaller or equal to 1·5 cm², as determined by doppler measurement.[27] Colour doppler was used to assess presence and severity of aortic[24] and mitral regurgitation.[25] Quantitative regurgitation measures were in development during the study period and, where done, were integrated into the grading of mitral and aortic valve regurgitation severity.[26]

Statistical analysis

We calculated the ratio of participants affected to those examined to estimate age-specific and sex-specific frequencies of valve diseases in the sampled population. Age-specific and sex-specific valve disease rates were compared between groups with *Z* scores; we tested for trends across age groups with the Cochran-Armitage test. Because the epidemiological studies oversampled older participants, the national prevalence of valvular heart diseases was estimated by adjustment of participant frequencies with data from the US 2000 population census. 95% CIs were calculated with Poisson standard errors. Logistic regression was done to test the association of sex and age with the presence of valve disease. We analysed the echo doppler and morphological (left ventricular and atrial) alterations associated with every valve disease and tested for significance with the Wilcoxon rank-sum test. Survival after diagnosis was estimated by the Kaplan-Meier method. Comparisons of survival between population-based participants with and without valve disease were done with the two-sample log-rank test and were adjusted for age, sex, left ventricular ejection fraction, hypertension, diabetes, and coronary artery disease with the Cox's proportional hazards model. Survival after diagnosis in community residents was compared with that of Minnesota white population, matched for age and sex, and tested with one-sample log-rank test. All p values were two-tailed.

Role of the funding source

The NHLBI designed the population studies, was made aware of the analysis done by the investigators, but did not influence data analysis and interpretation. The investigators designed this study and did the analysis and interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

There were 11 911 echocardiographs in the pooled population-based studies. The number of adult residents of Olmsted County alive in January, 2000, with available echocardiographs was 16 501, which represents 18·6% of the adult population of Olmsted County.

In the population-based studies, valvular heart disease was present in 615 (5·2%, 95% CI 4·8–5·6) participants.

	Age (years)					p value for trend	Frequency adjusted to 2000 US adult population
	18–44	45–54	55–64	65–74	≥75		
Participants (n)	4351	696	1240	3879	1745	..	209 128 094
Male, n (%)	1959 (45%)	258 (37%)	415 (33%)	1586 (41%)	826 (47%)	..	100 994 367 (48%)
Mitral regurgitation (n=449)	23, 0·5% (0·3–0·8)	1, 0·1% (0–0·8)	12, 1·0% (0·5–1·8)	250, 6·4% (5·7–7·3)	163, 9·3% (8·1–10·9)	<0·0001	1·7% (1·5–1·9)
Mitral stenosis (n=15)	0, 0% (0–0·1)	1, 0·1% (0–0·8)	3, 0·2% (0·1–0·7)	7, 0·2% (0·1–0·4)	4, 0·2% (0·1–0·6)	0·006	0·1% (0·02–0·2)
Aortic regurgitation (n=90)	10, 0·2% (0·1–0·4)	1, 0·1% (0–0·8)	8, 0·7% (0·3–1·3)	37, 1·0% (0·7–1·3)	34, 2·0% (1·4–2·7)	<0·0001	0·5% (0·3–0·6)
Aortic stenosis (n=102)	1, 0·02% (0–0·1)	1, 0·1% (0–0·8)	2, 0·2% (0·6–1·9)	50, 1·3% (1·0–1·7)	48, 2·8% (2·1–3·7)	<0·0001	0·4% (0·3–0·5)
Any valve disease							
Overall (n=615)	31, 0·7% (0·5–1·0)	3, 0·4% (0·1–1·3)	23, 1·9% (1·2–2·8)	328, 8·5% (7·6–9·4)	230, 13·2% (11·7–15·0)	<0·0001	2·5% (2·2–2·7)
Women (n=356)	19, 0·8% (0·5–1·3)	1, 0·2% (0·01–1·3)	13, 1·6% (0·9–2·7)	208, 9·1% (8·0–10·4)	115, 12·6% (10·6–15·0)	<0·0001	2·4% (2·1–2·8)
Men (n=259)	12, 0·6% (0·3–1·1)	2, 0·8% (0·1–2·8)	10, 2·4% (1·2–4·4)	120, 7·6% (6·3–9·0)	115, 14·0% (11·7–16·6)	<0·0001	2·5% (2·1–2·9)

Prevalence data are n, % (95% CI). Percentages are rounded to one decimal place.

Table 1: **Prevalence of valvular heart diseases in population-based studies**

The national prevalence of valve diseases, taking into account the oversampling of the elderly population, and after adjustment for the national age and sex distribution of the US 2000 population census, was 2·5% (95% CI 2·2–2·7; table 1). Of the diseases studied, mitral regurgitation was the most common, and mitral stenosis the least common. The prevalence of valve disease rose strikingly with advancing age (table 1 and figure 1). A large increase in the prevalence of mitral regurgitation was seen with ageing (table 1). Adjusted for sex, the odds ratio for the association of valve disease with increasing age (per 10 years) was significant for mitral regurgitation (1·84, 95% CI 1·70–1·99; p<0·0001), mitral stenosis (1·65, 1·12–2·43; p=0·01), aortic regurgitation (1·49, 1·30–1·70; p<0·0001), and aortic stenosis (2·51, 2·02–3·12; p<0·0001). There was no difference in age-adjusted valve disease rates in men versus women for most valve diseases (mitral regurgitation, p=0·67; mitral stenosis, p=0·74; aortic regurgitation, p=0·92). However, there was a trend for higher prevalence of aortic valve stenosis in men (p=0·06) than in women, and, after adjustment for age, men had higher rates of aortic stenosis than had women (odds ratio 1·52, 1·02–2·26; p=0·04).

In Olmsted County, clinically diagnosed valvular heart disease was identified in 1505 residents (1·8% adjusted to the adult US population). A significant increase in the prevalence of clinical valvular disease with age was seen in both men and women (figure 1 and table 2). Mitral regurgitation was the most commonly diagnosed valvular disease (1·0%, 0·9–1·1); the least common was mitral stenosis (0·04%, 0·03–0·05). The frequency of mitral valvular disease was higher than aortic valve disease (1·0% [0·9–1·1] *vs* 0·9% [0·8–0·9]; p=0·007). Valvular diseases were more commonly diagnosed in men than in women (p<0·0001 after adjustment for age. Odds ratio 0·90, 0·81–1·01, p=0·07 after adjustment for the entire county population and age).

Population-based participants with valvular diseases showed evidence of cardiac chamber remodelling (table 3), characteristic of volume or pressure overload. Compared with individuals without valvular disease, patients with mitral regurgitation showed left ventricular enlargement (measured by ventricular diameters) without hypertrophy (measured by ventricular mass), whereas those with aortic

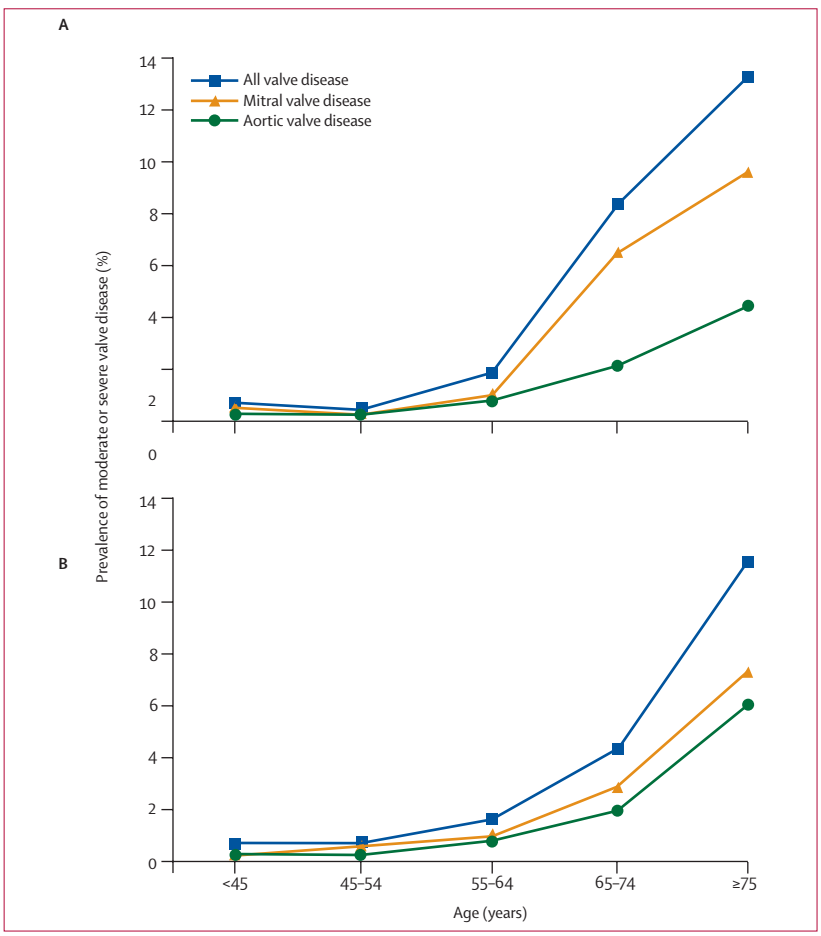


Figure 1: **Prevalence of valvular heart disease by age**
(A) Frequency in population-based studies and (B) in the Olmsted County community.

	Age (years)					p value for trend
	18–44	45–54	55–64	65–74	≥75	
Residents, n	49 957	16 306	10 241	6686	6663	..
Residents examined, n (% men)	4310 (38%)	2737 (48%)	2847 (53%)	2798 (53%)	3851 (41%)	..
Mitral regurgitation (n=874)	57, 0·1% (0·1–0·2)	62, 0·4% (0·3–0·5)	93, 0·9% (0·7–1·1)	186, 2·8% (2·4–3·3)	476, 7·1% (6·5–7·8)	<0·0001
Mitral stenosis (n=33)	5, 0·01% (0–0·02)	3, 0·02% (0–0·05)	3, 0·03% (0·01–0·1)	8, 0·1% (0·05–0·2)	14, 0·2% (0·1–0·4)	<0·0001
Aortic regurgitation (n=282)	55, 0·1% (0·08–0·1)	38, 0·2% (0·2–0·3)	33, 0·3% (0·2–0·5)	41, 0·6% (0·4–0·8)	115, 1·7% (1·4–2·1)	<0·0001
Aortic stenosis (n=547)	51, 0·1% (0·08–0·1)	35, 0·2% (0·2–0·3)	57, 0·6% (0·4–0·7)	96, 1·4% (1·2–1·8)	308, 4·6% (4·1–5·2)	<0·0001
Any valve disease						
Overall (n=1505)	144, 0·3% (0·2–0·3)	121, 0·7% (0·6–0·9)	166, 1·6% (1·4–1·9)	293, 4·4% (3·9–4·9)	781, 11·7% (11·0–12·5)	<0·0001
Women (n=803)	67, 0·3% (0·2–0·3)	47, 0·6% (0·4–0·7)	68, 1·3% (1·0–1·6)	148, 4·2% (3·5–4·9)	473, 10·9% (10·0–11·9)	<0·0001
Men (n=702)	77, 0·3% (0·3–0·4)	74, 0·9% (0·7–1·2)	98, 2·0% (1·6–2·4)	145, 4·7% (3·9–5·4)	308, 13·2% (11·8–14·6)	<0·0001

Data are n, % (95% CI) unless otherwise stated.

Table 2: **Valvular heart diseases diagnosed in Olmsted County**

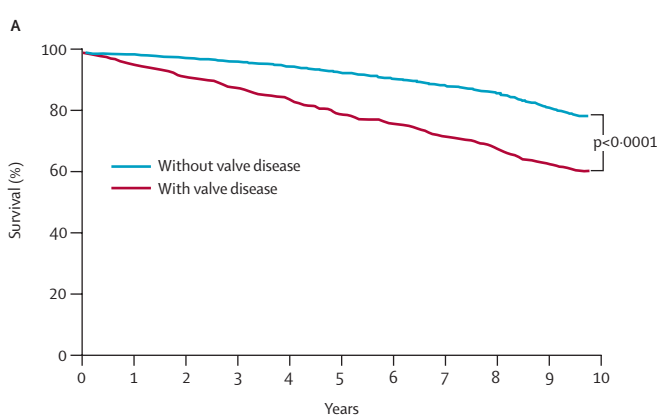
	No valve disease	Mitral regurgitation	Mitral stenosis	Aortic regurgitation	Aortic stenosis
Left ventricular diastolic diameter (mm)	48·9 (5·9)	51·2 (7·9)*	48·6 (6·1)	52·8 (8·4)*	50·5 (7·4)†
Left ventricular systolic diameter (mm)	30·2 (5·9)	31·4 (9·0)	29·7 (8·1)	32·7 (9·6)	30·2 (7·0)
Left ventricular mass (g)	171·1 (70·1)	170·6 (76·8)	176·9 (54·0)	219·2 (139·0)‡	198·7 (80·9)†
Left ventricular fractional shortening	38·4% (7·7)	39·5% (9·8)‡	38·8% (13·1)	38·8% (9·7)	40·7% (8·3)†
Left atrial diameter (mm)	37·3 (6·0)	40·4 (7·7)*	54·2 (8·3)*	41·4 (8·5)*	42·5 (7·8)*

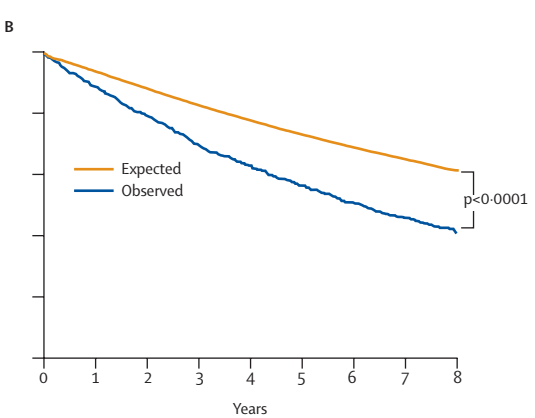
Data are mean (SD). *p<0·0001, †p<0·05, and ‡p<0·001 compared with individuals without valve disease.

Table 3: **Cardiac chamber remodelling associated with valvular heart diseases in the population**

regurgitation showed left ventricular enlargement with hypertrophy. Individuals with aortic stenosis had left ventricular hypertrophy without enlargement, whereas those with mitral stenosis showed substantial left atrial enlargement without left ventricular alteration. The characteristics of each type of valve disease and those of patients without valve diseases were much the same in Olmsted County as in the population-based studies.

In the population-based studies, survival of participants with valve diseases was 79% (SE 2) at 5 years and 68% (1·9) at 8 years, compared with 93% (0·2) and 86% (0·4) at the same time points in those





Number at risk

Valve disease	615	591	566	541	503	456	438	413	376	331
No valve disease	11 296	11 207	11 050	10 785	9507	8215	8001	7735	5054	3233

Number at risk	971	863	765	667	589	518	449	392	73
Expected survival	100%	94%	88%	83%	78%	73%	69%	65%	61%

Figure 2: **Survival after detection of moderate or severe valvular heart disease**
(A) Survival in population-based studies. (B) Expected versus observed survival in Olmsted County. The blue line represents survival of 971 residents diagnosed with valve diseases between 1990 and 1995; the yellow line represents the expected survival in the age-matched and sex-matched population of the county.

without such disease (p<0·0001, figure 2A). The adjusted relative risk of death associated with valvular disease was 1·36 (1·15–1·62; p=0·0005). In 971 Olmsted County residents diagnosed with valvular disease between 1990 and 1995, observed survival was 56% (1·6) at 5 years, compared with an expected survival of 73%. At 8 years, observed survival was 41% (1·7) versus an expected 61% (p<0·0001, figure 2B). The risk of death associated with valve diseases relative to expected (for same age and sex) in Olmsted County was 1·75 (1·61–1·90; p<0·0001).

Discussion

Our study has shown that the population burden of clinically noteworthy valvular heart diseases is considerable in the US population. This burden is also notable for clinically diagnosed valve disease in the community. The difference between the prevalence of such diseases in the population and the percentage of people diagnosed with valvular heart diseases in the community (2·5% *vs* 1·8%) is probably due to undiagnosed valve diseases.

Valve diseases detected in the general population and diagnosed in the community are not mere imaging peculiarities but are, in both settings, associated with characteristics of pressure or volume overload and independent determinants of subsequent mortality. Thus, these observations underscore the relevance of our findings and the need for enhanced research and therapeutic efforts directed towards valvular diseases. Men and women are affected by valve diseases to much the same extent in the population, but women are less often diagnosed in the community, suggesting a diagnostic imbalance that could have serious consequences for women with valve diseases.

The EuroHeart survey[11] attracted attention to the frequent and severe clinical presentation of valve diseases, but the burden of valve diseases cannot be fully appreciated by incident clinical cases of valve diseases that are mostly discovered on the basis of hospitalisation or surgical series. Our study provides information on valve disease in the general population (ie, diagnosed or not) and in the community (ie, individuals coming to clinical attention). Large, randomly selected samples of the US population provide a unique view of the burden of valve diseases in the general population. By use of the 2000 US population census to account for the prospective oversampling of the elderly population, our estimate of the prevalence of valve diseases in adults corresponds to a 2000 burden of 4·2–5·6 million adults with valve diseases in the USA.

Consistent patterns of distribution of valve diseases in the general population and in the community show that older age is an independent determinant of all forms of valve disease that arise with considerable frequency in elderly people, in accord with the notion that the burden of valve disease increases with ageing. Such a trend was suspected on the basis of the age and causal factors in patients with valve diseases who were referred to surgery and in those who participated in the prospective EuroHeart survey,[11] and from small population subsets.[6,14–16] Our study defines the prevalence of valve diseases in all adult segments of the population with robust estimates, which is a result of the coherent and comprehensive echocardiographic methodology in the series we analysed. Importantly, our study shows not only the trend of increasing prevalence with age but also very high absolute rates of valve diseases in elderly people. Indeed, more than one in eight people aged 75 and older have a moderate or severe valve disease. Thus, with the projected shift to an older and larger population,[12] the burden of valvular diseases will probably increase substantially in the future, despite the fall in rheumatic heart disease. The narrow CIs and high coherence between population and community data leave little doubt that this burden is high and will rise.

Not all patients with valve disease are diagnosed and treated, as shown by the lower detection of valve disease in the community than found in the general population. This difference is probably due to the need for echocardiography to be clinically indicated before diagnosis is made, and could have serious consequences for undiagnosed patients, in view of the outcome implications of valve diseases. Aortic stenosis showed the least difference between population and community, possibly because of poor clinical tolerance,[28] but its high prevalence in elderly individuals is confirmed by the population-based Helsinki Ageing Study.[16] This gap in clinical diagnosis of valve diseases, particularly in elderly patients, underscores the importance of quantitative echocardiography[29] whenever the diagnosis is suspected or is simply a possible explanation for unexplained symptoms.

Although most valvular diseases were equally diagnosed in men and women in the population groups, mitral and aortic regurgitation was more often diagnosed in men than in women in the community setting. Reported surgical series of mitral or aortic regurgitation consistently show a male predominance of 60–75%.[30,31] The imbalance of sex ratios between valve regurgitations identified in the general population and those diagnosed in the community or operated on in surgical series is important and could indicate a sex bias in referral patterns for diagnosis and treatment. The mechanisms for such an imbalance should be investigated prospectively.

The valve diseases detected here are not only benign imaging observations but have profound consequences, with cardiac remodelling and excess mortality recorded in the population and in the community despite the availability of radical treatment with surgical valve repair or replacement.[28] We adjusted excess mortality for coronary disease and for expected mortality to remove the potential role of coronary or comorbid

diseases in our estimation of the risk. The excess risk associated with valve disease indicates the importance of early detection of valve diseases. Early detection is key to improving prognosis, since the EuroHeart survey showed that many patients are denied intervention despite definite guideline-based indications, mostly because of older age.[32] Not all elderly patients can be candidates for surgery—eg, because of comorbid conditions—emphasising the importance of emerging percutaneous therapeutic approaches.

Echocardiography is the only method available to estimate the frequency and distribution of valve disease in large populations,[33] and cannot be corroborated by other tests (eg, catheterisation) because of the risk and cost. Studies where valve disease is the primary focus could provide higher sensitivity in detecting such diseases, but are not available. Valve disease aetiology encompasses many causes (eg, rheumatic *vs* degenerative), but our study does not address this issue. Nonetheless, we present a broad descriptive view of the distribution pattern of clinically significant valve diseases in the general population and community.

We did not reread original echocardiographs, and valve disease assessment in the population-based studies was either qualitative or semi-quantitative; detailed assessment with more quantitative measurements was not done.[26,34] However, those individuals identified with valve diseases showed cardiac remodelling consistent with the haemodynamics of each particular valve lesion,[35] which we judged appropriate for the identification of a particular valve disease. Nevertheless, future studies using quantitative measurements in the population are warranted.

The generalisability of the data presented here is essential. In a model that adjusted for age, the NHLBI studies showed no significant heterogeneity of valve disease assessment. Furthermore, the careful sampling of the general population in the NHLBI studies, and the coherence between population and community, provide a robust assessment of the burden of valve disease.

The high prevalence of valvular heart diseases, together with its increase with ageing, indicate a high and increasing burden of such conditions. Valve diseases are underdiagnosed in the community, especially in women, which could represent an important bias, since these diseases are associated with serious physiological and outcome consequences. Valvular heart diseases represent an underappreciated yet serious and growing public-health problem that should be addressed with appropriate resources to improve diagnosis, treatment, and research.

Contributors

V T Nkomo and M Enriquez-Sarano conceived this study and wrote the manuscript. J M Gardin, T N Skelton, and J S Gottdiener were principal investigators for the CARDIA, ARIC, and CHS population studies, and participated in the drafting and review of the manuscript. C G Scott was the data analyst and statistician, and participated in the drafting of the manuscript.

Conflict of interest statement

M Enriquez-Sarano is a consultant for, and has received honoraria from, Edwards Lifesciences, and has received research grants from Pfizer, Astra Zeneca, and Edwards Lifesciences. All other authors declare that they have no conflict of interest.

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