Valvular disease burden in the modern era of percutaneous and surgical interventions: the UK Biobank

Monica Tung,1 Gregory Nah,2 Janet Tang,2 Greg Marcus,3 Francesca N Delling3

ABSTRACT
Background The burden of valvular heart disease (VHD) has increased significantly among ageing populations, yet remains poorly understood in the present-day context of percutaneous and surgical interventions.

Objective To define the incidence, clinical correlates and associated mortality of VHD in the UK Biobank cohort.

Methods We interrogated data collected in the UK Biobank between 1 January 2000 and 30 June 2020. VHD incidence was determined using International Classification of Disease-10 codes for aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis, mitral regurgitation (MR) and mitral valve prolapse. We calculated HRs for incident VHD and all-cause mortality. Clinical correlates of VHD included demographics, coronary artery disease, heart failure and atrial fibrillation. Surgical and percutaneous interventions for mitral and aortic VHD were considered time-dependent variables.

Results Among 486,187 participants, the incidence of any VHD was 16 per 10,000 person-years, with highest rates for MR (8.2), AS (7.2) and AR (5.0). Age, heart failure, coronary artery disease and atrial fibrillation were significantly associated with all types of VHD. In our adjusted model, aortic and mitral VHD had an increased risk of all-cause death compared with no VHD (HR 1.62, 95% CI 1.44 to 1.82, p<0.001 and HR 1.25, 95% CI 1.09 to 1.44, p=0.002 for aortic and mitral VHD, respectively).

Conclusion VHD continues to constitute a significant public health burden, with MR and AR being the most common. Age and cardiac comorbidities remain strong risk factors for VHD. In the modern era of percutaneous and surgical interventions, mortality associated with VHD remains high.

INTRODUCTION
With the declining burden of rheumatic heart disease in non-endemic countries, valvular heart disease (VHD) has increasingly become a disease of ageing.1 2 Multiple cohort-based studies show the sharp rise of incident VHD with age, particularly for mitral regurgitation (MR) and aortic stenosis (AS). The shift in VHD epidemiology from rheumatic disease in younger patients to degenerative valve disease in older adults with comorbidities has translated into widespread use of percutaneous interventions.3 At the same time, improvement in postsurgical care has led to reduction of morbidity for surgical valve replacement4 and repair.5

Prior studies have investigated the overall prevalence, clinical determinants, and outcomes of VHD in both USA and European cohorts.1 2 6–8 Such investigations, some dating to the late 1990s and early 2000s, have highlighted the presence of modifiable risk factors such as hypertension and obesity,7 9 for the development and progression of VHD. These studies have also underlined the high mortality associated with VHD.1 8 However, they have not taken into account the more contemporary influence of percutaneous procedures and improved surgical techniques on VHD burden and outcomes.

By leveraging the UK Biobank, a large, contemporary prospective population-based study, we aimed to investigate (1) the incidence and clinical correlates of VHD taking...
into consideration current burden of known cardiovascular risk factors for VHD and (2) the all-cause and cardiovascular mortality associated with VHD in the modern era of percutaneous and surgical interventions.

**METHODS**

**Data sources**

The UK Biobank is a large biomedical cohort of adults age 40–69 who were recruited between 2006 and 2010 across 22 assessment centres in the UK, with follow-up assessment until 2020. Participant data include baseline interview of self-reported conditions, physical measurements and linkage to International Classification of Disease-10 (ICD-10) codes used by National Health Services for primary care visits, hospital admissions and death records. The UK Biobank includes a ‘first occurrence’ field for new diagnoses that appear in these data sources. Participant-level data provided to researchers are anonymised to protect identity. The study protocol was approved by the UK Biobank (Project 26751).

**Patient and public involvement**

The UK Biobank disseminates research generated from the database, including this study, for participants and the general public to view through their website and twitter feed (https://www.ukbiobank.ac.uk/). Given that the UK Biobank is a deidentified database, participants were not contacted or involved in the design and conduct of this retrospective study.

**Study cohort**

VHD was defined using ICD-10 codes and self-report codes for MR, mitral stenosis (MS), mitral valve prolapse (MVP), tricuspid regurgitation (TR), aortic regurgitation (AR) and AS (online supplemental table 1). Prior validation analyses using ICD-10 codes have found a high positive predictive value for all VHDs studied, with moderate or severe disease severity in the majority of cases, particularly for AS. Due to the rare occurrence of congenital pulmonary valve disease and tricuspid stenosis among adults, these valvular conditions were not included in our investigation, which was based on an adult cohort.

MVP was defined by specific ICD-10 codes (online supplemental table 1). For the purpose of our study, we placed participants with codes for both MVP and MR in the general MR category.

**Clinical correlates**

We chose cardiovascular covariates that are considered contributors or comorbid conditions to VHD. Systolic blood pressure (SBP) and body mass index (BMI) were measured at participant enrolment. Obesity was defined as BMI>30 kg/m². ICD-10 codes (online supplemental table 2) were used to identify the presence of smoking disorder, dyslipidaemia, diabetes, coronary artery disease (CAD), congestive heart failure (CHF), rheumatic fever, atrial fibrillation/flutter (AF), infective endocarditis and pulmonary hypertension.

**Valvular interventions**

The Office of Population Census and Surveys version 4 procedural coding system was used to identify mitral and aortic valve surgery (repair and replacement), and percutaneous interventions including annuloplasties and repairs. Mitral valve interventions included diagnostic codes for MR or MS with a corresponding procedural K code. Percutaneous interventions also included a Y code defining the approach. Aortic valve interventions included a procedural K code, with transcatheter aortic valve replacement (TAVR) defined using addition of Y code. Tricuspid valve interventions were defined in a similar fashion (online supplemental table 3).

**Outcomes**

Incident VHD was defined as ‘first occurrence’ VHD between January 2000 and June 2020, after excluding prevalent cases diagnosed in December 1999 or earlier. Mortality outcomes included all-cause mortality and cardiovascular mortality due to myocardial infarction, stroke, cardiac arrest or CHF (see online supplemental table 4).

**Statistical analysis**

Continuous variables were expressed as median and interquartile ranges or mean and SDs if normally distributed. Categorical data were expressed as number and percentage of total subjects in each group. Incident rates were calculated per 10 000 person years. The assessment period of participants with and without VHD ended at the date of death or June 2020. We used Cox proportional hazard cause-specific models to calculate HRs and 95% CIs. Demographics (age, male sex), risk factors (SBP, obesity, smoking, dyslipidaemia, diabetes, CAD, CHF and AF) and valve interventions were treated as time-dependent covariates when calculating HR for incident VHD. We calculated HR for any VHD as well as valve disease subtypes: TR, MR, MS, AR, AS. As MVP is considered a genetic condition, its development unrelated to typical cardiovascular risk factors, we did not run multivariate Cox models for this valvulopathy.

Next, we assessed any VHD, mitral valve disease (inclusive of MR, MS and MVP) and aortic valve disease (inclusive of AR and AS) as predictors of all-cause and cardiovascular mortality using Cox proportional hazards models. These models were adjusted for age, sex, SBP, obesity, smoking, dyslipidaemia, diabetes, CAD and CHF as well as valvular interventions. We included only those interventions that were relevant to the affected valve (eg, for our aortic valve model we only included aortic valve interventions). Assessments of Kaplan-Meier versus predicted survival plots and log-minus-log survival plots demonstrated that proportional hazards assumptions were met for each outcome.

Statistical analysis was performed using Stata V.14 (StataCorp) and SAS V.9.4 (SAS Institute). All reported p values are two sided, and statistical significance is reported for α=0.05.
RESULTS

Population characteristics

A total of 486,187 subjects were included in the analysis. There were 13,615 cases of new VHD, including 6,900 with MR, 6,020 with AS, 4,238 with AR, 2,095 with MS, 1,664 with TR and 1,119 with MVP. Incidence rate per 10,000 person-years was 16.3 (95% CI 16.0 to 16.5) for all VHD, with the highest for MR at 8.2 (95% CI 8.0 to 8.4), followed by AS at 7.2 (95% CI 7.0 to 7.3) and AR at 5.0 (95% CI 4.9 to 5.2) (Table 1). Demographic characteristics and comorbidities are summarised in Table 2. Compared with those without VHD, those with any VHD tended to be older and were more commonly men (56% vs 45%). Rheumatic fever was rare, but a significant contributor to MS (present in 44% of cases) and MR (present in 12% of cases). Male sex was slightly more prevalent (66% males) among those with MVP (Table 2). AF was common in all valve disease subtypes, but rare in the non-valvular population. There were 78 mitral valve (8 percutaneous), 238 aortic valve (36 percutaneous) and 25 tricuspid valve (5 percutaneous) interventions. Demographic characteristics and comorbidities of patients with VHD who did and did not receive interventions are summarised in online supplemental Table 5. Patients with VHD treated with surgical or percutaneous interventions were predominantly male, and more likely to have CAD or AF. Patients who did not undergo valvular procedures had more CHF.

Comorbidity profiles of incident VHD

Fully adjusted Cox proportional hazard models of incident valve disease are shown in Figure 1. All covariates studied were significantly associated with increased risk of incident VHD. Age significantly increased risk of all incident VHD types. Male sex was associated with incident AS, and AR, but not MS, MR or TR. The greatest HRs for development of any VHD were the following cardiac conditions: AF (HR 9.45, 95% CI 9.08 to 9.93), CAD (HR 5.41, 95% CI 5.12 to 5.71) and CHF (HR 5.2, 95% CI 4.91 to 5.51). Strong positive associations for AF and CHF were observed across all VHD subgroups (Figure 1). CAD was associated with increased hazard for all VHD subtypes except MS. Obesity, SBP, smoking, diabetes and dyslipidaemia were associated with increased risk of AS. Obesity and SBP were associated

Table 1  Valvular heart disease incidence rate and age of diagnosis

| Population   | N  | Age of diagnosis, years | IQR | IR (per 10000 person-years) | 95% CI   |
|--------------|----|-------------------------|-----|-----------------------------|----------|
| Any valve disease       | 13615 | 66                      | 60–72 | 16.3                        | 16.0 to 16.5 |
| MR           | 6900  | 64                      | 59–71 | 8.2                         | 8.0 to 8.4 |
| MS           | 2095  | 61                      | 55–67 | 2.5                         | 2.4 to 2.6 |
| MVP          | 1119  | 63                      | 57–70 | 1.3                         | 1.2 to 1.4 |
| AS           | 6020  | 66                      | 60–72 | 7.2                         | 7.0 to 7.3 |
| AR           | 4238  | 63                      | 58–70 | 5.0                         | 4.9 to 5.2 |
| TR           | 1664  | 68                      | 64–74 | 2.0                         | 1.9 to 2.1 |

AR, aortic regurgitation; AS, aortic stenosis; IR, incidence rate; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; TR, tricuspid regurgitation.

Table 2  Demographics and comorbidities of incident valve disease

|               | No valve disease (N=472328) | Any valve disease (N=13 615) | Mitral valve prolapse (N=1119) | Mitral regurgitation (N=6900) | Mitral stenosis (N=2095) | Aortic regurgitation (N=4238) | Aortic stenosis (N=6020) | Tricuspid regurgitation (N=1664) |
|---------------|------------------------------|------------------------------|-------------------------------|------------------------------|---------------------------|-------------------------------|-------------------------------|-----------------------------|
| Female, n (%) | 259,671 (55)                 | 5980 (44)                    | 497 (44)                      | 3242 (47)                    | 1107 (3)                  | 1829 (43)                    | 2443 (41)                    | 822 (49)                    |
| BMI >30 kg/m², n (%) | 114,072 (24)                  | 4418 (33)                    | 144 (13)                      | 1969 (27)                    | 557 (27)                  | 1320 (31)                    | 2228 (37)                    | 561 (34)                    |
| SBP (mmHg)   | 140±20                       | 145±21                       | 141±20                        | 144±21                       | 143±21                    | 145±21                       | 147±21                       | 144±21                      |
| Smoking (%)  | 6722 (1)                     | 513 (4)                      | 26 (2)                        | 207 (3)                      | 15 (1)                    | 94 (2)                       | 205 (3)                      | 86 (5)                      |
| Dyslipidaemia, n (%) | 9958 (2)                     | 1855 (14)                    | 105 (9)                        | 794 (11.5)                   | 47 (2.2)                  | 360 (8.5)                    | 776 (12.9)                   | 222 (13.3)                  |
| Diabetes, n (%) | 9564 (2.0)                   | 1527 (11.2)                  | 37 (3.3)                      | 590 (8.6)                    | 40 (1.9)                  | 225 (5.3)                    | 735 (12.2)                   | 229 (13.8)                  |
| CAD, n (%)   | 4491 (1.0)                   | 2069 (15.2)                  | 119 (10.6)                    | 911 (13.2)                   | 51 (2.4)                  | 417 (8.9)                    | 883 (14.7)                   | 202 (12.1)                  |
| CHF, n (%)   | 1545 (0.3)                   | 1801 (13.2)                  | 68 (6.1)                      | 1098 (15.9)                  | 99 (4.7)                  | 254 (6.0)                    | 430 (7.1)                    | 395 (23.7)                  |
| Rheumatic fever, n (%) | 30 (0.0)                     | 891 (6.5)                    | 32 (2.9)                      | 836 (12.1)                   | 927 (44.3)                | 146 (3.5)                    | 130 (2.2)                    | 214 (12.9)                  |
| Infective endocarditis, n (%) | 105 (0.0)                   | 974 (7.2)                    | 52 (4.7)                      | 902 (13.1)                   | 932 (44.5)                | 155 (3.7)                    | 125 (2.1)                    | 225 (13.5)                  |
| Atrial fibrillation and flutter, n (%) | 3965 (0.8)                  | 3840 (28.2)                  | 271 (24.2)                    | 2867 (41.6)                  | 1022 (48.8)               | 1994 (40.0)                   | 2002 (33.3)                  | 540 (32.5)                  |
| Pulmonary hypertension, n (%) | 54 (0.0)                     | 320 (2.4)                    | 38 (3.4)                      | 147 (2.1)                    | 35 (1.7)                  | 34 (0.8)                      | 48 (0.8)                      | 185 (11.1)                  |

Values are expressed as means±SD or n (%). BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; SBP, systolic blood pressure.
with increased risk of AR but smoking, diabetes and dyslipidaemia were not. Smoking and dyslipidaemia were associated with increased risk of MR but obesity, SBP and diabetes were not. None of these comorbidities (obesity, SBP, smoking, diabetes, dyslipidaemia) were associated with risk of incident MS.

Mortality and VHD

During 8465586 person-years of follow-up, there were 598 deaths among patients with incident valve disease, including 312 with aortic valve disease (0.37 deaths per 10000 person-years), 213 with mitral valve disease (0.25 deaths per 10000 person-years) and 43 with tricuspid valve disease (0.51 deaths per 10000 person-years). Of the total deaths, 193 (79 with aortic valve disease and 83 with mitral valve disease) were from cardiovascular causes, all driven by cardiac arrest.

After adjusting for covariates, and despite a progressive increase in number of valve interventions over the years (figure 2), all-cause and cardiovascular mortality remained higher for patients with any VHD (HR 1.65, 95% CI 1.52 to 1.81 and HR 1.72, 95% CI 1.47 to 1.97, respectively) compared with those without VHD (figure 3). When considered separately, aortic VHD (HR 1.62, 95% CI 1.44 to 1.82; HR 1.59, 95% CI 1.09 to 1.69), mitral VHD (HR 1.25, 95% CI 1.09 to 1.44; HR 1.46, 95% CI 1.16 to 1.76) and TR (HR 2.74, 95% CI 2.24 to 3.37; HR 3.00, 95% CI 2.12 to 4.16) exhibited higher all-cause and cardiovascular mortality when compared with no VHD (figure 3). There was a trend towards higher mortality among patients who did not receive interventions compared with those who did, although not statistically significant (online supplemental figure 1).
DISCUSSION

We leveraged the UK Biobank, a large, contemporary, prospective population-based study, to demonstrate the following: (1) VHD is common and continues to constitute a significant public health burden, (2) Age and cardiac comorbidities like AF, CHF and CAD remain strong risk factors for VHD, (3) In the modern era of percutaneous and advanced surgical interventions, mortality associated with VHD remains high. The strengths of this study are the large size of the
cohort, with inclusion of participants recruited from multiple community-based centres across the UK, and comprehensive record of diagnoses through linkage to both outpatient and inpatient visits across the entire National Health Service.

VHD burden
In our study, the incidence rate of any VHD was 16.3 per 10,000 person-years, and the most common valve lesions were MR, AS and AR. Although the incidence rate of VHD in the UK Biobank was high, it was lower compared with other contemporary cohorts. A study of the entire Swedish population from 2003 to 2010 determined an incidence rate of VHD of 6.4 per 10,000 person-years.6 Valve prevalence studies using transthoracic echocardiography to detect severe disease including the OxValve cohort in the UK14 and USA studies1 are in agreement with our findings that MR is the most common type of VHD, followed by AS and AR. TR incidence rate has not been previously defined in large cohorts, however, a community-based cohort identified a prevalence of 0.55% for moderate or greater TR by TTE, compared with a VA-based cohort where the prevalence was 15.6%.15,16

Risk factors for incident disease
Age and sex
Compared with other population-based studies where risk of VHD was assessed cross-sectionally, and only adjusting for age and sex,1,16 we assessed incident VHD over 20 years, and analysed the contribution of multiple risk factors in a multivariate model. After adjustment for confounders and potential mediators, we demonstrate that ageing remained an important risk for incident VHD of any aetiology, confirming the importance of age-related degenerative valvular changes.

In our study, men were at higher risk of developing VHD overall, and more so aortic valve disorders. The latter finding may be explained by hormonal differences17 or by a higher burden of other known risk factors such as aortopathies, endocarditis or bicuspid valves.6

The finding that MVP was slightly more common in men differs from other cohort-based and pedigree studies that have highlighted either a similar MVP burden in both sexes or a female predominance.18,19 This may be related to a different genetic background13,20 or different diagnostic definition (ICD codes in the UK Biobank, echocardiography in US studies).

Valvular comorbidities
Our finding that CAD and CAD risk factors (smoking, hypertension, obesity, hyperlipidaemia, diabetes) are significantly associated with incident AS supports the established paradigm that AS and its predecessor aortic sclerosis exist along the spectrum of atherosclerotic degeneration.21

Low BMI has previously been associated with both MR and TR.7 MVP typically is found in individuals with a thin body habitus,18 suggesting the coexistence of mild collagenopathies is some cases. We found that among cardiac conditions studied, AF was a strong predictor of all incident VHD subtypes. The interplay of left atrial dilation and AF has been well described and can explain this finding in the case of MR, where mitral annular dilation leads to failure of leaflets to coapt.22 Similarly, functional TR occurs in the setting of AF even in the absence of left sided heart disease.23 The heightened risk of AS among participants with AF was an unexpected finding and, to our knowledge, has not previously been described. This may reflect shared risk factors that lead to adverse remodelling of both the aortic valve and the atria. It is intriguing to consider the possibility that AF itself, such as due to a resultant unfavourable neurohormonal signalling, may lead to progression of AS.

There was a strong association between CHF and CAD with all incident VHD subtypes, which is consistent with other cohorts.6 CAD and myocardial ischaemia can cause MR and TR, while shared underlying mechanisms may underlie atherosclerosis and predisposing lesions to MS (mitral annular calcification) and AS (aortic sclerosis). Similarly, the association with CHF may be explained by the presence of functional MR and TR in this cohort. All VHD subtypes increase risk of CHF, so there is likely reverse causation or collinearity given presence of shared risk factors. Further, since most patients with CHF and CAD undergo echocardiography, VHD is more likely to be detected.

Valve disease and mortality
The presence of any VHD independently increased the risk of all-cause mortality by 65% and increased the risk of cardiovascular mortality by 72%, even after adjusting for percutaneous and modern-age surgical interventions. In comparison, a multivariate model from a Belgian cohort including age, left ventricular hypertrophy, left ventricular ejection fraction <50%, dyspnoea, Cumulative Illness Rating Scale (CIRS), found a 42% increase risk of all-cause mortality and a twofold increased risk of cardiovascular mortality, with moderate-to-severe valve disease.24 Adjustment for CIRS and echocardiographic abnormalities may explain the difference in mortality risk.

Only 316 patients in the UK Biobank cohort received aortic or mitral valve interventions. Even if we assume that only 10% of reported AS in this sample was severe, this would imply less than half received an aortic valve intervention, which is similar to a recent finding using the US-based Cardiovascular Health Study.25 A French population-based cohort found similar low uptake of valvular interventions despite high associated societal burden in mortality, readmissions and healthcare costs.26 Others have highlighted the under-referral of patients with severe MR for surgical repair27 or transcatheter edge-to-edge repair,28 and of patients with severe AS for TAVR or SAVR.29 The low absolute number of valvular interventions identified in our study may be a consequence of incorrect or insufficient coding efforts leading to underestimation of the true number of surgical or
percutaneous procedures. However, the persistent excess mortality related to VHD, and across different types of VHD (Figures 2 and 3), despite a cumulative increase in interventions over the past 20 years (Figure 2), raises the possibility of low adherence to guideline-directed therapy, including referral to valve centres and access to interventions, similar to what observed in other European and US cohorts. In addition, similar all-cause and cardiovascular mortality in untreated compared with treated VHD suggests that valvular interventions have yet to be incorporated into current practice in a way that offers survival benefit at the population level.

Study limitations
Our study has several limitations. First, UK Biobank participants have lower rates of self-reported chronic diseases and are on average less socioeconomically deprived and more white, compared with UK census data. Second, available ICD-10 codes did not allow grading of VHD severity, though prior studies in Sweden and the USA have shown presence of VHD codes predict moderate or severe disease. Further studies using echocardiography to quantify valvular disease severity are needed to confirm appropriateness of interventions and low-adherence to valvular guidelines in the UK. Third, participants did not undergo universal transthoracic echocardiography screening, and participants with known cardiac conditions like CAD, CHF and AF are more likely to get screened with echocardiography. Hence, VHD may be detected at higher rates among these individuals.

In the UK Biobank, VHD continues to constitute a significant public health burden, with MR and AS being the most common. Age and cardiac comorbidities, namely CHF, CAD and AF remain strong risk factors for VHD. In the modern era of percutaneous and advanced surgical interventions, mortality associated with VHD remains high. The link between excess mortality in VHD and low-adherence to guideline-directed therapies warrants further investigation.

Data availability statement Data may be obtained from a third party and are not publicly available. Data can be obtained by researchers through approved projects (ukbiobank.ac.uk/register-apply).

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID id
Monica Tung http://orcid.org/0000-0002-0508-0339

REFERENCES
1. Nikome VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke Statistics—2021 update: a report from the American heart association. Circulation 2021;143:e254–743.
3. Smith CR, Leon MB, Mack MJ, Svensson LG, Makkar RR, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
4. Saad AM, Kassis N, Isogai T, et al. Trends in outcomes of transcatheter and surgical aortic valve replacement in the United States (2012–2017). Am J Cardiol 2021;141:79–85.
5. Elbadawi A, Elgendy IV, Mohamed AH, et al. Temporal trends and outcomes of transcatheter mitral valve repair and surgical mitral valve intervention. Cardiovasc Revasc Med 2020;21:1560–6.
6. Andell P, Li X, Martinsson A, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017;103:1696–703.
7. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham heart study). Am J Cardiol 1999;83:897–902.
8. Coffey S, Cox B, Williams MJA. Lack of progress in valvular heart disease in the pre-transcatheter aortic valve replacement era: increasing deaths and minimal change in mortality rate over the past three decades. Am J Heart 2014;116:562–7.
9. Nazarzadeh M, Pinho-Gomes A-C, Smith Byrne K, et al. Systolic blood pressure and risk of valvular heart disease: a Mendelian randomization study. JAMA Cardiol 2019;4:788.
10. Sudiwow G, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
11. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res 2008;43:1424–41.
12. Keltie K, Cognigni P, Gross S, et al. Comparison of identifiable and non-identifiable data linkage: health technology assessment of MicroClip using registry, administrative and mortality datasets. BMJ Health Care Inform 2021;28:e100223.
13. Delling FN, Rong J, Larson MG, et al. Familial clustering of mitral valve prolapse in the community. Circulation 2015;131:263–8.
14. d’Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE population cohort study. Eur Heart J 2016;37:3515–22.
15. Topolosky Y, Maltsis S, Medina Inojosa J, et al. Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. JACC Cardiovasc Imaging 2019;12:433–42.
16. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405–9.
17. McRobb L, Handelsman DJ, Heather AK. Androgen-induced progression of arterial calcification in apolipoprotein E-null mice is uncoupled from plaque growth and lipid levels. Endocrinology 2009;150:841–8.
18 Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med 1999;341:1–7.
19 Devereux RB, Brown WT, Kramer-Fox R, et al. Inheritance of mitral valve prolapse: effect of age and sex on gene expression. Ann Intern Med 1982;97:826–32.
20 Delling FN, Li X, Li S, et al. Heritability of mitral regurgitation: observations from the Framingham heart study and Swedish population. Circ Cardiovasc Genet 2017;10:e001736.
21 Stewart BF, Slisovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease fn1 fn1This study was supported in part by contracts NO1-HC85079 through HC-85099E from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. J Am Coll Cardiol 1997;29:630–4.
22 Gertz ZM, Raina A, Saghy L, et al. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. J Am Coll Cardiol 2011;58:1474–81.
23 Utsunomiya H, Itabashi Y, Mihara H, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. Circ Cardiovasc Imaging 2017;10.
24 Rezzoug N, Vaes B, De Meester C, et al. The clinical impact of valvular heart disease in a population-based cohort of subjects aged 80 and older. BMC Cardiovasc Disord 2016;16:7.
25 Owens DS, Bartz TM, Buzkova P, et al. Cumulative burden of clinically significant aortic stenosis in community-dwelling older adults. Heart 2021;107:1493–502.
26 Messika-Zeitoun D, Candolfi P, Vahanian A, et al. Dismal outcomes and high societal burden of mitral valve regurgitation in France in the recent era: a nationwide perspective. J Am Heart Assoc 2020;9:e016086.
27 Dziadzko V, Clavel M-A, Dziadzko M, et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. Lancet 2018;391:960–9.
28 Iung B, Delgado V, Lazure P, et al. Educational needs and application of guidelines in the management of patients with mitral regurgitation. A European mixed-methods study. Eur Heart J 2018;39:1295–303.
29 Tang L, Gössl M, Ahmed A, et al. Contemporary reasons and clinical outcomes for patients with severe, symptomatic aortic stenosis not undergoing aortic valve replacement. Circulation 2018;11.
30 Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 2017;186:1026–34.