

One-year mortality and re-admission rate by disease etiology in National Heart Failure Registry of India.

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
NCOMMS-24-14377-T

We reviewed with interest the manuscript by Sivandasanpillai Harikrishnan et al titled "One-year mortality and re-admission rate in heart failure by disease etiology: Findings from the National Heart Failure Registry of India".

The authors evaluated mortality and re-admission rates in heart failure by etiology in a National Heart failure registry of 10850 patients. The study poses an important question previously evaluated in different populations. They reported that ischemic heart disease was the most common etiology accounting for 2/3 of the participants and that there were differences in one-year mortality rate according to several etiologies.

While the reviewers acknowledged the importance of studying heart failure in different populations given its major clinical and public health impact, the paper suffers from a number of methodological shortcomings that hinder enthusiasm.

Comments

1. Significance: The value of the findings in this report would be better contextualized with information about the registry, explicit discussion of participation bias and representativeness of the registry population vis-à-vis the rest of the population in India that experiences heart failure. It would also be critical to discuss the results in the context of similar studies and issues highlighted by Amezcua et al. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007218>

2. Methods

A. The authors note "wide heterogeneity in epidemiological transition, access to health care and health system readiness...". The authors should detail the source population from which registry participants are drawn and how participants may differ from non-participants. In particular, it is not clear if these were patients first seen at a multidisciplinary clinic or a tertiary center. This information is essential for the readership to understand the relevance of this data to the general population with heart failure in India.

B. The authors should clarify the selection criteria in particular cardiomyopathies such as drug-induced, and alcoholic cardiomyopathies are not included in the report. Conversely, the inclusion of endocarditis is not customary in studies of the epidemiology of heart failure and should be discussed in details. In addition, sensitivity analyses should be conducted with and without including endocarditis among the causes of heart failure.

C. Hypertension is not included as a cause for heart failure. The choice for the taxonomy emitting hypertension should be discussed. Indeed, hypertension is a major cause of heart failure and other countries, the United States in particular. And it would be of interest to adopt a similar taxonomy to facilitate cross study comparisons.

D. The authors should clarify the importance of educational level in the context of the study.

E. It would be of interest to have further details on the epidemiologic transition levels.

F. Methods: what is the average duration of hospital admission of the participants?

G. Methods: Please clarify that all the follow-ups (3 months, 6 months, 1 year) described in the report; nurse vs physician (family physician vs cardiologist?)

3. Results

A. Table 1 is missing information on key risk factors including obesity and smoking, medical history and comorbidities including atrial fibrillation, cerebrovascular disease, and liver disease. Yeah these are important clinical characteristics to understand the population to which this report pertains.

- B. The authors did not report on (a) the treatments received during follow-up and (b) whether the same treatment protocols were used across centers.
- C. The authors should clarify the socioeconomic representation and distribution in the current study considering the emphasis and comparison with high-income regions throughout the Discussion.
- D. Etiologies grouped as "Others" are not introduced in the Methods.
- E. Please address explicitly the capture rate of non fatal events in particular readmissions. Even at one year, there's conceivably significant loss of follow up.

4. Discussion

- A. To help contextualize the findings, the author should comment on the age of the patients in this study in light of the age in other national, multinational studies, or global cohorts.
- B. The authors state "Natriuretic peptides are not routinely done in the Indian context". Further clarification is needed since other studies on patients in India have reported some levels of natriuretic peptides. It would be helpful to clarify if any biomarkers are measured alongside the description of the management protocols followed across the centers, if any.
- C. There is a need to discuss the effect of the treatments received for specific etiologies in the course of follow-up
- D. This section can be improved by discussing the findings in the background of the burden of the disease, environmental contributors to HF risk and management, and gaps mentioned by Amezcua et al.
<https://doi.org/10.1161/CIRCHEARTFAILURE.120.007218>

5. Minor comments

- A. Line 189- 194, Further clarification and references needed.
- B. Please clarify for consistency: Line 81-82 refers to "Registry in 56 centers", but Line 203 refers to 53 hospitals.
- C. Table 3 is not mentioned in the text
- D. It would be of benefit if the same order is maintained in presenting the etiologies In Tables and Figures
- E. Clarify the difference in N for DCM and PPCM between Tables 1 and 2

Reviewer #2

(Remarks to the Author)

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #3

(Remarks to the Author)

This study is the disease specific description of patients recruited in Heart failure (HF) registry in India. More than 10,000 patients are included. The mortality and readmission rates have been analyzed for various disease etiologies of HF. In most cases, the mortality is higher than reported in the literature, the possible reasons are well described under the discussion section. I have the following comments;

1. The higher mortality in infective endocarditis could also be contributed by lack of early surgical intervention as has been reported in several studies from India. This may be mentioned in the discussion section.
2. Patients with unoperated congenital heart disease during adult age not only have heart failure due to pulmonary hypertension, but also due to ventricular dysfunction.
3. Was there any correlation between mortality with education status or were there any regional differences?
4. In Table 2 should mortality should replace event rates since events may include readmissions also.

Reviewer #4

(Remarks to the Author)

Comments to the author:

This is an important paper which deals in detail with the spectrum of HF in India. The important features are representation from across the country and not from one region. The analysis of mortality according to the etiology of HF is another noteworthy feature. The conclusions are justified and relevant for analysing the allotment of healthcare resources. As compared to the other HF registries published from India, the scope of this one is much wider.

Some points to be corrected, if possible:

- 1- Any information about the differences between rural and urban population?
- 2- Any information about up-titration of doses?
- 3- Any information about the use of GDMT from different regions of the country?
- 4- Any information about the use of devices?
- 5- Incidence of Hypertension in ischemic aetiology is not mentioned

The grammar needs to be cleaned up in some areas.

Version 1:

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Reviewer #2

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Reviewer #4

(Remarks to the Author)

The points raised by me have been addressed satisfactorily. No further comments

Reviewer #5

(Remarks to the Author)

I was asked to stand in for reviewer 1 and evaluate the rebuttal to the comments made by reviewer 1.

The authors seem to have appropriately addressed the concerns by reviewer 1. I did not re-review the entirety of the revised manuscript.

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NCOMMS-24-14377-T

Thank you for considering our manuscript and sharing the expert reviewers' comments. We provide below a detailed point by point reply to the comments. We have also modified the manuscript and included more data in supplementary files.

Recommendations from the guidelines

Please note that we require that the following recommendations from the guidelines are followed:

1. If the research findings apply to only one sex or gender, that must be indicated in the title and/or abstract.

Response: The research findings apply to both males and females.

2a. For studies involving vertebrates animal and cell lines- The Reporting Summary should include whether sex was considered in the study design.

Response: Not applicable.

2b. For studies involving human research participants- The Reporting Summary should include whether sex and/or gender was considered in the study design and whether sex and/or gender of participants was determined based on self-report or assigned (and methodology used).

Response: We collected self-reported data on sex.

3. Data should be reported disaggregated for sex and gender where this information has been collected and consent has been obtained for reporting and sharing individual-level data; disaggregated numbers for individual experiments must be provided in the source data as appropriate whereas overall numbers may be provided in the Nature Portfolio Reporting Summary.

Response: We have presented the combined data in the main manuscript text and provided the proportion of males and females in the study population stratified by the main exposure variable of interest. Furthermore, we provided the sex-disaggregated data in the supplementary files (Tables S1a, S1b, S2a, and S2b).

Information on the points above should be included in the revised manuscript and detailed in the cover letter.

Response: We have cited the supplementary tables (S1A, S1B, S2A, and S2B) in the main text and included the details in the cover letter.

In addition, please note that if sex- and gender-based analyses have been performed a priori, results should be reported regardless of positive or negative outcome. We discourage conducting post hoc sex- and gender-based analysis if the study design is insufficient (for example, low sample size) to enable meaningful conclusions.

If no sex- and gender-based analyses have been performed, please indicate the reasons for the lack of these analyses in the Reporting Summary.

Response: As mentioned in the previous comments, we have provided sex-disaggregated data.

All Nature Communications manuscripts must include a “Data Availability” section after the Methods section but before the References.

Response: We have added a data availability session. Anonymized and deidentified data will be made available as part of supplementary files.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

We reviewed with interest the manuscript by Sivandasanpillai Harikrishnan et al titled “One-year mortality and re-admission rate in heart failure by disease etiology: Findings from the National Heart Failure Registry of India”. The authors evaluated mortality and re-admission rates in heart failure by etiology in a National Heart failure registry of 10850 patients. The study poses an important question previously evaluated in different populations. They reported that ischemic heart disease was the most common etiology accounting for 2/3 of the participants and that there were differences in one-year mortality rate according to several etiologies.

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Comments

1. Significance: The value of the findings in this report would be better contextualized with information about the registry, explicit discussion of participation bias and representativeness of the registry population vis-à-vis the rest of the population in India that experiences heart failure. It would also be critical to discuss the results in the context of similar studies and issues highlighted by Amezcua et al.

<https://doi.org/10.1161/CIRCHEARTFAILURE.120.007218>

Response: The detailed Method of this study is already published (Harikrishnan et al. Indian Heart J. 2019 Nov-Dec; 71(6): 488–491). We established a hospital-based registry in 53 centres nationwide, with approximately 200 patients from each center. We included regions with various ethnicities and different epidemiological transition levels to improve the external validity of the study. This is the first registry from India with representation from multiple regions of India. We have recruited consecutive patients from these hospitals to minimize bias in patient selection. We did not recruit stable heart failure patients from the outpatient department.

We have already cited the paper by Martinez-Amezcu, P., et al. The Upcoming Epidemic of Heart Failure in South Asia. Circ Heart Fail 13, e007218 (2020) in our manuscript (ref 3). Our group has contributed and listed as authors in this paper. As suggested by the reviewer, we have discussed the results of our manuscript based on the summary results presented in the paper by Martinez-Amezcu, P., et al.

2. Methods

A. The authors note “wide heterogeneity in epidemiological transition, access to health care and health system readiness...”. The authors should detail the source population from which registry participants are drawn and how participants may differ from non-participants. In particular, it is not clear if these were patients first seen at a multidisciplinary clinic or a tertiary center. This information is essential for the readership to understand the relevance of this data to the general population with heart failure in India.

Response: *We recruited consecutive patients with acute decompensated HF from the participating centres. We had no refusal to participate in the registry. We did not recruit patients from OPDs or Clinics. Approximately 200 Consecutive patients were recruited from each of the participating centres. Since we wanted an echocardiogram in all patients to confirm the diagnosis, the study was restricted to centres where there was an echocardiography equipment. Therefore, patients admitted to other centres without access to Echo and with a clinical diagnosis of heart failure may not have been represented in our registry. We appreciate the concerns of the reviewer. However, it is a limitation of all registries from low and middle-income regions.*

B. The authors should clarify the selection criteria in particular cardiomyopathies such as drug-induced, and alcoholic cardiomyopathies are not included in the report. Conversely, the inclusion of endocarditis is not customary in studies of the epidemiology of heart failure and should be discussed in details. In addition, sensitivity analyses should be conducted with and without including endocarditis among the causes of heart failure.

Response: *They are included in “others” as the numbers were very small. We have explained the disease etiologies included in the ‘others’ category in the footnotes of the table 1. Infective endocarditis was the primary etiology in only 16 patients (0.2%). As the number of cases of IE was very small, there is no difference in the overall mortality rate with and without IE.*

C. Hypertension is not included as a cause for heart failure. The choice for the taxonomy emitting hypertension should be discussed. Indeed, hypertension is a major cause of heart failure and other countries, the United states in particular And it would be of interest to adopt a similar taxonomy to facilitate cross study comparisons.

Response: *The category of Hypertension induced HF is included in the “others” category. The proportion of patients with hypertension-induced HF was very small (0.69%), and the mortality was relatively low in this group. This is consistent with data from other HF registries in India such as the Trivandrum Heart Failure Registry (Eur J Heart Fail. 2015 Aug;17(8):794-800), Kerala Heart Failure Registry (European Heart Journal, Volume 43, Issue 9, 1 March 2022, Pages 908–915) and Medanta heart failure registry (Indian Heart J. 2019 May-Jun; 71(3): 242–248). The split up of the category of “others” is as follows. Hypertension (n=75), Chronic Obstructive Pulmonary Disease (n=3), Pulmonary embolism (n=2), pulmonary artery hypertension (n=9), constrictive pericarditis (n=3), and arrhythmia-induced CM (n=7).*

D. The authors should clarify the importance of educational level in the context of the study.

Response: *We have shown that HF affects all socio-economic groups, and there is a clear survival disadvantage in patients in the low socio-economic group compared to relatively higher educational groups (European Journal of Heart Failure (2015) 17, 794–800). We*

have used education as a proxy variable to assess socioeconomic status. Education as a proxy variable for socioeconomic status is widely accepted in Indian settings (Prev Med. 2011 Jun;52(6):471-2; Indian J Med Res. 2010 Nov;132(5):617-22; Proc Natl Acad Sci U S A 2007 Oct 9;104(41):16263-8). We have used educational status and classified participants into four different groups. It shows that the distribution is consistent with that of the general population and highlights the representation and internal/external validity of the study.

E. It would be of interest to have further details on the epidemiologic transition levels.

Response: Different states in India are in different epidemiological transition levels. For example, some Indian states like Kerala and Punjab are in advanced epidemiological transition but states like Bihar or Orissa are in early phases. The classification of states into different ETLs was based on the disease burden assessment using GBD methodology (Lancet 2017 Dec 2;390(10111):2437-2460). The ratio of disability-adjusted life years (DALYs) from communicable, maternal, neonatal, and nutritional diseases (CMNNDs) to those from non-communicable diseases (NCDs) and injuries combined was used for stratification into different ETLs. A smaller ratio indicates advancing epidemiological transition—ie, a higher burden of NCDs and injuries than CMNNDs. Since we have identified centres from regions with varying ETLs, our data represent different regions.

F. Methods: what is the average duration of hospital admission of the participants?

Response: The median duration of hospital stay was 7.63 (4-13) days.

G. Methods: Please clarify that all the follow-ups (3 months, 6 months, 1 year) described in the report; nurse vs physician (family physician vs cardiologist?)

Response: All the follow-ups were planned at the recruiting hospitals where the treating physician/cardiologist attended to the patient. If some patients cannot come in person, the follow-up data were collected over the telephone by the study nurse (trained by the study team) appointed at the respective hospitals.

3. Results

A. Table 1 is missing information on key risk factors including obesity and smoking , medical history and comorbidities including atrial fibrillation, cerebrovascular disease, and liver disease. Yeah these are important clinical characteristics to understand the population to which this report pertains.

Response: We have added information on obesity, smoking, alcohol use, AF, stroke, CKD, and COPD in Table 1. We have not collected information on liver disease. One-third of the participants were smokers (33.8%). One-sixth of the participants were alcohol users. The mean BMI was 24.2 kg/m². One-tenth of the participants reported AF. Stroke was reported in 2.9% of the participants.

B. The authors did not report on (a) the treatments received during follow-up and (b) whether the same treatment protocols were used across centers.

Response: The treating cardiologist/physician was encouraged to follow the ESC/ACC-AHA guidelines as part of the registry.

C. The authors should clarify the socioeconomic representation and distribution in the current study considering the emphasis and comparison with high-income regions throughout the Discussion.

Response: We have used education as a proxy for socioeconomic status. We have representation of participants from all four groups. We also have regional representation based on epidemiological transition levels. ETLs are also proxy variables for economic development. However, we agree that our study population will differ from high-income countries due to the gross differences in per-capita income between high-income and LMIC regions.

D. Etiologies grouped as “Others” are not introduced in the Methods.

Response: Since the numbers are small, it was not included in the tables. We have provided the detailed break-up in response to the comment 2C.

* The split up of the " others " category is as follows. Hypertension (n=75), Chronic Obstructive Pulmonary Disease (n=3), Pulmonary embolism (n=2), pulmonary artery hypertension (n=9), constrictive pericarditis (n=3), and arrhythmia-induced CM (n=7).

E. Please address explicitly the capture rate of non fatal events in particular readmissions. Even at one year, there's conceivably significant loss of follow up.

Response: All reported readmissions and procedures like angioplasty, CABG, ICD / CRT implantations were included in the data. We agree that 4.8% of patients were lost to follow-up. However, this is reasonable compared to other registries. We could achieve a relatively low attrition rate due to our active follow-up.

4. Discussion

A. To help contextualize the findings, the author should comment on the age of the patients in this study in light of the age in other national, multinational studies, or global cohorts.

Response: The mean age of the study population was 59.9 (SD = 13.5) years. This is at least ten years younger than that reported from the USA (ADHERE, Am Heart J. 2005; 149: 209–216), Europe (Eur J Heart Fail. 2016; 18: 613–625), and China (Li et al. HERO study Eur J Heart Fail. 2020 Apr;22 (4): 646-660. Other Indian studies reported similar age profiles for HF patients. (Jayagopal et al, Int J Cardiol . 2022 Jun 1;356:73-78.). We have added a statement to reflect the age differences in the discussion section.

B. The authors state “Natriuretic peptides are not routinely done in the Indian context”. Further clarification is needed since other studies on patients in India have reported some levels of natriuretic peptides. It would be helpful to clarify if any biomarkers are measured alongside the description of the management protocols followed across the centers, if any.

Response: Natriuretic peptides are not universally available in all hospitals across India and are costly. So, it was not mandated in the diagnosis of HF in our registry. We followed

the ESC 2016 criteria for diagnosis of HF. NP-guided management is not routinely followed in Indian hospitals.

C. There is a need to discuss the effect of the treatments received for specific etiologies in the course of follow-up.

Response: The vast majority (90%) of the patients had ischemic heart disease and dilated cardiomyopathy. Only 12.7% of the patients had an EF > 50%. Nearly 88% of the patients were eligible for guideline-directed therapy for HFrEF /HFmrEF as per the ESC / ACC-AHA guidelines). RHD patients underwent treatment for the respective valve diseases. HCM patients underwent Alcohol septal ablation or septal myectomy if their symptoms were not controlled with medications.

D. This section can be improved by discussing the findings in the background of the burden of the disease, environmental contributors to HF risk and management, and gaps mentioned by Amezcua et al. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007218>.

Response: We have limited space to expand the discussion section. Since we focus on etiology, we have not expanded on risk factors and disease burden. We have however, cited the key points in the article suggested by the reviewer.

5. Minor comments

A. Line 189- 194, Further clarification and references needed.

Response: We have added citations and improved the clarity of the sentences.

B. Please clarify for consistency: Line 81-82 refers to “Registry in 56 centers”, but Line 203 refers to 53 hospitals.

Response: The registry was initially planned in 56 centres, but recruitment could be done only in 53 centers. We have corrected this error in the manuscript.

C. Table 3 is not mentioned in the text

Response: Apologies for this omission. We have cited Table 3 along with Figure 2b.

D. It would be of benefit if the same order is maintained in presenting the etiologies In Tables and Figures

Response: We have clubbed some disease etiologies to reduce the cluttering in Figures 2A and 2B. The detailed break-up is provided in Tables 2 and 3.

E. Clarify the difference in N for DCM and PPCM between Tables 1 and 2

Response: Apologies for this error. DCM and PPCM are reported in 1877 and 49 participants, respectively.

Reviewer #2 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response: Thank you very much.

Reviewer #3 (Remarks to the Author):

This study is the disease specific description of patients recruited in Heart failure (HF) registry in India. More than 10,000 patients are included. The mortality and readmission rates have been analyzed for various disease etiologies of HF. In most cases, the mortality is higher than reported in the literature, the possible reasons are well described under the discussion section. I have the following comments;

1. The higher mortality in infective endocarditis could also be contributed by lack of early surgical intervention as has been reported in several studies from India. This may be mentioned in the discussion section.

Response: Thank you for the comments. We have modified the discussion and incorporated your suggestion.

2. Patients with unoperated congenital heart disease during adult age not only have heart failure due to pulmonary hypertension, but also due to ventricular dysfunction.

Response: Thank you for pointing out this correctly. We have added it to the discussion.

3. Was there any correlation between mortality with education status or were there any regional differences?

Response: Yes, there were differences. Mortality was relatively higher in lower education status. The regional differences among states in different epidemiological transition levels are being analyzed in a separate paper.

4. In Table 2 should mortality should replace event rates since events may include readmissions also.

Response: Thank you for pointing out this error. We have changed the title.

Reviewer #4 (Remarks to the Author):

Comments to the author:

This is an important paper which deals in detail with the spectrum of HF in India. The important features are representation from across the country and not from one region. The analysis of mortality according to the etiology of HF is another noteworthy feature. The conclusions are justified and relevant for analysing the allotment of healthcare resources. As compared to the other HF registries published from India, the scope of this one is much wider.

Response: Thank you for the positive comments.

Some points to be corrected, if possible:

1- Any information about the differences between rural and urban population?

Response: Thank you for this comment. There are regional and socio-economic differences in mortality. We are currently analyzing it as a separate paper. We have limitations in adding more text to the existing paper.

2- Any information about up-titration of doses?

Response: We have not collected information on the up-titration of drugs. We agree that titration data would have added more information.

3- Any information about the use of GDMT from different regions of the country?

Response: The analysis of the use of GDMT in different states based on ETL is being analyzed in a separate paper.

4- Any information about the use of devices?

Response: Device use is very low (1%).

5- Incidence of Hypertension in ischemic aetiology is not mentioned

Response: Hypertension in ischemic etiology is 53.5%. It is included in Table 1, S1A, S1B, S2, S2A and S2B.

The grammar needs to be cleaned up in some areas.

Response: Sorry that some grammatical mistakes had crept in. We have tried to modify the manuscript and corrected all grammatical mistakes.

Table 1. Baseline characteristics of the study population stratified by disease etiology

Variables	IHD (N=7800)	DCM (N=1877)	RHD (N=586)	NRHD (N=211)	HCM (N=92)	CHD (N=78)	PPCM (N=49)	RCM (N=38)	IE (N=16)	Others* (N=98)	Total (N=10845)
Age in years, mean(SD)	61.9(11.9)	56.8(14.7)	47.7(15.3)	63.3(15.3)	60.5(13.8)	44.3(15.1)	29.2(6.1)	59.1(13.6)	50.3(19.1)	57.4(15.5)	59.9(13.5)
Female, n(%)	2021(25.9)	706(37.6)	340(58.0)	95(45.0)	45(48.9)	40(51.3)	49(100.0)	17(44.7)	6(37.5)	47(47.9)	3366(31.0)
Education, n(%)											
0-4 years	1881(24.1)	571(30.4)	161(27.5)	53(25.1)	33(35.9)	13(16.7)	6(12.2)	8(21.1)	1(6.3)	37(37.8)	2764(25.5)
5-8 years	2009(25.8)	480(25.6)	175(29.9)	60(28.4)	20(21.7)	26(33.3)	9(18.4)	5(13.2)	4(25.0)	15(15.3)	2803(25.9)
9-12 years	2809(36.0)	600(32.0)	208(35.5)	69(32.7)	27(29.4)	27(34.6)	20(40.8)	13(34.2)	7(43.8)	34(34.7)	3814(35.2)
More than 13 years	1098(14.1)	224(11.9)	42(7.2)	29(13.7)	12(13.0)	12(15.4)	14(28.6)	12(31.6)	4(25.0)	12(12.2)	1459(13.5)
BMI, Mean (SD)	24.4(3.9)	24.1(4.2)	22.3(3.9)	24.7(4.57)	25.6(4.4)	22.7(3.5)	22.8(4.3)	24.3(3.9)	22.8(4.1)	24.5(5.1)	24.2(4.0)
Overweight, n(%)	2976(38.2)	709(37.9)	127(21.8)	91(43.1)	45(48.9)	21(26.9)	14(28.6)	14(37.8)	3(18.8)	39(40.2)	4,039(37.3)
Regions, n(%)											
Low ETLs	1706(21.9)	490(26.1)	152(25.9)	21(9.9)	9(9.8)	9(11.5)	17(34.7)	5(13.2)	0	15(15.3)	2424(22.4)
Lower-middle ETLs	813(10.4)	197(10.5)	37(6.3)	24(11.4)	2(2.2)	6(7.7)	6(12.2)	6(15.8)	1(6.3)	8(8.2)	1100(10.2)
Higher-middle ETLs	2749(35.2)	895(47.7)	254(43.3)	90(42.7)	63(68.5)	38(48.7)	18(36.7)	15(39.5)	7(43.8)	40(40.8)	4169(38.4)
High ETLs	2532(32.5)	295(15.7)	143(24.4)	76(36.0)	18(19.6)	25(32.0)	8(16.3)	12(31.6)	8(50.0)	35(35.7)	3152(29.1)
Comorbidities, n(%)											
Hypertension	4171(53.5)	733(39.1)	121(20.7)	114(54.0)	63(68.5)	14(17.9)	7(14.2)	15(39.5)	5(31.3)	60(61.2)	5303(48.9)
Diabetes mellitus	3830(49.1)	547(29.2)	88(15.0)	67(31.8)	31(33.7)	11(14.1)	0	8(21.1)	4(25.0)	30(30.6)	4616(42.6)
COPD	524(6.7)	139(7.4)	19(3.2)	18(8.5)	8(8.7)	7(8.9)	0	4(10.5)	1(6.3)	23(23.5)	743(6.9)
CKD	705(9.0)	143(7.6)	21(3.6)	18(8.5)	12(13.0)	3(3.9)	1(2.0)	5(13.2)	1(6.3)	11(11.2)	920(8.5)
AF	387(4.9)	216(11.5)	309(52.7)	53(25.1)	16(17.4)	17(21.8)	4(8.2)	15(39.5)	1(6.2)	11(11.2)	1029(9.5)
Stroke	221(2.8)	57(3.0)	21(3.6)	12(5.7)	4(4.3)	1(1.3)	0	0	1(6.2)	6(6.1)	323(2.9)

IHD=ischemic heart disease, DCM=dilated cardiomyopathy, RHD=rheumatic heart disease, NRHD=non-rheumatic valvular heart disease, HCM=hypertrophic cardiomyopathy, CHD=congenital heart disease, PPCM=peri-partum cardiomyopathy, RCM=restrictive cardiomyopathy, IE=infective endocarditis, SD=standard deviation, HF=heart failure, ETL=epidemiological transition level, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, AF=atrial fibrillation, BMI=body mass index. * The split up of the " others " category is as follows. Hypertension (n=75), Chronic Obstructive Pulmonary Disease (n=3), Pulmonary embolism (n=2), pulmonary artery hypertension (n=9), constrictive pericarditis (n=3), and arrhythmia-induced CM (n=7). Heart failure etiology was missing in five participants. BMI was missing in 23 participants.

Table S1A: Baseline Characteristics of the study population stratified by disease etiology (Men)

Variables	IHD (N=5779)	DCM (N=1171)	RHD (N=246)	NRHD (N=116)	HCM (N=47)	CHD (N=38)	RCM (N=21)	IE (N=10)	Others (N=51)	Total (N=7479)
Age	61.2(11.8)	56.4(14.7)	48.4(16.0)	61.8(16.0)	59(14.5)	44.1(14.5)	56.9(13.6)	46.3(16.8)	56.2(16.4)	59.9(13.4)
Education										
0-4years	1092(18.9)	276(23.6)	50(20.3)	17(14.7)	9(19.1)	4(10.5)	2(9.5)	0(0)	13(25.5)	1463(19.6)
4-8years	1473(25.5)	301(25.7)	72(29.3)	33(28.4)	10(21.3)	15(39.5)	2(9.5)	2(20.0)	7(13.7)	1915(25.6)
9-12years	2248(38.9)	436(37.3)	97(39.4)	47(40.5)	20(42.6)	13(34.2)	9(42.9)	4(40.0)	21(41.2)	2895(38.7)
>13years	963(16.7)	157(13.4)	27(11.0)	19(16.4)	8(17.0)	6(15.8)	8(38.1)	4(40.0)	10(19.6)	1202(16.1)
Tobacco, n(%)	2607(45.1)	522(44.6)	99(40.2)	45(38.8)	18(38.3)	13(34.2)	10(47.6)	6(60.0)	20(39.2)	3340(44.7)
Alcohol, n(%)	1319(22.8)	320(27.3)	44(17.9)	36(31.0)	9(19.1)	4(10.5)	6(28.6)	4(40.0)	16(31.4)	1758(23.5)
BMI, Mean (SD)	24.3(3.7)	23.9(4.0)	22.2(4.0)	24.5(4.4)	24.1(3.3)	22.8(3.6)	24.2(3.2)	24.3(4.3)	24.8(5.2)	24.2(3.8)
Obesity/overweight, n(%)	2175(37.7)	424(36.3)	56(22.8)	48(41.4)	15(31.9)	10(26.3)	8(38.1)	3(30.0)	23(45.1)	2762(36.9)
Regions, n (%)										
Low ETL	1285(22.2)	302(25.8)	68(27.6)	14(12.1)	5(10.6)	5(13.2)	2(9.5)	0(0)	7(13.7)	1688(22.6)
Lower-Middle ETL	618(10.7)	126(10.8)	13(5.3)	12(10.3)	2(4.3)	4(10.5)	5(23.8)	0(0)	5(9.8)	785(10.5)
Higher-Middle ETL	2067(35.8)	559(47.7)	106(43.1)	52(44.8)	29(61.7)	20(52.6)	7(33.3)	5(50.0)	20(39.2)	2865(38.3)
High ETL	1809(31.3)	184(15.7)	59(24.0)	38(32.8)	11(23.4)	9(23.7)	7(33.3)	5(50.0)	19(37.3)	2141(28.6)
Comorbidities, n(%)										
Hypertension	2896(50.1)	433(37.0)	48(19.5)	56(48.3)	27(57.4)	4(10.5)	8(38.1)	2(20.0)	30(58.8)	3504(46.9)
Diabetes Mellitus	2689(46.5)	335(28.6)	32(13.0)	27(23.3)	17(36.2)	3(7.9)	5(23.8)	2(20.0)	16(31.4)	3126(41.8)
COPD	418(7.2)	107(9.1)	11(4.5)	13(11.2)	4(8.5)	4(10.5)	3(14.3)	0(0)	12(23.5)	572(7.6)
CKD	534(9.2)	102(8.7)	13(5.3)	11(9.5)	6(12.8)	1(2.6)	2(9.5)	0(0)	6(11.8)	675(9.0)
AF	269(4.7)	139(11.9)	111(45.1)	25(21.6)	6(12.8)	11(28.9)	6(28.6)	0(0)	3(5.9)	570(7.6)
Stroke	169(2.9)	34(2.9)	6(2.4)	6(5.2)	1(2.1)	0(0)	0(0)	0(0)	4(7.8)	220(2.9)

IHD=ischemic heart disease, DCM=dilated cardiomyopathy, RHD=rheumatic heart disease, NRHD=non-rheumatic valvular heart disease, HCM=hypertrophic cardiomyopathy, CHD=congenital heart disease, PPCM=peri-partum cardiomyopathy, RCM=restrictive cardiomyopathy, IE=infective endocarditis, AF=atrial fibrillation, ETLs=epidemiological transition levels, BMI=body mass index, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, SD=standard deviation.

Table S1B: Baseline Characteristics of the study population stratified by disease etiology (Women)

Variables	IHD (N=2021)	DCM (N=706)	RHD (N=340)	NRHD (N=95)	HCM (N=45)	CHD (N=40)	PPCM (N=49)	RCM (N=17)	IE (N=6)	Others (N=47)	Total (N=3366)
Age	64(11.6)	57.5(14.6)	47.1(14.7)	64.9(14.3)	62(12.9)	44.5(15.8)	29.2(6.1)	61.8(13.3)	56.8(22.3)	58.5(14.4)	60.1(14.4)
Education											
0-4years	789(39.0)	295(41.8)	111(32.6)	36(37.9)	24(53.3)	9(22.5)	6(12.2)	6(35.3)	1(16.7)	24(51.1)	1301(38.7)
4-8years	536(26.5)	179(25.4)	103(30.3)	27(28.4)	10(22.2)	11(27.5)	9(18.4)	3(17.6)	2(33.3)	8(17.0)	888(26.4)
9-12years	561(27.8)	164(23.3)	111(32.6)	22(23.2)	7(15.6)	14(35.0)	20(40.8)	4(23.5)	3(50.0)	13(27.7)	919(27.3)
>13years	135(6.7)	67(9.5)	15(4.4)	10(10.5)	4(8.9)	6(15.0)	14(28.6)	4(23.5)	0(0)	2(4.3)	257(7.6)
Tobacco, n(%)	217(10.7)	66(9.3)	17(5.0)	6(6.3)	9(20.0)	2(5.0)	1(2.0)	0(0)	0(0)	12(25.5)	330(9.8)
Alcohol, n(%)	35(1.7)	9(1.3)	3(0.9)	1(1.1)	0(0)	0(0)	0(0)	0(0)	0(0)	1(2.1)	49(1.5)
BMI, Mean (SD)	24.5(4.3)	24.2(4.5)	22.3(3.9)	24.9(4.7)	27(4.9)	22.5(3.3)	22.7(4.3)	24.3(4.6)	20.2(2.0)	24.06(4.9)	24.2(4.4)
Obesity/overweight, n(%)	801(39.7)	285(40.4)	71(20.9)	43(45.3)	30(66.7)	11(27.5)	14(28.6)	6(37.5)	0(0)	16(34.8)	1277(38.0)
Regions, n (%)											
Low ETL	421(20.8)	188(26.6)	84(24.7)	7(7.4)	4(8.9)	4(10.0)	17(34.7)	3(17.6)	0(0)	8(17.0)	736(21.9)
Lower-Middle ETL	195(9.6)	71(10.1)	24(7.1)	12(12.6)	0(0)	2(5.0)	6(12.2)	1(5.9)	1(16.7)	3(6.4)	315(9.4)
Higher-Middle ETL	682(33.7)	336(47.6)	148(43.5)	38(40.0)	34(75.6)	18(45.0)	18(36.7)	8(47.1)	2(33.3)	20(42.6)	1304(38.7)
High ETL	723(35.8)	111(15.7)	84(24.7)	38(40.0)	7(15.6)	16(40.0)	8(16.3)	5(29.4)	3(50.0)	16(34.0)	1011(30.0)
Comorbidities, n(%)											
Hypertension	1275(63.1)	300(42.5)	73(21.5)	58(61.1)	36(80.0)	10(25.0)	7(14.3)	7(41.2)	3(50.0)	30(63.8)	1799(53.4)
Diabetes Mellitus	1141(56.5)	212(30.0)	56(16.5)	40(42.1)	14(31.1)	8(20.0)	0(0)	3(17.6)	2(33.3)	14(29.8)	1490(44.3)
COPD	106(5.2)	32(4.5)	8(2.4)	5(5.3)	4(8.9)	3(7.5)	0(0)	1(5.9)	1(16.7)	11(23.4)	171(5.1)
CKD	171(8.5)	41(5.8)	8(2.4)	7(7.4)	6(13.3)	2(5.0)	1(2.0)	3(17.6)	1(16.7)	5(10.6)	245(7.3)
AF	118(5.8)	77(10.9)	198(58.2)	28(29.5)	10(22.2)	6(15.0)	4(8.2)	9(52.9)	1(16.7)	8(17.0)	459(13.6)
Stroke	52(2.6)	23(3.3)	15(4.4)	6(6.3)	3(6.7)	1(2.5)	0(0)	0(0)	1(16.7)	2(4.3)	103(3.1)

IHD=ischemic heart disease, DCM=dilated cardiomyopathy, RHD=rheumatic heart disease, NRHD=non-rheumatic valvular heart disease, HCM=hypertrophic cardiomyopathy, CHD=congenital heart disease, PPCM=peri-partum cardiomyopathy, RCM=restrictive cardiomyopathy, IE=infective endocarditis, AF=atrial fibrillation, ETLs=epidemiological transition levels, BMI=body mass index, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, SD=standard deviation.

Table S2A: Mortality rate by disease etiology in men

Disease etiology	Participants, n(%)	Events, n	Event rate at one year, %	Person-time in days	Event rate per 100 person-years(95% CI)
IHD	5779(77.3)	1184	20.5	1745108	24.8(23.4-26.2)
DCM	1171(15.7)	287	24.5	343736	30.5(27.1-34.2)
RHD	246(3.3)	68	27.7	70061	35.4(27.9-44.9)
NRHD	211(1.9)	30	25.9	32973	33.2(23.2-47.5)
HCM	47(0.6)	9	19.2	14510	22.6(11.8-43.5)
CHD	38(0.5)	13	34.2	9430	50.8(29.5-87.5)
PPCM	NA	NA	NA	NA	NA
RCM	21(0.3)	7	33.3	5811	44.0(21.0-92.3)
IE	10(0.1)	4	40.0	2343	92.9(46.5-185.9)
Others	51(0.7)	14	27.5	14512	62.3(23.4-166.0)
Total	7479	1616	21.6	2239854	26.3(25.1-27.7)

IHD=ischemic heart disease, DCM=dilated cardiomyopathy, RHD=rheumatic heart disease, NRHD=non-rheumatic valvular heart disease, HCM=hypertrophic cardiomyopathy, CHD=congenital heart disease, PPCM=peri-partum cardiomyopathy, RCM=restrictive cardiomyopathy, IE=infective endocarditis.

Table S2B: Mortality rate by disease etiology in women

Disease etiology	Participants, n(%)	Events, n	Event rate at one year, %	Person-time in days	Event rate per 100 person-years(95% CI)
IHD	2021(60.0)	465	23.0	596784	28.5(25.9-31.2)
DCM	706(21.0)	157	22.2	211904	27.1(23.2-31.7)
RHD	340(10.1)	93	27.3	95744	34.5(28.9-43.4)
NRHD	95(2.8)	23	24.2	27745	30.3(20.1-45.5)
HCM	45(1.3)	3	6.7	15661	6.9(2.3-21.7)
CHD	40(1.2)	14	35.0	10626	48.1(28.5-81.2)
PPCM	49(1.5)	6	12.2	15510	14.1(6.3-31.4)
RCM	17(0.5)	7	41.1	4084	62.6(29.8-131.2)
IE	6(0.2)	4	66.7	798	182.9(68.7-487.5)
Others	47(1.4)	14	29.8	12975	39.4(23.3-66.5)
Total	3366	786	23.4	992196	28.9(26.9-31.0)

IHD=ischemic heart disease, DCM=dilated cardiomyopathy, RHD=rheumatic heart disease, NRHD=non-rheumatic valvular heart disease, HCM=hypertrophic cardiomyopathy, CHD=congenital heart disease, PPCM=peri-partum cardiomyopathy, RCM=restrictive cardiomyopathy, IE=infective endocarditis.

