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Title: The Upcoming Epidemic of Heart Failure in South Asia

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Word Counts: Main Text: 5,360; Abstract: 249

Tables: 4; Figures: 4

Journal Subject Terms:

Epidemiology; Heart Failure; Race and Ethnicity

Declaration of Conflicts of Interest: S.J.S. has received research grants from Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and has received consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Ionis, Ironwood, Merck, Novartis, Pfizer, Sanofi, and United Therapeutics. All other authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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KEYWORDS

epidemiology; heart failure; non-communicable diseases; prevention; South Asian

ABSTRACT

Currently, South Asia accounts for a quarter of the world population, yet it already claims ~60% of the global burden of heart disease. Besides the epidemics of type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD) already faced by South Asian (SA) countries, recent studies suggest that SAs may also be at an increased risk of heart failure (HF), and that it presents at earlier ages than in most other racial/ethnic groups. Although a frequently underrecognized threat, an eventual HF epidemic in the densely populated SA nations could have dramatic health, social and economic consequences, and urgent interventions are needed to "flatten the curve" of HF in South Asia. In this review we discuss recent studies portraying these trends, and describe the mechanisms that may explain an increased risk of premature HF in SAs compared to other groups, with a special focus on highly relevant features in SA populations including premature CHD, early T2DM, ubiquitous abdominal obesity, exposure to the world's highest levels of air pollution, highly prevalent pre-transition forms of HF such as rheumatic heart disease, and underdevelopment of healthcare systems. Other rising lifestyle-related risk factors such as use of tobacco products, hypertension and general obesity are also discussed. We evaluate the prognosis of HF in SA countries and the implications of an anticipated HF epidemic. Finally, we discuss proposed interventions aimed at curbing these adverse trends, management approaches that can reduce the burden of prevalent HF in SA countries, and research gaps in this important field.

ABBREVIATIONS AND ACRONYMS

ACEI	angiotensin-converting enzyme inhibitors
ARB	angiotensin II receptor blockers
ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure
CHD	coronary heart disease
CVD	cardiovascular disease
GLP-1	glucagon-like peptide-1
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
ICMR-INDIAB	Indian Council of Medical Research–India Diabetes
INTER-CHF	International Congestive Heart Failure
INTERHEART	Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction
LMIC	low- and middle-income countries
MI	myocardial infarction
NCDs	non-communicable diseases
SA	South Asian
SGLT-2	sodium-glucose co-transporter 2
T2DM	type 2 diabetes mellitus
THFR	Trivandrum Heart Failure Registry
WHO	World Health Organization

TEXT

Introduction

In 2020, the population of South Asian (SA) countries —India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan, and Maldives— is 1.8 billion, comprising 23% of the world's population (**Figure 1**).[1] Also, in countries such as the US, Canada, the UK and other European and Asian nations, persons of SA ancestry represent one of the largest and/or fastest-growing minority groups.[2–5]

With rapid industrialization, increased survival from acute conditions and population aging, chronic non-communicable diseases (NCDs) and particularly cardiovascular disease (CVD) are becoming a major concern in low- and middle-income countries (LMICs), including the densely populated SA nations.[6–11] A wealth of research has shown that SAs are at increased risk of type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD),[6,12–18] resulting in calls to enhance the prevention of these conditions in SA countries and migrant groups.[16–18] On the other hand, awareness about the current and anticipated importance of heart failure (HF) in SAs remains limited.

HF is a devastating, resource-intensive syndrome that results in premature mortality, disability, impaired functional capacity, reduced quality of life, and need for multiple pharmacotherapies.[7,8] HF is also a main cause of hospitalization and healthcare expenditure in many countries.[7,8,19–22] For these reasons, HF represents a major threat to patients, health systems and societies; particularly in nations with resource-constrained systems and economies. In this context, recent studies suggest that SAs may also be at increased risk of HF, and that it may manifest in average 10 to 15 years earlier in life in SAs than in other geographical and

racial/ethnic groups.[15,23–30] These phenomena combined with a very large,[1] progressively aging population in South Asia may result in a massive number of cases of HF in the coming decades, with the potential to have large health and economic consequences.

In this narrative review, we discuss recent studies portraying these trends, describe the mechanisms that may explain an increased risk of premature HF in SAs compared to other groups, and evaluate the implications of an anticipated HF epidemic in SA countries. We then discuss proposed interventions aimed at curbing these adverse trends, as well as management approaches that can reduce the burden of prevalent HF in SA countries.

HF in SAs living in diaspora countries and multinational studies

Studies of migrant and local subgroups living in Asian, European and North American countries allow to compare the characteristics of various racial/ethnic groups in settings in which the quality of the health information tends to be high and reasonably homogeneous across strata. This research has yielded valuable insights, consistently pointing towards an increased risk of HF and particularly of premature HF in SAs compared with several other racial/ethnic groups. A summary of key studies from the Middle East, Europe and North America is presented in **Table 1**, **Figures 2** and **3**.

Although the findings of those studies might be influenced, at least in part, by the adverse socioeconomic circumstances faced by first generation SA immigrants in many countries, the burden of HF in SAs has also been shown to be higher than that observed among immigrants from other LMICs.[15,23–25,28,29] Also, several of those trends, particularly an earlier age of presentation, are consistent with those portrayed in multinational studies comparing the characteristics of HF patients across various nations, including the Asian Sudden Cardiac Death

in Heart Failure (ASIAN-HF)[30] and the International Congestive Heart Failure (INTER-CHF) (**Table 1**).[33]

Epidemiology of HF in SA countries

Granular epidemiological data on the incidence and prevalence of HF from SA countries is currently limited. This is the consequence of scarce surveillance systems and patient registries particularly at the national level, together with the challenges associated with the complex diagnosis of HF, which may represent a big barrier in resource-constrained settings. Recently, the Indian Council of Medical Research has funded a HF registry that aims to collect information from 10,000 patients from 53 hospitals in India.[34] Although results are not available yet, this pivotal effort will provide crucial data to inform evidence-based interventions.

Epidemiologic transition, population aging and implications for HF

Despite limited available data, the consequences of fast epidemiologic transition, which are particularly relevant to HF, are evident in South Asia. On the one hand, life expectancy has increased markedly in the last two decades in the region. SA populations are aging, with an estimated ~500 million individuals above the age of 60 living in South Asia by 2050.[35] It is estimated that the population will surpass 1.94 billion during 2020, a 13% increase since the year 2010.[36] On the other hand, industrialization, westernization of lifestyles and aging come with a rising incidence and prevalence of cardiovascular risk factors, while CVD prevention efforts are still in their early stages in SA nations.[10,11,16,18,37] The strong association between these processes and NCDs, particularly CVD, is evident in South Asia: for example, from 1990 to 2016 all states in India experienced a shift from the majority of disease burden from communicable conditions to NCDs, with CVD representing the number one cause of death.[10]

These phenomena together with the very large size of the population herald the potential for a large absolute number of cases of HF in SA countries in the coming years. Currently, South Asia accounts for a quarter of the world population, yet it already claims ~60% of the global burden of heart disease.[38] Also, despite rapid industrialization in certain areas, SA countries are highly heterogeneous in terms of urbanization and development, and still face a large burden of conditions typical of earlier stages of the epidemiological transition, including infectious, nutritional and congenital diseases. Many of these have the potential to lead to HF, such as rheumatic fever, tuberculosis, peripartum cardiomyopathy, congenital heart diseases, and various nutritional deficits.

Preliminary estimates and local registries

The limited available estimates of the prevalence of HF in SA suggest that as of 2014 the number of cases of HF in India ranged between 1.3 to 4.6 million.[11] Pakistan had an estimated 2.8 million HF patients in 2006.[39] For Bangladesh, there are no prevalence estimates available, although it was reported that among all adult hospitalizations occurring in the country in 2016, 14%–25% were due to HF.[40] The incidence of HF in India is estimated to be at least between 0.5–1.7 cases per 1,000 person per year, for a total of 492,000 to 1.8 million new cases per year. This would be similar to that of South American countries, the US, or Portugal, and lower than Spain or the UK.[41] Nevertheless, the age-specific incidence for India is unknown, and because HF is strongly associated with age and the population of India is on average younger than that of those countries, incidence comparisons without adjusting for age are misleading—although they suggest an increased risk of HF in India at earlier ages than in countries such as the US. HF incidence estimates for Pakistan and Bangladesh are currently not available.

Local HF registries

Consistent with the findings from diaspora and multinational studies, local HF registries confirm a lower average age at admission in SA patients compared to that of patients from reference HF populations in Western countries.[42] For instance, in the Trivandrum Heart Failure Registry (THFR) in India which included 1,205 HF hospital admissions during 2013, mean age was 61 years. The most common etiology of HF was CHD (72%), and hospital length of stay was longer than that in Western registries, and so was the in-hospital mortality. HF patients in other SA countries may be even younger on average: in a small HF registry from Lahore, Pakistan, mean age was 54 years, ~7 years lower than that of Trivandrum and ~18 years lower than that of a reference US HF population.[43]

Key mechanisms potentially contributing to an increased risk of HF in SAs compared to other groups

The very large size of the SA population together with its within-group heterogeneity call for caution when making generalizations in terms of risk factors and mechanisms of disease. Also, HF is a complex syndrome resulting from multiple, heterogenous causes.[44,45] Nonetheless, some characteristics highly prevalent in SA countries and migrant subgroups are of particular relevance to understanding a potentially increased risk of HF and especially of premature HF in SAs compared to other groups, such as Caucasians (**Figure 4**).

CHD

The higher burden of CHD among SAs compared to most other racial/ethnic groups has been well documented in the literature, the potential underlying factors being multiple.[6,12–16] CHD is one of the strongest risk factors for the development of HF, particularly of HF with

reduced ejection fraction (HFrEF) but also with preserved ejection fraction (HFpEF).[45,46] In several diaspora HF studies a large proportion of SAs either presented with a concurrent myocardial infarction (MI) or had a history of CHD. Increasing rates of CHD in SA countries combined with suboptimal management (e.g., limited use of acute revascularization therapies, door-to-balloon delays, low use of chronic medications)[11,18] will likely contribute to a prolonged surge in the incidence of HF in coming years. Of note, the Effect of Potentially Modifiable Risk Factors Associated with MI (INTERHEART) study demonstrated that first MIs occur an average of 10 years earlier in SA countries than in other geographic regions,[12] and reports of premature CHD are ubiquitous in SA migrants living elsewhere.[13–16,47] Precocious CHD is likely to play a relevant part in the early presentation of HF in SAs.

T2DM

Besides its role as a key risk factor for CHD, T2DM is also a strong, independent risk factor for the development of HF even among individuals without clinically overt CHD. Diabetic cardiomyopathy leads to myocardial dysfunction and eventually to clinical HF through various mechanisms, including not only atherogenesis but also myocardial fibrosis, dysfunctional remodeling and associated diastolic dysfunction, and eventual systolic dysfunction.[48,49] Importantly, the prevalence of T2DM in the densely populated SA nations is among the world's highest, resulting in a very large absolute number of individuals with diabetes, which often presents at early age.[6,15,16,50] In addition, poor metabolic control of T2DM further accentuates HF risk.[48,49] In SA countries this is often suboptimal—for instance, average levels of glycosylated hemoglobin are 9% in diabetic patients in India,[51] with only one third of patients achieving the <7% treatment goal.[18] The same has been reported in some SA migrant studies.[52,53] Importantly, the prevalence of prediabetes and metabolic syndrome are also disproportionately high in SAs.[16]

Body composition and abdominal obesity

SAs have a higher proportion of total, abdominal, subcutaneous abdominal, and visceral fat for a given body mass index compared with Caucasians. Abdominal obesity is highly prevalent among SAs, particularly SA men, even in those with a normal body mass index.[16] In India, according to the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB), the prevalence of abdominal obesity ranged between 17% and 36% in 2015,[54] resulting once again in a very large absolute number of cases. The prevalence increases with age and is even more striking among SAs living in some Western countries. For example, in the US among 40- to 80-year-old CVD-free participants included in the Mediators of Atherosclerosis in SAs Living in America (MASALA) study, the majority of whom were of Indian ancestry, abdominal obesity is highly prevalent.[55] Compelling research has demonstrated an independent association between obesity and incident HF,[56] and studies have also reported associations between abdominal obesity, the risk of HF and adverse HF outcomes independent of body mass index.[57,58]

Air pollution and pesticides

Levels of various air pollutants are extremely high in many SA urban areas, particularly in large Indian cities. According to international air quality data for 2019, 21 of the 30 most polluted cities in the world were in India, 5 in Pakistan, and one in Bangladesh.[59] Robust evidence suggests that levels of carbon monoxide, sulfur dioxide and nitrogen dioxide, and increases in particulate matter concentration are independently associated with HF hospitalization and mortality.[60] Potential mechanisms include cardiac dysrhythmias, systemic vasoconstriction leading to increased systemic blood pressure, pulmonary vasoconstriction, increased diastolic filling pressures in both ventricles, reduced myocardial contractility, myocardial injury, adverse ventricular remodeling, and myocardial fibrosis, the combination of

which leads to acute decompensated HF and death.[60] Exposure to other persistent organic pollutants such as pesticides is also very high in countries such as India, and these have also been associated with incident HF.[61] These factors would not be so relevant among SA immigrants living in less polluted world areas, particularly among second and subsequent generation immigrants.

Pre-transition diseases: Rheumatic heart disease and other conditions

While many SA diaspora groups face adverse socioeconomic circumstances and these likely contribute to their burden of HF, in SA countries poverty is a powerful contributor to the local burden of the disease. For example, in spite of rapid industrialization, LMICs including SA nations still face a large burden of pre-transition diseases. Specifically, rheumatic heart disease remains an important cause of HF in South Asia,[11] although prevalence estimates are limited by insufficient surveillance systems and marked heterogeneity across published epidemiological studies. In INTER-CHF, among 2,661 Asian participants, 32% of which were Indian, 10% of HF cases were considered secondary to rheumatic valvular disease.[33] Because exposure to group A streptococci usually occurs early in life, rheumatic heart disease is likely to be a relevant contributor to the early presentation of HF in SAs. Another example of a pre-transition condition with implications for HF is tuberculosis, which remains highly prevalent in SA countries and can cause HF through constrictive pericarditis.[62]

Underdeveloped healthcare systems

The risk factors described above are further compounded by the underdevelopment of public healthcare systems in many SA regions, which are overloaded particularly in densely populated rural areas and lowest-income states.[11,18] Infrastructures are often insufficient to serve a very large population, and there is a scarcity of quality control measures. These features have

direct implications for access and quality of care, and commonly result in the suboptimal acute and chronic management of key risk factors relevant to the development of HF, such as T2DM and CHD.[11,18] Of note, epidemic cardiovascular diseases in SA countries likely contribute to perpetuating this situation and the economic underlying factors through loss of productivity, years of disability-free life lost, and direct and indirect costs (**Figure 4**). Limited health insurance coverage and affordability of therapies are also relevant issues in South Asia.

Other key lifestyle contributors to HF risk in SAs

Besides the features described above, which are particularly relevant in SA populations, expansion of other lifestyle risk factors in SA countries resulting from rapid industrialization and westernization of lifestyles further contributes to an increased population-level risk of HF. Although the prevalence of these risk factors is currently not as high as in other world areas, in the densely populated SA nations these translate into in a very large absolute number of individuals at risk of developing HF. Moreover, these combined with the features described above can create a "perfect storm" for the eventual onset of HF.

Tobacco products

Use of tobacco products (not only cigarettes, but also bidis and chewable tobacco) is very common in South Asia.[16] In 2003, 47% of Indian men and 14% of women either smoked or chewed tobacco.[63] With regards to smoked tobacco, while taxation initiatives have been recently implemented in India resulting in promising declining trends, tobacco control efforts have so far been insufficient in other SA countries:[18,64] in 2010, 29% of the SA male population and 4% of SA women smoked tobacco for a total of 171 million tobacco smokers, the prevalence being highest among Bangladeshi and Pakistani men.[64] According to most recent estimates from the

World Health Organization (WHO), the age-standardized prevalence of tobacco smoking in India, Pakistan and Bangladesh is now 20%, 42% and 40%, respectively.[65] For reference, the age-adjusted prevalence is 19.5% in the US, 30% in France, 48% in China, and 59% in Russia. Besides its effects as a risk factor for CHD, studies have demonstrated that smoking tobacco is independently associated with higher N-terminal pro-BNP levels, incident left ventricle hypertrophy, systolic dysfunction, and HF admission after accounting for CHD.[66,67] Bidis and smokeless tobacco, which account for 80% of tobacco product use in India,[11] also have deleterious cardiovascular effects, including a marked increase in the risk of MI.[68]

Hypertension

High blood pressure is a major contributor to CVD in South Asia.[6,11,16,18] The prevalence of hypertension continues to grow in SA countries: in India, recent nationally representative studies reported an age-standardized prevalence in 2014 of 24.5% in men and 20% in women.[69,70] Although this is lower than that of Western countries such as the US,[71] there is an increasing trend since 1950,[69,70] with a projected surge from 118 million cases in year 2000 to 214 million in 2025.[11] This is believed to be the consequence of population aging, industrialization, adoption of Western lifestyles, high salt intake, and accumulation of precipitating factors such as obesity and tobacco use, particularly in most developed states and urban areas.[70] Of concern, awareness of hypertension status is low and blood pressure control is often suboptimal in South Asia.[70,72] High blood pressure is not only a strong risk factor for CHD but also a major cause of HF.[73] Longstanding hypertension causes diastolic dysfunction in the left ventricle, hypertrophy and concentric remodeling, which eventually lead to clinically overt hypertensive heart disease. In some patients, pressure and volume overload eventually lead to dilated cardiomyopathy and impaired left ventricular ejection fraction.[73]

General obesity

General obesity is independently associated with incident HF.[56] Besides the epidemiological importance of highly prevalent abdominal obesity as a risk factor for HF particularly among SA men, recent data suggest that generalized obesity is also growing in South Asia. For example, according to the ICMR-INDIAB the prevalence in India ranged between 12% and 31% in 2015,[54] with a greater prevalence in urban areas and among older SA women.[74] This has also been reported in various migrant studies—for example, in a 2017 study in Catalonia (Spain), SA immigrant women had a much higher prevalence of obesity than local Caucasians.[15] The prevalence of obesity was also high among Newcastle (UK) SAs,[44] as well as among other SA subgroups living in Western countries.[16] The association between obesity and HF occurs through a number of mechanisms including inflammation, adipokine release, insulin resistance, endothelial dysfunction, and atherogenesis, all of which may lead to deleterious changes in cardiac hemodynamics, structure, function and conduction. Also, obesity is associated with an increased risk of conditions strongly associated with incident HF, such as most traditional CVD risk factors, atrial fibrillation, and chronic kidney disease.[74,75]

The role of genetics

To date, the role of genetic and epigenetic factors as underlying causes of the increased burden of CVD among SAs remains a matter of debate. Formal genetic studies have failed to identify SA-specific genetic variants linked with T2DM or CHD,[76] and INTERHEART demonstrated that the excess burden of CHD in SA countries could be mostly explained by a higher burden of traditional risk factors.[12] Moreover, in the UK, where individuals of SA ancestry now have access to high-quality healthcare similar to that of other racial/ethnic groups,

their cardiovascular outcomes in the presence of diabetes are now similar or even better than those of Caucasian patients with diabetes, arguing against a strong genetic cause leading to CVD in this group.[77]

Nevertheless, metabolic risk factors indeed have a genetic component, and there is consensus regarding the importance of (genetically determined) features such as body composition in the increased odds of T2DM and subsequent CHD observed in SAs.[16,54,55] Specifically for HF, some genetic variants associated with the development of cardiomyopathies, such as a variant of MYBPC3 (Cardiac Myosin Binding Protein C), have been noted to be highly frequent in SAs.[78] However, whether these significantly contribute to the higher population-level burden of HF observed among SAs living in diaspora studies, and/or to the premature presentation of HF described in multinational studies and local SA registries, in uncertain. Further research is therefore needed to better understand the contribution of these and other potential genetic mechanisms to the burden of HF in SAs. Should a role of genetics be confirmed, opportunities for genetic screening and novel therapeutic targets would have to be explored.

HF prognosis

In the recent Global Non-interventional Heart Failure Disease Registry (REPORT-HF), a patient registry including HFpEF and HFrEF patients evaluating post-discharge outcomes in 18,102 patients hospitalized for HF across 44 countries on 6 continents, patients from lower-income regions and those from areas with greater income inequality had 58% and 25% higher 1-year mortality compared with HF patients from regions with the highest income and/or lowest income inequality, respectively.[79] Of note, HF patients from lower-income regions were more

frequently Asian (83%) than those from high income regions (14%). Sub-analyses among Asian countries revealed that HF patients from South Asia and Southeast Asia had higher 1-year mortality rates (17% and 23%, respectively) than those from Northeast Asia and Western Pacific (both 15%) despite a younger mean age.[79]

One-year mortality in INTER-CHF participants from India was also high, particularly among hospitalized HF patients, only surpassed by that observed in African patients.[33] The fact that in most diaspora studies the prognosis of cardiovascular conditions, including HF, was similar in SAs and in native local populations suggests that the worse HF outcomes observed in South Asia may likely the consequence of limited resources and suboptimal management, rather than of any underlying biological mechanisms. Indeed, 1-year mortality rates in SA participants in ASIAN-HF were significantly lower than in INTER-CHF and REPORT-HF, likely the consequence of the inclusion criteria of each study together with greater use of guideline-endorsed HF therapies specifically in ASIAN-HF.[80]

Time to curb the HF epidemic in South Asia—An urgent call for action

If the observed trends described above are confirmed and eventually result in a surge of HF cases in SA nations in the coming decades, this would have catastrophic consequences for the public's health, for the sustainability of the local healthcare systems, and for the societies of those countries. Moreover, the economic impact of a very large absolute number of HF cases would perpetuate the disadvantage with higher-income world regions. Frequent presentation of HF at early age would accentuate these issues further, resulting in premature mortality, additional years of life lost and lower productivity. These potential consequences stress the need for timely, effective interventions.

Prevention

The recent coronavirus pandemic has confirmed once again the central importance of implementing preventive interventions in a timely manner to avoid overwhelming healthcare systems and the resulting dramatic increases in morbidity and mortality. In the coming years, health officials in SA countries will need to prioritize reducing the incidence of CVD, with special attention to HF. The latter will have to be accomplished through the primordial and primary prevention of its risk factors and of CHD, together with their early detection and aggressive management. Preventive interventions already recommended for curtailing T2DM and CHD[16–18] in SA countries and migrant groups become even more relevant in light of their potential to curb this additional cardiovascular epidemic.

Table 2 summarizes proposed approaches that may be particularly relevant to the prevention of HF in SA populations. Importantly, in a context of resource-constrained economies, the widespread use of costly, individual-level preventive interventions, of tests for the early diagnosis of the disease, and of costly therapies once present, without reducing the number of at-risk individuals may not be affordable. Policies aimed at reducing population exposure to preventable risk factors through sensible regulations (e.g., ban tobacco products, reduce the content of refined sugar, salt and trans fatty acids in foods) represent the most cost-effective, fast, impactful preventive actions.[11,18,64,81,82] Also, physical activity will have to be aggressively promoted as means to simultaneously curb various cardiovascular epidemics.[16,17] Similar preventive actions should also target SA migrant groups.[17] Reduction of air pollution levels and pesticides should also become a top policy priority.

In parallel, development and strengthening of public healthcare systems should be considered a national priority in South Asian countries (**Table 3**).[18] In rural Pakistan, the Control

of Blood Pressure and Risk Attenuation - Bangladesh, Pakistan, and Sri Lanka (COBRA-BPS) investigators demonstrated that availability of public high-quality care not only improved the management of risk factors such as blood pressure, but also reduced mortality in a dramatic manner (more than 30% after only two years of follow-up).[83]

Management of HF

Even if much warranted prevention efforts were further developed, in a context of population aging the number of cases of HF will most likely grow in South Asia in the coming years in a dramatic manner. This will require optimized acute and chronic management approaches aimed at reducing mortality, morbidity, disability, need for re-hospitalizations, and costs. The substantially higher HF case fatality rate in LMICs illustrates the importance of health system strengthening and quality improvement, which should occur at all levels. Of particular importance will be the development of sustainable chronic care models including cardiac rehabilitation and structured follow-up, which have proven effective in SA communities and will need to be widely implemented.[84,85]

Special attention will also have to be paid to the early detection of HF, as well as to its aggressive, optimal management since the very early stages of the disease process. Although SAs have been underrepresented in most landmark HF trials and research specifically in SA patients is warranted,[86] there is no *a priori* reason to expect that currently recommended class I HF therapies would be less effective in SAs.[45,87] Indeed, subgroup analyses by geographical region of landmark randomized controlled HFrEF trials have not identified significant effect modification by region, and observational studies of Asian HF patients suggest a consistent beneficial effect of guideline-endorsed pharmacotherapies and devices in these populations.[88,89]

Access to such therapies will therefore need to be enhanced through generic drugs, polypill combination therapies for patients with established disease, and other initiatives.[90]

Of concern, available data across Asia demonstrate large gaps in the use of evidence-based HF therapies in the region. In the ASIAN-HF HFrEF registry, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) were prescribed to 77%, betablockers to 79%, and mineralocorticoid receptor antagonists to 58% of Asian patients. Nevertheless, there was substantial variation across South, Southeast and Northeast Asian regions, with India having the second lowest use of betablockers.[89] Moreover, guideline-recommended drug doses were achieved in only 17% for ACEIs/ARBs, 13% for betablockers, and 29% for mineralocorticoid receptor antagonists overall. There was also marked heterogeneity in the utilization of implantable cardioverter defibrillators among eligible patients, ranging from 1.5% in Indonesia, 1.8% in the Philippines and 4.9% in India, to 21.1% in Hong Kong and 52.5% in Japan.[88] Use of key HF therapies was also low in the Trivandrum THFR patient registry (only 25% received optimal medical therapy), and patients in which management was suboptimal had increased mortality.[42] These treatment gaps may contribute to the higher mortality rates among HF patients from specific Asian countries, including SA nations, and warrant urgent attention.

Of note, some novel therapies for T2DM have demonstrated cardiovascular benefits, such as glucagon-like peptide-1 (GLP-1) receptor agonists;[91] and medications originally intended for the management of T2DM have now expanded their breadth as therapeutic options for patients with HFrEF (e.g., dapagliflozin, a sodium-glucose co-transporter 2 [SGLT-2] inhibitor).[92] GLP-1 receptor agonists will represent relevant therapeutic options in SA patients with diabetes to reduce their risk of CVD, so will SGLT-2 inhibitors in SA patients with HF with and without

diabetes. Again, cost may represent a barrier for the uptake of GLP-1s, SGLT-2s and other medications in SA countries, and cost-reduction strategies will need to be explored.

Importantly, in 2018 the Cardiological Society of India released a position statement describing standards for the prevention and management of HF in India.[93] This is a crucial step forward and should be followed by similar initiatives in other SA countries. Implementation of the recommendations included in this document in the coming years will be key to reduce the incidence and improve the outcomes of Indian patients with HF. Of note, an improved management of HF in SA countries in the coming years will most likely have overall beneficial effects for the local health systems, as well as for other patient subpopulations. For example, optimal chronic HF management may result in a better design and enhanced implementation of chronic care models for other diseases such as diabetes, CHD and chronic obstructive pulmonary disease; greater experience in the use of novel therapies such as SGLT-2s; or potential developments driven by this public health threat, such as lower-cost defibrillators or additional generic drug options.

A global priority

The same way that no nation would ignore the health needs of 25% of their citizens, we pose that in our current globalized world a coordinated response is needed to address epidemic NCDs, particularly CVDs such as HF, in SA nations, as these may not be able to tackle these challenges alone.[18,93] The same is true for other LMICs: indeed, while the central thrust of this review focuses on HF in South Asia, other low- and middle-income regions of the world may face HF epidemics only a few years later than in South Asia. For example, in sub-Saharan Africa, acute HF is already the leading cause for patient admission into cardiac units.[94] Southeast Asia is also becoming a hotspot of T2DM, CHD and premature HF.[30,95–98] Therefore, the

recommendations provided here should stimulate discussion about timely HF prevention and optimized management in other LMICs as well.

The WHO, the World Bank, the International Monetary Fund, and other international development agencies and non-profit institutes can play a key role through expert evidence-based guidance, provision of support in the implementation of key prevention policies, and financial assistance in the strengthening of public health, health promotion and healthcare systems in South Asia. This is consistent with the WHO Millennium Development Goals' actions to support countries.[98] Also, international efforts aimed at enhancing the economies of SA and other LMICs may be the most powerful root intervention towards improved health and sustainability. A global coordinated response is likely to have enormous benefits, as the global annual financial burden of HF is estimated to be $108 billion.[99]

A call for further research

More research is needed to better establish the true incidence and prevalence of HF in SA countries, the characteristics and prognosis of HF in SA populations, as well as further characterize the absolute and relative contributions of different risk factors, including genetics and epigenetics. In addition, evidence-based prevention and management of HF specifically in SA populations both need to be further improved. **Table 4** presents a summary of key prevailing research gaps in this field. These research initiatives should be pursued both in SA countries as well as in nations hosting large SA immigrant populations. Increased attention towards HF in the coming years driven by an eventual epidemic in the very large SA population may further our understanding of its pathophysiology, mechanisms, prevention, optimal management approaches,

and novel therapeutic targets, overall as well as among key patient subgroups such as those with HFpEF.

Similar research should also be pursued in other LMICs. Ongoing international HF studies such as the Global Congestive Heart Failure (G-CHF) registry, which aims to include 25,000 HF patients from 335 sites in 42 countries will provide valuable updated insights on the global and regional epidemiology of the disease.[100] The study was started in 2016 and is planned to extend until 2024.

Conclusions

Although frequently underrecognized compared to CHD and T2DM, international studies suggest that SAs may also be at an increased risk of HF compared to other racial/ethnic groups, and that HF presents at earlier ages in SAs. These phenomena are likely the consequence of a high, double burden of key pre- and post-epidemiological transition HF risk factors in SA populations since young ages. Combined with the very large size of progressively aging populations in SA countries, this would most likely result in a surge of HF cases in the coming decades. An eventual HF epidemic could have dramatic consequences, and urgent interventions are needed to "flatten the curve" of HF in South Asia. We call for urgent action to curb these trends, with a focus on interventions aimed at reducing the incidence of HF, particularly through policy action and strengthening of healthcare systems, and optimizing the management of prevalent HF. This will require aggressive health protection policies, local prioritization of resources in SA countries towards the prevention and management of NCDs, and a global collaborative effort.

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FIGURE LEGENDS

Figure 1. Population of South Asian countries in 2020.

Numbers presented in millions of persons.

Figure 2. Relative risk of first hospitalization and/or mortality for HF in the Scottish Health and Ethnicity Linkage (SHELS) Study.

Age range was 30 to 74 years. Adapted from: Bhopal RS, Bansal N, Fischbacher CM, Brown H, Capewell S; Scottish Health and Ethnicity Linkage Study. Ethnic variations in heart failure: Scottish Health and Ethnicity Linkage Study (SHELS). Heart. 2012;98(6):468–473.

Abbreviations: CI = confidence interval; RR = rate ratios; SA = South Asian

Figure 3. Prevalence and incidence of HF in Catalonia (Spain) by geographic group, age and sex.

The number of SA men ages ≥65 years included in the database was low.

Reproduced with permission from Cainzos-Achirica M, Vela E, Cleries M, et al. Cardiovascular risk factors and disease among non-European immigrants living in Catalonia. Heart. 2019;105(15):1168–1174.

Abbreviations: HF = heart failure

Figure 4. Potential mechanisms leading to an increased risk HF in SAs.

Abbreviations: CHD = coronary heart disease; CKD = chronic kidney disease; HF = heart failure; LV = left ventricle; PM = particulate matter; RV = right ventricle; SA = South Asian

1 **TABLES**

2 **Table 1.** Summary of studies of HF epidemiology in SA living in *diaspora* countries and multinational studies of HF patients.

Region/Author	Country(ies)	Year	Study population	Key findings
Middle East				
Panduranga P[23]	Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen	2012	4,539 hospitalized patients with acute decompensated chronic HF or new-onset acute HF from the Gulf Acute Heart Failure Registry, a clinical registry comprising 47 hospitals	HF patients of Indian ancestry were 6 years younger than the native Middle Easterners and 16 years younger than patients in similar European and US HF registries, such as EHFS II and ADHERE.[31,32] Indian patients presented with concurrent acute coronary syndromes more often (46% vs. 26%), were more likely to be smokers (36 vs. 21%), to have diabetes (56% vs. 49%) and had a higher frequency of HFrEF (76% vs. 65%). In-hospital mortality similar in both groups.
Europe				
Blackledge HM[24]	England (Leicestershire)	1998 to 2001	5,789 consecutive patients newly admitted with HF	SAs had higher age-adjusted HF admission rates than the white population (rate ratios of 3.8 for men, 5.2 for women), higher hospital incidence rates (rate ratios of 2.2 and 2.9, respectively), and were on average 8 years younger (70 vs. 78 years). SAs more frequently had either a history of or concurrent MI, and 46% had diabetes compared to 16% among whites.

Bhopal RS[25]	Scotland	2001 (Census data) onward	Cohort study of 4.65 million people living in Scotland (SHELS)	SAs particularly Pakistanis, Bangladeshis, and Indian men had the highest rates of HF admission compared with the local white population and all other immigrant groups, including persons of African and Chinese origin. SHELS also confirmed that UK SAs were the youngest group at the time of a first HF admission. Differences between SAs and whites in terms of HF rates were less striking than in the study by Blackledge[24]
van Oeffelen AA[26]	The Netherlands	1998 to 2010	Nationwide prospective cohort study of 189,069 first HF admissions	Local SAs were much younger than the Dutch population (median ages 58 and 79 years, respectively).
Cainzos-Achirica M[15]	Spain (Catalonia)	2017	Regionwide study including ~60,000 mostly-Pakistani SA immigrants	SA women ≥65 years of age had a much higher prevalence of HF than the local Spanish population or any other LMIC immigrant group. Also, SA men had the highest prevalence of HF at ages 55–65 years and also led the prevalence of HF among men ≥80 years among all groups evaluated
North America				
Singh N[27]	Canada	1997 to 1999	Retrospective cohort of patients hospitalized with a primary diagnosis of HF	SAs were younger than local white patients and had diabetes more frequently. In-hospital survival was similar between the 2 groups, although SAs had a higher prevalence of high-risk features at discharge.

Choi D[28]	Canada (Ontario)	2000 to 2011	1,671 HF patients followed in 2 specialized HF clinics	Average mean age was ~8 years lower in SAs compared with Chinese patients and ~5 years lower than in non-Asian individuals. SAs more frequently had a history of diabetes, MI and 3-vessel disease, and needed coronary revascularization procedures more often than the other groups.
Jose PO[29]	United States	2003 to 2010	Study of more than 10.4 million death records evaluated cardiovascular mortality trends among the six largest local Asian-American subgroups	Women of SA ancestry had the highest age-adjusted yearly mortality rates from HF among all Asian subgroups evaluated (11.3 per 100,000 persons), and SA men had the second-highest rate (8.7 per 100,000) only surpassed by Filipinos (11.5 per 100,000). Nevertheless, mortality rates from HF were higher among non-Hispanic Whites. US SAs comprise a highly educated, high-income, healthier SA diaspora subgroup.[16]
Multinational				
Lam CS[30]	Various	2012 to 2015	ASIAN-HF international registry of 5,276 chronic HFrEF patients from China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand	SAs were the youngest patients in the registry (mean age 57.8 years, compared to 62.1 in Northeast Asians and 58.9 in Southeast Asians) yet had a higher burden of underlying CHD and diabetes (51% and 37%, respectively) than Northeast Asians (38% and 31%, respectively). Rheumatic valvular disease was an exclusion criterion, which may explain the slightly higher mean age of SA participants compared to other studies.

Abbreviations: ADHERE = Acute Decompensated Heart Failure National Registry; ASIAN-HF = Asian Sudden Cardiac Death in Heart Failure; EHFS II = EuroHeart Failure Survey II; HF = heart failure; HFrEF = HF with reduced ejection fraction; LMIC = low- and middle-income countries; MI = myocardial infarction; SA = South Asian; SHELS = Scottish Health and Ethnicity Linkage Study; UK = United Kingdom; US = United States

Table 2. Proposed interventions for the prevention of HF in SAs.

Primordial
• National prioritization of policies and strategies aimed at reducing exposure to cardiovascular risk factors and increasing exposure to health factors • Increase taxation, enforce public smoking bans, warnings on packets, and advertisement restrictions, affecting smoked tobacco but also other tobacco products (including branded *bidis* and smokeless tobacco) • Decrease content of salt, refined sugars and trans fatty acids in foods through national policies; use of mandatory food labels • Taxations for sugar-sweetened beverages, saturated and trans fats, coconut oil, palm oil, Vanaspati, ghee • Aggressively promote a culture of increased levels of physical activity both at the workplace and during leisure time • Promote a cultural shift towards healthy diets and foods • Provision of health education to the general population, including since early ages (interventions at schools, healthy living included in the curriculum) • Target entire households and communities • Enhance cultural competency of interventions • Policies to reduce air pollution: cooking fuel, industry and transportation regulations • Policies to minimize the use of pesticides with deleterious health effects • Enhance the detection, acute-phase management and follow-up of rheumatic fever
Primary

• Aggressive detection of cardiovascular risk factors at early adult ages with special attention to diabetes, obesity, hypertension and atherogenic dyslipidemia • Develop local, regional and nationwide cardiovascular risk factor screening programs • Optimized lifestyle and pharmacological management since early stages
Secondary
• Optimized acute-phase management of CHD once present: increase awareness, develop primary angioplasty networks, minimize door to balloon delays • Enhanced chronic management of CHD: optimize lifestyle and pharmacological management during follow-up, long-term use of class I therapies such as statins and ACE inhibitors • Culturally appropriate CHD rehabilitation, such as yoga and Bollywood dance • Early detection and aggressive management of subclinical left ventricular systolic dysfunction (Stage B HF) following relevant clinical practice guidelines

Abbreviations: ACE = angiotensin converting enzyme; HF = heart failure; SA = South Asian

Table 3. Proposed health systems strengthening approaches aimed at improving the prevention and management of HF in SA countries.

General approaches
• Political prioritization of CVD prevention and of quality of care
• Increase the % of gross domestic product devoted to healthcare
• Provide public universal healthcare coverage
• Improve health education and CVD health awareness in the general population
• Expansion of healthcare workforce to meet WHO recommendations
• Strengthen primary care systems with special attention to the management of complex, resource-intensive chronic conditions such as HF
• Enhance involvement of cardiovascular scientific societies in the design, implementation and evaluation of relevant health policies
• Development and implementation of clinical practice guidelines
• Implement and monitor quality and practice improvement programs, periodic audits
Approaches specific to key HF risk factors
• Develop protocols and units for the optimal management of rheumatic fever
• Train cardiovascular prevention and cardiometabolic medicine specialists
• Improve availability of weight-loss and tobacco cessation services and clinics
• Develop and monitor primary angioplasty networks
• Facilitate access to class I pharmacological and invasive therapies for T2DM, hypertension and CHD, reduce costs
• Expand availability of cardiac rehabilitation units

- Develop, expand and improve T2DM and CHD surveillance systems and registries

Specific approaches aimed at enhancing HF care

- Expand access to tools (echocardiography, NT-proBNP) and implement protocols for the early detection of left ventricle systolic dysfunction in patients with key risk factors particularly CHD
- Develop HF clinics and chronic HF management programs
- Enhance post-discharge transitional care and coordination
- Further involvement of non-physician health workers (e.g., nurses, chronic care case managers) in the care of HF patients, and enhance coordination between relevant specialists: primary care, internal medicine, cardiology, case managers, nurses
- Facilitate access to class I lifestyle, pharmacological and invasive therapies for HF, reduce costs
- Empower HF patients to improve their self-care, monitor vital signs and early detect HF exacerbations
- Day hospitals for the management of mild HF exacerbations
- Leverage novel technologies: telemedicine, remote monitoring, self-monitoring wearable devices
- Develop, expand and improve HF surveillance systems and patient registries

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; NT-proBNP = N-terminal pro b-type natriuretic peptide; SA = South Asian; T2DM = type 2 diabetes mellitus; WHO = World Health Organization

Table 4. Key evidence gaps and research needs in SA populations.

HF surveillance and epidemiology
• National and regional estimates of HF prevalence and incidence
• Descriptive epidemiological studies: HF demographics, subtypes, risk factors, temporal trends, comorbidities, mortality
• Characterization of national, subnational and cultural heterogeneity in HF epidemiology
• HF direct and indirect costs, healthcare expenditure
Mechanistic research
• Further identification of unique underlying determinants of excess HF risk in SAs, overall and by HF subtypes (HFrEF, HFpEF)
• Further characterization of genetic variants and mechanisms associated with HF in SAs
• Identification of novel pharmacological therapeutic targets relevant to SA populations
• Identification of opportunities to improve care of CHD patients and CVD risk factors
HF management
• HF trials with enhanced representation of SA participants
• Epidemiology of HF drug prescription, use and adherence
• Characterization of HF therapy costs to patients and affordability in SA countries
• Effectiveness of HF guideline-recommended pharmacotherapies in SAs compared to other groups
Translational science
• Evaluation of NTproBNP and other biomarkers for the diagnosis of HF in SAs

• Definition of SA-specific biomarker cut-points, overall and by sex and age groups • Evaluation of screening approaches aimed at the early detection of HF in the general population and in specific subgroups at higher risk (e.g., CHD and diabetes)
Policy
• Comparative effectiveness of different primary prevention policies • Cost-effectiveness evaluations
Outcomes research
• Identification of optimal acute HF management algorithms • Identification and characterization of chronic HF management strategies aimed at improving transitional and chronic care and preventing early rehospitalization after discharge for a hospital admission for HF • Cost-effectiveness studies

Abbreviations: CHD = coronary heart disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NTproBNP = N-terminal pro b-type natriuretic peptide; SA = South Asian

FIGURES

Figure 1.

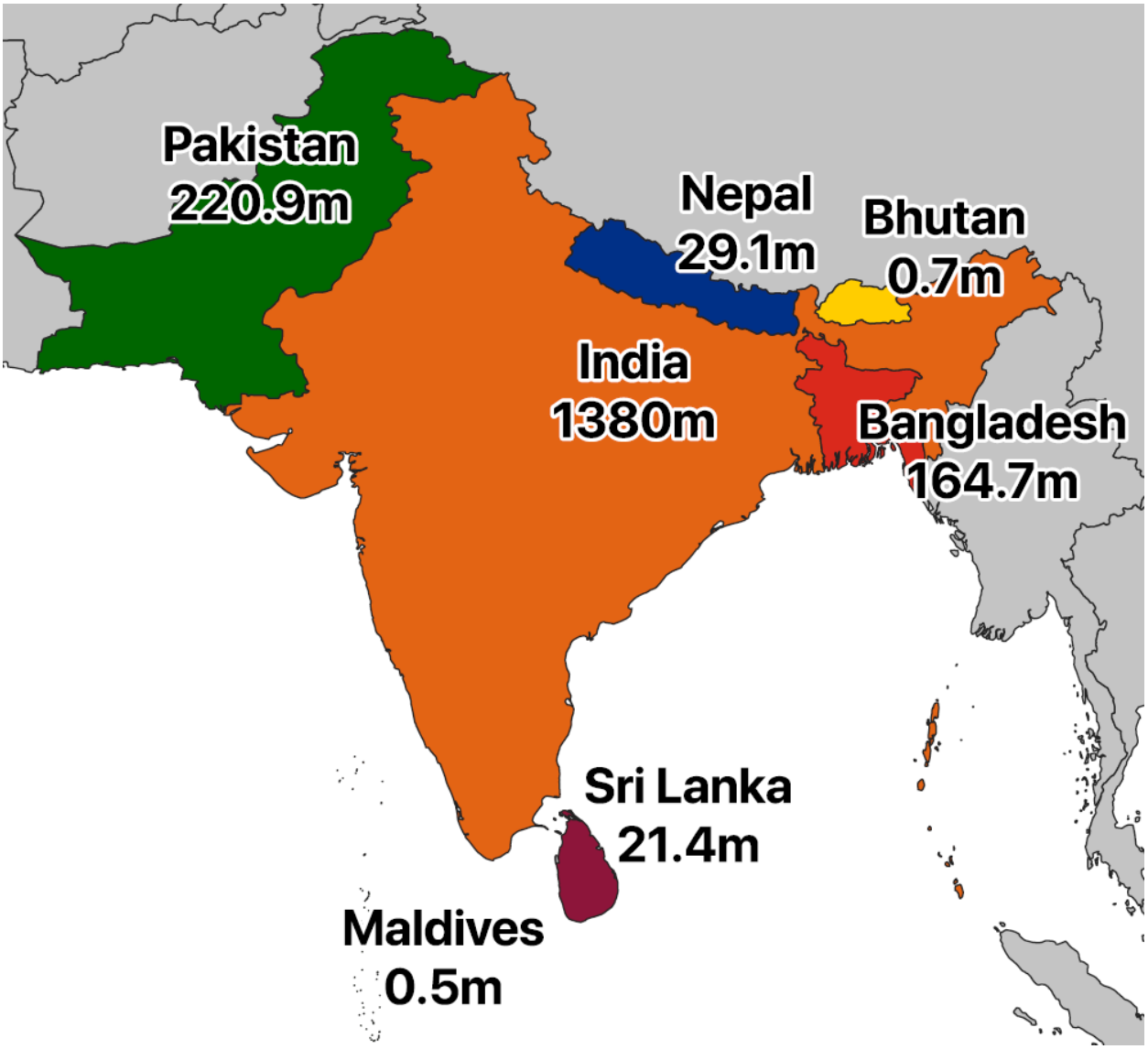


Figure 2.

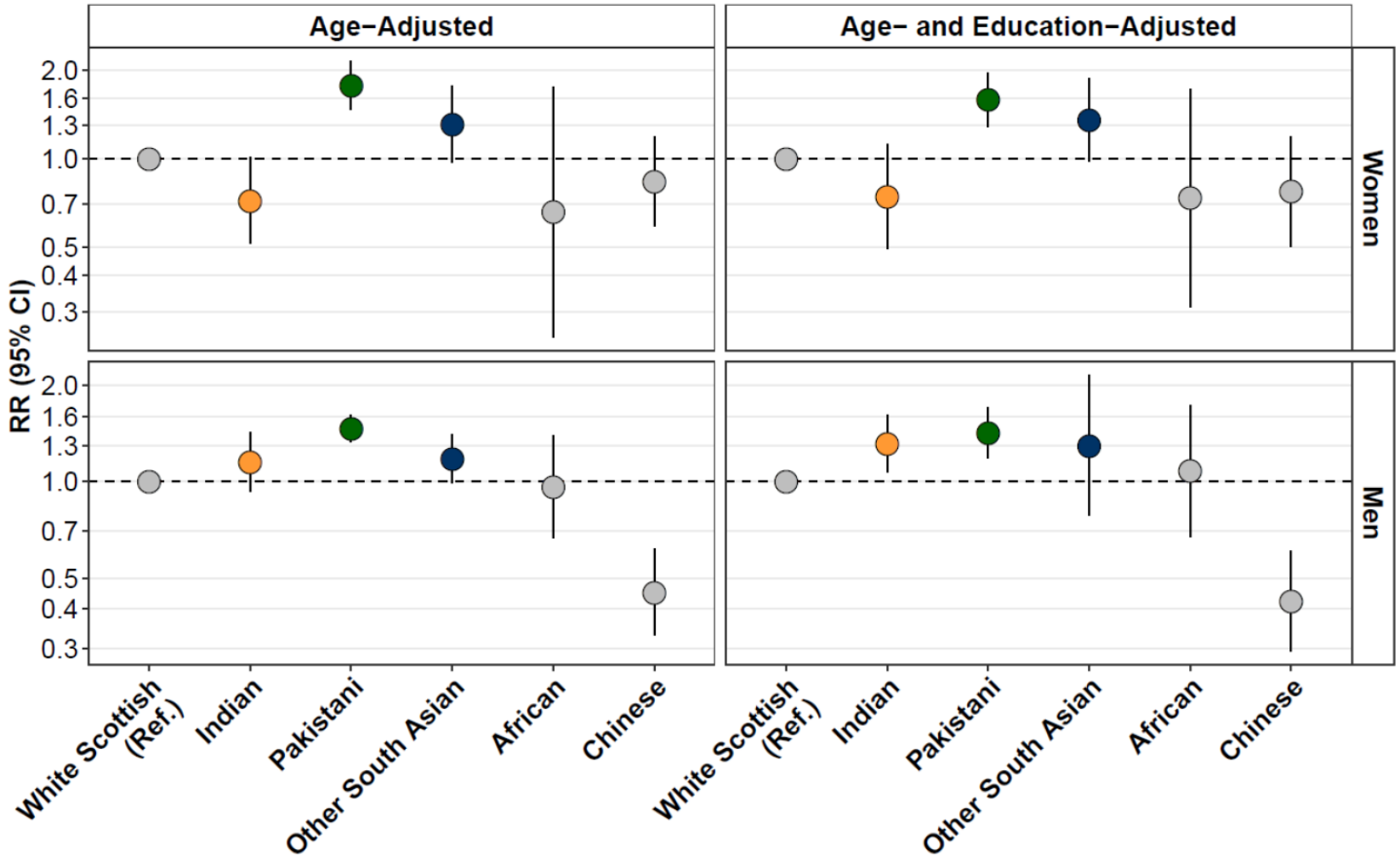

Age−Adjusted
Age− and Education−Adjusted
RR (95% CI)
2.0
1.6
1.3
1.0
0.7
0.5
0.4
0.3
Women
Men
White Scottish (Ref.)
Indian
Pakistani
Other South Asian
African
Chinese

Figure 3.

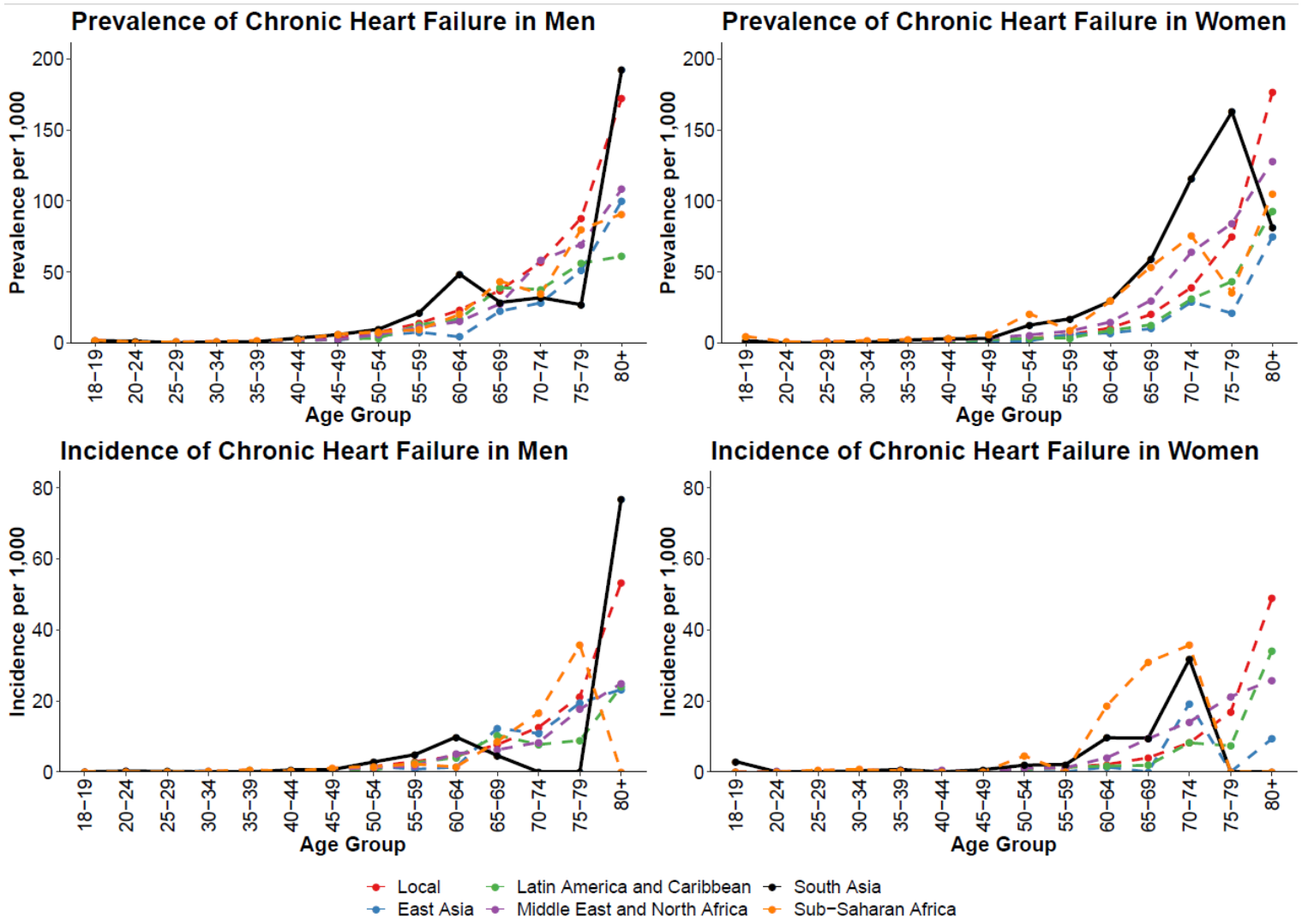
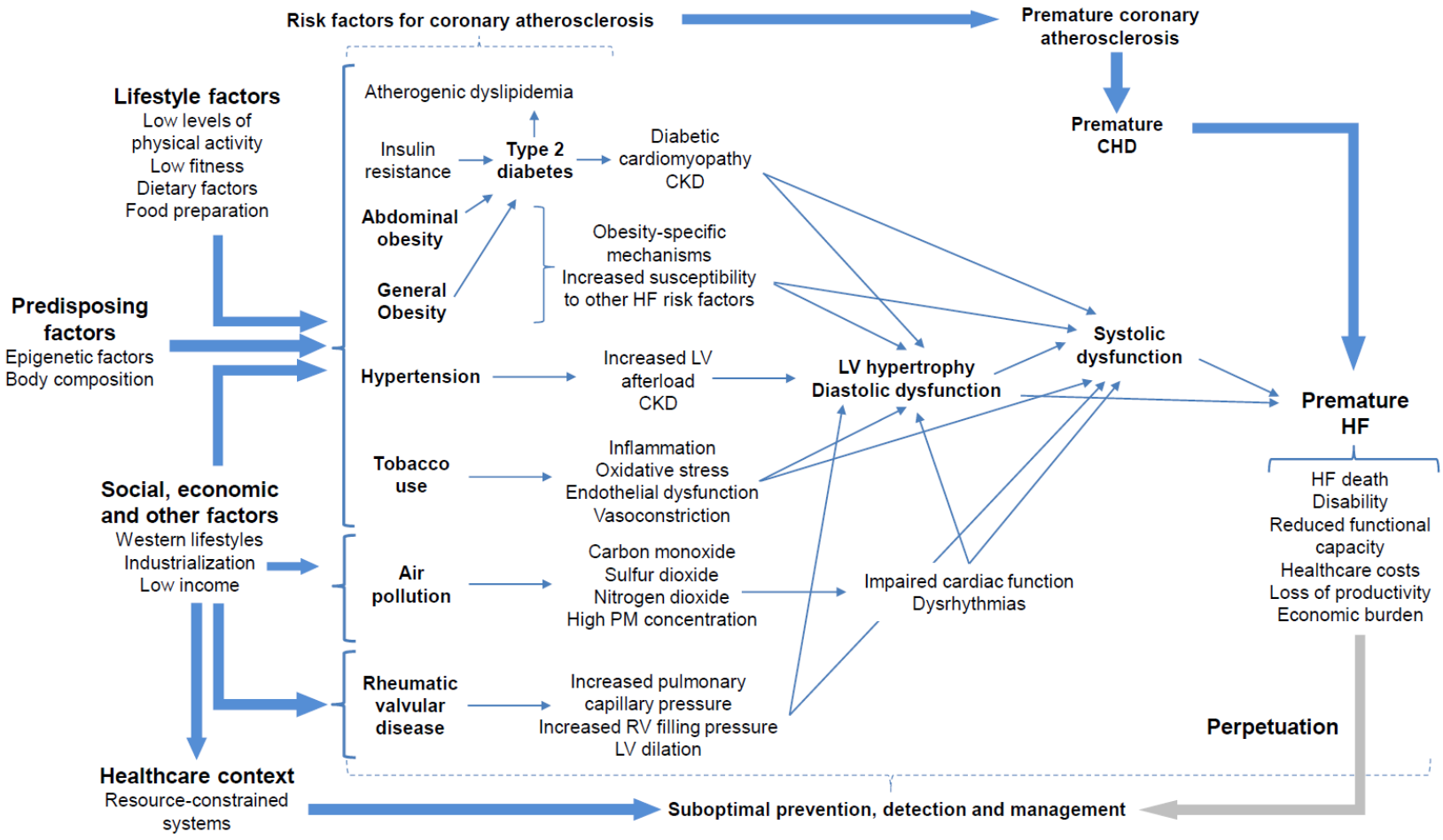

Prevalence of Chronic Heart Failure in Men
Prevalence of Chronic Heart Failure in Women
Incidence of Chronic Heart Failure in Men
Incidence of Chronic Heart Failure in Women
Prevalence per 1,000
Incidence per 1,000
Age Group
18–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65–69
70–74
75–79
80+
Local
East Asia
Latin America and Caribbean
Middle East and North Africa
South Asia
Sub−Saharan Africa

Figure 4.


Risk factors for coronary atherosclerosis
Premature coronary atherosclerosis
Premature CHD
Lifestyle factors
Low levels of physical activity
Low fitness
Dietary factors
Food preparation
Atherogenic dyslipidemia
Insulin resistance
Type 2 diabetes
Diabetic cardiomyopathy
CKD
Abdominal obesity
General Obesity
Obesity-specific mechanisms
Increased susceptibility to other HF risk factors
Predisposing factors
Epigenetic factors
Body composition
Hypertension
Increased LV afterload
CKD
LV hypertrophy
Diastolic dysfunction
Systolic dysfunction
Premature HF
Tobacco use
Inflammation
Oxidative stress
Endothelial dysfunction
Vasoconstriction
Social, economic and other factors
Western lifestyles
Industrialization
Low income
Air pollution
Carbon monoxide
Sulfur dioxide
Nitrogen dioxide
High PM concentration
Impaired cardiac function
Dysrhythmias
HF death
Disability
Reduced functional capacity
Healthcare costs
Loss of productivity
Economic burden
Rheumatic valvular disease
Increased pulmonary capillary pressure
Increased RV filling pressure
LV dilation
Perpetuation
Healthcare context
Resource-constrained systems
Suboptimal prevention, detection and management

1