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Title: Heart Failure Burden in 15-44 Year Olds: Global Analysis 1990-2021 with 2050 Projections

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Clinical Question Box

What is the Global Burden and Etiological Profile of Heart Failure in Adolescents and Young Adults Aged 15–44 Years?

Heart failure in adolescents and young adults (AYA) is an emerging public health challenge with distinct epidemiological features compared to older populations. This study quantifies the global prevalence, years lived with disability (YLDs), and underlying causes of HF in individuals aged 15–44 from 1990 to 2021, with projections to 2050. Findings indicate a substantial and growing burden, characterized by male predominance, a peak in the 40–44 age group, and a leading etiological role of cardiomyopathy, contrasting with the ischemic-driven profile in older adults. These results underscore the need for early screening, etiology-specific prevention, and targeted public health interventions in this demographic.

Abstract

Introduction: Heart failure (HF) persists as a critical public health priority globally, and comprehensive epidemiological assessments of the rising number of young HF patients remain limited. This study aimed to quantify the global burden of HF among individuals aged 15-44 from 1990 to 2021 and predict until 2050. **Methods:** Using data from the Global Burden of Disease Study (GBD) 2021, we quantified HF burden among adolescents and young adults (AYA) aged 15-44 years from 1990 to 2021 globally, with stratified by six 5-year age subgroups, sex, sociodemographic index (SDI). **Results:** In 2021, HF affected 5.45 million cases (age-standardized prevalence rate [ASPR]: 156.43/100,000), with 525,221 YLDs (age-standardized YLD rate [ASYR]: 15.07/100,000) from 1990 to 2021, representing a substantial increase. High SDI regions bore the highest burden. Analyses revealed a consistent male predominance, with the highest burden observed in the 40-44 year age group. Etiologically, cardiomyopathy dominated globally (25.84%). Projections to 2050 forecast continued increase. **Conclusion:** This study shows HF burden in AYA aged 15-44 years is substantial and continuously growing, characterized by significant gender, age, socio-economic, and geographic differences; cardiomyopathy dominates, highlighting the need for early screening and targeted global health actions.

Keywords: adolescent and young adult (AYA); global burden of disease (GBD); heart failure; joinpoint regression; public health

Introduction

Heart Failure (HF) is a clinical syndrome characterized by structural and/or functional cardiac impairment leading to objective evidence of cardiopulmonary congestion, typically confirmed by elevated natriuretic peptide levels and imaging findings[1,2]. HF imposes a substantial global health and economic burden, with estimated worldwide costs reaching $284.17 billion across 179 countries in 2021[3,4].

Historically, HF predominantly affects older populations, with peak incidence occurring among adults aged ≥60 years. Ischemic heart disease (IHD), hypertension, and chronic obstructive pulmonary disease (COPD) constitute the primary etiologies[5-9]. While overall HF incidence has declined since the 1990s due to improved cardiovascular prevention and management, epidemiological trends reveal an alarming in incidence among adolescent and young adult (AYA)[10-14]. Data from New Zealand documented a significant annual increase of 1.5% among 20-49 year-olds from 2006 to 2018[15-17]. 61,729 HF-related deaths occurred globally in AYA populations from 1990-2019[14], underscoring the substantial disease burden in this demographic[18]. While incidence remains approximately 1% in adults under 55 years, it escalates dramatically to 46% among healthy 46 year old, signaling mid-adulthood as a pivotal period for preventive intervention[18-20]. AYA remain markedly underrepresented in both clinical research and public health policies, resulting in critical evidence gaps regarding disease mechanisms, optimal interventions, and burden stratification specific to this demographic. However, as a critical window for curbing HF progression through early

lifestyle and medical intervention, the 15-44 year age group lacks tailored prevention strategies and dedicated resource allocation in global health agendas.

Based on Global Burden of Disease (GBD) 2021 dataset, this study quantifies the disease burden of HF among AYA aged 15-44 years from 1990 to 2021. We systematically evaluated temporal trends stratified by sex, age cohort, and the Socio-Demographic Index (SDI) and project future trajectories, and the etiological spectrum in this population. This comprehensive epidemiological assessment provides critical evidence to guide targeted public health interventions, optimize resource distribution, and mitigate the HF burden in the 15-44 age demographic globally.

Materials and methods

Study population and data sources

This study utilized primary data from the GBD 2021, a comprehensive epidemiological database coordinated by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington that collates 371 diseases and 88 risk factors across 204 countries and territories[21].

Our analysis focuses specifically on HF burden among AYA aged 15-44 years. Data were stratified by six age subgroups (15-19, 20-24, 25-29, 30-34, 35-39, and 40-44 years) and sex (both/male/female) to quantify age-specific trends and sex-based disparities. Primary metrics included prevalence and YLDs. The complete dataset is publicly accessible through the GBD Results Tool (https://ghdx.healthdata.org/gbd-results-tool).

Definition

HF is clinically defined as a complex syndrome arising from structural or functional cardiac impairment that compromises ventricular filling or blood ejection capacity, leading to characteristic symptoms and signs, as defined by the Global Burden of Disease Study 2021 (GBD 2021) Data Resources (GHDx)[1].

Based on systematic literature review and alignment with GBD 2021, this study identified 17 underlying causes of HF among AYA aged 15-44 years[22,23]. ICD codes in Table S1. Additionally, for atrial fibrillation and flutter (AF/AFL), due to the lack of data for individuals under 30 years, the analysis for AF/AFL commenced at age 30[24].

While the GBD database predominantly defines AYA as individuals aged 15-39 years, this study extends the upper age limit to 44 years to capture the critical window for cardiovascular disease intervention prior to mid-adulthood[25,26]. This adjustment aligns with epidemiological evidence indicating that cardiovascular risk trajectories undergo significant shifts before age 45, necessitating expanded surveillance in this demographic[27].

To mitigate demographic heterogeneity, all burden metrics were age-standardized using the GBD global reference population[28]. The formula as follows:

$$ASR = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i} \times 1000{,}000$$

where: a_i =number of events (e.g., incident cases, deaths) in the ith age group; w_i =weight of the ith age group in the GBD standard population; A =total number of age groups[29].

YLDs, a standardized measure of non-fatal health loss, are calculated through multiplicative integration of cause-age-sex-location-year-specific sequelae prevalence and their corresponding disability weights (ranging 0-1), thereby capturing the morbidity burden attributable to functional impairment[29].

UIs quantify the robustness of estimates, expressed as 95% UIs derived from the 2.5th and 97.5th percentiles of 1000 posterior draws. This incorporates stochastic uncertainty from data inputs, model specification, and disability weight assignments, ensuring statistical rigor in reporting data[28].

SDI serves as a composite indicator of development status, ranging from 0 (lowest)

to 1 (highest). It integrates lag-distributed income per capita, average educational attainment in individuals aged ≥15 years, and the total fertility rate among those <25 years[30].

2.3. Statistical analysis

Joinpoint regression analysis

Temporal trends in HF burden among AYA aged 15-44 years from 1990 to 2021 were evaluated using Joinpoint regression analysis (v5.2.0, NCI). This segmented linear modeling approach identified inflection points ("joinpoints") where significant shifts in trend directionality occurred, minimizing residual sum of squared errors via iterative grid searches constrained to a maximum of five joinpoints. Annual Percent Change (APC) characterized segment-specific trends, while the Average Annual Percent Change (AAPC), a geometric weighted mean of APCs, summarized the overall trajectory. Monte Carlo permutation testing (9,999 iterations) assessed statistical significance ($P < 0.05$). Trends were deemed increasing if the AAPC and its 95% confidence interval (CI) were >0, decreasing if <0, and stable if the CI spanned 0[31].

This analytical approach was selected for its specific capacity to identify discrete inflection points in temporal trends, a key advantage over methods that estimate a single, smoothed average trend, such as the Estimated Annual Percentage Change (EAPC)[32]. While EAPC provides a summarized annual rate of change over an entire period, our Joinpoint analysis reveals the specific timing and magnitude of significant shifts in disease burden trajectory. This enables a more dynamic interpretation of trends, linking epidemiological changes to potential period-specific drivers that may be obscured by

average estimates.

Bayesian Age–Period–Cohort Analysis

The Bayesian Age-Period-Cohort (BAPC) model, implemented via R packages `BAPC` and Integrated Nested Laplace Approximation (`INLA`), projected the burden to 2050. This framework integrated prior epidemiological knowledge with GBD 2021 data to decompose temporal trends into orthogonal age, period, and cohort effects, addressing multicollinearity through Bayesian regularization. The intrinsic estimator method resolved identifiability constraints (Age = Period - Cohort).

In GBD studies, UIs are used to quantify overall uncertainty from multiple sources, such as data inputs, model parameters, and multi-stage modeling processes. Compared with conventional confidence intervals, UIs provide a more comprehensive measure of statistical uncertainty in complex, hierarchical modeling frameworks. Our projections were derived from a BAPC model, which inherently accounts for uncertainty in future estimates. To remain consistent with the source data and propagate this foundational uncertainty through our analysis, we report projections with 95% UIs instead of confidence intervals. Model fitting was conducted using the `INLA`, a deterministic approach that approximates marginal posterior distributions and unlike Markov Chain Monte Carlo methods, avoids convergence-related challenges[33,34]. Previous studies have shown that `INLA` offers comparable or superior coverage and accuracy relative to other Bayesian estimation techniques, supporting the reliability of our projections[35].

All epidemiological analyses and statistical modeling were performed using R software, version 4.3.2 (R Foundation for Statistical Computing). Joinpoint regression

analysis was conducted using version 5.2.0 to perform segmented trend analysis with Monte Carlo permutation testing. Statistical significance for all inferential analyses was defined a two-tailed $P < 0.05$.

Results

Global trends

HF among AYA aged 15-44 years caused 5,452,015 global cases (95% UI: 4,058,028-7,104,938) in 2021, corresponding to an ASPR of 156.43 per 100,000 persons (95% UI: 116.59-203.71). This is a substantial increase from the 1990 of 3,277,464 cases (95% UI: 2,431,379-4,259,270) and an ASPR of 134.51 (95% UI: 99.26-175.24). Similarly, HF-related YLDs in this demographic reached 525,221 cases (95% UI: 325,285-793,006) in 2021, with ASYR of 15.07 (95% UI: 9.34-22.75), compared to 314,059 cases (95% UI: 192,971-473,785) and an ASYR of 12.87 (95% UI: 7.88-19.46) in 1990 (Table 1).

Joinpoint regression analysis revealed a significant upward trend in ASPR from 1990 to 2021 (AAPC =0.50%; 95% CI: 0.49%-0.50%; P <0.001), with a marked increase between 2000 and 2005 (APC =1.19%). The ASYR trend paralleled this rise (AAPC =0.52%; 95% CI: 0.51%-0.52%; P <0.001), peaking from 2000 to 2005 (APC =1.26%) (Table 1 and Fig. 1A, 1B).

Socio-Demographic level trends

In 2021, High SDI regions demonstrated the highest ASPR of 183.58 (95% UI: 140.68-235.29) and ASYR of 17.45 (95% UI: 11.00-25.98), while high-middle SDI regions showed the lowest burden (ASPR: 135.43 [95% UI: 101.07-176.29]; ASYR: 13.01 [95% UI: 8.03-19.60]) (Table 1). All SDI quintiles showed increasing trends from 1990 to 2021 (all AAPC >0, P <0.05). Regions experiencing lower baseline burdens exhibited the most accelerated growth, with middle SDI regions demonstrating the highest

increases. In contrast, high-SDI regions, which bore the highest absolute burden, displayed a significant decrease after 2019 (Table 1 and Fig. 1C, 1D).

Regional trends

In 21 GBD regions, High-income North America exhibited the highest ASPR at 250.31 per 100,000 (95% UI: 195.58-313.76) and ASYR at 23.55 (95% UI: 14.76-34.83), closely followed by North Africa and the Middle East (ASPR: 200.49; ASYR: 19.19). Conversely, Oceania (ASPR: 100.94; ASYR: 9.59), Southeast Asia (ASPR: 109.15; ASYR: 10.93), and East Asia (ASPR: 114.74; ASYR: 11.24) demonstrated the lowest burdens in 2021(Table 1). The majority exhibited increasing trends, with East Asia showing the most accelerated growth (AAPC ASPR: 1.44%; ASYR: 1.43%). In contrast, only four regions experienced declines: Southern Latin America, Andean Latin America, High-income North America, and Tropical Latin America (Table 1 and Figure S1).

Notably, the relationship between SDI and HF burden showed a nonlinear W-shaped distribution across 21 GBD regions. This pattern signifies elevated burdens in both low SDI and high SDI regions, reflecting the dual influence of limited healthcare access in developing economies and lifestyle-associated risk factors in affluent societies.

National trends

In 2021, Canada showed the highest ASPR (269.20 per 100,000; 95% UI: 191.28-356.07), followed by the United States (248.10; 194.30-310.10) and Qatar (236.53; 160.52-325.00). Conversely, Iceland (79.34; 55.39-108.36) and Greece (87.40; 62.08-117.66) exhibited the lowest burden in 2021 (Fig.2A and Table S2). Among 184

countries (90.2% of analyzed territories), HF burden significantly increased (all AAPC >0, P <0.05). The most accelerated growth occurred in China (ASPR AAPC: 1.49%; 95% CI: 1.43-1.55), the Netherlands (0.79%; 0.69-0.92), and the United Kingdom (0.61%; 0.47-0.72). Conversely, 19 nations demonstrated declining trends, with Bolivia exhibiting the steepest reduction (AAPC: -1.29%), followed by Sweden (-0.91%) and Argentina (-0.87%) (Fig. 2C and Table S2). While low SDI regions showed marginally elevated ASPR, the heaviest absolute burdens concentrated in high SDI countries (Figure S3). This pattern was also mirrored in ASYR, confirming consistent disability-adjusted burden metrics across countries and regions level (Fig. 2B, 2D; Table S2 and Figure S3).

Sex pattern

In 2021, Males exhibited higher ASPR (175.05 per 100,000; 95% UI: 127.36-222.65) and ASYR (16.48 per 100,000; 95% UI: 10.20-24.81) compared to females (ASPR: 141.43; ASYR: 13.63 per 100,000). This male predominance persisted universally across different age subgroups, and all countries and territories (Table 1 and Table S3). Temporal trends from 1990 to 2021 revealed consistent increases for both sexes globally. Males had an AAPC of 0.47% (95% CI: 0.46-0.48) for ASPR and 0.50% (0.50-0.51) for ASYR, while females showed slightly higher growth. Notably, the period 2000-2005 marked the most rapid acceleration, with APC of 1.12% (males) and 1.41% (females) in ASPR (Fig. 1A, 1B and Table 1). Stratification by SDI further confirmed no significant gender-based divergence in trend trajectories across development strata, reinforcing the robustness of these patterns (Figure S4).

Age pattern

Distinct age-dependent patterns in the global burden of HF among AYA aged 15-44 years were observed in 2021. The 40-44 year cohort demonstrated the highest ASPR (223.38; 95% UI: 156.15-301.71) and ASYR (21.29; 12.67-32.00), followed by the 35-39 year and 15-19 year groups. Conversely, the lowest burden was observed in the 30-34 year and 25-29 year cohorts (Table 1). This age gradient persisted across most GBD regions (Figure S5). All age groups demonstrated increases from 1990 to 2021. The most accelerated growth occurred in the 20-24 year cohort (Table 1). Notably, the 30-34 year subgroup experienced the sharpest short-term acceleration during 2000-2004 (ASPR APC: 2.12%), indicating critical period-specific influences (Fig. 1E). ASYR trends paralleled ASPR patterns (Table 1, Fig. 1F, and Figure S6).

Underlying causes analysis

Analysis of 17 underlying causes of HF among AYA aged 15-44 years revealed CM as the predominant etiology globally in 2021, accounting for 25.84% of the ASPR. IHD and rheumatic heart disease (RHD) constituted the next largest proportions (25.16% and 14.85%, respectively), followed by hypertensive heart disease (HHD) (13.79%) and congenital birth defects (CBD) (7.67%). Other causes collectively represented minor contributors (<1% individually) (Fig 3 and Table S4). Age-stratified etiology patterns demonstrated significant transitions, in which CM, CBD, and RHD proportions decreased with advancing age, whereas IHD and HHD exhibited substantial increases (Fig. 3 and Table S4). Geographical stratification revealed CM as the primary driver across high SDI, high-middle SDI, and low SDI regions. Conversely, IHD

predominated in middle SDI and low-middle SDI regions (Figure S8). ASYR patterns mirrored ASPR distributions (Figure S7, S9 and Table S5).

Prediction to 2050

By 2050, HF cases of AYA are predicted to reach 6,895,715 (95% UI: 4,745,769-9,045,662), corresponding to an ASPR of 178.44 per 100,000 (95% UI: 122.81-234.07). Concurrently, YLDs will rise to 673,591 (462,245-884,937), with an ASYR of 17.43 per 100,000 (11.96-22.90) (Fig. 4A, 4B and Table S6). Stratified analyses indicate uniform upward trajectories across both sexes and all age subgroups during this period, reflecting compounded effects of demographic momentum and evolving risk factor exposures (Fig. 4C-F, Figure S10 and Table S7, S8). Projected etiological patterns reveal divergent trajectories. While most underlying causes exhibit increasing burdens, PAH and RHD will be marginally declining, with IHD showing the steepest reduction (Figure S11 and Table S9).

Discussion

This study presents the first comprehensive assessment of HF burden among AYA aged 15-44 years across global, regional, and national levels from 1990 to 2021. First, our analyses reveal a sustained increasing trajectory in this disease burden, with projections indicating continued escalation through 2050. Second, persistent male predominance and distinct age-dependent patterns were observed. Third, a nonlinear relationship emerged between socioeconomic development and disease burden. High SDI regions exhibited the highest absolute burden yet slowest growth, while middle SDI regions demonstrated the steepest increases. Finally, etiologically, contrasting with ischemic-driven patterns in elderly populations, non-ischemic factors are the causes of HF in this age group.

Our findings, derived from a focused analysis of the 15–44-year cohort, reveal critical distinctions from the recent report on 15–49-year-olds by Shu et al. (2025), underscoring the necessity of finer age stratification[36]. First, burden distribution: approximately 77.4% of the prevalent cases and 87.6% of the ASMR within the broader 15–49-year cohort are concentrated in our younger 15–44-year population, identifying this subgroup as the core driver of the young-adult HF epidemic.Second, identification of critical transitions: By applying Joinpoint regression to the 15–44-year cohort, we were able to identify not only the magnitude but also the precise timing of significant shifts in HF burden trends. This capability to detect and date such inflection points offers a more dynamic understanding of disease progression than approaches that report

only average trends. Third, national profiles: the country-level peak shifted from the United Arab Emirates to Canada, a change potentially attributable to high-risk Indigenous Canadian subpopulations characterized by early-onset cardiac lipid abnormalities[37]. Most importantly, etiological profile: whereas IHD dominated in the 15–49-year cohort, CM emerges as the primary etiology in the 15–44-year group. This aligns with the early-life manifestation of non-ischemic pathologies like CM, rheumatic and congenital heart diseases, contrasting with IHD which typically follows decades of risk factor exposure. Therefore, stratifying the young-adult population into 15–44 years is not merely a subset analysis but reveals a distinct epidemiological entity with unique burden drivers, necessitating tailored preventive strategies.

Our study reveals that globally, the burden of HF among AYA exhibited a consistent upward trend from 1990 to 2021. This finding contrasts with previous reports of declining in ASPR of HF in the general population[38,39], which may be attributable to the predominance of elderly individuals in HF epidemiology[39]. Actually, a study in the United States demonstrated a decrease in hospitalization rates for HF among those aged 55 and older[40]. Similarly, research in Australia found that the decline in HF hospitalization rates was primarily confined to older cohorts[41]. Such stratified trajectories highlight an important limitation of population-wide analyses, namely their potential to obscure rising morbidity in specific demographic subgroups.

Furthermore, our findings reveal a nuanced trend within specific socioeconomic groups. Contrary to a previous study reporting declining HF prevalence among those under 50 in high and high-middle SDI regions from 1990 to 2021[42], our analysis shows

an upward trajectory in these quintiles until 2019, followed by a marked post-2019 decline specifically in high-SDI regions. This inflection point coincides with several developments: (i) the expansion of telemedicine during the COVID-19 pandemic, which may have improved continuity of chronic HF management[43]; (ii) a therapeutic paradigm shift following trials such as EMPEROR-Preserved (2017-2021) and the subsequent 2021 ESC guidelines endorsing SGLT-2 inhibitors as first-line therapy for HF[44,45]; and (iii) greater healthcare resources and health literacy in high-SDI settings, which can facilitate preventive behaviors and early treatment[46]. Despite these contextual factors, high-SDI regions retained the highest HF burden in 2021. This paradox may reflect underlying structural disparities. For instance, in many North African and Middle Eastern countries, healthcare expenditure constitutes less than 5% of GDP, which is below the global average, and physician distribution is uneven, with densities as low as two per 10,000 people in some nations[47]. Concurrently, escalating behavioral risks in affluent societies contribute to the burden; in the United States, for example, an obesity/overweight rate of 57.4% among young adults (18-25 years) is a potential driver of its elevated HF ranking[48]. Conversely, Oceania, Southeast Asia, and East Asia exhibited the lowest HF burdens, attributable to multiple protective factors: (i) Tobacco control successes, such as Japanese male smoking prevalence reduction from 55% to 30% (2000-2020)[49]; (ii) Cardioprotective diets rich in vegetables, fish, and olive oil. Asian diets are predominantly vegetable, and Japanese dietary patterns resembling the Mediterranean diet[50]; and (iii) Hypertension management excellence. Countries such as Japan, South Korea, Singapore, and Thailand exhibit relatively high

awareness, treatment, and control rates of hypertension[51,52].

Among 204 countries and territories analyzed, Iceland and Greece demonstrated the lowest HF burden, possibly attributed to distinct cardioprotective lifestyle patterns. Greek populations exhibit high adherence to the Mediterranean die[53], characterized by annual per capita olive oil consumption of 12.08 kg[54]. A large number of studies have shown that olive oil is a key source of monounsaturated fats and polyphenols that confer anti-inflammatory, antioxidant, and vasodilatory benefits, collectively mitigating atherosclerotic progression and myocardial dysfunction[55,56]. Concurrently, Icelandic residents display exceptional physical activity engagement, with 56% of adults meeting WHO-recommended exercise targets (≥150 minutes/week moderate-to-vigorous activity), markedly surpassing the European Union average of 33% and enhancing cardiovascular resilience through improved endothelial function and metabolic regulation[57]. This contrasts sharply with the accelerating HF burden observed in >90% of nations. China exhibits the steepest growth (ASPR AAPC: 1.49%), driven by rising cardiometabolic risks despite the "Healthy China 2030" hypertension control initiative[58]. The Netherlands (AAPC: 0.79%) and the United Kingdom (AAPC: 0.61%) similarly reflect persistent healthcare access disparities and suboptimal risk factor control in these countries and territories. Therefore, introducing policies targeting the primary causes of HF, such as taxation on sugar-sweetened beverages, and addressing socioeconomic health disparities could be important strategies for effective HF prevention and management in these regions.

Males exhibitied a systematically higher burden of HF than females across all

353 geographic regions and age subgroups during 1990-2021. This disparity can be
354 attributed to a confluence of divergent behavioral and metabolic risk profiles, potential
355 biological contributors, and sex-specific patterns in healthcare utilization. Men have
356 historically demonstrated a higher prevalence of modifiable risk factors, including
357 smoking, diabetes, and central obesity[59-61]. Additionally, biological differences may
358 play a role; premenopausal females benefit from relative cardioprotection linked to
359 estrogen, which is associated with favorable vascular physiology and a lower incidence
360 of heart failure compared to age-matched males[62-64].

361 Crucially, healthcare engagement patterns significantly influence recorded burden.
362 The peak burden observed in the 40–44 year age group in 2021 coincides temporally
363 with the expansion of structured cardiovascular screening programs, such as the UK's
364 "Men's Health MOT," which enhance case detection specifically among middle-aged
365 men. This pattern indicates that the elevated burden metric reflects not only the
366 acceleration of cardiometabolic risk in mid-adulthood but also the sensitivity of burden
367 estimates to diagnostic intensity and access to care.

368 The study addresses a critical evidence gap cardiovascular epidemiology. We
369 demonstrated that this demographic exhibits unique etiological profiles, with CM
370 constituting the primary HF etiology, contrasting sharply with ischemic-driven disease
371 in older cohorts. However, this global finding masks significant regional variation,
372 which is principally mediated by socioeconomic development. In high-middle SDI
373 settings, economic advancement generates a dual force: it enhances diagnostic capacity
374 to identify CM while concurrently promoting lifestyle transitions that increase

cardiometabolic risk-related CM subtypes[65]. Conversely, in low-middle SDI regions, the CM burden remains closely linked to preventable infectious antecedents such as RHD, reflecting persistent gaps in primary healthcare. This divergence is crystallized in high-burden middle SDI nations like Indonesia, which faces a composite burden of persistent infectious causes and rising metabolic cardiomyopathies[66]. Consequently, the specific CM profile in a region acts as a direct marker of its stage in the epidemiological transition. Despite declining age-standardized HF incidence in the general, AYA experience a sustained burden escalation, attributable to rising cardiometabolic risks, diagnostic advancements, and socioeconomic transitions. This etiological stratification necessitates equally development-stratified interventions: high-income regions require enhanced cardiomyopathy surveillance and early pharmacotherapy, while low-middle-income regions must prioritize rheumatic fever prevention and hypertension control programs targeting young populations.

This study has several limitations. First, substantial heterogeneity in primary data quality and availability across regions, particularly in low- and middle-income nations. While this variation contributes to wider uncertainty intervals for burden estimates in these settings, the GBD modeling framework employs strategies, such as spatiotemporal smoothing and crosswalk adjustments, to mitigate potential source bias. Consequently, these regional estimates should be interpreted with due caution, with a focus on their reported uncertainty ranges. Second, we did not further analyze the different pressure types of HF, which limits pathophysiological mechanism exploration and targeted intervention assessment. Third, the absence of HF-specific mortality data

precludes analysis of fatality trends among AYA, restricting comprehensive burden assessment. Fourth, an important limitation from the ecological nature of the GBD data. While robust for describing population-level trends, the GBD framework cannot statistically adjust for potential unmeasured confounders, such as simultaneous policy reforms, healthcare access disparities, or environmental exposures, that may independently influence HF burden. Therefore, the observed associations between burden metrics and socioeconomic or healthcare factors represent correlations, not established causal effects. Fifth, the projections from the BAPC model offer baseline forecasts based on historical trends. As a static framework, the model cannot simulate the effect of future interventions, policy changes, or clinical advances. Consequently, our estimates do not include their potential mitigation, and sensitivity analyses of hypothetical strategies were not performed, as this study aimed to establish a data-informed reference scenario. These projections should therefore be interpreted as a benchmark for guiding public health planning, not as a definitive outcome. Sixth, although we discuss hormonal differences as a potential explanation for the observed sex disparity in HF burden, our analysis did not include individual-level data on menopausal status. We were therefore unable to stratify female participants to test whether HF risk rises following menopause. Future detailed clinical data are needed to directly examine this hormonal hypothesis. Finally, the observed associations between HF burden and SDI should be interpreted as correlation rather than causation. While socioeconomic gradients demonstrate significant ecological correlations, unmeasured confounders such as healthcare infrastructure variability and environmental exposures

may drive these relationships. Future studies should incorporate causal inference methods to delineate direct SDI effects from contextual mediators.

Conclusion

The HF burden increased steadily among AYA aged 15-44 years globally from 1990 to 2021, predominantly driven by non-ischemic causes and disproportionately affecting males and females. Geographical disparities in HF burden correlate strongly with regional variations in dietary patterns, healthcare resource allocation, economic development and policy implementation gaps. The projected continued increase in HF burden among AYA underscores the urgent need for more proactive strategies to address its underlying causes.

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Data Availability: The datasets supporting this study are publicly available via the Global Burden of Disease (GBD) 2021 database. Detailed information regarding data sources and access is provided in the Methods section.

Ethical Statement: Not applicable

Conflict of Interest: The authors report no conflicts of interest in this work.

Reference:

1. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. Mar 2021;23(3):352–380. doi:10.1002/ejhf.2115
2. Sinescu C, Axente L. Heart failure--concepts and significance. Birth of a prognostic model. *J Med Life*. Oct–Dec 2010;3(4):421–9.
3. Darvish M, Shakoor A, Feyz L, et al. Heart failure: assessment of the global economic burden. *Eur Heart J*. Aug 14 2025;46(31):3069–3078. doi:10.1093/eurheartj/ehaf323
4. Heidenreich PA, Fonarow GC, Opsha Y, Sandhu AT, Sweitzer NK, Warraich HJ. Economic Issues in Heart Failure in the United States. *J Card Fail*. Mar 2022;28(3):453–466. doi:10.1016/j.cardfail.2021.12.017
5. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med*. Jan 11 1999;159(1):29–34. doi:10.1001/archinte.159.1.29
6. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. Feb 10 2018;391(10120):572–580. doi:10.1016/s0140-6736(17)32520-5
7. Yang R, Zhang X, Bai J, Wang L, Wang W, Cai J. Global, regional, and national burden of hypertensive heart disease among older adults in 204 countries and territories between 1990 and 2019: a trend analysis. *Chin Med J (Engl)*. Oct 20 2023;136(20):2421–2430. doi:10.1097/cm9.0000000000002863
8. Qu C, Liao S, Zhang J, et al. Burden of cardiovascular disease among elderly: based on the Global Burden of Disease Study 2019. *Eur Heart J Qual Care Clin Outcomes*. Mar 1 2024;10(2):143–153. doi:10.1093/ehjqcco/qcad033
9. Zhi H, Yang Y, Zhao J, Mao C, Shen J, Wang X. Global, regional, and national burdens of ischemic heart disease in the older adults aged 60-89 years: a systematic analysis for the Global Burden of Disease Study 2019. *Front Cardiovasc Med*. 2025;12:1443881. doi:10.3389/fcvm.2025.1443881
10. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. Jun 2015;175(6):996–1004. doi:10.1001/jamainternmed.2015.0924
11. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. Oct 31 2002;347(18):1397–402. doi:10.1056/NEJMoa020265
12. Zarrinkoub R, Wettermark B, Wändell P, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail*. Sep 2013;15(9):995–1002. doi:10.1093/eurjhf/hft064
13. Khera R, Kondamudi N, Zhong L, et al. Temporal Trends in Heart Failure Incidence

Among Medicare Beneficiaries Across Risk Factor Strata, 2011 to 2016. *JAMA Netw Open*. Oct 1 2020;3(10):e2022190. doi:10.1001/jamanetworkopen.2020.22190
14. Wang Y, Wang X, Wang C, Zhou J. Global, Regional, and National Burden of Cardiovascular Disease, 1990-2021: Results From the 2021 Global Burden of Disease Study. *Cureus*. Nov 2024;16(11):e74333. doi:10.7759/cureus.74333
15. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J*. Jan 2014;35(1):25–32. doi:10.1093/eurheartj/eht278
16. Christiansen MN, Køber L, Weeke P, et al. Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. *Circulation*. Mar 28 2017;135(13):1214–1223. doi:10.1161/circulationaha.116.025941
17. Chan DZL, Kerr A, Grey C, et al. Contrasting trends in heart failure incidence in younger and older New Zealanders, 2006-2018. *Heart*. Feb 2022;108(4):300–306. doi:10.1136/heartjnl-2021-319853
18. Jain V, Minhas AMK, Morris AA, et al. Demographic and Regional Trends of Heart Failure-Related Mortality in Young Adults in the US, 1999-2019. *JAMA Cardiol*. Sep 1 2022;7(9):900–904. doi:10.1001/jamacardio.2022.2213
19. Age dependent associations of risk factors with heart failure: pooled population based cohort study. *Bmj*. Apr 1 2021;373:n880. doi:10.1136/bmj.n880
20. Huffman MD, Berry JD, Ning H, et al. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol*. Apr 9 2013;61(14):1510–7. doi:10.1016/j.jacc.2013.01.022
21. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. May 18 2024;403(10440):2162–2203. doi:10.1016/s0140-6736(24)00933-4
22. Yang C, Jia Y, Zhang C, et al. Global, regional, and national burdens of heart failure in adolescents and young adults aged 10-24 years from 1990 to 2021: an analysis of data from the Global Burden of Disease Study 2021. *EClinicalMedicine*. Jan 2025;79:102998. doi:10.1016/j.eclinm.2024.102998
23. Ran J, Zhou P, Wang J, et al. Global, regional, and national burden of heart failure and its underlying causes, 1990-2021: results from the global burden of disease study 2021. *Biomark Res*. Jan 23 2025;13(1):16. doi:10.1186/s40364-025-00728-8
24. Cheng S, He J, Han Y, et al. Global burden of atrial fibrillation/atrial flutter and its attributable risk factors from 1990 to 2021. *Europace*. Jul 2 2024;26(7)doi:10.1093/europace/euae195
25. Huang Z, Wang J, Liu H, et al. Global trends in adolescent and young adult female cancer burden, 1990-2021: insights from the Global Burden of Disease study. *ESMO Open*. Nov 2024;9(11):103958. doi:10.1016/j.esmoop.2024.103958
26. Sun J, Qiao Y, Zhao M, Magnussen CG, Xi B. Global, regional, and national burden of cardiovascular diseases in youths and young adults aged 15-39 years in 204 countries/territories, 1990-2019: a systematic analysis of Global Burden of Disease Study 2019. *BMC Med*. Jun 26 2023;21(1):222. doi:10.1186/s12916-023-02925-4

27. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol*. Apr 2018;15(4):230–240. doi:10.1038/nrcardio.2017.154
28. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. May 18 2024;403(10440):2133–2161. doi:10.1016/s0140-6736(24)00757-8
29. Yang K, Yang X, Jin C, et al. Global burden of type 1 diabetes in adults aged 65 years and older, 1990-2019: population based study. *Bmj*. Jun 12 2024;385:e078432. doi:10.1136/bmj-2023-078432
30. Wang F, Ma B, Ma Q, Liu X. Global, regional, and national burden of inguinal, femoral, and abdominal hernias: a systematic analysis of prevalence, incidence, deaths, and DALYs with projections to 2030. *Int J Surg*. Apr 1 2024;110(4):1951–1967. doi:10.1097/js9.0000000000001071
31. National Cancer Institute. Joinpoint Regression Program (Version 5.2.0). 2024. Available from: https://surveillance.cancer.gov/joinpoint/
32. Tian Q, Zheng Y, Li Y, Wu R, Lin Y, Chen Z. Global trends, inequalities, and pathogen shifts in infectious diarrhea among children under five: a comprehensive analysis of the global burden of disease study 1990-2021. *Front Nutr*. 2025;12:1679081. doi:10.3389/fnut.2025.1679081
33. Bai Z, Han J, An J, et al. The global, regional, and national patterns of change in the burden of congenital birth defects, 1990-2021: an analysis of the global burden of disease study 2021 and forecast to 2040. *EClinicalMedicine*. Nov 2024;77:102873. doi:10.1016/j.eclinm.2024.102873
34. Chen A, Zeng L, Yan Y, Gao G, Xie L. Global pulmonary arterial hypertension trends and projections to 2046: a multi-method analysis of epidemiologic and demographic drivers using GBD 2021. *J Thorac Dis*. Jul 31 2025;17(7):4420–4438. doi:10.21037/jtd-2025-305
35. Knoll M, Furkel J, Debus J, Abdollahi A, Karch A, Stock C. An R package for an integrated evaluation of statistical approaches to cancer incidence projection. *BMC Med Res Methodol*. Oct 15 2020;20(1):257. doi:10.1186/s12874-020-01133-5
36. Shu S, Zeng Z, Yang Y, et al. Trends and projections of heart failure among adolescents and young adults: an in-depth analysis for the Global Burden of Disease Study 2021. *Eur Heart J Qual Care Clin Outcomes*. Nov 4 2025;11(7):1108–1122. doi:10.1093/ehjqcco/qcaf040
37. Garner RC, Gisèle; Sanmartin, Claudia; et al. *<The Health of First Nations Living Off-Reserve, Inuit, and Métis Adults in Canada: The Impact of Socio-economic Status on Inequalities in Health.pdf>*. 2010.
38. Yan T, Zhu S, Yin X, et al. Burden, Trends, and Inequalities of Heart Failure Globally, 1990 to 2019: A Secondary Analysis Based on the Global Burden of Disease 2019 Study. *J Am Heart Assoc*. Mar 21 2023;12(6):e027852. doi:10.1161/jaha.122.027852
39. Liu Z, Li Z, Li X, et al. Global trends in heart failure from 1990 to 2019: An age-period-cohort analysis from the Global Burden of Disease study. *ESC Heart Fail*. Oct

2024;11(5):3264–3278. doi:10.1002/ehf2.14915
40. Chen J, Dharmarajan K, Wang Y, Krumholz HM. National trends in heart failure hospital stay rates, 2001 to 2009. *J Am Coll Cardiol*. Mar 12 2013;61(10):1078–88. doi:10.1016/j.jacc.2012.11.057
41. Teng TH, Finn J, Hobbs M, Hung J. Heart failure: incidence, case fatality, and hospitalization rates in Western Australia between 1990 and 2005. *Circ Heart Fail*. Mar 2010;3(2):236–43. doi:10.1161/circheartfailure.109.879239
42. Li X, Zhao C, Liu M, Zhao W, Pan H, Wang D. Sociodemographic index-age differences in the global prevalence of cardiovascular diseases, 1990-2019: a population-based study. *Arch Public Health*. Jan 9 2025;83(1):2. doi:10.1186/s13690-024-01454-7
43. Cleland JGF, Clark RA, Pellicori P, Inglis SC. Caring for people with heart failure and many other medical problems through and beyond the COVID-19 pandemic: the advantages of universal access to home telemonitoring. *Eur J Heart Fail*. Jun 2020;22(6):995–998. doi:10.1002/ejhf.1864
44. Bu S, Jung MH, Lee D, et al. Empagliflozin and Dapagliflozin Outcomes in Heart Failure. *JAMA Netw Open*. Dec 1 2025;8(12):e2546865. doi:10.1001/jamanetworkopen.2025.46865
45. Sharma A, Verma S, Bhatt DL, et al. Optimizing Foundational Therapies in Patients With HFrEF: How Do We Translate These Findings Into Clinical Care? *JACC Basic Transl Sci*. May 2022;7(5):504–517. doi:10.1016/j.jacbts.2021.10.018
46. Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. *Lancet Glob Health*. Jun 2019;7(6):e748–e760. doi:10.1016/s2214-109x(19)30045-2
47. OECD. *<Governing for Sustainable Prosperity in the Middle East and North Africa.pdf>*. OECD Public Governance Reviews. OECD Publishing; 2024.
48. Xinhua. New study finds adolescent obesity surges alarmingly in U.S. *Xinhua / Xinhuanet (englishnewscn)*. https://english.news.cn/northamerica/20240806/da63f164e53549d8abbd09a42c2deaff/c.htm
49. Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation*. Dec 16 2008;118(25):2702–9. doi:10.1161/circulationaha.108.790048
50. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. Mar–Apr 2014;136-137:148–62. doi:10.1016/j.mad.2014.01.002
51. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. Sep 11 2021;398(10304):957–980. doi:10.1016/s0140-6736(21)01330-1
52. WHO. Regional Health Forum: WHO South-East Asia Region. https://www.uncclearn.org/resources/library/regional-health-forum-who-south-east-asia-region/

53. Hackauf HW, Gerda. *Information and communication network concerning health-related prevention projects for young people in the European Union*. 2004.
54. Bouhaddane SMM. Delphi-Based Foresight of Global Olive Oil Market Trends 2019;
55. Nocella C, Cammisotto V, Fianchini L, et al. Extra Virgin Olive Oil and Cardiovascular Diseases: Benefits for Human Health. *Endocr Metab Immune Disord Drug Targets*. 2018;18(1):4–13. doi:10.2174/1871530317666171114121533
56. Milena E, Maurizio M. Exploring the Cardiovascular Benefits of Extra Virgin Olive Oil: Insights into Mechanisms and Therapeutic Potential. *Biomolecules*. Feb 14 2025;15(2)doi:10.3390/biom15020284
57. Policies ECOEOoHSa. *State of Health in the EU: Iceland Country Health Profile 2023*. 2023. *State of Health in the EU (Country Health Profile)*. 2023–09.
58. Sun Y, Sun G, Chang Y. Current Status and Future Direction of Community-based Management of Hypertension in China. *J Transl Int Med*. Jun 2021;9(2):61–64. doi:10.2478/jtim-2021-0022
59. Barrett-Connor E. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. *Circulation*. Jan 7 1997;95(1):252–64. doi:10.1161/01.cir.95.1.252
60. Bu S, Ruan D, Yang Z, et al. Sex-Specific Prevalence of Diabetes and Cardiovascular Risk Factors in the Middle-Aged Population of China: A Subgroup Analysis of the 2007-2008 China National Diabetes and Metabolic Disorders Study. *PLoS One*. 2015;10(9):e0139039. doi:10.1371/journal.pone.0139039
61. Yerly A, van der Vorst EPC, Baumgartner I, Bernhard SM, Schindewolf M, Döring Y. Sex-specific and hormone-related differences in vascular remodelling in atherosclerosis. *Eur J Clin Invest*. Jan 2023;53(1):e13885. doi:10.1111/eci.13885
62. Arcones AC, Martínez-Cignoni MR, Vila-Bedmar R, et al. Cardiac GRK2 Protein Levels Show Sexual Dimorphism during Aging and Are Regulated by Ovarian Hormones. *Cells*. Mar 17 2021;10(3)doi:10.3390/cells10030673
63. Sickinghe AA, Korporaal SJA, den Ruijter HM, Kessler EL. Estrogen Contributions to Microvascular Dysfunction Evolving to Heart Failure With Preserved Ejection Fraction. *Front Endocrinol (Lausanne)*. 2019;10:442. doi:10.3389/fendo.2019.00442
64. van Essen BJ, Emmens JE, Tromp J, et al. Sex-specific risk factors for new-onset heart failure: the PREVEND study at 25 years. *Eur Heart J*. Apr 22 2025;46(16):1528–1536. doi:10.1093/eurheartj/ehae868
65. Zeljkovic I, Gauthey A, Manninger M, et al. Genetic testing for inherited arrhythmia syndromes and cardiomyopathies: results of the European Heart Rhythm Association survey. *Europace*. Aug 30 2024;26(9)doi:10.1093/europace/euae216
66. Polo JM, Jeng KS, Lim B, et al. Transgenic mice support replication of hepatitis delta virus RNA in multiple tissues, particularly in skeletal muscle. *J Virol*. Aug 1995;69(8):4880–7. doi:10.1128/jvi.69.8.4880-4887.1995

664 **Figure legends**

665 **Figure 1.** Joinpoint regression analysis of HF patients aged 15-44 years, 1990-2021.
666 (A) ASPR by sex; (B) ASYR by sex; (C) ASPR by SDI level; (D) ASYR by SDI level;
667 (E) ASPR by age groups; (F) ASYR by age groups. APC =annual percent change; ASPR
668 =age-standardized prevalence rate; ASYR =age-standardized years lived with disability
669 rate; HF =heart failure; SDI=socio-demographic index; * =P <0.05.

670 **Figure 2.** Map of HF aged 15-44 years and AAPCs, 1990-2021. (A) ASPR in 2021; (B)
671 ASYR in 2021; (C)AAPCs in ASPR; (D) AAPCs inASYR. AAPC =average annual
672 percentage changes; ASPR =age-standardized prevalence rate; ASYR =age-
673 standardized years lived with disability rate; HF=heart failure.

674 **Figure 3.** Underlying causes at different age groups. (A) The proportion of main
675 underlying causes in 1990; (B) The proportion of main underlying causes in 2021.
676 ASPR =age-standardized prevalence rate; HF=heart failure.

677 **Figure 4.** Prediction to 2050 at global. (A) ASPR prediction to 2050 in both sex; (B)
678 ASYR prediction to 2050 in both sex; (C) ASPR prediction to 2050 in female; (D)
679 ASYR prediction to 2050 in female; (E) ASPR prediction to 2050 in male; (F) ASYR
680 prediction to 2050 in male. ASPR =age-standardized prevalence rate; ASYR =age-
681 standardized years lived with disability rate; HF =heart failure; UI=uncertainty interval.