Journal of Clinical and Translational Hepatology **2025** vol. 13(8) | 609–618
DOI: 10.14218/JCTH.2025.00101

Original Article

Global Trends and Cross-country Inequalities of Acute Hepatitis E in the Elderly, 1990–2021: A Comprehensive Analysis

Deliang Huang[1,2*], Jinyan Jiang[1,2], Jinghan Peng[1,2], Zhibin Zhu[1,2], Yuanyuan Chen[1,2], Siyu Zhang[1,2], Huiyi Lai[1,2], Hong Yu[1,2], Qi Zhao[1,2], Yanna Wu[1,2], Yanping Chen[1,2] and Jun Chen[1,2*]

[1]*Department of Liver Diseases, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong, China;* [2]*National Clinical Research Center for Infectious Diseases, Shenzhen, Guangdong, China*

Received: March 05, 2025 | **Revised:** April 25, 2025 | **Accepted:** May 14, 2025 | **Published online:** May 30, 2025

Abstract

Background and Aims: Acute hepatitis E (AHE) in the elderly can lead to severe complications including liver failure and mortality, yet the epidemiological landscape remains poorly characterized. This study aimed to assess the burden, trends, and health inequalities of AHE among the elderly over the past three decades, and to further predict its changes by 2030. ***Methods:*** Data on AHE in the elderly were obtained from the Global Burden of Disease 2021. The burden of AHE was analyzed by trends, decomposition, cross-country inequalities, and predictive analysis. ***Results:*** In 2021, the global incidence and Disability-Adjusted Life Years (DALYs) for AHE among the elderly were recorded as 1,130,013.35 and 20,084.77, respectively. Although there were significant differences in the incidence and DALYs across countries, the number of incident cases increased from 1990 to 2021, with a slight rise in age-standardized rates, while the number and age-standardized rate of DALYs showed a declining trend. Decomposition analysis revealed that population growth and aging are the drivers of changes in incidence, while epidemiological changes somewhat offset the increases in DALYs driven by population growth. Low socio-demographic index countries bear a disproportionate burden of elderly AHE, although inequality gaps have narrowed over time. Notably, up to 2030, the number of incident cases and DALYs will continue increasing. The burden in elderly women was more pronounced than in men. ***Conclusions:*** The burden of elderly AHE, as a major public health issue, remains substantial. While cross-country inequities have been alleviated over time, the pressure on lower socio-demographic index countries to control the disease remains high. AHE in elderly women requires further attention. This emphasizes the significant challenges faced in controlling and managing elderly AHE.

Keywords: Hepatitis E; Elderly; Aged; Trends; Health inequalities; Projection.
*__Correspondence to:__ Jun Chen and Deliang Huang, Department of Liver Diseases, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong 518100, China. ORCID: https://orcid.org/0000-0002-9744-792X (JC) and https://orcid.org/0000-0002-6154-017X (DH). Tel: +86-755-61222333, E-mail: drchenjun@163.com (JC) and huangdeliang2020@163.com (DH).

Citation of this article: Huang D, Jiang J, Peng J, Zhu Z, Chen Y, Zhang S, *et al*. Global Trends and Cross-country Inequalities of Acute Hepatitis E in the Elderly, 1990–2021: A Comprehensive Analysis. J Clin Transl Hepatol 2025;13(8): 609–618. doi: 10.14218/JCTH.2025.00101.

Introduction

Hepatitis E virus (HEV) is a hepatotropic pathogen that can cause acute hepatitis E (AHE), posing a significant threat to global public health.[1–4] Although AHE is typically a self-limiting disease with mild symptoms and a low mortality risk, recent studies have highlighted that in certain high-risk groups, HEV infection can lead to acute fulminant liver failure, which carries a high fatality rate.[1,5,6] Moreover, research indicates that AHE can evolve into a chronic condition, imposing an additional burden on health and medical systems.[7,8] Data from the 2019 Global Burden of Disease (GBD) report indicate a 19% increase in AHE cases worldwide—from 16,279,700 in 1990 to 19,469,888 in 2019. The age-standardized rate (ASR) of incidence for AHE decreased from 278.14 per 100,000 people in 1990 to 267.44 in 2019.[9] Despite this overall decrease in incidence ASR, the absolute number of cases continues to rise, making prevention and control of AHE a challenging endeavor.

The elderly represent a high-incidence demographic and are at increased risk for severe and chronic AHE.[10–15] Research has shown that the elderly experience the highest incidence of AHE among all age groups, with the risk of HEV infection increasing with age.[10,11] In geriatric patients, AHE frequently manifests as hyperbilirubinemia and cholestasis, potentially progressing to acute, sub-acute, or acute-on-chronic liver failure.[15] This progression presents a variety of novel challenges for clinical diagnosis and treatment. Geriatric patients with pre-existing conditions are at higher risk of progressing to chronic hepatitis, cirrhosis, and liver failure, with mortality rates ranging from 25% to 75%.[14,16–19] The precise mechanisms underlying progression to severe AHE in the elderly remain incompletely understood. However, recent advances using animal models—particularly studies involving gerbils and rabbits infected with HEV—have provided valuable insights into the pathogenesis of liver injury.[20,21] Furthermore, research has identified that HEV genotypes 3 and 4 are more likely to infect older individuals, often resulting in severe liver damage.[22,23]

The elimination of viral hepatitis and addressing the health issues of an aging population are key objectives of the World Health Organization's 2030 sustainable development plan.[24] As populations age, the health concerns of the elderly have become a significant public health priority. The impact and importance of the health and disease burden among the elderly are multifaceted, extending beyond quality of life to encompass social structure, economic factors, and the allocation of healthcare resources. The impact of AHE on the health of geriatric populations is substantial; however, the global epidemiological patterns of AHE in this group remain unclear, making a comprehensive global overview and burden analysis urgently needed. To advance epidemiological understanding, this study utilizes data from the GBD 2021 to conduct a comprehensive assessment of AHE burden, trends, and health inequalities. The study primarily includes: (1) an epidemiological descriptive analysis of AHE in the elderly at global, regional, and national levels; (2) dynamic trend analysis of AHE using estimated annual percentage change (EAPC) and Joinpoint regression models; (3) a decomposition analysis based on demographic changes, age structure, and epidemiological factors; (4) an analysis of cross-national inequalities related to the socio-demographic index (SDI) using standard health equity methods; and (5) a predictive analysis of the global burden through 2030 using Bayesian models.

Methods

Data source

The incidence and disability-adjusted life-years (DALYs) data for AHE among individuals aged 60 years and older from 1990 to 2021 were obtained from GBD 2021. The GBD data, provided by the Institute for Health Metrics and Evaluation, encompass the latest epidemiological studies on the burden of 371 diseases and injuries across 204 countries and territories.[25] The GBD integrates an extensive array of health data sources, including censuses, household surveys, vital records, disease registries, health service utilization, ambient air quality data, satellite imagery, and disease reports. Each data source is assigned a unique identification code within the Global Health Data Exchange.[25] Epidemiological estimates of HEV infection incidence were derived from population-based seroprevalence studies using anti-HEV IgG as a biomarker. This analytical process incorporated bias adjustment for non-reference data through log-transformed Bayesian priors with regularization and trimming (MR-BRT). The epidemiological model for AHE was developed using DisMod-MR 2.1, a Bayesian meta-regression tool.[25] The anti-HEV IgG seroconversion incidence derived from DisMod-MR served as a proxy for AHE infection incidence.

Definitions

The GBD categorizes diseases into four levels based on different etiologies, with AHE classified as a fourth-level cause under the broad category of infectious diseases. In the GBD 2021 framework, AHE is defined as an infection caused by HEV that results in the seroconversion of anti-HEV IgG. According to the 10th revision of the International Classification of Diseases, HEV is coded as B17.2.

The SDI is a composite metric that evaluates the developmental status of a country or region by integrating key indicators including fertility rates, educational attainment, and per capita income. The SDI scale ranges from 0 to 1, with higher values indicating more advanced socioeconomic development. Based on SDI values from GBD 2021, the 204 countries and territories are stratified into five quintiles: low, lower-middle, middle, upper-middle, and high SDI regions.[26]

Ethics

For the use of identified data in the GBD study, the Institutional Review Board of the University of Washington has approved a waiver of informed consent.

Descriptive and trend analysis

Descriptive analyses of the disease burden of AHE in the elderly at global, regional, and national levels were conducted using the ASR and the numbers of incidence and DALYs from 1990 to 2021. To explore the dynamic trends of AHE from holistic, regional, and multidimensional perspectives, we employed two methods: the EAPC and joinpoint regression analysis.[27,28] Initially, we utilized EAPC to quantify ASR trends, assessing the overall pattern of AHE. Previous studies have indicated that EAPC is a reliable metric for monitoring changes in epidemiological disease patterns.[27] Furthermore, we applied the joinpoint regression analysis model to analyze overall and regional trends in the AHE burden. Joinpoint regression (using NCI joinpoint regression software) segments the overall trend into multiple sub-trends based on inflection points and calculates the annual percentage change (APC) with its 95% confidence interval (CI) for each segment, assessing the magnitude of epidemiological changes in each phase.[28,29] Joinpoint regression estimates both APC and average APC, determining the direction and magnitude of changes and statistically verifying the significance of inflection points identified in the trend lines.[29]

Decomposition analysis

To gain a deeper understanding of the factors contributing to changes in AHE incidence and DALYs from 1990 to 2021, we conducted a decomposition analysis using three factors: population size, age structure, and epidemiological changes.[29,30] The study was stratified by gender to decompose the contributions of population growth, aging, and epidemiological changes on the epidemiology of AHE over the past three decades. The contribution of each factor to the change in AHE burden is defined as the impact of that factor's change while all other factors remain constant.

Health inequality analysis

Analyses of health inequalities provide an evidence base for health planning, helping improve prevention and control policies and programs to reduce disparities in health distribution.[31,32] This study employed two standard metrics, the slope index of inequality and the CI, representing absolute and relative inequality gradients, respectively, to assess and quantify the distributional inequality of the AHE burden across countries.[31,32] The slope index of inequality was derived from regression of the country's index rate for all age groups on a scale of relative position associated with the SDI, defined by the midpoint of the population's cumulative range sorted by SDI. The concentration index was determined by numerically integrating the area under the Lorenz concentration curve, which was fitted using the cumulative proportion of the index and the cumulative relative distribution of the population sorted by SDI.

Predictive analysis

To better inform public health policies and healthcare resource allocation, we predicted the future burden of AHE. The study utilized the integrated nested Laplace approximation with the Bayesian age-period-cohort model to forecast the global burden of AHE through 2030. The use of the integrated nested Laplace approximation with the Bayesian age-period-cohort model allows approximation of the marginal posterior distribution, avoiding some mixing and convergence issues associated with traditional Bayesian methods relying on Markov chain Monte Carlo sampling techniques.[3,33]

Statistics

ASRs of incidence and DALYs were expressed as estimates per 100,000 population with their 95% uncertainty intervals (UIs). All statistical analyses and graphs were conducted using R Studio software (version 4.2.1). A two-tailed *p*-value of less than 0.05 was considered statistically significant for all analyses.

Results

Descriptive analysis of AHE burden in older adults at global, regional, and national levels

Data on the incidence and DALYs of AHE among the elderly for the years 1990 and 2021 are summarized in Table 1. From 1990 to 2021, a notable upward trend was observed in the number of AHE incidence cases worldwide among the elderly, while the ASR remained relatively stable with a slight increase. Conversely, both the number and ASR of DALYs exhibited a downward trend (Fig. 1). When examining gender subgroups, an increasing trend in incidence numbers and ASRs was observed for both males and females, with females consistently having higher rates than males. In contrast, males demonstrated higher DALYs numbers and ASRs compared to females. However, females showed an increasing trend in DALYs numbers, whereas males experienced a decline (Fig. 1).

Across the five SDI regions, the middle SDI region had the highest number of AHE incident cases in 2021. An upward trend in incidence numbers was noted across all SDI regions, with the middle SDI experiencing the most rapid growth. The low SDI region had the highest incidence ASR, which decreased as SDI increased. Compared to 1990, incidence ASRs across the five SDI regions remained relatively stable in 2021. The low-middle SDI region had the highest number of DALYs in 2021. From 1990 to 2021, DALYs cases increased in the high SDI and low-middle SDI regions, while they decreased in the other SDI regions. The low SDI region had the highest DALYs ASR, with ASRs decreasing as SDI increased. All five SDI regions experienced a decline in DALYs ASR from 1990 to 2021.

At the GBD regional level, the highest incidence and DALYs of AHE among the elderly were found in Asia, with the lowest rates in Oceania. The highest ASRs were observed in Sub-Saharan Africa and Asia, while Southern Latin America had the lowest rates (Supplementary Tables 1 and 2). Significant variations in AHE incidence and DALYs among the elderly were noted at national and regional levels. In 2021, China and India, the two most populous countries, had the highest number of incident cases, while Tokelau reported the fewest. Poland had the highest incidence ASR, and Argentina the lowest. India had the highest number of DALYs cases, and Tokelau the lowest. Zimbabwe reported the highest DALYs ASR, and Uruguay the lowest.

Overall trends in AHE among older adults using the broad estimation method

Globally, from 1990 to 2021, the ASR of incidence for AHE among the elderly increased by 0.04%, while the ASR of DALYs decreased by 3.3%. The incidence ASR rose more rapidly in females than in males, whereas the DALYs ASR declined more slowly in females compared to males. Among SDI quintiles, only the high-middle SDI region showed a decreasing trend in incidence ASR; other SDI regions remained relatively stable (Table 1). The DALYs ASR showed a downward trend across five SDI regions, with the high-middle SDI experiencing the largest decrease.

Among the 21 GBD regions, East Asia had the fastest-growing incidence ASR, while Western Europe showed the steepest decline. The largest decrease in DALYs ASR was observed in East Asia, whereas Western Europe experienced the fastest increase (Supplementary Tables 1 and 2). Across the 204 countries and territories, substantial variation existed in the overall trend of AHE burden among the elderly (Fig. 2). Incidence ASR increased in 59 countries and territories, with Greece experiencing the fastest growth and Italy the steepest decline. DALYs ASR decreased in 154 countries and territories, with the largest decline in Nigeria and the fastest increase in Germany (Fig. 2).

Trends of AHE burden in older adults using joinpoint regression analysis

The results of joinpoint regression analysis for AHE burden among the elderly are illustrated in Figure 3. From 1990 to 2021, the incidence ASR generally trended upward with fluctuations, characterized by periods of increase followed by declines and then a rapid rise. Specifically, increases occurred during 1990–1991, 1994–2001, 2010–2015, and 2015–2021, with the most significant rise between 2010 and 2015. Conversely, declines were observed between 2001–2004 and 2004–2010. The DALYs ASR showed a consistent decline, with the largest drop between 2001 and 2004, and a slower decrease during 2013–2021. Joinpoint regression analyses stratified by gender for incidence and DALYs trends are shown in Supplementary Figure 1.

Decomposition analysis

Over the past 30 years, global incidence has substantially increased, with the middle SDI quintile experiencing the highest surge (Fig. 4A). Aging, population growth, and epidemiological changes contributed 4.33%, 93.92%, and 1.74% respectively to the global incidence increase. The largest contributions of aging, population growth, and epidemiological changes were observed in the high SDI (7.82%), low-middle SDI (97.57%), and middle SDI (2.36%) regions, respectively. Gender subgroup analysis revealed that older females bear a higher burden of AHE incidence than males globally and five SDI regions, with population growth having the most notable impact.

Conversely, global DALYs have significantly declined over the past 30 years (Fig. 4B). However, at the five SDI levels, the burden increased in the high and low-middle SDI regions, with the low-middle SDI showing the largest increase and the high-middle SDI experiencing the fastest decrease. Aging, population growth, and epidemiological changes accounted for 17.49%, −1,368.79%, and 1,451.30% of the global DALYs burden change, respectively. Population growth was the main contributing factor to the burden, while epidemiological changes contributed to its reduction. When stratified by gender, females bore a higher DALYs burden than males globally and five SDI

Table 1. The number and ASR of incidence and DALYs of AHE among the elderly in 1990 and 2021 by global and SDI quintiles, with EAPC from 1990 to 2021

	1990		2021		1990–2021
	Number (95 % UIs)	**ASR (95 % UIs), per 100 000**	**Number (95 % UIs)**	**ASR (95 % UIs), per 100 000**	**EAPC (95 % CI)**
Incidence					
Global	479,620.59 (265,300.11 to 797,925.32)	104 (57.03 to 173.09)	1,130,013.35 (613,176.99 to 1,882,306.83)	105.5 (57.2 to 175.61)	0.04% (0.03 to 0.05)
Female	271,892.17 (150,185.99 to 451,290.88)	104.66 (57.4 to 173.79)	624,510.77 (338,017.97 to 1,041,532.86)	106.34 (57.65 to 177.23)	0.05% (0.04 to 0.06)
Male	207,728.42 (114,735.69 to 346,251.7)	103.42 (56.48 to 172.5)	505,502.57 (274,900.5 to 841,423.16)	104.65 (56.67 to 174.12)	0.03 % (0.01 to 0.04)
Five SDIs					
Low SDI	27,109.85 (14,421.1 to 45,370.98)	116.4 (61.68 to 194.86)	61,375.35 (32,967.49 to 102,236.94)	116.97 (62.48 to 194.96)	0.02 % (0.01 to 0.03)
Low-middle SDI	74,634.67 (40,359.32 to 124,515.45)	116.16 (62.35 to 194.18)	187,652.17 (100,963.87 to 311,777.65)	116.04 (62.16 to 193.1)	0.01 % (0 to 0.01)
Middle SDI	118,882.69 (64,714.37 to 199,519.17)	107.59 (58.1 to 180.62)	349,586.12 (187,257.18 to 585,473.57)	110.07 (58.81 to 184.12)	0.07 % (0.06 to 0.08)
High-middle SDI	121,096.39 (67,549.75 to 200,958.35)	101.84 (56.18 to 169.21)	256,533.78 (139,171.82 to 427,920.3)	101.32 (54.91 to 168.94)	−0.03% (−0.07 to 0)
High SDI	137,288.46 (74,485.72 to 228,837.65)	95.73 (51.7 to 159.64)	273,787.38 (146,442.64 to 456,421.08)	95.73 (51.55 to 159.54)	0% (−0.01 to 0.02)
DALYs					
Global	21,462.56 (9,495.1 to 38,887.74)	4.32 (1.92 to 7.82)	20,084.77 (12,325.55 to 38,537.13)	1.84 (1.13 to 3.52)	−3.3% (−3.58 to −3.02)
Female	4,365.08 (1,966.6 to 8,910.99)	1.62 (0.73 to 3.31)	5,936.24 (2,730.74 to 11,334.03)	1.01 (0.47 to 1.94)	−1.87% (−2.02 to −1.72)
Male	17,097.47 (5,473.15 to 33,922.39)	7.64 (2.47 to 15.15)	14,148.53 (7,156.55 to 30,981.93)	2.78 (1.41 to 6.09)	−3.86% (−4.18 to −3.53)
Five SDIs					
Low SDI	5,051.98 (1,506.67 to 13,261.48)	19.69 (5.97 to 51.53)	3,926.01 (1,641.26 to 8,747.46)	7.13 (2.96 to 15.92)	−3.84% (−4.13 to −3.55)
Low-middle SDI	5,813.58 (2,797.81 to 10,528.7)	8.25 (3.97 to 15.05)	7,291.04 (3,852.2 to 14,761.17)	4.24 (2.23 to 8.63)	−2.54% (−2.69 to −2.39)
Middle SDI	5,481.46 (2,293.05 to 10,018.79)	4.44 (1.87 to 8.13)	5,415.38 (3,215.09 to 10,682.07)	1.62 (0.97 to 3.19)	−3.82% (−4.25 to −3.39)
High-middle SDI	4,010.77 (1,187.38 to 8,820.56)	3.13 (0.94 to 6.88)	2,167.68 (1,346.54 to 3,552.84)	0.84 (0.52 to 1.38)	−4.97% (−5.5 to −4.43)
High SDI	1,094.74 (452.9 to 1,948.36)	0.76 (0.31 to 1.35)	1,271.58 (833.12 to 1,918.1)	0.46 (0.3 to 0.68)	−2.23% (−2.79 to −1.67)

ASIR, age-standardized incidence rate; DALYs, disability-adjusted life-years; SDI, sociodemographic index; EAPC, estimated annual percentage change; UIs, uncertainty intervals; CI, confidence interval.

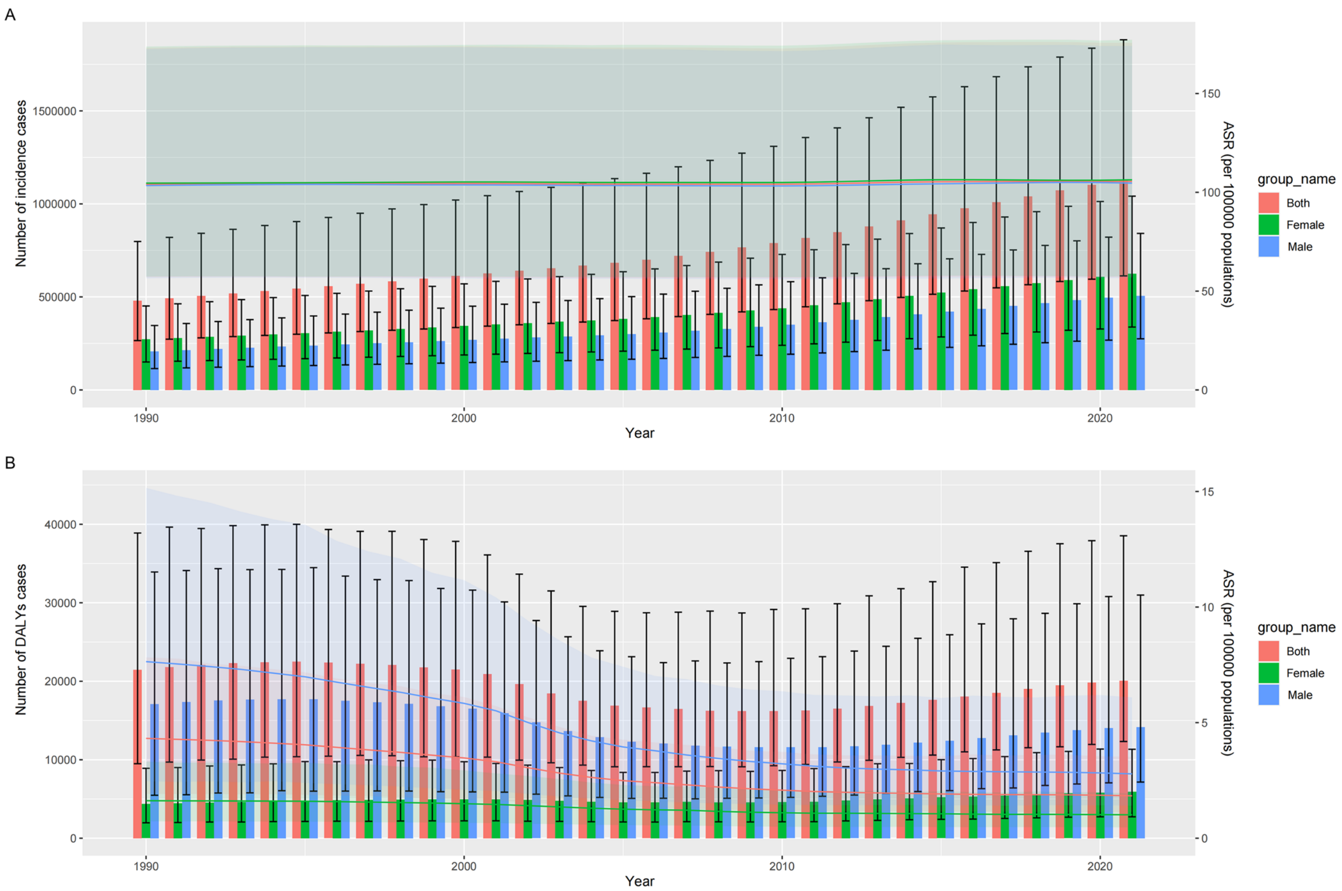

Fig. 1. The numbers and ASIR of Acute Hepatitis E (A) incidence and (B) DALYs globally among the elderly from 1990 to 2021. ASIR, age-standardized incidence rate; DALYs, disability-adjusted life-years.

regions, with the burden declining for males overall but increasing for females.

Cross-country inequality analysis

In the burden of AHE among the elderly, both absolute and relative SDI-related inequalities were observed, although these disparities gradually narrowed over time (Fig. 5). The DALYs burden was disproportionately concentrated in regions with lower SDI. The slope index of inequality indicated that in 1990, the difference in DALYs per 100,000 people between the highest and lowest SDI countries was 11 [−10.65 (95% CI: −12.27 to −9.03)], which reduced to 3 [−3.11 (95% CI: −3.72 to −2.51)] by 2019. The concentration index, measuring relative inequality, was −0.56 (95% CI: −0.68 to −0.44) in 1990 and −0.51 (95% CI: −0.66 to −0.37) in 2019, indicating that while the AHE burden became less concentrated among countries with different SDI levels, it remained focused in lower SDI countries. Cross-country inequality analyses of AHE incidence and DALYs by gender are shown in Supplementary Figure 2.

Predictive analysis of AHE burden among the elderly to 2030

Based on the predictive model, Figure 6 illustrates that from 2022 to 2030, the projected incidence and DALYs numbers for AHE among the global elderly population are expected to continue increasing. The incidence ASR is predicted to remain relatively stable with a slight upward trend. By gender, incidence numbers for both males and females are rising, with females exceeding males. However, the incidence ASR is projected to increase in females while decreasing in males. Globally, the DALYs ASR is projected to rise slightly by 2030 for both males and females, with a greater increase anticipated in females.

Discussion

This study provides the most recent global, regional, and national estimates of the incidence and DALYs of AHE among the elderly from 1990 to 2021. Our analysis encompassed temporal trends, decomposition of contributing factors, assessment of international inequalities, and future projections. Despite substantial heterogeneity in the AHE burden across countries and regions, the overall incidence has gradually increased, while DALYs have exhibited a declining trend in both absolute numbers and age-standardized rates. Decomposition analysis revealed that population growth and aging were the primary drivers of increased incidence, whereas epidemiological changes contributed to the reduction in DALYs. Notably, countries with low SDI bore a disproportionately high burden of AHE, though SDI-related disparities have diminished over time. Projections indicate that while ASRs for incidence and DALYs will remain stable through 2030, absolute case numbers will continue to rise, underscoring persistent challenges in AHE management. Furthermore, gender

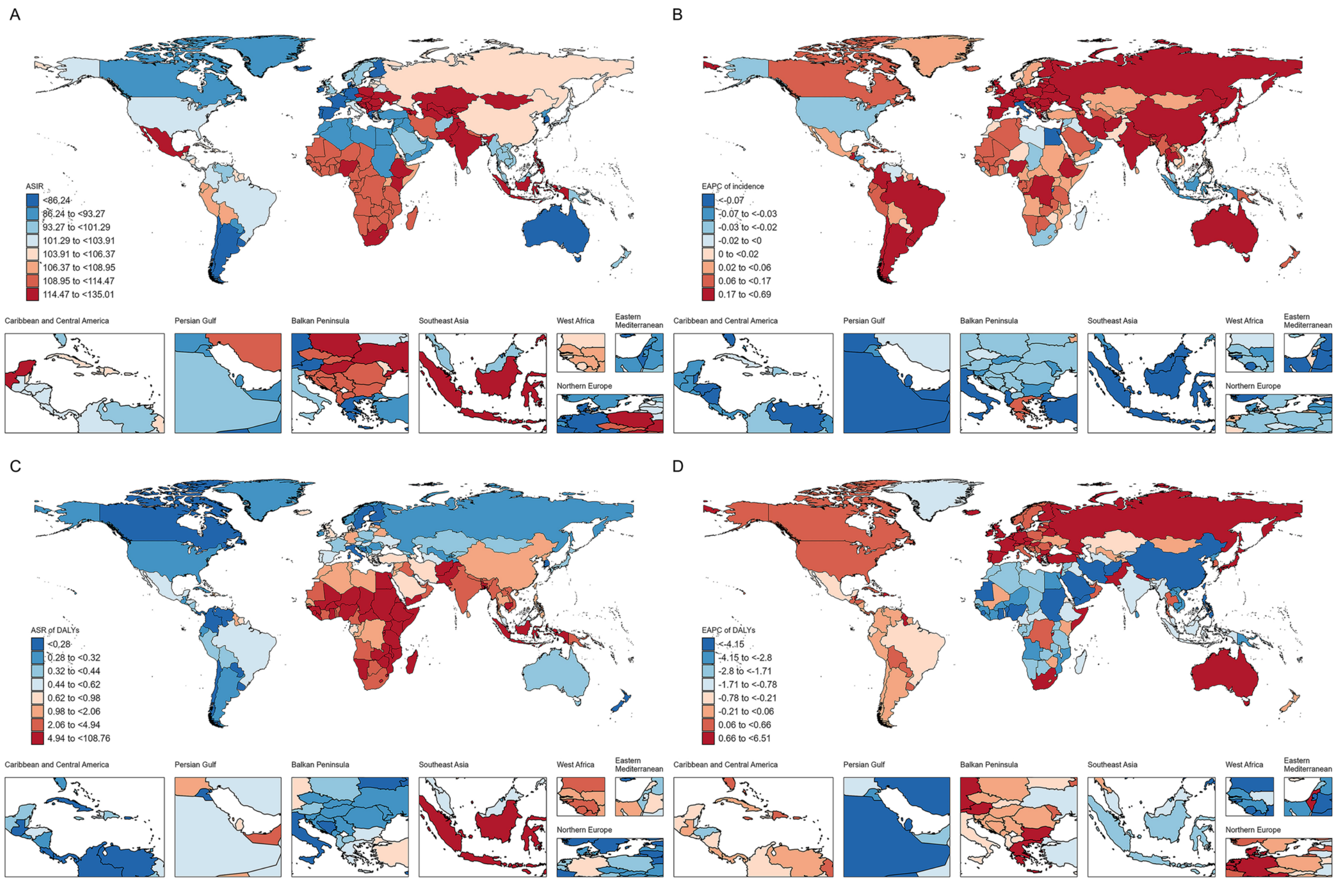

Fig. 2. (A) ASR of incidence in 2021; (B) Trend (EAPC) in ASR of incidence from 1990 to 2021; (C) ASR of DALYs in 2021; (D) Trend (EAPC) in ASR of DALYs from 1990 to 2021 for AHE in the elderly across 204 countries and territories. ASR, age-standardized rate; DALYs, disability-adjusted life-years; EAPC, estimated annual percentage change.

disparities were evident, with elderly women facing a higher burden than men, necessitating targeted interventions.

In 2021, global AHE incidence and DALYs among the elderly reached 1,130,013.35 (95% UI: 613,176.99–1,882,306.83) and 20,084.77 (95% UI: 12,325.55–38,537.13), respectively. The Asian region reported the highest numbers, with

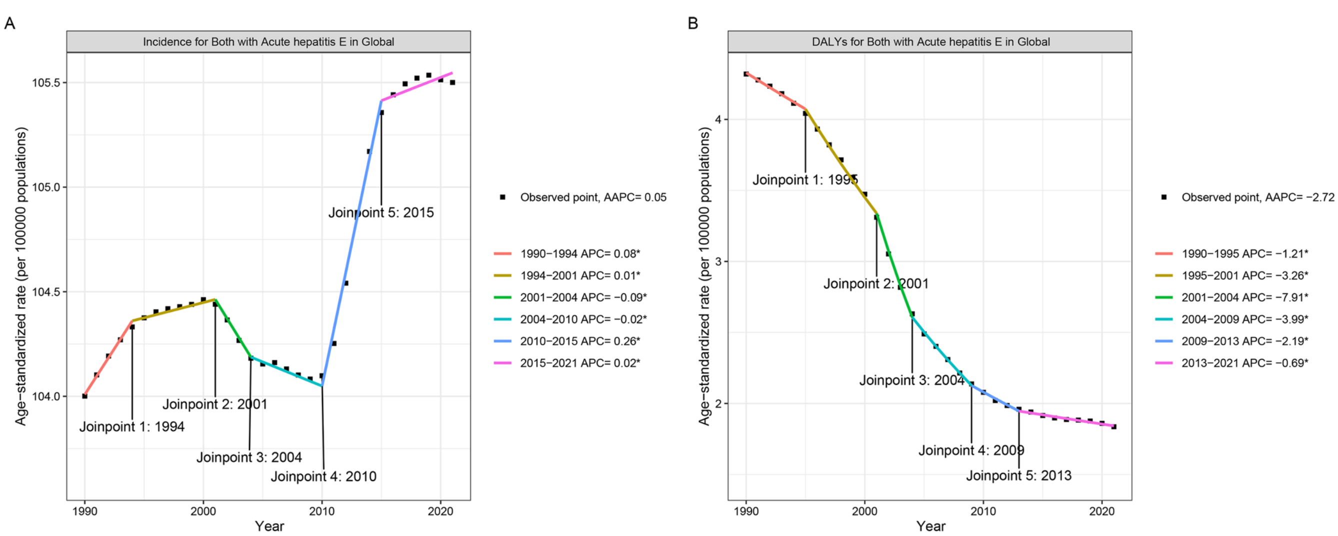

Fig. 3. Joinpoint regression analysis on the ASR of (A) incidence and (B) DALYs of AHE among the elderly from 1990 to 2021. ASR, age-standardized rate; AHE, Acute hepatitis E; DALYs, disability-adjusted life-years; *$p < 0.001$.

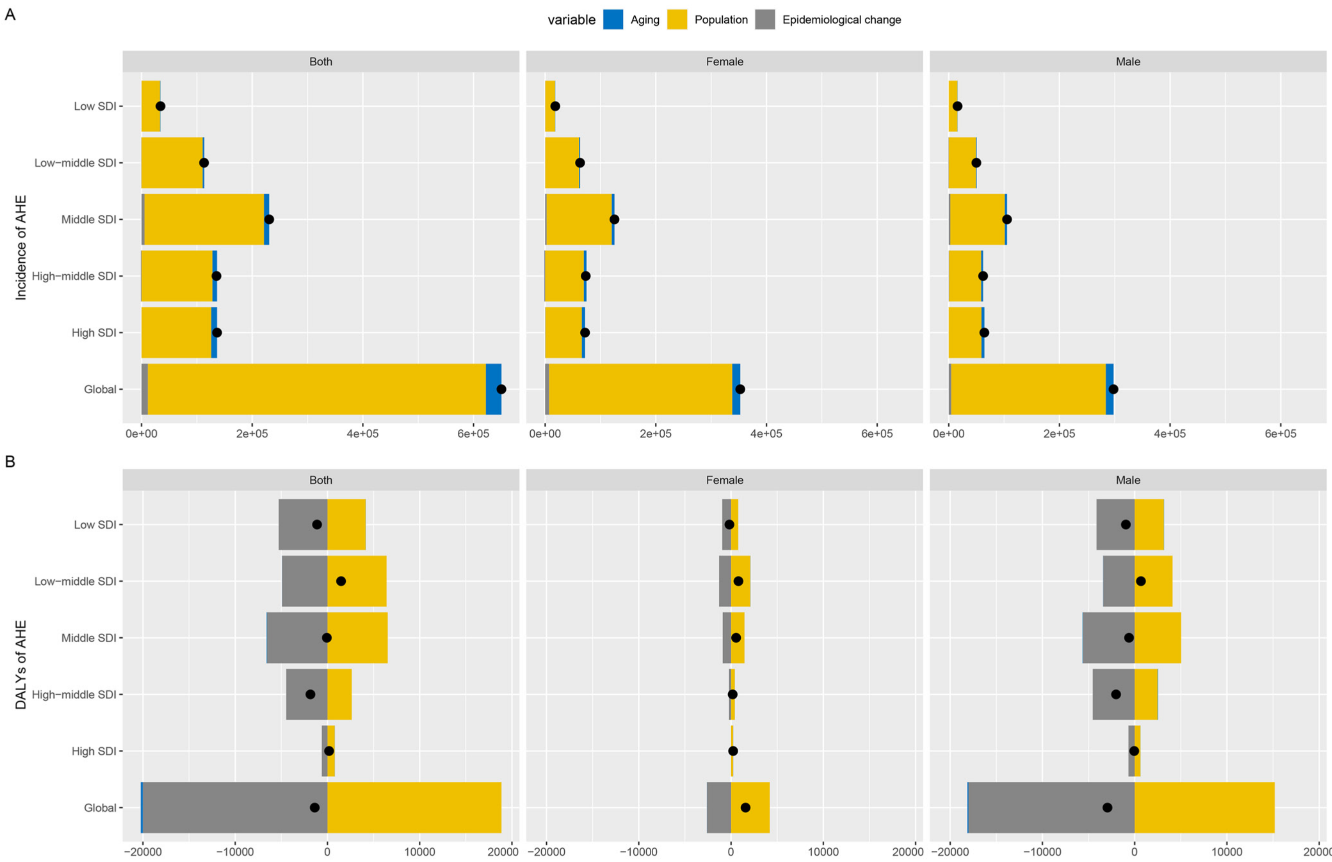

Fig. 4. Changes in incidence and DALYs of AHE among the elderly attributed to aging, population growth, and epidemiological changes from 1990 to 2021 at the global level by SDI quintile and gender. AHE, Acute hepatitis E; DALYs, disability-adjusted life-years; SDI, socio-demographic index.

Sub-Saharan Africa and Asia having the highest ASRs, reflecting a sustained burden over the past three decades. East Asia demonstrated the most rapid increase in incidence (EAPC: 0.14%), yet DALYs declined significantly—a contrast to Western Europe, where incidence decreased but DALYs rose (EAPC: 2.74). These findings highlight the need for region-specific surveillance, particularly in areas with escalating burdens.

Nationally, China and India accounted for the highest incidence numbers in 2021, driven by their large populations and middle SDI status. China's steadily increasing incidence signals the necessity for improved healthcare resource distribution and economic development to bolster AHE control. India's elevated burden, compounded by challenges such as poor hand hygiene, contaminated water, and uneven healthcare access, demands urgent public health attention. Conversely, Poland, a high-income nation, recorded the highest incidence ASR, with minimal change over 30 years—a trend also observed in other developed regions. This may be attributed to distinct transmission pathways, particularly foodborne exposure (e.g., contaminated meat and seafood),[34,35] suggesting the need for tailored prevention strategies beyond conventional water and hygiene measures.[2]

AHE, though typically self-limiting, poses significant risks to the elderly, who are more susceptible to severe complications.[10–15] The resultant economic burden—encompassing direct medical costs, productivity losses, and intangible personal tolls—underscores the urgency of optimized disease management. Encouragingly, from 1990 to 2021, the ASR of incidence for elderly AHE has shown a slight overall upward trend, while the ASR for DALYs has consistently declined. This suggests notable progress in global efforts to control and prevent AHE, likely associated with improvements in hand hygiene and water sanitation, coupled with partial protective effects of worldwide HEV vaccination campaigns.

Decomposition analysis indicated that population growth and aging remain key drivers of incidence, with regional variations: aging predominates in high-SDI regions, whereas population growth exerts greater influence in low-SDI settings. While epidemiological improvements have offset DALY increases globally, this effect is less pronounced in high-SDI areas, possibly due to already low baseline DALYs.

Our study found an inverse relationship between the ASR of incidence and DALYs for AHE and SDI. Previous research similarly suggested that areas with lower SDI bear a relatively higher burden of AHE, consistent with our findings.[9,36] Inequality analysis further quantified this disparity, linking it to inadequate sanitation, limited healthcare infrastructure, and economic constraints. However, the observed narrowing of SDI-related inequalities over time highlights the positive impact of international initiatives, such as World Health Organization-led hygiene campaigns and targeted healthcare aid. The degree of inequality in AHE burden is primarily concentrated in countries with lower SDI, which can be attributed to two main factors. Firstly, countries with low SDI often lack clean water sources and exhibit insufficient awareness of hand hygiene prac-

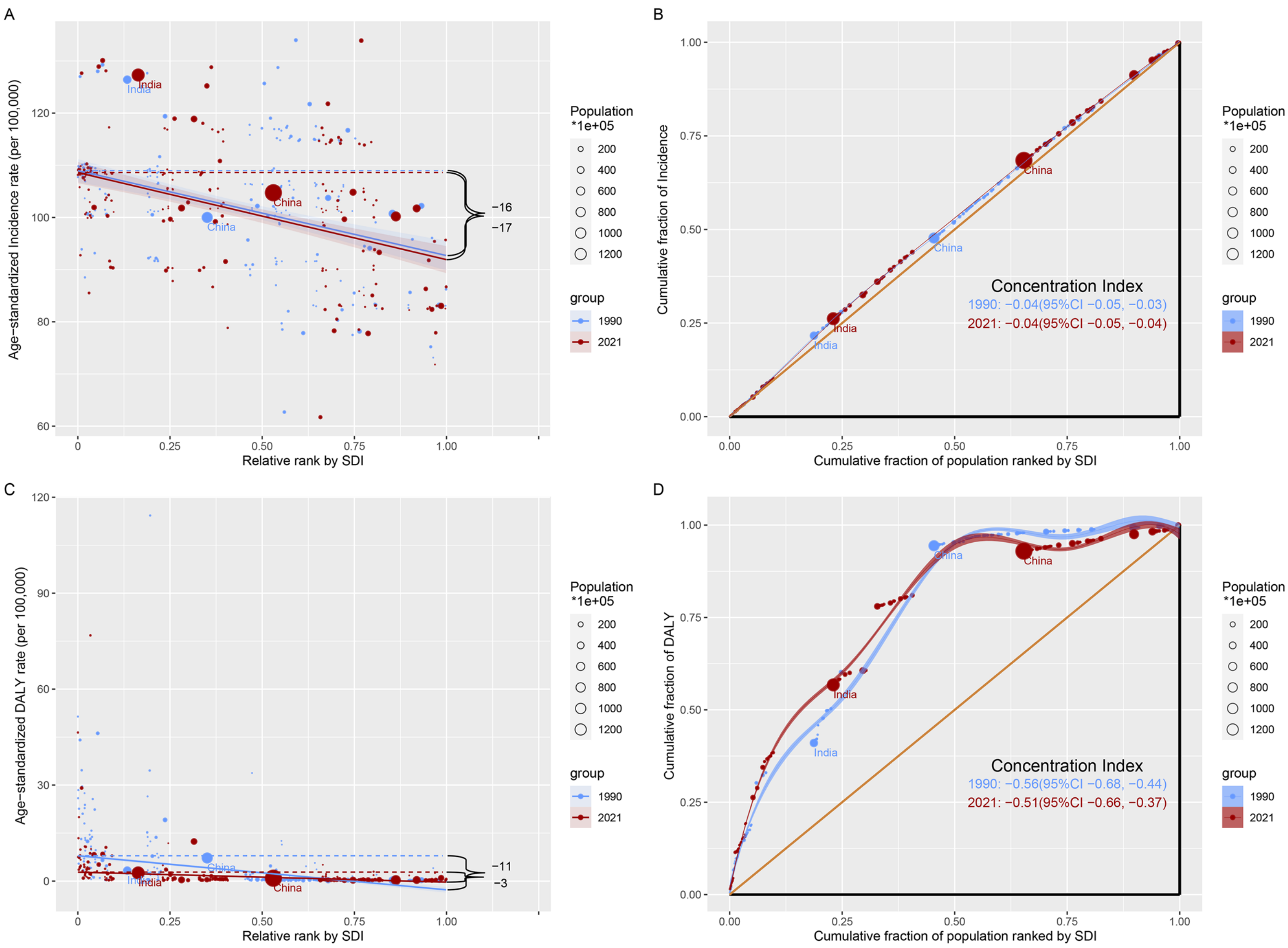

Fig. 5. SDI-related health inequality regression and concentration curves for the (A) incidence and (B) DALYs of AHE among the elderly worldwide in 1990 and 2021. AHE, Acute hepatitis E; DALYs, disability-adjusted life-years; SDI, socio-demographic index.

tices. Secondly, due to their lower economic status, these countries typically have substandard medical interventions and limited capacity for medical rescue. To mitigate these disparities, countries should develop tailored, individualized policies and allocate medical resources appropriately based on their specific circumstances. It is noteworthy that over time, these inequality gaps have gradually narrowed, indicating that, over the past decades, with focused efforts by the World Health Organization and the United Nations, implementation of effective prevention and control policies, such as improved hand hygiene, clean water access, and medical aid in lower-income countries, has significantly reduced the burden of AHE.

Projections suggest a continued rise in AHE cases through 2030, driven by demographic shifts including global population growth and aging. By 2050, 80% of the elderly will reside in low- and middle-income countries, exacerbating AHE challenges in these regions.[37,38] Proactive measures, such as healthcare system strengthening and equitable resource allocation, are imperative to mitigate this impending burden.

Gender-specific analyses revealed a less favorable trajectory for elderly women, who exhibited higher incidence and DALYs than men. Overall, future prevention and control strategies for AHE must not overlook the management of elderly women. Additionally, it is important to recognize that the elderly constitute a vulnerable group; as age increases, immune function weakens and susceptibility to chronic diseases such as hypertension, diabetes, liver disease, and malignancies rises.[39–41] The risk of severe illness and death from AHE co-infections in this population significantly increases, shortening lifespan and imposing additional societal burdens. Therefore, countries worldwide should enhance management of this group, including considering early vaccination to reduce the risk of infection and severe disease.[42–44]

Our study has several limitations. Firstly, misdiagnosis, underdiagnosis, and documentation losses in less developed countries may result in underestimation of AHE within the GBD. Secondly, the primary data feeding into the GBD originate from various nations with inconsistent quality. However, the application of data cleansing, correction techniques, and sophisticated statistical modeling by GBD collaborators helps mitigate these effects. Despite these limitations, our research adopts a multifaceted and multidimensional analytical approach, encompassing descriptive, trend, decomposition, health inequality, and predictive analyses. This comprehensive methodology advances understanding of AHE epidemiology among the elderly and provides a foundation for in-

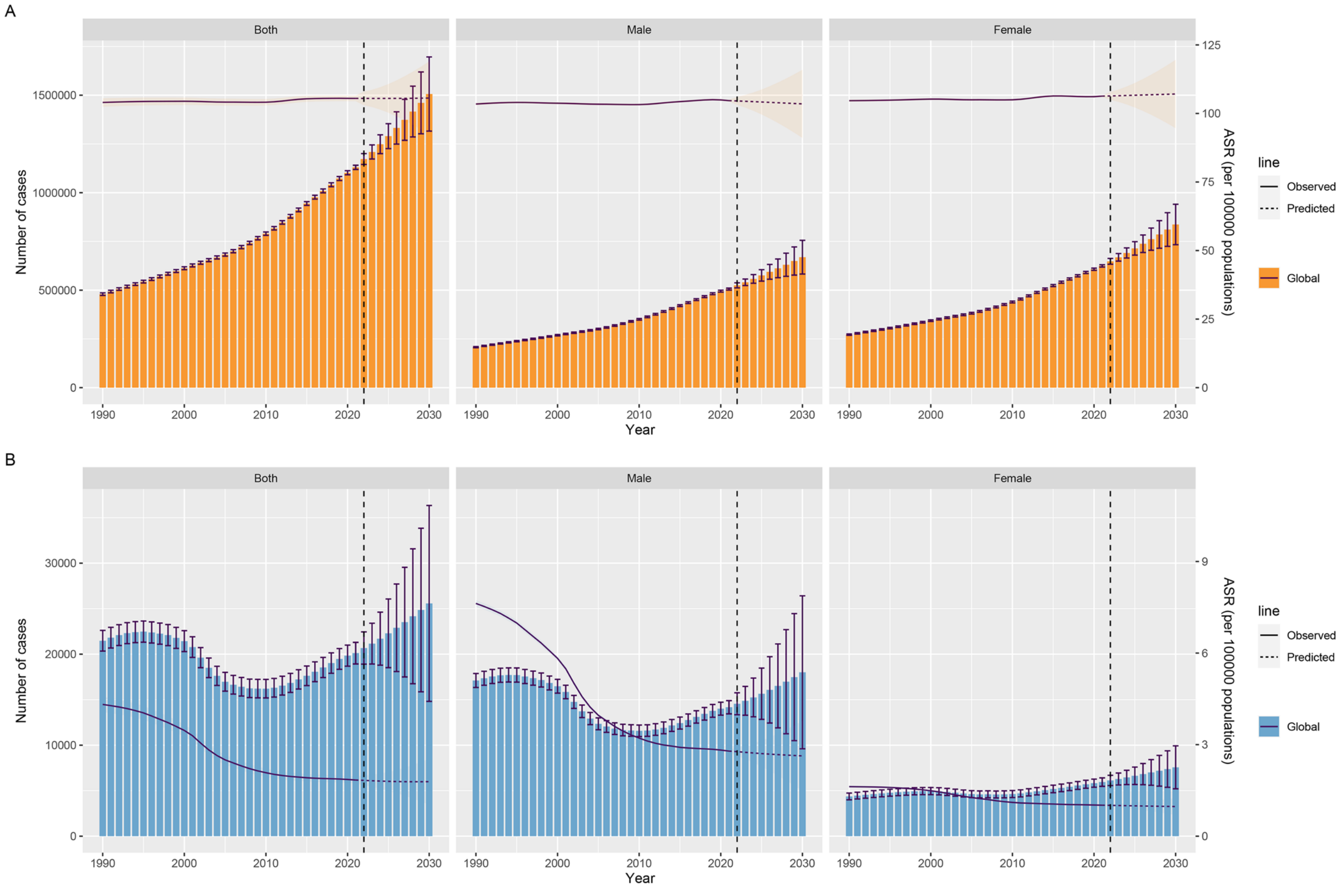

Fig. 6. Projected ASR and numbers of (A) incidence and (B) DALYs of AHE among the elderly worldwide from 2022 to 2030. AHE, Acute hepatitis E; ASR, age-standardized rate; DALYs, disability-adjusted life-years.

forming public health policy and medical resource allocation worldwide.

Conclusions

AHE remains a critical public health challenge for the elderly, with rising global incidence and persistent disparities. Population growth and aging are key drivers of this trend, necessitating enhanced prevention strategies to counterbalance their impact. Although SDI-related inequalities have diminished, lower-SDI countries continue to bear a disproportionate burden. Moving forward, tailored interventions that account for regional transmission dynamics, demographic shifts, and gender disparities are essential to reduce the AHE burden and safeguard elderly health worldwide. Policymakers must prioritize adaptable, context-specific measures to strengthen healthcare systems and ensure equitable resource distribution.

Acknowledgments

We appreciate the excellent work of the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 collaborators.

Funding

This study was supported by the funds for the construction of key medical disciplines in Shenzhen (No. SZXK076 to JC) and the Shenzhen High-level Hospital Construction Fund.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (JC, DH), analysis and interpretation of data (JJ, JP, ZZ, YuC, SZ, HL, HY, QZ, YW, YaC), manuscript writing (JC, DH), and critical funding (JC). All authors have read and agreed to the published version of the manuscript.

Ethical statement

Ethical approval was not required as this study used publicly available data. This study follows the Guidelines for Accurate and Transparent Health Estimates Reporting Guidelines for cross-sectional studies. For the use of identified data in the GBD study, the Institutional Review Board of the University of Washington has approved a waiver of informed consent.

Data sharing statement

The data used in this study can be accessed from the GBD 2021 (available at: https://ghdx.healthdata.org/gbd-2021).

References

[1] Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med 2012;367(13):1237–1244. doi:10.1056/NEJMra1204512, PMID:23013075.
[2] WHO| Hepatitis E. [cited 20 Jun 2024]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e.
[3] Huang D, Lai H, Shi X, Jiang J, Zhu Z, Peng J, *et al*. Global temporal trends and projections of acute hepatitis E incidence among women of childbearing age: Age-period-cohort analysis 2021. J Infect 2024;89(4):106250. doi:10.1016/j.jinf.2024.106250, PMID:39181413.
[4] Larrue H, Abravanel F, Peron JM. Hepatitis E, what is the real issue? Liver Int 2021;41(Suppl 1):68–72. doi:10.1111/liv.14880, PMID:33975382.
[5] Sedhom D, D'Souza M, John E, Rustgi V. Viral Hepatitis and Acute Liver Failure: Still a Problem. Clin Liver Dis 2018;22(2):289–300. doi:10.1016/j.cld.2018.01.005, PMID:29605067.
[6] Dong R, Chang D, Luo Z, Zhang M, Guan Q, Shen C, *et al*. The burden of HEV-related acute liver failure in Bangladesh, China and India: a systematic review and meta-analysis. BMC Public Health 2023;23(1):2369. doi:10.1186/s12889-023-17302-2, PMID:38031080.
[7] Ma Z, de Man RA, Kamar N, Pan Q. Chronic hepatitis E: Advancing research and patient care. J Hepatol 2022;77(4):1109–1123. doi:10.1016/j.jhep.2022.05.006, PMID:35605741.
[8] Lai JC, Wong GL, Yip TC, Tse YK, Lam KL, Lui GC, *et al*. Chronic Hepatitis B Increases Liver-Related Mortality of Patients With Acute Hepatitis E: A Territorywide Cohort Study From 2000 to 2016. Clin Infect Dis 2018;67(8):1278–1284. doi:10.1093/cid/ciy234, PMID:30265321.
[9] Ouyang G, Pan G, Li Q, Li S, Liu T, Yi X, *et al*. Global burden of acute hepatitis E between 1990 and 2019 and projections until 2030. Liver Int 2024;44(6):1329–1342. doi:10.1111/liv.15883, PMID:38426633.
[10] Man S, Fu J, Yang X, Ma Y, Bao H, Du J, *et al*. Prevalence and Incidence of Hepatitis E Infection in China. Clin Gastroenterol Hepatol 2024. doi:10.1016/j.cgh.2024.07.026, PMID:39181429.
[11] Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis 2008;8(11):698–709. doi:10.1016/S1473-3099(08)70255-X, PMID:18992406.
[12] Yoon Y, Jeong HS, Yun H, Lee H, Hwang YS, Park B, *et al*. Hepatitis E Virus (HEV) seroprevalence in the general population of the Republic of Korea in 2007-2009: a nationwide cross-sectional study. BMC Infect Dis 2014;14:517. doi:10.1186/1471-2334-14-517, PMID:25248488.
[13] Rapicetta M, Monarca R, Kondili LA, Chionne P, Madonna E, Madeddu G, *et al*. Hepatitis E virus and hepatitis A virus exposures in an apparently healthy high-risk population in Italy. Infection 2013;41(1):69–76. doi:10.1007/s15010-012-0385-8, PMID:23264095.
[14] Tseng TC, Liu CJ, Chang CT, Su TH, Yang WT, Tsai CH, *et al*. HEV superinfection accelerates disease progression in patients with chronic HBV infection and increases mortality in those with cirrhosis. J Hepatol 2020;72(6):1105–1111. doi:10.1016/j.jhep.2020.01.012, PMID:32006586.
[15] Nimgaonkar I, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. Nat Rev Gastroenterol Hepatol 2018;15(2):96–110. doi:10.1038/nrgastro.2017.150, PMID:29162935.
[16] Kilonzo SB, Wang YL, Jiang QQ, Wu WY, Wang P, Ning Q, *et al*. Superinfective Hepatitis E Virus Infection Aggravates Hepatocytes Injury in Chronic Hepatitis B. Curr Med Sci 2019;39(5):719–726. doi:10.1007/s11596-019-2097-0, PMID:31612388.
[17] Yadav KK, Kenney SP. Hepatitis E Virus Immunopathogenesis. Pathogens 2021;10(9):1180. doi:10.3390/pathogens10091180, PMID:34578211.
[18] Zhao H, Ye W, Yu X, Hu J, Zhang X, Yang M, *et al*. Hepatitis E virus superinfection impairs long-term outcome in hospitalized patients with hepatitis B virus-related decompensated liver cirrhosis. Ann Hepatol 2023;28(2):100878. doi:10.1016/j.aohep.2022.100878, PMID:36417965.
[19] Nasir M, Wu GY. HEV and HBV Dual Infection: A Review. J Clin Transl Hepatol 2020;8(3):313–321. doi:10.14218/JCTH.2020.00030, PMID:33083255.
[20] Liu T, He Q, Yang X, Li Y, Yuan D, Lu Q, *et al*. An Immunocompetent Mongolian Gerbil Model for Hepatitis E Virus Genotype 1 Infection. Gastroenterology 2024;167(4):750–763.e10. doi:10.1053/j.gastro.2024.03.038, PMID:38582270.
[21] Liu T, Li J, Yin X, Lu F, Zhao H, Wang L, *et al*. Establishment of enterically transmitted hepatitis virus animal models using lipid nanoparticle-based full-length viral genome RNA delivery system. Gut 2025;74(3):467–476. doi:10.1136/gutjnl-2024-332784, PMID:39353724.
[22] Zhu FC, Huang SJ, Wu T, Zhang XF, Wang ZZ, Ai X, *et al*. Epidemiology of zoonotic hepatitis E: a community-based surveillance study in a rural population in China. PLoS One 2014;9(1):e87154. doi:10.1371/journal.pone.0087154, PMID:24498033.
[23] Tang WF, Kong DG, Wang YH, Liu MQ, Hu Q. Hepatitis E virus infection in Wuhan, Central China. Arch Virol 2019;164(1):27–32. doi:10.1007/s00705-018-4036-y, PMID:30229302.
[24] Sustainable Development Goals. [cited 8 Jul 2024]. Available from: https://www.who.int/data/gho/data/themes/sustainable-development-goals.
[25] Global Health Data Exchange | GHDx. [cited 8 Jul 2024]. Available from: https://ghdx.healthdata.org/.
[26] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Socio-Demographic Index (SDI) 1950–2021. Seattle, USA: Institute for Health Metrics and Evaluation (IHME), 2024.
[27] Liu Z, Jiang Y, Yuan H, Fang Q, Cai N, Suo C, *et al*. The trends in incidence of primary liver cancer caused by specific etiologies: Results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. J Hepatol 2019;70(4):674–683. doi:10.1016/j.jhep.2018.12.001, PMID:30543829.
[28] Yang P, Huang W, Xu Y, Teng Y, Shu P. Trends and projections of the burden of gastric cancer in China and G20 countries: a comparative study based on the global burden of disease database 2021. Int J Surg 2025. doi:10.1097/JS9.0000000000002464, PMID:40359560.
[29] Cao F, Xu Z, Li XX, Fu ZY, Han RY, Zhang JL, *et al*. Trends and cross-country inequalities in the global burden of osteoarthritis, 1990-2019: A population-based study. Ageing Res Rev 2024;99:102382. doi:10.1016/j.arr.2024.102382, PMID:38917934.
[30] Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, *et al*. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. Kidney Int 2018;94(3):567–581. doi:10.1016/j.kint.2018.04.011, PMID:30078514.
[31] Howe LD. Handbook on Health Inequality Monitoring. Int J Epidemiol 2014;43:1345–1346. doi:10.1093/ije/dyu124.
[32] WHO. Handbook on health inequality monitoring with a special focus on low- and middle-income countries. Geneva, Switzerland: WHO; 2013.
[33] GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2023;402(10397):203–234. doi:10.1016/S0140-6736(23)01301-6, PMID:37356446.
[34] Sridhar S, Lo SK, Xing F, Yang J, Ye H, Chan JF, *et al*. Clinical characteristics and molecular epidemiology of hepatitis E in Shenzhen, China: a shift toward foodborne transmission of hepatitis E virus infection. Emerg Microbes Infect 2017;6(12):e115. doi:10.1038/emi.2017.107, PMID:29259325.
[35] Rafieepoor M, Mohebbi SR, Hosseini SM, Tanhaei M, Niasar MS, Kazemian S, *et al*. Detection of human enteric viruses in fresh produce of markets, farms and surface water used for irrigation in the Tehran, Iran. Sci Total Environ 2024;912:169575. doi:10.1016/j.scitotenv.2023.169575, PMID:38143000.
[36] Zeng DY, Li JM, Lin S, Dong X, You J, Xing QQ, *et al*. Global burden of acute viral hepatitis and its association with socioeconomic development status, 1990-2019. J Hepatol 2021;75(3):547–556. doi:10.1016/j.jhep.2021.04.035, PMID:33961940.
[37] Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel J-P, *et al*. The World report on ageing and health: a policy framework for healthy ageing. The Lancet 2016;387:2145–2154. doi:10.1016/S0140-6736(15)00516-4, PMID:26520231.
[38] Chen X, Giles J, Yao Y, Yip W, Meng Q, Berkman L, *et al*. The path to healthy ageing in China: a Peking University-Lancet Commission. Lancet 2022; 400(10367):1967–2006. doi:10.1016/S0140-6736(22)01546-X, PMID:36423650.
[39] Wang L, Peng W, Zhao Z, Zhang M, Shi Z, Song Z, *et al*. Prevalence and Treatment of Diabetes in China, 2013-2018. JAMA 2021;326(24):2498–2506. doi:10.1001/jama.2021.22208, PMID:34962526.
[40] Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, *et al*. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet 2018; 392(10159):2052–2090. doi:10.1016/S0140-6736(18)31694-5, PMID:30340847.
[41] Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, *et al*. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018;6(5):e555–e567. doi:10.1016/S2214-109X(18)30127-X, PMID:29653628.
[42] Yu XY, Chen ZP, Wang SY, Pan HR, Wang ZF, Zhang QF, *et al*. Safety and immunogenicity of hepatitis E vaccine in elderly people older than 65 years. Vaccine 2019;37(32):4581–4586. doi:10.1016/j.vaccine.2019.04.006, PMID:31262585.
[43] Huang S, Zhang X, Su Y, Zhuang C, Tang Z, Huang X, *et al*. Long-term efficacy of a recombinant hepatitis E vaccine in adults: 10-year results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2024;403(10429):813–823. doi:10.1016/S0140-6736(23)02234-1, PMID:38387470.
[44] Peron JM, Larrue H, Izopet J, Buti M. The pressing need for a global HEV vaccine. J Hepatol 2023;79(3):876–880. doi:10.1016/j.jhep.2023.03.024, PMID:37003442.