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Trends in pulmonary arterial hypertension: insights from Global Burden of Disease 1990–2021

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ABSTRACT

Objective This study aimed to assess the global, regional and national burden of pulmonary arterial hypertension (PAH) from 1990 to 2021 using data from the Global Burden of Disease Study 2021. The focus was on evaluating trends in incidence, prevalence, mortality and disability-adjusted life-years (DALYs) associated with PAH and examining these trends by age, gender and sociodemographic index (SDI).

Design This is a systematic analysis leveraging data from the Global Burden of Disease Study 2021. The analysis focused on both crude and age-standardised rates to track temporal trends in PAH burden, with data stratified by region and SDI.

Setting The study used global, regiona, and national data from 204 countries and regions, spanning from 1990 to 2021.

Participants The participants in this study include individuals diagnosed with PAH, with data representing populations globally, categorised by age, gender and SDI.

Primary and secondary outcome measures Primary outcome measures included global, regional and national incidence, prevalence, mortality and DALYs related to PAH. Secondary outcomes consisted of age-standardised rates (age-standardised incidence rate (ASIR), age-standardised mortality rate (ASMR)) and trends over the study period. A key strength of this study is the detailed stratification by SDI, revealing how PAH burden varies across different socio-economic settings. This extended temporal analysis offers new insights into long-term trends, highlighting the rising burden in lower-SDI regions and significant regional disparities in disease management and outcomes.

Results From 1990 to 2021, global PAH cases showed substantial increases in both incidence (85.62%) and prevalence (81.46%), while age-standardised rates remained stable. Across SDI levels, high-SDI regions maintained stable ASIRs (0.37 per 100 000) with a slight decline (estimated average percentage change (EAPC) −0.06%), while low-SDI regions demonstrated the most significant reduction (EAPC −0.30%). Deaths increased by 48.36% globally, though the ASMR decreased from 0.35 to 0.27 per 100 000. The disease burden measured by DALYs decreased by 6.59%, with high-SDI regions showing better improvements in age-standardised DALY rates (−1.39% EAPC) compared with other SDI levels. Gender analysis revealed persistent female predominance (female-to-male ratio 1.62:1), particularly pronounced in populations over 50 years across all SDI quintiles.

Conclusions While global age-standardised rates have declined, PAH remains a significant global health burden, particularly in low-SDI regions. These findings underscore the need for targeted prevention and intervention strategies, especially for high-risk populations, such as females and the elderly, to reduce the global health impact of PAH.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our analytical approach incorporates sociodemographic index stratification to systematically examine health disparities across development levels.
⇒ We employ advanced modelling tools (DisMod-MR 2.1 and CODEm) with robust statistical procedures to ensure temporal consistency and handle missing data.
⇒ The methodology relies on modelled estimates rather than primary clinical data, which may affect accuracy in regions with limited data collection.
⇒ Despite standardised adjustment procedures, variations in source data quality across healthcare systems may impact estimate precision.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive and incurable disease[1] characterised by elevated pulmonary vascular resistance, resulting in right ventricular failure.[2] PAH is classified into different subtypes according to the underlying disease pathogenesis, including idiopathic PAH (IPAH), heritable PAH and PAH associated with other conditions such as connective tissue disease.[3 4]

PAH is a rare but severe cardiovascular condition characterised by increased pulmonary vascular resistance, leading to right heart failure and premature death.[5] The disease significantly impacts patients' quality of life through reduced exercise capacity, chronic fatigue, chest pain and psychological distress.[6] Multiple risk factors contribute to PAH development, including genetic predisposition (particularly BMPR2 gene

mutations,[7] SMAD5 as new[8]), connective tissue diseases, congenital heart defects and certain medications such as appetite suppressants.[9] Metformin and sotatercept appear as promising therapeutic drugs for PAH.[10]

According to the Global Burden of Disease (GBD) study, approximately 192 000 people worldwide were affected by PAH in 2021, with around 22 000 reported deaths.[11]The disease presents a substantial economic burden on healthcare systems due to high treatment costs, frequent hospitalisations and reduced workforce participation among affected individuals.[12]

Despite significant advances in diagnosis and treatment over recent decades, PAH remains a major global health challenge, particularly in resource-limited settings.[13] The disease impact varies considerably across regions due to differences in diagnostic capabilities, environmental exposures and socio-economic conditions.[14–18]

Current research on the global burden of PAH has primarily focused on broad assessments at global and regional levels. Previous studies have estimated global trends and attributable risks of PAH from 1990 to 2021, explored associations with socio-economic status (SES) and provided predictions for future disease burden.[11] However, these studies often lack comprehensive data from regions with limited healthcare access, where PAH may be underreported or misdiagnosed.[19 20]

To address these gaps, this study uses data from the GBD 2021 to provide a more detailed assessment of PAH burden globally, regionally and nationally from 1990 to 2021.[21] A key innovation of our study is the inclusion of SDI-based stratifications, which were not addressed in previous research, offering a deeper understanding of how PAH burden varies by socio-economic development.[22 23] Additionally, we have expanded our analysis to include previously unassessed or data-scarce regions using predictive covariates adjusted for SDI levels and individual country data.[24] This allows for a more nuanced understanding of the disease burden, particularly in regions with limited healthcare infrastructure.[25]

The findings aim to inform targeted prevention and control strategies and serve as a valuable reference for health policy development and resource allocation, with a particular emphasis on regions that were previously underrepresented in the literature.

METHODS

Data source and classification

This study analysed data from the GBD 2021 data set, a comprehensive database documenting disease patterns across 204 countries and regions.[26] In the GBD framework, PAH is classified under cause code B.4.2, corresponding to the International Classification of Diseases 11th Revision codes 1B50-1B52.[27] The data set integrates information from multiple sources, including cohort studies, randomised controlled trials and civil surveys, encompassing over 50 000 studies.[28]

Disease definition and diagnostic considerations

PAH diagnostic criteria vary across healthcare settings. In high-resource environments, diagnosis follows the World Symposium on Pulmonary Hypertension guidelines, requiring right heart catheterisation with specific haemodynamic criteria (mean pulmonary arterial pressure >20 mm Hg, pulmonary vascular resistance ≥3 Wood units).[29] Resource-limited settings often rely on echocardiographic screening and clinical presentation, which may affect case definition consistency. This diagnostic heterogeneity presents a methodological challenge for accurate disease burden estimation.[30–32]

Modelling assumption

We employed two primary analytical tools: DisMod-MR 2.1 and the Cause of Death Ensemble Model (CODEm).[33] DisMod-MR 2.1, a Bayesian meta-regression tool, was selected for its advanced capabilities in handling sparse data and accounting for age-sex patterns. This tool has been extensively validated in previous global burden studies and offers improved modelling strategies for geographical location and covariate adjustments compared with earlier versions.[34–37]

CODEm analysed mortality data through multiple modelling methods, selecting covariates based on out-of-sample predictive validity testing. These tools enabled systematic assessment of PAH's epidemiological parameters from 1990 to 2021, facilitating exploration of temporal and geographical distribution patterns.[38–40]

Data extraction and analysis

We extracted data on incidence rates, prevalence rates, mortality rates and disability-adjusted life-years (DALYs) from the Global Health Data Exchange (GHDx) and its affiliated tools. Our analysis encompassed global, regional and national levels from 1990 to 2021. The study adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).[41] The data used in this study are publicly available through the GBD 2021 database.[42] All data were accessed from the GHDx platform (http://ghdx.healthdata.org/gbd-results-tool) and are compliant with ethical guidelines for the use of public health data. No special permissions were required for the use of these data as they are freely accessible to researchers and do not require specific authorisation.

Statistical analysis

The variables extracted from the database included prevalent cases, number of deaths, number of DALYs and their corresponding age-standardised rates (ASRs) at the global, regional and national levels. The prevalence rate (per 100 000 people) was defined as the number of aggregated cases (including new and existing cases) divided by the population size; the mortality rate (per 100 000 people) was defined as the annual number of deaths divided by the total population.

The average annual percentage change (AAPC) and corresponding 95% CI were calculated using Joinpoint

software (National Cancer Institute, Rockville, MD, USA) to assess disease burden trends.[43 44] The logarithmic age-standardised indicators were fitted into a regression model: $\ln(y) = \alpha + \beta x + \varepsilon$, where y represents the age-standardised indicator, and x represents the calendar year. The AAPC was calculated as $100 \times (\exp(\beta) - 1)$, and the 95% CI was derived from the model. If the CI of the AAPC estimate was >0, the indicator showed an increasing trend; if <0, it showed a decreasing trend; and if it included 0, the trend was stable. Joinpoint software (V.4.9.1.0) was used to analyse trends in PAH incidence, mortality and DALYs from 1990 to 2021, providing insights into the changes in PAH burden and informing prevention and control strategies.

The data were stratified by age (1–4, 5–9, every 5-year age group up to 95 years and 95 years and older), calendar year (1990–2021), region and country or territory. Geographically, the world was divided into 21 regions, and 204 countries and territories were classified into five categories according to the sociodemographic index (SDI), constructed based on the geometric mean of total fertility rate, income per capita and average years of schooling among those aged 15 years or older, ranging from 0 to 1. A higher SDI indicates a more developed country.[45]

Estimated average percentage changes (EAPCs) were used to evaluate trends in the ASRs of prevalence, deaths and DALYs over a specified period. The natural logarithm of ASR was assumed to be linearly associated with time: $y = \alpha + \beta x + \varepsilon$, where $y = \ln(\text{rate})$, x = calendar year, and ε = error term. Based on this formula, β represents the positive or negative ASR trends. The EAPC was calculated as $100 \times (\exp(\beta) - 1)$, and its 95% CI was derived from the model.[46] A positive CI indicated an upward trend, a negative CI indicated a downward trend and a CI that included zero indicated a stable trend. All statistical analyses and visualisations were conducted using R statistical software (V.4.3.3), with $p<0.05$ considered statistically significant.

Patient and public involvement

Patient and public involvement was not applicable to this study as it represents a secondary analysis of the GBD 2021 data using population-level statistics and epidemiological models. The study used existing public health data that adhere to the GATHER. The findings from this analysis are intended to inform public health policies and interventions for PAH.

RESULTS

Incidence of PAH

Global trends in PAH incidence

From 1990 to 2021, the global incidence of PAH increased by 85.62% (95% CI: 77.92% to 92.85%). Despite this rise in absolute numbers, the age-standardised incidence rate (ASIR) remained stable, with an estimated annual percentage change (EAPC) of 0.05% (95% CI: 0.03% to 0.07%) (online supplemental table 1 and figure 1). Joinpoint regression analysis identified five distinct periods of annual percentage change (APC), indicating a decelerated but persistent upward trend in PAH incidence over the past decade (online supplemental figure 2A).

SDI analysis

Distinct patterns in PAH incidence were observed across SDI levels. High-SDI regions maintained a stable ASIR of 0.37 per 100 000 (95% CI: 0.29 to 0.44) with a slight decline (EAPC −0.06%). High-middle-SDI regions showed a marginal increase (EAPC 0.03%), while middle-SDI regions remained stable at approximately 0.53 per 100 000 (EAPC −0.02%). Lower-middle-SDI regions experienced a modest decrease (from 0.60 to 0.59 per 100 000; EAPC −0.17%), and low-SDI regions showed the most significant reduction (from 0.78 to 0.71 per 100 000; EAPC −0.30%) (online supplemental figures 3A and 4A).

Regional variations in disease occurrence

PAH incidence showed significant geographical variations. The highest ASIRs were in Eastern Europe (0.43 per 100 000), Central Asia (0.44) and Central Europe (0.47), while lower rates were recorded in high-income Asia Pacific (0.33) and North America (0.30). Central Europe (EAPC 0.40%) and the Caribbean (EAPC 0.27%) saw notable increases, whereas Western Sub-Saharan Africa (EAPC −1.15%) and North Africa and the Middle East (EAPC −0.45%) experienced the steepest declines. These patterns reflect the influence of regional socio-economic factors, healthcare accessibility and environmental exposures (online supplemental figure 3B).

Country-level analysis

At the country level, significant variations in disease occurrence were observed. Several high-SDI nations, including France (ASIR 0.47 per 100 000), Germany (0.37 per 100 000) and Japan (0.34 per 100 000), maintained relatively stable rates. In contrast, some low- and low-middle-SDI countries showed markedly different patterns. Ethiopia maintained a high ASIR of 1.00 per 100 000 (95% CI: 0.82 to 1.19), while Benin demonstrated a significant decrease in incidence (EAPC −1.32%) (online supplemental table 2). These trends may reflect differences in healthcare quality, disease awareness and diagnostic capabilities across countries.

Gender-specific patterns

The analysis revealed comparable ASIRs between males (0.48 per 100 000; 95% CI: 0.39 to 0.58) and females (0.55 per 100 000; 95% CI: 0.45 to 0.66). Incident cases increased similarly for both genders, with male cases rising from 10 684 to 19 831 and female cases from 12 617 to 23 420, representing an 85.62% increase for both groups. The EAPC was slightly higher for females (0.06%) compared with males (0.03%) (figure 1A, online supplemental figure 4A). In low-SDI and low-moderate-SDI areas, males tend to have a higher prevalence than females, while in

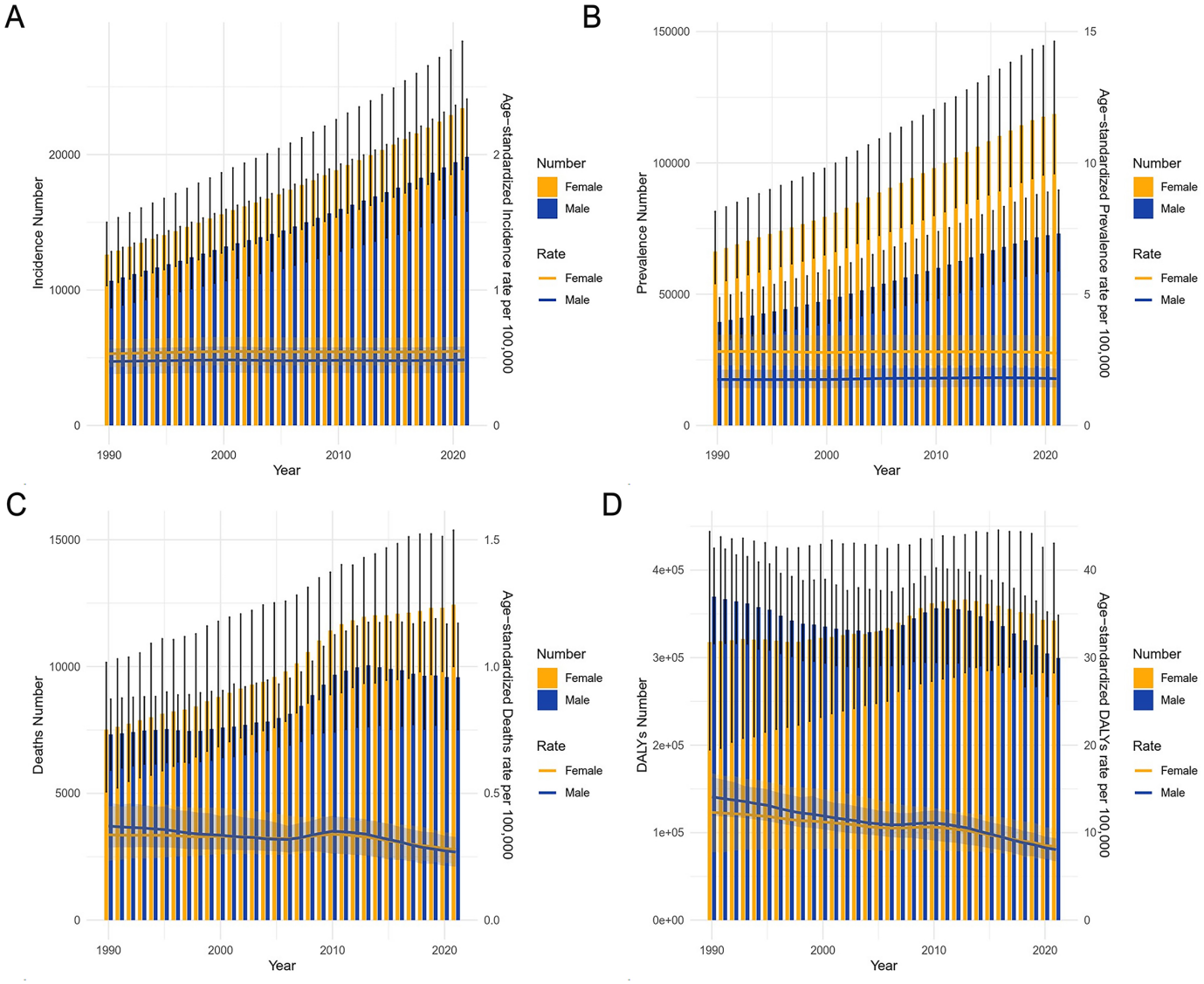

Figure 1 Global trends in pulmonary arterial hypertension burden: incidence (A), prevalence (B), mortality (C) and disability-adjusted life-years (DALYs) (D) by sex, 1990–2021.

high- and medium-high-SDI areas, the prevalence rates are closer for males and females (figure 2A).

Age-related patterns

PAH incidence increased significantly with age, particularly in individuals aged 60 years and older. Middle-aged and older men exhibited higher incidence rates, likely due to greater exposure to risk factors such as smoking and occupational hazards (online supplemental figure 5A). While the ASIR initially increased as the SDI level decreased, trends from 1990 to 2021 showed a significant ASIR decline in low-SDI areas, with stability or minor fluctuations in other SDI subgroups (figure 3).

Prevalence of PAH

Global trends in disease prevalence

Globally, the prevalence of PAH remained relatively stable from 1990 to 2021 (table 1).

The global prevalence of PAH increased from 105 703 cases to 191 808 cases between 1990 and 2021, representing an 81.46% increase. The age-standardised prevalence rate (ASPR) showed minimal change, decreasing slightly from 2.30 to 2.28 per 100 000 population (EAPC 0.04, 95% CI: 0.01 to 0.06) (figure 4). Joinpoint analysis revealed multiple significant trend changes over the past 30 years, with five joinpoints identified. Overall, the ASPR decreased in the 1990s, rebounded in the early 2000s, stabilised between 2005 and 2016, and turned downwards again in recent years (online supplemental figure 2B).

Sociodemographic patterns

SDI analysis revealed distinct patterns across regions. High- and high-middle-SDI regions showed moderate increases in case numbers (48.36% and 50.85%, respectively) with minor decreases in ASPR. Middle-, low-middle-, and low-SDI regions experienced more substantial increases in case numbers, ranging from 106.43% to 120.38%. Low-SDI regions, while showing a 119.21% increase in total

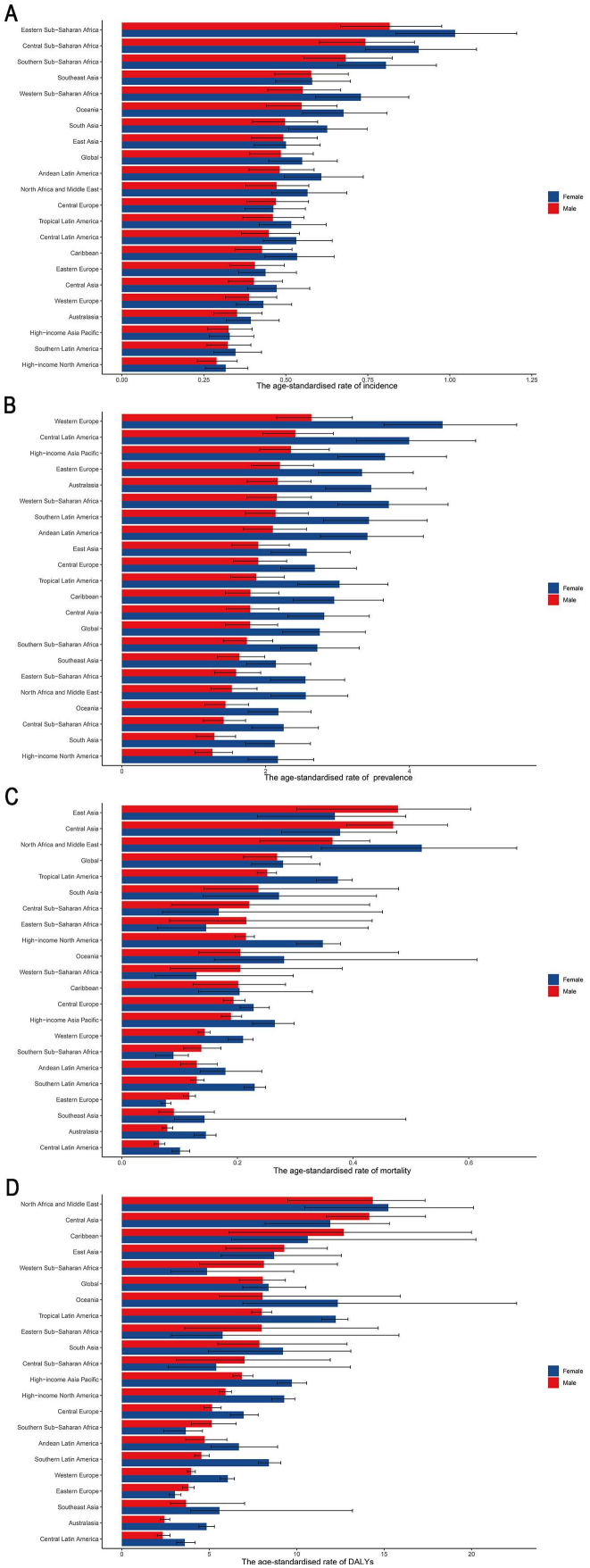

Figure 2 The age-standardised rates of incidence (A), prevalence (B), mortality (C) and disability-adjusted life-years (DALYs) (D) due to pulmonary arterial hypertension, by sex, across 21 regions in 2021. Error bars indicate the 95% uncertainty interval for the age-standardised rates.

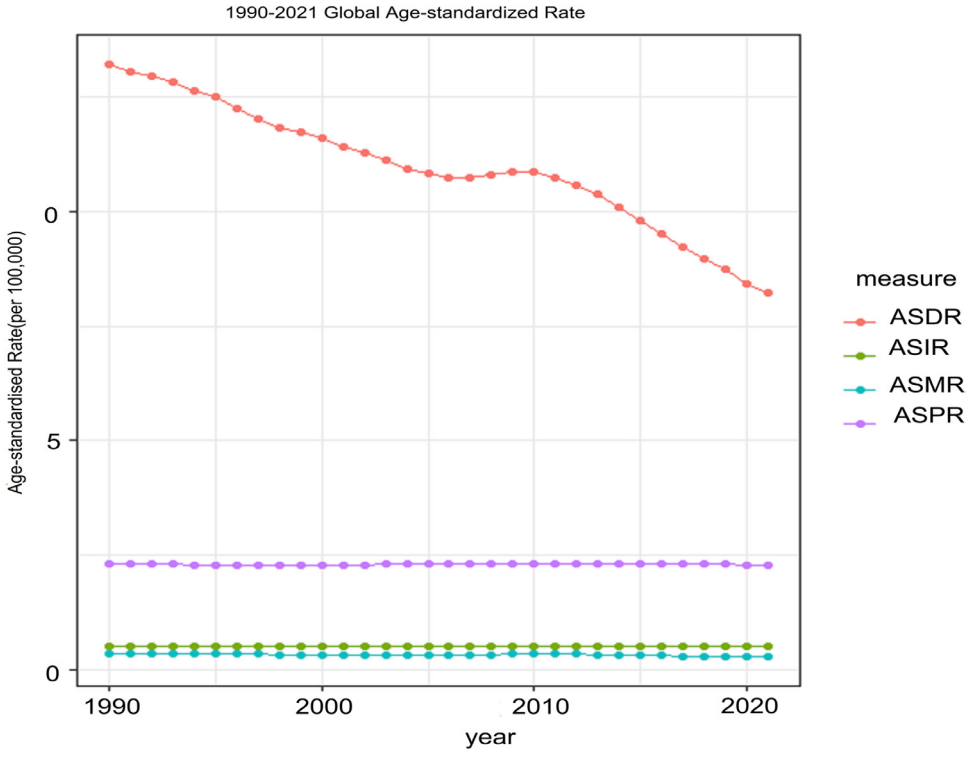

Figure 3 Comparison of trends in age-standardised incidence rate (ASIR), age-standardised prevalence rate (ASPR), age-standardised mortality rate (ASMR) and age-standardised disability-adjusted life-years (ASDR) rate of pulmonary arterial hypertension worldwide from 1990 to 2021.

cases, demonstrated a declining ASPR from 2.08 to 1.94 per 100 000 population (online supplemental figures 3C and 4B).

Geographical distribution

Regional variations in disease occurrence were significant. Western Sub-Saharan Africa saw the largest increase in cases (214.21%) despite a decline in ASPR from 3.22 to 2.97 per 100 000. Central Latin America (160.30%) and South Asia (136.39%) also showed substantial case increases, with divergent PR trends: Central Latin America rose from 2.71 to 3.25, while South Asia declined from 1.98 to 1.71 per 100 000. More modest increases were observed in Western Europe (44.65%) and high-income Asia Pacific (44.12%). Eastern Europe experienced a 6.52% reduction in cases, with PR decreasing from 3.21 to 2.83 per 100 000 (online supplemental figure 3D).

Country-level variations

The most pronounced changes occurred in specific low-middle-SDI nations, with the United Arab Emirates and Qatar showing increases of 615.52% and 717.15% in cases, respectively. In contrast, high-SDI countries generally demonstrated more modest increases while maintaining relatively stable ASPRs (online supplemental table 3).

Gender-specific patterns

Female cases increased from 66 282 to 1 18 682 (79.06%), while male cases rose from 39 421 to 73 127 (85.50%). The female-to-male ratio remained approximately 1.62:1 in 2021. ASPRs showed persistent gender differences: female rates decreased slightly from 2.82 to 2.75 per 100 000 (EAPC −0.02, 95% CI: −0.04 to 0.00), while male rates increased marginally from 1.75 to 1.78 per 100 000 (EAPC 0.15, 95% CI: 0.12 to 0.17). This gender disparity was particularly evident in low- and middle-income regions (figure 1B, online supplemental figure 4B). In most regions, particularly in low- and middle-income areas, the prevalence among females consistently exceeds that of males (figure 2B).

Age-related distribution

The prevalence of PAH showed distinct age-related patterns, with female predominance becoming more pronounced in populations over 50 years. This pattern, consistent across all SDI quintiles, suggests the influence of both biological factors and healthcare access on gender-specific differences in disease occurrence (online supplemental figure 5B).

Mortality of PAH

Global trends in PAH mortality

Global deaths from PAH increased from 14 842 in 1990 to 22 020 in 2021, representing a 48.36% increase (95% CI: 20.97% to 78.48%). Despite this increase in absolute numbers, the age-standardised mortality rate (ASMR) showed a favourable trend, decreasing from 0.35 to 0.27 deaths per 100 000 population, with an EAPC of −0.57% (95% CI: −0.73% to −0.41%) (online supplemental table 4 and figure 6).

Table 1 All-age cases and age-standardised prevalence rates for pulmonary arterial hypertension in 1990 and 2021 at the global and regional levels

	Prevalence no. (95% UI)					
	1990		2021		1990–2021	
Location	Prevalent cases	ASPR per 100 000	Prevalent cases	ASPR per 100 000	Cases change	EAPC*
Global	105703.31 (86381.45 to 130334.30)	2.30 (1.87 to 2.82)	191808.22 (155356.95 to 235787.14)	2.28 (1.85 to 2.80)	81.46 (73.47 to 89.06)	0.04 (0.01 to 0.06)
Sex						
Male	39421.32 (32159.43 to 48676.72)	1.75 (1.43 to 2.13)	73126.54 (58943.78 to 89629.37)	1.78 (1.44 to 2.17)	85.50 (76.34 to 94.03)	0.15 (0.12 to 0.17)
Female	66282.00 (54058.16 to 81489.14)	2.82 (2.29 to 3.46)	118681.68 (95923.29 to 146291.08)	2.75 (2.24 to 3.39)	79.06 (71.54 to 86.05)	−0.02 (−0.04 to 0.00)
SDI quintile						
High SDI	27053.75 (21977.20 to 33298.35)	2.67 (2.17 to 3.27)	41452.29 (33444.95 to 51587.94)	2.64 (2.15 to 3.23)	48.36 (42.48 to 53.78)	−0.02 (−0.05 to 0.01)
High-middle SDI	27439.19 (22296.22 to 33800.48)	2.61 (2.12 to 3.21)	42635.88 (34236.20 to 52931.66)	2.54 (2.07 to 3.12)	50.85 (42.83 to 57.95)	0.11 (0.01 to 0.22)
Middle SDI	29051.33 (23769.47 to 35768.60)	2.08 (1.68 to 2.54)	59666.73 (48064.58 to 73648.38)	2.22 (1.80 to 2.71)	106.43 (91.49 to 121.24)	0.21 (0.14 to 0.28)
Low-middle SDI	15078.70 (12416.61 to 18609.14)	1.77 (1.43 to 2.15)	32714.76 (26546.45 to 40620.35)	1.90 (1.53 to 2.33)	120.38 (111.10 to 128.09)	0.27 (0.24 to 0.30)
Low SDI	6965.74 (5736.97 to 8608.69)	2.08 (1.68 to 2.53)	15180.80 (12474.43 to 18747.09)	1.94 (1.58 to 2.36)	119.21 (114.61 to 123.22)	−0.21 (−0.30 to −0.13)
GBD region						
Andean Latin America	812.23 (666.88 to 996.56)	2.91 (2.35 to 3.58)	1777.16 (1434.00 to 2193.65)	2.77 (2.24 to 3.40)	120.19 (104.43 to 135.52)	−0.23 (−0.33 to −0.12)
Australasia	669.77 (543.50 to 828.03)	2.99 (2.45 to 3.70)	1166.81 (935.86 to 1444.34)	2.83 (2.29 to 3.44)	71.99 (60.47 to 83.96)	−0.14 (−0.18 to −0.10)
Caribbean	778.03 (634.80 to 953.72)	2.56 (2.08 to 3.13)	1228.93 (987.13 to 1505.96)	2.39 (1.93 to 2.93)	58.56 (49.10 to 68.14)	−0.32 (−0.43 to −0.21)
Central Asia	1408.73 (1145.19 to 1726.77)	2.46 (2.10 to 3.00)	2161.86 (1757.90 to 2676.53)	2.33 (1.90 to 2.86)	51.35 (43.57 to 58.84)	−0.06 (−0.15 to 0.04)
Central Europe	3455.75 (2820.58 to 4227.73)	2.52 (2.08 to 3.05)	3520.66 (2863.67 to 4311.25)	2.30 (1.89 to 2.79)	2.78 (−2.51 to 8.53)	−0.12 (−0.22 to −0.02)
Central Latin America	3262.25 (2678.67 to 3991.26)	2.71 (2.21 to 3.30)	8421.49 (6855.57 to 10382.57)	3.25 (2.65 to 3.99)	160.30 (141.62 to 180.97)	0.28 (0.07 to 0.49)
Central Sub-Saharan Africa	971.97 (795.46 to 1205.95)	2.79 (2.26 to 3.44)	1693.37 (1377.93 to 2093.53)	1.86 (1.50 to 2.24)	70.90 (58.79 to 83.04)	−1.15 (−1.30 to −0.10)
East Asia	22867.49 (18512.91 to 28350.61)	2.07 (1.68 to 2.55)	42486.04 (33929.79 to 53043.15)	2.23 (1.81 to 2.75)	83.96 (66.84 to 100.80)	0.38 (0.33 to 0.43)
Eastern Europe	8178.82 (6670.46 to 10049.29)	3.21 (2.65 to 3.91)	7686.23 (6263.74 to 9489.33)	2.83 (2.32 to 3.43)	−6.52 (−10.23 to −3.25)	−0.15 (−0.48 to 0.20)
Eastern Sub-Saharan Africa	2874.64 (2358.67 to 3535.65)	2.40 (1.95 to 2.92)	5907.48 (4822.15 to 7343.53)	2.09 (1.70 to 2.53)	105.16 (99.79 to 110.89)	−0.71 (−0.87 to −0.55)
High-income Asia Pacific	6368.84 (5211.58 to 7811.87)	2.30 (1.87 to 2.82)	9167.25 (7427.03 to 11361.78)	3.01 (2.47 to 3.68)	44.12 (34.07 to 55.52)	−0.21 (−0.24 to −0.17)
High-income North America	5984.09 (4856.05 to 7324.59)	3.25 (2.67 to 3.97)	8625.44 (6917.78 to 10745.03)	1.73 (1.396 to 2.12)	39.63 (32.94 to 45.64)	−0.24 (−0.35 to −0.13)
North Africa and Middle East	4967.64 (4055.92 to 6153.23)	1.87 (1.53 to 2.29)	11590.78 (9389.49 to 14435.62)	2.03 (1.64 to 2.49)	130.68 (117.71 to 143.14)	0.03 (−0.21 to 0.26)
Oceania	91.52 (74.65 to 112.48)	2.02 (1.64 to 2.49)	196.27 (158.79 to 241.29)	1.80 (1.45 to 2.18)	112.88 (97.48 to 126.52)	0.03 (−0.10 to 0.16)
South Asia	12896.59 (10582.38 to 15994.26)	1.98 (1.60 to 2.40)	29560.95 (23835.10 to 36926.63)	1.71 (1.38 to 2.09)	136.39 (125.54 to 146.90)	0.28 (0.27 to 0.30)
Southeast Asia	6365.98 (5233.68 to 7851.60)	1.58 (1.28 to 1.93)	13615.88 (11019.31 to 16956.99)	1.90 (1.54 to 2.32)	101.54 (87.60 to 115.69)	0.24 (0.08 to 0.41)
Southern Latin America	1280.90 (1039.53 to 1574.37)	1.77 (1.43 to 2.17)	2227.32 (1800.20 to 2759.99)	2.82 (2.29 to 3.48)	73.51 (65.12 to 82.39)	0.10 (0.05 to 0.15)
Southern Sub-Saharan Africa	795.76 (658.44 to 966.58)	2.69 (2.18 to 3.30)	1596.23 (1287.45 to 1944.80)	2.28 (1.852 to 2.76)	100.75 (89.79 to 111.32)	0.09 (0.03 to 0.16)
Tropical Latin America	2885.30 (2356.80 to 3541.16)	2.12 (1.73 to 2.56)	6238.60 (5019.81 to 7679.45)	2.48 (2.00 to 3.04)	118.43 (102.26 to 134.31)	0.12 (−0.06 to 0.29)
Western Europe	15675.19 (12581.68 to 19293.62)	2.35 (1.91 to 2.88)	23620.94 (19120.73 to 29197.29)	3.56 (2.92 to 4.35)	44.65 (39.41 to 49.27)	0.32 (0.28 to 0.35)
Western Sub-Saharan Africa	3111.80 (2565.50 to 3828.73)	3.22 (2.616 to 3.95)	9318.55 (7635.34 to 11570.12)	2.97 (2.40 to 3.63)	214.21 (203.23 to 229.00)	0.98 (0.78 to 1.18)

*EAPC is expressed as 95% CIs.
ASPR, age-standardised prevalence rate; EAPC, estimated annual percentage change; GBD, Global Burden of Disease; SDI, sociodemographic index; UI, uncertainty interval.

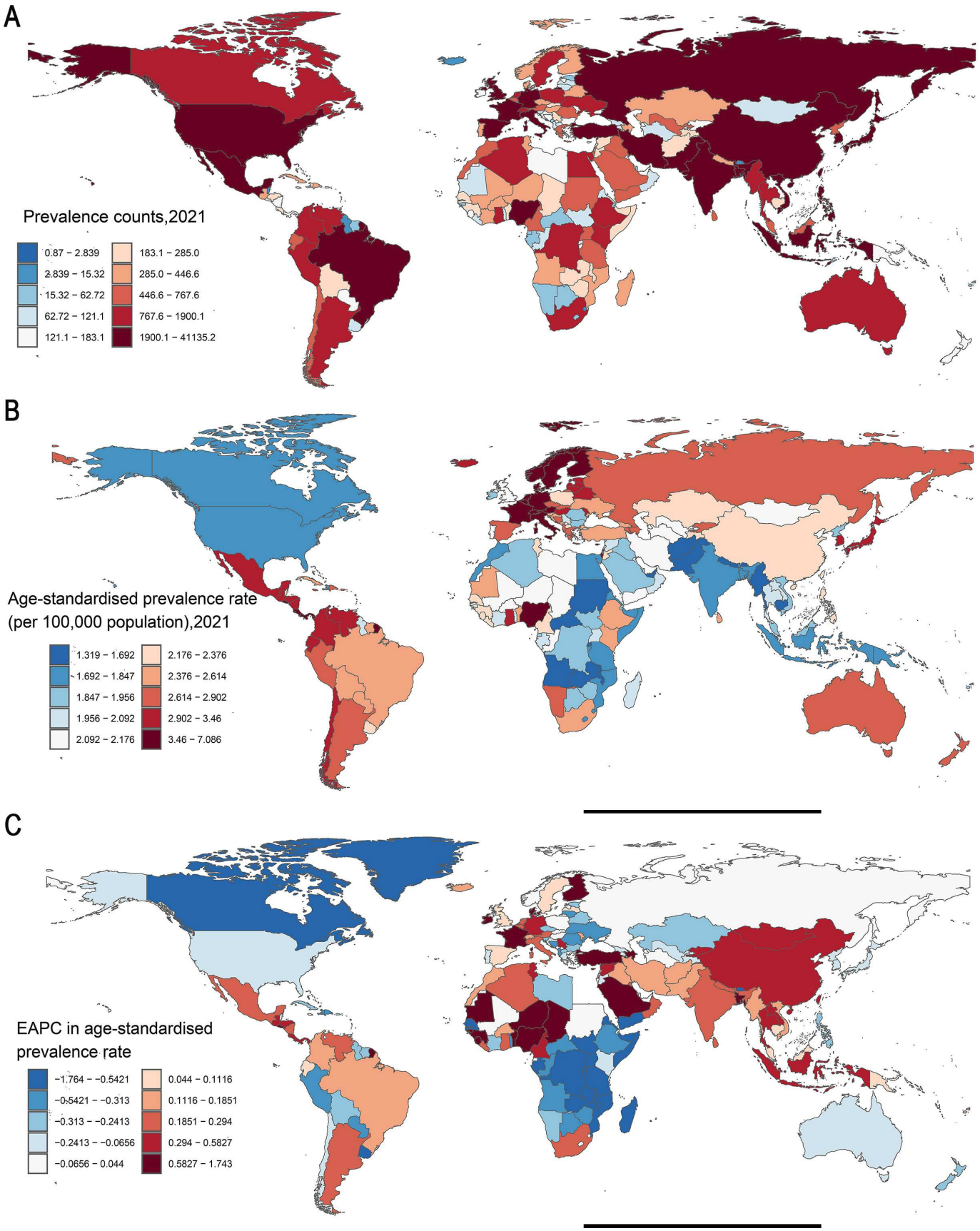

Figure 4 The global prevalence burden of pulmonary arterial hypertension (PAH) in 204 countries and territories. (A) The absolute number of PAH prevalence counts in 2021. (B) The age-standardised prevalence rate (per 100 000 population) of PAH in 2021. (C) The estimated annual percentage change (EAPC) of age-standardised prevalence rate for PAH between 1990 and 2021.

Trend analysis identified four distinct phases in PAH mortality. These findings suggest that PAH control measures have varied over time, with recent sustained declines since 2010 indicating effective interventions (online supplemental figure 2C).

SDI analysis

SDI analysis revealed varying patterns across different development levels. High-SDI regions experienced an 84.72% increase in deaths (from 2616 to 4620), with their ASMR declining from 0.26 to 0.22 per 100 000 (EAPC −0.56%, 95% CI: −0.75% to −0.37%). Similar patterns were observed across other development levels, with varying magnitudes of change (online supplemental figures 3E and 4C).

Regional variations in PAH mortality

The analysis of PAH mortality rates reveals distinct regional patterns in 2021. The highest ASMRs were concentrated in Central Asia (0.41 per 100 000), East Asia (0.41) and North Africa and Middle East (0.44). In contrast, Central Latin America (0.08) and Eastern Europe (0.09) demonstrated the lowest rates. Trend analysis from 1990 to 2021 indicates Central Asia as the only region with a positive change (EAPC +0.30%). Most regions experienced declining trends, with Eastern Europe (−3.78%), the Caribbean (−2.53%) and Central Latin America (−2.54%) showing the most substantial improvements. East Asia carried the highest absolute mortality burden with 7489.97 deaths in 2021, followed by high-income North America (1879.78) and Western Europe (1787.52). Notably, high-income Asia Pacific recorded the largest relative increase in cases (167.52%), while Eastern Europe showed the most significant decrease (−51.65%) (online supplemental figure 3F).

Country-level variations

ASMRs varied significantly between countries. Substantial reductions were observed in Costa Rica (−5.69% annual change), Puerto Rico (−6.64%) and Guatemala (−5.93%), reflecting successful healthcare interventions. Conversely, ASMR increases in Kuwait (3.62%), Latvia (5.63%) and Georgia (4.74%) highlighted the need for targeted measures.

High-income countries, such as the USA, Germany and Australia, experienced increased PAH-related deaths but stable or declining ASMRs due to medical advancements. In contrast, low- and middle-income countries, particularly in Africa and South Asia, saw rising deaths and variable ASMRs, likely due to insufficient healthcare resources.

Mortality reductions in Serbia and Slovenia were achieved through improved medical management, while fluctuations in smaller nations (eg, Monaco, Liechtenstein) reflected population size. Rising mortality in Middle Eastern countries underscored healthcare resource challenges and socio-economic disparities (online supplemental table 5).

Gender-specific analysis

Gender-specific analysis revealed distinct patterns. Female deaths increased from 7516 to 12 441 (65.53% increase), while male deaths rose from 7326 to 9578 (30.74% increase). The ASMR showed declining trends for both genders, with males decreasing from 0.37 to 0.27 per 100 000 (EAPC −0.73%, 95% CI: −0.92% to −0.54%) and females from 0.34 to 0.28 per 100 000 (EAPC −0.43%, 95% CI: −0.57% to −0.29%) (figures 1C and 2C).

Age-specific patterns

Deaths were highest among children under 5 years (2000–3000 cases), with ASMRs peaking at approximately 2 per 100 000—significantly higher than other age groups. Mortality declined with age and was lowest in those over 85 years. ASMR remained relatively stable across older age groups, with females consistently showing higher rates than males. These findings highlight the vulnerability of young children and the need for targeted interventions to reduce PAH mortality across all age groups (online supplemental figure 5C).

DALYs attributable to PAH

Global trends in disease impact

The global impact of PAH, measured in DALYs, decreased from 687 419 cases in 1990 to 642 104 cases in 2021, representing a 6.59% reduction (95% CI: −26.78% to 17.77%). The age-standardised DALY rate (ASDR) demonstrated a more substantial improvement, declining from 13.21 to 8.24 per 100 000 population, with an EAPC of −1.31% (95% CI: −1.44% to −1.19%) (online supplemental table 6 and figure 7)

Temporal trends in DALYs identified five distinct phases in the APC from 1989 to 2021. This overall trend reflects a sustained, although fluctuating, reduction in the disease burden of PAH over three decades (online supplemental figure 2D).

SDI analysis

The impact varied significantly across different SDI levels. High SDI regions experienced a 13.93% increase in DALY cases (81 792 to 93 182), though their ASDR decreased from 9.16 to 6.16 per 100 000 (EAPC −1.39%, 95% CI: −1.58% to −1.21%). High-middle-SDI regions showed substantial improvement, with a 22.09% reduction in DALY cases (127 638 to 99 448) and ASDR declining from 13.14 to 6.48 per 100 000 (EAPC −2.20%, 95% CI: −2.36% to −2.04%) (online supplemental figures 3G and 4D).

Regional analysis

East Asia reported the highest absolute DALY impact, with cases increasing marginally by 2.07% (151 596 to 154 740) but achieving a significant reduction in the ASDR from 15.78 to 8.84 per 100 000 (EAPC −1.32%). Eastern Europe demonstrated notable progress, with DALY cases decreasing by 59.49% (20 628 to 8357) and ASDR declining from 9.23 to 3.32 per 100 000 (EAPC −3.99%).

Other regions showed diverse trends. High-income North America and East Asia saw ASDR declines despite increased DALY cases, while significant reductions in North Africa and the Middle East likely reflect effective public health measures. Stabilisation in South Asia suggests some success in disease control. These variations underscore the critical influence of socio-economic conditions and healthcare resource allocation on PAH management (online supplemental figure 3H).

Country-level variations

Significant country-level differences in DALY impact were observed. Substantial reductions were noted in Egypt (−69.84%, EAPC −4.71%) and the Russian Federation (−65.61%, EAPC −4.81%). Conversely, increases were reported in Kuwait (+202.17%, EAPC 3.11%) and Taiwan (+273.94%, EAPC 4.76%).

These trends reflect disparities in healthcare resources, disease management capacity and socio-economic conditions across countries. Tailored public health strategies are needed to address these differences and reduce the global burden of PAH effectively (online supplemental table 7).

Gender-specific analysis

Male DALY cases decreased by 18.95% (369 686 to 299 636; EAPC −1.54%), while female cases increased by 7.78% (317 734 to 342 468; EAPC −1.07%). The ASDR declined for both genders, with males dropping from 14.09 to 8.06 per 100 000 and females from 12.32 to 8.39 (online supplemental figure 4D). High-burden regions for females included Central America, Australia, Eastern Europe, Southeast Asia, Western Europe and South America, where DALY rates exceeded 10 per 100 000. The gender gap was most pronounced in Europe and South America, likely due to biological, social or healthcare access factors (figure 2D).

Age-specific patterns

PAH had the greatest impact on the elderly (≥75 years, >90 000 DALYs) and children aged 0–10 years (50 000–70 000 DALYs). Infants, particularly young girls, emerged as a high-risk group, with significantly higher DALY rates in girls under 5 compared with boys. These findings highlight the need for targeted prevention and gender-specific interventions in early-childhood PAH (online supplemental figure 5D).

DISCUSSION

Global trends and regional disparities in PAH burden

Our longitudinal analysis from 1990 to 2021 reveals a complex pattern in the global burden of PAH. While most nations demonstrated declining trends in ASRs (incidence, prevalence and mortality), the magnitude of improvement varied substantially across regions. The disease burden exhibits marked geographical inequalities, with high-income nations, particularly in Europe and North America, reporting higher prevalence rates compared with developing regions in Asia and Africa. This disparity likely reflects enhanced diagnostic capabilities and robust healthcare infrastructure rather than true differences in disease occurrence.

Environmental and lifestyle risk factors

Environmental exposures, particularly air pollution in urbanised areas, remain significant contributors to PAH risk through multiple pathophysiological mechanisms. Recent epidemiological investigations have revealed a complex relationship between long-term air pollution exposure and adverse health outcomes, with particularly pronounced effects observed in specific demographic groups.[47 48] The impact of prolonged air pollution exposure demonstrates notable sex-specific differences in health outcomes, with males showing increased vulnerability to hospitalisation, particularly in the context of COVID-19 complications.[49] Of particular significance is the role of ozone, a prevalent urban air pollutant, in early-life exposure scenarios.[50]

The impact of modernisation manifests through lifestyle factors, including increased sedentary behaviour, dietary changes and tobacco consumption. The distribution of risk factors for PAH demonstrates significant regional heterogeneity, closely associated with urbanisation patterns and economic development levels.[51] Digital health interventions, specifically e-learning modules focused on nutrition, have demonstrated potential in improving patients' dietary behaviours and, consequently, their quality of life.[52] PAH imposes significant psychological burdens on affected individuals, leading to a reduced Quality of Life (QOL) due to factors such as emotional distress, limitations in daily activities, and physical symptoms.[53]

Mortality patterns and healthcare access

Despite overall improvements in PAH mortality globally, significant regional disparities persist. The pattern of mortality reduction follows a distinct geographical distribution, with more substantial improvements observed in Western nations and the Southern Hemisphere. These regions benefit from advanced diagnostic capabilities, comprehensive treatment options and robust healthcare infrastructure. Conversely, developing nations in Asia, Africa and parts of the Northern Hemisphere demonstrate slower progress, primarily due to limited healthcare resources and reduced disease awareness.

Quality indicators serve as essential tools for standardising care and improving outcomes in PAH management.[54] Recent evidence suggests that combination therapy incorporating inhaled or oral treprostinil can benefit PAH patients with cardiovascular comorbidities, highlighting the importance of tailored therapeutic approaches.[55]

Health disparities significantly impact outcomes of patients with PAH through their influence on medical care accessibility. Recent data from the Pulmonary

Hypertension Association Registry reveal concerning disparities: Hispanic patients demonstrate higher rates of Medicaid coverage or lack of insurance compared with non-Hispanic white patients (25% vs 12% and 7.1% vs 1.4%, respectively), resulting in increased hospitalisation frequencies despite comparable disease severity.[56]

Geographical location emerges as a significant determinant of patient outcomes.[57] A national cohort study identified elevated all-cause mortality risk among patients residing in rural counties compared with metropolitan areas (HR 1.48; 95% CI: 1.14 to 1.92; p=0.003).[58] Additionally, socio-economic factors correlate with specific risk behaviours; notably, methamphetamine use, more prevalent among lower socio-economic groups, is associated with a 42% increased risk of PAH development (HR 1.42; 95% CI: 1.26 to 1.60).[59–61]

Vulnerable population groups

Demographic factors significantly influence PAH outcomes. Women and children represent critical demographic groups requiring specialised attention, with distinct disease manifestations and treatment needs.[62]

While males show higher exposure to certain risk factors, females often experience more severe disease progression. While the condition demonstrates a marked female predominance in occurrence, the disease trajectory reveals unexpected gender-based variations in outcomes. The role of sex hormones, particularly oestrogens, appears central to understanding these differential patterns. Research has identified the TGF-β signalling pathway as a critical mediator in these sex-specific manifestations.[63] Notably, despite the higher disease prevalence among women, female patients generally demonstrate more favourable prognoses compared with their male counterparts. This apparent contradiction, termed the 'oestrogen paradox', has emerged as a significant focus of research interest.[64]

The elderly population faces particularly high mortality rates, emphasising the need for targeted management strategies. We need enhanced perioperative management during the neonatal period.[65] Paediatric PAH differs significantly from adult forms of the disease in terms of aetiology and clinical presentation, underscoring the need for early and accurate diagnosis.[66] PAH presents significant challenges during pregnancy, requiring careful consideration and specialised management. Key aspects of management include thorough patient counselling regarding pregnancy implications, appropriate therapeutic intervention for both new and existing patients, continuous risk assessment, strategic delivery timing and intensive care during the critical periods of delivery and postpartum phase.[67]

Further research into sex-specific and age-specific mechanisms driving these disparities is crucial to inform more effective and targeted prevention efforts.

Treatment accessibility and regional variations

Analysis of PAH outcomes across SDI regions reveals substantial disparities attributable to variations in treatment accessibility and healthcare infrastructure. High-SDI regions demonstrate superior outcomes through widespread implementation of advanced diagnostic tools and targeted therapeutic interventions, including prostacyclin, endothelin receptor antagonists and phosphodiesterase-5 inhibitors.[68 69] These advancements have manifested in declining ASMRs and reduced DALYs over the past three decades.

In contrast, low-SDI regions continue to face significant challenges in PAH management. A lower SES is strongly associated with a higher risk of death in IPAH.[70] Resource constraints limit access to essential diagnostic tools and specialised treatments, frequently resulting in delayed diagnoses and compromised outcomes.[71] These socio-economic barriers impede the adoption of life-saving therapies, contributing to disproportionately elevated disease burden in these regions.

Risk factor distribution and regional impact

The epidemiological profile of PAH demonstrates marked regional variation in risk factor distribution. Substance use patterns differ significantly across geographical regions, with higher prevalence of stimulant-related PAH in North America and Europe compared with lower incidence in regions with stricter regulatory frameworks. HIV infection emerges as a significant contributor to PAH burden in Sub-Saharan Africa,[72 73] where limited healthcare resources and variable antiretroviral therapy coverage compound the challenges of early diagnosis and effective treatment.

Competing health risks further complicate the PAH landscape. High-income regions face substantial competing risks from cardiovascular diseases and malignancies, while low- and middle-income countries contend with infectious diseases and nutritional deficiencies.[74–76] The increasing prevalence of chronic conditions and demographic ageing introduces additional complexity to PAH management, particularly affecting diagnostic accuracy and treatment outcomes in the elderly populations.

Strategic framework for global PAH control

The imperative to address global disparities in PAH necessitates the implementation of sophisticated prevention strategies tailored to regional socio-economic contexts. This comprehensive framework articulates three interconnected dimensions that collectively aim to enhance PAH management and outcomes worldwide.

The cornerstone of effective global PAH management lies in establishing a robust international prevention network.[77] Through coordinated efforts among international organisations, this network serves as a catalyst for policy harmonisation and research collaboration across borders. Such collaboration facilitates the systematic transfer of knowledge and successful prevention models from high-resource environments to limited-resource

settings, ensuring that proven interventions can be appropriately adapted and implemented in diverse healthcare contexts.

A dual approach to infrastructure development emerges as essential for comprehensive PAH management.[78–80] High-income nations must strategically leverage their technological and economic advantages to pioneer advanced diagnostic and treatment innovations. Simultaneously, these nations bear responsibility for fostering international collaboration and supporting knowledge dissemination. In contrast, interventions in low-resource regions demand careful prioritisation of fundamental healthcare infrastructure development. This includes systematic investment in healthcare professional training programmes and ensuring sustainable access to essential medical resources, thereby building lasting capacity for PAH management.

The framework's third dimension focuses on implementing differentiated prevention measures for identified high-risk populations.[81–83] This targeted approach requires particular attention to children, elderly individuals and women, each presenting unique challenges in PAH management. Through enhanced screening protocols and early intervention strategies, healthcare systems can significantly impact morbidity rates and improve survival outcomes. Furthermore, dedicated gender-specific research initiatives hold promise for developing innovative therapeutic approaches that address the distinct biological and clinical needs of different patient populations.

Through the coordinated implementation of these three dimensions, healthcare systems worldwide can work towards reducing PAH disparities while ensuring that interventions remain appropriately tailored to local contexts and capabilities.[84] This strategic framework provides a comprehensive foundation for advancing global PAH care while acknowledging and addressing the diverse challenges faced by different healthcare environments.

Database structure and analytical challenges

The GBD database architecture presents unique challenges in PAH burden assessment. Data heterogeneity across regions, with more robust collection systems in high-income countries, affects the comparability and completeness of global estimates. The application of advanced statistical models, including DisMod-MR and CODEm, while sophisticated, faces limitations in analysing rare conditions like PAH, particularly in regions with limited data availability.[85]

The infrequent nature of data updates and integration poses additional challenges for long-term trend analysis and real-time monitoring. These methodological considerations underscore the importance of strengthening global health surveillance systems while acknowledging current limitations in burden estimation for rare conditions.[86]

This comprehensive analysis highlights the necessity for coordinated international efforts to address PAH disparities through enhanced healthcare infrastructure, targeted interventions and improved data collection methodologies.

Methodological considerations and data quality assessment

Our investigation into the global burden of PAH encountered several significant methodological challenges that warrant careful consideration. The fundamental structure of the GBD database, while comprehensive, presents distinct complexities in accurately estimating PAH burden, particularly given the condition's relative rarity and heterogeneous presentation across populations.

In addressing these challenges, we employed sophisticated statistical frameworks, notably DisMod-MR and CODEm. These advanced modelling approaches were specifically selected for their capacity to handle complex epidemiological data. However, their predictive accuracy demonstrates notable sensitivity to data availability, potentially compromising their effectiveness in regions with limited surveillance infrastructure. The models' reliance on prior information and related disease patterns, while methodologically sound, may introduce systematic biases when extrapolating to populations with distinct healthcare characteristics.

A critical consideration in our analysis stems from the substantial heterogeneity in data quality and completeness across regions. High-income countries, benefiting from robust health surveillance systems, generally provide more comprehensive and reliable data. Conversely, resource-limited settings often face significant challenges in maintaining systematic data collection, potentially leading to underestimation of disease burden. This disparity is particularly pronounced in regions affected by political instability, armed conflicts or natural disasters, where healthcare infrastructure disruption severely compromises data collection capabilities.

The evolution of diagnostic standards throughout the study period introduces additional complexity to our longitudinal analyses. Changes in diagnostic criteria, technological capabilities and clinical practices over time potentially affect the consistency of case identification and classification. This temporal variability necessitates careful interpretation of trend analyses and may impact on the comparability of data across different time periods.

The culmination of these methodological challenges significantly influences the study's external validity and generalisability. While our statistical approaches employ state-of-the-art methods to address data gaps, including Bayesian modelling and multivariable regression techniques, these cannot fully compensate for fundamental limitations in primary data collection. The resultant uncertainties in burden estimates underscore the critical importance of strengthening global health surveillance systems, particularly in regions currently under-represented in international health databases.

These methodological considerations collectively emphasise the need for a cautious interpretation of our findings while highlighting opportunities for enhancing future global health research infrastructure and analytical approaches.

Future directions and strategic recommendations

Based on our findings, we propose several strategic initiatives: the establishment of a comprehensive global PAH prevention network through enhanced international collaboration represents a critical priority. This should be accompanied by targeted support mechanisms for low- and middle-income countries to strengthen their healthcare capacity. The development of differentiated prevention strategies for high-risk populations requires particular attention, alongside improvements in data collection systems, especially in resource-limited settings. Furthermore, increased investment in research examining region-specific risk factors and treatment approaches is essential.

These strategic initiatives should prioritise the reduction of global health disparities while acknowledging the varying resource constraints and healthcare system capabilities across regions. Success in these efforts requires sustained commitment from the international healthcare community and coordinated action across multiple stakeholders.

CONCLUSIONS AND POLICY IMPLICATIONS

Our study highlights the complex and uneven burden of PAH worldwide, emphasising the need for targeted interventions that address regional and demographic disparities. Strengthening healthcare systems, improving diagnostic and treatment capabilities, and focusing on high-risk groups are crucial steps towards reducing the global impact of PAH and achieving equitable health outcomes.

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