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Original Article

Hemolysis-associated Disorder and Natural Product Exposures: Underrecognized Drivers of an Escalating Global Pulmonary Arterial Hypertension Burden—An Ecological Study of 204 Countries and Territories

Caibin Zhang, Tianyang Huang, Xiaokai Guo, Xiaolin Cui* and Yisheng He*

School of Medicine, The Chinese University of Hong Kong, Shenzhen, Guangdong, China

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Abstract

Background and objectives: Pulmonary arterial hypertension (PAH) is a progressive cardiovascular disease with an increasing global burden. Although hemolytic disorders are established causes of PAH, their contribution to the global PAH burden remains unclear. This study aimed to evaluate the association between hemolysis-associated disorders and PAH incidence and to identify the relative contribution of hemolytic disorder subtypes compared with socio-demographic factors.

Methods: Using Global Burden of Disease 2021 data, temporal trends in the age-standardized incidence rate (ASIR) of PAH were analyzed using Joinpoint regression. Pearson correlation analysis assessed associations between PAH ASIR and the age-standardized prevalence rates of hemolytic disorder subtypes, hemolysis-related infections, malnutrition, and the Socio-demographic Index (SDI). Random forest regression was used to quantify the contributions of hemolytic disorders to PAH ASIR. Geographic distributions of PAH incidence and hemolytic disorder prevalence were compared, and Bayesian age-period-cohort modeling was used to project their burdens through 2050.

Results: Global PAH ASIR increased from 0.50 to 0.52 per 100,000 from 1990 to 2021. The prevalence of hemoglobinopathies and hemolytic anemias correlated positively with PAH ASIR ($R = 0.61$, $P = 7.70 \times 10^{-22}$). The random forest model explained 73% of the variance in PAH ASIR ($R^2 = 0.73$, $P = 0.01$), with G6PD trait (percentage increase in mean squared error [%IncMSE]: 18.43), other hemoglobinopathies/hemolytic anemias of unknown etiology (%IncMSE: 18.38), and vitamin A deficiency (%IncMSE: 17.27) identified as the top predictors, surpassing SDI (%IncMSE: 13.25) and sex (%IncMSE: 1.25). Temporal changes in hemolytic disorder prevalence strongly mirrored changes in PAH incidence ($R = 0.76$, $P = 6.34 \times 10^{-39}$). Exploratory analyses suggested that natural product exposures may contribute to the unexplained hemolytic burden that drives PAH. Projections indicated a continued rise through 2050 in both PAH burden (ASIR increasing from 0.52 in 2022 to 0.57 per 100,000) and hemolytic disease burden (prevalence rising from 27,760.54 to 31,863.72 per 100,000).

Conclusions: Hemolysis-associated disorders, particularly G6PD trait, other hemoglobinopathies/hemolytic anemias, and vitamin A deficiency, are the predominant contributors to the global PAH burden. The projected continued rise in hemolytic disorder prevalence through 2050 signals a persistent exacerbation of the global PAH burden, underscoring the urgent need for targeted prevention strategies.

Keywords: Pulmonary arterial hypertension; Hemolytic disorders; Natural products; Herbal Medicine; G6PD trait; Ecological study.

***Correspondence to:** Yisheng He and Xiaolin Cui, School of Medicine, The Chinese University of Hong Kong, Shenzhen, Guangdong 518172, China. ORCID: https://orcid.org/0000-0002-2217-6758 (YH); https://orcid.org/0000-0001-5118-0169 (XC). Tel: +86-755-23516154 (YH); +86-755-19042 (XC), E-mail: heyisheng@cuhk.edu.cn (YH); stevencui@cuhk.edu.cn (XC)

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Introduction

Pulmonary arterial hypertension (PAH), characterized by progressive vascular remodeling and pulmonary arterial stenosis, remains incurable. Historically, untreated patients have exhibited a mean survival of only 2.8 years.[1] Although therapeutic advances have increased the 3-year survival rate to 70–76%,[2,3] PAH continues to impose a significant global health burden. Given this, research into primary prevention risk factors is important for

reducing the global PAH burden.

Hemolytic anemias represent a particularly significant yet underappreciated contributor to the PAH burden. In patients with hemolytic disorders, PAH has emerged as a leading cause of morbidity and mortality.[4-6] The pathophysiological mechanism is well established: hemoglobin released during erythrocyte destruction acts as a potent oxidant, scavenging nitric oxide and generating reactive oxygen species that trigger endothelial activation.[7,8] This endothelial dysfunction subsequently initiates the characteristic pathological processes of PAH.[8-10] Experimental studies have demonstrated that intravascular hemolysis directly causes pulmonary vascular dysfunction through nitric oxide depletion and oxidative injury, establishing a causal basis for the hemolysis–PAH pathway.[11,12] Approximately 10% of patients with hemolytic anemias develop moderate-to-severe PAH.[13] According to Global Burden of Disease (GBD) 2021 data, hemoglobinopathies and hemolytic anemias (including carrier states such as G6PD trait, sickle cell trait, and thalassemia trait) collectively affect an estimated 27,789.88 per 100,000 population globally, and these disorders represent a potentially substantial but poorly quantified contributor to the worldwide PAH burden.

Although PAH is a well-established complication of hemolytic diseases, hemolysis-associated PAH remains systematically overlooked in global health assessments.[4,5] Previous studies examining the global burden of PAH have predominantly focused on demographic factors such as age and sex, along with the Socio-demographic Index (SDI), while no systematic investigation has specifically evaluated the contribution of hemolytic disorders. As a result, the global burden of PAH attributable to hemolysis remains unquantified, representing a knowledge gap in our understanding of PAH epidemiology.

This study aimed to elucidate the association between hemolysis-associated disorders and PAH incidence and to identify the relative contribution of hemolytic disorder subtypes compared with socio-demographic factors. Using GBD 2021 data across 204 countries and territories, we employed an ecological study design to evaluate this relationship at the national level. Through random forest regression modeling, we quantified and compared the relative contributions of specific hemolytic disorder subtypes, sex, and SDI to PAH burden. Furthermore, we analyzed temporal associations between changes in hemolytic disorder prevalence and PAH incidence trends from 2011 to 2021 and projected future burden through 2050. These findings provide critical evidence for developing targeted PAH prevention strategies and inform policymakers about the escalating health challenges associated with PAH, particularly in regions with high hemolytic disorder prevalence.

Materials and methods

Study design

This study employed an ecological design, analyzing population-level data from 204 countries and territories to examine the association between the prevalence of hemolytic disorders and the incidence of PAH. Because this is an ecological study using aggregated national-level data from the GBD 2021 database, individual-level inclusion and exclusion criteria for patients are not applicable. The case definitions described below reflect the standardized diagnostic criteria used by the GBD study framework. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies. The analytical workflow is illustrated in Figure 1.

Data source

The GBD 2021 project generated comprehensive estimates covering 371 diseases and injuries in 204 countries and territories from 1990 to 2021. These estimates are based on data gathered from multiple sources, including national censuses, household surveys, civil registration records, disease-specific registries, documentation of health service use, air quality monitoring networks, and satellite remote sensing data. All GBD data used in this study were obtained from the GBD Results Tool (https://vizhub.healthdata.org/gbd-results/).

GBD data extraction parameters

All data were extracted from the GBD 2021 Results Tool on April 10, 2025. For PAH, the selected cause was "pulmonary arterial hypertension", the measure was "incidence", and the metrics included "rate" for age-standardized incidence rate (ASIR) analyses and "number" for incident case analyses. Locations included the global level, 21 GBD regions, and 204 countries and territories. Age selections included "age-standardized" for ASIR analyses and all available age groups for age-specific analyses and projection modeling. Sex selections included "both", "male", and "female". Years from 1990 to 2021 were extracted.

For hemolysis-associated disorders, the measure was "prevalence" and the metrics included "rate" for age-standardized prevalence rate (ASPR) analyses and "number" for prevalence case analyses and projection modeling. The extracted causes included "hemoglobinopathies and hemolytic anemias" and its subcategories: "G6PD deficiency", "G6PD trait", "sickle cell disorders", "sickle cell trait", "thalassemias", "thalassemia trait", and "other hemoglobinopathies and hemolytic anemias of unknown etiology". Additional hemolysis-related conditions included "AIDS", "schistosomiasis", and "vitamin A deficiency". Locations included the global level, 21 GBD regions, and 204 countries and territories, as applicable to each analysis. Age selections included "age-standardized" for ASPR analyses and all available age groups for projection modeling. Sex selections included "both", "male", and "female", and years from 1990 to 2021 were extracted.

The SDI was obtained from the GBD 2021 covariate estimates for the corresponding locations and years. For the 2021 cross-sectional correlation and random forest analyses, country-level PAH ASIR, ASPRs of hemolysis-associated disorders, SDI, and sex-specific population proportions were matched by location and year. For temporal change analyses, changes in PAH incidence and hemolytic disorder prevalence were calculated over 2011–2021 using matched country-level estimates.

Case definitions

According to hemodynamic criteria established by right heart catheterization, PAH is characterized by a mean pulmonary artery pressure at rest exceeding 20 mmHg, along with a pulmonary capillary wedge pressure ≤15 mmHg and a pulmonary vascular resistance ≥2 Wood units.[14]

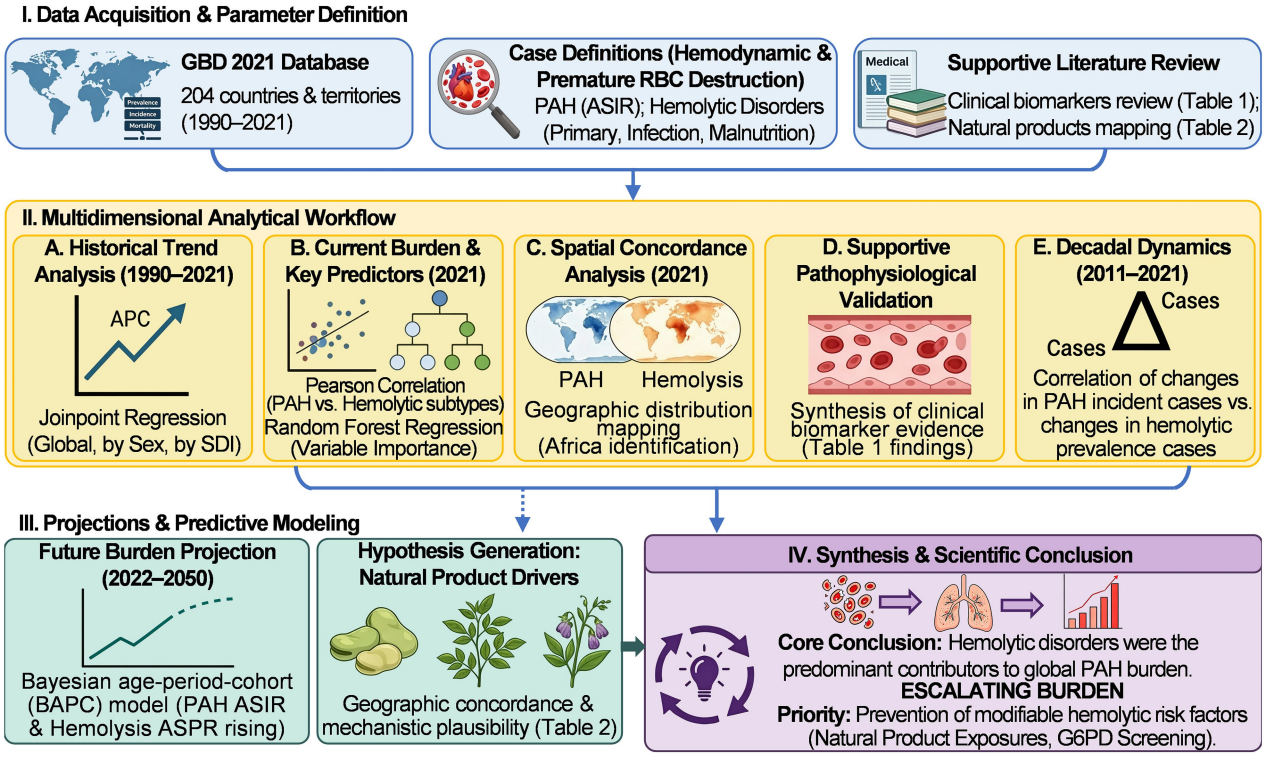

Fig. 1. Analytical workflow of this ecological study illustrating the data sources, study variables, statistical methods, and analytical steps employed. This study used GBD 2021 data from 204 countries and territories to evaluate the association between hemolysis-associated disorders and the global burden of PAH. The workflow included data acquisition and case definition, historical trend analysis, assessment of current burden and key predictors, spatial concordance analysis, supportive pathophysiological evidence synthesis, decadal dynamics analysis, future burden projection, hypothesis generation regarding natural product exposures, and final synthesis of scientific conclusions. APC, annual percent change; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; BAPC, Bayesian age-period-cohort; G6PD, glucose-6-phosphate dehydrogenase; GBD, Global Burden of Disease; PAH, pulmonary arterial hypertension; RBC, red blood cell; SDI, Socio-demographic Index.

In this study, hemolytic disorders were defined as conditions involving the premature destruction of red blood cells, shortening their lifespan to below the normal 120 days. Consistent with the GBD 2021 framework, these disorders were categorized as follows. Primary hemolytic disorders include hemoglobinopathies and hemolytic anemias, including G6PD deficiency, G6PD trait, sickle cell disorders, sickle cell trait, thalassemias, thalassemia trait, and other hemoglobinopathies and hemolytic anemias of unknown etiology. Infection-related disorders with hemolytic complications include AIDS and schistosomiasis. Malnutrition-related disorders in which hemolysis may occur include vitamin A deficiency.

Statistical analysis

The Joinpoint Regression Program (version 5.4.0.0) was employed to assess trends in the global ASIR of PAH from 1990 to 2021 and to calculate the annual percent change (APC) and average annual percent change.

Pearson correlation analysis was used to evaluate correlations between PAH ASIR and socio-demographic factors, as well as between PAH ASIR and the ASPR of hemolytic disorder subtypes.

Random forest, an ensemble learning algorithm that constructs multiple decision trees, is widely recognized for its effectiveness in assessing variable importance.[15] It demonstrates superior accuracy and improved capability in identifying features in large-scale simulations compared with other classification models.[16] Random forest regression was used to quantify the relative contribution of hemolysis-associated disorder subtypes, hemolysis-related infections and malnutrition, sex, and SDI to the global PAH burden across 204 countries and territories in 2021. The random forest regression model was fitted using the R package "randomForest" (version 4.7-1.2). The dependent variable was the country-level age-standardized incidence rate (ASIR) of PAH, and all selected predictors were entered simultaneously. To ensure reproducibility, the random seed for model construction was set to 2. The model was built with 500 trees (ntree = 500), with variable importance estimation (importance = TRUE) and proximity matrix calculation (proximity = TRUE) enabled. The number of variables randomly sampled at each split (mtry) was retained at the default setting for regression in the "randomForest" package, calculated as floor(p/3), where p

denotes the total number of predictors. The minimum terminal node size (nodesize) was also kept at the default value for regression (5 observations). Bootstrap samples were drawn with replacement from the full dataset, and the default sample size was equal to the total number of observations. No maximum number of terminal nodes was specified. As the primary objective of the analysis was to evaluate the relative importance of explanatory variables rather than to develop a predictive model for external application, and given the limited sample size of 204 country-level observations, no separate training and validation datasets were created. Instead, model performance was internally evaluated using the out-of-bag prediction error generated during bootstrap aggregation. The proportion of variance explained (R^2) was derived from the final out-of-bag estimate after 500 trees. Overall model significance was assessed using the rf.significance function in the "rfUtilities" package with 99 permutations and 500 trees, using the same random seed. Variable-level significance for the percentage increase in mean squared error (%IncMSE) was further evaluated using the "rfPermute" package with 100 permutations, 500 trees, and one computational core. Variable importance was quantified by %IncMSE, with higher values indicating a greater contribution to model prediction accuracy.

The Bayesian age-period-cohort (BAPC) model allows concurrent estimation of age, period, and cohort effects, providing reliable projections of disease trends over time.[17] In this study, we used the BAPC model to project the global ASIR of PAH and the ASPR of hemoglobinopathies and hemolytic anemias from 2022 to 2050. For BAPC projection, age-specific disease counts were used as model inputs. Historical PAH incidence counts and hemoglobinopathy/hemolytic anemia prevalence counts from 1990 to 2021 were obtained from the GBD 2021 database. The corresponding historical age-specific population denominators for 1990 to 2021 were obtained from GBD population estimates. Future population denominators for 2022 to 2050 were downloaded from the Global Health Data Exchange platform: Global Fertility, Mortality, Migration, and Population Forecasts 2017–2100 (https://ghdx.healthdata.org/record/ihme-data/global-population-forecasts-2017-2100). Projections were performed separately for both sexes combined, males, and females. Age groups were harmonized into 20 categories: <5, 5 to 9, 10 to 14, 15 to 19, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, 75 to 79, 80 to 84, 85 to 89, 90 to 94, and ≥95 years. Male and female population projections were summed to generate the population denominator for both sexes combined when required. Age-specific disease counts and population denominators were then reshaped into year-by-age matrices for BAPC modeling. The BAPC model was fitted using the "BAPC" package (version 0.0.36) and the "INLA" package (version 24.12.11) in R. The age-period-cohort input object was generated using APCList, with a 5-year age-group interval (gf = 5). The number of predicted years was set to 29, corresponding to the period from 2022 to 2050. Age-standardized rates were calculated using 20-age-group standard population weights matched to the age categories used in the model. Internal model validation was conducted using the retrospective prediction option in the BAPC model (retro = TRUE). This approach allowed the model-fitted estimates for the observed period to be compared with the corresponding GBD estimates. The consistency between observed and fitted age-standardized rates was visually assessed by plotting the observed data points together with the posterior estimates and prediction intervals. Because independent observed data after 2021 were not available, no external validation dataset was used.

All statistical analyses were performed using R (version 4.4.2). Statistical significance was defined as a P-value < 0.05.

Results

Temporal trends in global PAH incidence burden, 1990–2021: overall growth with accelerated rise post-2019

From 1990 to 2021, the global ASIR of PAH increased from 0.50 (95% uncertainty interval [UI]: 0.40–0.60) to 0.52 (95% UI: 0.42–0.62) per 100,000 population. Sex-specific analysis revealed rising ASIRs for both sexes. Among males, the ASIR increased from 0.47 (95% UI: 0.38–0.57) to 0.49 (95% UI: 0.39–0.58), while among females it rose from 0.53 (95% UI: 0.43–0.63) to 0.55 (95% UI: 0.45–0.66). Females maintained consistently higher incidence rates than males throughout the study period (Supplementary Table 1).

Joinpoint regression analysis revealed distinct phases in global PAH ASIR trends from 1990 to 2021 (Fig. 2). The global ASIR increased significantly from 1990 to 2000 (APC = 0.29; 95% CI: 0.29–0.30; $P < 0.05$), followed by a significant decline between 2000 and 2005 (APC = −0.17; 95% CI: −0.19 to −0.16; $P < 0.05$). Subsequent fluctuations included a slight increase from 2005 to 2011 (APC = 0.03; 95% CI: 0.02–0.04; $P < 0.05$) and a decrease from 2011 to 2015 (APC = −0.09; 95% CI: −0.11 to −0.06; $P < 0.05$). A modest increase resumed from 2015 to 2019 (APC = 0.11; 95% CI: 0.09–0.14; $P < 0.05$), before a substantial rise from 2019 to 2021 (APC = 0.45; 95% CI: 0.39–0.50; $P < 0.05$; Fig. 2a).

Mirroring global trends, both male and female ASIRs increased modestly starting in 2015 (males: APC = 0.13, 95% CI: 0.09–0.16; females: APC = 0.07, 95% CI: 0.01–0.14; both $P < 0.05$). From 2019 to 2021, rates rose markedly in both sexes (males: APC = 0.40, 95% CI: 0.33–0.47; females: APC = 0.50, 95% CI: 0.37–0.63; both $P < 0.05$; Fig. 2b and c). These findings indicate an escalating global PAH burden, particularly pronounced after 2019.

Sex- and age-specific patterns in PAH ASIR and their association with SDI levels, 1990–2021

The ASIR of PAH increased with advancing age in both 1990 and 2021. Across nearly all age groups, females exhibited higher ASIRs than males. In 1990, the highest ASIR for males (1.61, 95% UI: 1.06–2.31) was observed in the 75–79 age group, while for females the peak ASIR (1.61, 95% UI: 1.04–2.36) occurred in the 70–74 age group. In 2021, the highest ASIRs for both males (1.62, 95% UI: 1.07–2.31) and females (1.70, 95% UI: 1.11–2.44) were recorded in the 75–79 age group. Compared with 1990, the ASIR in 2021 increased across all age groups for males except the 5–9 and 70–74 age groups. Similarly, the ASIR among females increased in all age groups between 1990 and 2021 (Fig. 3a and b).

We analyzed the correlation between SDI and the ASIR of PAH across 204 countries and territories in 2021 to assess the impact of SDI on PAH burden. Our analysis revealed a significant negative correlation between SDI and the ASIR of PAH in 2021 (

Table 1. Summary of hemolysis-related indicator levels in PAH patients

Indicator	PAH patients, mean (SD) or median (IQR)	Sample size	Reference
Cell-free hemoglobin (mg/dL) Normal level: <5 mg/dL			
	13.8 (2.2)	138	Brittain *et al*.[18]
	14 (2)	121	Meegan *et al*.[19]
	7.0 (8.8)	12	Hekmat *et al*.[20]
	14	1	Lode *et al*.[21]
Haptoglobin (mg/dL) Normal level: 30-200 mg/dL			
	3.1 (3.2)	54	Taylor *et al*.[25]
	27.0 (21.7)	6	Taylor *et al*.[25]
	<2	1	Yoshida *et al*.[22]
	29% of PAH patients decreased	24	Nakamura *et al*.[35]
Indirect bilirubin (mg/dL) Normal level: 0.1-0.8 mg/dL			
	3.0 (1.8)	82	Lobo *et al*.[23]
	4.8 (7.1)	20	Huang *et al*.[24]
	1.8	1	Yoshida *et al*.[22]
Lactate dehydrogenase (U/L) Normal level: 109-245 U/L			
	472.8 (224.7)	68	Taylor *et al*.[25]
	487 (58)	17	Villagra *et al*.[26]
	430 (189)	16	Mehari *et al*.[27]
	458 (192)	13	Liem *et al*.[28]
	425.67 (99.58)	3	Liu *et al*.[29]
	796	1	Yoshida *et al*.[22]
	740	1	Jung *et al*.[30]
	321	1	Taniyama *et al*.[31]
	985	1	Liu *et al*.[32]
	359	1	Kamiya *et al*.[33]
Ferritin (μg/L) Normal level: 20-200 μg/L			
	1,263.3 (1569.4)	74	Taylor *et al*.[25]
	573.1 (728.6)	8	Taylor *et al*.[25]
	1,780 (77.9–7180)	41	Chuncharunee *et al*.[34]
Transferrin (mg/dL) Normal level: 215-380 mg/dL			
	187.2 (46.9)	70	Taylor *et al*.[25]

IQR, interquartile range; PAH, pulmonary arterial hypertension; SD, standard deviation.

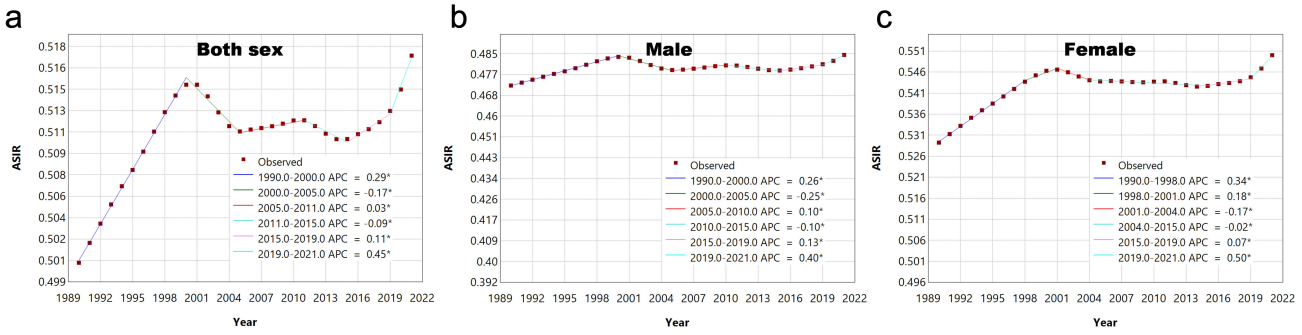

Fig. 2. Joinpoint regression analysis of global PAH ASIR (1990–2021). (a) APC for both sexes combined. (b) APC for global males. (c) APC for global females. ∗ indicates that the APC is statistically significant at $P < 0.05$. APC, annual percent change; ASIR, age-standardized incidence rate; PAH, pulmonary arterial hypertension.

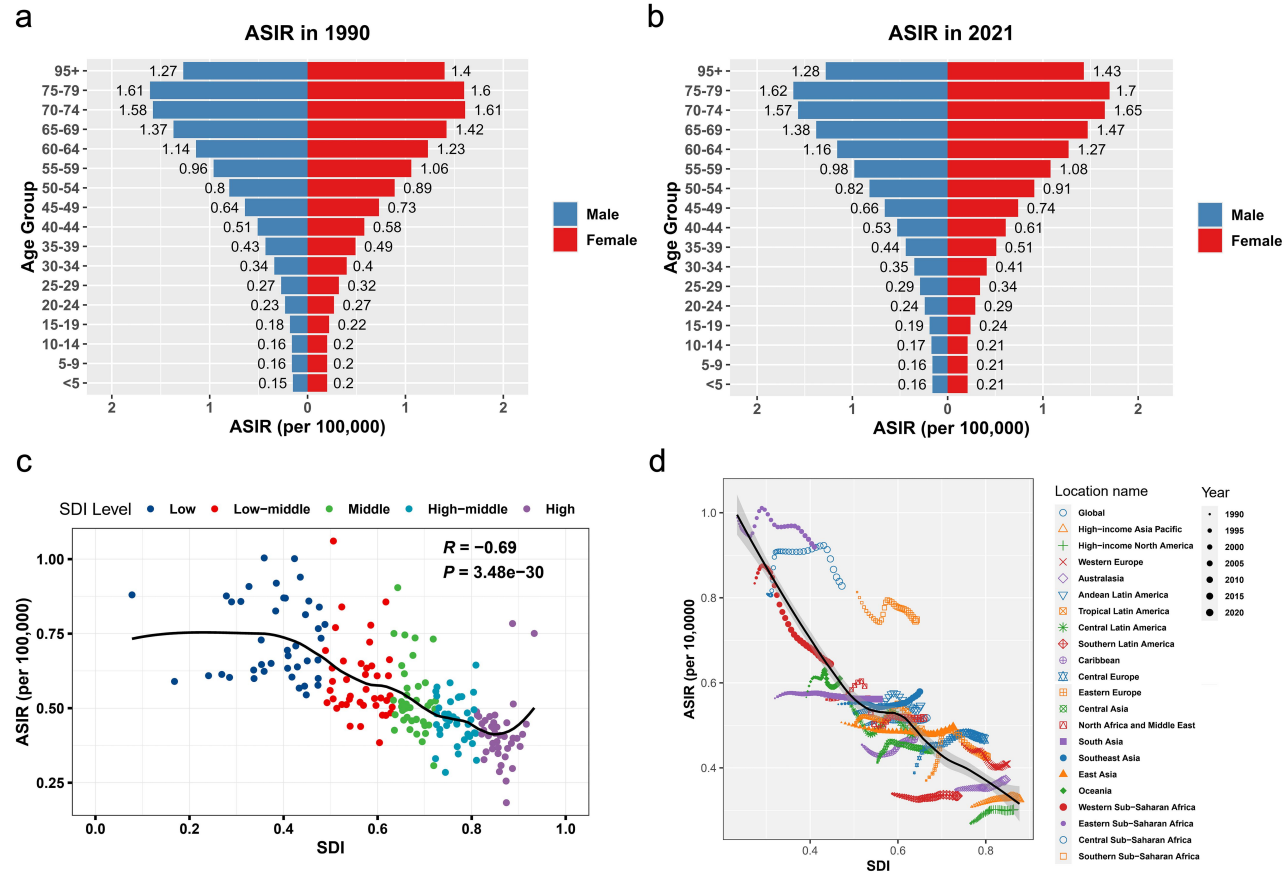

Fig. 3. Global trends and sociodemographic associations of PAH incidence. (a) ASIR of PAH by sex and age group in 1990. (b) ASIR of PAH by sex and age group in 2021. (c) Global correlation between PAH ASIR and SDI across 204 countries and territories, 2021. (d) Regional correlation between PAH ASIR and SDI across 21 GBD regions, 1990–2021. ASIR, age-standardized incidence rate; GBD, Global Burden of Disease; PAH, pulmonary arterial hypertension; SDI, Socio-demographic Index.

$R = -0.69$, $P = 3.48 \times 10^{-30}$; Fig. 3c), indicating that higher SDI was associated with lower PAH incidence. This inverse correlation was even stronger in 1990 ($R = -0.73$, $P = 1.94 \times 10^{-35}$; Supplementary Fig. 1), suggesting that although the influence of SDI on PAH burden modestly attenuated between 1990 and 2021, it remained substantial.

Regional analysis across 21 GBD regions from 1990 to 2021 revealed a nonlinear, inverse sigmoidal relationship between SDI and PAH ASIR. The association showed gradual decreases in ASIR with increasing SDI in the 0.5–0.6 range, with steeper

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declines observed at SDI levels below 0.5 or above 0.6 (Fig. 3d).

Clinical evidence for hemolysis in PAH and global burden assessment

Abnormal hemolysis-related biomarkers from clinical studies indicated that hemolysis is a characteristic pathophysiological process in PAH. Direct hemolytic indicators (including cell-free hemoglobin,[18-21] indirect bilirubin,[22-24] and lactate dehydrogenase[22,25-33]) released from erythrocyte rupture were consistently elevated in PAH patients (Table 1).[34] Haptoglobin, the endogenous scavenger of free hemoglobin, decreases in concentration as free hemoglobin levels rise during hemolysis. Multiple studies have reported significantly reduced haptoglobin levels in PAH,[22,25,35] further indicating hemolysis (Table 1). These data demonstrate that hemolysis is a pervasive feature of PAH. Given that hemolysis is a well-established etiology of PAH, particularly as a common complication in hereditary and acquired hemolytic disorders,[4,5] hemolytic diseases likely contribute significantly to the PAH disease burden.[13]

Analysis using GBD 2021 data revealed a strong association between the prevalence of hemolytic disorders and the incidence of PAH. The ASPR of hemoglobinopathies and hemolytic anemias showed a significant positive correlation ($R = 0.61$, $P = 7.70 \times 10^{-22}$) with the ASIR of PAH across 204 countries and territories in 2021 (Supplementary Fig. 2). This finding supports the hypothesis that hemolytic diseases drive the escalation in the global PAH burden. PAH and hemoglobinopathies/hemolytic anemias also exhibited similar geographic distributions. Analysis of the 2021 GBD data identified Africa as the continent with the highest PAH ASIR globally. The top four subregions for PAH ASIR were Eastern Africa, Middle Africa, Southern Africa, and Western Africa (Fig. 4a). Hemoglobinopathies and hemolytic anemias also demonstrated their highest ASPR predominantly within Africa in 2021 (Fig. 4b). These same four African subregions also exhibited very high ASPRs for these hemolytic disorders. This geographic concordance further strengthens the evidence linking hemolytic diseases to an elevated PAH burden. The high PAH burden in African nations therefore warrants particular attention, especially regarding the contribution of hemolytic diseases.

Contribution of hemolysis-associated disorder subtypes to PAH burden

The GBD database incorporates diverse subtypes of hemoglobinopathies and hemolytic anemias, including G6PD deficiency, G6PD trait, sickle cell disorders, sickle cell trait, thalassemias, thalassemia trait, and other hemoglobinopathies and hemolytic anemias of unknown etiology. Analysis of the correlation between ASPRs of these subtypes and the ASIR of PAH across 204 countries and territories in 2021 revealed robust positive correlations between PAH ASIR and ASPRs of G6PD deficiency ($R = 0.55$, $P = 9.57 \times 10^{-18}$), G6PD trait ($R = 0.66$, $P = 2.04 \times 10^{-26}$), sickle cell disorders ($R = 0.26$, $P = 1.59 \times 10^{-4}$), sickle cell trait ($R = 0.35$, $P = 2.95 \times 10^{-7}$), and other hemoglobinopathies and hemolytic anemias of unknown etiology ($R = 0.61$, $P = 1.58 \times 10^{-22}$) (Fig. 5a–e). Thalassemia-related disorders showed no significant correlation with PAH ASIR ($P > 0.05$; Supplementary Fig. 3).

Aside from primary hemolytic disorders, hemolysis-related infections and malnutrition also demonstrated significant associations with PAH burden. PAH ASIR increased substantially with rising prevalence of AIDS ($R = 0.49$, $P = 5.61 \times 10^{-14}$), schistosomiasis ($R = 0.54$, $P = 5.63 \times 10^{-17}$), and vitamin A deficiency ($R = 0.59$, $P = 3.97 \times 10^{-20}$) across the 204 countries and territories in 2021 (Fig. 5f–h), indicating that these conditions also contribute meaningfully to national PAH burden.

To quantify the relative importance of these factors, we employed random forest regression analysis incorporating hemoglobinopathy/hemolytic anemia subtypes, hemolysis-related infections and malnutrition, and demographic indicators (including SDI and sex) as predictors of global PAH ASIR burden across 204 countries and territories in 2021. The final model incorporated the following variables: G6PD trait, other hemoglobinopathies and hemolytic anemias of unknown etiology, vitamin A deficiency, AIDS, SDI, schistosomiasis, G6PD deficiency, and sickle cell trait. This model demonstrated good explanatory power ($R^2 = 0.73$, $P = 0.01$), accounting for approximately 73% of the variability in PAH ASIR burden. The ASPRs of G6PD trait (%IncMSE: 18.43), other hemoglobinopathies and hemolytic anemias of unknown etiology (%IncMSE: 18.38), and vitamin A deficiency (%IncMSE: 17.27) emerged as the top three contributors to PAH ASIR ($P < 0.01$; Fig. 5i; Supplementary Table 2). These exceeded the impact of both SDI (%IncMSE: 13.25) and the proportion of females (%IncMSE: 1.25) on PAH burden. These findings indicate that hemolysis-associated disorders substantially contribute to the global burden of PAH, with G6PD trait, other hemoglobinopathies/hemolytic anemias of unknown etiology, and vitamin A deficiency exerting the greatest influence on PAH ASIR.

Impact of changes in hemoglobinopathies and hemolytic anemia prevalence on PAH burden, 2011–2021

Given the chronic nature of hemolysis-induced PAH development, we examined the relationship between changes in hemoglobinopathy/hemolytic anemia prevalence and PAH incidence over the decade from 2011 to 2021. During this period, PAH incident cases increased in 191 countries while decreasing in only 13, reflecting substantial global burden growth. The eight countries with the most pronounced increases in PAH incidence were China, India, Indonesia, Nigeria, Pakistan, the United States, Bangladesh, and Ethiopia (Fig. 6a). Parallel analysis of hemoglobinopathy and hemolytic anemia prevalence revealed increases in 161 countries and decreases in 43 between 2011 and 2021. The eight countries with the largest prevalence increases substantially overlapped with those showing the greatest PAH burden growth: India, Nigeria, China, the Democratic Republic of the Congo, the United States, Pakistan, Indonesia, and Bangladesh (Fig. 6b).

Correlation analysis across 204 countries and territories from 2011 to 2021 revealed a strong positive association between changes in PAH incidence and the prevalence of hemoglobinopathies and hemolytic anemias ($R = 0.76$, $P = 6.34 \times 10^{-39}$; Fig. 6c). This indicates that variations in the prevalence of hemoglobinopathies and hemolytic anemias significantly influenced PAH incidence during this period. Changes in the prevalence of specific hemoglobinopathy and hemolytic anemia subtypes from 2011 to 2021 also demonstrated significant

Table 2. Natural products, traditional remedies, and related exposure sources associated with hemolytic disorders

Natural product/Source	Active compound(s)	Mechanism of hemolysis	At-risk population	Geographic distribution
Fava beans[36] (*Vicia faba*)	Vicine, Convicine	Oxidative stress via glutathione depletion	G6PD deficiency (primarily males)	Mediterranean, Middle East, Africa, Asia
Henna[37-39] (*Lawsonia inermis*)	Lawsone (2-hydroxy-1,4-naphthoquinone)	Oxidative damage to RBC membrane	G6PD deficiency, infants	North Africa, Middle East, South Asia
Comfrey[8] (*Symphytum officinale*)	Pyrrolizidine alkaloids	Metabolic activation to pyrrole derivatives	General population (dose-dependent)	Europe, North America, traditional medicine use
Motherwort/Ragwort[40] (*Senecio* species)	Pyrrolizidine alkaloids	Direct membrane damage, metabolic toxicity	General population, livestock	Worldwide (contaminated grains/honey)
Senna[41] (*Cassia* species)	Anthraquinones	Oxidative stress and membrane instability	G6PD deficiency, chronic users	Worldwide (laxative use)
Naphthalene[42] (mothballs, traditional remedies)	Naphthalene	Oxidative hemolysis via methemoglobin formation	G6PD deficiency, infants	Worldwide (household/medicinal use)
Copper-containing preparations[43]	Copper salts	Direct oxidative damage to RBC	General population (dose-dependent)	Traditional Ayurvedic, Chinese medicine

G6PD, glucose-6-phosphate dehydrogenase; RBC, red blood cell.

associations with PAH incidence. These included G6PD deficiency ($R = 0.54$, $P = 1.21 \times 10^{-16}$), G6PD trait ($R = 0.70$, $P = 9.34 \times 10^{-32}$), sickle cell trait ($R = 0.54$, $P = 1.16 \times 10^{-16}$), and other hemoglobinopathies and hemolytic anemias of unknown etiology ($R = 0.43$, $P = 1.76 \times 10^{-10}$) (Fig. 6d–g).

These findings demonstrate that temporal changes in hemolytic disorder prevalence substantially influenced PAH burden dynamics during this critical decade.

Future burden projections: increasing PAH incidence linked to rising hemolytic disorders

The BAPC model was used to project the global disease burden of PAH and hemolytic disorders from 2022 to 2050. Our projections indicate a continued rise in the global ASIR of PAH. The ASIR for both sexes is projected to increase from 0.52 to 0.57 per 100,000 population. The ASIR for males is estimated to rise from 0.49 to 0.53 per 100,000, while the ASIR for females is anticipated to increase from 0.55 to 0.61 per 100,000 (Fig. 7a–c). The global ASPR of hemoglobinopathies and hemolytic anemias is also projected to increase. The ASPR for both sexes is expected to rise from 27,760.54 to 31,863.72 per 100,000 population. The ASPR for males is forecasted to increase from 17,577.99 to 20,836.33 per 100,000, while the ASPR for females is projected to increase from 37,812.16 to 42,011.27 per 100,000 (Fig. 7d–f).

Given the established contribution of hemoglobinopathies and hemolytic anemias to PAH incidence, their rising prevalence will continue to drive future PAH burden growth. The hemolytic disorder prevalence remains approximately twice as high in females as in males through 2050, suggesting that hemolytic disorders will contribute disproportionately to PAH burden in women. These findings highlight the importance of targeting hemolytic disorder prevention and management as a primary strategy for mitigating future global PAH burden.

Natural product exposures contributing to hemolytic disorders and PAH burden: a hypothesis-generating analysis

The substantial contribution of "other hemoglobinopathies and hemolytic anemias of unknown etiology" to global PAH burden identified in our analysis highlights important knowledge gaps regarding specific etiologic factors. While this category includes chemical exposures and drug-

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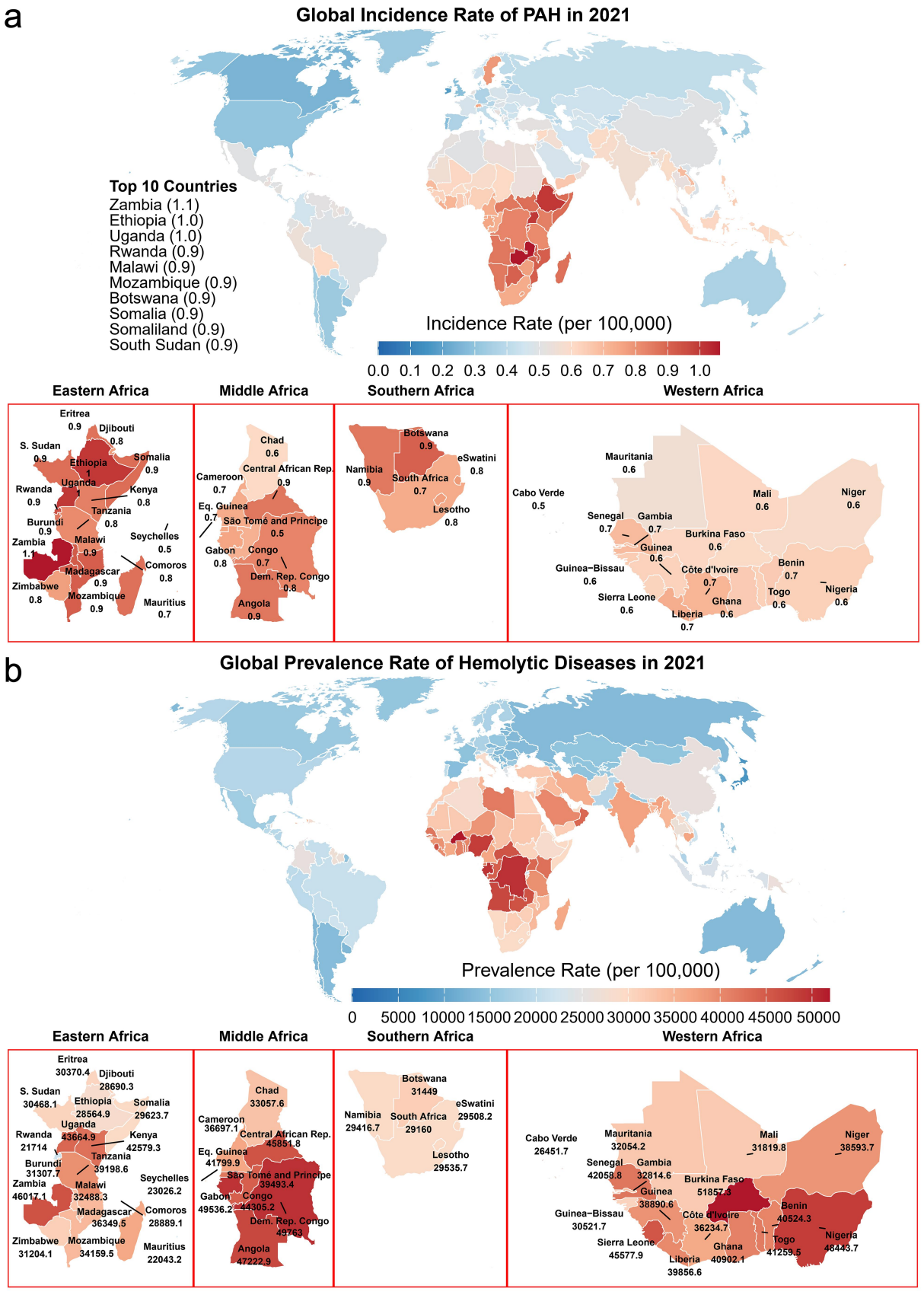
a
Global Incidence Rate of PAH in 2021
Top 10 Countries
Zambia (1.1)
Ethiopia (1.0)
Uganda (1.0)
Rwanda (0.9)
Malawi (0.9)
Mozambique (0.9)
Botswana (0.9)
Somalia (0.9)
Somaliland (0.9)
South Sudan (0.9)
Incidence Rate (per 100,000)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Eastern Africa
Middle Africa
Southern Africa
Western Africa
Eritrea 0.9
Djibouti 0.8
S. Sudan 0.9
Somalia 0.9
Ethiopia 1
Uganda 1
Rwanda 0.9
Kenya 0.8
Tanzania 0.8
Burundi 0.9
Seychelles 0.5
Zambia 1.1
Malawi 0.9
Comoros 0.8
Madagascar 0.9
Zimbabwe 0.8
Mozambique 0.9
Mauritius 0.7
Chad 0.6
Cameroon 0.7
Central African Rep. 0.9
Eq. Guinea 0.7
São Tomé and Principe 0.5
Gabon 0.8
Congo 0.7
Dem. Rep. Congo 0.8
Angola 0.9
Botswana 0.9
eSwatini 0.8
Namibia 0.9
South Africa 0.7
Lesotho 0.8
Mauritania 0.6
Cabo Verde 0.5
Mali 0.6
Niger 0.6
Senegal 0.7
Gambia 0.7
Burkina Faso 0.6
Guinea 0.6
Guinea−Bissau 0.6
Côte d'Ivoire 0.7
Benin 0.7
Sierra Leone 0.6
Ghana 0.6
Togo 0.6
Nigeria 0.6
Liberia 0.7
b
Global Prevalence Rate of Hemolytic Diseases in 2021
Prevalence Rate (per 100,000)
0 5000 10000 15000 20000 25000 30000 35000 40000 45000 50000
Eastern Africa
Middle Africa
Southern Africa
Western Africa
Eritrea 30370.4
Djibouti 28690.3
S. Sudan 30468.1
Ethiopia 28564.9
Somalia 29623.7
Uganda 43664.9
Rwanda 21714
Kenya 42579.3
Tanzania 39198.6
Burundi 31307.7
Seychelles 23026.2
Zambia 46017.1
Malawi 32488.3
Comoros 28889.1
Madagascar 36349.5
Zimbabwe 31204.1
Mozambique 34159.5
Mauritius 22043.2
Chad 33057.6
Cameroon 36697.1
Central African Rep. 45851.8
Eq. Guinea 41799.9
São Tomé and Principe 39493.4
Gabon 49536.2
Congo 44305.2
Dem. Rep. Congo 49763
Angola 47222.9
Botswana 31449
eSwatini 29508.2
Namibia 29416.7
South Africa 29160
Lesotho 29535.7
Mauritania 32054.2
Cabo Verde 26451.7
Mali 31819.8
Niger 38593.7
Senegal 42058.8
Gambia 32814.6
Burkina Faso 51857.3
Guinea 38890.6
Guinea−Bissau 30521.7
Côte d'Ivoire 36234.7
Benin 40524.3
Sierra Leone 45577.9
Ghana 40902.1
Togo 41259.5
Nigeria 48443.7
Liberia 39856.6

Fig. 4. The global burden of PAH and hemoglobinopathies/hemolytic anemias in 2021. (a) ASIR of PAH in 204 countries and territories. (b) Global distribution of ASPR of hemoglobinopathies and hemolytic anemias. ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; PAH, pulmonary arterial hypertension.

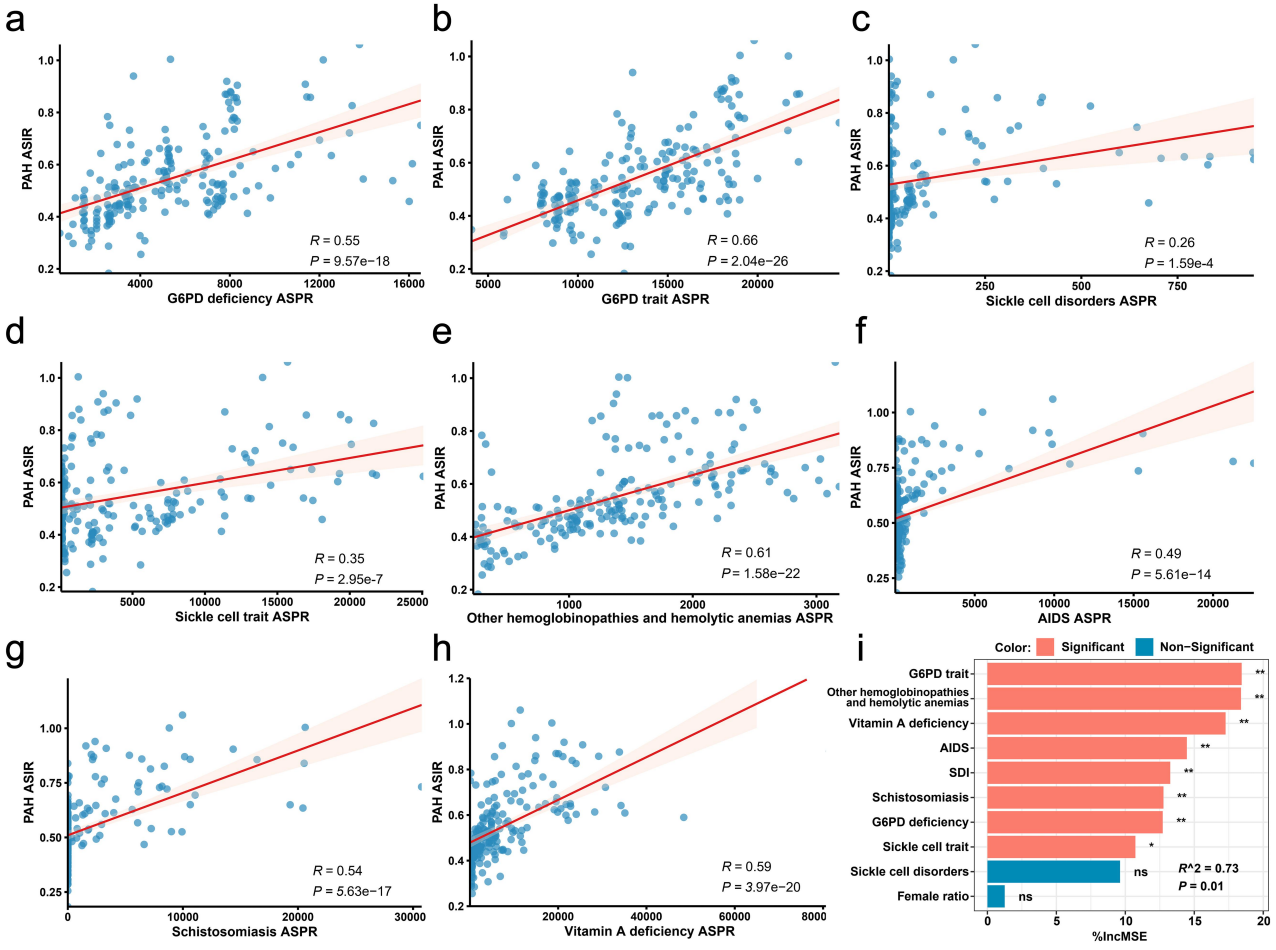

Fig. 5. The impact of hemolysis-associated disorder subtypes on PAH burden: Pearson correlation and random forest analyses. (a–e) ASPRs of hemoglobinopathies and hemolytic anemia subtypes significantly correlate with PAH ASIR: (a) G6PD deficiency, (b) G6PD trait, (c) sickle cell disorders, (d) sickle cell trait, and (e) other hemoglobinopathies and hemolytic anemias of unknown etiology. (f–h) PAH ASIR also significantly correlated with ASPRs of (f) AIDS, (g) schistosomiasis, and (h) vitamin A deficiency. (i) Random forest regression analysis of contributors to global PAH ASIR across 204 countries and territories in 2021. The importance of each contributor (hemoglobinopathy and hemolytic anemia subtypes, hemolysis-related diseases/malnutrition, sex, and SDI) was measured by the percentage increase in mean squared error (%IncMSE). A higher %IncMSE indicates greater variable importance. AIDS, acquired immunodeficiency syndrome; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; G6PD, glucose-6-phosphate dehydrogenase; PAH, pulmonary arterial hypertension; SDI, Socio-demographic Index; %IncMSE, percentage increase in mean squared error.

induced hemolysis, natural product exposures represent a significant yet underrecognized contributor to hemolytic disorders and subsequent PAH development. The following analysis is hypothesis-generating, drawing on geographic concordance observed in our data and mechanistic plausibility from published literature, rather than direct causal evidence from this ecological study. Direct measurement of specific exposure biomarkers in high-risk populations will be needed to establish causal links (Table 2).[36-43]

Pyrrolizidine alkaloids (PAs) from herbal medicines and contaminated foods

PAs found in traditional herbal medicines and food contaminants present a global health concern with direct relevance to PAH pathogenesis.[44,45] These compounds occur in over 6,000 plant species, including *Symphytum* (comfrey), *Tussilago* (coltsfoot), and *Senecio* species, which are widely used in traditional medicine systems across Africa, Asia, and South America.[46] PA exposure occurs through contaminated grains, honey, and herbal

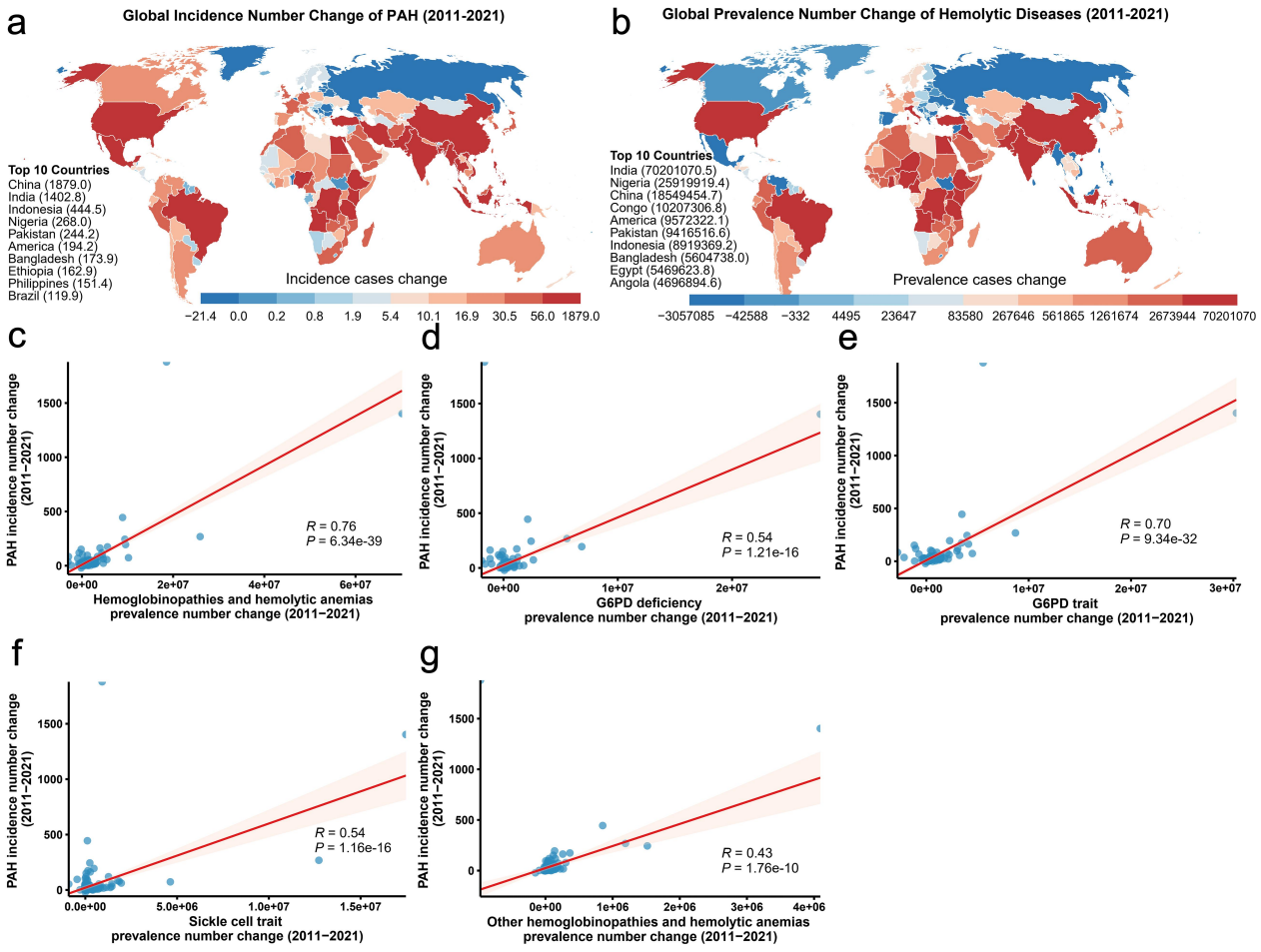

Fig. 6. Association between changes in PAH incidence and the prevalence of hemoglobinopathies/hemolytic anemias (2011–2021). (a) Change in PAH incidence from 2011 to 2021 across 204 countries and territories. (b) Global distribution of changes in the prevalence of hemoglobinopathies and hemolytic anemias (2011–2021). (c–g) Significant correlations between changes in PAH incidence cases (2011–2021) and changes in prevalence cases (2011–2021) of: (c) hemoglobinopathies and hemolytic anemias, (d) G6PD deficiency, (e) G6PD trait, (f) sickle cell trait, and (g) other hemoglobinopathies and hemolytic anemias of unknown etiology. G6PD, glucose-6-phosphate dehydrogenase; PAH, pulmonary arterial hypertension.

preparations, particularly in regions with high PAH burden identified in our global analysis.[8]

PAs induce hemolysis through multiple mechanisms. These compounds are metabolized to reactive pyrrole derivatives that bind covalently to red blood cell membranes, causing membrane instability and premature cell destruction.[47] The resulting hemolysis releases cell-free hemoglobin, which depletes nitric oxide and generates reactive oxygen species, directly contributing to the endothelial dysfunction characteristic of PAH development.[8] The geographic overlap between regions with documented high PA exposure and elevated PAH burden observed in our findings suggests this pathway may contribute to the unexplained hemolytic disorders driving global PAH incidence, although this hypothesis requires verification through direct biomarker studies, such as measurement of blood pyrrole–protein adducts or urinary PA metabolites in high-risk populations.

Natural oxidative stressors interacting with G6PD deficiency

Our analysis identified G6PD trait as the largest single contributor to global PAH burden (%IncMSE: 18.43). This finding gains additional significance when considering interactions between G6PD deficiency and natural oxidative stressors commonly encountered through traditional medicine use and dietary practices.

Individuals with G6PD deficiency have reduced capacity to regenerate glutathione, making their red blood cells particularly vulnerable to oxidative damage from natural compounds.[48] Common natural oxidative stressors include fava beans containing vicine and convicine, which can trigger severe hemolytic crises in G6PD-deficient individuals.[36] Other plant-derived compounds include quinones from henna, primaquine-like alkaloids from antimalarial plants, and phenolic compounds from various medicinal herbs that can induce hemolysis in susceptible populations.[49,50]

The widespread use of traditional medicines in regions with high G6PD deficiency prevalence, particularly across Africa and Mediterranean countries, creates a concerning intersection

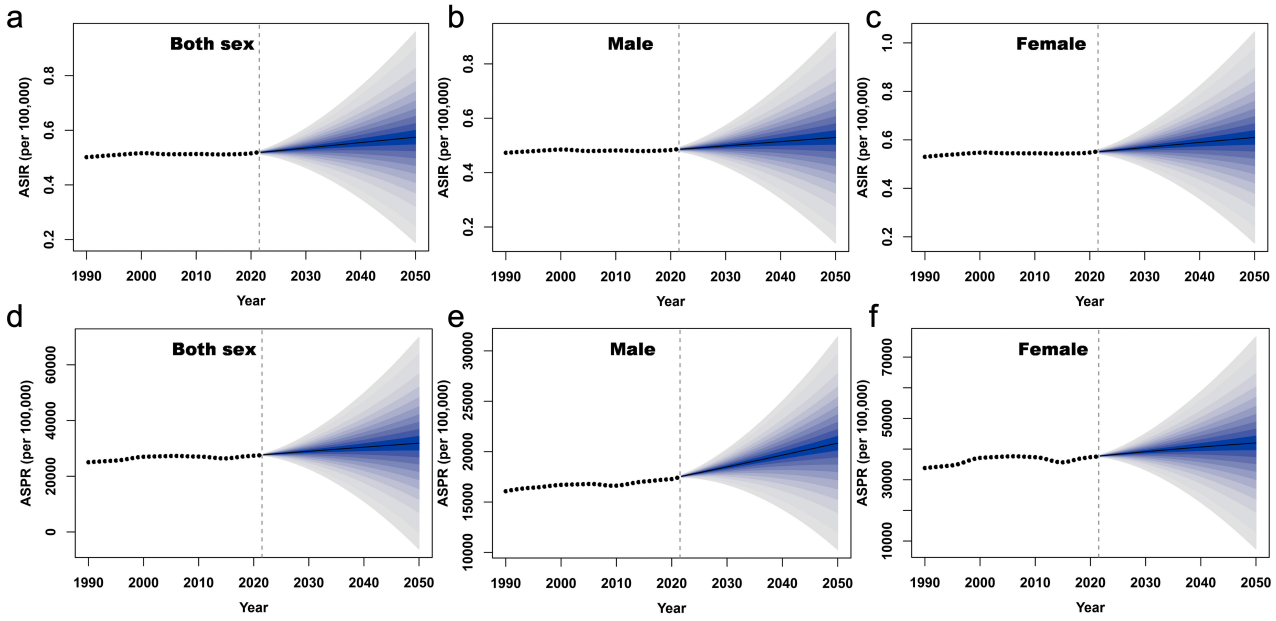

Fig. 7. BAPC model projections of global PAH ASIR and hemoglobinopathies/hemolytic anemias ASPR from 2022 to 2050. (a) PAH ASIR for both sexes is estimated to increase from 0.52 to 0.57 per 100,000 persons. (b) PAH ASIR for males is projected to increase from 0.49 to 0.53 per 100,000 persons. (c) PAH ASIR for females is anticipated to increase from 0.55 to 0.61 per 100,000 persons. (d) Hemolytic disease ASPR for both sexes is projected to increase from 27,760.54 to 31,863.72 per 100,000 persons. (e) Hemolytic disease ASPR for males is expected to increase from 17,577.99 to 20,836.33 per 100,000 persons. (f) Hemolytic disease ASPR for females is forecasted to increase from 37,812.16 to 42,011.27 per 100,000 persons. Black dots indicate observed GBD estimates from 1990 to 2021, the blue fan plots indicate posterior projections with uncertainty intervals, and the vertical dashed line indicates the start of the projection period. ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; BAPC, Bayesian age-period-cohort; GBD, Global Burden of Disease; PAH, pulmonary arterial hypertension.

between genetic susceptibility and environmental exposure. Analysis of the geographic distribution shows remarkable overlap between regions with high G6PD trait prevalence and elevated PAH burden in our 2021 data. This interaction between natural oxidative stressors and G6PD deficiency may partly explain the disproportionate PAH burden observed in these regions, where traditional medicine practices involving oxidative plant compounds could trigger repeated hemolytic episodes leading to chronic hemolysis-induced PAH development. However, this remains a hypothesis that warrants investigation through prospective studies quantifying specific natural product exposures in G6PD-deficient populations with and without PAH.

Hemolytic herbal remedies

Several traditional herbal remedies directly cause hemolysis and warrant specific attention in PAH prevention strategies. Henna (*Lawsonia inermis*), widely used for cosmetic and medicinal purposes across Africa, Asia, and the Middle East, contains lawsone, a naphthoquinone derivative that induces hemolysis, particularly in G6PD-deficient individuals. Clinical case reports have documented severe hemolytic anemia following henna application, including life-threatening hemolysis in G6PD-deficient children and oxidative hemolysis with neonatal hyperbilirubinemia in G6PD-deficient infants.[37,38] These clinical observations confirm that henna exposure can trigger acute hemolytic episodes in susceptible individuals.

Other hemolytic herbal remedies include *Cassia* species used as laxatives, which contain anthraquinones that can cause red blood cell damage, and various traditional preparations containing copper or lead compounds that directly induce hemolysis.[51,52] The widespread use of these remedies in regions with high PAH burden suggests they may contribute to the "other hemoglobinopathies and hemolytic anemias of unknown etiology" category that emerged as the second-largest contributor to PAH burden in our random forest analysis (%IncMSE: 18.38).

Geographic concordance of herbal medicine use and PAH burden

The geographic patterns observed in our analysis support the hypothesis that natural product exposures contribute to regional variations in PAH burden. African regions showing the highest PAH incidence (Eastern, Middle, Southern, and Western Africa) correspond to areas with extensive traditional medicine use and high prevalence of both G6PD deficiency and exposure to PA–containing plants. Similarly, countries showing rapid increases in PAH burden between 2011 and 2021 (India, Nigeria, China, Pakistan, and Bangladesh) are regions where traditional herbal medicine use remains common and regulatory oversight of herbal products may be limited.

Recognition of these natural product exposures is essential for developing comprehensive PAH prevention strategies. Healthcare systems in high-burden regions should consider implementing education programs about hemolytic risks associated with traditional medicines, particularly for individuals with G6PD

deficiency. Screening for natural product exposures should be considered in the evaluation of patients with unexplained hemolytic anemia or PAH development.

These findings suggest that a portion of the global PAH burden attributed to hemolytic disorders may be preventable through targeted interventions addressing natural product exposures. This represents a potentially cost-effective approach to PAH prevention, particularly relevant for resource-limited settings where traditional medicine use is prevalent and PAH incidence continues to rise. Future studies should directly measure exposure biomarkers to quantify the contribution of natural product exposures to the hemolytic PAH burden.

Discussion

This study provides evidence supporting a fundamental reorientation in how the global PAH burden is understood and addressed. Our findings indicate that a substantial portion of PAH can be viewed as a vascular complication of underlying hemolytic disorders rather than as an isolated cardiovascular disease driven primarily by demographic factors. This perspective implies that prevention of modifiable hemolytic risk factors should be prioritized as a strategy of equal importance to treating established PAH. Specifically, PAH incidence has risen over the past three decades and accelerated markedly in recent years (2019–2021; APC = 0.45), and projections indicate this upward trajectory will persist through 2050. While previous research has predominantly examined the influence of demographic factors such as age, sex, and SDI on PAH burden, the contribution of hemolytic disorders has remained systematically overlooked despite their established association with PAH development.[4,5] Our analysis demonstrates that hemolysis-associated disorders constitute a major driver of global PAH burden and that these conditions not only contribute substantially to current PAH incidence but are projected to exacerbate this burden through 2050 as their prevalence continues to rise. These results underscore the importance of integrating hemolytic disorder prevention and management into PAH mitigation strategies, particularly in high-prevalence regions such as Africa and rapidly growing countries including India, Nigeria, China, the Democratic Republic of the Congo, the United States, Pakistan, Indonesia, and Bangladesh.

The accelerated growth of global PAH ASIR after 2019 warrants specific discussion. Several factors may contribute to this acceleration. The COVID-19 pandemic and SARS-CoV-2 infection have been associated with pulmonary vascular injury, endothelial dysfunction, and microangiopathy,[53] which could directly contribute to PAH development. SARS-CoV-2 has also been reported to induce hemolysis in some patients, potentially amplifying hemolysis-driven PAH pathways.[54] Improved diagnostic awareness and advances in echocardiographic and catheterization-based screening may also have contributed to increased case detection during this period. In addition, rising prevalence of underlying risk factors, including hemolytic disorders, may have cumulatively driven the observed acceleration. However, the relative contribution of each factor remains to be determined, and the possibility that GBD modeling effects partly account for the observed trend cannot be excluded. Future studies should specifically investigate the impact of the COVID-19 pandemic on PAH epidemiology.

The mechanistic basis linking hemolysis to PAH pathogenesis is well supported by experimental and clinical evidence. Hemolysis-derived cell-free hemoglobin depletes vascular nitric oxide and generates reactive oxygen species, directly causing endothelial dysfunction.[8,55] This endothelial dysfunction, in turn, drives the vasoconstriction, vascular remodeling, and in situ thrombosis characteristic of PAH pathogenesis.[8,56] These downstream processes are shared with other recognized PAH pathogenic mechanisms. While bone morphogenetic protein receptor type 2 (BMPR2) mutations represent a distinct genetic pathway, hemolysis and BMPR2 dysfunction converge on shared downstream endothelial pathology, including impaired endothelial cell survival, dysregulated proliferation, and vascular remodeling.[8,57] Clinical studies have consistently reported elevated hemolytic biomarkers in PAH patients, including cell-free hemoglobin, indirect bilirubin, and lactate dehydrogenase across multiple studies, providing evidence that hemolysis is a pervasive feature of PAH.[18-33] These findings establish a biological foundation for the epidemiological associations observed in our global burden analysis and highlight the need for greater recognition of hemolytic disorders in PAH pathogenesis.

The random forest regression analysis yielded several striking insights. Most notably, G6PD trait emerged as the single largest contributor to PAH burden (%IncMSE: 18.43), substantially exceeding the impact of the more widely recognized sickle cell trait (%IncMSE: 10.73). G6PD, the rate-limiting enzyme in glutathione regeneration, is essential for protecting erythrocytes against oxidative stress.[58] Its dysfunction directly causes hemolysis and consequently increases the risk of PAH.[59] However, G6PD deficiency-related PAH remains even more overlooked than sickle cell disease–induced PAH. To date, only Kurdyukov *et al*.[60] have clinically reported reduced G6PD activity in 5 of 22 PAH patients. The 2021 ASPR for G6PD trait was 14,178.15 per 100,000 population, markedly higher than the ASPR for sickle cell trait (5,332.29 per 100,000) or sickle cell disorders (108.54 per 100,000). Given that the G6PD trait represents the hemolytic disorder subtype contributing most substantially to PAH burden, coupled with its high prevalence, we propose that G6PD deficiency-related PAH warrants significantly greater attention. Future efforts should specifically prioritize mitigating the PAH burden attributable to G6PD deficiency. We therefore advocate implementing routine G6PD activity screening in regions with high PAH incidence. This targeted strategy holds significant potential for reducing PAH risk associated with G6PD deficiency. We further note that the other hemoglobinopathies/hemolytic anemias subtype is the second-largest contributor to PAH ASIR among hemolytic disorders (%IncMSE: 18.38). The specific etiologies underlying this category remain poorly defined, potentially including chemical exposures or drug-induced hemolysis.[61,62] Given its substantial contribution to PAH ASIR and undefined etiology, future research should prioritize stratifying this heterogeneous group by underlying cause. Such stratification is essential to identify novel, significant drivers of PAH burden, paving the way for targeted prevention and management strategies.

Prior studies have established that AIDS can induce autoimmune hemolysis and has been implicated as a potential leading cause of PAH.[13] Similarly, schistosomiasis has been

demonstrated to cause hemolysis and is likewise suspected as a common etiological factor for PAH.[13] Vitamin A, an antioxidant that mitigates oxidative stress, protects red blood cell membranes and reduces hemolysis.[63] However, vitamin A deficiency compromises this protective effect, rendering red blood cells vulnerable to oxidative damage and consequently triggering hemolysis. This pathophysiological relationship is corroborated by clinical evidence linking vitamin A deficiency to exacerbated hemolysis.[64] Given their established roles in hemolysis and suspected contributions to PAH pathogenesis, we included AIDS, schistosomiasis, and vitamin A deficiency in our analysis. Our findings reveal that elevated ASPR for these conditions correlates with increased PAH ASIR. Random forest regression analysis confirmed their substantial contributions to PAH burden: AIDS (%IncMSE: 14.46), schistosomiasis (%IncMSE: 12.76), and vitamin A deficiency (%IncMSE: 17.27).

These findings reframe PAH prevention strategies by identifying a substantial portion of the disease burden as potentially preventable through targeted management of underlying hemolytic conditions. Implementing comprehensive interventions against hemolysis-associated disorders, including routine G6PD screening, improved management of hemoglobinopathies, and addressing nutritional deficiencies, represents a critical and novel approach to reducing global PAH burden. This imperative is particularly urgent in high-prevalence regions and countries experiencing rapid case growth, where such interventions could yield the greatest public health impact.

Although the contribution of natural product exposures to PAH burden remains hypothesis-generating and requires confirmation through direct biomarker studies, our findings suggest that future public health interventions should address these exposures. This includes regulating herbal medicines containing PAs, educating communities about hemolytic risks associated with traditional remedies, and implementing comprehensive G6PD screening programs that include counseling about oxidative plant exposures. These targeted interventions represent practical, cost-effective approaches to reducing PAH burden, particularly in resource-limited settings where traditional medicine use is common and PAH incidence is highest.

The practical implementation of these strategies faces important challenges that must be acknowledged. The cost-effectiveness of widespread G6PD screening in high-burden, resource-limited settings requires careful evaluation, although point-of-care G6PD tests with decreasing costs may improve feasibility. Regulation of herbal medicines poses particular complexity given the deep cultural significance of traditional medicine practices in many high-burden regions. Effective regulation will require culturally sensitive approaches that engage traditional healers and community leaders rather than simply restricting access. Health education programs about hemolytic risks must be designed to be culturally appropriate, linguistically accessible, and delivered through trusted community channels. Despite these challenges, the high PAH burden in affected regions and the modifiable nature of many hemolytic risk factors suggest that even partial implementation of these strategies could yield meaningful public health benefits.

Limitations

Several limitations of this study should be acknowledged. First, this is an ecological study using aggregated population-level data, and the associations observed at the national level cannot be directly inferred as individual-level causal relationships. The ecological design precludes adjustment for individual-level confounders, including comorbidities such as chronic obstructive pulmonary disease, coronary heart disease, and connective tissue diseases that commonly coexist with PAH. Individual-level cohort studies and clinical trials are needed to confirm the causal relationships suggested by our ecological analysis. Second, our analysis was constrained by the spectrum of hemolytic disorders available in the GBD database, which may underestimate the full contribution of hemolysis to PAH burden. Conditions such as hereditary spherocytosis, autoimmune hemolytic anemia, and drug- or chemical-induced hemolysis are not separately quantified in the GBD framework and could not be individually assessed.[62,65,66] Third, the GBD estimates themselves are modeled from heterogeneous data sources of varying quality across countries, and the accuracy of these estimates may differ between high-income countries with robust disease registries and low-income countries with limited surveillance infrastructure. This differential data quality could influence the observed associations, particularly in African regions where PAH burden is highest. Fourth, our temporal analysis focused on a decade-long window to assess the impact of changes in hemolytic disorder prevalence on PAH incidence. The chronic nature of hemolysis-induced PAH development means that the optimal lag period between hemolytic exposure and PAH manifestation remains uncertain, and future research could explore varying timeframes to better characterize this progression. Fifth, the natural product exposure analysis is hypothesis-generating and based on geographic concordance and mechanistic plausibility rather than direct exposure assessment. Future studies should directly measure specific natural product biomarkers (such as blood levels of PA metabolites or pyrrole-protein adducts) in high-risk populations to provide more direct evidence linking exposure to outcome. Sixth, the random forest model, while explaining 73% of PAH ASIR variance, leaves 27% unexplained, suggesting that additional unmeasured factors contribute to PAH burden.

Conclusions

This ecological study of 204 countries and territories identified hemolysis-associated disorders as major drivers of the escalating global PAH burden. G6PD trait, other hemoglobinopathies/hemolytic anemias of unknown etiology, and vitamin A deficiency were the predominant contributors to PAH incidence, exceeding the impact of SDI and sex. Furthermore, given the projected continued rise in hemolytic disorder prevalence through 2050, these conditions are expected to persistently exacerbate the global PAH burden. These findings highlight hemolytic disorders as a critical, underrecognized driver of PAH that requires prioritized attention in global health policy.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/FIM.2026.00004.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization (CZ, YH), investigation (CZ, TH, XG), resources (CZ, TH, XG, XC), original draft preparation (CZ), visualization (CZ, TH), writing - review and editing (XC, YH), and supervision (YH). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study used publicly available, aggregated, and de-identified data from the Global Burden of Disease 2021 database. No individual-level human or animal data were used. Therefore, ethics approval and informed consent were not required.

Data sharing statement

All Global Burden of Disease (GBD) data used in this study were obtained from the GBD Results Tool (https://vizhub.healthdata.org/gbd-results/).

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