Original Article

Pulmonary hypertension associated mortality in the United States from 2003 to 2020: an observational analysis of time trends and disparities

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Background: Pulmonary hypertension (PH) is an independent risk factor for morbidity and mortality. In the last two decades, significant advances have been made in management of World Health Organization (WHO) group 1 PH. However, there are no approved targeted pharmacotherapies for PH secondary to left-sided heart diseases or chronic hypoxic lung diseases which are thought to account for more than 70–80% of the disease burden. No recent investigation has analyzed and compared the mortality burden related to WHO group 1 PH with the mortality burden with WHO groups 2–5 PH at the national level in the United States (US). We hypothesize that WHO group 1 PH-related mortality has improved over the last two decades in comparison to WHO groups 2–5 PH.

Methods: In this study, we used data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) the underlying cause of death database to study age-standardized mortality rates related to PH in the US from 2003 to 2020.

Results: A total of 126,526 deaths were recorded from PH in the US between 2003 and 2020. Across the study period, PH-related ASMR increased from 17.81 per million population in 2003 to 23.89 in 2020 with a percentage change (PC) of +34%. However, there are contrasting mortality trends in WHO group 1 PH when compared to WHO groups 2–5 PH. Data demonstrated a decline in mortality from group 1 PH regardless of gender. In contrast, an increase in mortality from WHO groups 2–5 PH was observed, accounting for the major proportion of the overall PH mortality burden in recent years.

Conclusions: PH-related mortality continues to an increase primarily due to increase in mortality attributed to WHO groups 2–5 PH. These findings have notable public health implications. Screening and risk assessment tools for secondary PH, risk factor modification, and novel management strategies are vital to improve outcomes.

Keywords: Pulmonary hypertension (PH); mortality; United States (US)

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Submitted Oct 18, 2022. Accepted for publication May 12, 2023. Published online Jun 13, 2023.
doi: 10.21037/jtd-22-1468
View this article at: https://dx.doi.org/10.21037/jtd-22-1468

Introduction

Pulmonary hypertension (PH) is a syndrome characterized by elevated pressures in the pulmonary vasculature. Regardless of the underlying pathology, PH is an independent risk factor for morbidity, and mortality (1-4). The World Health Organization (WHO) subdivides PH into five groups based on the underlying etiology (5) (*Table 1*).

More than forty different etiologies are associated with PH; however, clinicians, researchers and the pharmaceutical industry have focused mainly on WHO group 1 PH, a relatively less common group. In the last two decades, significant advances in pharmacotherapy have been made in the management of WHO group 1 PH. Some studies have shown the benefits of pulmonary artery hypertension (PAH) specific pharmacotherapy in interstitial lung disease-related PH (6) and chronic thromboembolic PH (7). However, despite multiple studies exploring the role of targeted pharmacotherapy in PH secondary to left-sided heart diseases or chronic hypoxic lung diseases, there are no approved pharmacotherapies with the mortality benefits. The amplitude of this disparity in advances in treatment gap becomes more significant when we consider the much higher prevalence of WHO groups 2–5 PH. Recent studies have demonstrated an emerging epidemic of diseases associated with PH which is likely to have significant population health and economic implications (2-5). Wijeratne and colleagues reported a substantial increase in the incidence and prevalence of PH and accompanying low 5-year survival (37%) in Ontario, Canada (1). Studies from Australia, the Netherlands, and the United Kingdom demonstrated similar trends and low 5-year survival, ranging from 23-35% (2-4). In the United States (US), studies reported a reversal of the decline in PH-related mortality in males and continuous worsening in females in the first decade of the millennium (8,9). No recent investigation has analyzed and compared PH-associated mortality burden from WHO group 1 PH with WHO groups 2–5 PH. We hypothesize that WHO group 1 PH-associated mortality has improved over the last two decades in comparison to WHO groups 2–5. It is important to understand the current trends to help drive further care planning, resource allocation, and policy making.

The first objective of the present study is to evaluate PH-related mortality rates and trends from 2003 to 2020 in the US. The second objective is to compare the mortality burden from WHO group 1 PH with WHO groups 2–5 PH. The final objective is to explore any disparities by sex, race, age groups, and urbanization status. For this analysis we utilized data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1468/rc).

Highlight box

Key findings

- Our study reports an increase in PH-related mortality in the United States from 2003 to 2020.
- The rising PH-related mortality is primarily driven by WHO groups 2 and 3.
- Females died more often from PH when compared with males over study period.
- Among all races, the highest PH mortality burden was observed in African American population.

What is known and what is new?

- There has been a steady decline in WHO group 1 PH mortality, which corresponds to the progress of PAH-specific pharmacotherapies and the establishment of specialized PH centers.
- But there is limited literature reporting overall mortality burden and temporal trends related to WHO groups 2–5 PH. Present study compared PH mortality burden from WHO group 1 PH with WHO groups 2–5 PH.

What is the implication, and what should change now?

- The higher burden and worsening trends in mortality from WHO groups 2 and 3 PH underscores the growing need to shift our attention towards non-PAH PH.
- The racial disparity in mortality from PH needs to be explored.

Methods

Study design and data source

This is a retrospective study exploring PH-related mortality from 2003 through 2020 utilizing CDC WONDER

Table 1 WHO clinical classification of PH (groups 1–5) by the sixth world symposium on PH

PAH
Idiopathic PAH
Heritable PAH
Drug- and toxin-induced PAH
PAH-associated with:
Connective tissue disease
Human immunodeficiency virus infection
Portal hypertension
Congenital heart disease
Schistosomiasis
PAH long-term responders to calcium channel blockers
PAH with overt features of venous/capillaries (PVOD/PCH) involvement
Persistent PH of the newborn syndrome
PH due to left heart disease
PH due to heart failure with preserved left ventricular ejection fraction
PH due to heart failure with reduced left ventricular ejection fraction
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to post-capillary PH
PH due to lung diseases and/or hypoxia
Obstructive lung disease
Restrictive lung disease
Other lung disease with mixed restrictive/obstructive pattern
Hypoxia without lung disease
Developmental lung disorders
PH due to pulmonary artery obstructions
Chronic thromboembolic PH
Other pulmonary artery obstructions
PH with unclear and/or multifactorial mechanisms
Haematological disorders: chronic hemolytic anemia, extramedullary hematopoiesis
Systemic and metabolic disorders: sarcoidosis, glycogen storage disease, and PLCH
Others: fibrosing mediastinitis
Complex congenital heart disease

WHO, World Health Organization; PH, pulmonary hypertension; PAH, pulmonary artery hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hypertension; PLCH, pulmonary Langerhans cell histiocytosis.

underlying cause of death (UCOD) datafiles, an online health information system built and maintained by the National Center for Health Statistics (NCHS), a subdivision of the CDC (https://wonder.cdc.gov/Deaths-by-Underlying-Cause.html). NCHS compiles the mortality database from death certificates of the US decedents. The information from all death certificates filed is collected by state registries and provided to the NCHS through the National Vital Statistics System. Details of data inputs, processing, and translation into UCOD files have been reported in detail before (10,11). The UCOD is defined by the WHO as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." When more than one diagnosis is documented in the death certificate, UCOD is determined by the sequence of conditions on the certificate and provisions of the International Classification of Diseases-10 (ICD-10) codes. Up to 20 contributing causes of death can be reported in addition to UCOD which all together constitutes multiple cause of death (MCOD) datafiles. We have performed similar studies previously to assess mortality trends attributed to lung cancer (12) and cardiovascular disease (13).

Study definitions, variables, and statistical analysis

PH-related deaths were defined as those where the deceased's death certificate had ICD-10 code I27 reported as the primary underlying cause of death. Mortality rates were stratified by sex, race, urbanization status, age groups, and subtypes of PH [WHO group 1 PH (ICD-10 code: I27.0); and WHO groups 2–5 (ICD-10 codes: I27.2, I27.8, and I27.9)]. The resident populations from the US Census Bureau were used to calculate death rates per million population. The US standard population in 2000 was utilized to calculate age standardized mortality rates (ASMRs). The ASMR is an average of the age-specific mortality rates weighted to the distribution of mortality per 5-year age group according to the appropriate standard population. ASMR eliminates the effect of differences in age structures in populations and allows for more accurate comparisons. Urbanization status was classified by the 2013 NCHS Urban-Rural Classification Scheme for Counties (14). Counties with population >50,000 were categorized as urban and those with population less than 50,000 were categorized as rural.

The annual ASMRs from 2003 to 2020 were further analyzed using the joinpoint regression model to assess

the statistical significance of changes in mortality rates over time. Joinpoint (Command Line Version 4.5.0.1) is a statistical software developed by the US National Cancer Institute Surveillance Research Program (15). The software takes trend data and fits the simplest Joinpoint model that the data allows to analyze overall trends in mortality and tests for significant changes in the model with the sequential addition of joinpoints where there is a significant change in the slope of the line. The model computes average annual percentage changes (AAPCs) from the start to the end of the study period and estimates annual percentage changes (EAPCs) for each trend segment by fitting a regression line to the natural logarithm of ASMRs. The null hypothesis testing (Monte Carlo Permutation method) of EAPCs or AAPCs was performed to report the statistical significance of changes. Due to the lower number of annual deaths (<10 per annum) related to WHO group 1 PH in American Indian/Alaska Native and Asian/Pacific Islander races, data was suppressed by CDC to ensure confidentiality. Therefore, we were not able to report time trends for these variables.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All the data are covered by the statute of the Public Health Service Act [42 U.S.C. 242 m (d)] and an Institutional Review Board endorsement and patient consent were not necessary for this study because the deidentified data are publicly available in the CDC data repository.

Post hoc analysis

In response to the reviewers' comments and re-examining our primary analysis, we performed two post hoc analyses using CDC multiple cause of death data files investigating mortality related to WHO groups 2–5 PH. Firstly, we extracted ASMRs attributed to PH with comorbid conditions which cause group 2 PH (ICD-10 codes: I05-08, I11.0, I13, I20-25, I34-37, and I42). Second, we explored ASMRs attributed to PH with comorbid conditions which cause group 3 PH (ICD-10 codes: G47.3, J43, J44, J45, and J84). The comorbid conditions were not mutually exclusive for each analysis. Similar to the primary analysis, we performed the Joinpoint analysis to elucidate the statistical significance of the temporal trends.

Additionally, we calculated the median age of death along with 25% to 75% interquartile range (IQR) in both cohorts from 2003 to 2010, and 2011 to 2020 by sex, race, and urbanization status.

Results

A total of 126,526 deaths were recorded from PH in the US from 2003 through 2020. 83,147 (66%) deaths were observed in females and 43,379 (34%) deaths were observed in males. A total of 120,168 (95%) deaths were related to WHO groups 2–5 PH and 6,358 (5%) deaths were related to WHO group 1 PH. The average ASMR related to WHO group 1 PH was 1.04 per million population [95% confidence interval (CI): 1.01 to 1.06) and the average ASMR related to WHO groups 2–5 PH was 19.34 (95% CI: 19.23 to 19.45). In both WHO group 1 PH, and WHO groups 2–5 PH cohorts, a higher mortality burden was observed in females, African American race, and rural population. Rural-urban disparity gap was wider in group 1 PH in comparison to groups 2–5 cohort (group 1: rural, 1.22, 95% CI: 1.14 to 1.29; urban, 0.99, 95% CI: 0.97 to 1.02), and (groups 2–5: rural, 20.49, 95% CI: 20.21 to 2.77; urban, 19.11, 95% CI: 18.99 to 19.24) (*Table 2*). Highest PH-related deaths and crude mortality rates (CMRs) were observed in the 85+ age group population: PH group 1: deaths, 1,471; CMR, 14.36 per million population (95% CI: 13.63 to 15.09) and PH groups 2–5: deaths 37,279; CMR, 363.91 (95% CI: 360.22 to 367.61) (*Table 3*).

PH-related ASMR increased from 17.81 per million population (95% CI: 17.32 to 18.3) in 2003 to 23.89 (95% CI: 23.41 to 24.37) in 2020 [percentage change (PC), +34%]. In females, ASMR increased from 19.85 (95% CI: 19.17 to 20.53) to 27.19 (95% CI: 26.5 to 27.87); PC, +37%) and in males, ASMR increased from 15.27 (95% CI: 14.56 to 15.98) to 19.51 (95% CI: 18.85 to 20.18); PC +28%) (*Table 4*). Females had higher PH-attributed mortality in comparison to males (Table S1).

In WHO group 1 PH, there was a decline in group 1 PH mortality from 2.81 per million population (95% CI: 2.61 to 3) in 2003 to 0.67 (95% CI: 0.59 to 0.75) in 2020 (PC, –76%). Individually in males, ASMR decreased from 2.03 (95% CI: 1.78 to 2.29) to 0.42 (95% CI: 0.33 to 0.54); PC, –79%) and in females, from 3.5 (95% CI: 3.21 to 3.79) to 0.88 (95% CI: 0.76 to 1.01); PC, –75%) (*Table 4*). Mortality burden was higher in females in comparison to males throughout the study period (Table S1). WHO group 1 PH-related ASMRs decreased across both races (White: PC, –64%; African American: PC, –70%) and independent of urbanization status (urban: PC, –74%; rural: PC, –80%) (*Table 3*).

The overall PH mortality trends were driven by an

Table 2 PH-related average ASMRs per million population (UCOD) by demographic characteristics in the US, 2003–2020

Variables	PH WHO group 1			PH WHO groups 2–5		
	Deaths	Average ASMRs	95% CI	Deaths	Average ASMRs	95% CI
Overall	6,358	1.04	1.01–1.06	120,168	19.34	19.23–19.45
Gender						
Males	1,827	0.68	0.65–0.71	41,552	15.92	15.76–16.07
Females	4,531	1.32	1.28–1.36	78,616	21.84	21.69–22
Race						
White	5,324	1.02	0.99–1.04	98,144	18.36	18.25–18.48
Males	1,571	0.7	0.66–0.73	34,446	15.39	15.23–15.55
Females	3,753	1.29	1.25–1.34	63,698	20.51	20.35–20.68
African American	834	1.31	1.22–1.4	19,018	30.61	30.16–31.05
Males	200	0.79	0.67–0.9	6,001	23.41	22.77–24.04
Females	634	1.72	1.58–1.85	13,017	35.58	34.96–36.2
American Indian/Alaska Native	48	0.74	0.54–1.01	611	14.7	13.19–16.21
Males	10	1.16	0.81–1.61	214	9.79	8.32–11.26
Females	38	NA	NA–NA	397	14.7	13.19–16.21
Asian/Pacific Islander	152	0.54	0.45–0.63	2,395	9.4	9.01–9.78
Males	46	0.37	0.27–0.5	891	8.22	7.66–8.78
Females	106	0.66	0.53–0.79	1,504	10.27	9.75–10.8
Urbanization						
>50K	5,165	0.99	0.97–1.02	98,363	19.11	18.99–19.24
<50K	1,193	1.22	1.14–1.29	21,805	20.49	20.21–20.77

Data from underlying cause of death CDC WONDER data set, 2003–2020. Urbanization >50K: large to small metropolitans; <50K: non-metro. PH, pulmonary hypertension; ASMRs, age-standardized mortality rates; CI, confidence interval; UCOD, underlying cause of death; US, United States; WHO, World Health Organization; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.

increase in mortality from WHO groups 2–5 PH. WHO groups 2–5 PH-related ASMR including both sexes increased from 14.95 per million population (95% CI: 14.51 to 15.4) in 2003 to 23.2 (95% CI: 22.73 to 23.68) in 2020 (PC, +55%). Similar trends were seen independently in males [13.22 (95% CI: 12.56 to 13.8) to 19.09 (95% CI: 18.44 to 19.75); PC, + 44%] and females [16.34 (95% CI: 15.72 to 16.95) to 26.3 (95% CI: 25.62 to 26.97); PC, +61%] (*Table 3*). Similar to WHO group 1 PH, mortality burden from WHO groups 2–5 was higher in females compared to males throughout the study period (Table S1). WHO groups 2–5 PH-related ASMRs increased in all races (White: PC, 56%; African American: PC, 54%; American Indian/Alaska Native: PC, 52%; and Asian/Pacific Islander: PC, 44%). Similarly, ASMRs increased over the study period in the urban and rural area, however, a higher percentage change was observed in rural areas (urban PC, 40%; rural PC, 64%). Mortality rate from WHO groups 2–5 PH was 32 times higher than WHO group 1 PH in 2020 (*Table 4*).

Joinpoint mortality trends

Joinpoint analysis showed one trend indicating an increase in PH-associated mortality from 2003 to 2020 [EAPC, 2.3% (95% CI: 2% to 2.6%); P<0.001]. In males, there was an

Table 3 PH-related crude mortality rates per million population (UCOD) by age groups in the US, 2003–2020

Age groups	PH WHO group 1			PH WHO groups 2–5		
	Deaths	Average CMRs	95% CI	Deaths	Average CMRs	95% CI
<1 year	139	1.95	1.62–2.27	1,428	20.01	18.98–21.05
1–4 years	44	0.15	0.11–0.21	363	1.26	1.13–1.39
5–14 years	63	0.09	0.07–0.11	260	0.35	0.31–0.4
15–24 years	115	0.15	0.12–0.18	534	0.69	0.63–0.75
25–34 years	194	0.25	0.22–0.29	1,345	1.77	1.67–1.86
35–44 years	338	0.45	0.4–0.5	3,030	4.03	3.89–4.18
45–54 years	585	0.76	0.69–0.82	7,157	9.25	9.03–9.46
55–64 years	826	1.24	1.15–1.32	13,977	20.97	20.62–21.32
65–74 years	1,148	2.63	2.48–2.78	22,478	51.45	50.78–52.12
75–84 years	1,435	5.77	5.47–6.07	32,315	130.01	128.59–131.43
85+ years	1,471	14.36	13.63–15.09	37,279	363.91	360.22–367.61

Data from underlying cause of death CDC WONDER data set, 2003–2020. CI, confidence interval; CMRs, crude mortality rates; PH, pulmonary hypertension; UCOD, underlying cause of death; US, United States; WHO, World Health Organization; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.

initial non-significant decline from 2003 to 2005 [EAPC, –5.3% (95% CI: –14.4% to 4.8%); P=0.266], followed by a significant increase from 2005 through 2020 [EAPC, 2.7% (95% CI: 2.2% to 3.1%); P<0.001]. Overall, this represents a statistically significant increase from 2003 to 2020 [EAPC, 1.7% (95% CI: 0.6% to 2.9%); P=0.004]. In females, there was also a significant increase in mortality between 2003 and 2020, with one Joinpoint trend observed [EAPC, 2.3% (95% CI: 2.1% to 2.6%); P<0.001] (*Table 5*, *Figure 1*).

In WHO group 1 PH, joinpoint analyses including both males and females showed two trends. On combined analysis of both genders, there was a precipitous reduction in mortality from 2003 to 2005 [EAPC, –34.5% (95% CI: –50.8% to –12.8%); P<0.007], followed by a flattened although statistically significant decline from 2005 to 2020 [EAPC, –5.8 % (95% CI: –8.7% to –2.7%; P<0.001] (*Table 5*, *Figure 2*). For males, there was a single downward trend in mortality from 2003 to 2020 [EAPC, –2.5% (95% CI: –5.2% to –0.4%); P=0.085]. For females, there were two trends in mortality. There was an initial fast reduction in mortality between 2003 and 2005 [EAPC, –33.3% (95% CI: –45.7% to –18.2%); P<0.001]. This trend flattened but remained statistically significant from 2005 through 2020 [EAPC, –1.8% (95% CI: –2.8% to –1%); P<0.001]. This resulted in an overall decrease in EAPC from 2003 through 2020 [EAPC, –6.2% (95% CI: –8.3% to –4%); P<0.001] (*Table 5*, *Figure 3*). In the White and African American population, the ASMRs decreased [AAPC, –5.5% (95% CI: –8.7% to –2.2%); P<0.001 and AAPC, –6% (95% CI: –11.9% to 0.2%); P<0.056] respectively (*Table 5*, *Figure 4*). By urbanization status, ASMRs decreased in both urban and rural populations [AAPC, –5.3% (95% CI: –8.7% to –1.8%); P<0.001 and AAPC, –7.6% (95% CI: –10% to –5%); P<0.001] respectively. The urban-rural gap in mortality decreased from 2003 to 2020 (*Table 5*, *Figure 5*).

In WHO groups 2–5, only one trend was observed on Joinpoint including both sexes [EAPC, 2.7% (95% CI: 2.5% to 2.9%); P<0.001] (*Table 5*, *Figure 2*) and individually in males and females. EAPC in males increased from 2003 through 2020 by 2.5% (95% CI: 2.2% to 2.9%) (P<0.001). A similar trend was observed in females with an EAPC of 2.8% (95% CI: 2.6% to 3%) and P<0.001 (*Table 5*, *Figure 6*). In White, African American, and Asian/Pacific Islander ASMRs decreased [AAPC, 2.8% (95% CI: 2.6% to 3%); P<0.001, and AAPC, 2.5% (95% CI: 2.2% to 2.8%); P<0.001, and AAPC, 2.7% (95% CI: 1.7% to 3.7%); P<0.001] respectively. No joinpoint trend was observed in American Indian/Alaska Native (*Table 4*, *Figure 7*). By urbanization status, ASMRs increased in both urban and rural populations [AAPC, 2.6% (95% CI: 2.5% to 2.8%); P<0.001 and AAPC, 3.1% (95% CI: 2.8% to 3.5%); P<0.001] respectively. The urban-rural gap in mortality

Table 4 Changes in PH-related ASMRs per million population (UCOD) in the US, 2003–2020

Variables	Start (year 2003)		End (year 2020)		Absolute change	Percentage change
	ASMRs	95% CI	ASMRs	95% CI		
Overall PH	17.81	17.32–18.3	23.89	23.41–24.37	6.08	34
Males	15.27	14.56–15.98	19.51	18.85–20.18	4.24	28
Females	19.85	19.17–20.53	27.19	26.5–27.87	7.34	37
PH WHO group 1	2.81	2.61–3	0.67	0.59–0.75	–2.14	–76
Gender						
Males	2.03	1.78–2.29	0.42	0.33–0.54	–1.61	–79
Females	3.5	3.21–3.79	0.88	0.76–1.01	–2.62	–75
Race						
White	2.8	2.59–3	1.02	0.99–1	–1.78	–64
African American	3.1	2.48–3.82	0.92	0.65–1.27	–2.18	–70
Others*	NA					
Urbanization						
>50K	2.57	2.37–2.77	0.66	0.57–0.75	–1.91	–74
<50K	4.14	3.58–4.71	0.83	0.61–1.1	–3.31	–80
PH WHO groups 2–5	14.95	14.51–15.4	23.2	22.73–23.68	8.25	55
Gender						
Males	13.22	12.56–13.88	19.09	18.44–19.75	5.87	44
Females	16.34	15.72–16.95	26.3	25.62–26.97	9.96	61
Race						
White	14.07	13.6–14.53	21.94	21.43–22.44	7.87	56
African American	24.78	22.88–26.67	38.15	36.26–40.05	13.37	54
American Indian/Alaska Native**	10.84	6.53–16.93	16.44	12.51–21.2	5.6	52
Asian/Pacific Islander	7.44	5.73–9.5	10.68	9.28–12.08	3.24	44
Urbanization						
>50K	14.92	14.43–15.41	22.93	22.41–23.44	6.01	40
<50K	15.11	14.05–16.17	24.84	23.6–26.08	9.73	64

Data from underlying cause of death CDC WONDER data set, 2003–2020. *, data suppressed due to low number of decedents as per CDC policy to ensure confidentiality; **, start date 2004. ASMRs, age-standardized mortality rates; CI, confidence interval; NA, not available; PH, pulmonary hypertension; UCOD, underlying cause of death; US, United States; WHO, World Health Organization; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.

increased from 2003 to 2020 (*Table 5*, *Figure 8*).

Post hoc analysis

Using MCOD datafiles, ASMR attributed to PH with comorbid conditions causing group 2 PH increased from 13.6 per million population (95% CI: 13.1 to 14.0) in 2003 to 27.0 (95% CI: 26.5 to 27.5) (PC, 99%) with AAPC of 4% (95% CI: 3.2% to 4.9%); P<0.001) (*Table 6*, Table S2, *Figure 9*). ASMRs of decedents who have PH and concurrent disease conditions associated with group 3 PH increased from 22.99 (95% CI: 22.44 to 23.55) in 2003 to 29.17 (95%

Table 5 Joinpoint analysis of PH-related ASMRs per million population (UCOD) in the US, 2003–2020

Variables	Trend 1			Trend 2			Overall from 2003–2020	
	Years	EAPC (95% CI)	P value	Years	EAPC (95% CI)	P value	AAPC (95% CI)	P value
Overall PH	2003–2020	2.3 (2 to 2.6)	<0.001				2.3 (2 to 2.6)	<0.001
Males	2003–2005	−5.3 (−14.4 to 4.8)	0.266	2005–2020	2.7 (2.2 to 3.1)	<0.001	1.7 (0.6 to 2.9)	0.004
Females	2003–2020	2.3 (2.1 to 2.6)	<0.001				2.3 (2.1 to 2.6)	<0.001
PH WHO group 1	2003–2005	−34.5 (−50.8 to −12.8)	<0.007	2005–2020	−1.1 (−2.3 to 0)	0.071	−5.8 (−8.7 to −2.7)	<0.001
Gender								
Males	2003–2020	−2.5 (−5.2 to 0.4)	0.085				−2.5 (−5.2 to 0.4)	0.085
Females	2003–2005	−33.3 (−45.7 to −18.2)	0.001	2005–2020	−1.8 (−2.7 to −1)	<0.001	−6.2 (−8.3 to −4)	<0.001
Race								
White	2003–2005	−34.4 (−51.8 to −10.8)	0.011	2005–2020	−0.8 (−2.1 to 0.5)	0.201	−5.5 (−8.7 to −2.2)	0.001
African American	2003–2005	−34.5 (−63 to 16)	0.134	2005–2020	−1.4 (−3.8 to 1)	0.224	−6 (−11.9 to 0.2)	0.056
Others*	NA							
Urbanization								
>50K	2003–2005	−32.5 (−51.4 to −6.4)	0.022	2005–2020	−1 (−2.3 to 0.4)	0.16	−5.3 (−8.7 to −1.8)	<0.001
<50K		−41.4 (−54.1 to −25.3)	<0.001		−1.8 (−2.8 to −0.7)	0.003	−7.6 (−10 to −5)	<0.001
PH WHO groups 2–5	2003–2020	2.7 (2.5 to 2.9)	<0.001				2.7 (2.5 to 2.9)	<0.001
Gender								
Males	2003–2020	2.5 (2.2 to 2.9)	<0.001				2.5 (2.2 to 2.9)	<0.001
Females	2003–2020	2.8 (2.6 to 3)	<0.001				2.8 (2.6 to 3)	<0.001
Race								
White	2003–2020	2.8 (2.6 to 3)	<0.001				2.8 (2.6 to 3)	<0.001
African American	2003–2020	2.5 (2.2 to 2.8)	<0.001				2.5 (2.2 to 2.8)	<0.001
American Indian/Alaska Native**								
Asian/Pacific Islander	2003–2020	2.7 (1.7 to 3.7)	<0.001				2.7 (1.7 to 3.7)	<0.001
Urbanization								
>50K	2003–2020	2.6 (2.5 to 2.8)	<0.001				2.6 (2.5 to 2.8)	<0.001
<50K	2003–2020	3.1 (2.8 to 3.5)	<0.001				3.1 (2.8 to 3.5)	<0.001

Data from underlying cause of death CDC WONDER data set, 2003–2020. *, data suppressed due to low number of decedents as per CDC policy to ensure confidentiality. **, no joinpoint trends observed. AAPC, average annual percentage change; ASMRs, age-standardized mortality rates; CI, confidence interval; EAPC, estimated annual percentage change; NA, not available; PH, pulmonary hypertension; UCOD, underlying cause of death; US, United States; WHO, World Health Organization; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.

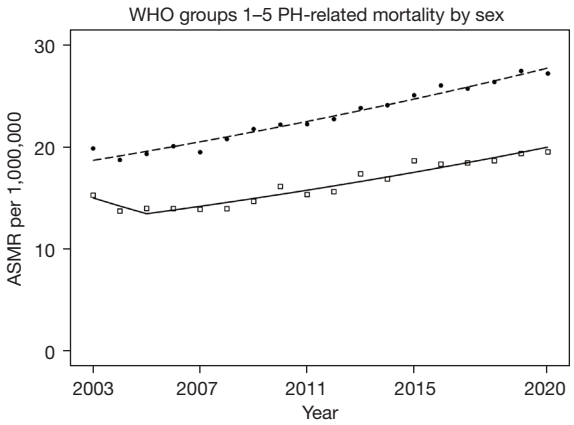

Figure 1 Joinpoint trends of age-standardized mortality rates per million population attributed to PH in the United States, 2003–2020. Squares indicate males, whereas circles indicate females. PH, pulmonary hypertension.

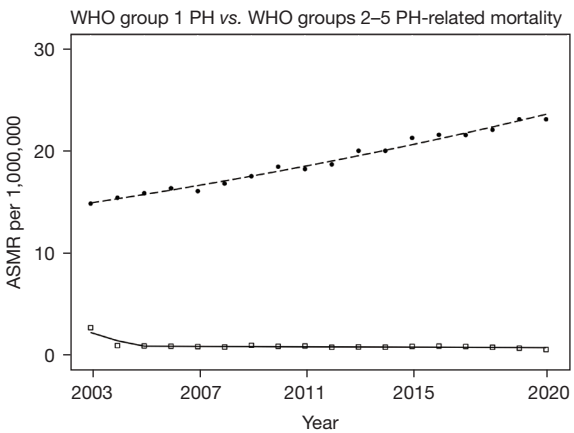

Figure 2 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO group 1 PH and WHO groups 2–5 PH in the United States, 2003 to 2020. Squares indicate WHO group 1 PH, whereas circles indicate WHO groups 2–5 PH. WHO, World Health Organization; PH, pulmonary hypertension.

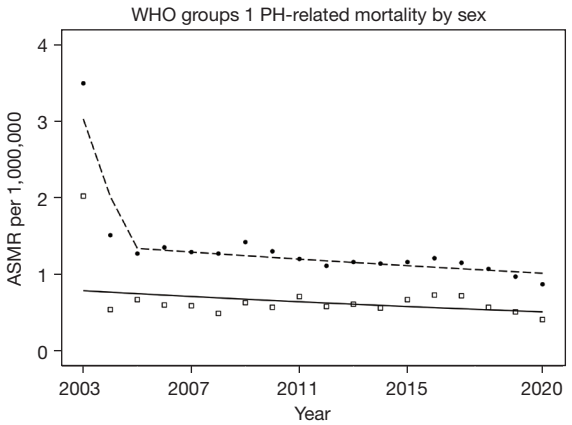

Figure 3 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO group 1 PH in the United States, 2003–2020. Squares indicate males, whereas circles indicate females. WHO, World Health Organization; PH, pulmonary hypertension.

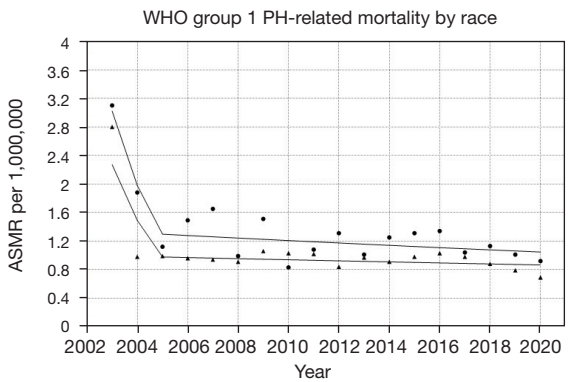

Figure 4 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO group 1 PH by race in the United States, 2003–2020. Circles indicate the African Americans, whereas triangles indicate White population. WHO, World Health Organization; PH, pulmonary hypertension.

CI: 28.64 to 29.69) (PC, 27%) with AAPC of 1.4% (95% CI: 0.7% to 2%) (P<0.001; *Table 6*, Table S2, *Figure 10*). These trends indicate that increased mortality in WHO groups 2–5 PH over the study period is secondary to increased burden from both WHO groups 2 and 3 subtypes with relatively higher contribution from WHO group 2 PH.

Median age of death in WHO group 1 PH decedents increased from 66 years (IQR, 49 to 79 years) in 2003 through 2010 to 76 years (IQR, 62 to 86 years) in 2011 through 2020. On similar lines, though smaller in magnitude, the median age of death in WHO groups 2–5 PH increased from 75 years (IQR, 62 to 84 years) to 78.5 years (IQR, 66.5 to 87 years) (*Table 7*).

Discussion

Our study indicates a rise in PH-associated mortality from 2003 to 2020 in the US population. This trend was identified in both males and females and driven primarily

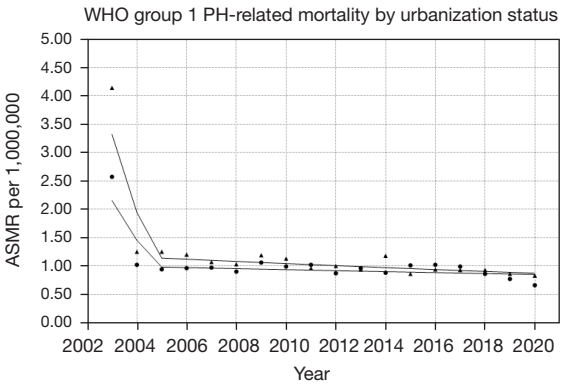

Figure 5 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO group 1 PH by urbanization status in the United States, 2003–2020. Circles indicate urban, whereas triangles indicate rural population. WHO, World Health Organization; PH, pulmonary hypertension.

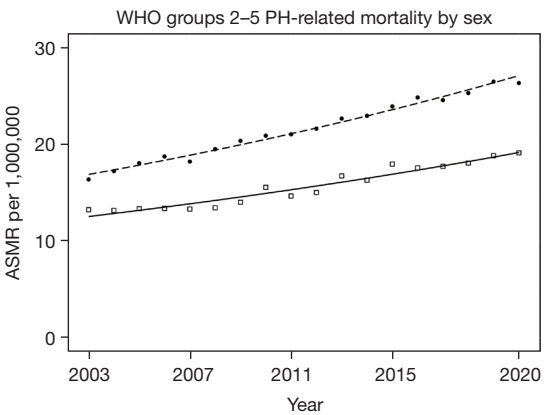

Figure 6 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO groups 2–5 PH in the United States, 2003–2020. Squares indicate males, whereas circles indicate females. WHO, World Health Organization; PH, pulmonary hypertension.

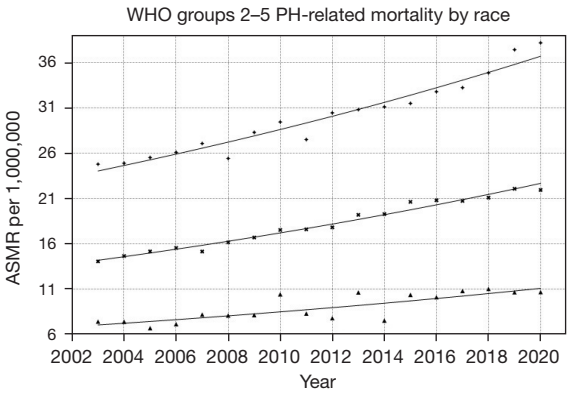

Figure 7 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO groups 2–5 PH by race in the United States, 2003–2020. Plus, signs indicate the African Americans, cross signs indicate the White population, triangles indicate the Asian/Pacific Islander. WHO, World Health Organization; PH, pulmonary hypertension.

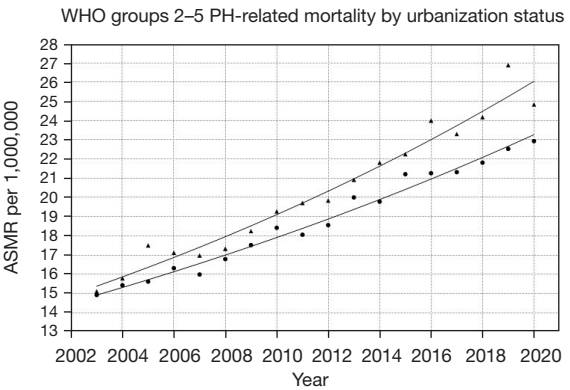

Figure 8 Joinpoint trends of age-standardized mortality rates per million population attributed to WHO groups 2–5 PH by urbanization status in the United States, 2003–2020. Circles indicate urban, whereas triangles indicate rural population. WHO, World Health Organization; PH, pulmonary hypertension.

by WHO groups 2–5 PH. Overall, PH was more often reported as the underlying cause of death in females, with the sex gap widening over the study period. Similarly, the mortality burden from each subtype was higher in females. When WHO group 1 PH and groups 2–5 PH were analyzed individually, there was a striking difference in trends. Deaths associated with WHO group 1 showed the fast decline independent of sex in the early years of the study, followed by a steady decline from 2006 to 2020. WHO groups 2–5 PH mortality rates increased, and there was a steeper rise in females as compared to males. Post hoc analysis indicated WHO group 2 PH-related mortality as the primarily driving subcategory contributing to worsening trends in WHO groups 2–5 cohort. The highest PH-related mortality burden was observed in African American population.

Temporal trends in PH-associated deaths have been reported previously. This study builds upon previous studies with new data from the last two decades (8,16). Hyduk *et al.* (16) reported stable PH mortality in the US population from 1980 through 2002. In contrast, our study showed

Table 6 Joinpoint analysis of PH-related ASMRs per million population with comorbid conditions (MCOD) in the US, 2003–2020

PH WHO groups 2–5	Trend 1			Trend 2			Trend 3			Overall from 2003–2020	
	Years	EAPC (95% CI)	P value	Years	EAPC (95% CI)	P value	Years	EAPC (95% CI)	P value	AAPC (95% CI)	P value
Group 2 related comorbid conditions	2003–2008	5.7 (4.2–7.2)	0	2008–2018	2.3 (1.7–2.9)	0	2018–2020	9.1 (2.4–16.3)	0.012	4 (3.2–4.9)	0
Group 3 related comorbid conditions	2003–2010	1.3 (0.6–2)	0.002	2010–2014	−0.5 (−3.1 to 2.2)	0.71	2014–2020	2.6 (1.7–3.6)	0	1.4 (0.7–2)	0

Data from underlying cause of death CDC WONDER data set, 2003–2020. AAPC, average annual percentage change; ASMRs, age-standardized mortality rates; CI, confidence interval; EAPC, estimated annual percentage change; PH, pulmonary hypertension; MCOD, multiple cause of death; US, United States; WHO, World Health Organization; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.

Figure 9 Joinpoint trends of age-standardized mortality rates per million population attributed to PH with comorbid conditions associated with WHO group 2 PH in the United States, 2003–2020. WHO, World Health Organization; PH, pulmonary hypertension.

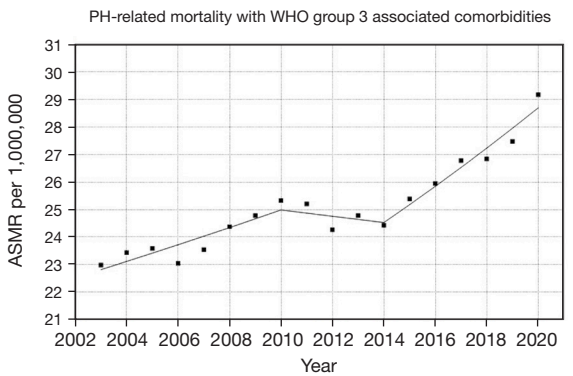

Figure 10 Joinpoint trends of age-standardized mortality rates per million population attributed to PH with comorbid conditions associated with WHO group 3 PH in the United States, 2003–2020. WHO, World Health Organization; PH, pulmonary hypertension.

a significant rise in ASMRs from 2003 to 2020, including the increase from 2005 to 2020 in males and throughout the study period in females. These trends are in alignment with observations by George and colleagues, who reported data relating to the first decade of the millennium (8). However, we report lower absolute mortality figures as compared to Hyduk *et al.* and George *et al.* (8,16). The difference in the absolute mortality rate is because both previous studies reported PH as any contributing cause of death out of the possible twenty conditions reported in death certificates, including a primary underlying cause of

Table 7 PH-related median age of death in years (UCOD) by demographic characteristics in the US, 2003–2020

Variables	WHO group 1 PH, median (Q1-Q3)		WHO groups 2–5 PH, median (Q1-Q3)	
	2003–2010	2011–2020	2003–2010	2011–2020
Overall	66 (49 to 79)	76 (62 to 86)	75 (62 to 84)	78.5 (66.5 to 87)
Gender				
Males	64.5 (46 to 77)	74 (60 to 84)	73 (59 to 82)	76 (64 to 85)
Females	67 (49.5 to 80)	77 (63 to 87)	77 (63 to 85)	80 (68 to 88)
Race				
White	68 (51 to 80.5)	77 (64.5 to 87)	77 (65 to 85)	80.5 (69 to 87.5)
African American	58 (40 to 73)	68 (56 to 80)	65 (51 to 77)	68.5 (57 to 79.5)
American Indian/Alaska Native	NA		NA	NA
Asian/Pacific Islander	NA		71 (52 to 81.5)	76 (62 to 86)
Urbanization*				
>50K	65.5 (48 to 79)	76 (62 to 86)	75 (61 to 84)	78.5 (66.5 to 87)
<50K	68 (50 to 80)	75 (62 to 85)	76 (64 to 84)	78.5 (67 to 87)

Data from underlying cause of death CDC WONDER data set, 2003–2020. *, urbanization >50K: large to small metropolitans; <50K: non-metro. PH, pulmonary hypertension; NA, not available due to low number of decedents and suppression of data by CDC to ensure confidentially; Q1, 25% quartile; Q3, 75% quartile; UCOD, underlying cause of death; US, United States; WHO, World Health Organization; CDC WONDER, Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.

death, while our study reports mortality burden from PH as the primary underlying cause of death (8,16). To our knowledge, this is the first study exploring the nationwide mortality burden with PH as the primary underlying cause of death. Our analysis also identified that PH deaths from WHO groups 2 PH were predominantly responsible for worsening mortality trends, a finding consistent with other small studies (1,2,17).

PH from secondary causes is encountered frequently in clinical practice and may be underrecognized. More than 40 different etiologies of PH are reported. PH secondary to left-sided heart disease (WHO group 2) and chronic lung diseases (WHO group 3) are the most common etiologies. Although the exact prevalence is unknown, approximately 70 to 80% of PH burden is thought to be due to left-sided heart disease and chronic lung disease, and the presence of PH in these diseases strongly correlates with increased morbidity and mortality (2,8,18-21). Our study documents nineteen times higher mortality rates in groups 2–5 PH in comparison to the PAH group, a 55% increase in mortality burden related to groups 2–5 PH, and an increase in the median age of death. Post hoc analysis showed hundred percent increase in mortality from PH with comorbid conditions associated with WHO group 2 PH and a 27% increase in mortality attributed to PH with comorbid conditions associated with WHO group 3 PH. These findings signal that the aging population and comorbid clinical conditions such as left-sided heart disease, systemic hypertension, obstructive sleep apnea, chronic obstructive lung diseases, and interstitial lung diseases are responsible for the increasing mortality burden from secondary PH. Other possible explanations for increasing rate of PH deaths may be secondary to greater awareness of PH among physicians, shifting in documentation from congestive heart failure to PH as the primary cause of death, better diagnostics, and changes in the reporting of PH (22-24). The concerning mortality trends from PH have notable public health implications supporting the need for more research and resources to better understand non-PAH PH groups especially PH-related to left-sided heart diseases, chronic hypoxic lung diseases, and sleep apnea.

Multiple PAH-specific pharmacotherapies have been studied in both groups. Apart from a few studies indicating some morbidity benefit from pulmonary vasodilators in individuals with groups 2, 3, and 4 PH (6,7,25-28), numerous other studies have failed to demonstrate any morbidity or mortality benefit, with some studies even producing a signal toward deleterious effects (29-32).

Despite of guidelines recommending the use of PAH-specific pharmacotherapies in only a few non-PAH conditions (6,7), trends suggesting off-label use of PAH-targeted drugs have emerged (1). In the Giessen PH registry, 47% of patients with WHO group 2 and 77% of patients with WHO group 3 were on PAH-specific therapies at the time of referral to PH-specialized centers (33). The prognosis in both groups was worse compared to PAH. Studies from pulmonary vascular disease centers in the US have mirrored similar off-label use of PAH-specific pharmacotherapies (34,35). Worsening overall mortality trends from WHO groups 2–5 in our study coincide with a dramatic increase in the number of new commercially available pulmonary vasodilators. However, the importance or relevance of this cannot be determined by the present study.

Females are more susceptible to PAH; however, previous studies described better survival in females than males, a phenomenon referred to as the "estrogen paradox" (16,36,37). Mortality data analyzing gender differences relating to PAH and all forms of PH are sparse. One nationwide study reported higher mortality rates in males over a 20-year period, but the gap closed in 2000, secondary to a decrease in mortality in males and an increased burden in females (16). In our study, PH ASMRs were uniformly higher in females relative to males and the difference increased over time. However, we observed a higher median age of death in female decedents in comparison to males in both PAH and non-PAH PH pointing toward better survival in females. Similarly, in a large cohort of US veterans with PH, females had improved survival compared to their male counterparts (38). In contrast, a recent registry report described increasing trends in PH-related deaths and hospitalization in females (8,9). Similarly, Chang *et al.* (39) observed higher mortality rates in females when compared with age-matched males, despite male sex being a risk factor for mortality. Thus, the effect of sex on PH mortality remains unclear. Some studies have implicated the effect of estrogens or differential sex hormone metabolism in enhancing damage to the pulmonary vasculature in females (40-42) whereas others reported an adaptive effect of estrogen on the pulmonary vasculature and the right ventricle (43). Most of the animal studies in this area have observed a protective effect of female sex, and a preventive as well as therapeutic role of estrogen in group 1 PH (44,45). Although the role of multiple sex hormones and their metabolites remains unknown, further investigation in this field has the potential to establish new PH pharmacotherapies especially for WHO groups 2 and 3.

We observed a precipitous decline in PAH-associated ASMRs in females from 2003 to 2006, followed by a steady and statistically significant decline over the remainder of the study period. Similar trends have been reported by others (46-48). The sudden decrease in reported mortality coincides with an ICD coding system change occurring in October 2003; the addition of ICD-10 code I27.2 for "other secondary PH" in the death certificate index and rearranging the death certificate index order (8,49). The changes in mortality trends around this time period warrant cautious interpretation.

The steady decline in PAH mortality corresponds to the introduction of PAH-specific pharmacotherapies. Since FDA approval in 1995 of epoprostenol, the first PAH-specific medical therapy, 14 drugs have received FDA approval for PAH. Apart from new PAH-specific pharmacotherapy, significant progress has been made in the use of combination therapies, alternate modes of systemic delivery with implantable devices, more sensitive diagnostics, and specialized PH referral centers. All of these advances have led to an improvement in median survival of 7 years as compared to 2.8 years in the pre-epoprostenol era (50-52). Our study reflects similar trends in PAH-associated mortality in both sexes.

Our study demonstrated the highest PH-related mortality and the lower median age of death in African American population as compared to White and other races. The racial disparity in mortality widened in the WHO groups 2–5 PH over the study period. There are no previous study reporting time trends of racial disparity in WHO groups 2–5 PH. However, Kang *et al.* (48) reported worsening racial disparity on combined analysis of all five subgroups of PH. Our study also exhibited higher mortality rates related to WHO group 1 PH in the African American population as compared to other races. Previous studies evaluating racial disparities related to WHO group 1 PH have variable results. Davis *et al.* reported higher PAH related mortality in African American population as compared to Caucasians (53). In contrast, Medrek *et al.* observed no survival difference across races after adjusting for variables of prognostic impact (54). Fortunately, we noticed a decrease in the WHO group 1 PH-related mortality disparity among African American and White races. The precise reasons for such disparity are not clear. Some studies have suggested a difference in the baseline physiological characteristics of African Americans. While one paper reported a poorer response to estrogen receptor antagonists for PAH amongst African Americans as compared to

Whites, another reported that African Americans had a significantly higher end-diastolic pulmonary regurgitation gradient as compared to Caucasians and other races, possibly suggesting higher baseline PA pressures in African Americans. There is also a report of higher incidence of diseases that cause PH (such as systemic sclerosis) in African American (54-57). Furthermore, the social and economic disparity amongst African Americans and its effects on healthcare and outcomes is well established. However, there is limited literature on the impact of socioeconomic disparity on PH outcomes. One paper by Parikh *et al.* found that the higher mortality from PH amongst African Americans was attenuated when insurance status was taken into account. They suggested that insurance status was an important prognosticator of increased PH mortality. Further exploration of high-risk baseline characteristics as well as other social or economic factors can help identify opportunities for improvement in PH management (58,59).

One of the key points from the current study is that mortality data reporting, especially for relatively uncommon diseases such as PH, is critical to investigate changes in epidemiology and assess the impact of new diagnostic and treatment modalities at a national level. ICD codes serve as the primary foundation for analysing disease statistics. Although separate ICD codes have been assigned to each WHO PH group, we were not able to investigate discrete mortality rates for each WHO group because this level of detail is not captured in the CDC WONDER UCOD database. Perhaps future iterations of the database will include this level of data stratification.

The present study has several strengths. Most of the previous studies are based on specialized registries and are therefore less likely to represent "real world" estimates. This study is nationwide and provides a more comprehensive evaluation of the US population. To our knowledge, this is the first study exploring the burden of PH as a primary underlying cause of death in the US population. There are several limitations of this study. Although the CDC WONDER database provides abundant and reliable data, it is based on information from death certificates, which may contain reporting errors or misclassify the cause of death. In current study, PAH is defined an ICD code I27.0 only, however, some forms of PAH such as PAH secondary to connective tissue diseases might be reported under ICD code I27.2. Centralized data sources have been reported to underestimate mortality in prior studies (60,61) and similar bias could have occurred in the current study. Revision of the ICD codes at the beginning of the study period and changes in the death certificate index might be responsible for some of the observed trends, especially regarding PAH mortality. Mortality estimates using the CDC database don't take into account any changes in prevalence and any differences in absolute mortality rates across gender or races could be due to differences in prevalence or case fatality, or misclassification. To make the comparison feasible, we reported median age of death as a surrogate marker of survival across different variables. Other confounders may not be accounted for by stratifying mortality rates by age and sex. Finally, in an observational study, results cannot be used to determine causality.

Conclusions

PH-related mortality continues to increase. Mortality trends for WHO group 1 and WHO groups 2–5 combined together are divergent. There has been a decline in mortality and an increase in the median age of death for PAH in both males and females. In contrast, there has been an increase in mortality for WHO groups 2–5 PH, which accounts for the higher observed overall PH mortality. These findings have notable public health implications. Screening and risk assessment tools for secondary PH, risk factor modification, and novel management strategies are vital to improve outcomes. Tracking mortality based on the latest WHO PH classification groups is vital to assess the mortality burden for each group.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1468/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1468/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1468/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional Review Board endorsement and patient consent were not necessary for this study because the deidentified data are publicly available in the CDC data repository.

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Cite this article as: Singh H, Agarwal L, Jani C, Bhatt P, Hartley A, Shalhoub J, Kurman JS, Al Omari O, Ahmed A, Marshall DC, Salciccioli JD. Pulmonary hypertension associated mortality in the United States from 2003 to 2020: an observational analysis of time trends and disparities. J Thorac Dis 2023;15(6):3256-3272. doi: 10.21037/jtd-22-1468

Supplementary

Table S1 Temporal trends of PH-related ASMRs per million population (UCOD) with 95% CI in the US, 2003–2020

Variables	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
PH	17.81 (17.32–18.3)	16.55 (16.09–17.02)	16.98 (16.51–17.44)	17.43 (16.96–17.9)	17.14 (16.68–17.6)	17.82 (17.35–18.28)	18.72 (18.25–19.2)	19.58 (19.09–20.06)	19.34 (18.87–19.82)	19.7 (19.23–20.18)	21.07 (20.58–21.55)	21.03 (20.55–21.5)	22.35 (21.86–22.83)	22.69 (22.2–23.18)	22.64 (22.16–23.12)	23.07 (22.59–23.55)	24.01 (23.53–24.5)	23.89 (23.41–24.37)
Males	15.27 (14.56–15.98)	13.72 (13.05–14.38)	13.98 (13.32–14.64)	13.96 (13.3–14.61)	13.89 (13.24–14.54)	13.95 (13.3–14.59)	14.67 (14.02–15.33)	16.13 (15.44–16.81)	15.34 (14.68–15.99)	15.62 (14.96–16.27)	17.36 (16.68–18.04)	16.86 (16.2–17.53)	18.65 (17.97–19.34)	18.31 (17.63–18.98)	18.43 (17.76–19.1)	18.65 (17.98–19.31)	19.35 (18.69–20.02)	19.51 (18.85–20.18)
Females	19.85 (19.17–20.53)	18.73 (18.07–19.38)	19.31 (18.65–19.97)	20.07 (19.41–20.74)	19.48 (18.83–20.13)	20.77 (20.1–21.44)	21.75 (21.07–22.43)	22.18 (21.51–22.86)	22.23 (21.55–22.9)	22.72 (22.04–23.39)	23.8 (23.12–24.48)	24.08 (23.4–24.76)	25.06 (24.38–25.75)	26.02 (25.32–26.71)	25.71 (25.03–26.39)	26.36 (25.67–27.04)	27.43 (26.74–28.12)	27.19 (26.5–27.87)
PH WHO group 1	2.81 (2.62–3)	1.06 (0.94–1.18)	1.02 (0.9–1.13)	1 (0.89–1.11)	0.96 (0.85–1.07)	0.92 (0.81–1.02)	1.08 (0.96–1.19)	0.99 (0.88–1.1)	1.02 (0.91–1.13)	0.89 (0.79–0.99)	0.93 (0.82–1.03)	0.9 (0.8–1)	0.98 (0.88–1.08)	1.01 (0.91–1.11)	0.97 (0.87–1.07)	0.89 (0.79–0.99)	0.81 (0.72–0.9)	0.67 (0.59–0.75)
Gender																		
Males	2.03 (1.78–2.29)	0.55 (0.43–0.7)	0.68 (0.54–0.83)	0.61 (0.49–0.76)	0.6 (0.47–0.74)	0.5 (0.39–0.64)	0.64 (0.52–0.79)	0.58 (0.46–0.72)	0.72 (0.58–0.86)	0.59 (0.47–0.73)	0.62 (0.5–0.76)	0.57 (0.46–0.7)	0.68 (0.55–0.81)	0.74 (0.6–0.87)	0.73 (0.6–0.87)	0.58 (0.47–0.71)	0.52 (0.42–0.65)	0.42 (0.33–0.54)
Females	3.5 (3.21–3.79)	1.52 (1.32–1.71)	1.28 (1.11–1.46)	1.36 (1.18–1.54)	1.3 (1.13–1.48)	1.28 (1.11–1.45)	1.43 (1.25–1.61)	1.31 (1.14–1.47)	1.21 (1.05–1.37)	1.12 (0.97–1.28)	1.17 (1.01–1.32)	1.15 (1–1.3)	1.17 (1.02–1.32)	1.22 (1.07–1.37)	1.16 (1.02–1.31)	1.08 (0.94–1.22)	0.98 (0.84–1.11)	0.88 (0.76–1.01)
Race																		
White	2.8 (2.59–3)	0.98 (0.86–1.1)	0.99 (0.87–1.11)	0.96 (0.84–1.08)	0.94 (0.82–1.06)	0.91 (0.8–1.03)	1.06 (0.94–1.19)	1.03 (0.91–1.15)	1.02 (0.9–1.14)	0.84 (0.73–0.94)	0.97 (0.85–1.08)	0.91 (0.8–1.02)	0.98 (0.87–1.1)	1.03 (0.91–1.15)	0.98 (0.87–1.09)	0.88 (0.78–0.99)	0.79 (0.69–0.88)	0.69 (0.6–0.78)
African American	3.1 (2.48–3.82)	1.88 (1.41–2.46)	1.12 (0.77–1.57)	1.49 (1.1–1.97)	1.65 (1.22–2.18)	0.99 (0.66–1.42)	1.51 (1.11–2.01)	0.83 (0.55–1.19)	1.08 (0.75–1.49)	1.31 (0.94–1.76)	1.01 (0.69–1.43)	1.25 (0.91–1.67)	1.31 (0.95–1.75)	1.34 (0.99–1.77)	1.04 (0.74–1.42)	1.13 (0.81–1.54)	1.01 (0.72–1.38)	0.92 (0.65–1.27)
Others*	NA																	
Urbanization																		
>50K	2.57 (2.37–2.77)	1.02 (0.89–1.15)	0.94 (0.82–1.06)	0.96 (0.84–1.08)	0.97 (0.84–1.09)	0.9 (0.79–1.02)	1.06 (0.93–1.18)	0.99 (0.87–1.11)	1.02 (0.9–1.14)	0.87 (0.76–0.97)	0.96 (0.85–1.08)	0.88 (0.77–0.98)	1.01 (0.89–1.12)	1.02 (0.91–1.14)	0.99 (0.88–1.1)	0.86 (0.76–0.97)	0.77 (0.67–0.86)	0.66 (0.57–0.75)
<50K	4.14 (3.58–4.71)	1.25 (0.95–1.61)	1.25 (0.96–1.6)	1.2 (0.92–1.55)	1.07 (0.8–1.4)	1.03 (0.78–1.35)	1.19 (0.9–1.54)	1.13 (0.86–1.45)	0.96 (0.72–1.26)	1 (0.75–1.31)	0.94 (0.69–1.24)	1.18 (0.9–1.52)	0.86 (0.63–1.14)	0.94 (0.71–1.21)	0.93 (0.7–1.2)	0.93 (0.71–1.21)	0.86 (0.64–1.14)	0.83 (0.61–1.1)
PH WHO groups 2–5	14.95 (14.51–15.4)	15.52 (15.07–15.97)	15.97 (15.52–16.42)	16.45 (15.99–16.9)	16.17 (15.72–16.62)	16.91 (16.45–17.36)	17.63 (17.17–18.09)	18.56 (18.09–19.03)	18.33 (17.87–18.79)	18.79 (18.33–19.25)	20.12 (19.65–20.6)	20.12 (19.65–20.59)	21.38 (20.9–21.85)	21.68 (21.2–22.16)	21.66 (21.19–22.14)	22.17 (21.7–22.64)	23.2 (22.72–23.67)	23.2 (22.73–23.68)
Gender																		
Males	13.22 (12.56–13.88)	13.15 (12.5–13.8)	13.32 (12.67–13.96)	13.36 (12.72–14.01)	13.29 (12.66–13.93)	13.42 (12.79–14.05)	13.99 (13.35–14.63)	15.53 (14.86–16.2)	14.63 (13.99–15.27)	15 (14.36–15.64)	16.71 (16.05–17.38)	16.27 (15.62–16.92)	17.93 (17.26–18.61)	17.54 (16.88–18.2)	17.69 (17.03–18.34)	18.04 (17.39–18.69)	18.8 (18.14–19.45)	19.09 (18.44–19.75)
Females	16.34 (15.72–16.95)	17.21 (16.58–17.83)	18.03 (17.39–18.67)	18.72 (18.07–19.36)	18.19 (17.56–18.82)	19.48 (18.84–20.13)	20.33 (19.68–20.99)	20.86 (20.2–21.51)	21 (20.35–21.65)	21.59 (20.94–22.25)	22.63 (21.97–23.3)	22.91 (22.25–23.58)	23.89 (23.22–24.56)	24.81 (24.14–25.49)	24.54 (23.88–25.21)	25.26 (24.59–25.93)	26.45 (25.77–27.13)	26.3 (25.62–26.97)
Race																		
White	14.07 (13.6–14.53)	14.66 (14.19–15.13)	15.17 (14.69–15.64)	15.55 (15.07–16.03)	15.16 (14.69–15.62)	16.17 (15.7–16.65)	16.7 (16.22–17.18)	17.53 (17.04–18.02)	17.6 (17.11–18.09)	17.82 (17.34–18.31)	19.2 (18.7–19.7)	19.28 (18.79–19.78)	20.63 (20.12–21.14)	20.8 (20.29–21.31)	20.73 (20.23–21.23)	21.09 (20.59–21.59)	22.07 (21.56–22.57)	21.94 (21.43–22.44)
African American	24.78 (22.88–26.67)	24.88 (23–26.75)	25.51 (23.63–27.39)	26.09 (24.21–27.96)	27.06 (25.14–28.98)	25.41 (23.58–27.23)	28.28 (26.38–30.18)	29.43 (27.51–31.36)	27.49 (25.65–29.33)	30.44 (28.54–32.34)	30.8 (28.91–32.69)	31.1 (29.22–32.98)	31.48 (29.63–33.33)	32.77 (30.91–34.64)	33.21 (31.37–35.05)	34.84 (32.98–36.7)	37.39 (35.49–39.29)	38.15 (36.26–40.05)
American Indian/Alaska Native	NA	10.84 (6.53–16.93)	14.39 (9.12–21.6)	13.23 (8.38–19.85)	9.33 (5.77–14.26)	8.16 (4.67–13.26)	12.12 (7.76–18.03)	12.4 (8.1–18.17)	12.44 (8.26–17.97)	9.89 (6.12–15.11)	14.29 (9.64–20.4)	14.61 (10.34–20.06)	15.7 (11.16–21.46)	13.2 (9.38–18.04)	11.23 (7.82–15.61)	10.59 (7.33–14.79)	12.32 (8.84–16.71)	16.44 (12.51–21.2)
Asian/Pacific Islander	7.44 (5.73–9.5)	7.43 (5.73–9.47)	6.72 (5.12–8.67)	7.15 (5.54–9.08)	8.21 (6.54–10.18)	8.11 (6.49–10)	8.15 (6.49–9.81)	10.44 (8.55–12.32)	8.32 (6.69–9.94)	7.81 (6.32–9.31)	10.64 (8.95–12.33)	7.55 (6.16–8.94)	10.38 (8.82–11.94)	10.12 (8.61–11.64)	10.81 (9.3–12.32)	11.03 (9.53–12.54)	10.66 (9.22–12.09)	10.68 (9.28–12.08)
Urbanization																		
>50K	14.92 (14.43–15.41)	15.43 (14.93–15.92)	15.62 (15.12–16.11)	16.32 (15.82–16.82)	15.99 (15.5–16.48)	16.79 (16.29–17.28)	17.52 (17.01–18.02)	18.42 (17.91–18.94)	18.06 (17.56–18.57)	18.56 (18.06–19.06)	20 (19.48–20.52)	19.78 (19.27–20.29)	21.21 (20.69–21.72)	21.26 (20.74–21.78)	21.32 (20.81–21.83)	21.81 (21.3–22.32)	22.53 (22.02–23.05)	22.93 (22.41–23.44)
<50K	15.11 (14.05–16.17)	15.79 (14.71–16.86)	17.5 (16.37–18.62)	17.12 (16.01–18.23)	16.98 (15.88–18.07)	17.33 (16.23–18.43)	18.25 (17.12–19.38)	19.27 (18.12–20.41)	19.71 (18.56–20.86)	19.84 (18.69–20.99)	20.92 (19.74–22.1)	21.81 (20.61–23)	22.25 (21.06–23.45)	24 (22.75–25.25)	23.3 (22.1–24.51)	24.18 (22.95–25.41)	26.89 (25.61–28.18)	24.84 (23.6–26.08)

Data from underlying cause of death CDC WONDER data set, 2003–2020. *, data suppressed due to low number of decedents (<10 per annum) as per CDC policy to ensure confidentiality. ASMRs, age-standardized mortality rates; CI, confidence interval; NA, not available; PH, pulmonary hypertension; UCOD, underlying cause of death; US, United States; and WHO, World Health Organization.

Table S2 Temporal trends of PH-related ASMRs per million population with comorbid conditions (MCOD) with 95% CI in the US, 2003–2020

PH WHO groups 2–5	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Absolute change	Percentage change
Group 2 related comorbid conditions	13.6 (13.1–14)	14.7 (14.2–15.1)	15.3 (14.9–15.7)	15.9 (15.4–16.3)	17.1 (16.6–17.5)	18.1 (17.6–18.5)	18.3 (17.9–18.8)	19.1 (18.6–19.6)	19.9 (19.4–20.4)	19.7 (19.2–20.2)	19.9 (19.4–20.3)	20 (19.6–20.5)	20.6 (20.1–21.1)	21.7 (21.2–22.2)	22.6 (22.1–23)	22.8 (22.4–23.3)	24.4 (23.9–24.9)	27 (26.5–27.5)	13.4	99
Group 3 related comorbid conditions	22.99 (22.44–23.55)	23.44 (22.88–23.99)	23.59 (23.04–24.14)	23.05 (22.51–23.59)	23.55 (23.01–24.1)	24.38 (23.83–24.93)	24.78 (24.24–25.33)	25.33 (24.78–25.88)	25.21 (24.67–25.75)	24.27 (23.75–24.8)	24.78 (24.26–25.31)	24.43 (23.92–24.95)	25.39 (24.87–25.91)	25.95 (25.43–26.47)	26.78 (26.26–27.3)	26.84 (26.33–27.36)	27.48 (26.97–27.99)	29.17 (28.64–29.69)	6.18	27

Data from underlying cause of death CDC WONDER data set, 2003–2020. ASMRs, age-standardized mortality rates; CI, confidence interval; MCOD, multiple cause of death; PH, pulmonary hypertension; and WHO, World health Organization.

https://dx.doi.org/10.21037/jtd-22-1468