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Racial and ethnic differences in reported haemophilia death rates in the United States

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Abstract

Introduction: People with haemophilia's life expectancies have improved over time. Whether progress has been experienced equitably is unknown.

Aim: To examine recorded haemophilia death (rHD) rates according to race and ethnicity in the United States (US).

Methods: In this cohort study, rHDs were examined with US National Vital Statistics' 1999–2020 Multiple Cause-of-Death data. rHD was defined as having a haemophilia A (D66) or B (D67) ICD-10 code in the death certificate (underlying or multiple causes of death). Age-adjusted rHD rates were compared with age-adjusted rate ratios (aRR) and 95% Confidence Intervals (CI).

Results: There were 3115 rHDs in males with an rHD rate of 0.98 per 1 million males. Between 1999 and 2020, rHD rates declined by 46% in NH (Non-Hispanic) White, 44% in NH Black (aRR = 0.56, 95%CI 0.43, 0.74), and 42% in Hispanic (aRR = 0.58, 95%CI 0.39, 0.88) males. However, rHD rates remained higher and were on average 30% greater in NH Black versus NH White males (aRR = 1.30 95% CI 1.16, 1.46). Among males with rHD, the median age at death rose from 54.5 to 65.5 years between 1999 and 2020 and was 12 years lower in NH Black (56 years) versus NH White (68 years) males in 2010–2020. There were 930 females with rHD, with an age-adjusted rate of 0.22 per 1 million females, which was consistent between 1999 and 2020.

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AUTHOR CONTRIBUTIONS

Christine L. Kempton and Stacey A. Fedewa conceived of the project and created the analysis plan. Stacey A. Fedewa performed the analysis. All authors drafted the manuscript.

CONFLICT OF INTEREST STATEMENT

Christine L. Kempton: Has received honoraria for participation in advisory boards from Biomarin, Pfizer, Genentech, and Spark.

ETHICS STATEMENT

The US National Death Certificate data were deidentified with no means to identify individual participants and the definition of a human subject was not met. This study was thus considered nonhuman subject research by the Emory University institutional review board.

Conclusion: Reported haemophilia-death rates improved in males across all race/ethnicities, but rates were higher Black versus White males. Given the inherent limitations of the current study's data source, further investigation of survival rates and disparities in haemophilia are needed.

Keywords

death; disparities; ethnicity; haemophilia; outcomes; race

1 | INTRODUCTION

Haemophilia is an X-linked blood clotting disorder where people are deficient in Factor VIII (haemophilia A) or IX (haemophilia B), resulting in an increased risk of spontaneous bleeding, bleeding following injuries or surgery, and premature death. Death rates and the life expectancy for people with haemophilia (PwH) have drastically improved in the past 20 years after a period of oscillation.[1] Life expectancy rose in the 1970′s with the introduction of factor-replacement therapies, then quickly declined beginning in the early 1980′s as people with haemophilia became infected with human immune deficiency (HIV) and hepatitis C virus (HCV) due to contaminated blood products used for treatment of haemophilia. Mortality rates began to improve in the 1990s in part due to more widespread use of highly active antiretroviral therapy (HAART) that prevents HIV replication and it increased survival among people with severe haemophilia infected with HIV.[2,3] Plasma-derived products were routinely screened, viral inactivation procedures were implemented, and recombinant blood products were introduced beginning in the early 1990s.[1,4] Recent and further improvements in life expectancy have been attributed to more robust prophylaxis treatment that better prevent and control bleeding events.[1] The underlying causes of death have also shifted throughout time where HIV and HCV-associated liver disease were the leading cause of death up until the early 2000′s and heart disease and cancer became more common by 2010.[4,5]

However, it is unknown if recent improvements in haemophilia death rates have been experienced equitably across all race/ethnicities. In earlier studies of United States' (US) death certificate data, Black and White males had similar recorded haemophilia death rates between 1979 and 1995, but it is not known if patterns changed in recent time periods where factor products are abundant, and prophylaxis is the standard of care.[2] In this study, we examined trends in reported haemophilia-death rates, the median age at death, and the cause of death according to race and ethnicity with historical and contemporary US death certificate data between 1999 and 2020.

2 | MATERIALS AND METHODS

This cohort study utilized the US National Vital Statistics' 1999−2020 Final Multiple Causes of Death database with bridged race categories.[6] The database contains death certificate data for all US residents and each death certificate includes a person's underlying causes of death and up to 20 multiple causes of death, and sociodemographic information (sex, age, race and ethnicity). Recorded haemophilia deaths were defined as having a haemophilia A or B ICD-10 code (D66 for Factor VIII deficiency, D67 for Factor IX

deficiency) listed as either an underlying or multiple cause of death. US death certificate data have not been linked to haemophilia registries or medical records to validate diagnosis. Denominators were based on US Bureau of Census population estimates as of July 1 during the year in which deaths occurred.[7] The total population was used for the denominator because there is not a US registry that captures all people with haemophilia. The US American Thrombosis and Hemostasis Network and Community Counts registries collect data from those seen at Haemophilia Treatment Centers and access to US Haemophilia Treatment Centers could vary over time period, socioeconomic status and/or race and ethnicity.[8,9] The data in the current study were deidentified with no means to identify individual participants and the definition of a human subject was not met. This study was thus considered nonhuman subject research by the Emory University institutional review board.

Age-adjusted recorded haemophilia death (rHD) rates were directly standardized to the 2000 US population and presented as the number of deaths per 1,000,000 (1 million) males or females. Race and ethnicity was coded using the National Center for Health Statistics' bridged race and ethnicity variable to ensure consistency of coding over time and grouped as Hispanic, Non-Hispanic White (hereafter referred to as White), Non-Hispanic Black (hereafter referred to as Black), Asian, and American Indian/Alaska Native (AI/AN). Rates were also computed according to age (<25, 25−64, ≥65 years), and time-period at death (1999–2004; 2005–2009; 2010–2014; 2015–2020). Additionally, all rates were stratified according to sex (male/female) as females are more likely to be carriers of haemophilia and experience less severe disease compared to males.

Age-adjusted death rate ratios (aRR) and 95% confidence intervals (CI) were calculated to compare rates across racial and ethnic groups as well as time period and age. These aRRs were used to test statistical significance, if aRR's 95%CI did not include the null (i.e., '1'), differences were considered to be statistically significant. Among people with haemophilia listed in their death certificate, the median age of death and underlying cause of death were considered. For these outcomes, time periods were condensed into two categories (1999–2009; 2010–2020) to ensure adequate sample sizes for statistical reliability for Hispanic and Black populations. For Asian and American Indian/Alaska Native persons, the median age and causes of death were not stratified as there were fewer deaths in these groups. The underlying cause of death was categorized using mutually exclusive ICD-10 sub-chapter death groupings, with three modifications: (1) liver disease, viral hepatitis, and liver cancer were combined into one category; (2) non-liver cancers (includes all cancers except liver cancers) were grouped together; and (3) heart diseases were combined into one category (ischemic, myocardial infarction, heart failure). Based on the ICD-10 sub-chapter subgrouping, deaths due to coagulation defects included people who died from Factor VIII or Factor IX deficiencies, whereas intercranial haemorrhage and other haemorrhage were considered separately. Analyses were conducted with SAS version 9.4.

3 | RESULTS

In the US, there were 3115 males with haemophilia listed as a cause of death between 1999 and 2020. Approximately 76.1% of deaths occurred in White males (n = 2370), 13.3%,

7.4%, 2.2% and 0.9% occurred in Black (n = 413), Hispanic (n = 233), Asian (n = 69), and American Indian/ Alaska Native males (n = 28), respectively (Table 1). There were two rHD with missing race and ethnicity data.

During the 21-year study period (1999–2020) the age-adjusted rHD rate declined by nearly half from 1.37 in 1999–2004 to 0.76 in 2015–2020 per 1 million males in all race/ethnicities combined. Between 1999−2004 and 2015−2020, rates declined by 46% in White (aRR = 0.54, 95%CI 0.48, 0.60), 44% in Black (aRR = 0.56, 95%CI 0.43, 0.74), and 42% in Hispanic (aRR = 0.58, 95%CI 0.39, 0.88) males. During the study period, rates were statistically significantly higher among Black males (aRR = 1.30, 95%CI 1.16, 1.46) and statistically significantly lower among Hispanic (aRR = 0.67, 95%CI 0.57, 0.78) and Asian males (aRR = 0.50, 95%CI 0.39, 0.64) relative to White males during the entire study period (1999–2020) (Table 1). There were no statistically significant differences between American Indian/Alaska Native males' age-adjusted rHD rates when compared to White males. In period stratified analyses, Black males' age-adjusted rHD rates were higher than White males during 1999−2004 (aRR = 1.27, 95%CI 1.03, 1.53), 2005−2009 (aRR = 1.33, 95%CI 1.05, 1.70), and 2015−2020 (aRR = 1.33, 95%CI 1.06, 1.65) (Figure 1, Table 1). When stratified according to age, Black (aRR = 2.52, 95%CI 1.46, 4.33) and Hispanic (aRR = 1.75, 95%CI 1.01, 3.04) males aged < 25 years had significantly higher rates compared to White males, and Black males' recorded haemophilia death rate (aRR = 1.33, 95%CI 1.11, 1.58) was also elevated in the ≥65 years age group.

Among males with rHD, the median age at death rose 11 years, from 54.5 years in 1999−2009 to 65.5 years in 2010−2020 (Table 2). The increase in the median age of rHD was observed for each racial and ethnic group analysed but remained 12 years younger in Hispanic (56 years) and Black (56 years) persons relative to White males (68 years) in the most recent period (2010–2020). As a result of this gap, the average age of death among Black males with recorded haemophilia death in 2010−2020 (56 years) approximated what was observed in White males a decade earlier (56.5 years in 1999−2009). During the entire study period, the median age of death was on average 10 years lower for Black and Hispanic males compared to White males.

In terms of the underlying cause of death, coagulation defects (34.0%) were the most common during 1999−2009, followed by HIV (18.8%) and liver disease (9.8%) (Table 3). In the most recent 10 years of data (2010–2020), coagulation defects (33.9%), liver disease (11.5%), heart disease (9.4%), and non-liver cancers (8.3%) were the leading causes of death among White males. In 2010−2020, coagulation defects were the leading underlying cause of death (40.3%) among Black men as well, with a higher proportion than what was observed among White males (33.9%). HIV was the second leading cause of death among Black males (11.0%) between 2010 and 2020. Also, liver-related diseases were not among the top five causes of death for Black males with recorded haemophilia death during 2010−2020. Intracranial and intracerebral hemorrhage (ICH) was the underlying cause of death in 55 (or 1.7%) of the males included. This proportion did not vary across race and ethnicity nor age.

There were 930 reported haemophilia deaths among females with an age-adjusted death rate of 0.22 per 1 million females (Table 4). Age-adjusted haemophilia death rates were steady during the study period, ranging from 0.22 per 1 million females in 1999−2009 to 0.20 per 1 million females in 2010−2020, and remained similar across the study period for NH White, Black, and Hispanic females (Figure 2). The rHD rate was statistically significantly higher in Black versus White females (aRR = 2.46, 95%CI 2.10, 2.90) and non-significantly lower in Hispanic versus White females (aRR = 0.74, 95%CI 0.53, 1.01). The overall median age of death among females with recorded haemophilia death was 79.5 years and due to insufficient numbers of racial and ethnic single-age at deaths, the proportion of deaths by broad age groups were computed according to race and ethnicity. Over 60% of reported haemophilia deaths were in White (69.0%) and in Black (62.7%) women who were ≥75 years, with nearly a third occurring in women 85 years and older. The leading causes of death were coagulation defects (n = 517, 55.6%), heart disease (n = 125, 13.4%), and cancer (n = 55, 5.9%).

4 | DISCUSSION

In our study of US death certificate data, reported haemophilia death rates improved between 1999 and 2020 among males across all race/ethnicities. However, Black males had persistently higher rHD rates. Among males with haemophilia listed as a cause of death, the median age at death rose from 54.5 to 65.5 years between 1999 and 2020. However, Black males' average age at death was 10 years younger compared to White males in the most recent time period (2010–2020). This exploratory study suggests that progress in haemophilia outcomes may not be experienced equitably across minoritized racial and ethnic groups.

Our study showed that Black males experienced higher recorded haemophilia death rates in the past 21 years. Death rates are a function of both disease occurrence and survival. While it's not fully known whether there are racial and ethnic differences in haemophilia occurrence, several previous studies support the hypothesis that occurrence may be similar. Based on a global study, haemophilia occurrence at birth does not vary across country of origin showing similar prevalence across countries with national registries.[10] Furthermore, there is no known biological or other reason for racial and ethnic differences in Factor VIII or IX deficiencies. Based on data from US Haemophilia Treatment Centers (HTCs), the prevalence of haemophilia is slightly lower in Black males (12.4 cases per 100,000 males) compared to White (15.1 cases per 100,000) males, these prevalence differences could be due to lower survival rates in Black versus White persons.[11] It could also be that Black males' lower prevalence of haemophilia in US HTC data is related to racial and ethnic differences in access to HTC care and/or underdiagnosis of mild and moderate haemophilia among Black persons in the US.[9]

If haemophilia occurrence is similar across race/ethnicities, our finding of higher recorded haemophilia death rates among Black versus White males suggests lower haemophilia-specific survival among Black males. Earlier studies of death certificate data showed similar reported haemophilia death rates in Black and White males between 1979 and 1995, when prophylaxis was not widely used, and HCV/HIV infection became common.[2,12] In the US,

HIV and HCV transmission were prevalent during the early 1980′s due to contaminated blood products, but transmission declined in the mid 1980′s due to viral inactivation procedures.[13] HIV and HCV-associated liver disease were the leading cause of death up until the early 2000′s due to ongoing consequences of these infections.[5] Our observation that Black men had a lower median age at death and that HIV continues to be a leading cause of death among Black males with haemophilia listed in their death certificate in both earlier and recent years could signal ongoing survival disparities among Black people with haemophilia and an HIV infection. In a study among those in the general population with HIV, Black persons were less likely to be treated with antiretroviral drugs that suppress HIV replication, and HIV is less controlled relative to White persons.[14] Whether this is also true in people with haemophilia who have an HIV infection is not yet known.

Other characteristics associated with haemophilia-specific survival include age, severity, and the development of inhibitors.[4,15] The extent to which these characteristics might account or explain racial and ethnic differences in haemophilia survival are not yet known. However, age-adjusted rates and ratios were used to standardize known racial and ethnic differences in underlying age distributions.[16] In terms of severity, a higher proportion of Black or Hispanic males have severe haemophilia in the US HTC registry; however, this may partly reflect lower use or access to HTCs for non-White persons with mild or moderate haemophilia.[9] Also, it’s unclear if there’s a biological basis for racial and ethnic differences in the level of Factor VIII or IX deficiency. For inhibitors, previous studies note that both Black and Hispanic males may be more likely to develop inhibitors, although the underlying aetiology is uncertain.[17]

To close potential gaps in haemophilia survival, identifying disparities in treatment is crucial, given that treatment can be intervened upon. People with severe haemophilia and some with moderate disease are recommended to receive prophylaxis, which has been attributed to population-wide increases in life-expectancy.[1] For example, among people with severe haemophilia A in the US, prophylaxis use doubled between 1999 and 2010 from 31% to 59%.[18] Prophylaxis treatment among people with moderate and severe haemophilia B were mostly similar in Black versus White males and another study found similar adherence to prophylaxis in non-white and White people with haemophilia.[19–21] In people with haemophilia who have inhibitors, immune tolerance induction (ITI) is used to eradicate inhibitors and restore factor-replacement effectiveness. Earlier investigations found that while most people with severe haemophilia A with inhibitors received ITI, its use were lower among a relatively small number of Black versus White people with an inhibitor and a recent and nation-wide study, showed lower receipt of ITI among Black versus White males with severe haemophilia A and inhibitors.[22,23]

On a broader scale, Black males in the US general population have higher death rates than White males, due to disparities in economic mobility, as well as lower educational attainment, barriers in accessing to healthcare, and greater comorbidity burden.[24,25] In the current study, we did not have information on whether a person had haemophilia, so we were unable to explicitly tease out whether mortality disparities for those with haemophilia were on par with those among people without haemophilia. However, the magnitude of Black versus White age-adjusted rate ratios in the general population (aRR = 1.35) was comparable

with what was observed for recorded haemophilia deaths (aRR = 1.29). Our findings of lower aRRs for Asian and Hispanic males versus White males were analogous to what is observed in the general US population.[26,27] The lower mortality rates among Hispanic persons in the general US population despite disadvantageous risk profiles has been referred to as the 'Hispanic paradox', perhaps due to 'health migrant' effects, advantageous survival and resilience.[28] Asian Americans live approximately 8 years longer than the US average possibly due to the 'health migrant' effect as well, 'salmon-bias' where people return to their home country at the end of life, and healthier behaviors.[29] The applicability of these general patterns to the US Hispanic and Asian haemophilia population is not yet known.[29] It is also noteworthy that while the overall age-adjusted haemophilia death rate is much lower in those aged <25 years, Black and Hispanic males' age-adjusted haemophilia death rates were higher than White males in this age group, suggesting that racial and ethnic differences in recorded haemophilia deaths may not be related to comorbidities, which often develop later in life. Studies to better understand how haemophilia-specific factors as well as general healthcare and societal factors might contribute to racial and ethnic disparities in haemophilia mortality are warranted.

Recorded haemophilia death rates for females were far lower than what was observed in males, and the median age of death was similar to the US general population. This lower rate of death among females is also seen in other data sources; among 2501 deaths among persons with haemophilia reported to CDC's bleeding disorder data collection system, only 59 or 3.8% of decedents were female.[30] In our study using US death certificate data, there were 4045 recorded haemophilia deaths (either listed as the underlying or leading cause of death), and 930 or 22.9% of them were among women and girls. It is not known the extent to which haemophilia is considered as a cause of death when healthcare providers fill out death certificates, especially among women and girls. Haemophilia is an X-linked condition, most female haemophilia carriers are either asymptomatic or have mild disease (>5 and <40% factor levels of normal).[31,32] It has been estimated that for each male with haemophilia, 1.6 female carriers can be identified and among people seen at US HTCs, about one in every five people with mild haemophilia were women or girls.[33] Females with mild haemophilia experience complications that include heavy menstrual bleeding, bleeding during pregnancy, and after medical procedures.[34] Female carriers with factor levels 0.41–0.60 have also been reported experience spontaneous bleeding and in response to medical interventions more frequently than non-carriers.[35] In terms of complications and contributions to death, it is not known if healthcare providers completing the death certificates were aware of haemophilia carriership and/or factor activity level of each female decedent. Female decedents whose causes of death included haemophilia as a leading cause may have been among the small proportion of female haemophilia carriers who have severe haemophilia.

Our study has several limitations. Information on whether a person had been diagnosed with haemophilia was not available in the US death certificate data, and it is not known what proportion of people with haemophilia have it listed as a cause of death on their certificate. Recorded haemophilia deaths are also a function of receiving a diagnosis and those with fewer resources and minoritized racial and ethnic minorities may be less likely to have their milder forms diagnosed, possibly driving down the number of deaths in these groups. Another limitation is accurate coding of the cause of death. Previous auditing

studies in the general population have noted errors in the reporting of underlying and immediate causes of death and inconsistent coding of the leading cause of death among people with haemophilia is plausible.[36,37] For example, if a person with haemophilia died from intercranial haemorrhage, their death could be coded as 'hemophilia' or 'ICH'; thus, the cause of death data should be interpreted with caution. The National Center for Health Statistics has implemented quality improvement projects (e.g., clinician and non-clinician training, providing feedback) to improve the overall accuracy of death certificate recording in more recent years.[38] Furthermore, there could be misreporting of race and ethnicity in death certificates, though a NCHS validation study found that the accuracy of race coding is higher for White and Black persons but is less accurate for Asian, American/Indian Alaska Native, and Hispanic persons.[39] Another limitation of our study is that disparities in death rates during the current study period (1999–2020) could be influenced by previous trends, for example if Black persons with haemophilia died at a faster rate than White persons in earlier time periods, the number of older Black persons at risk of dying from haemophilia during our study period would be lower, possibly underestimating death rates. However, previous studies of US death certificates report similar recorded haemophilia death rates in Black versus White males from 1979 through 1995.[2,12]

In conclusion, recorded haemophilia death rates declined between 1999 and 2020 among White, Black, and Hispanic males. However, rates were higher, and deaths occurred earlier in life among Black males compared to White males. Nonetheless, given the inherent limitations of the data source used for this analysis, further studies of survival rates and disparities in haemophilia are needed.

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DATA AVAILABILITY STATEMENT

The US National Death Certificate data is publicly available. It can be accessed through the Centers for Disease Control and Prevention WONDER portal: https://wonder.cdc.gov/mcd.html

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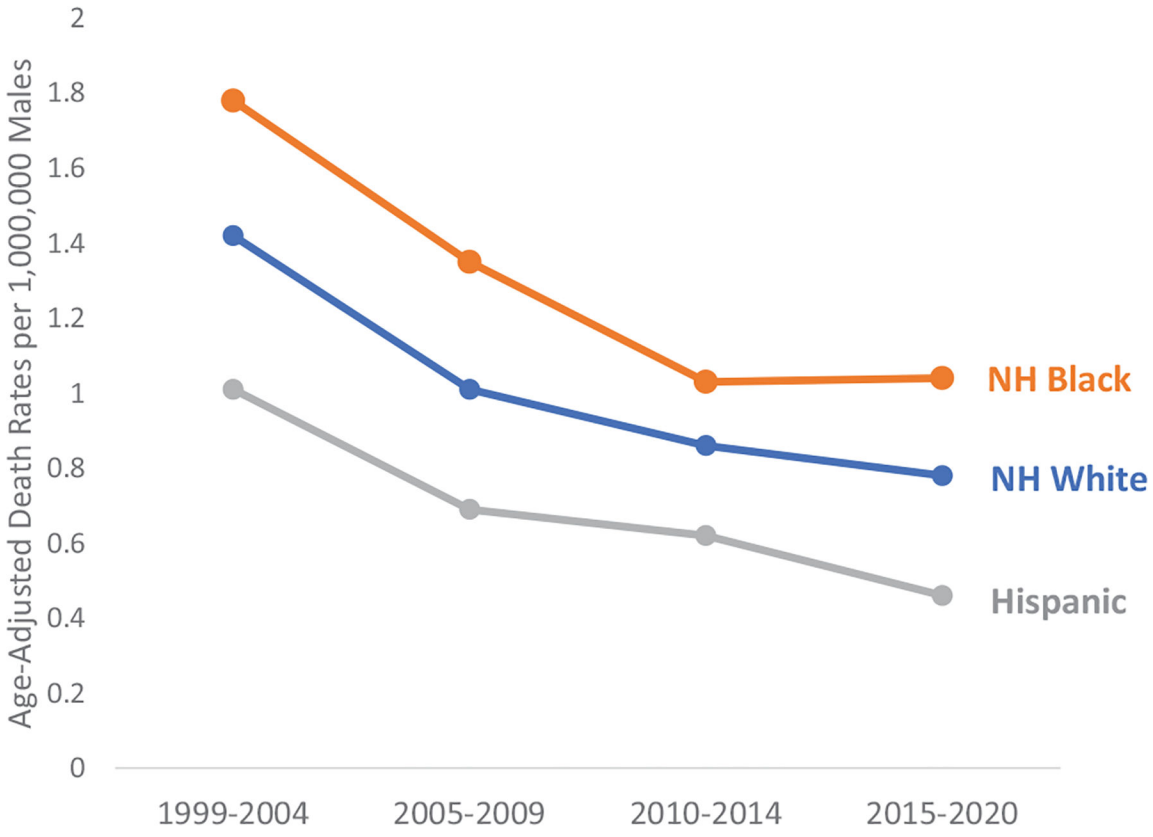

FIGURE 1.
Age-adjusted death rates among males according to race and ethnicity, National Vital Statistics 1999−2020. NH, non-Hispanic.

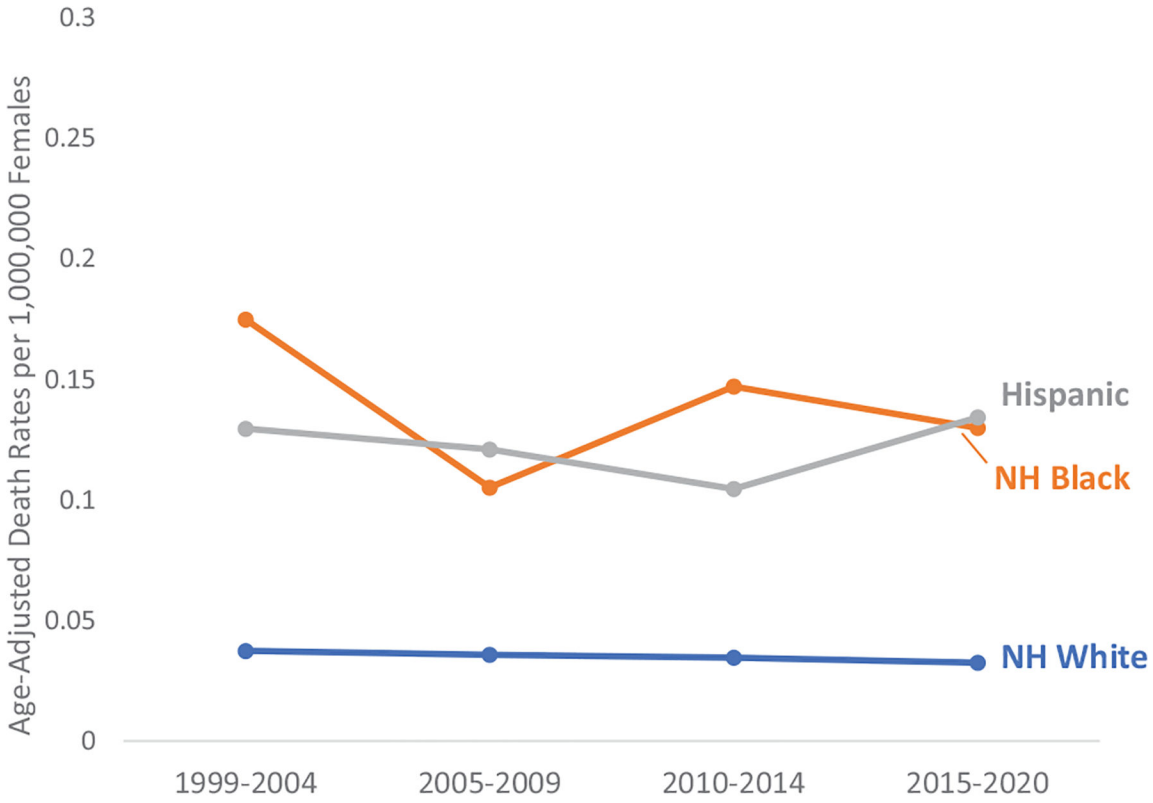

FIGURE 2.
Age-adjusted death rates among females according to race and ethnicity, National Vital Statistics 1999−2020.

TABLE 1

Age-adjusted recorded haemophilia death rates and rate ratios among males according to race and ethnicity, 1999–2020.[a]

	Total	White	Black	Hispanic	Asian	American Indian/Alaska Native
No. of deaths	3115	2370	413	233	69	28
Age-adjusted recorded haemophilia death rates (age-adjusted haemophilia death rates) per 1,000,000 males and (95%CI)						
1999–2020	0.98 (0.95,1.01)	1.02 (0.98,1.06)	1.33 (1.12,1.46)	0.69 (0.59,0.79)	0.51 (0.39,0.64)	1.09 (0.67,1.52)
1999–2004	1.37 (1.28,1.45)	1.42 (1.32,1.52)	1.78 (1.45, 2.11)	1.01 (0.73,1.30)	–	–
2005–2009	0.98 (0.90,1.05)	1.01 (0.92,1.11)	1.35 (1.04,1.65)	0.69 (0.46,0.92)	–	–
2010–2014	0.84 (0.76,0.91)	0.86 (0.78,0.94)	1.03 (0.77,1.27)	0.62 (0.43,0.83)	–	–
2015–2020	0.76 (0.70,0.81)	0.78 (0.72,0.85)	1.04 (0.83,1.25)	0.46 (0.32,0.64)	–	–
<25 years	0.12 (0.09,0.14)	0.08 (0.05,0.11)	0.21 (0.13,0.30)	0.15 (0.08,0.21)	–	–
25–64 years	0.73 (0.69,0.76)	0.80 (0.75,0.85)	0.91 (0.80,1.02)	0.47 (0.39,0.55)	–	–
65+ years	3.75 (3.55, 3.94)	3.80 (3.60,4.01)	5.02 (4.16, 5.88)	2.77 (2.10,3.48)	–	–
Age-adjusted death rate ratios (95%CI)						
1999–2020	–	1.00 (ref)	1.30 (1.16,1.46)	0.67 (0.57,0.78)	0.50 (0.39,0.64)	1.06 (0.72,1.57)
1999–2004		1.00 (ref)	1.27 (1.03,1.53)	0.71 (0.52,0.96)	–	–
2005–2009		1.00 (ref)	1.33 (1.05,1.70)	0.68 (0.48,0.97)	–	
2010–2014		1.00 (ref)	1.19 (0.92,1.54)	0.73 (0.52,1.01)	–	
2015–2020		1.00 (ref)	1.33 (1.06,1.65)	0.70 (0.53,0.94)	–	
<25 years		1.00 (ref)	2.52 (1.46,4.33)	1.75 (1.01, 3.04)	–	
25–64 years		1.00 (ref)	1.13 (0.99,1.30)	0.58 (0.49,0.69)	–	
65+ years		1.00 (ref)	1.33 (1.11,1.58)	0.73 (0.57,0.94)	–	

Abbreviations: CI, Confidence Interval; No, Number.

[a]White and Black are among non-Hispanic White and non-Hispanic Black males, respectively. Number were not computed for certain racial and ethnic groups for certain age and time period strata due to sample sizes. Age-adjustment used 10-year age groupings.

TABLE 2

Median age of death among males with haemophilia listed in cause of death according to race and ethnicity, 1999–2020.[a]

	Total	White	Black	Hispanic	Asian	American Indian/Alaska Native
No. of deaths	3115	2370	413	233	69	28
Median age of death (IQR)						
1999–2020	59.5 (43, 76.5)	62 (45.5, 78.5)	52 (37, 71)	51.5 (32,71.5)	61 (43, 52)	46 (23, 60)
1999–2009	54.5 (38.5, 72.5)	56.5 (40.5,76.5)	48 (33.5, 68)	40 (26.5, 60)	54.5 (31,72)	40 (10, 59.5)
2010–2020	65.5 (51, 78.5)	68 (54.5,80)	56 (43.5, 74)	56 (34.5, 72)	65 (50, 79)	46 (22.5, 58)

Abbreviations: IQR, Interquartile range; No, Number.

[a]White and Black are among non-Hispanic White and non-Hispanic Black males, respectively. Numbers were not computed for certain racial and ethnic groups for certain age and time period strata due to sample sizes.

TABLE 3

Underlying cause of death among males with recorded haemophilia death according to race and ethnicity, 1999–2020.[a,b]

	Total	White	Black	Hispanic	Asian	American Indian/ Alaska Native
No. of deaths(%)	3115 (100%)	2370 (76.1%)	413 (13.3%)	233 (7.5%)	69 (2.2%)	28 (0.9%)
Underlying cause of death based on NCHS-sub chapter deaths 1999–2020 *n* (%)						
1	Coagulation defects 1079 (34.6%)	Coagulation Defects 861 (33.2%)	Coagulation Defects 174 (41.4%)	Coagulation Defects 79 (33.9%)	Coagulation Defects 29 (42.0%)	Coagulation Defects 15 (51.7%)
2	HIV 410 (13.2%)	HIV 339 (13.1%)	HIV 63 (15.0%)	Liver Cancer, Disease, and Viral Hep 29 (12.4%)	Liver Cancer, Disease, and Viral Hep 8 (12.4%)	HIV 3 (10.3%)
3	Liver Cancer, Disease, and Viral Hep. 310 (10.0%)	Liver Cancer, Disease, and Viral Hep 275 (11.6%)	Heart Disease 34 (8.2)	HIV 26 (8.2%)	Heart Disease 6 (8.7)	Liver and Viral Hep 3 (10.3%)
4	Heart Disease 244 (7.8%)	Non-Liver Cancer 195 (8.2%)	Accidents/Wounds 21 (5%)	Heart Disease 16 (6.9)	HIV 5 (7.2%)	Accidents 2 (6.9%)
5	Non-liver cancer 210 (6.7%)	Heart Disease 190 (8.0)	Non-liver cancer 19 (4.6%)	Cerebrovascular 12 (5.2%)	Non-liver cancer 4 (5.8%)	Surgical Complications 2 (6.9%)
Underlying cause of death based on NCHS sub chapter death 1999–2009 *n* (%)						
1	Coagulation defects 587 (34.0%)	Coagulation Defects 432 (32.5%)	Coagulation Defects 97 (41.8%)	Coagulation Defects 37 (31.4%)	-	-
2	HIV 325 (18.8%)	HIV 258 (19.4%)	HIV 43 (18.5%)	HIV 19 (16.1%)		
3	Liver Cancer, Disease and Viral Hep 167 (9.8%)	Liver Cancer, Disease and Viral Hep 134 (10.0%)	Heart Disease 17 (7.3)	Liver Cancer, Disease and Viral Hep 16 (13.6%)		
4	Heart Disease 119 (6.9%)	Heart Disease 92 (6.9%)	Accidents 11 (4.7%)	Non-liver Cancer 7 (5.9%)	-	-
5	Non-liver Cancer 104 (6.1%)	Non-liver Cancer 91 (6.8%)	Liver Disease, Cancer and Viral Infections 10 (4.3%)	Heart Disease 6 (5.1)	-	
Underlying cause of death based on NCHS sub-chapter death 2010–2020 *n* (%)						
1	Coagulation Defects 492 (35.4%)	Coagulation defects 353 (33.9%)	Coagulation defects 73 (40.3%)	Coagulation defects 42 (36.5%)	-	-
2	Liver Cancer, Disease and Viral Hep 143 (10.4%)	Liver Cancer, Disease, and Viral Hepatitis 120 (11.5%)	HIV 20 (11.0%)	Liver Cancer, Disease, and Hepatitis 12 (10.0%)		
3	Heart Disease 125 (9.0%)	Heart Disease 98 (9.4%)	Heart Disease 17 (9.4)	Cerebrovascular 9 (7.8%)	-	-
4	Non-liver Cancer 106 (7.7%)	Non-liver Cancer 86 (8.3%)	Non-liver Cancer 11 (6.0%)	Heart Disease 8 (6.9%)		
5	HIV85 (6.1%)	Accidents 59 (5.7%)	Cerebrovascular 10 (5.5%)	Non-liver cancer 5 (4.3%)	-	-

Abbreviations: age-adjusted haemophilia death rate, age-adjusted haemophilia-related death; CI, Confidence Interval; Hep, Hepatitis; HIV, Human Immunodeficiency Virus; IQR, Interquartile range; NCHS, National Center for Health Statistics; No, Number.

[a] White and Black are among non-Hispanic White and non-Hispanic Blackmales, respectively. Numbers were not computed for certain racial and ethnic groups for certain age and time period strata due to sample sizes.

[b] Based on NCHS subgrouping with the following modifications: three modifications: (1) liver disease, viral hepatitis, and liver cancer were combined into one category; (2) non-liver cancers (includes all cancers except liver cancers) were grouped together; and (3) heart diseases were combined into one category (ischemic, myocardial infarction, heart failure).

TABLE 4

Age-adjusted recorded-haemophilia death rates, rate ratios, proportion of deaths according to age group and leading causes of death among females, 1999–2020.[a,b]

	Total	White	Black	Hispanic
No. of deaths[a]	930	674 (72.4%)	190 (20.4%)	43 (4.6%)
Age adjusted death rates 1999–2020	0.22	0.20	0.48	0.15
aRR 1999–2020	–	1.00 (ref)	2.46 (2.10, 2.90)	0.74 (0.53,1.01)
Proportion of deaths according to age				
<65 years	138 (14.8%)	89 (13.2%)	28 (14.7%)	
65–74 years	174 (18.7%)	120 (17.8%)	41 (21.6%)	
75–84 years	320 (34.4%)	233 (34.6%)	67 (35.3%)	
85+years	298 (32.0%)	232 (34.4%)	54 (28.4%)	
Underlying cause of death based on NCHS-sub chapter deaths 1999–2020 *n* (%)				
1	Coagulation defects, 517 (55.6%)	Coagulation defects, 361 (53.6%)	Coagulation defects, 104 (94.7%)	
2	Heart disease 125 (13.4%)	Heart disease 88 (13.0%)	–	
3	Cancer 55 (5.9%)	Cancer 43 (6.4%)	–	

[a]Therewere 16 deaths among Asian females, data are not presented due to unreliable estimates. There were seven death certificates without information on race and ethnicity.

[b]Based on NCHS subgrouping with the following modifications: three modifications: (1) liver disease, viral hepatitis, and liver cancer were combined into one category; (2) non-liver cancers (includes all cancers except liver cancers) were grouped together; and (3) heart diseases were combined into one category (ischemic, myocardial infarction, heart failure).