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Article type : Review Article

**Mortality in congenital hemophilia A – A systemic literature review**

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**Short title:** Mortality in congenital hemophilia A [36/50 characters]

**Target journal:** *Journal of Thrombosis and Haemostasis*

**Type:** Review

**Word count:** 5210/5000

**Figure and tables:** 2 figures, 4 tables/8

**References:** 74/100

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JTH.15189](https://doi.org/10.1111/JTH.15189)

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**Abstract** [Unstructured, 247/250]

Against a background of a rapidly evolving treatment landscape, a contemporary, evidence-based consolidated understanding of mortality in people with congenital hemophilia A (PwCHA) is lacking. This systematic literature review examines the available data on mortality and causes of death in PwCHA, to enable a better understanding of fatalities in PwCHA and evaluate the impact of new treatment paradigms on mortality.

A systematic literature review of observational studies was conducted by searching Medline, Embase, and clinical trials registries for articles published from January 2010 to March 2020, using the search terms: hemophilia A (HA), mortality, cause of death. Interventional studies, studies not reporting fatalities, and those reporting only on hemophilia B, acquired HA, or mixed other coagulopathies were excluded.

Overall, 7818 unique records were identified and 17 were analyzed. Of these, six reported mortality rates and five reported mortality ratios. Mortality generally decreased over time, despite a spike associated with human immunodeficiency virus (HIV)/hepatitis C virus (HCV) infection in the 1980s-1990s. Mortality was strongly correlated with age and hemophilia severity. People with hemophilia had a raised mortality risk compared with the general population, particularly in severe hemophilia, and when infected with HIV or HCV. Causes of death varied across populations, countries, and time in 15 identified studies; however, incomplete and heterogeneous reporting limits evidence. Hemorrhage, HIV, HCV, and hepatic disease were the leading causes of death.

A unified approach to reporting mortality and cause of death is needed to understand mortality in PwCHA as treatments continue to advance.

**Keywords:** benchmarking, cause of death, hemophilia A, mortality, systematic review

## 1 | INTRODUCTION

Hemorrhage, particularly hemarthrosis, is the principal hallmark of hemophilia A (HA), and its damaging impact on the life expectancy of people with congenital hemophilia A (PwCHA) is well established [1,2]. Although hemophilia was recognized in the 1800s, and transfusion of blood and plasma slightly improved life expectancy in the 1900s, treatment remained largely unchanged until the 1964 discovery of factor VIII (FVIII) in cryoprecipitate prepared from blood plasma [3,4]. Lyophilized plasma FVIII concentrates revolutionized treatment, and the 1970s saw huge leaps in the life expectancy of PwCHA [5]. Unfortunately, this breakthrough brought devastation in its wake: the

life expectancy of PwCHA was severely affected during the 1980s and early 1990s by human immunodeficiency virus (HIV) and hepatitis C virus (HCV), contracted from contaminated blood products [6]. HIV-infected blood caused the first reported case of acquired immunodeficiency 5 - syndrome (AIDS) in a person with hemophilia in 1982, which was followed by thousands of others across the globe and a significant rise in mortality among PwCHA [4,7,8]. It is estimated that in the USA almost 5000 people with hemophilia (PwH) became infected with HIV, and over 4000 of the 10 000 PwH in the USA died [4].

Despite this, the life expectancy of PwCHA has generally improved over recent decades [9]. Clotting factor product safety measures have been implemented, including exclusion of at-risk plasma donors, viral screening of blood donations such as nucleic acid testing, and a number of in-process viral inactivation and/or removal steps (eg, solvent-detergent and heat treatment, nanofiltration) [10]. The viral attenuation of plasma-derived concentrates, availability of recombinant factor concentrates, and widespread adoption of FVIII prophylaxis in place of on-demand treatment have dramatically reduced the treatment risk and severity of hemophilic arthropathy, and led to a substantial fall in mortality rates [11-14]. However, around 30% of PwCHA develop FVIII inhibitors, which may render FVIII replacement therapy ineffective for those individuals and require use of alternative and less effective therapies. The presence of FVIII inhibitors has a significant detrimental impact on quality of life and life expectancy [1,15].

In recent years, innovative therapeutics have been introduced, including extended half-life FVIII products and non-factor replacement products such as a humanized bispecific monoclonal antibody, which replaces the function of missing activated FVIII [16]. Further products are under development, including gene therapies [16], a ribonucleic acid (RNA) interference therapeutic targeting antithrombin [17], tissue factor pathway inhibitors [18], and new delivery forms for FVIII concentrates [16]. The introduction of these therapeutics, and the shift towards comprehensive, lifelong prophylaxis, might be expected to increase life expectancy and decrease mortality rates for PwCHA.

Advances in the care of PwCHA have progressively improved life expectancy, almost to the level observed in the general population [12]. While there are existing publications on mortality in PwCHA, many are historical and none reflect recent therapeutic advances. The literature is lacking a contemporary, evidence-based evaluation of mortality in PwCHA. An understanding of past and present mortality and causes of death in PwCHA is vital, as these will change over time and continue to evolve as innovative new treatments are developed [12]. It is therefore crucial that relevant study and registry data are collected and published to provide benchmark data on life expectancy and cause of death and to identify any gaps.

This systematic literature review aims to examine the available data on mortality in PwCHA. Specifically, the scope covers mortality in observational studies in PwCHA, with or without FVIII inhibitors, including all age groups and mild, moderate, and severe disease. Additionally, this review evaluates causes of death in PwCHA, providing an essential part of the evidence base supporting the development of an algorithm to assess mortality in PwCHA (please see Pipe et al publication in this supplement).

## 2 | METHODS

**2.1 | Search scope.** A comprehensive search of Medline, Embase, the Cochrane Central Register of Controlled Studies, clinicaltrials.gov, and conference abstracts was conducted on February 05, 2020 using search terms associated with *h(a)emophilia A, therapy, mortality, or cause of death*. For exact search terms used, please refer to the supporting information. The search was updated on March 17, 2020 to identify observational studies that did not mention specific therapies, and the final analysis captured records published between January 2010 and March 17, 2020.

**2.2 | Study population.** Interventional studies, studies not reporting on fatalities, studies reporting only on hemophilia B (HB) or acquired HA, and those with populations mixed with other coagulopathies were excluded. Although the search was intended to focus on congenital HA only, it was updated to include mixed populations of HA and HB and/or acquired and congenital hemophilia, as most historical cohort records were not able to differentiate between hemophilia types, and therefore studies with these mixed populations were included in the analysis. Studies encompassed all age groups and disease severities.

**2.3 | Outcome criteria.** Studies reporting on mortality rates, ratios or cause of death were included in the analysis.

**2.4 | Historical data.** Bibliographies of the studies reporting mortality rates were screened to identify pre-2010 records reporting on mortality rates or ratios in PwH, to provide historical context.

**2.5 | Data extraction.** Findings were screened by a single reviewer and the data were extracted into an Excel spreadsheet for analysis. Records selected for analysis were then manually searched to identify the study population, number of deaths, location, data collection period and type of study (as described in the primary reference), to give context to the results.

### 3 | RESULTS

In total, 7818 unique records were identified through the original and updated searches; 20 reported on mortality rates/ratios and/or cause of death; however, two of these only reported the cause of a single death [19,20], and the study population of one [21] overlapped with another record [22]. Therefore, 17 records are analyzed in this review. A PRISMA flow chart describes the selection process of the searches and reasons for record exclusion (Fig 1). Six records reported mortality rates (Table 1) [23-28], five reported mortality ratios (Table 2) [23,27,29-31], and 15 reported causes of death (Table 3) [15,22-26,28,29,31-37]. Many records did not specifically report on PwCHA; therefore, those analyzed included mixed populations of HA and HB, as well as congenital and acquired HA, where no differentiation was made. In this analysis, PwH refers to all people with hemophilia, including HA and HB; PwHA refers to people with HA, including congenital and acquired HA, and PwCHA refers only to people with congenital HA. The study period among all publications spanned 1968 through 2018, and most publications focused on the developed world.

#### 3.1 | Mortality rates and ratios

Nine observational studies published between 2010 and 2020 reported on crude mortality rates and/or mortality ratios; the data in these studies spanned 1968 to 2018 [23-31]. The mortality ratio (standardized mortality ratio [SMR] or hazard ratio [HR]) is an age-adjusted measure of excess risk in PwH compared with the general population where these PwH were drawn from [38]. Many studies did not differentiate by disease severity or presence of FVIII inhibitors, and none differentiated by treatment regimen.

Six records published crude mortality rates for PwHA or combined populations of HA and HB of all severities, which ranged from 0.2 to 1.0/100 person years (PY; Table 1) [23-28]. Five reported SMRs or HRs, comparing the observed mortality with expected mortality (that of the general male population), which ranged from 0.9 to 2.2 in the overall hemophilia population, and from 2.2 to 8.2 in the severe hemophilia population, including those with HIV and/or HCV/hepatitis B (HBV) infection (Table 2) [23,27,29-31]. When compared with age- and sex-matched controls in a Swedish cohort study, PwH of all severities had a greater risk of death, regardless of HIV or HCV/HBV infection (HR, 2.2;  $P < .001$ ) [29]. As expected, mortality was strongly correlated with age in the two studies that investigated age-specific mortality rates [26,27]. One study reported a lower HR in PwH without HIV infection, compared with all PwH [29], and one reported a lower SMR in PwH without HIV infection, or current or previous HCV infection, compared with all PwH [30]; these were identified as risk factors, along with hepatic disease [22].

**3.1.1 | Disease severity and mortality.** Studies indicated that severe HA is correlated with poorer clinical outcomes and an increased risk of mortality, compared with mild and moderate disease [23,30]. Four studies reported mortality rates for people with mild and moderate HA [23,26,28,30]. Eckhardt et al conducted a retrospective cohort study across 34 European and Australian centers (n = 2709) [26], while Lim et al utilized the American Thrombosis and Hemostasis Network database (n = 6606) [28]; both calculated a mortality rate of 0.2/100 PY (95% confidence interval [CI], 0.2-0.3) [26,28]. An Italian study by Tagliaferri et al found mortality rates of 0.2/100 PY (95% CI, 0.1-0.3) and 0.5/100 PY (95% CI, 0.3-0.7) for mild and moderate hemophilia, respectively (443 deaths) [23]. One publication, a cohort study from the Netherlands (n = 1031) by Hassan et al, reported SMRs for people with mild and moderate hemophilia: 1.0 (95% CI, 0.8-1.3) and 1.1 (95% CI, 0.7-1.7), respectively, compared with the Dutch male population [30].

Three studies reported on mortality for people with severe hemophilia [23,29,30]. Tagliaferri et al calculated a mortality rate of 0.9/100 PY (95% CI, 0.8-1.0; 443 deaths) among people with severe hemophilia [23]. A registry-based study in Sweden calculated a HR of 2.2 (95% CI, 1.8-2.7;  $P < .001$ ) for all PwH (n = 1431), compared with age- and sex-matched healthy controls (n = 7150), rising to 6.6 (95% CI, 4.5-10.0;  $P < .001$ ) for severe cases [29]. Hassan et al reported a SMR for people with severe hemophilia of 2.4 (95% CI, 1.8-3.0), again compared with the Dutch general male population [30].

**3.1.2 | Presence of FVIII inhibitors and mortality.** Two studies investigated a link between FVIII inhibitors in people with mild and moderate HA and the risk of mortality, with conflicting results [26,28]. The aforementioned study by Eckhardt et al found the all-cause mortality rate was 5.6 times higher among PwHA with FVIII inhibitors (2.1/100 PY; 95% CI, 1.2-3.3) than in PwHA without FVIII inhibitors [26]. In contrast, Lim et al found no association between mortality and FVIII inhibitors ( $P = .790$ ), with a mortality risk ratio between those without and those with FVIII inhibitors of 1.0 (95% CI, 0.3-3.1) [28].

**3.1.3 | Mortality rates over time.** Three publications reported mortality rates/ratios of PwH over time [23,30,31]. An Italian cohort study including people with severe HA found the SMR decreased from 1990-1999 (4.1; 95% CI, 2.6-6.3) to 2000-2007 (3.3; 95% CI, 1.8-5.7).[23] In the Netherlands, mortality in PwH had clearly decreased from 1992-2001 to 2001-2018, but was still higher than in the general population [30]. Finally, in Brazil, the SMR was calculated in 2-year intervals from 2000

to 2014 for PwH, progressively decreasing from 1.5 (95% CI, 1.3-1.74) in 2000-2002 to 0.9 (95% CI, 0.7-1.0) in 2012-2014 [31].

**3.1.4 | Mortality rates and ratios in pre-2010 publications.** Although eligibility for this review was limited to studies published since January 2010, six pre-2010 studies were identified through screening references to provide historical context (Table 4) [2,39-43]. Plug et al reported SMRs of 2.3 (95% CI, 1.9-2.8) among PwH of all severities (n = 967; 5% with FVIII inhibitors) and 5.1 (95% CI, 3.8-6.8) among people with severe hemophilia, respectively, compared with the general male population from 1992 to 2001 in the Netherlands [2]. The main cause of death was AIDS (26%), but HCV (22%) was also an important contributor in this time period [2]. Soucie et al analyzed mortality among 2950 PwH of all severities (5% with FVIII inhibitors) between 1993 and 1995 in six US states, calculating a mortality rate of 3.5/100 PY for PwHA [39]. Increased risk of death was associated with AIDS, infection with HIV, and hepatic disease ( $P < .001$ ) [39]. A survival analysis by Reitter et al (n = 226) found the cumulative relative survival ratio of PwH (9.3% with FVIII inhibitors) from 1983 to 2006 compared with the general Austrian male population was worse for severe cases (0.5; 95% CI, 0.4-0.6), but similar for mild and moderate cases (1.0; 95% CI, 0.9-1.1) [40]. Survival was lowest in PwH infected with HIV (0.3; 95% CI, 0.2-0.4) [40].

Finally, three publications reported mortality rates exclusively in PwH who were HIV-negative [41-43]. In 2004 and 2007 publications, Darby et al reported the mortality rate of the UK hemophilia population between 1977 and 1999 using the UK Haemophilia Centre Doctors' Organization database [41,42]. In 2004, Darby et al (n = 6078) reported mortality rates (/100 PY) of 2.0 (95% CI, 1.3-2.8) in 1977-1984, 2.3 (95% CI, 1.4-3.3) in 1985-1992, and 1.2 (95% CI, 0.5-1.9) in 1993-1999 for those with severe hemophilia with FVIII inhibitors, and 1.0 (95% CI, 0.8-1.2) in 1977-1984, 1.0 (95% CI, 0.7-1.3) in 1985-1992, and 1.2 (95% CI, 0.9-1.5) in 1993-1999 for those with severe hemophilia without FVIII inhibitors [41]. For people with severe hemophilia without HIV infection, FVIII inhibitors doubled the risk of mortality compared with those without FVIII inhibitors during 1977-1992, but in the latest time period of 1993-1999, mortality rates were identical between those with and without [41]. In 2007, Darby et al (n = 6018) found that all-cause mortality in people with severe hemophilia without HIV infection was higher than in the general population by a factor of 2.7 (95% CI, 2.4-3.1;  $P < .001$ ) [42]. PwH were more likely to die as a result of hemorrhage, hepatic disease, and Hodgkin disease, but less likely to die due to ischemic heart disease, compared with the general population [42]. Diamondstone et al published the Multicentre Hemophilia Cohort Study (n = 751) [43]. Crude mortality rates from 1986 to 1988 were 0.5/100 PY, 0.9/100 PY, and 1.3/100 PY for those with mild,

moderate, and severe coagulopathy, respectively, including HA (51%), HB (25%), von Willebrand disease (VWD; 7%), or other coagulopathies (5%) [43].

In summary, these pre-2010 studies estimated mortality rates of 0.5-3.5/100 PY and SMRs/HRs of 0.6-5.1 in comparison with 0.2-1.0/100 PY and 0.9-8.2 in the post-2010 studies, across all severities and with or without FVIII inhibitors, HIV, and/or HCV infection.

### 3.2 | Causes of death

Fifteen observational studies reported on cause of death in PwH (Table 3, Fig 2), with data collection spanning from 1968 to 2018 [22-26,28,29,31-37,44]. Causes were inconsistently categorized, and the most common causes varied according to the population, country, and time period. The most frequently observed causes of death were HIV/HCV/HBV and hepatic disease (32.4%), hemorrhage (21.4%), other (19.4%), and malignancy (9.9%; Fig 2A).

Of the 15 records, only one examined the relationship between cause of death and presence of FVIII inhibitors: Walsh et al (1998-2011) found a 70% increased risk of death among people with severe HA with current FVIII inhibitors, compared with those without ( $P < .01$ ), and these deaths were significantly more likely to be bleeding-related (42% versus 12%;  $P < .0001$ ) [22]. The majority of these were as a result of intracranial hemorrhage (ICH), which accounted for 70% and 67% of bleeding-related deaths in those with and without FVIII inhibitors, respectively [22].

Similarly, only one study accounted for disease severity. Lovdahl et al reported a higher proportion of immunodeficiency- and bleeding-related deaths and a lower proportion of malignancy-related deaths among Swedish people with severe hemophilia, compared with the overall hemophilia population [29].

**3.2.1 | Bleeding-related deaths.** The proportion of bleeding-related deaths varied greatly across countries and time periods, from 5.9% in a US-based study from 2010 to 2018 [28] to 52.6% in a report from Korea from 1991 to 2012 [34]. In a Brazilian study of PwH from 2000 to 2014, Jardim et al reported a 32.4% death rate from hemorrhage, of which the majority of deaths (54.0%) were due to ICH [31]; a similar pattern was seen in studies by Eckhardt et al in non-severe HA in Europe and Australia and by Yoo et al in HA in Korea, in which ICH occurred in 89.5% and 67.2% of bleeding-related deaths, respectively [26,34]. In two studies, the proportion of deaths due to bleeding episodes increased over time: an increase was seen from 1990-1999 to 2000-2007 in a study by Tagliaferri et al [23], and from 1973 to 2015 in a cohort of people with HA, HB, or VWD with HCV infection in a study by Eyster et al [35].



**3.2.2 | Virus-related deaths.** Complications from HIV/HCV infection were one of the most frequent causes of death, and were associated with a higher mortality rate [23,29]. The proportion of deaths from HIV varied widely, from 1% in 2000-2010 in a study of people with non-severe HA in Europe/Australia, to 55.9% in 1980-1989 in an Italian study of PwH [23,26]. Seven studies reported a peak of HIV-related deaths during the AIDS epidemic in late 1980s and early 1990s (Fig 2B) [23,25,28,29,33,36], which decreased from then on [23-26,31,33,35]. The proportion of deaths due to HCV/HBV infection or hepatic disease ranged from 6% (severe hemophilia) to 32% (severe hemophilia without FVIII inhibitors) [22,29]. Two studies also noted that coinfection with HIV/HCV may confer a greater mortality risk than either separately [25,35].

**3.2.3 | Deaths due to malignancy.** Malignancy was the most common primary cause of death for PwH in three studies [24,26,28], and ranged from 4.8% in a pediatric hemophilia study [44] to 26.0% in a study of people with non-severe HA [26]. Three studies observed an increase in cancer-related mortality over recent years [23,26,31], although this was equal to or lower than in the general population, presumably due to a lower life expectancy in PwH [23,29,33]; one exception was deaths due to hepatocellular carcinoma (HCC) [23,33], a complication of blood-borne infections. However, many publications were unclear whether they classified this under 'malignancy' or 'virus-related' deaths.

**3.2.4 | Deaths due to cardiovascular causes.** The proportion of deaths due to cardiovascular disease ranged from 4.8% of deaths in Italian people from 1980 to 2007 [23] to 25.5% in Brazilian people from 2012 to 2014 [31]. Two studies noted an increasing proportion of deaths from cardiovascular causes in PwH over recent years [23,31]. Nevertheless, several studies acknowledged that mortality due to cardiovascular events is still lower than in the general population [23,29,31,33], although it is worth noting that these events may be categorized differently in PwH than in the general population. For example, Franssen van de Putte et al reported that 13% of PwH died of stroke (including ICH and ischemic stroke) versus 6.5% of the general population, but in PwH 90% of fatal strokes were hemorrhagic, compared with 21% in the general population [33]. Hemophilia-related and non-hemophilia-related causes of death overlap, and a hemorrhagic stroke may be viewed as a cardiovascular event in the general population, but as a bleeding event in the hemophilia community. This may confound the findings, as discussed further in publications by Pipe et al and Peyvandi et al in this supplement.

## 4 | DISCUSSION

#### 4.1 | Incomplete reporting limits evidence on mortality in PwH

Studying mortality rates in a rare disease is challenging for many reasons. Firstly, small sample sizes are inevitable, and relevant reports may be scarce. Nationwide registries are often used to report mortality and causes of death, but may have poorer quality data than clinical trials, due to a lack of rigorous quality checks or standardized reporting [45]. Heterogeneity of medical terminologies, misclassification of the underlying cause of death, incomplete death certification, and inconsistencies across regions or time periods are all problems that frequently plague mortality registry data [46]. Moreover, data on mortality and causes of death in a rare disease are frequently handicapped by the absence of a standardized reporting framework; therefore, the already limited literature surrounding rare diseases is more complicated to interpret [47].

Limited reports on long-term outcomes lead to incomplete evidence on mortality in PwH, particularly in lower-income and developing countries [29,31,37]. The majority of studies identified by this systematic literature search included data from Western European countries or the USA, with only two from countries not classed as high-income using the World Bank Atlas method: Iran and Brazil [31,37], both of which are considered 'upper-middle-income economies' [48]. There are substantial differences in health services and hemophilia care across the countries in the included studies, therefore mortality rates are expected to vary. Study populations were also extremely heterogeneous, encompassing those with congenital and acquired HA/HB of different severities and with various comorbidities, including a pediatric study [44] and a study in PwH over 60 years of age [36]. Therefore, it is difficult to draw conclusions specifically about PwCHA.

In the one study that used a control group, PwH had a greater risk of death than the age- and sex-matched controls (HR, 2.2;  $P < .001$ ) [29]. This finding is in alignment with a study not assessed in this review (as it did not present mortality rates/ratios), in which the authors calculated a crude ratio of the prevalence of HA to its prevalence at birth. This ratio can be used as a raw measure of the survival disadvantage associated with the disease and alternative measure of life expectancy and mortality. In high-income countries (Canada, France, and the UK), the life expectancy disadvantage was 30% and 37% in all PwHA and people with severe HA, respectively, across 1991 to 2015 [49]. This suggests a substantial impact of HA on mortality, particularly severe HA [49], which is in agreement with the studies analyzed in this review.

Two studies published post 2010, by Eckhardt et al and Lim et al, both in mild and moderate HA [26,28], and one study published pre 2010, by Darby et al, in people with severe hemophilia without HIV infection [41], evaluated the association between FVIII inhibitors and mortality, with conflicting results [26,28]. Lim et al and Darby et al classified individuals as positive for FVIII inhibitors if they ever had a positive FVIII inhibitor test; it was not specified if these individuals were

still positive for FVIII inhibitors at the time of their death, and since FVIII inhibitors are often transient, this may have biased the results towards a finding of no association [28]. However, a study by Walsh et al in people with severe HA [22] also addressed the risk of death associated with FVIII inhibitors (although the publication provided no general measure of mortality). Walsh et al found a significantly increased risk of death, particularly hemorrhagic death, in PwH with current FVIII inhibitors compared with PwH without current FVIII inhibitors, suggesting the life expectancy of people with severe HA with FVIII inhibitors may be adversely affected by the limited efficacy of bypassing FVIII replacement therapy in this population [22,50].

Methodological differences led to a mixture of measures being used to capture mortality, which are not directly comparable. These included mortality rates, which measure the number of deaths in a population per PY and can be adjusted for age or other variables, and SMRs or HRs, which in this case compare the number of deaths in a select population with the overall population, can also be standardized to account for variables, and are presented as a ratio. Although SMRs and HRs use the same method of calculation, it has been found that using an internal control group (as when calculating an HR) may be more appropriate, and indirect standardization against national data may underestimate mortality risk [51]. Overall, the studies were disparate in their use or lack of a control group, with studies reporting mortality rates not using controls and those reporting ratios using the general male population or a selected group of healthy controls. These limitations and the relatively small datasets employed suggest that the current literature is not adequate to establish a benchmark mortality rate for PwCHA.

#### **4.2 | Categorization of causes of death was inconsistent**

In studies reporting cause of death among PwCHA [15,22-26,28,29,31-37], there were numerous disparities in categorization, such as whether bleeding-related events were due to trauma or spontaneous, and whether HCC was related to viral infection or malignancy. This review provides evidence for a framework for consistent mortality reporting in PwCHA (please see Pipe et al publication in this supplement). Despite these limitations, broad trends were consistently observed across different studies.

#### **4.3 | Primary cause of death changed over time**

Deaths relating to HIV infection in PwH peaked in the 1980s and early 1990s and decreased dramatically thereafter [23-26,31,33,35]. The variability in these reports is accounted for by the time span of the mortality calculations and the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s [52]. Deaths due to complications of HCV infection such as end-stage liver

disease or HCC exhibited a longer and later peak [23,35], perhaps due to the time taken to develop and succumb to these complications [53,54] or the development of highly effective antiviral therapies against HCV [55]. Two studies reported higher mortality rates when PwH were coinfecting with HIV and HCV [25,35]. HIV/HCV coinfection accelerates the progression of hepatic disease as the individual becomes significantly immunocompromised [56,57]. However, the impact of coinfection on life expectancy cannot be easily dissected out, since many coinfecting PwH had severe hepatic disease and AIDS at the time of death. After the introduction of triple therapy, both HIV-related and hepatic disease-related deaths declined considerably [58].

The proportion of deaths from hemorrhage increased as a primary cause of death in two studies [23,35]. However, Eyster et al noted that in their study, the increase in bleeding-related deaths may have been confounded by the development of thrombocytopenia secondary to portal hypotension as a result of progressive hepatic disease increasing the risk of bleeding, an important factor in a cohort with HCV infection [35]. The increase may also be confounded by a decline in deaths due to viral causes rather than an elevated risk from bleeding episodes, as virus-related deaths have generally fallen as the aftermath from contaminated blood products diminishes [23-26,31,33,35], and treatments to prevent bleeding in PwH continue to improve [14].

Two studies noted a recent fall in infant mortality due to ICH, not seen in the elderly in the study that included adults [31,44]. This may be a result of early primary prophylaxis in pediatric care [31,59]. Hemorrhage was a more prominent primary cause of death in the two countries without high-income economies, Brazil and Iran [31,37], highlighting the difficulties in comparing outcomes across countries. Treatment availability and overall hemophilia management varies greatly across countries, and the data from lower-income economies cannot be extrapolated to high-income economies, due to the gap in life expectancy [49]. It is predicted that bleeding-related mortality will decrease over time, particularly in the low- and middle-income countries, as prophylaxis is more broadly implemented and overall care improves [60].

Cancer and cardiovascular disease are increasingly prevalent causes of death in PwH, as improved treatment and prophylaxis options lead to impressive leaps in life expectancy and an expanding population of elderly PwH. The studies reviewed here suggest that malignancy rates in PwH are, with the exception of HCC and other virus-related malignancies [23,33,61], similar to or lower than in the general population [23,29,31]. Although cardiovascular disease accounts for a minority of deaths in PwH, four studies suggest mortality risk associated with cardiovascular disease may be lower in PwH than the general population [23,29,31,33]. It is speculated that the lower mortality rate could be due to the hypocoagulable state of PwH, since PwH appear to present with identical cardiovascular risk factors to the general population [62]. Moreover, PwH and HIV are

typically treated with HAART, which is associated with side effects such as dyslipidemia and diabetes, notable risk factors for cardiac events [62]. Despite these risk factors, PwH have a lower incidence of myocardial infarction than the general population [63,64]. The hypocoagulable state of PwH may be protective against thrombotic cardiac events by preventing the formation of the final blood clot which occludes the vessel and causes a myocardial infarction [65,66]. However, there is no scientific consensus, and the possible protective effect and death rates due to cardiovascular events among PwH have been disputed and may be reduced as treatment intensity increases [67-69]. A lower mortality rate from cardiovascular causes may be explained by a competing risk of death from bleeding- or virus-related causes [33]. Age may also account for a decreased proportion of deaths due to cardiovascular events, as mortality in PwH typically occurs at a younger age than the general population [36]. Additionally, inconsistent categorization of incidents such as hemorrhagic stroke, which may be considered to be bleeding-related in PwH but cardiovascular in the general population, may be another confounding factor. Some studies suggest that ageing PwH have a similar risk of cardiovascular disease to the general population, which may be exacerbated by a more sedentary lifestyle [70-72]. It is theorized that if a protective effect does exist, it may be eroded by new, more effective prophylaxis which achieves consistent FVIII levels [69], and increased use of prophylaxis to target higher FVIII activity levels and prevent all bleeds [73]. This may cause progression towards normalized cardiovascular risk for PwH as they achieve hemostasis [62].

The trends noted in this review were also recognized by a Norwegian study on life expectancy and causes of death in PwH from 1986 to 2018, published after the search was conducted for this review [74]. The publication reflects the findings of this review, reporting a shift away from hemophilia-related causes of death, such as hemorrhage and HIV infection, towards age-related causes of death more typical in the general population, such as cancer [74].

#### **4.4 | Limitations of this review**

This review is limited by the small number of deaths reported in some of the studies, the inability of some observational studies to capture all deaths and causes of death (Fig 2B), and the great variability in populations (sometimes including mixed populations, not only HA) and time periods across the studies (Table 4). This variability may lead to either over- or under-estimation of mortality depending on the context. The wide range of countries, and therefore access to care, is also likely to affect mortality substantially. As many studies did not specify type of hemophilia, mortality and causes of death could not be explored specifically in PwCHA. Severity of disease, presence of FVIII inhibitors, or treatment regimen, all of which are expected to influence mortality and cause of

death, were also frequently not specified. Finally, the categorization when recording cause of death was heterogeneous across the studies, hampering the analysis.

#### **4.5 | Conclusions**

In conclusion, although there are a number of historic reports on mortality in PwCHA, current evidence surrounding the mortality rates and causes of death among PwCHA is disparate. In particular, categorization of causes of death is inconsistent. This systematic literature review presents the available evidence concerning mortality rates in PwCHA, for consideration when comparing the risks and benefits of emerging therapies and monitoring future progress in a rapidly evolving treatment landscape. However, there is a need to collect more evidence regarding current mortality rates and long-term outcomes from registries and studies in PwCHA. Moreover, there is a need for clearer and more consistent communication of the causes of death among PwCHA, as there is currently no standardized reporting framework. This review forms part of an evidence base used in developing an algorithm for assessing mortality in PwCHA, which aims to address this absence (please see Pipe et al publication in this supplement).

#### **AUTHOR CONTRIBUTIONS**

C. R. M. Hay, F. Nissen, and S. W. Pipe all made substantial contributions to the conception and design of the work, as well as the analysis and interpretation of data for the work. All authors revised the manuscript critically and provided final approval of the version to be published. They all agree to be accountable for all aspects of the work.

#### **ACKNOWLEDGMENTS**

Literature searches were carried out by Elvira Schmidt, Monika Neumann, and Linnea Koller of Certara, Lorrach, Germany. Editorial assistance for the development of this manuscript, under the direction of the authors, was provided by Phoebe Tate, MSc, of Gardiner-Caldwell Communications, Macclesfield, UK and funded by F. Hoffmann-La Roche Ltd.

#### **CONFLICT OF INTEREST DISCLAIMER**

None of the authors received honoraria or fees for their contribution to the development of this manuscript or supplement. F. N. is a current employee of F. Hoffmann-La Roche Ltd. C. R. M. H. has received consultancy and honoraria from Shire Plc., Alnylam Pharmaceuticals Inc., Novo Nordisk, Swedish Orphan Biovitrum AB (Sobi), and F. Hoffmann-La Roche Ltd, has participated in speakers' bureaus for Shire Plc., Sobi, F. Hoffmann-La Roche Ltd, and Pfizer Inc., has received research funding

from Bayer, Shire Plc., Sobi, Novo Nordisk, and Pfizer Inc., and has received travel and accommodation expenses from F. Hoffmann-La Roche Ltd, Sobi, CSL Behring, and Shire Plc. S. W. P. has received consultancy and honoraria from Apcintex Ltd., Bayer AG, BioMarin Pharmaceutical, Catalyst Biosciences, CSL Behring, HEMA Biologics Inc., F. Hoffmann-La Roche Ltd., Freeline Therapeutics, Novo Nordisk, Pfizer Inc., Sangamo Therapeutics Inc., Sanofi, Takeda Pharmaceutical Company Ltd., Spark Therapeutics Inc., and uniQure NV; has received research funding from Siemens AG; and is a member of the board of directors/advisory committee for the Medical and Scientific Advisory Council to the National Hemophilia Foundation and the Medical Advisory Board to World Federation of Hemophilia.

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**FIGURE 1** PRISMA CONSORT diagram describing the search results and screening.

A total of 10 083 records reporting on mortality and cause of death in PwCHA were identified searching both the Medline and Embase databases, as well as clinical trial registries (clinicaltrials.gov; Cochrane Central Register of Controlled Studies). A primary search identified 9512 of these; an updated search, limited to observational studies, identified a further 571. After the removal of duplicated records, a total of 7818 unique records were screened, and 1144 were excluded because they lacked discussion of haemophilia or mortality in their titles or abstracts. After all exclusions, 17 articles met the eligibility criteria for this systematic literature review. HA, hemophilia A; PwCHA, people with congenital hemophilia A.

**FIGURE 2** Primary cause of death in 15 observational studies.

A, Primary cause of death in publications ordered by study period [22-26,28,29,31-37,44]

B, Primary cause of death among studies that were conducted pre 2010 [23,29,33] versus post 2010 [25,28,36]<sup>§</sup>

A, Publications reporting the primary cause of death in PwH were ordered by study period, from earliest to most recent. Number of deaths in each study is displayed across the top of the chart. B, Publications reporting the primary cause of death in PwH were divided into those with study periods pre and post 2010. Publications with study periods that spanned across 2010 were excluded.

\*Lovdahl et al only reported the number of deaths for the five most frequent causes of death'; †Of the nine deaths attributed to fulminant sepsis ('other infection'), all were people with HIV infection;

‡Some people presented with more than one related cause of death; §Includes: Fransen van de Putte et al, Lovdahl et al, and Tagliaferri et al pre 2010 and Lim et al, Miesbach et al, and Schramm et al 2013 post 2010. Records were ordered by record period, from earliest to most recent. Ischemic heart disease and pulmonary embolism were categorized as 'thrombosis', and if exact cause of death was unclear, the death was categorized as 'unknown'. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwH, people with hemophilia.

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**TABLE 1** Overview of mortality rates in PwH observational studies from 2010 onwards [23-28]

Study	Population	Number of PwH	Country	Data collection period	Type of study	Mortality rate by disease severity or FVIII inhibitor status/100 PY (95% CI)					Overall mortality rate /100 PY
						Mild	Moderate	Severe	With FVIII inhibitors	Without FVIII inhibitors	
Tagliaferri 2010[23]	Mild-severe hemophilia HA: 78%; HB: 22%	84.5% of Italian PwH (443 deaths)	Italy	1980-2007	Retrospective data collection from hemophilia centers	0.2 (0.1-0.3)	0.5 (0.3-0.7)	0.9 (0.8-1.0)	NR	NR	0.6 (0.5-0.6)
Schramm 2012[24]	2008/2009: HA/HB 2009/2010: HA, 86.3%; HB, 13.7% FVIII inhibitors: 1.41% (HA), 1.97% (HB)	4453	Germany	2008-2010	Annual multicenter survey	NR	NR	NR	NR	NR	2008/2009: 0.4 2009/2010: 0.5
Schramm 2013[25]	PwH; no population characteristics	3331	Germany	2011-2012	Annual multicenter survey	NR	NR	NR	NR	NR	0.6
Chang 2014[27]	HA: 85.8%; HB: 14.2%	493	Taiwan	1997-2009	Population-based data from the National Health Insurance Research Database	NR	NR	NR	NR	NR	0.7 (average annual crude death rate) 1.0 (standardized crude death rate)
Eckhardt 2015[26]	Non-severe HA (with and without FVIII inhibitors)	2709	Europe (10 countries) and Australia	1980-2011	Retrospective cohort study	0.2		NR	NR	NR	Mild and moderate: 0.2 (0.2-0.3)



<b>Lim 2019[28]</b>	Non-severe HA FVIII inhibitors: 2.59%	6606	USA	2010-2018	Retrospective data from the American Thrombosis and Hemostasis Network	0.2	NR	0.2	0.2	Mild and moderate: 0.2 (0.2- 0.3)
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Abbreviations: CI, confidence interval; FVIII, factor VIII; HA, hemophilia A; HB, hemophilia B; NR, not reported; PwH, people with hemophilia; PY, person years; USA, United States of America.

**TABLE 2** Overview of mortality ratios in PwH in observational studies from 2010 onwards [23,27,29-31]

Study	Population	Number of PwH	Country	Data collection period	Type of study	Mortality ratio by disease severity (95% CI)			Overall mortality ratio (SMR or hazard ratio) (95% CI)
						Mild	Moderate	Severe	
<b>Tagliaferri 2010 [23]</b>	Mild-severe hemophilia HA: 78%; HB: 22%	84.5% of Italian PwH; 443 deaths	Italy	1980-2007	Retrospective data collection from hemophilia centers	NR	NR	HA: 4.1 (2.7-6.3) in 1990-1999 HA: 3.3 (1.8-5.7) in 2000-2007 (SMR)	HA/HB: 2.0 (1.5-2.5) in 1990-1999 HA/HB: 1.1 (0.8-1.4) in 2000-2007 (SMR)
<b>Lovdahl 2013 [29]</b>	HA and HB (proportions not specified)	PwH, 1431; controls, 7150	Sweden	1968-2009	Registry study	NR	NR	All: 6.6 (4.5-10.0; <i>P</i> < .001*) No HIV: 3.3 (1.9-5.6; <i>P</i> < .001*) No HIV/viral hepatitis: 8.2 (3.2-20.8; <i>P</i> < .001*) (hazard ratios)	All: 2.2 (1.8-2.7; <i>P</i> < .001*) No HIV: 1.6 (1.2-2.0; <i>P</i> < .001*) No HIV/viral hepatitis: 1.7 (1.3- 2.2; <i>P</i> < .001*) (hazard ratios)

<b>Chang 2014 [27]</b>	HA: 86% HB:14%	493	Taiwan	1997-2009	Population-based data from National Health Insurance Research Database	NR	NR	NR	1.98 (SMR)
<b>Hassan 2019 [30]</b>	PwHA in the Netherlands between 1973 and 2018	1031	The Netherlands	2001-2018	Cohort study	All: 1.0 (0.8-1.3) No HIV/HCV: 1.0 (0.7-1.3) (SMR)	All: 1.1 (0.7-1.7) No HIV/HCV: 1.1 (0.6-1.9) (SMR)	All: 2.4 (1.8-3.0) No HIV/HCV: 2.2 (1.3-3.6) (SMR)	All: 1.4 (1.2-1.7) No HIV/HCV: 1.2 (0.9-1.5) (SMR)
<b>Jardim 2019 [31]</b>	Congenital HA/HB (proportions not specified)	784 (deaths)	Brazil	2000-2014	Retrospective study using the Brazilian National Mortality Information System	NR		NR	1.5 (1.3-1.7) 2000-2002 1.3 (1.1-1.5) 2003-2005 1.2 (1.0-1.4) 2006-2008 0.9 (0.7-1.0) 2009-2011 0.9 (0.7-1.0) 2012-2014 1.1 (1.0-1.2) 2000-2014 (SMR)

Mortality ratios were standardized to the general male population of the country in which the study was located, except where otherwise indicated: \*Compared with age- and sex-matched controls.

Abbreviations: CI, confidence interval; HA, hemophilia A; HB, hemophilia B; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NR, not reported; PwH, people with hemophilia; PwHA, people with hemophilia A; SMR, standardized mortality ratio.

**TABLE 3** Overview of studies reporting cause of death [22-26,28,29,31-37,44]

Study	Population	No. of deaths	Country	Data	
				collection period	Type of study
Tagliaferri 2010 [23]	Mild-severe hemophilia HA: 78%; HB: 22%	443	Italy	1980-2007	Retrospective data collection from hemophilia centers
Au 2011 [32]	Mild-severe HA/HB	12	China (Hong Kong)	1993-2011	Retrospective survey of the Hospital Authority
Fransen van de Putte 2012 [33]	All males with hemophilia	78	The Netherlands	1985-2010	Retrospective medical record data collection
Schramm 2012 [24]	HA/HB	34	Germany	2009-2010 2010-2011	Annual multicenter survey
Lovdahl 2013 [29]	HA/HB	PwH: 382; Controls: 1351	Sweden	1968-2009	Registry study
Schramm 2013 [25]	HA/HB	20	Germany	2011-2012	Annual multicenter survey
Yoo 2014 [34]	HA: 81.8%; HB: 18.2% Mild: 11.1%; Moderate: 22.2%; Severe: 66.6%	120	Korea	1993-2012	20-year cohort study
Eckhardt 2015 [26]	Non-severe HA (with and without FVIII inhibitors)	148	Europe and Australia	1980-2011	Retrospective cohort study
Walsh 2015 [22]	Severe HA	432	USA	1998-2011	Retrospective study of hemophilia centers
Witmer 2015 [15]	Males <21 years old with hemophilia	21	USA	2002-2011	Retrospective multicenter cohort study
Eyster 2016 [35]	PwH or VWD with transfusion-induced chronic HCV infections	111	USA	1973-2011	Single-center cohort study
Miesbach 2017 [36]	People with hemophilia >60 years old	25	Germany, Austria, and Switzerland	2010-2012	Retrospective multicenter data collection study
Mansouritorghabeh 2018 [37]	HA/HB	40	Iran	1975-2015	Epidemiological retrospective study
Jardim 2019 [31]	Congenital HA/HB	784	Brazil	2000-2014	Retrospective study using the Brazilian National Mortality

Lim 2019 [28]	Non-severe HA	136	USA	2010-2018	Retrospective data from the American Thrombosis and Hemostasis Network
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Abbreviations: FVIII, factor VIII; HA, hemophilia A; HB, hemophilia B; HCV, hepatitis C virus; PwH, people with hemophilia; USA, United States of America; VWD, von Willebrand disease.

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**TABLE 4** Overview of mortality rates and ratios in PwH in observational studies published before 2010 [2,39-43]

Study	Population	Number of PwH	Country	Data collection period	Type of study	Mortality rate or ratio																												
<b>Plug 2006 [2]</b>	HA (87%) and HB (13%)	967 (HA, 796)	The Netherlands	1992-2001	Prospective cohort study	HA or HB (SMR): mild (1.3 [0.9-1.9]); moderate (2.6 [1.5-4.3]); severe (5.1 [3.8-6.8])		HA (SMR): all (2.3 [1.9-2.9]); HIV-negative (1.7 [1.4-2.2])																										
<b>Soucie 2000 [39]</b>	HA (79%) and HB (21%)	2950 (HA, 2334)	USA	1993-1995	Medical record review	HA: 3.5/100 PY (Mortality rate)																												
<b>Reitter 2009 [40]</b>	HA (92%) and HB (8%)	226	Austria	1983-2006	Retrospective survival analysis	All: 0.7 (95% CI, 0.6-0.8) Mild and moderate: 1.0 (95% CI, 0.9-1.1) Severe: 0.5 (95% CI, 0.4-0.6) HIV-positive: 0.3 (95% CI, 0.2-0.4) (Cumulative relative survival compared with general Austrian male population)																												
<b>Darby 2004 [41]</b>	HA and HB, HIV-negative	7250 (HA, 6078)	UK	1977-1999	Nationwide database study	<table border="1"> <thead> <tr> <th></th> <th colspan="2">With FVIII inhibitors (death rate /100 PY)</th> <th colspan="2">Without FVIII inhibitors (death rate /100 PY)</th> </tr> <tr> <th></th> <th>Mild and moderate</th> <th>Severe</th> <th>Mild and moderate</th> <th>Severe</th> </tr> </thead> <tbody> <tr> <td>1977-84</td> <td>3.1 (95% CI, 1.1-5.2)</td> <td>2.0 (95% CI, 1.3-2.8)</td> <td>0.7 (95% CI, 0.5-0.8)</td> <td>1.0 (95% CI, 0.8-1.2)</td> </tr> <tr> <td>1985-92</td> <td>1.5 (95% CI, 0.0-3.0)</td> <td>2.3 (95% CI, 1.4-3.3)</td> <td>0.6 (95% CI, 0.5-0.7)</td> <td>1.0 (95% CI, 0.7-1.3)</td> </tr> <tr> <td>1993-99</td> <td>1.3 (95% CI, 0.2-2.4)</td> <td>1.2 (95% CI, 0.5-1.9)</td> <td>0.6 (95% CI, 0.5-0.7)</td> <td>1.2 (95% CI, 0.9-1.5)</td> </tr> </tbody> </table>					With FVIII inhibitors (death rate /100 PY)		Without FVIII inhibitors (death rate /100 PY)			Mild and moderate	Severe	Mild and moderate	Severe	1977-84	3.1 (95% CI, 1.1-5.2)	2.0 (95% CI, 1.3-2.8)	0.7 (95% CI, 0.5-0.8)	1.0 (95% CI, 0.8-1.2)	1985-92	1.5 (95% CI, 0.0-3.0)	2.3 (95% CI, 1.4-3.3)	0.6 (95% CI, 0.5-0.7)	1.0 (95% CI, 0.7-1.3)	1993-99	1.3 (95% CI, 0.2-2.4)	1.2 (95% CI, 0.5-1.9)	0.6 (95% CI, 0.5-0.7)	1.2 (95% CI, 0.9-1.5)
	With FVIII inhibitors (death rate /100 PY)		Without FVIII inhibitors (death rate /100 PY)																															
	Mild and moderate	Severe	Mild and moderate	Severe																														
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<b>Darby 2007 [42]</b>	HA and HB, HIV-negative	6018 (HA, 4874)	UK	1977-1999	Nationwide database study	Mild and moderate: 1.2 (95% CI, 1.1-1.3; $P < .001$ ) Severe: 2.7 (95% CI, 2.4-3.1; $P < .001$ )																												

(SMR, compared with the general male population)

<b>Diamondstone 2002 [43]</b>	HA, HB, and VWD HIV- negative	751	USA and Europe	1986-1988	Cohort study	All coagulopathies (crude mortality rate): mild (0.5/100 PY); moderate (0.9/100 PY); severe (1.3/100 PY)	HA (crude mortality rate): with FVIII inhibitors (2.1/100 PY); without FVIII inhibitors (0.7/100 PY)
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Mortality ratios were standardized to the general male population of the country in which the study was located.

Abbreviations: CI, confidence interval; FVIII, factor VIII; HA, hemophilia A; HB, hemophilia B; HIV, human immunodeficiency virus; PwH, people with hemophilia; PY, person years; SMR, standardized mortality ratio; UK, United Kingdom; USA, United States of America; VWD, von Willebrand disease.

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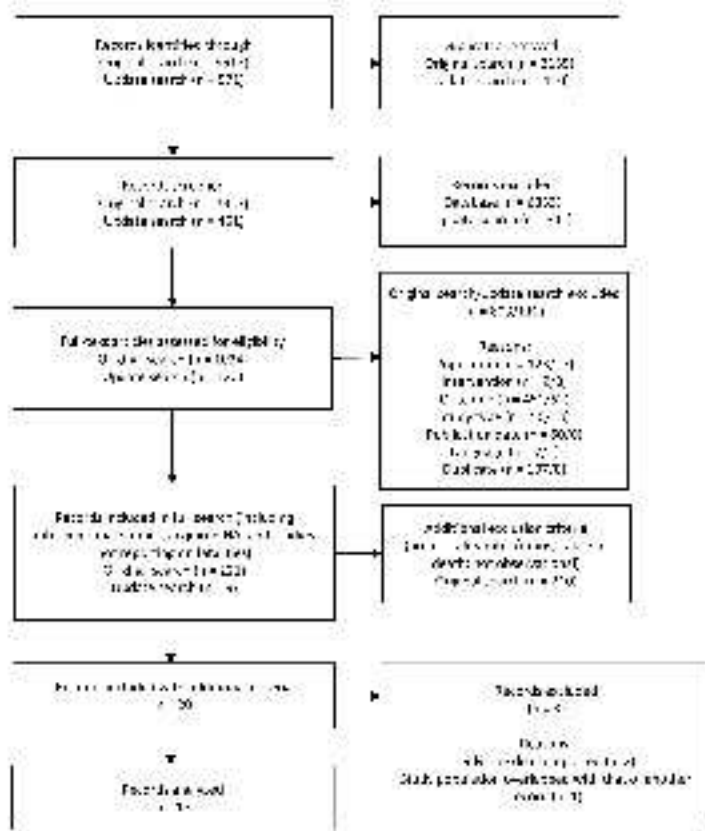
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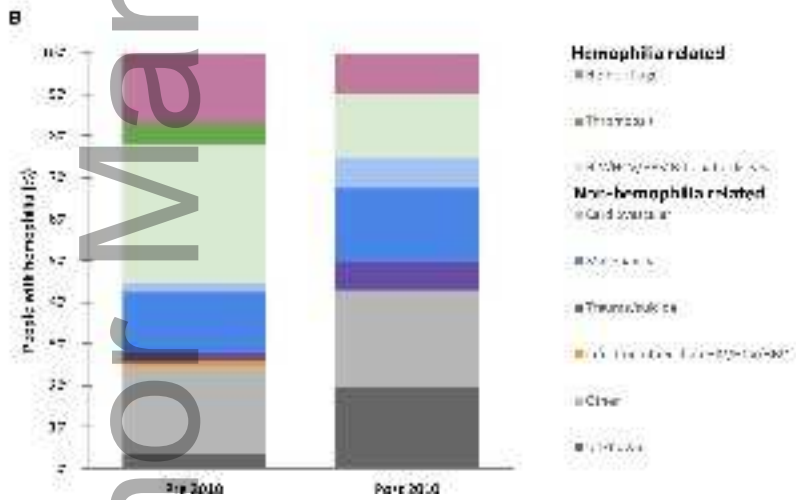
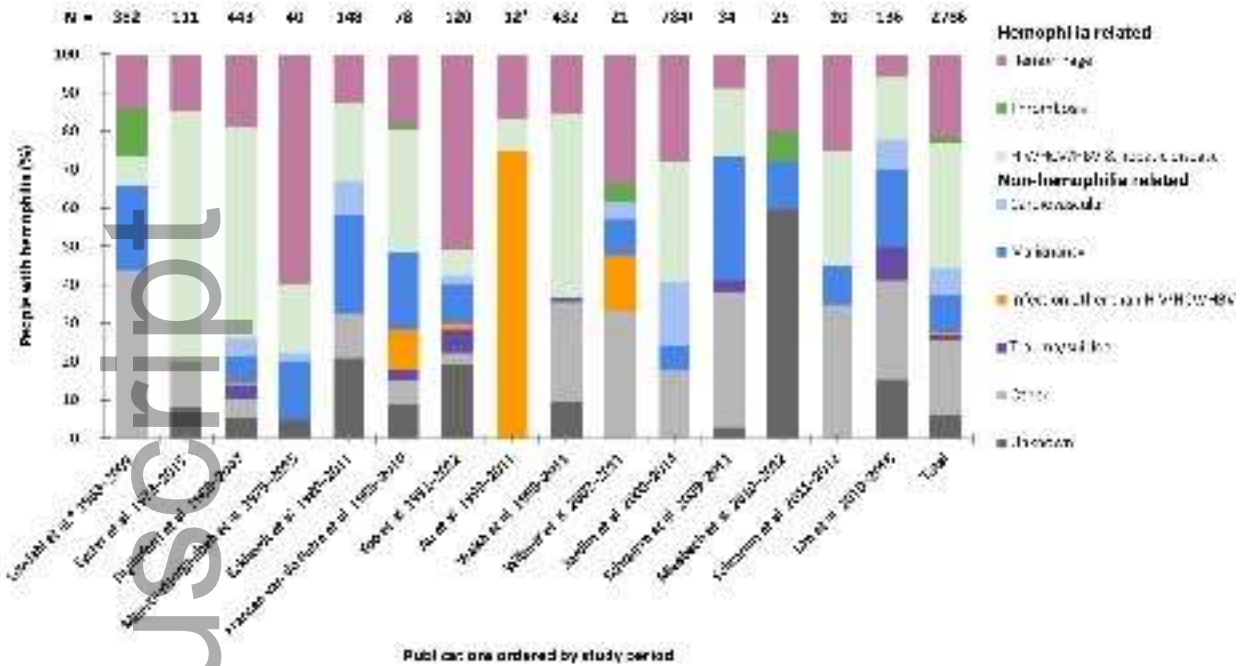
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