

Von Willebrand Disease Epidemiology, Burden of Illness and Management: A Systematic Review

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Introduction: Although hereditary von Willebrand disease (VWD) is the most common bleeding disorder, its epidemiology is not well understood. A systematic review (PROSPERO CRD42020197674/CRD42021244374) on the epidemiology/burden of illness of VWD was conducted to better understand patients' unmet needs.

Methods: Observational studies (published January 1, 2010 to April 14, 2021) were identified in MEDLINE and Embase databases, using free-text keywords and thesaurus terms for VWD and outcomes of interest. Pragmatic web-based searches of the gray literature, including conference abstracts, were performed, and reference lists of retained publications were manually searched for additional sources. Case reports and clinical trials (phase 1–3) were excluded. Outcomes of interest were incidence, prevalence, mortality, patient characteristics, burden of illness, and therapeutic management/treatments currently used for VWD.

Results: Of the 3095 identified sources, 168 were included in this systematic review. Reported VWD prevalence (22 sources) ranged from 108.9 to 2200 per 100,000 in population-based studies and from 0.3 to 16.5 per 100,000 in referral-based studies. Reported times between first symptom onset and diagnosis (two sources; mean 669 days; median 3 years) highlighted gaps in timely VWD diagnosis. Bleeding events reported in 72–94% of the patients with VWD (all types; 27 sources) were mostly mucocutaneous including epistaxis, menorrhagia, and oral/gum bleeding. Poorer health-related quality of life (three sources) and greater health care resource utilization (three sources) were reported for patients with VWD than in general populations.

Conclusion: Available data suggest that patients with VWD experience high disease burden in terms of bleeding, poor quality of life, and health care resource utilization.

Keywords: disease burden, epidemiology, health-related quality of life, health care resource utilization, systematic review, von Willebrand disease

Introduction

von Willebrand disease (VWD) is an inherited bleeding disorder characterized by defects in the concentration, structure, or function of von Willebrand factor (VWF), a glycoprotein that acts as a carrier protein for factor VIII (FVIII) and facilitates platelet adhesion at vascular injury sites.^{1–3} There are three main types of VWD that differ according to the degree of disease severity and inheritance pattern.² Types 1 and 3 are characterized by quantitative defects in the VWD protein: type 1 VWD is characterized by partial quantitative VWF deficiency, resulting in a mild to moderate bleeding phenotype, whereas type 3, the most severe form of VWD, results from near-complete absence of VWF.^{2,4} Type 2 VWD represents a group of disease phenotypes resulting from qualitative defects in VWF, affecting formation of multimers (types 2A and 2B), platelet adhesion (type 2M), or FVIII binding (type 2N).^{2,4} Bleeding complications in patients with VWD vary depending on the level of residual VWF activity, disease type, age, and sex.⁵ Patients most often experience mucocutaneous bleeding, including epistaxis, easy bruising, and heavy menstrual bleeding (HMB), as well as bleeding after surgery/trauma.^{4,5}

VWD is considered the most common hereditary bleeding disorder,⁶ but information on the epidemiology of VWD is limited. This systematic review was, therefore, conducted to better understand the disease and related unmet needs for the patients. Data on the epidemiology of VWD worldwide were reviewed, including incidence, prevalence, mortality, patient characteristics, natural history, burden of illness, and therapeutic management/treatments received in the real-world clinical practice setting.

Methods

A systematic review was conducted between January 1, 2010 and April 14, 2021 (date last searched) using methods developed by the Cochrane group and the National Academy of Medicine, formerly the Institute of Medicine of the National Academy.^{7,8} This time period was selected to provide comprehensive search results for the outcomes of interest that were also reflective of recent trends in disease burden, epidemiology and clinical management strategies. The protocol was registered under the International Prospective Register of Systematic Reviews. The original protocol, which covered searches through to July 1, 2020, was registered on August 8, 2020 (PROSPERO CRD42020197674). An updated protocol was registered on May 12, 2021, and covered pragmatic searches from July 1, 2020 to April 14, 2021, and literature searches from July 1, 2020 to March 22, 2021, as well as from January 2010 to March 22, 2021, for publications not covered by the original protocol (ie, scientific communications without abstracts) (PROSPERO CRD42021244374).

Search Strategy and Information Sources

Comprehensive literature searches of MEDLINE and Embase were conducted to identify publications written in English. Search strategies were based on free-text keywords and thesaurus terms (ie, Medical Subject Headings [MeSH] and Emtree terms) combining the following concepts: population and data of interest. Search strategies are detailed in [Supplemental Table 1](#). In addition, pragmatic searches were performed using Google, Google Scholar, the Cochrane Library, and websites of relevant scientific societies involved in VWD, as well as abstracts from related conferences ([Supplemental Table 2](#)). The reference lists of retained publications were manually searched for additional relevant sources (“snowballing”).

Eligibility Criteria

Observational (non-interventional) studies, literature reviews, or meta-analyses involving patients with VWD and reporting on epidemiologic, burden of illness, and management data of interest were included. [Table 1](#) provides a complete list of inclusion and exclusion criteria.

Table 1 Eligibility Criteria for the Selection of Sources Included in This Systematic Review

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Studies published in English between January 1, 2010 and March 22, 2021 • Studies conducted in humans • Non-interventional (observational) studies • Studies that included patients with von Willebrand disease, either as the study population or as a subgroup analysis • Studies that reported epidemiologic data of interest (epidemiologic parameters, patient characteristics, natural history of disease, burden of illness, disease management) • Original research articles • Full-text articles, letters to the editors, editorials, conference proceedings, abstracts, reports • Literature reviews (systematic or non-systematic) and meta-analyses (both types to be used for snowballing only) • For studies with multiple publications, only the latest publication was retained 	<ul style="list-style-type: none"> • Case reports • Opinions • Clinical trials (phase 1–3) • Non-clinical and experimental studies • Studies reporting preliminary results (later published in full text)

Selection of Studies

During the first stage, titles and/or abstracts were screened using the predefined eligibility criteria by two independent reviewers, with conflicts resolved by a third assessor, and during the second stage, eligibility was confirmed by in-depth review of full texts. Reasons for exclusion at second stage were documented. For studies with multiple publications, only the most recent reporting on each outcome of interest was retained.

Data Extraction and Data Synthesis

Data from relevant publications were extracted into a standardized data extraction form and the extracted data evaluated for completeness. Data items extracted included general information (source, citation, publication type, geographical coverage); study methods (study period, study design, data source); target population (age); VWD type; study population (diagnostic criteria); number of patients with VWD; and definition of the reference population. The following study outcomes were also extracted: patient characteristics (sociodemographics and medical history), incidence/prevalence estimates, all-cause and VWD-related mortality, time from symptoms onset to diagnosis, disease severity, disease progression, bleeding events at diagnosis and during follow-up, disease management/treatment used in clinical practice, health care resource utilization (HCRU), and health-related quality of life (HRQoL).

For each study, the methodology was assessed qualitatively. Specific attention was paid to the robustness of study methods and the generalizability of findings, and these results were used to inform data synthesis. Risk-of-bias tools were not used.

Results of the systematic review were synthesized qualitatively; there was no pooling of estimates through a meta-analysis. For prevalence, incidence, and mortality, a range of estimates was reported according to country/region. Ranges of estimates were provided, and outliers identified using qualitative appraisal and reason for outlying estimates qualitatively assessed; no statistical tests were conducted. Details regarding characteristics of patients and natural history of disease were reported according to VWD type, if available. The burden of illness was described in terms of HCRU and impact of the disease on patients' HRQoL.

Results

Study Selection

A total of 3095 references were identified through the combined search of electronic bibliographical databases (Medline $n = 735$, Embase $n = 2360$). Following removal of duplicates, titles/abstracts of 2671 unique references ([Supplemental Table 1](#)) were screened independently by two assessors and 2368 references were excluded. Of the 303 full-text articles assessed for eligibility, 136 met the eligibility criteria; a further 32 references were identified through pragmatic searches ([Supplemental Table 2](#)). Thus, 168 sources (ie, unique references) ([Supplemental Table 3](#)) were retained for this systematic review ([Figure 1](#)).

VWD Epidemiology

Prevalence

Estimates of the prevalence of VWD (overall or by specific type) were available from 22 of the 168 sources and varied according to the method of estimation. Referral-based estimates were derived from the number of symptomatic patients attending hemophilia treatment centers or health care facilities based on national registries or surveillance studies. Population-based estimates relied on the identification of patients with VWD in cohort studies based on specific diagnostic criteria.

Multinational estimates for VWD (all types) were reported from two global sources, and a cross-sectional study conducted in Western Europe and Israel. Based on expert opinion, Orphanet reported that globally 0.6–1.3% of the general population was affected by VWD (unspecified data source and time period), and that the prevalence of symptomatic VWD was approximately 10 per 100,000.⁹ The 2019 annual global survey of the World Federation of Hemophilia yielded a referral-based estimate of 1.5 per 100,000 based on the number of patients (with all types of VWD)

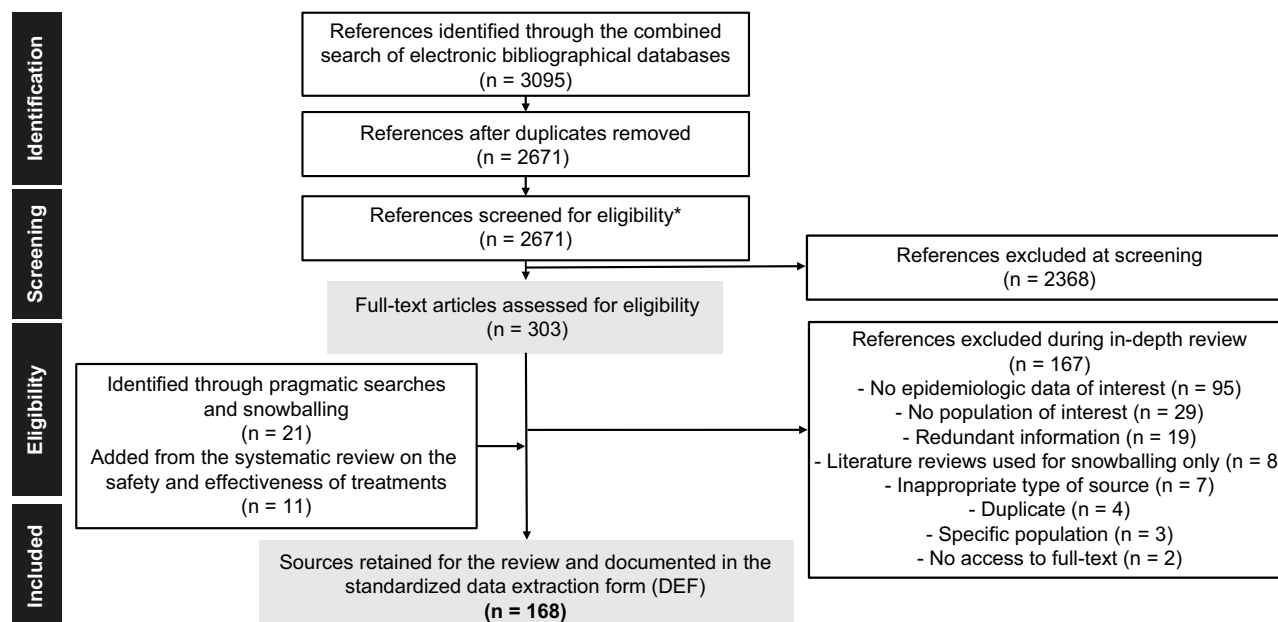


Figure 1 Flow chart for the identification and selection of published sources included for this systematic review. *Independently by two assessors.

registered in hemophilia treatment centers.¹⁰ The European cross-sectional study yielded a population-based estimate of 0.05 per 100,000 for type 3 VWD.¹¹

Country-specific prevalence estimates for VWD were reported from 17 sources: five from Europe, three from Americas, and nine from other regions (Table 2). Referral-based prevalence estimates for overall VWD ranged from 4.4 to 16.5 per 100,000 in Europe,^{12–16} from 0.1 to 8.8 per 100,000 in Western Pacific,^{17–21} and from 1.8 to 2.0 per 100,000 in Eastern Mediterranean^{22,23} (Table 2). Referral-based data were also available for the Czech Republic²⁴ and the USA,²⁵ however, as sizes of the catchment populations were not reported, prevalence could not be estimated.

Estimates by VWD type were available from two registries in Europe (Italy¹² and the UK¹⁵) and one registry in the Western Pacific (Australia^{18,26}). Each of these sources reported higher prevalence estimates for type 1 disease than type 2 or type 3: 2.7–7.2 per 100,000 for type 1 VWD, 0.8–2.5 per 100,000 for type 2, and 0.1–0.3 per 100,000 for type 3. Higher prevalence estimates were also reported for adults than for children in the National Register of Congenital Coagulopathies in Italy.¹²

Population-based estimates, which were mostly conducted in pediatric populations, were higher than referral-based estimates, varying between 800 and 1000 per 100,000 in Europe,^{27,28} 1500 per 100,000 in Eastern Mediterranean,²⁹ 108.9 and 1300 per 100,000 in the Americas,^{30,31} and 2200 per 100,000 in Africa.³²

Incidence

Referral-based incidence estimates of VWD according to the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) report, based on the National Hemophilia Database, were 0.6 (all subtypes), 0.3 (type 1 VWD), 0.2 (type 2 VWD), and 0.01 (type 3 VWD) per 100,000.¹⁵ There were no incidence estimates found for the Americas, Eastern Mediterranean, Western Pacific, or Africa regions. The Orphanet database reported that the incidence rate of type 3 VWD varied across countries from 0.05 to 0.1 per 100,000 person-years in Europe and the USA; sources of estimates and time period were not reported.³³

Patient Demographic Characteristics

Reported demographic characteristics of patients with VWD are presented in Table 3. Patients diagnosed with VWD were predominantly white, with a blood group O and a family history of VWD or other bleeding disorder. The proportion of female patients with VWD (all types) ranged from 45% to 68%.^{10,12,13,15,18,19,22,24,25,28–31,34–48}

Table 2 Reported Country-Based Prevalence Estimates of VWD (17 Sources)

Region	Country	Source (Citation)	Prevalence Estimate (per 100,000)	Prevalence Estimation (Time Period)
Referral-based estimates				
Europe	France	FranceCoag Network ^{13,105}	4.4	Based on 2963 patients with VWD (March 31, 2021) and French population of 67,407,241 (January 21, 2021)
	Italy	National Register of Congenital Coagulopathies ^{12,14,16}	<ul style="list-style-type: none"> • Overall: 5.4 (2016 and 2018) • Adults (>18 years; 2016): <ul style="list-style-type: none"> ◦ 5.8 (all types); 4.3 (type 1); 1.2 (type 2); 0.2 (type 3) • Children (≤18 years; 2016): <ul style="list-style-type: none"> ◦ 3.6 (all types); 2.7 (type 1); 0.8 (type 2); 0.1 (type 3) • All ages, type 3 (2015): 0.2 	
	UK	National Hemophilia Database (NHD) ¹⁵	16.5 (all types); 7.2 (type 1); 2.5 (type 2); 0.3 (type 3)	Based on 11,120 patients diagnosed with VWD (April 2019 to March 2020) and UK population of 67,195,769 in 2020
Americas	US/ Canada	Screening program under supervision of National Institute of Health (NIH) ^{11,106}	0.1 (severe VWD)	Time period: 1977 Case definition for severe VWD: <ul style="list-style-type: none"> • VWF:Ag or plasma ristocetin cofactor levels (VWF:RCo) <10 U/dL or • Bleeding time >20 min and FVIII coagulant activity <5 U/dL
Western Pacific	Australia	Australian Bleeding Disorders registry ^{18,26}	8.8 (all types); 5.6 (type 1); 2.2 (type 2); 0.2 (type 3)	Based on 2221 patients diagnosed with VWD (fiscal year of 2018–2019) and Australian population of 25,365,745 in 2019
	China	Systematic review and meta-analysis ²¹	0.09 (all types)	Time period: 1985–2010
	Japan	Research Committee for the National Surveillance on Coagulation Disorders ^{19,107}	0.7 (all types)	Based on 944 patients diagnosed with VWD (June 11, 2010) and Japanese population of 128,070,000 in 2010
	South Korea	Korea Hemophilia Foundation ^{17,108}	0.3 (all types)	Based on 152 patients diagnosed with VWD (December 31, 2020) and Korean population of 51,709,098 in 2019
	South Korea	Korean Health Insurance Review and Assessment Service (HIRA) database ²⁰	0.1 (all types)	Based on 517 patients with VWD (identified through ICD-10 code D68.0) between 2010 and 2015 and Korean population of 51,529,338
Eastern Mediterranean	Iran	Cross-sectional study using referral data ²³	1.8 (all types)	Based on 50 patients with VWD identified in 3 referral hospitals (September 2009–March 2011)
	Oman	Cross-sectional study ad hoc data collection (EMRs and questionnaire) ²²	2.0 (all types)	101 patients with VWD identified based on ISTH criteria in 2 referral tertiary care hospitals (June 2019)

(Continued)

Table 2 (Continued).

Region	Country	Source (Citation)	Prevalence Estimate (per 100,000)	Prevalence Estimation (Time Period)
Population-based estimates				
Europe	Italy	Prospective cohort study using ad hoc data collection (questionnaires and laboratory values) ²⁷	800	School-aged children (aged 11–14 years) Case definition: <ul style="list-style-type: none"> • Family history of bleeding • VWF levels below normal range • ≥1 other member, on the hemorrhagic side of the subject's family, with low VWF level
	Turkey	Cross-sectional study using ad hoc data collection (questionnaires) ²⁸	1000 (all type I)	Children aged 14–19 years attending high school (October 2006 and March 2007) Case definition: <ul style="list-style-type: none"> • Decrease of VWF:RCo and/or VWF:Ag • Presence of meaningful bleeding symptoms • Similar symptoms in ≥1 family member according to ISTH criteria
Americas	Canada	Prospective cohort using ad hoc data collection (questionnaire and laboratory values) ³⁰	108.9 (symptomatic VWD)	Unselected children aged ≤18 years attending primary care pediatric clinic (November 2006–June 2008) Case definition: <ul style="list-style-type: none"> • Significant bleeding symptoms (BS ≥2) • Abnormal VWF laboratory profile
	US	Cross-sectional using ad hoc data collection (questionnaire, medical history and laboratory values) ³¹	1300 (all types)	Healthy children (aged 2–18 years; N=600) attending routine school examination at 2 military hospitals and 1 urban hospital (March 1989–June 1991) Case definition: <ul style="list-style-type: none"> • ≥1 significant bleeding symptom • A family member with bleeding symptoms • VWF activity <2.5 units percentile of the study population distribution
Eastern Mediterranean	Saudi Arabia	Cross-sectional study using ad hoc data collection (questionnaire and laboratory values) ²⁹	1500 among individuals with suspected bleeding disorders	In students aged 17–22 years (February 2014–January 2016) Case definition: <ul style="list-style-type: none"> • Decrease of VWF:Ag/activity and FVIII
Africa	Nigeria	Cross-sectional study using ad hoc data collection ³²	2200 (all types)	VWD identified in 4 of 182 healthy individuals aged 15–35 years Case definition: <ul style="list-style-type: none"> • VWF:Ag and FVIII coagulant levels

Abbreviations: BS, bleeding score; FVIII, factor VIII; ISTH, International Society on Thrombosis and Haemostasis; VWF, von Willebrand factor; VWF:Ag, VWF antigen.

Table 3 Reported Patient Demographic Characteristics

	Overall VWD	Type 1 VWD	Type 2 VWD	Type 3 VWD
Overall age distribution	<ul style="list-style-type: none"> • Median age: 33–43 years^{13,16,24} • Adult patients (aged ≥18 years): 81.8–84.7%^{15,18} • Majority of patients 11–44 years age group (66%)²⁵ <ul style="list-style-type: none"> ◦ 20–44 years age group (53.3%)¹⁷ 	<ul style="list-style-type: none"> • Median age: 33–42 years^{14,24} • Adult patients (aged ≥18 years): 82.5–87.0%^{15,18} • Majority of patients: 11–44 years age group (68%)²⁵ 	<ul style="list-style-type: none"> • Median age: 41–46 years^{16,24} • Adult patients (aged ≥18 years): 79.2–80.7%^{15,18} • Majority of patients: 11–44 years age group (58%)²⁵ 	<ul style="list-style-type: none"> • Median age: 40–41 years^{16,24} • Adult patients (aged ≥18 years): 71.8–73.5%^{15,18} • Majority of patients: 11–44 years age group (58%)²⁵
Age at symptom onset	<ul style="list-style-type: none"> • Median age at first bleeding event: 1.5–8.5 years^{38,57,62} 	<ul style="list-style-type: none"> • Median age at first bleeding event: 2–7 years^{38,57} 	<ul style="list-style-type: none"> • Median age at first bleeding event: 1–8 years^{38,57} 	<ul style="list-style-type: none"> • Median age at first bleeding event: 0.8–1 year^{38,57}
Age at diagnosis	<ul style="list-style-type: none"> • Median age at diagnosis: <ul style="list-style-type: none"> ◦ General population: 32–33 years^{34,52} ◦ Pediatric population: 2.0–5.5 years^{44,57} 	<ul style="list-style-type: none"> • Median age at diagnosis: <ul style="list-style-type: none"> ◦ General population: 35 years³⁴ ◦ Pediatric population: 3.0–5 years^{44,57} 	<ul style="list-style-type: none"> • Median age at diagnosis <ul style="list-style-type: none"> ◦ Pediatric population: 0.8–7.5 years^{40,44,57} 	<ul style="list-style-type: none"> • Median age at diagnosis: <ul style="list-style-type: none"> ◦ General population: 28 years³⁴ ◦ Pediatric population: 0.8–3 years^{38,44,57,58}
Sex distribution	<ul style="list-style-type: none"> • Female predominance: 55.3%¹⁰ • Proportion of female patients:^{10,12,13,15,18,19,22,24,25,28–31,34–48} <ul style="list-style-type: none"> ◦ General population: 45.2–68.2% ◦ Adult population: 60–75.4% ◦ Pediatric population: 43.2–75.8% 	<ul style="list-style-type: none"> • Female predominance: 55.3–83.3%^{15,24,25,34,35,38,42,44,53,54,75} 	<ul style="list-style-type: none"> • Proportion of female patients: 46.6–58.8%^{15,24,25,34,35,38,40,42,44,54,75} 	<ul style="list-style-type: none"> • Proportion of female patients: 41.7–65.8%^{15,18,24,25,34,35,38,42,44,58}
Ethnicity	<ul style="list-style-type: none"> • White: 50–83.1%^{25,31,40,41} 	<ul style="list-style-type: none"> • White: 83.9%²⁵ 	<ul style="list-style-type: none"> • White: 82.0%²⁵ 	<ul style="list-style-type: none"> • White: 79.0%²⁵
Blood type	<ul style="list-style-type: none"> • Group O: 39.8–87.5%^{24,29–31,37,39,57,62} 	<ul style="list-style-type: none"> • Group O: 47.5–93.6%^{24,53,54,62,75} 	<ul style="list-style-type: none"> • Group O: 32.0–62.5%^{24,54,62,75} 	<ul style="list-style-type: none"> • Group O: 35.3–45.4%^{24,58}
Family history	<ul style="list-style-type: none"> • Family history of VWD: 13.2–68.9%^{22,23,38,42,55,62,77} • Family history of bleeding: <ul style="list-style-type: none"> ◦ 15.2–60.0% (bleeding disorders)^{40,43,62} ◦ 18.9% (hemophilia A)⁶² ◦ 51.2% (bleeding tendencies)⁴⁷ 	<ul style="list-style-type: none"> • Family history of VWD: 22.4%⁵⁴ • Family history of bleeding: 50% in patients with severe VWD³⁸ 	<ul style="list-style-type: none"> • Family history of VWD: 37.5%⁵⁴ • Family history of bleeding: 78.1% in patients with severe VWD³⁸ 	<ul style="list-style-type: none"> • Family history of VWD (siblings): 21.1%⁴⁵ • Family history of bleeding: 33.3% in patients with severe VWD³⁸
Consanguinity	<ul style="list-style-type: none"> • 36–48.5% in pediatric population (<18 years)^{43,44} 	<ul style="list-style-type: none"> • 27.7% in pediatric population (<18 years)⁴⁴ 	<ul style="list-style-type: none"> • 25.0% in pediatric population (<18 years)⁴⁴ 	<ul style="list-style-type: none"> • 67–71.9% in pediatric population (<18 years)^{44,56}

Abbreviation: VWD, von Willebrand disease.

Mortality and Causes of Death

Mortality rates were available from seven sources ([Supplemental Table 4](#)),^{15,36,41,44,46,48–51} none of the publications reported mortality according to VWD type. Based on studies conducted in Sweden and the USA, VWD does not appear to be associated with an increased risk of death compared with populations without VWD. In a cohort study including 2790 patients with VWD in Sweden, all-cause mortality over a 22-year observation period (1987–2009) was estimated at 10.8% (equivalent to 235 per 100,000 person-years), and the risk of death in patients with VWD was not statistically different from that of age- and sex-matched individuals without VWD (hazard ratio 0.90; 95% confidence interval [CI], 0.80–1.05).⁴⁹ All-cause mortality in a single-center cohort study (1985–2010) conducted in the USA was 5.1% in 198 patients with VWD compared with 2.0% in 198 patients without VWD matched for age, sex, and cardiovascular comorbidities ($P=0.1$).⁴⁸ A lower inpatient mortality rate was reported for adult patients with VWD (7556 admissions) than for those without VWD (19,918,970 admissions) in a retrospective US cohort study (2009–2011) using inpatient discharge data (1.3% vs 2.2% [$P<0.0001$]).^{41,46} Another retrospective cohort study (2003–2011) using the same database, and focusing on pregnant women, found similar inpatient mortality rates for women with ($n=15,258$) or without VWD ($n=40,602,254$; 0.03% vs 0.02%, respectively [$P=0.970$]).⁵¹

Other studies have reported mortality rates for 11,120 patients with VWD newly registered at hemophilia centers in the UK (0.6% over period of April 2019 to March 2020),¹⁵ 161 children aged <18 years in Turkey (1.2% over period of 1985–2017),⁴⁴ and 506 pregnant women in the USA (0% over period of 2007–2011).⁵⁰

Data on cause of death were limited to two publications. In a retrospective US single-center cohort study (1985–2010), among 10 deaths in 198 patients with VWD, 7 were due to cancer or cancer-related complications.⁴⁸ In the UK, among 69 deaths in patients with VWD ($n=11,120$) recorded in the UKHCDO (2019–2020), carcinoma (7.2%) and bacterial infection (2.9%) were the most common known cause of death; the majority (79.7%) of deaths had an unknown cause.¹⁵

Burden of Illness

In total, 36 sources were identified that described bleeding events and disease-related complications. The burden of illness was also described in eight sources that reported on HRQoL and nine that reported on the HCRU of patients with VWD.

Timing of VWD Diagnosis

The time from onset of symptoms to VWD diagnosis was poorly documented in the literature, with only two sources being identified. One source was a retrospective US cohort study, which was based on administrative claims data ($N=18,182$) and estimated the mean time from the first billing claim for a bleeding event to a VWD diagnosis as 669 days (range, 2–3284 days).⁵² The second source was a European retrospective cohort study based on medical records for 103 patients with severe VWD from 2010 to 2013 in which the estimated median time between the first bleeding event and VWD diagnosis was 3 years (interquartile range [IQR] 0–18).³⁸

Bleeding Events and Disease-Related Complications

Patients with VWD frequently experience bleeding events. Based on data collected from patient questionnaires or chart reviews, between 72% and 94% of the patients had a history of bleeding events.^{40,44,53} Bleeding events commonly occurred at mucocutaneous sites ([Table 4](#)), with epistaxis, HMB, and oral/gum bleeding being the most frequently reported events in the overall VWD population.

HMB occurred frequently, affecting 61–100% of the women of reproductive age with VWD.^{23,31,34,42,44,54–58} Lower estimates (43% and 53%) were found in studies that used medical records.^{47,59} Postpartum hemorrhage occurred less frequently than HMB, occurring in 5.5–12.7% of the deliveries in women with VWD.^{42,47,50,59–63} Miscarriages were reported in 3–29% of the pregnant women with VWD.^{64–66} Rates of anemia and iron deficiency in women with VWD (including pregnant women) ranged from 13% to 21.4%^{50,52,65} and 4.2 to 22.5%.^{67,68}

Wound-related bleeding was also a common non-spontaneous type of bleeding event that was reported in 38–79% of the patients.^{28,34,37,42,54,55,57,58} Post-surgical bleeding events occurred in 2.4–71.9% of the patients with

Table 4 Reported Disease-Related Complications

	Overall VWD	Type 1 VWD	Type 2 VWD	Type 3 VWD
Epistaxis	55–86% ^{23,28,34,42,56,57,62}	38.8–52.9% ^{34,54}	43.8–56.6% ^{34,54}	36.8–77.3% ^{34,45,58}
Hematoma	13.0–71.7% ^{34,37,62}	10.2–11.9% ^{34,54}	10.5% ³⁴	24–51.9% ^{34,56,58}
Wound-related bleeding	38–79% ^{28,34,37,42,54,55,57,58}	35.0–51.0% ^{34,54}	39.1–43.8% ^{34,54}	24–54.5% ^{34,58}
Oral cavity bleeding	37.5–100% ^{31,55,57}	–	–	48–69.9% ^{56,58}
Gum/gingival bleeding ^a	31.9–62.5% ^{23,34,42,45,47,62}	27.0–49.0% ^{34,54}	35.7–56.3% ^{34,54}	57.6% ³⁴
GI bleeding	3.7–24% ^{b23,34,37,42,47,54,59,62,69,70}	4.0–14.3% ^{34,54}	10.3–33.3% ^{34,37,54}	4.6–29% ^{34,45,56,58}
Post-dental extraction bleeding	6.1–84.6% ^{23,28,34,37,43,47,62}	42.0–53.2% ^{34,54}	40.9–60.0% ^{34,54}	40.9–44% ^{34,58}
Post-surgical bleeding	2.4–71.9% ^{31,34,37,47,59}	23.9–35.9% ^{34,54}	21.4–52.3% ^{34,37,54}	28–45.5% ^{34,56,58}
Heavy menstrual bleeding	61–100% ^{23,31,34,42,44,54–58}	79.9–83.3% ^{34,54}	66.7–75.6% ^{34,54}	61.0–69.2% ^{34,56,58}
Postpartum hemorrhage	5.5–12.7% ^{42,47,50,59–63}	30.0% ⁵⁴	20.0% ⁵⁴	15.0–16.0% ^{56,58}
Hemarthrosis ^c	3.8–38% ^{23,37,39,42,44,47,62,73}	7.6% ⁷¹	16.3% ⁷¹	36.6–51% ^{56,58}
Joint bleeding ^c	6.3–32.3% ^{34,39,71–73}	1.9–22.0% ^{34,39,72,73}	7.9–20.6% ^{34,39,72,73}	9.5–47.8% ^{34,39,72,73}
CNS bleeding ^d	1–2% ^{34,37,44,55,69}	0.6% ³⁴	0.8% ³⁴	1.8–9.1% ^{34,56,58}
Anemia	5–58% ^{50,52,65,109,110}	–	–	–
Iron deficiency	4.2–22.5% in females and 4.5% in males ^{67,68}	–	–	–

Notes: ^a9.1% reported in an additional study involving 33 patients.⁴³ ^bIn studies involving adults or patients of all ages; lower rates reported for pediatric patients.^{43,44} ^cSelf-reported by patients in majority of studies. ^dRate of 8.8% (based on the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool [ISTH-BAT] completed by physician) reported in pediatric study in patients with moderate or severe VWD;⁵⁷ other studies based on medical record, International Classification of Diseases, 9th or 10th Revision, codes, or questionnaire.

Abbreviations: CNS, central nervous system; GI, gastrointestinal; VWD, von Willebrand disease.

VWD,^{31,34,37,47,54,56,58,59} with the highest rate observed in patients aged 65–85 years in a sub-analysis of the cross-sectional von Willebrand in the Netherlands (WiN) study.³⁷ Gastrointestinal (GI) bleeding events were reported in 3.7–24% of the overall VWD population, with studies indicating that these events occur less frequently in the pediatric population.^{23,34,37,42–45,47,54,56,58,59,62,69,70} The reported proportions of patients who experienced joint bleeds^{34,39,71–73} or hemarthrosis^{23,37,39,42,44,47,56,58,62,71,73} were heterogenous across the identified studies, ranging from 6.3% to 32.3% and 3.8% to 38%, respectively. Bleeding events occurring in the central nervous system were rarely reported.^{34,37,44,55–58,69}

Bleeding Score

In total, bleeding scores (BSs) in patients with VWD (all types) were reported in eight studies.^{24,37,53,55,57,58,72,74} In the Dutch WiN study (N = 666), the Tosetto BS varied from 10 to 12 in patients with VWD (aged ≥16 years) (normal Tosetto BS score defined as <3).^{37,53,55} In a subgroup analysis of the WiN study that focused on 113 pediatric patients with VWD (aged 0–15 years), the median BS assessed according to the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT) was 9.0 (IQR 5.0–12.5) (normal range defined as <3 in children).⁵⁷ In a Canadian study that included 100 pediatric patients with VWD (aged <18 years), the median (range) Pediatric Bleeding Questionnaire (PBQ) score was estimated to be 7.0 (0–29) (PBQ score of ≥2 is predictive of VWD diagnosis).⁷⁴

BSs were higher/worse in patients with type 2 or 3 than in those with type 1 VWD. In the Dutch WiN study, the median (range) Tosetto BS for patients with either type 1 or type 2 VWD was 10 (–1 to 31) and 13 (0–33), respectively, compared with 19.5 (2–35) in patients with type 3 VWD.⁵⁵ Similarly, in the pediatric subgroup analysis of the WiN study (aged 0–15 years), median (IQR) ISTH-BAT score was 6.5 (4.0–10.0), 10.5 (6.3–12.8), and 17.0 (11.5–25.5) for patients

with type 1, 2, or 3 VWD, respectively.⁵⁷ In the Canadian study, median (range) PBQ score was estimated to be 9 (2–18) for type 1 VWD, 14 (3–17) for type 2 VWD, and 12 (4–29) for type 3 VWD.⁷⁴

Comorbidities

Cardiovascular-Related Comorbidities

Eight sources reported estimates of cardiovascular comorbidities in patients with VWD.^{37,41,46,48,50,64,69,75} The reported proportions of patients with cardiovascular disease (CVD) in the overall VWD population were 15%^{41,46} and 31%³⁷ based on two sources; reported hypertension rates ranged from 20.0% to 64.8% in patients >16 years of age.^{37,41,46,48,64,75} In a retrospective US cohort study based on hospital discharge data, the proportion of patients with at least one CVD or hypertension was lower in patients with (7556 admissions) versus without (19,918,970 admissions) VWD (15% vs 26% [$P < 0.001$] and 37.4% vs 49.4% [$P < 0.0001$], respectively).^{41,46} In a US single-center case–control study involving 198 patients with VWD, atrial fibrillation was reported in 7.6% and hypertension in 37.4% of the patients.⁴⁸ In the Dutch WiN study involving 536 adult patients (aged ≥ 16 years) with type 1 or 2 VWD (type 3 excluded), the comorbidities of hypertension, hypercholesterolemia, and history of arterial thrombotic events were reported in 21.8%, 9.5%, and 4.3% of the patients, respectively.⁷⁵

Digestive System-Related Comorbidities

In a subgroup analysis of the Dutch WiN study focusing on elderly patients with VWD (aged 65–85 years, $n = 71$), 15.5% of the patients had GI diseases.³⁷ In the retrospective US study based on discharge data, the proportion of patients with liver disease was higher in the population of patients with (7556 admissions) versus without (19,918,970 admissions) VWD (1.0% vs 0.8% [$P = 0.0458$]).⁴¹ Chronic liver disease was also reported in 1.9% of the adult patients with type 1 or 2 VWD ($n = 536$) in the WiN study.⁷⁵

Blood-Borne Diseases

The rate of infections with hepatitis B virus in patients with VWD was 0–1.5% across the identified studies.^{23,24,37} Across six studies, the rate of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections in patients with VWD were reported at 0.1–0.4% and 1.1–3.8%, respectively.^{10,12,16,25,41,71} In the retrospective US study, the proportion of patients with HCV was higher in patients with (7556 admissions) versus without (19,918,970 admissions) VWD (3.8% vs 1.8% [$P < 0.0001$]), whereas the proportion with HIV infection was lower in patients with VWD versus without VWD (0.4% vs 0.8% [$P = 0.0001$]).⁴¹

Metabolic and Endocrine Comorbidities

The rates of metabolic and endocrine comorbidities in patients with VWD were reported in five studies.^{41,46,48,50,59,69,75} Rates of hypothyroidism ranged from 2.4% in the Dutch WiN study in patients with type 1 or 2 VWD ($n = 536$)⁷⁵ to 16.2% in the US single-center case–control study involving all types of VWD ($n = 197$); this latter rate was significantly higher than in patients without VWD (5.6%, $P < 0.0001$).^{48,59} In the overall VWD population, reports of diabetes mellitus in three studies ranged from 6.7% to 16.2%,^{41,48,50} whereas 3.7% of the patients with type 1 or 2 VWD ($n = 536$) had diabetes mellitus in the WiN study.⁷⁵ In the retrospective US study, the proportion of patients with diabetes mellitus and obesity was lower in patients with (7556 admissions) versus without (19,918,970 admissions) VWD (13.5% vs 23.4% [$P < 0.0001$] and 9.2% vs 10.0% [$P = 0.028$], respectively).⁴¹

Other Comorbidities

Across three studies, cancer rates ranged from 4.3% (in patients aged ≥ 16 years with type 1 or 2 VWD) to 23.9% (in patients aged 65–85 years with all VWD types); rates based on self-reporting by patients tended to be lower than those based on medical chart review.^{37,75,76} Across the studies identified through the systematic review, none reported on comorbidities involving renal, skin, allergic, or hypersensitivity disorders in patients with VWD.

Health-Related Quality of Life

Eight studies assessed HRQoL in patients with VWD (Table 5).^{39,40,67,73,77–82} VWD was associated with lower/poorer HRQoL scores than reference or general populations in three of these studies. In children aged 0–5 years ($n=46$) from the Dutch WiN study, mean (SD) scores for general health perception (70 [15] vs 79 [15]) and parental time (83 [27] vs 93 [11]) from the Infant/Toddler Quality of Life (ITQOL) questionnaire were lower than those reported in the reference population (Dutch preschool children without VWD).⁷⁷ Similarly, in children aged 6–15 years ($n=87$), physical functioning (96 [13] vs 99 [4]), role functioning–emotional/behavioral (95 [15] vs 98 [7]), general health perceptions (76 [20] vs 83 [13]), and physical summary (54 [8] vs 56 [6]) scores from the Child Health Questionnaire Parent Form 50 (CHQ-PF50) and Child Form 87 (CHQ-CF87) were lower than those for the reference population.⁷⁷ A Swedish retrospective study ($N=29$) reported significantly lower median scores in the 36-item Short Form Health Survey (SF-36) for bodily pain in women with VWD and HMB than in those women from the general population.⁸² In a Canadian cross-sectional study, adult patients (aged ≥ 18 years) with VWD ($N=102$) were found to have significantly lower scores ($P<0.05$) in all SF-36 domains (except role–emotional limitations), compared with age- and sex-normative data from the general population.⁸⁰ The physical (PCS) and mental component summary (MCS) scores were also significantly lower (by 2.4 and 3.9 points, respectively [$P<0.005$]) than the general population.⁸⁰

Data from the Dutch WiN study also showed that within the patient population with VWD ($n=804$), HRQoL (based on SF-36 scores) was poorer in patients with joint bleeding than in those without these clinical symptoms/conditions (PCS, 73 vs 77 [$P=0.005$]; MCS, 47 vs 50 [$P=0.006$]).³⁹ In another analysis from the WiN study, patients with VWD and joint bleeding ($n=48$) had significantly higher (worse) hemophilia joint health scores (HJHS; median total score 5 [IQR 1–15] vs 1.5 [IQR 0–5]; $P<0.01$) and more functional limitations on the Hemophilia Activities List (HAL) (median total score 88 [IQR 69–98] vs 100 [IQR 87–100]; $P<0.01$) than patients with VWD but without joint bleeding ($n=48$).^{79,81}

Table 5 Reported HRQoL Outcomes in Patients with VWD

	Overall VWD	Type 1 VWD	Type 2 VWD	Type 3 VWD
SF-36 PCS scores	42.3–80.5 ^{39,78,80}	–	–	–
SF-36 MCS scores	45.5–70.0 ^{39,78,80}	–	–	–
HJHS score	–	6 ⁸¹	2.5 ⁸¹	14 ⁸¹
HAL score	–	85 ⁸¹	92 ⁸¹	77 ⁸¹
ITQOL general health perception score ^a	70 ⁷⁷	73 ⁷⁷	70 ⁷⁷	61 ⁷⁷
ITQOL parental time score ^a	83 ⁷⁷	80 ⁷⁷	88 ⁷⁷	73 ⁷⁷
CHQ-PF50 and CHQ-CF87 physical functioning score ^b	96 ⁷⁷	97 ⁷⁷	95 ⁷⁷	92 ⁷⁷
CHQ-PF50 and CHQ-CF87 role functioning – emotional/behavioral score ^b	95 ⁷⁷	97 ⁷⁷	93 ⁷⁷	93 ⁷⁷
CHQ-PF50 and CHQ-CF87 general health perceptions score ^b	76 ⁷⁷	79 ⁷⁷	78 ⁷⁷	54 ⁷⁷
CHQ-PF50 and CHQ-CF87 physical summary score ^b	54 ⁷⁷	55 ⁷⁷	53 ⁷⁷	47 ⁷⁷
Unrestricted physical activity ^c	–	96.6% ⁴⁰	96.5% ⁴⁰	91.6% ⁴⁰
Mean HUI [®] score	0.70 for females 0.77 for males ⁶⁷	–	–	–

Notes: In pediatric populations: ^a0–5 years, ^b6–15 years, ^c2–12 years.

Abbreviations: CHQ-CF87, Child Health Questionnaire Child Form 87; CHQ-PF50, Child Health Questionnaire Parent Form 50; HAL, Hemophilia Activities List; HJHS, hemophilia joint health score; HRQoL, health-related quality of life; HUI, Health Utilities Index; ITQOL, Infant/Toddler Quality of Life; MCS, mental component summary; PCS, physical component summary; SF-36, 36-item Short Form Health Survey; VWD, von Willebrand disease.

Based on data from the Universal Data Collection, a surveillance system funded by the US Centers for Disease Control and Prevention, 4.3% of the children with VWD (aged 2–12 years, $n=2712$) used a cane, crutches, walker, or wheelchair for mobility assistance, with this rate higher in patients with type 3 VWD than in those with type 1 or 2 (22.6% vs 3.3% or 3.5%, respectively).⁴⁰

Health Care Resource Utilization

The burden of VWD on outpatient/emergency department visits and hospitalizations was reported in nine studies (Table 6). No publications reporting on admissions to intensive care units were identified. In a Swedish population-based case–control study, a twofold increase in the rate of outpatient hospital visits and hospitalizations was recorded in patients with VWD ($n=2790$) compared with age- and sex-matched controls ($n=5$ controls per case).⁸³ In this study, the most common causes of outpatient visits were menorrhagia and epistaxis, and GI bleeding was the most common cause of hospitalizations. A retrospective cohort study based on US administrative claims data ($N=5058$) also showed that patients with VWD and major bleeding events were significantly ($P<0.0001$) more likely to be admitted to hospital (incidence rate ratio [IRR] 3.2; 95% CI, 2.8–3.8) and to have emergency department (IRR 2.0; 95% CI, 1.8–2.3) and outpatient visits (IRR 1.3; 95% CI, 1.2–1.3) than patients with VWD who had no major bleeding events.⁶⁹ In another retrospective cohort study based on US administrative claims data in patients undergoing major surgery, IRRs for the patients with VWD ($n=2972$) were 1.2 (95% CI, 1.1–1.2; $P<0.0001$) for outpatient visits and 1.4 (95% CI, 1.3–1.6; $P<0.0001$) for emergency department visits in comparison to the patients without VWD.⁸⁴

VWD Disease Management

Data on VWD treatment with an unspecified indication (ie, on-demand, surgery, or prophylaxis) were available from seven sources.^{15,24,34,62,85,86} The main products and doses used in clinical practice are summarized by indication in Table 7. Patterns of on-demand treatment for VWD were reported in 12 sources. On-demand treatments included desmopressin, replacement therapy with VWF (including VWF/FVIII concentrates), antifibrinolytics, and blood transfusion.^{38,51,63,72,85,87–91} There were 17 sources reporting on the use of situational/conditional prophylaxis (ie, for surgical procedures or childbirth), and nine sources on the use of long-term prophylaxis. Treatments for situational/conditional prophylaxis included desmopressin, plasma-derived VWF and VWF/FVIII-containing concentrates (as monotherapy or in combination), recombinant VWF, and tranexamic acid.^{61,73,85,88,92–94} Plasma-derived VWF/FVIII and VWF concentrates were used for long-term prophylaxis (Table 7).^{81,91,92,95–101} The age, sex, and type of VWD of patients receiving long-term prophylaxis varied across studies: median age was 15.9–60 years,^{92,95,96,98,100} more than half were male;^{95,97,99,100} and 3.1–12.5% had VWD type 1, 17.6–46.9% type 2, and 40.6–74.5% type 3.^{92,95–97,99,100,102} Indications for long-term prophylaxis were reported in eight studies: joint bleeding in 13–43.8%, epistaxis or oral bleeding in 23–34.4%, and GI bleeding in 6.3–63.6% of patients with VWD in general, and HMB in 5–21.9% of the women with VWD.^{92,95–100,102}

Discussion

This systematic review shows that there are limited data available on the epidemiology of VWD, indicating the need for more research to be conducted. Prevalence data that were identified varied depending on method, region/country, VWD type, and patient age.^{9–23,27–32} Incidence data were limited to two sources.^{15,33} The systematic review also highlighted high disease burden, with a high proportion of patients with VWD reporting a history of bleeding events.^{23,28,31,34,37,39,42–45,47,54–63,67,68,70–73} Patients with VWD were also reported to have lower/poorer HRQoL scores versus general populations,^{77,80,82} as well as increased HCRU.^{83,84}

VWD prevalence estimates varied highly according to the study populations and method of estimation. Population-based estimates were higher than referral-based estimates (108.9–2200 per 100,000^{27–32} vs 0.1–16.5 per 100,000^{9,10,12–15,17–23}). This is perhaps not surprising given that the population-based studies mostly involved healthy school children or college students (aged ≤ 35 years) or unselected children (aged ≤ 18 years) attending one or more local hospitals.^{27–32} By contrast, the referral-based studies (with the exception of two cross-sectional studies^{22,23}) identified symptomatic patients of all ages in national registry programs or surveillance databases.^{10,12–15,17–20} Therefore, the population-based studies are more likely to identify a greater

Table 6 Reported Outpatient Visits, Emergency Department Visits, and Hospitalizations for Patients with VWD

	Outpatient Visits	Emergency Department Visits	Hospitalizations
≥1 hemophilia treatment center visit per year	<ul style="list-style-type: none"> 68.6% in the pediatric population⁴⁰ 	–	–
Most common causes of visits	<ul style="list-style-type: none"> Menorrhagia: 22.5 visits/1000 PY Epistaxis: 20.4 visits/1000 PY⁸³ 	–	–
Incidence rate ratio of visits	<ul style="list-style-type: none"> Patients with VWD vs age- and sex-matched controls: 2.3 (95% CI, 2.0–2.7)⁸³ Patients with vs without VWD undergoing major surgery: 1.2 (95% CI, 1.1–1.2; $P < 0.0001$)⁸⁴ VWD patients with vs without major bleeding events: 1.3 (95% CI, 1.2–1.3; $P < 0.0001$)⁶⁹ 	<ul style="list-style-type: none"> Patients with vs without VWD undergoing major surgery: 1.4 (95% CI, 1.3–1.6; $P < 0.0001$)⁸⁴ VWD patients with vs without major bleeding events: 2.0 (95% CI, 1.8–2.3; $P < 0.0001$)⁶⁹ 	<ul style="list-style-type: none"> VWD patients vs age- and sex-matched controls: 2.2 (95% CI, 2.1–2.4)⁸³ Patients with vs without VWD undergoing major surgery: 1.5 (95% CI, 1.4–1.6; $P < 0.0001$)⁸⁴ VWD patients with vs without major bleeding events: 3.2 (95% CI, 2.8–3.8; $P < 0.0001$)⁶⁹
Main reasons for admission	–	<ul style="list-style-type: none"> Emergency hospitalizations due to menorrhagia: 2/26 (7.7%)⁵⁷ Traumatic bleeding: 49.0%⁹⁰ Post-operative bleeding (10.2%)⁹⁰ Epistaxis (8.7%)⁹⁰ 	<ul style="list-style-type: none"> GI bleeding: 4.1/1000 PY⁸³ Menorrhagia: 3.5/1000 PY⁸³ Epistaxis: 3.4/1000 PY⁸³ Coronary heart disease: 4.0/100 PY³⁶ Ischemic stroke: 1.8/100 PY³⁶ Pulmonary embolism: 0.5/100 PY³⁶ DVT: 0.5/100 PY³⁶ Surgery: 69.2%³⁷ Bleeding: 15.4%³⁷ First bleeding event: 4.9%³⁸
Mean (standard error) length of stay	–	–	<ul style="list-style-type: none"> 4.6 (0.07) days^{41,46}

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; GI, gastrointestinal; PY, person-years; VWD, von Willebrand disease.

Table 7 Disease Management in the Real-World Clinical Practice Setting

Treatment Indication	Main Product	Dose
Spontaneous bleeds (2 studies)	Haemate [®] P ⁹¹ Wilate ^{®87}	<ul style="list-style-type: none"> • 46.9 FVIII IU/kg for 1–21 days • 40.2 IU/kg for a mean of 5.3 ± 12.2 days
Long-term prophylaxis of overall VWD (6 studies)	Humate-P [®] , Fanhdi [®] and Alphanate ^{®95} Wilfactin ^{®92} Alphanate [®] , Fanhdi [®] or Humate-P ^{®97} Humate-P ^{®96} Fanhdi [®] and Alphanate ^{®98} FVIII ¹⁰¹	<ul style="list-style-type: none"> • Median (IQR) (VWF:RCo, IU/kg): <ul style="list-style-type: none"> ◦ Epistaxis: 48 (40–60) ◦ GI bleeding: 60 (47–60) ◦ Joint bleeding: 40 (30–50) ◦ Other^a: 59 (17–70) ◦ Mixed^b: 42 (33–49) ◦ Abnormally heavy bleeding at menstruation: 39 (38–40) • Median of 43.5 VWF:RCo IU/kg per infusion, for patients on long-term prophylaxis (4239 IU/kg) • After the first bolus: 40 FVIII IU/kg twice a week for joint bleeding and every other day or 3×/week for GI bleeding • VWF:RCo: 40–80 IU/kg • FVIII:C 20–40 IU/kg • Median (range) long-term secondary prophylaxis dose: 42 (17–74) VWF:RCo IU/kg • Mean of 24 FVIII IU/kg 1–3×/week
Situational prophylaxis (11 studies)	Wilfactin ^{®92,111,112} Veyvondi [®] /Vonvendi ^{®113} Haemate [®] /Humate-P ^{®93,96,114,115} Fanhdi [®] and Alphanate ^{®98} Wilate ^{®116} Biostate ^{®88} Voncento ^{®117}	<ul style="list-style-type: none"> • Minor surgery: 54.0 VWF:RCo IU/kg • Major surgery: 44.5 VWF:RCo IU/kg • Dental procedures: 30 VWF:RCo IU/kg • Cesarean delivery: 27 VWF:RCo IU/kg • Vaginal delivery: 33–42 VWF:RCo IU/kg • Minor surgery: 35 VWF:RCo IU/kg pre-operatively and 34 VWF:RCo IU/kg maintenance • Major surgery: 36 VWF:RCo IU/kg pre-operatively and 26 VWF:RCo IU/kg maintenance • Minor surgery: initial bolus of 46–62 VWF:RCo IU/kg • Major surgery: initial bolus of 58–89 VWF:RCo IU/kg • Surgery: 40–80 VWF:RCo IU/kg; 20–40 FVIII:C IU/kg • Surgery: 80 VWF:RCo IU/kg at surgery and 40–50 VWF:RCo IU/kg post-operatively • Prior to delivery: 2000 IU • Surgery: preoperative dose: 48 VWF:RCo IU/kg; post-operative dose: 44 VWF:RCo IU/kg • Minor surgery: 42.5 IU/kg • Major surgery: 49 IU/kg • Dental procedures: 30 IU/kg • Minor surgery: 45 FVIII:C IU/kg for a median of 3 days • Major surgery: 51 FVIII:C IU/kg for a median of 7 days • Minor surgery: 38.9 ± 10.2 VWF:RCo IU/kg for a median of 1 day • Major surgery: 44.8 ± 19.0 VWF:RCo IU/kg for a median of 4.6 days

Notes: ^aOther: the primary indication occurred with low frequency. This category includes intracranial hemorrhage, hematomas in soft tissue, oral, dental extraction, scraped knees, ovarian cysts, or bleeding. ^bMixed: bleeding pattern was mixed with no primary indication.

Alphanate[®] (human FVIII/human VWF, Instituto Grifols, S.A., Barcelona, Spain); Biostate[®] (human FVIII/human VWF complex, CSL Behring (Australia) Pty Ltd, Broadmeadows, Australia); Fanhdi[®] (high-purity, double-inactivated plasma-derived FVIII/VWF concentrate, Instituto Grifols, S.A., Barcelona, Spain); Haemate[®]/Humate-P[®] (antihemophilic factor/VWF complex [human], CSL Behring GmbH, Marburg, Germany); Veyvondi[®]/Vonvendi[®] (recombinant VWF, Takeda Pharmaceuticals USA, Lexington, MA, USA); Voncento[®] (human FVIII/human VWF, CSL Behring GmbH, Marburg, Germany), Wilate[®] (human FVIII/human VWF, Octapharma AG, Lachen, Switzerland); Wilfactin[®] (human VWF, LFB-BIOMEDICAMENTS, Les Ulis, France).

Abbreviations: FVIII, factor VIII; FVIII:C, factor VIII concentration; GI, gastrointestinal; IQR, interquartile range; VWD, von Willebrand disease; VWF:RCo, von Willebrand factor:ristocetin cofactor.

number of patients with VWD, with less severe bleeding symptoms, than referral-based studies identifying symptomatic patients seeking care for VWD in specialist centers. The wide range in population-based estimates reflects variations in population size ($N = 182\text{--}4592$), as well as in timescale (study periods varied across a range of years from around 1985 to 2018 [exact timing not provided for study by Rodeghiero et al]).^{27–32} Definitions used to identify patients with VWD in the population-based studies also varied. Whereas all six population-based studies providing estimates for VWD overall^{27–32} included VWF levels with or without FVIII levels in the definition, the presence of bleeding symptoms was only required in three studies.^{28,30,31} Variations in referral-based estimates likely reflect several factors, including diagnostic facilities, physician awareness, subtype of VWD, and/or severity of bleeds.

Estimates of VWD prevalence also varied by disease type, age, and sex. Prevalence was lower in pediatric than in adult populations,¹² which could reflect the accumulation of non-fatal cases or increased diagnosis in adulthood. Type 3 VWD was the rarest reported (0.1–0.3 per 100,000), followed by type 2 VWD (0.8–2.5 per 100,000), and type 1 VWD (2.7–7.2 per 100,000).^{12,15,18} Reports suggest that more women than men are affected by VWD globally, despite VWD having an autosomal inheritance pattern.⁵ This may be because VWD is diagnosed more often in women due to female-specific hemostatic challenges such as HMB and intra-/postpartum bleeding. The studies reviewed suggest that HMB occurs frequently (>60%) in patients with VWD,^{23,31,34,42,44,54–58} while postpartum bleeding can occur in up to 13% of women with VWD.^{42,47,50,59–63}

This systematic review also suggests that there are important gaps in VWD diagnosis that could delay care and result in adverse health outcomes. Although the time from symptom development to diagnosis was poorly documented in the literature,^{38,52} the 3-year difference between median age at overt symptom onset and median age at diagnosis reported in this review³⁸ highlights the need for improved disease awareness for both patients and health care providers. According to international guidelines for VWD diagnosis, an accurate and timely diagnosis remains a major challenge for patients with VWD, with barriers identified as difficulties in distinguishing between normal and abnormal bleeding symptoms, limited clarity regarding an appropriate diagnostic approach, and limited access to specialized laboratory testing.¹⁰³ To facilitate VWD diagnosis, the multidisciplinary review panel recommended the use of bleeding-assessment tools in patients suspected of having VWD in a primary care setting to help identify patients who require laboratory testing, as well as specific diagnostic approaches for types 1 and 2 VWD.¹⁰³

Patients with VWD had a high burden of bleeding events even after VWD diagnosis or if receiving VWD treatment. Bleeding was reported in 72–94% of the patients with VWD,^{40,44,53} with mucocutaneous bleeds such as menorrhagia, GI bleeds, epistaxis, and oral bleeds being the most frequent.^{23,28,31,34,37,39,42–45,47,54–63,67,68,70–73,84} Life-threatening bleeding involving critical organs (eg, central nervous system^{34,37,44,55,69}) were also reported, although these were rare and studies have not found a difference in mortality between VWD and general populations.^{41,46,48,49,51} Only one study compared bleeding rates across all three VWD types.³⁴ In this retrospective Italian study ($N = 1234$), GI bleeding was more common in patients with types 2A or 3, central nervous system and joint bleeding events in those with type 3, and hematomas in patients with types 2N and 3, relative to other VWD types. However, the frequency of mucosal bleeding (epistaxis, HMB, and gum bleeding) did not differ significantly across VWD types. Lower bleeding rates were reported in studies that used medical records (vs those using questionnaires) or focused on specific patient populations, which suggests that bleeding events are not always reported or captured in medical records. Only one study used a validated bleeding assessment tool (the ISTH-BAT) completed by the physician to evaluate bleeding rates.⁵⁷ Bleeding assessment tools provide a standardized approach to assessment and can educate patients and physicians regarding bleeding symptoms and possible interventions.¹⁰³

The reported real-world treatment patterns show a range of treatment options with respect to VWD types and severity,^{92,95–97,99,100,102} with only a small proportion of patients with VWD reported to be receiving long-term VWF prophylaxis in a multinational VWD Prophylaxis Network study and in the Czech National Hemophilia Programme registry (0.7% and 1.6%, respectively).^{24,102} Long-term prophylaxis was administered most often in patients with type 3 VWD,^{92,95–97,99,100,102} and mostly for joint or GI bleeding.^{92,95–100,102} The current VWD management guidelines conditionally recommend long-term prophylaxis for patients with VWD and a history of severe and frequent bleeds.⁴ The guideline panel, however, acknowledged the low certainty of evidence for a net health benefit for long-term prophylaxis in this population. Thus, future research is needed to better understand bleeding outcomes and unmet needs of patients with VWD who may benefit from long-term prophylaxis.

Findings from the identified sources also suggest that VWD is associated with poorer HRQoL scores^{77,80,82} as well as higher HCRU^{83,84} compared with general populations. A variety of measurements were used across the eight studies evaluating HRQoL, including quality-of-life measures (SF-36 in adults, and ITQOL, CHQ-PF50, and CHQ-CF87 in children), and joint health measures (HJHS and HAL).^{39,40,67,73,77–82} In children, scores for physical functioning, emotional/behavioral functioning, and general health perceptions were lower than in children without VWD,⁷⁷ while in adults, both SF-36 PCS and MCS scores were lower than the general population.⁸⁰ All nine studies reporting HCRU were observational studies,^{36,38,40,41,46,57,69,83,84,90} mostly retrospective cohort studies. Although not covered by this review, decreased HRQoL and increased HCRU would be expected to have a substantial economic and societal impact. Studies evaluating VWD prophylaxis continue to demonstrate reductions in HCRU, such as hospitalizations,^{83,104} further supporting the overall benefit of long-term prophylaxis for eligible patients.

Limitations

Large variations in outcomes reported in this review reflect the heterogeneity of bleeding phenotype in VWD, as well as variability in study populations and research methodologies. Differences in disease awareness, diagnosis, and clinical management of VWD across the large geographic areas and different time periods covered by this review will also have contributed to the heterogeneity of the data.

Some relevant sources may not be captured in this review if they were not indexed in the electronic bibliographic databases used for this literature search, not classified under the MeSH or Emtree terms, or did not contain the keywords used in the search. To mitigate this limitation, the comprehensiveness of the search strategy was verified against articles known to be pertinent for the search. Keywords were reverse generated using a sample of articles deemed relevant for the review. Furthermore, some relevant sources may not have been captured in the systematic literature search, as some sources do not publish their studies in peer-reviewed journals. To mitigate this limitation, pragmatic searches of the gray literature as well as “snowballing” were conducted. Single-entry data extraction was employed for this systematic review. However, the completeness of the data was assessed by a separate reviewer.

Summary

This systematic review highlights the limited data available on the epidemiology of VWD, as well as the high disease burden and related impact on HRQoL and HCRU for patients with VWD. More real-world studies are needed to better understand the characteristics of VWD patient populations and help inform timely VWD diagnosis and care.

Data Sharing Statement

The datasets, including the template data extraction form and data extracted from the included studies, are available upon request from corresponding author, Ping Du.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

PD, GÖ, and ST are employees of Takeda Development Center Americas, Inc., and Takeda stockholders. AB and YM are employees of YOLARX Consultants and received fees from Shire Human Genetic Therapies, Inc., a Takeda company, for conducting this analysis. FTB is an employee of Takeda Pharmaceuticals International AG, and a Takeda stockholder. The authors report no other conflicts of interest in this work.

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