HHS Public Access

Author manuscript

Am J Hematol. Author manuscript; available in PMC 2022 May 23.

Published in final edited form as:

Am J Hematol. 2020 January ; 95(1): 10–17. doi:10.1002/ajh.25656.

Higher rates of bleeding and use of treatment products among young boys compared to girls with von Willebrand disease

Karon Abe, PhD[1], **Brandi Dupervil, MPH, DHSc**[1], **Sarah H. O'Brien, MD**[2], **Meredith Oakley, MPH, DVM**[1], **Roshni Kulkarni, MD**[3], **Joan Cox Gill, MD**[4,†], **Vanessa Byams, MPH, DrPH**[1], **Michael J. Soucie, PhD**[1] **on behalf of US Hemophilia Treatment Center Network**

[1]Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[2]Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, Ohio

[3]Centers for Bleeding and Clotting Disorders, Department of Pediatrics and Human Development, Michigan State University, East Lansing, Michigan

[4]Bloodcenter of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin

Abstract

There are limited observational studies among children diagnosed with von Willebrand Disease (VWD). We analyzed differences in bleeding characteristics by sex and type of VWD using the largest reported surveillance database of children with VWD (n = 2712), ages 2 to 12 years old. We found that the mean ages of first bleed and diagnosis were lowest among children with type 3 VWD. It was even lower among boys than girls among all VWD types, with statistically significant difference among children with type 1 or type 3 VWD. Children with type 3 VWD also reported higher proportions of ever having a bleed compared to other VWD types, with statistically higher proportions of boys compared to girls reporting ever having a bleed with type 1 and type 2 VWD. A similar pattern was observed with the use of treatment product, showing higher usage among type 3 VWD, and among boys than girls with type 1 and type 2 VWD. While there were no differences in life quality or in well-being status by sex, children with type 3 VWD showed a greater need for mobility assistance compared to children with type 1 and type 2 VWD. In an adjusted analysis among children with type 1 VWD, boys showed a significant association of ever bleeding [hazard ratio 1.4; *P*-value <.001)] compared to girls. Understanding phenotypic

Correspondence: Karon Abe, PhD, Centers for Disease Control and Prevention, 4770 Buford Hwy, Mail-Stop S106-4, Atlanta, GA, 30341. kabe@cdc.gov.

†Deceased.

AUTHOR CONTRIBUTIONS

K.A., B.D. M.S. conceived and designed study. S.O. evaluated VWD subtype coding for categorization. K.A. and B.D. performed data analyses. K.A., B.D., M.O., V.B., M.S., R.K., and S.O. made substantial contributions to the interpretation of the data. K.A. and B.D. drafted the manuscript with critical expert input with regards to clinical importance, surveillance methodology and epidemiology by MO., V.B., M.S., R.K., and S.O. Final approval was required by all authors.

CONFLICT OF INTEREST AND DISCLAIMER STATEMENT

The authors K.A., B.D., M.O., V.B., M.S., R.K., and S.O. report no actual or potential conflicts of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

bleeding characteristics, well-being status, treatment, and higher risk groups for bleeding among pre-adolescent children with VWD will aid physicians in efforts to educate families about bleeding symptoms.

1 INTRODUCTION

Von Willebrand Disease (VWD) is recognized as the most common inherited bleeding disorder, with a reported prevalence of 0.6% to 1.3% in the general population.[1–3] The condition is characterized by clinically significant mucocutaneous or post-surgical bleeding. The bleeding symptoms are a result of decreased or dysfunctional von Willebrand factor (VWF), a protein that plays a role both as a carrier of coagulation factor VIII (FVIII), and as an intermediator of platelet adhesion and aggregation during hemostasis.[4] There are three main designated disease types of VWD based on the quantitative reduction (type 1), qualitative activity or functionality (type 2), or absence (type 3) of VWF.[5] Diagnosis of VWD is complex and often requires evaluation through bleeding assessment tools (BAT), family history, and extensive laboratory testing. Bleeding symptoms do not always align with VWF levels or VWF or FVIII activity, and can also vary by type, age and sex, adding additional complexity to both diagnosis and treatment.[6–8] Management in type 1 and type 2 VWD is intent on increasing the levels of functional VWF with desmopressin, a synthetic derivative of the antidiuretic vasopressin, with or without other treatment options such as antifibrinolytic agents, hormonal therapy, or surgical hemostasis, as appropriately indicated[6] The most rare and severe form of VWD is type 3, which requires infusion of VWF concentrates (with or without recombinant or monoclonal FVIII) as treatment.[6]

The prevalence of symptomatic VWD in children ≤18 years of age has been estimated to be 1 in 1000, similar to adults in primary care.[3,9] Diagnosis of VWD in children can be more clinically challenging compared to adults, since children can remain asymptomatic in the relative absence of any major hemostatic encounters.[9] Also, bleeding disorder symptoms such as epistaxis and bruising are frequent among even healthy children.[10] Several studies have developed or evaluated BATS with or without pediatric specific questions to identify children who may require further testing, validate the sensitivity of a tool among children with VWD or estimate the prevalence of clinically significant bleeding symptoms of VWD in a pediatric population to facilitate treatment.[2,9,11–16] However, a more complete characterization of the bleeding symptoms among children with diagnosed VWD could help to improve management of this disorder in this younger population.[17]

There are very few studies with large cohorts of children diagnosed with VWD. Studies have grouped children up to 18 years of age, despite age-related and sex differences in pre-adolescence, adolescence, and in early adulthood.[9,11] These stages of development present different bleeding challenges by sex that may go undetected when analyzed together. The autosomal inheritance pattern of VWD indicates an equal distribution among males and females. However, VWD is often perceived as predominantly affecting females, especially with the onset of puberty. There is little information on the differences by sex and by type of VWD during the pre-adolescent years. Early identification of significant bleeding characteristics by sex during these years may have important clinical implications.

Therefore, our objective was to evaluate the differences in bleeding characteristics, treatment, and well-being status by sex and by type of VWD using surveillance data with the largest reported number of children with diagnosed VWD.

2 | METHODS

The Universal Data Collection (UDC) was a surveillance system funded by the Centers for Disease Control and Prevention (CDC) to monitor the health of people with bleeding disorders, receiving care at one of the 135 federally funded Hemophilia Treatment Centers (HTCs) across the U.S.[18] Patients Of all ages who had a bleeding disorder and received care at an HTC were eligible to enroll in the project. Standardized data collection spanned from May 1998 through September 2011. Trained HTC staff collected demographic and clinical information based on medical and clinic records using standardized data collection forms. A registration form was used to collect baseline and historical data on sex, race/ethnicity (self-reported), VWD diagnosis, age of diagnosis, month and year of birth, family history, age at first HTC visit, and bleeding history, including the age and site of the first bleeding episode. An annual visit form (the first completed at the time of registration) was also used to collect height and weight, information on health insurance, joint, muscle, or other bleeds, treatment products, HTC utilization, physical activity, and joint range of motion during annual comprehensive clinic visits. The UDC had Institutional Review Board oversight at each HTC and parents of all minor children provided informed consent.

2.1 | Study population

There were 2776 children ages 2 to 12 years with a VWD diagnosis in UDC. Children with VWD diagnosed with an additional bleeding disorder were excluded from this study (n = 64). The remaining 2712 children formed the study population.

2.2 | Data collection

Month and year of birth data were converted to a birthdate by assuming the 15th of the month and the resulting date was subtracted from the registration date to calculate age at registration. We then categorized age of registration into ages 2 to 5 years and 6 to 12 years to correspond with preschool and elementary school ages. Age of diagnosis was categorized into three age groups (<2 years, 2–5 years, 6–12 years) to differentiate children diagnosed before 2 years of age. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander (PI) or American Indian/ Alaskan Native (AI/AN), and other.

Diagnosis of VWD was at the discretion of the physician at the HTCs. The UDC did not specify laboratory definitions nor diagnostic criteria for subtypes. The VWD type 2 subtypes were collapsed into a type 2 VWD category. Additionally, the text from an “other specify” option was reclassified into type 1, type 2, type 3, or unknown VWD by coauthor Sarah O’Brien. For subjects with a history of bleeding, the site of the first bleed was categorized on the form as head (intracranial/extracranial), circumcision, intramuscular injection, oral mucosa, joint, unknown, and other. The HTC staff provided text to specify the location in ‘other’. These text responses were reclassified by Sarah O’Brien. Based on the International

Society on Thrombosis and Haemostasis (ISTH)-BAT.[7] At registration, the presence of a bleeding history was based on the response to the yes/no question "Has the patient ever had a bleed?" Information on the type of health insurance was categorized as private (commercial insurance), public (Medicare, Medicaid, state plan, TRICARE), other insurance or uninsured. Measurements of height and weight were used to calculate body mass index (BMI) as weight (kg)/[height (m)],[2] and the corresponding BMI-for-age percentile, based on the CDC growth charts for children ages 2 to 19 years was used to categorize BMI ranges as underweight, normal, overweight or obese.[19]

Treatment products used by subjects in practice, reported at any annual visit, were grouped into one of three product categories: non-plasma and topical products (i.e., intravenous or intranasal desmopressin (DDAVP), antifibrinolytics, fibrin glue, or other); blood bank products (ie, cryoprecipitate, fresh frozen plasma, platelets, packed red blood cells or whole blood); or factor concentrates (ie, human FVIII containing VWF).

We analyzed frequency of HTC utilization at registration categorized as frequent (one visit/ year), infrequent (one visit/ 2–3 years), or rare (one visit/4+ years) or first visit to an HTC. To evaluate well-being status, the use of assistive devices for ambulation or mobility including a cane, crutches, walker or a wheelchair at any annual visit was assessed and categorized as any or none. The use of a central venous access device (CVAD) for treatment administration on any annual visit was also assessed. The number of days missed from school or work due to joint problems was calculated by combining the reported number of missed days for both upper and lower extremities for all annual visits.

Data on the use of orthopedic appliances (cast, splint, orthosis, brace), and invasive procedures (arthrodesis, joint replacement, arthroscopic synovectomy, open synovectomy, radiosynovectomy, other invasive procedure) at any annual visit were assessed. Level of activity at registration was assessed by a check box on the following statements: (a) Unrestricted school/work and recreational activities; (b) Full school/work with limited recreational activity levels due to pain, loss of motion, weakness; (c) Limited school/work and recreational activity levels due to pain, loss of motion, weakness; (d) Limited school/ work, recreational activity levels, and self-care activity levels due to pain, loss of motion, weakness; (e) Requires assistance from another person for school/work/self-care, and unable to participate in recreation due to pain, loss of motion, weakness. We categorized levels 3 to 5 into an "limited activity" category.

2.3 | Data analysis

For analysis, data from any annual visit prior to age 13 were assessed. Clinical characteristics were assessed by sex and by type of VWD using chi-square analysis and Wilcoxon rank sum tests, as appropriate. To assess associations between patient characteristics and the prevalence of ever bleeding among children with type 1 VWD, we used Cox proportional hazard (PH) regression with discrete ties, and estimated adjusted hazard ratios (HRS) and Wald 95% confidence limits (Cl). We used time to first bleed in years as the survival time/failure event and censored the children without any bleeding episodes at the time of registration into UDC. All variables used in the model (sex, health insurance, race/ethnicity, family history, and BMI) were reported at the time of

registration. All analyses were performed using SAS version 9.4 and *P*-values were considered statistically significant when $P \leq .05$.

3 | RESULTS

Table 1 describes the characteristics of 2712 children with VWD, 2 to 12 years old, enrolled in UDC during 1998 to 2011. In this population there were more males (56.8%) than females (43.2%). Approximately 76% of the population had type 1, 13% had type 2, 4% had type 3, and 7% had unknown/other type VWD. The majority of children (68.7%) were registered in UDC between 6 to 12 years of age. Sixty-seven percent of children had been diagnosed with VWD prior to 6 years of age, with almost a quarter diagnosed before 2 years of age. Approximately 98% of the population had some form of health insurance and nearly two-thirds of the population were non-Hispanic white. Sixty percent of the children had a family history of a bleeding disorder. Almost 40% of children were overweight/obese and 57.3% were normal according to their BMI.

3.1 | Bleeding characteristics

Differences in bleeding characteristics according to VWD type and sex are shown in Table 2. The mean age of first bleed was lower by approximately a year among children with type 3 VWD compared to other VWD types and was lower among boys than girls among all types of VWD, with a statistically significant difference among children with type 1 VWD [3.3 year (boys) vs 4.3 year (girls); $P < .001$]. The mean age of diagnosis was also much lower among children with type 3 VWD compared to the other types and was significantly lower among the boys compared to girls with type 1 (4.2 year vs 5.0 year; $P < .001$) or type 3 VWD (0.8 year vs 1.5 year, $P < .01$). Among children with type 1 VWD, boys were younger at their first HTC visit and at registration than girls. At the time of registration, a higher proportion of boys than girls reported ever having had a bleeding episode among children with type 1 (77.5% vs 72.8%; $P = .01$) and type 2 (87.7% vs 78.7%; $P = .02$). When accounting for bleeds reported at registration and any annual visit prior to age 13, boys reported significantly more bleeding episodes compared to girls with type 1, but not with type 2. At registration, a higher percentage of treatment product use was reported among children with type 3 compared to type 1 and type 2 VWD and boys reported receiving treatment product significantly more often than girls among type 1 VWD (19.7% vs 11.9%, $P < .01$). When using the registration and annual visit forms, a significantly higher proportion of treatment product use was seen among boys than girls with type 1 and type 2.

3.2 | Well-being status

The results of analyses of five life quality or well-being status questions by VWD type are shown in Table 3. Children with type 3 VWD utilized HTCs more frequently than those with type 1 or type 2. About 2% of children with VWD had a CVAD, with children with type 3 VWD having a higher proportion of usage (16%) than children with type 1 or type 2. Greater than 95% of children with type 1 (n = 2006; 96.9%) and type 2 (n = 327; 96.5%) reported unrestricted physical activity, however, the proportion was lower among those with type 3 VWD (n = 109; 91.6%). No child reported any days missed from school due to joint

problems and there was only one reported invasive joint procedure performed in a child with type 3 VWD (data not shown).

In contrast, a far higher proportion of children with type 3 reported any use of a cane, crutches, walker, or wheelchair for mobility assistance compared to those with type I or type 2 VWD. Less than 1% of children among all types of VWD had any use of an orthopedic appliance reported at any annual visit; among children with type 3 VWD, usage was less than 5%.

3.3 | First bleed and treatment usage

The results of analyses of the site of the first bleed among the children who experienced a bleed based on registration form (n = 1965) are shown in Table 4. The most common sites of first bleed were epistaxis and oral cavity bleeding among all children. However, boys experienced a higher proportion of epistaxis and girls experienced a higher proportion of oral cavity bleeding as the site of their first bleed. Children with type 3 had lower rates of epistaxis compared to type 1 or type 2 VWD. Boys with type 3 VWD showed equivalent frequencies of reporting both circumcision (21%) and epistaxis (21%) as site of first bleed. Surgical sites were also reported among children with type 1 as a site of first bleed more frequently than type 2 or type 3 VWD.

We also evaluated treatment product usage among children who received treatment (n = 1893) and did not see any significant differences by sex. This population was coming out of the HIV hepatitis epidemic and none of the plasma-derived products that contained VWF (and currently used for VWD) were FDA approved for this indication. From our data, 2% of the clinicians prescribed FVIII concentrate to the VWD population. Usage of human FVIII containing VWF among children was 13.8% with type 1, 48.4% with type 2, and 85.7% with type 3 VWD. For non-plasma and topical products, usage was 65.1% (30.9% DDAVP) with type 1, 58.7% (19.2% DDAVP) with type 2, and 59.7% (1.7% DDAVP) with type 3 VWD. For blood bank products, usage was 0.2% with type 1, 0.9% with type 2, and 4.2% with type 3 (Figure S1). Sixteen percent of children used more than one treatment product.

3.4 | Risk Factors for bleeds among type I VWD

Table S5 shows the proportion of children with type 1 VWD who experienced a bleeding episode and the adjusted HRS for associations with demographic characteristics. Children with type 1 VWD who had experienced a bleed were more likely to be male (HR 1.4; 95% Cl 1.2–1.5), be Asian/Pl/Al/AN race (HR 1.4; 95% a 1.1–1.8) or Hispanic ethnicity (HR 1.3; 95% Cl 1.2–1.6). We did not have a large enough sample to perform a Cox proportional hazard regression among children with type 2 or type 3 VWD.

4 | DISCUSSION

This study shows the utility of surveillance data to report bleeding characteristics, treatment, and well-being status of children with diagnosed VWD. It is the largest sample of children with diagnosed VWD to date, and it is also the first to report statistically significant differences by sex in a pre-adolescent sample. Boys show statistically higher proportions of bleeding episodes, earlier age of diagnosis, and treatment product use compared to girls.

4.1 | Bleeding characteristics by sex

It is not clear why boys compared to girls would show different bleeding characteristics resulting, for example, in almost a year difference in first bleed episode among children with type 1 VWD. Boys may be experiencing both hemostatic challenges (eg, circumcision) and bleeding episodes much earlier compared to girls. There may be a higher index of suspicion for a bleeding disorder among boys, such as hemophilia, resulting in earlier testing and diagnosis. Boys have been reported to be more physically active than girls, even as infants [20,21] which could result in more frequent bleeding episodes. Only one other study, the Willebrand in the Netherlands (WiN) study, evaluated children with moderate to severe VWD by sex.[11] The WiN study (n = 113, 0–16 year olds) included girls who experienced menstruation, which may have precluded any observable bleeding score differences by sex. Only 5% (n = 35) of girls reported heavy menstrual bleeding as a site of first bleed in our study. Other studies have only evaluated bleeding characteristics by sex among undiagnosed children in need of further hematologic evalution.[3,9,12] Our study underscores the importance of using a large dataset to gain a comprehensive understanding of the bleeding history and symptoms among children with diagnosed VWD by age, stages of development, and sex.

4.2 | Bleeding characteristics

Consistent with other clinical studies, our surveillance data also showed a more severe bleeding phenotype among children with type 3 VWD, compared to children with type 1 or type 2 VWD. [1,11] Sanders et al[11] reported ISTH-BAT pediatric bleeding symptoms and scores to be the highest among children with type 3, then type 2, and then type 1, as well as an earlier mean age of diagnosis among children with type 3 VWD. The study also reported cutaneous bleeding (32%) and epistaxis (31%) as the top sites of first bleed among children with VWD, but did not analyze by sex. [11] We observed that among the two most frequently reported sites of first bleed, epistaxis and oral cavity bleeding, boys frequently reported more epistaxis and girls reported more oral cavity bleeding among all types of VWD.

4.3 | Well-being

As with other bleeding disorders such as hemophilia, severe bleeding symptoms in people with VWD can also result in a decrease of quality of life.[22,23] Van Galen et al[22] reported that 23% of patients with VWD reported joint bleeds, 47% among patients with type 3 VWD. Individuals who reported joint bleeds also self-reported joint damage and lower health-related quality of life (HR-QoL) measures compared to patients with VWD without joint bleeds. The study also found that the majority of joint bleeds occurred before 16 years of age.[22] A decrease in the joint range of motion was also noted in a 2005 UDC report among VWD participants, as early as two years of age.[23.24] We did not evaluate individual joint bleeding or range of motion in our study, but assessed missed days due to joint problems (data not shown), of which, there were no reported cases. Although we did not implement standardized HR-QoL measures, the surveillance data did assess other well-being type indicators. Our findings further emphasize the early age onset of these bleeding episodes and its impact on mobility and physical activity.

Of clinical importance is the identification of potential higher risk populations for bleeding among children with VWD in order to conduct more patient and provider awareness and education for prevention and treatment. We found that children with type 1 VWD who were Hispanic or Asian/Pl/Al/AN were significantly more likely to have experienced a bleed, compared to non-Hispanic white children at the time of registration. Further attention is needed to address potential reasons for this health disparity. The HR was not statistically significant for an association between obesity and ever bleeding. But there were proportional increases in the population ever experiencing a bleed by increasing weight category, the lowest among the underweight (71.1%) to the highest among the obese (80%). Studies in the hemophilia population using UDC data have found an association between obesity and decreases in joint range of motion over time.[25] The VWD population should be advised of the potential outcomes with obesity, especially among children with type 3 VWD.

This study has many strengths. It is the largest cohort of pre-adolescent children with VWD reported to date, allowing for more robust analysis of bleeding characteristics, treatment and well-being status by type and sex. We were able to evaluate risk factors for bleeding among children with type 1 VWD. However, there are several limitations. The UDC is a surveillance system, designed to capture minimal data elements. Therefore, bleeding scores were not collected as part of UDC, nor was information on VWF:antigen levels or VWF ristocetin cofactor activity, blood type, and presence of anemia. Therefore, the number of low von Willebrand levels included as type 1 VWD is not known. Diagnosis of VWD by a physician should not have differed by sex. Also, data on bleeding episodes were based on recall of the patient, but again the recall bias should not have differed by sex. There also was no data collection regarding age of menarche, long-term prophylaxis, or any standardized HR-QoL questionnaires. So our well-being status questions were inferred based on other survey questions, and diagnosis for VWD may not have been uniformly interpreted across HTCs.

This study contributes to the understanding of the pre-adolescent history of bleeding among children with diagnosed VWD in the U.S. Boys showed higher proportions of bleeding episodes and treatment product use than girls with type 1 VWD. Minority children (Hispanic or Asian/Pl/Al/AN) in the U.S. are at higher risk of ever bleeding, compared to children who are non-Hispanic white. Children with type 3 VWD also show the early stages of lower well-being status compared to children with type 1 VWD and type 2 VWD. Awareness of these bleeding differences and continued vigilance of care may improve outcomes for children with VWD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The UDC project was funded by a cooperative agreement (“Prevention of Bleeding Disorder Complications through Regional Hemophilia Treatment Centers”) between the CDC and the United States Hemophilia Treatment Center Network (US HTCN). This is comprised of >130 clinical centers located throughout the United States. The authors acknowledge with gratitude the staff of the US HTCN for recruiting patients to the UDC surveillance project and

collecting the data. The authors also thank the regional coordinators, regional directors, patients and their families for their participation.

REFERENCES

1. Leebeek FW, Eikenboom JC. Von Willebrand's disease. N Engl J Med. 2016;375(21):2067–2080. [PubMed: 27959741]
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987;69(2):454–459. [PubMed: 3492222]
3. Werner EJ, Broxson EH, Tucker EL Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. J Pediatr. 1993;123(6):893–898. [PubMed: 8229521]
4. Zimmerman TS, Ratnoff OD, Powell AE. Immunologic differentiation of classic hemophilia (factor 8 deficiency) and von Willebrand's disease, with observations on combined deficiencies of antihemophilic factor and proaccelerin (factor V) and on an acquired circulating anticoagulant against antihemophilic factor. J Clin Invest. 1971;50(1): 244–254. [PubMed: 5543879]
5. Sadler JE, Budde IJ, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006;4(10):2103–2114. [PubMed: 16889557]
6. Nichols WI, Hultin MB, James AH, et al. Von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert panel report (USA). Haemophilia. 2008;14(2):171–232. [PubMed: 18315614]
7. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. J Thromb Haemost. 2010;8(9):2063–2065. [PubMed: 20626619]
8. Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis Of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). J Thromb Haemost. 2006;4(4):766–773. [PubMed: 16634745]
9. Bowman M, Hopman WM, Rapson D, Lillicrap D, Silva M, James P. A prospective evaluation of the prevalence of symptomatic von Willebrand disease (VWD) in a pediatric primary care population. Pediatr Blood Cancer. 2010;55(1):171–173. [PubMed: 20213845]
10. Nosek-Cenkowska B, Cheang MS, Pizzi NJ, Israels ED, Gerrard JM. Bleeding/bruising symptomatology in children with and without bleeding disorders. Thromb Haemost. 1991;65(3):237–241. [PubMed: 2048048]
11. Sanders YV, Fijnvandraat K, Boender J, et al. Bleeding spectrum in children with moderate or severe von Willebrand disease: relevance of pediatric-specific bleeding. Am J Hematol. 2015;90(12):1142–1148. [PubMed: 26375306]
12. Malec LM, Moore CC, Bennett CM, et al. Validation study of the composite score to identify Von Willebrand disease in children. J Pediatr Hematol Oncol. 2016;38(2):139–142. [PubMed: 26535774]
13. Bowman ML, James PD. Bleeding scores for the diagnosis of von Willebrand disease. Semin Thromb Hemost. 2017;43(5):530–539. [PubMed: 28196380]
14. Sidonio RF Jr, Gunawardena S, Shaw PH, Ragni M. Predictors of von Willebrand disease in children. Pediatr Blood Cancer. 2012;58(5):736–740. [PubMed: 22237978]
15. Marcus PD, Nire KG, Grooms L, Klima J, O'Brien SH. The power of a standardized bleeding score in diagnosing paediatric type 1 von Willebrand's disease and platelet function defects. Haemophilia. 2011;17(2):223–227. [PubMed: 20860605]
16. Bidlingmaier C, Grote V, Budde U, Olivieri M, Kurnik K. Prospective evaluation Of a pediatric bleeding questionnaire and the ISTH bleeding assessment tool in children and parents in routine clinical practice. J Thromb Haemost. 2012;10(7):1335–1341. [PubMed: 22578063]
17. Sidonio RF, Haley KM, Fallaize D. Impact of diagnosis of von Willebrand disease on patient outcomes: analysis of medical insurance claims data. Haemophilia. 2017;23(5):743–749. [PubMed: 28636092]
18. Soucie JM, McAlister S, McClellan A, Oakley M, Su Y. The universal data collection surveillance system for rare bleeding disorders. Am J Prev Med 2010;389(4 Suppl):S475–S481.

19. Blinder MA, Vekeman F, Sasane M, Trahey A, paley C, Duh MS. Age-related treatment patterns in sickle cell disease patients and the associated sickle cell complications and healthcare costs. Pediatr Blood Cancer. 2013;60(5):828–835. [PubMed: 23335275]

20. Ekelund U, Luan J, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. JAMA. 2012;307(7):704–712. [PubMed: 22337681]

21. Campbell DW, Eaton WO. Sex differences in the activity level of infants. Infant and Child Development 1999;8(1):1–17.

22. van Galen KP, Sanders YV, Vojinovic U, et al. Joint bleeds in von Willebrand disease patients have significant impact on quality of life and joint integrity: a cross-sectional study. Haemophilia. 2015;21(3):e185–e192. [PubMed: 25854528]

23. Abshire T The role of prophylaxis in the management of von Willebrand disease: today and tomorrow. Thromb Res. 2009;124 (Suppl 1):S15–S19. [PubMed: 19944256]

24. Centers for Disease Control and Prevention. Report On The Universal Data Collection Program. 2005;7(No.1): 1–39.

25. Soucie JM, Wang C, Siddiqi A, et al. The longitudinal effect of body adiposity on joint mobility in young males with Haemophilia A. Haemophilia. 2011;17(2):196–203. [PubMed: 21332880]

TABLE 1

Demographics of children ages 2–12 years of age (n = 2712) diagnosed with VWD, UDC1998–2011

Characteristics	n (%)
Gender	
Male	1540 (56.8)
Female	1172 (43.2)
VWD Type	
Type 1	2070 (76.3)
Type 2	339 (12.5)
Type 3	119 (44)
Other VWD	43 (1.6)
Unknown	141 (5.2)
Age at registration	
2–5 years	849 (31.3)
6–12 years	1863 (68.7)
Age at diagnosis of VWD	
<2 years	662 (244)
2–5 years	1152 (42.5)
6–12 years	862 (31.8)
Unknown/Missing	36(1.3)
Health Insurance	
Private	1513 (55.8)
Public	965 (35.6)
Insured Other	191 (7)
Uninsured	43 (1.6)
Race/Ethniclty	
White (Non-Hispanic)	1762 (65)
Black (Non-Hispanic)	228 (84)
Hispanic	459 (16.9)
Asian/PI AI/AN	110 (4.1)
Other	153 (5.6)
Family History of a bleeding disorder	
No	1086 (40)
Yes	1626 (60)
BMI (at registration)	
Obese	541 (20)
Overweight	471 (17.4)
Normal	1605 (59.2)
Underweight	80 (2.9)
Unknown/Missing	14 (0.5)

Abbreviations: PI, Pacific Islander; AI/AN, American Indian/Alaskan Native.

TABLE 2

Bleeding characteristics among children by VWD type 1,2, and 3 and sex (n = 2528)

	Type 1 n = 2070			**Type 2 n = 339**			**Type 3 n = 119**		
	Male n = 1169 n [SD]	**Female n = 901**	***P*-value**	**Male n = 203 n [SD]**	**Female n = 136**	***P*-value**	**Male n = 68 n [SD]**	**Female n = 51**	***P*-value**
Mean age in years at first bleed[a]	3.3 [2.7]	4.3 [3.3]	<.001	2.0 [2.3]	2.4 [2.8]	.2	0.7 [1.4]	1.2 [1.7]	.1
Mean age in years of diagnosis	4.2 [3.0]	5.0 [3.2]	<.001	2.6 [2.9]	3.3 [3.3]	.06	0.8 [1.3]	1.5 [2.1]	.01
Mean age in years at first HTC visit[a]	4.7 [3.1]	5.4 [3.3]	<.001	3.2 [3.1]	3.7 [3.4]	.14	1.5 [2.0]	2.2 [2.4]	.12
Mean age in years at registration[a]	7.4 [3]	7.7 [3.1]	.02	6.5 [3.2]	6.7 [3.2]	.55	6.5 [3.7]	6.1 [3.2]	.49
Ever had a bleed registration only[a] n (%)									
No	263 (22.5)	245 (27.2)	.01	25 (12.3)	29 (21.3)	.02	-	-	.79
Yes	906 (77.5)	656 (72.8)		178 (87.7)	107 (78.7)		-	-	
Ever had a bleed registration and annual visit[a] n (%)									
No	191 (16.3)	183 (20.3)	.02	19 (9.4)	19 (14.0)	.19	-	-	0.84
Yes	978 (83.7)	718 (79.7)		184 (90.6)	117 (86.0)		-	-	
Ever received product or dotting factor concentrate at registration only[a] n (%)									
No	939 (80.3)	794 (88.1)	<.01	100 (49.3)	81 (59.6)	.06	13 (19.1)	9 (17.6)	.84
Yes	230 (19.7)	107 (11.9)		103 (50.7)	55 (40.4)		55 (80.9)	42 (82.4)	
Ever received product or dotting factor concentrate registration and annual visit[b] n (%)									
No	320 (274)	285 (31.6)	.03	33 (16.3)	36 (26.5)	.02	-	-	.63
Yes	849 (72.6)	616 (68.4)		170 (83.7)	100 (73.5)		-	-	

[a] As reported at registration.

[b] As reported at registration and annual visits. Data cells with a dash represents cell sizes with 5 or less data points. Complementary cells were also not shown consistent with UDC standards.

TABLE 3

Well-being status among children with VWD by type (n = 2528)

	Type 1 n = 2070 n (%)	**Type 2 n = 339 n (%)**	**Type 3 n = 119 n (%)**	***P*-value**
HTC utilization[a]				
Frequent	1393 (67.3)	241 (71.1)	101 (84.9)	.003
Infrequent	295 (14.3)	45 (13.3)	-	
Rare	29 (1.4)	7 (2.1)	-	
First visit	352 (17)	46 (13.6)	9 (7.6)	
CVAD use[b]				
No	2049 (99)	326 (96.2)	100 (84)	<.001
Yes	21 (1)	13 (3.8)	19 (16)	
Physical activity level[a]				
Unrestricted	2006 (96.9)	327 (96.5)	109 (91.6)	.11
Full school and work, limited recreation	50 (2.4)	-	-	
Other[c]	13 (0.6)	-	-	
Ever used cane, crunches, walker, or wheelchair for mobility[b]				
No	2001 (96.7)	327 (96.5)	92 (77.3)	<.001
Yes	69 (3.3)	12 (3.5)	27 (22.7)	
Orthopedic applicance[b]				
No	2054 (99.2)	-	-	-
Yes	16 (0.8)	-	-	

[a]As reported at registration.

[b]As reported at any annual visit

[c]Other = limited school/work and recreational activity levels due to pain, loss of motion, weakness, limited school/work recreational activity levels, and self-care activity levels due to pain, loss of motion, weakness, and requires assistance from another person for school/work/self-care, and unable to participate In recreation due to pain, loss of motion, weakness; data cells with a dash represent cell sizes with 5 or less data points. Complementary cells also were not shown consistent with UDC standards.

TABLE 4

Site of first bleed based on registration form among children that experienced a bleed (n = 1962) by sex and type of VWD[b]

	Type 1 n = 1562		Type 2 n = 285		Type 3 n = 115	
	Male n = 906 n (%)	Female n = 656	Male n = 178 n (%)	Female n = 107	Male n = 66 n (%)	Female n = 49
Site of Bleed						
Circumcision	33 (3.6)	n/a	18 (10.1)	n/a	14 (21.2)	n/a
Cutaneous	46 (5.1)	48 (7.3)	4 (2.2)	2 (1.9)	0	1 (2.0)
Dental extraction	2 (0.2)	1 (0.2)	0	0	0	0
Epistaxis	317 (35.0)	207 (31.6)	59 (33.1)	28 (26.2)	14 (21.2)	6 (12.2)
Gastrointestinal	15 (1.7)	12 (1.8)	3 (1.7)	0	0	1 (2.0)
Head	45 (5.0)	21 (3.2)	8 (4.5)	5 (4.7)	5 (7.6)	6 (12.2)
Heavy menstrual bleeding	n/a	33 (5.0)	n/a	2 (1.9)	n/a	0
Intramuscular injection	2 (0.2)	4 (0.6)	9 (5.1)	5 (4.7)	2 (3.0)	4 (8.2)
Joint	12 (1.3)	6(0.9)	1(0.6)	0	2 (3.0)	1 (2.0)
Minor wounds	19 (2.1)	14 (2.1)	3 (1.7)	2 (1.9)	2 (3.0)	4 (8.2)
Musde hematoma	6 (0.7)	0	0	0	1 (1.5)	0
Hematoma other, or unspecified	5 (0.6)	2 (0.3)	0	1 (0.9)	0	0
Oral cavity	262 (28.9)	220 (33.5)	41 (23.0)	48 (44.9)	21 (31.8)	22 (44.9)
Other	37 (4.1)	15 (2.3)	7 (3.9)	6 (5.6)	1 (1.5)	1 (2)
Surgical[a]	48 (5.3)	36 (5.5)	4 (2.2)	1 (0.9)	1 (1.5)	1 (2)
Umbilicus	2 (0.2)	2 (0.3)	0	0	0	0
Unknown	65 (7.2)	43 (6.6)	23 (12.9)	7 (6.5)	3 (4.5)	3 (6.1)

[a]The following surgeries were reported: adenoidectomy, appendectomy, tonsillectomy, cardiac, colostomy, ear, eye, spinal tap, hydrocelectomy, mole removal, port-a cath insertion, endoscopy, and other non-spedfied surgical procedures.

[b]Multiple sites of first bleed were reported for some partidpants so cell numbers will not add up to the total.