Published in final edited form as:

Haemophilia. 2013 May ; 19(3): 385–391. doi:10.1111/hae.12014.

Bleeding disorders, menorrhagia and iron deficiency: impacts on health-related quality of life

C. RAE^{*}, W. FURLONG^{*,†}, J. HORSMAN^{*,†}, E. PULLENAYEGUM[‡], C. DEMERS[§], J. ST-LOUIS[¶], D. LILLICRAP^{**}, and R. BARR^{††}

^{*}Centre for Health Economics and Policy Analysis, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

[†]Health Utilities Inc., Dundas, ON, Canada

[‡]Father Sean O'Sullivan Research Centre, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

[§]Department of Hematology, Hôpital Enfant-Jesus, Quebec City, QC, Canada

[¶]Department of Hematology/Oncology, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada

^{**}Department of Pathology, Queen's University, Kingston, ON, Canada

^{††}Departments of Pediatrics, Pathology and Medicine, McMaster University, Hamilton, ON, Canada

Summary

von Willebrand disease (VWD) is a bleeding disorder that occurs in up to 1% of the general population. The great majority of females with VWD experience menorrhagia. The morbidity burden in females with VWD may relate to iron deficiency resulting from menorrhagia. To explore relationships between bleeding disorders, menorrhagia, iron deficiency and the outcomes of health-related quality of life (HRQL) and educational attainment. All subjects with VWD, and females with other bleeding disorders, in the Canadian national registry who were more than 12 years of age were eligible for survey. Survey measures included the HEALTH UTILITIES INDEX[®]; abridged Clinical History Assessment Tool; socio-demographic questions and serum ferritin. Statistical analyses included testing differences among groups of means using analysis of variance and of proportions using chi-squared test. Significant size differences in mean HRQL

© 2012 Blackwell Publishing Ltd

Correspondence: Ronald Barr, Room 3N27B, Health Sciences Centre, McMaster University, 1200 Main Street West, Hamilton ON, L8S 4J9, Canada. Tel.: +1 905 521 2100 X 73464; fax: +1 905 521 1703; rbarr@mcmaster.ca.

Author contributions

Ronald Barr, William Furlong, David Lillicrap, Christine Demers and Jean St-Louis designed the research study. Eleanor Pullenayegum and Charlene Rae analysed the data. Ronald Barr, William Furlong, John Horsman and Charlene Rae performed the research and wrote the article. The authors also acknowledge staff at the Canadian Regional Hemophilia Centres and the Children's Health Utilities Group at McMaster University for their assistance in conducting this national study.

Disclosures

William Furlong has a proprietary interest in, and is an officer of, Health Utilities Incorporated (HUInc). John Horsman and Charlene Rae are paid consultants for HUInc. HUInc distributes copyrighted HEALTH UTILITIES INDEX[®] (HUI[®]) materials and provides methodological advice on the use of HUI. The other authors state that they have no interests which might be perceived as posing a conflict of interest or bias.

scores were detected between VWD females and both females with other bleeding disorders [diff = (-0.08) ; $P = 0.017$] and VWD males [diff = (-0.07) ; $P = 0.039$]. Mean HRQL scores differed between females with and without menorrhagia ($P < 0.001$). Mean HRQL scores were not significantly different between females with and without iron deficiency. Educational attainment was not associated with disease group, menorrhagia status or iron status. Females with VWD have a greater morbidity burden than females in the general population, females with other bleeding disorders and males with VWD. Menorrhagia is associated with low HRQL scores in females with bleeding disorders, including VWD. Further investigation should assess how menorrhagia impacts HRQL in females with bleeding disorders.

Keywords

bleeding disorder; health-related quality of life; iron status; menorrhagia; von Willebrand disease

Introduction

Health-related quality of life (HRQL) is often impaired in individuals with bleeding disorders [1–3], and impairment in females is likely to differ greatly from that in males. von Willebrand disease (VWD), occurring equally in males and females affects approximately 1% of the general population, making this family of diseases much more prevalent than the haemophilias [4]. Most patients have the Type 1 disorder, which has relatively mild clinical manifestations [5,6]. The most serious form of VWD, Type 3, is rare and its manifestations include gastrointestinal bleeding and haemarthrosis [6]. The majority of females (47–60%) with VWD experience menorrhagia [6–10] and are at increased risk for postpartum haemorrhage [9,11–14]. A recent review, examining HRQL in females with bleeding disorders, suggests that menorrhagia may impact HRQL significantly; however, studies examining this issue are limited [3].

With the use of desmopressin, most patients with VWD do not receive blood products [4], and so transfusion-transmitted hepatitis and HIV infection are less common than among haemophiliacs who formerly experienced added burdens of morbidity from these complications [1]. Little has been reported about the overall HRQL among females with VWD, especially within large cohorts [15]. In previous studies, age, type of disease and gender were identified as important factors [3]. In a study to determine ‘willingness to pay’, the average ‘perceived self-report of health status’ of patients with VWD ($n = 290$) was 4 on a Likert scale of 1 (excellent) to 5 (poor) [16]. A high prevalence of ‘generalised anxiety disorder’ has been reported in female VWD patients [17], and pain, especially related to menstruation, was reported by the great majority (86%) [8]. Not surprisingly, a notable minority (up to 25%) of females with VWD have undergone hysterectomy at an early age [8–10]. Other investigators have reported significant correlations between emotional role and educational level, and between physical functioning and educational level, in patients with VWD [18].

A study from a single regional haemophilia programme in Canada, of subjects who were 13 years of age or older ($n = 36$), measured health status and HRQL among Type 1 and Type 2

VWD patients using the HEALTH UTILITIES INDEX[®] (HUI[®]) [2]. Significant morbidity compared with the general population was detected in the attributes of emotion, cognition and pain as well as overall HRQL. There was also significantly greater morbidity among female than male patients for overall HRQL and for the single attributes of emotion, cognition and pain. Most of the female respondents were between menarche and menopause, suggesting that menorrhagia may be a contributory factor in the observed morbidity burdens. Previous studies have investigated the effect of menstruation [7,8] and menorrhagia [3] on HRQL in females with bleeding disorders, although the validity of the measurement instruments was not established.

The large burden of morbidity and the low rate of attainment of postsecondary education by females with VWD identified by Barr *et al.* [2] is concerning. It is possible that these issues reflect iron deficiency resulting from menorrhagia. A mechanism for cognitive deficits in iron deficiency has been proposed [19]. A prospective study found that the HRQL of females with iron deficiency anaemia was lower than national norms, but was significantly improved by iron supplementation [20]. At least two randomized controlled trials attest to the cognitive benefits of iron supplementation in iron deficient females, even in those who were not anaemic [21,22].

This study conducted a national population-based survey involving patients of all regional haemophilia centres in Canada to compare the health status and overall HRQL of females with VWD to females with other bleeding disorders, to males with VWD and to females in the general population. The study also aimed to assess the effects of menorrhagia and iron status on HRQL, and on educational attainment, among females with VWD and other bleeding disorders. These relationships are important for public health because of the high prevalence of VWD in the general population, the great likelihood of large negative effects on overall HRQL and the potential for identifying a highly cost-effective intervention.

Materials and methods

Subjects

A national cross-sectional survey was conducted between 2004 and 2007 of females with VWD and other bleeding disorders, and males with VWD, who were greater than 12 years of age at the time of survey. Females who had had a hysterectomy were neither identified as such nor systematically excluded. The survey package consisted of three questionnaires: social and demographic information, the HUI [Health Utilities Inc., Canada] [23–25] and a portion of the Clinical History Assessment Tool (CHAT) [26–28]. Subjects were also asked to provide a blood sample as part of their routine standard of care. Eligible subjects were identified from the Canadian Hemophilia Registry (<http://fhs.mcmaster.ca/chr/>) and by staff at 23 of the comprehensive inherited bleeding disorder clinics across Canada. Normative data for the general population were obtained from the 2002/3 Joint Canada/United States Survey of Health for HRQL data (<http://www.statcan.gc.ca/pub/82m0022x/82m0022x2003001-eng.htm>), a published study for levels of iron status [29] and the CHAT development survey for menstrual symptoms. Research ethics board approval was obtained at all participating institutions and informed consent was obtained from all participants.

Measures

Health status and HRQL—A standard self-complete HUI questionnaire was used to measure self-assessed health status during the past 4 weeks and the HUI3 results were analysed. HUI3 measures HRQL based on levels of eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. HUI3 measures include utility scores with interval-scale properties based on community preferences, for each attribute and for overall HRQL. HRQL scores are on a scale such that dead = 0.00 and perfect health = 1.00, and negative scores represent health states considered worse than dead. Differences in mean utility scores 0.03 for HRQL, and 0.05 for single attributes, are considered clinically important [25].

Educational attainment—Subjects were asked to report their highest level of education completed and responses were coded into three categories: less than high school diploma; high school diploma and more than high school diploma.

Menstruation and menorrhagia—Information regarding menstruation was collected from responses to selected questions from the CHAT. A binary variable indicating the presence or absence of a symptom for menorrhagia was coded from responses to each of seven CHAT questions (see Table 1), where a code of '1' represents a positive symptom and '0' represents a negative symptom. The seven codes per patient were then summed, producing an integer variable from zero to seven, the frequency distribution of which was compared between female disease groups and controls. A breakpoint of five symptoms or more was chosen to represent menorrhagia, based on cumulative percentages.

Secondary outcomes of menstrual pain and interference of menstruation with daily activities were self-reported using other CHAT questions. Menstrual pain was reported as: none, a little pain (mild), quite a lot of pain (moderate) and very severe pain (severe). For analytical purposes, a binary classification was defined of none/mild or moderate/severe pain. Interference of menstruation with daily activities was measured using a binary (yes/no) question of whether the 'heaviness of menstrual flow interfered with the ability to work, go to school or do social activities'.

Iron status—Subjects were defined as iron deficient with serum ferritin <15 mcg L⁻¹ or not iron deficient with serum ferritin ≥ 15 mcg L⁻¹. This threshold is conservative in estimating iron deficiency in the context of variations in normative values across Canada [29] and has broad acceptance [30].

Statistical techniques

Statistical analyses were completed using IBM SPSS Statistics version 19 [SPSS Inc., USA]. Effects on the primary and secondary outcome measures, HRQL and educational attainment, respectively, were assessed for three major factors: study group, iron status and menorrhagia status. Differences in mean utility scores were assessed using analysis of variance. Differences in proportions were assessed using a chi-squared test. Analysis of co-variance was used to assess the relationship between continuous variables and multiple predictors; *P*-values were bootstrapped in the presence of non-normality and heteroscedascity.

Study-wide statistical significance was set at $P < 0.05$. Bonferroni's correction was used to adjust the critical P -value of individual tests involving the eight sets of single-attribute utility scores to $P = 0.006$ ($P = 0.05/8$).

Results

Study sample

Eighteen institutions and 417 subjects participated. Sample sizes varied due to differences in analytical eligibility criteria and missing data. The study sample represented 26% of the eligible population in the Registry ($n = 1589$). Clinical and demographic characteristics, by study group, are summarized in Table 2.

Effects of disease type—There were no significant differences in mean HRQL scores by severity/type of disease ($P = 0.914$); and therefore this factor was not considered in further analyses. Females with VWD had lower mean HRQL scores (Table 3) than females with other bleeding disorders (difference = -0.08 , $P = 0.017$) and males with VWD (difference = -0.07 , $P = 0.039$). After accounting for the effect of age at the time of survey, differences in HRQL between study groups remained statistically significant ($P = 0.004$). Pain was the only attribute with a significant and clinically important difference in mean scores among the three study groups. Among females age 20 through 85 years of age (most appropriate interval for which normative results are available), mean HRQL scores were importantly lower (difference > 0.150 , $P < 0.05$) for females with VWD and other bleeding disorders than for females in the general population. There was no association between study group (females with VWD, females with other bleeding disorders and females in the general population) and educational attainment ($P = 0.415$).

Effects of iron deficiency—The prevalence of iron deficiency among females with VWD (22%; 29/129) and other bleeding disorders (15%; 6/40) was not significantly different ($P = 0.812$) than that in non-pregnant, adult females (22%) in the Canadian general population [29]. There was no significant difference in the prevalence of iron deficiency between female study groups ($P = 0.376$). Only 4% (2/44) of males with VWD were iron deficient. Female study groups were pooled ($n = 167$) for iron deficiency analyses related to outcome measures. There was no significant difference ($P = 0.459$) in mean HRQL scores between iron deficient and non-deficient females. No association ($P = 0.528$) was observed between the level of educational attainment and iron status among females.

Effects of menorrhagia—The effects of menorrhagia were assessed using the subsample of females ($n = 185$) consisting of those with valid HRQL scores who had begun menstruation and were less than 45 years of age.

A total of 45% (70/155) of females with VWD and 37% (11/30) of females with other bleeding disorders were classified as having menorrhagia, compared with 11% (7/66) of female controls from the CHAT development survey. The differences in the proportions with and without menorrhagia were significant for both VWD ($P < 0.001$) and other bleeding disorders ($P = 0.006$) compared with controls. There was no difference in the

proportion of menorrhagia between females with VWD and those with other bleeding disorders ($P = 0.391$).

There was no difference ($P = 0.100$) between mean HRQL scores of females with VWD ($n = 155$, mean = 0.73, SD = 0.257) and females with other bleeding disorders ($n = 30$, mean = 0.81, SD = 0.197), therefore these groups were pooled for subsequent analyses of menorrhagia effects. Females with bleeding disorders and menorrhagia had a mean HRQL score importantly lower than those without menorrhagia (difference = -0.173 ; $P < 0.001$) (Table 4). After adjusting for multiple testing, significant and clinically important differences were observed for the attributes of cognition (difference = 0.091, $P < 0.001$) and pain (difference = 0.075, $P = 0.002$).

More ($P = 0.016$) females with menorrhagia reported moderate or severe pain (64.1%) during menstruation than did females without menorrhagia (46.0%). A majority ($P < 0.001$) of females with menorrhagia (77.5%) reported menstrual bleeding interfering with daily activities. In females without menorrhagia this proportion was 42.7%. There was no significant association between menorrhagia status and educational attainment ($P = 0.058$) or iron deficiency ($P = 0.740$).

Discussion

Important deficits in HRQL are associated with four subject characteristics: having a bleeding disorder; being female; the bleeding disorder being VWD and having menorrhagia. Health status disabilities associated with the HRQL deficits are in the attributes of emotion, cognition and pain. The lack of variation in HRQL by severity of VWD is explained by the small number of patients in the study sample with types 2 and 3 disease. There were no significant associations between educational achievement and each of the three main study factors: gender/disease study group; iron deficiency and menorrhagia.

Females with bleeding disorders, especially those with VWD, showed remarkable morbidity in relation to other diagnostic groups and the general population (Table 5).

In the Canadian general population aged 35–44 years, the mean HUI scores for males and females are 0.927 and 0.923, respectively, i.e. very similar. The mean scores for females with VWD (0.70), females with other bleeding disorders (0.78) and males with VWD (0.77) are less than the lower confidence bounds in the general population (HUI Reference Scores. Health Utilities Inc. <http://www.healthutilities.com/>, accessed May 7, 2012). The relatively low HRQL of females with bleeding disorders may be due to menorrhagia, which is prevalent in this group [31]. The mean HRQL of females with bleeding disorders and menorrhagia was similar to that of HIV-positive males with severe haemophilia and lower than that reported for adults with arthritis (Table 5). The low HRQL observed in females with bleeding disorders and menorrhagia suggests that effective screening for these factors may be the key to improving overall HRQL for females.

Iron deficiency was not associated with lower mean HRQL scores or with menorrhagia. However, this study was limited by a small sample size and a cross-sectional analysis of iron status. It is possible that treatment with iron supplementation has the potential to improve

mean HRQL, but this study lacked the power to show the potential for improvement. Further exploration of the effects of iron deficiency and its management is needed in a longitudinal study which also tracks the use of iron supplements. The high prevalence of menstrual pain suggests that this may be an important factor contributing to poor HRQL in females with bleeding disorders, especially in conjunction with menorrhagia. Further examination of menstrual pain is required to better understand how this factor influences HRQL.

Studies of HRQL in VWD have been limited. In addition to this study, there have only been two other large scale studies. One, the WiN study, examined HRQL in an adult population [15] whereas the other focused on children [32]. The WiN study [15] utilized the generic SF-36 instrument to assess the associations between HRQL, type of VWD and bleeding severity. Similar to this study, females with VWD had lower general health scores than the general population. These lower scores were related mainly to the vitality and physical function domains. Unlike this study, in which lower scores were observed in the HUI attributes of emotion, cognition and pain, there were no significant differences between VWD patients and the general population for similar SF-36 domains of mental component summary and bodily pain. Bleeding phenotype severity was found to be a strong determinant of HRQL in the WiN population study, which did not examine the effects of menstruation on HRQL. However, the authors noted that lower scores in the vitality domain than in the general population may be related to menorrhagia. Our results also support previous findings that females with VWD have poorer HRQL than females with other bleeding disorders [7]. These findings also provide evidence that menorrhagia may play a significant role in the HRQL of females with bleeding disorders, as suggested in a recent review [3]. The study did not identify the type of VWD as a factor influencing HRQL, which was deemed an important factor in that review [3]. It is likely that the analysis of VWD type in that study was hindered by diagnostic issues, as discussed below.

A major limitation of this study was the difficulty in diagnosing Type 1 VWD [5], making it difficult to determine how many subjects actually had the disease. Diagnostic criteria for Type I VWD include abnormal laboratory values, personal bleeding history and family history [5]. However, in Type 1 VWD, in which the principal laboratory diagnostic characteristic is a mild/moderate reduction in VWF levels, variable results and interpretation of data have lead consistently to diagnostic uncertainty [33]. In a recent study by Hyatt et al. [33], only 4.5% of paediatric patients diagnosed with Type I VWD met the diagnostic criteria of the International Society on Thrombosis and Haemostasis, whereas 34% met the diagnostic criteria defined by the Hospital for Sick Children in Toronto [34]. It is likely that there was variability in the diagnosis across participating institutions in the current study and therefore it is difficult to determine if all patients included in the survey actually had VWD.

In the current version of the Canadian Registry for VWD, 85% of patients are listed as having Type 1 disease, 12% as Type 2 and <1% as Type 3. In this study of HRQL, the proportions of study subjects with each of the types of VWD varies significantly from this distribution, with fewer Type 1 cases and more of the severe Type 3 cases. The classification of 16–22% of the cases in this study as of ‘unknown’ VWD type reflects the uncertainty of diagnosis that often accompanies Type 1 disease. Overall, in considering the interpretation of the results of this study, it should be kept in mind that the study population comprised

more severe cases of VWD than is found in the general population. The generalizability of our results may also be limited by a sampling bias resulting from low response rates. Further work should focus on regional level sampling with intensive follow-up to improve overall response rates.

As there is no reason to believe that the effects of menorrhagia are any different among females with and without VWD [35], the results of this study identify a need for further investigation of the incidence and costs of menorrhagia among females in the general population. Further research should focus on better understanding the mechanisms and factors, especially menorrhagia, that result in poor HRQL using both generic and disease-specific instruments. Work should also focus on developing interventions to improve the HRQL of these females.

Conclusions

Females with VWD have a greater morbidity burden than males with this disease, females with other bleeding disorders and females in the general population. Menorrhagia is a significant factor associated with lower HRQL scores in females with bleeding disorders. Given the level of morbidity observed in this study, it is important that health professionals develop more effective interventions for females with bleeding disorders and for females with menorrhagia.

Acknowledgments

This work was supported by grants from the Bayer Hemophilia Awards Foundation and the Canadian Hemophilia Society.

References

1. Barr RD, Saleh M, Furlong W, Horsman J, Sek J, Pai M, et al. Health status and health-related quality of life associated with hemophilia. *Am J Hematol*. 2002; 71:152–60. [PubMed: 12410568]
2. Barr RD, Sek J, Horsman J, Furlong W, Saleh M, Pai M, et al. Health status and health-related quality of life associated with von Willebrand disease. *Am J Hematol*. 2003; 73:108–14. [PubMed: 12749012]
3. Von Mackensen S. Quality of life in women with bleeding disorders. *Haemophilia*. 2011; 17(Suppl 1):33–7. [PubMed: 21692927]
4. Lillicrap D, James P. von Willebrand disease: an introduction for the primary care physician. *World Federation of Hemophilia Monograph*. 2009; 47:1–7.
5. Bolton-Maggs PH, Lillicrap D, Goudemand J, Berntorp E. von Willebrand disease update: diagnostic and treatment dilemmas. *Haemophilia*. 2008; 14(Suppl 3):56–61. [PubMed: 18510523]
6. Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, 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; 14:171–232. [PubMed: 18315614]
7. Kadir RA, Sabin CA, Pollard D, Lee CA, Economides DL. Quality of life during menstruation in patients with inherited bleeding disorders. *Haemophilia*. 1998; 4:836–41. [PubMed: 10028306]
8. Kouides PA, Phatak PD, Burkart P, Braggins C, Cox C, Bernstein Z, et al. Gynaecological and obstetrical morbidity in women with type I von Willebrand disease: results of a patient survey. *Haemophilia*. 2000; 6:643–8. [PubMed: 11122390]
9. Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. *Haemophilia*. 1999; 5:313–7. [PubMed: 10583512]

10. Foster PA. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. The reproductive health of women with von Willebrand disease unresponsive to DDAVP: results of an international survey. *Thromb Haemost.* 1995; 74:784–90. [PubMed: 8585022]
11. Lee CA. Bleeding problems in women. *Br J Haematol.* 2000; 108(Suppl 1):14.
12. Kadir RA. Bleeding disorders and pregnancy. *Br J Haematol.* 2000; 108(Suppl 1):15.
13. James AH, Jamison MG. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. *J Thromb Haemost.* 2007; 5:1165–9. [PubMed: 17403089]
14. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol.* 1998; 105:314–21. [PubMed: 9532993]
15. de Wee EM, Mauser-Bunschoten EP, Van Der Bom JG, Degenaar-Dujardin ME, Eikenboom HC, Fijnvandraat K, et al. Health-related quality of life among adult patients with moderate and severe von Willebrand disease. *J Thromb Haemost.* 2010; 8:1492–9. [PubMed: 20345712]
16. Eastaugh SR. Willingness to pay in treatment of bleeding disorders. *Int J Technol Assess Health Care.* 2000; 16:706–10. [PubMed: 10932435]
17. Rozeik C, Scharer I. Defekt des von Willebrand faktor-proteins. Gynakologische und psychische probleme bei frauen mit von Willebrand-Syndrom. *Gynakologische Geburtshilfe.* 1998; 3:70–5.
18. Solovieva S. Clinical severity of disease, functional disability and health-related quality of life. Three-year follow-up study of 150 Finnish patients with coagulation disorders. *Haemophilia.* 2001; 7:53–63. [PubMed: 11136382]
19. Youdim MB, Yehuda S. The neurochemical basis of cognitive deficits induced by brain iron deficiency: involvement of dopamine-opiate system. *Cell Mol Biol (Noisy-le-grand).* 2000; 46:491–500. [PubMed: 10872737]
20. Ando K, Morita S, Higashi T, Fukuhara S, Watanabe S, Park J, et al. Health-related quality of life among Japanese women with iron-deficiency anemia. *Qual Life Res.* 2006; 15:1559–63. [PubMed: 16826432]
21. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet.* 1996; 348:992–6. [PubMed: 8855856]
22. Patterson AJ, Brown WJ, Roberts DC. Dietary and supplement treatment of iron deficiency results in improvements in general health and fatigue in Australian women of childbearing age. *J Am Coll Nutr.* 2001; 20:337–42. [PubMed: 11506061]
23. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. *Med Care.* 1996; 34:702–22. [PubMed: 8676608]
24. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. *Med Care.* 2002; 40:113–28. [PubMed: 11802084]
25. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes.* 2003; 1:54. [PubMed: 14613568]
26. McKay H, Derome F, Haq MA, Whittaker S, Arnold E, Adam F, et al. Bleeding risks associated with inheritance of the Quebec platelet disorder. *Blood.* 2004; 104:159–65. [PubMed: 15026313]
27. Pai M, Liu Y, Whittaker S, Arnold E, Seecharan JL, Moffat KA, et al. Gender differences in bleeding problems and implications for the assessment of a bleeding disorder. *Blood.* 2007; 110(11 Pt 1):2148. [PubMed: 17537994]
28. Pai M, Lui Y, Whittaker S, Arnold E, Seecharan J, Moffat K, et al. High prevalence of iron deficiency among patients referred for evaluation of a bleeding disorder. *J Thromb Haemost.* 2007; 5(Suppl 2):P-T-215.
29. Valberg LS, Sorbie J, Ludwig J, Pelletier O. Serum ferritin and iron status of Canadians. *Can Med Assoc J.* 1976; 114:417–21. [PubMed: 1253085]

30. Milman N. Serum ferritin in Danes: studies of iron status from infancy to old age, during blood donation and pregnancy. *Int J Hematol.* 1996; 63:103–35. [PubMed: 8867722]
31. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet.* 1998; 351:485–9. [PubMed: 9482440]
32. de Wee EM, Fijnvandraat K, de Goede-Bolder A, Mauser-Bunschoten EP, Eikenboom JC, Brons PP, et al. Impact of von Willebrand disease on health-related quality of life in a pediatric population. *J Thromb Haemost.* 2011; 9:502–9. [PubMed: 21166992]
33. Hyatt SA, Wang W, Kerlin BA, O'Brien SH. Applying diagnostic criteria for type 1 von Willebrand disease to a pediatric population. *Pediatr Blood Cancer.* 2009; 52:102–7. [PubMed: 18816699]
34. Dean JA, Blanchette VS, Carcao MD, Stain AM, Sparling CR, Siekmann J, et al. von Willebrand disease in a pediatric-based population – comparison of type 1 diagnostic criteria and use of the PFA-100[®] and a von Willebrand/collagen-binding assay. *Thromb Haemost.* 2000; 84:401–9. [PubMed: 11019962]
35. James A, Matchar DB, Myers ER. Testing for von Willebrand disease in women with menorrhagia: a systematic review. *Obstet Gynecol.* 2004; 104:381–8. [PubMed: 15292016]
36. Grootendorst P, Feeny D, Furlong W. Health Utilities Index Mark 3: evidence of construct validity for stroke and arthritis in a population health survey. *Med Care.* 2000; 38:290–9. [PubMed: 10718354]

Table 1

Coding for menorrhagia symptom status from CHAT questionnaire responses.

CHAT		Code as	
Question #	Characteristic	'Menorrhagia' symptom (1)	'Non-menorrhagia' symptom (0)
6	How long do your menstrual periods last?	7+ days	<7 days
8	Do you have problems with flooding?	Yes	No
9	Do you have to double up pads/tampons to prevent accidents?	Yes	No
10	On average, how many days of heavy flow do you have with a typical period?	3+days	<3 days
11	On the heaviest days of flow, how long does it take for you soak through pads/tampon?	1 h	>1 h
13	Do you have clots with periods?	Yes	No
15	Do you have break-through bleeding between periods?	Yes	No

Table 2

Subject characteristics by study groups.

Variable	Females with VWD	Females with other bleeding disorders	Males with VWD
<i>n</i> (% of sample)	259 (62.1%)	56 (13.4%)	97 (23.3%)
Missing gender data <i>n</i> = 5			
Age at survey (years), missing age data <i>n</i> = 6			
Mean	40.5 (<i>n</i> = 258)	42.0 (<i>n</i> = 56)	39.1 (<i>n</i> = 97)
Median	40.0	43.1	40.3
Min	12.7	14.3	13.7
Max	82.6	77.3	84.8
SD	15.68	14.84	19.43
Type of VWD <i>n</i> (%)			
1	165 (63.7%)	n/a	52 (53.6%)
2	24 (9.3%)	n/a	18 (18.6%)
3	13 (5.0%)	n/a	12 (12.4%)
Unknown	57 (22.0%)	n/a	15 (15.5%)

n/a, not applicable.

Table 3

HRQL and single-attribute utility scores of study groups.

HUI3 measure	Females VWD (<i>n</i> = 259) Mean (SD)	Females other (<i>n</i> = 56) Mean (SD)	Males VWD (<i>n</i> = 97) Mean (SD)
HRQL	0.70 (0.270)	0.78 (0.218) *	0.77 (0.255) *
Vision	0.95 (0.090)	0.95 (0.087)	0.97 (0.046)
Hearing	0.95 (0.183)	0.93 (0.176)	0.95 (0.175)
Speech	0.98 (0.103)	0.97 (0.097)	0.98 (0.081)
Ambulation	0.97 (0.096)	0.98 (0.068)	0.99 (0.047)
Dexterity	0.98 (0.078)	0.99 (0.027)	0.99 (0.065)
Emotion	0.89 (0.176)	0.94 (0.151)	0.91 (0.172)
Cognition	0.90 (0.163)	0.93 (0.114)	0.92 (0.160)
Pain	0.84 (0.203)	0.91 (0.100) **	0.88 (0.172)

Significantly different than females with VWD

* $P < 0.05$;** $P < 0.001$.

Table 4

HRQL and single-attribute utility scores by menorrhagia status.

	Menorrhagia (<i>n</i> = 84) Mean (SD)	No menorrhagia (<i>n</i> = 104) Mean(SD)	Difference <i>P</i>-value
HRQL	0.64 (0.279)	0.82 (0.195)	<0.001
Vision	0.96 (0.069)	0.96 (0.063)	0.604
Hearing	0.92 (0.228)	0.98 (0.111)	0.033
Speech	0.94 (0.184)	0.99 (0.041)	0.018
Ambulation	0.99 (0.045)	0.98 (0.078)	0.615
Dexterity	0.98 (0.074)	1.00 (0.017)	0.034
Emotion	0.87 (0.173)	0.93 (0.145)	0.013
Cognition	0.85 (0.202)	0.95 (0.111)	<0.001
Pain	0.82 (0.181)	0.90 (0.115)	0.002

Table 5

Mean HUI3 utility scores of HRQL for various groups.

Score	Clinical group
1.00	Perfect health state – upper HRQL utility scale anchor
0.90	General population – adults [36]
0.78	Female adults with other bleeding disorders
0.77	Adults with arthritis [36]
0.77	Male adults with VWD [2]
0.73	Moderate haemophiliacs [1]
0.71	HIV negative severe haemophiliacs [1]
0.70	Female adults with VWD[2]
0.64	Female adults with bleeding disorders <45 years of age with menorrhagia
0.57	HIV-positive severe haemophiliacs [1]
0.54	Adults who have experienced a stroke [36]
0.00	Dead – conventional HRQL utility scale anchor
-0.36	Pits State – lower HRQL utility scale anchor