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ORIGINAL ARTICLE

Sexuality and bleeding in von Willebrand disease

Calvin B. van Kwawegen[1] | Hester Pastoor[2] | Jeroen Eikenboom[3] | Karin Fijnvandraat[4] | Paula Ypma[5] | Floor C. J. I. Heubel-Moenen[6] | Karin P. M. van Galen[7] | Evelien P. Mauser-Bunschoten[7] | Karina Meijer[8] | Saskia E. M. Schols[9] | Marjon H. Cnossen[10] | Johanna G. van der Bom[11] | Joke de Meris[12] | Ferdows Atiq[1] | Marieke J. H. A. Kruip[1] | Frank W. G. Leebeek[1] | for the WiN Study Group

[1]Department of Hematology, Erasmus Medical Center, University Medical Center, Rotterdam, the Netherlands

[2]Division of Reproductive Medicine, Department of Obstetrics and Gynecology, Erasmus University Medical Center, Rotterdam, the Netherlands

[3]Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Centre, Leiden, the Netherlands

[4]Department of Pediatric Hematology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands

[5]Department of Hematology, Hagaziekenhuis, Den Haag, the Netherlands

[6]Department of Hematology, Maastricht University Medical Center, Hemophilia Treatment Centre Nijmegen-Eindhoven-Maastricht, Maastricht, the Netherlands

[7]Department of Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

[8]Department Hematology, University Medical Center Groningen, Groningen, the Netherlands

[9]Department of Hematology, Radboud University Medical Center, Hemophilia Treatment Center Nijmegen-Eindhoven-Maastricht, Nijmegen, the Netherlands

[10]Department of Pediatric Hematology and Oncology, Erasmus Medical Center, Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, the Netherlands

[11]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

[12]Netherlands Hemophilia Society, Nijkerk, the Netherlands

Correspondence
Frank W. G. Leebeek, Department of Hematology, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, CA Rotterdam3000, the Netherlands.
Email: F.leebeek@erasmusmc.nl

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Abstract

Background: Sexuality is a fundamental aspect of quality of life, often impacted by chronic or inherited diseases like von Willebrand disease (VWD), an inherited bleeding disorder characterized by mucosal bleeding, including heavy menstrual bleeding (HMB). To date, no studies have investigated the impact of VWD on sexuality.

Objectives: This study aimed to identify sexual restrictions and symptoms in VWD patients, differentiating between men and women and between premenopausal and nonmenstruating women.

Methods: We performed a nationwide, multicenter, prospective cohort study, the Willebrand in the Netherlands-Prospective study, including adult VWD patients (>18 years) who completed questionnaires on sexuality and health-related quality of life (SF-36). Additional data were collected via blood tests and a self-reported bleeding assessment tool (International Society on Thrombosis and Haemostasis Bleeding Assessment Tool).

Results: We included 549 VWD patients with a median age of 51 years (IQR, 37-66 years), of whom the majority were women (n = 347; 63.2%). Patients were diagnosed with type 1 (57.2%), type 2 (39.2%), or type 3 VWD (3.6%). Sexual restrictions due to VWD were reported by 3.5% of men (n = 7) and 9.8% of women (n = 34; P < .01). Bleeding during sexual activity was reported by 33.1% (n = 115) of women. Premenopausal patients more often reported sexual restrictions than nonmenstruating patients (15.5% vs 5.2%, P = .01), with HMB as the most important determinant (odds ratio, 1.60; 95% CI, 1.12-2.46). Most patients (n = 455; 82.9%) reported that sexuality was not discussed during routine clinic visits.

Conclusion: Women with VWD experience more sexual restrictions than men and report more postcoital bleeding than the general population. Premenopausal women are particularly affected, mostly due to HMB. This highlights the need for health care providers to address sexual health during consultations and treat HMB to improve overall care for VWD patients.

KEYWORDS
hemorrhage, menorrhagia, quality of life, sexuality, von Willebrand disease

Essentials

- The impact of Von Willebrand disease (VWD) on sexuality has not been extensively studied.
- Large studies have found that chronic disease may negatively impact sexuality.
- This study showed that heavy menstrual bleeding was the most important determinant for reporting sexual restrictions in VWD patients.
- Discussion of sexual health during consultations and treatment of heavy menstrual bleeding may improve overall care for VWD patients.

1 | INTRODUCTION

von Willebrand disease (VWD) is the most prevalent inherited bleeding disorder and is caused by dysfunction or deficiency of von Willebrand factor (VWF) [1]. VWF, a multimeric protein that plays an important role in the adhesion and aggregation of platelets, is either reduced (type 1), dysfunctional (type 2), or absent (type 3) [2]. The disease is characterized by mucosal bleeding but may also lead to joint or muscle bleeding in more severe phenotypes [1]. It has been previously described that VWD is associated with major impairments in quality of life (QoL) [3,4].

Sexuality is qualified by the World Health Organization as a fundamental component contributing to QoL, irrespective of being in a relationship [5–7]. Sexual problems occur frequently in the general population, self-reported by 11% of men and 15% of women in a national questionnaire in the Netherlands among 17,000 respondents aged 18 to 80 years [8]. Results showed that in the general public, men most often experience erection problems or premature ejaculation, which are most common among those aged >70 years. Women most often experience at least 1 sexual problem between 18 and 24 years (21%) or between 55 and 69 years (19%), presenting with more diverse complaints than men. Moreover, 6% of women report substantial problems due to lack of lubrication, and 5% because of dyspareunia [8].

Chronic disease is the second most important determinant of at least 1 sexual problem in patients aged >25 years and is only preceded by a history of sexual violence [8]. In addition, the likelihood of experiencing a sexual problem is approximately twice as high for individuals with a chronic illness [8]. The effects of inherited bleeding disorders on sexuality have been studied previously in patients with hemophilia, an X-linked disease and, therefore, primarily seen in men [9,10]. In the study by Gianotten and Heijnen [9], it was demonstrated that sexuality is mostly impaired due to bleeding, pain, side effects of medication, and posture adjustment during sexual activity.

For women, the negative impact of heavy menstrual bleeding (HMB) on health-related QoL has been shown in patients with and without bleeding disorders [11]. In addition, several studies show positive effects of treatment for HMB on sexual functioning [12,13]. In women with VWD, HMB is reported in 80% to 90% of patients and is persistently undertreated [14,15]. Although the importance of sexuality in holistic care is widely acknowledged, and a strong patient-physician partnership is known to reduce disease burden, proactive discussions of sexual health issues by health care professionals lag behind [16,17]. Similarly, there is a lack of research on the relationship between VWD and sexuality, and it is notable that bleeding symptoms are often left out of standardized sexual function questionnaires [18–20].

Our primary study aim was to identify restrictions and symptoms related to sexual activity that are experienced by patients with VWD. Additionally, we planned to compare the consequences of these restrictions between men and women. Specifically, we tried to assess the influence of HMB by comparing menstruating and nonmenstruating patients. Finally, we intend to address the experiences of patients in discussing the topic of sexuality in healthcare. By addressing these study aims, to our knowledge, we are the first to study the effects of VWD on sexual health in a large and well-defined patient cohort.

2 | METHODS

The Willebrand in the Netherlands-Prospective study (WiN-Pro) is a nationwide multicenter, prospective, observational cohort study conducted in all 7 Dutch hemophilia treatment centers (HTCs) between January 1, 2019, and December 31, 2023. Patients of all ages were included at baseline, with a 2-year prospective follow-up phase. They all had historically the lowest VWF antigen (VWF:Ag) and/or VWF activity (VWF:GPIbM) and/or VWF collagen binding <0.30 IU/mL and/or factor (F)VIII:C <0.40 IU/mL. The historically lowest VWF and factor VIII activity (FVIII:C) levels ever measured were provided by the patients' HTC. Patients with acquired VWD or a known concomitant bleeding disorder were excluded from the study cohort. The study was approved by the Medical Ethical Committee of the Erasmus MC and was approved by the respective boards of the other participating centers. All patients signed informed consent.

2.1 | Assessment methods

All patients were invited for a single visit to their HTC for study inclusion. During this visit, in addition to blood sampling, patients or parents filled out an extensive questionnaire, including questions on comorbidity, medication use, pedigree, and health-related QoL by means of the short form 36 (SF-36) questionnaire and a self-reported bleeding assessment tool (BAT). Adult patients aged ≥18 years also received questions about sexuality, which were derived from the sexual functioning questionnaire used in the Hemophilia in the Netherlands 6 study and modified for VWD patients [10].

For this analysis, participants who completed the sexuality-related sections of the questionnaire were included in the analysis. Stratification was based sex, defined as biological sex assigned at birth, as recorded in the electronic patient file of the participating centers. Individuals who did not respond to menstruation-related questions were excluded from the analyses concerning menstrual bleeding. Participants were categorized as premenopausal if they were potentially menstruating at the time of study inclusion, after which those on hormonal therapy or (post) pregnancy were separately classified. Nonmenstruating patients were further classified as either postmenopausal or as having undergone hysterectomy or endometrial ablation (Figure 1).

The SF-36 questionnaire represents 8 domains, covering physical and mental properties [21]. For this study, the physical component summary (PCS) and mental component summary (MCS) were computed with reference to the international standard [21–25]. The scores for these components have been validated across patient groups and cultures and have been further specified for several countries, including the Netherlands [25–27].

International Society on Thrombosis and Haemostasis (ISTH) BAT scores were obtained by each participant completing a self-BAT and verified by the study investigator [28]. Higher scores reflect a more severe bleeding phenotype; scores > 3 are considered abnormal for men and >5 for women [29].

2.2 | Laboratory assessment

Blood was drawn at study inclusion for laboratory studies. VWF:Ag, VWF:GpIbM, and FVIII:C levels were centrally measured in the laboratory of the Erasmus MC. VWF:Ag was measured using an in-house ELISA, VWF:GpIbM was measured with the VWF:GPIbM Innovance assay from Siemens, and FVIII:C was measured using a one-stage clotting assay with FVIII-deficient plasma [30,31].

2.3 | Statistical analysis

Statistical analyses were performed using R version 4.3.1 (2023-06-16; R Development Core Team). Data normality was assessed visually with histograms, and missing data were not replaced. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means and SDs for normally distributed data and medians and IQRs for skewed data.

Chi-squared tests with Bonferroni correction applied to post hoc tests to correct for multiple testing were performed to compare between VWD types. For comparisons between men and women and menstruating and nonmenstruating patients, we computed contingency tables and performed chi-squared tests or Fischer's exact test for small sample sizes. Independent *t*-tests were performed for comparisons involving QoL measures. Logistic regression was used to identify determinants of independent binary variable sexual restriction. The dependent variables were the ISTH-BAT bleeding score for menorrhagia, VWD type, blood group, hysterectomy, and age at study inclusion.

To determine the clinical significance of statistically significant differences, we estimated effect sizes (Cohen's d) by calculating the difference in mean scores between 2 groups and dividing it by the largest SD [32]. Effect sizes were then interpreted according to Cohen's guidelines: a small effect is indicated by $0.2 \leq d < 0.5$; a moderate effect by $0.5 \leq d < 0.8$; and a large effect by $d \geq 0.8$ [33].

3 | RESULTS

We included 549 patients with VWD from the WiN-Pro cohort in this study (Figure 1). The majority of patients were women (*n* = 347; 63.2%). Most participants had type 1 VWD (*n* = 314; 57.2%), and the

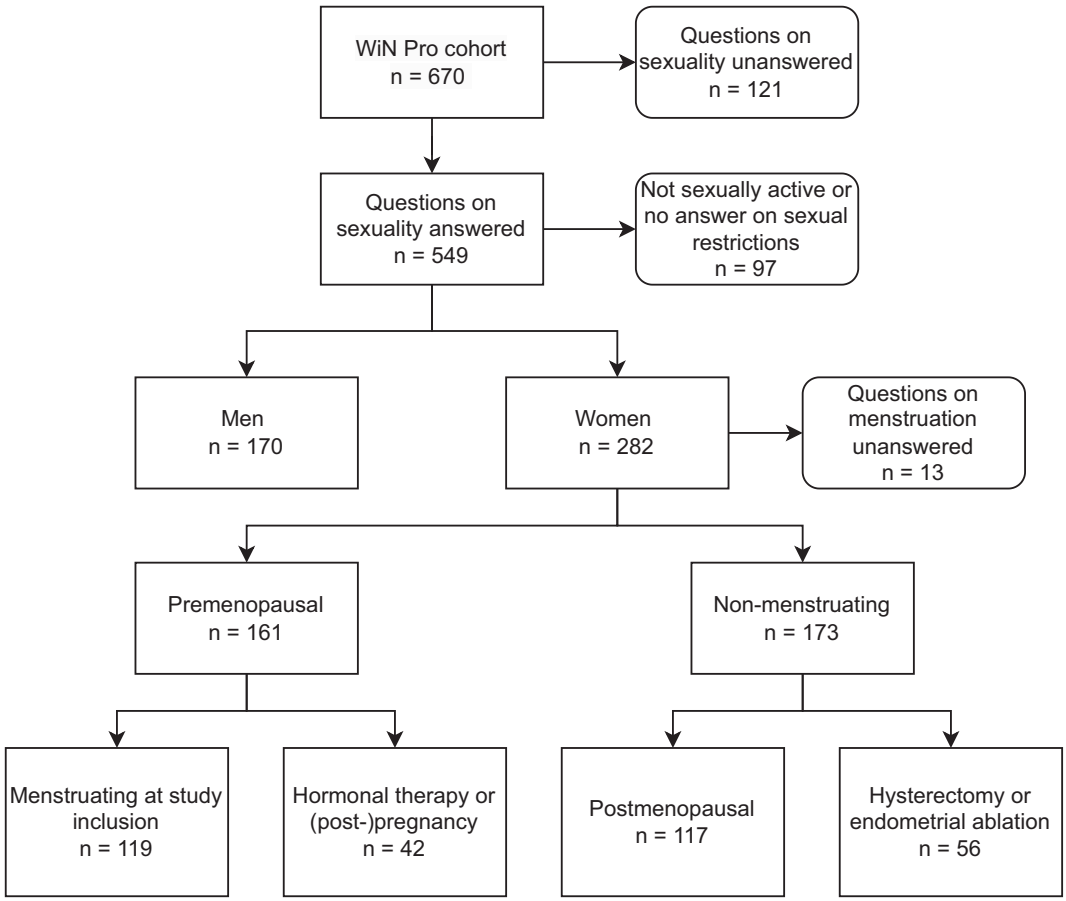

FIGURE 1 Flowchart of study participants. A flowchart was computed to clarify the percentages provided in the results section. Patients were included in the study if they answered the questionnaire section on sexuality. They were then stratified into groups of men and women. The group of women was divided into premenopausal and nonmenstruating patients at study inclusion. Patients were excluded from analyses on menstrual bleeding if they did not answer questions on menstruation.

others had type 2 (*n* = 215; 39.2%) or type 3 (*n* = 20; 3.6%) VWD. The median age was 51 years (IQR, 37-66 years; range, 18-92), and the median ISTH-BAT bleeding score was 11 (IQR, 8-16). The group of women contained a higher proportion of type 1 patients compared with the group of men (Table 1).

3.1 | Sexuality and VWD

A total of 41 out of 549 patients (7.5%) reported sexual restrictions as a result of VWD, according to the questionnaire (Supplementary Material). Seventy-one patients (12.9%) were not or no longer sexually active, and 26 (4.7%) did not answer this particular question. The majority of patients (74.9%) reported no problems pertaining to sexuality because of their disease.

Seven patients (1.3%) reported the use of painkillers around sexual activity. Patients requiring analgesia before sexual activity had a median age of 49 years (IQR, 36-63 years). This group included 3 men and 4 women. Of these, 5 had type 1 VWD, 1 had type 2A, and 1 had type 2M. Others changed their posture or sexual position to reduce complaints (*n* = 19; 3.5%), either due to the risk of or because of joint pain due to joint bleeding or arthropathy. Patients who adjusted their posture during sexual activity had a median age of 39 years (IQR, 53-66 years). This group consisted of 4 men and 15 women. Among them, 12 had type 1 VWD, 1 had type 2A, 2 had type 2M, and 4 had type 3. None of the patients reported that they stopped sexual activity completely as a result of their disease.

QoL measured in the physical domain of the SF-36 questionnaire was similar for patients who reported restrictions pertaining to sexual activity compared with those who reported no restrictions (47.0 vs 50.0, *P* = .08; Figure 2A). The mental domain scores between these groups were also similar (48.8 vs 52.0, *P* = .06; Figure 2B). The clinical effect sizes, according to Cohen's d, were small for both physical health (−0.30) and mental health (−0.35).

3.2 | Men vs women

In the questionnaire, 3.5% of men (7/202) and 9.8% of women (34/347) self-reported restrictions regarding sexual activity in relation to VWD (*P* < .01; Figure 2C). Men reported bleeding (*n* = 3), medication (*n* = 3), and pain (*n* = 1) as the reasons for sexual restrictions

TABLE 1 Patient characteristics of the study population.

Variables	Total (*N* = 549)	Men (*n* = 202)	Women (*n* = 347)
Age (y), median (IQR)	51 (37-66)	50 (36-65)	53 (38-66)
Blood group O, (%)	59.9	55.9	62.2
Type, (%)			
1[a]	57.2	46.0	63.6
2[a]	39.2	49.5	33.1
3	3.6	4.5	3.2
VWF:Ag (IU/mL), median (IQR)[a,b]	0.41 (0.23-0.62)	0.33 (0.21-0.55)	0.46 (0.25-0.65)
VWF:GPIbM (IU/mL), median (IQR)[a,b]	0.24 (0.10-0.51)	0.17 (0.06-0.36)	0.28 (0.13-0.58)
FVIII:C (IU/mL), median (IQR)[a,b]	0.63 (0.35-0.97)	0.46 (0.30-0.78)	0.74 (0.42-1.05)
ISTH-BAT, median (IQR)[c]	11 (8-16)	10 (6-14)	13 (9-18)

FVIII:C, factor VIII activity; ISTH-BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; VWF:Ag, von Willebrand factor antigen; VWF:GPIbM, von Willebrand factor activity.

[a]$P < .05$: calculated as the difference between men and women.

[b]As a result of missing data, these numbers are based on $n = 519$: 193 men and 326 women.

[c]ISTH-BAT abnormal levels are >3 in adult men and >5 in adult women.

(Figure 3A). Of all men, 4.5% (9/202) reported an observation of blood in their ejaculate (hematospermia) at least once. Only 1 individual sought medical consultation for this issue. Women reported various reasons for sexual restrictions, including pain (9/347; 2.6%), joint problems (5/347; 1.4%), HMB (15/347; 4.3%), and other bleeding symptoms (15/347; 4.3%; Figure 3B). Of all women, 115/347 (33.1%) reported blood loss during sexual activity.

Men reported higher QoL scores based on the physical domain than women (PCS: 51.6 vs 47.7, $P < .01$; Figure 2A). These differences were not seen in the mental domain (MCS: 52.3 vs 51.2, $P = .15$; Figure 2B). This was confirmed in the effect sizes for clinical significance, with a small effect for PCS (Cohen's d = 0.37) and a negligible effect for MCS (Cohen's d = 0.12). No differences in QoL between men and women for either the PCS or the MCS were found after stratification by those who reported restrictions during sexual activity.

3.3 | Influence of menstrual bleeding

The majority of women (84.1%) had a bleeding score > 0 on the ISTH-BAT item for menorrhagia, indicating symptoms of current or past HMB. Patients with current or past HMB reported sexual restrictions in 10% of all cases (32/292) compared with only 3.8% (2/55) for patients without HMB. Eighty-five (24.5%) women reported that menstrual bleeding has a negative influence on sexual activity. Most of these patients experienced restrictions due to bleeding ($n = 78$) or loss of self-confidence ($n = 3$).

At study inclusion, 119 out of 347 women were of reproductive age, premenopausal, and menstruating (34.3%), whereas 42 (19.5%) were not menstruating temporarily at the time of study inclusion due to hormonal therapy, pregnancy, or recent child delivery. In the patients not menstruating anymore, 117 out of 215 participants (54.4%) were postmenopausal, 55 participants had undergone a hysterectomy (25.6%), and one was successfully treated with an endometrial ablation procedure. The other 13 participants did not answer the questions on menstruation (Figure 1).

Sexual restrictions were reported more often by premenopausal patients compared with nonmenstruating patients (15.5% vs 5.2%, $P = .01$; Figure 2C), specifically the hysterectomy subgroup (3.6%; $P < .05$). Despite this, premenopausal patients reported higher physical health scores on the SF-36 compared with nonmenstruating patients (51.1 vs 44.4, $P < .01$; Figure 2B) and the hysterectomy subgroup (43.5; $P < .01$). The mental health domain scores were similar between the 2 groups (50.4 vs 51.8, $P = .06$; Figure 2C). The effect sizes were medium for the physical health score (Cohen's d = 0.63) and small for the mental health score (Cohen's d = −0.14). There were no significant differences between sexual restrictions in premenopausal patients and postmenopausal patients (15.5% vs 6.0%, $P = .09$). However, SF-36 physical health scores remained significantly higher in premenopausal patients compared with postmenopausal patients (51.1 vs 44.8, $P < .01$). There were no differences in sexual restrictions between actively menstruating premenopausal patients and those temporarily not menstruating (15.1% vs 16.7%, $P = 1.00$).

There was an undeniable age difference between the premenopausal and nonmenstruating patients (mean ± SD, 36 ± 10 years vs 66 ± 10 years). Despite this, logistic regression analysis revealed that the ISTH-BAT item for menstrual bleeding emerged as the most important determinant of sexual restriction (odds ratio [OR], 1.60; 95% CI, 1.12-2.46). This finding persisted even after accounting for the confounding effects of age at inclusion (OR, 0.97; 95% CI, 0.94-0.99; Table 2). The probability of sexual restriction was lower for hysterectomy patients (OR, 0.26; 95% CI, 0.04-1.07), but this procedure was not an independent determinant.

3.4 | Discussing sexuality in the outpatient clinic

Most patients (82.9%) reported that sexuality is not brought up and discussed at all during visits to the outpatient clinic or that it is only

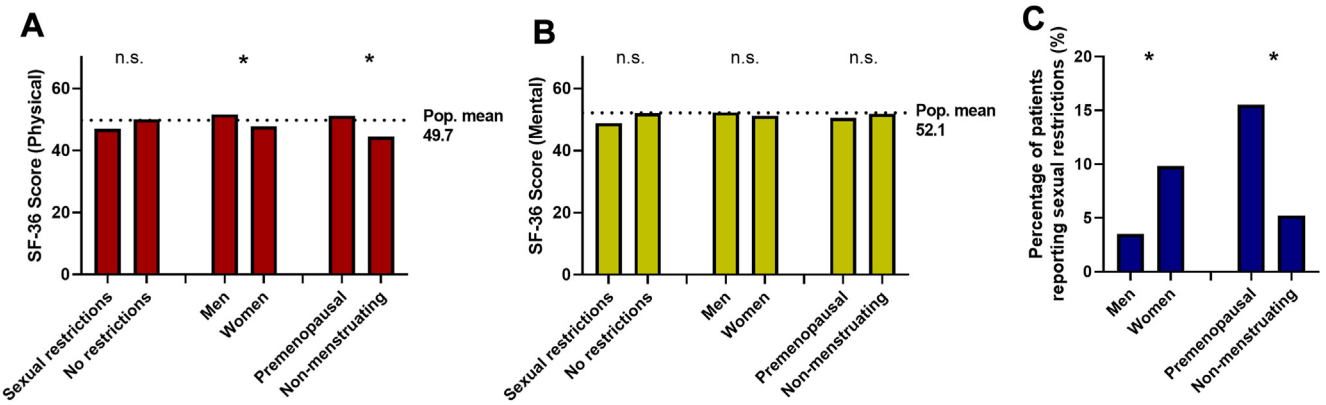

FIGURE 2 Comparisons of reported sexual restriction and quality of life. A comparison was made between men and women and between menstruating and nonmenstruating patients. (A) Shows the differences between the physical domain scores of the short form (SF)-36 questionnaire. The dotted line shows the mean physical component summary score (49.7) referenced to the general population (Pop.) in the Netherlands. (B) Shows the differences between the mental domain scores of the SF-36 questionnaire. The dotted line shows the mean score (52.1) referenced to the general Pop. in the Netherlands. (C) Shows the differences between the percentage of patients who reported sexual

discussed if it is brought up by the patient (2.0%). A small group of 31 of the 549 VWD patients (5.6%) reported that they would appreciate sexuality as a standard topic during outpatient clinic visits, whereas 34.2% of patients would not. The majority of patients (47.4%) had no strong preference for or against discussing sexuality during clinic visits. Of the 41 patients who reported restrictions in sexuality due to VWD, 13 (31.7%) patients would prefer sexuality to be a standardized topic during outpatient clinic visits.

4 | DISCUSSION

To our knowledge, this study is the first investigation on sexuality and sexual restrictions in the most common inherited bleeding disorder, VWD. It demonstrates that having VWD may negatively impact sexual activity in both men and women. In a large cohort of well-defined patients with VWD, we found that 10% of women and <5% of men report sexual restrictions due to their bleeding disorder. Among women, a range of symptoms and complaints were noted. A substantial group of participants indicated that HMB, which is a consequence of VWD, adversely impacted their sexual activity. Our data show that premenopausal patients reported sexual restrictions more frequently than nonmenstruating patients.

To our knowledge, we are the first to have studied sexuality in a large VWD patient cohort, focusing on the patient perspective. Many studies on the subject of sexuality and chronic disease are characterized by methodological drawbacks, such as a lack of standardized

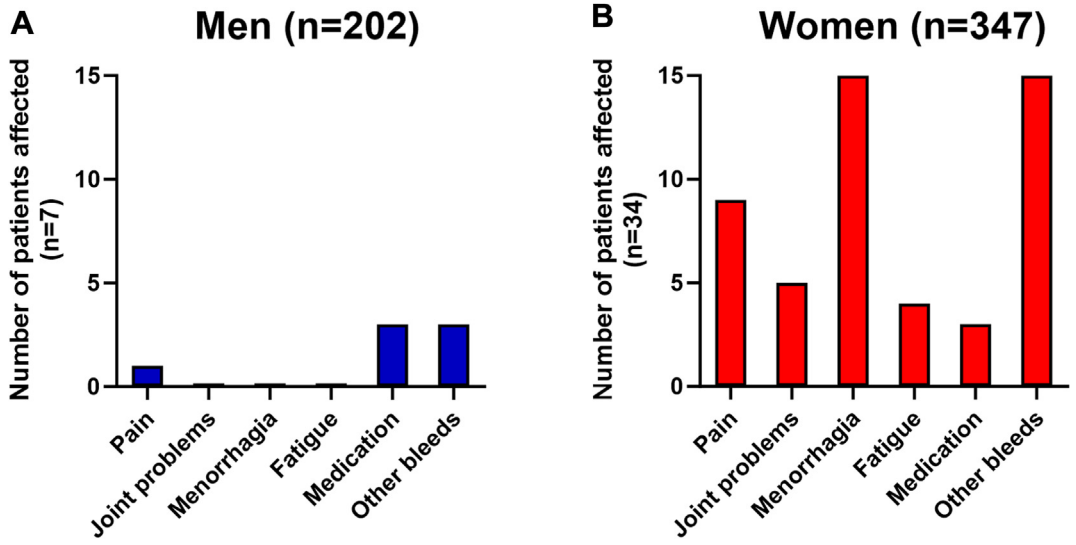

FIGURE 3 Self-reported reasons for sexual restriction due to von Willebrand disease. The distribution of reasons is shown for men and women who reported to have experienced sexual restriction as a result of von Willebrand disease.

TABLE 2 Logistic regression model.

Determinant	OR	95% CI
ISTH-BAT menstruation[a]	1.60	1.12-2.46
Blood group	0.46	0.18-1.07
Type 3[b]	3.97	0.46-24.87
Hysterectomy	0.26	0.04-1.07
Age at inclusion[a]	0.97	0.94-0.99

ISTH-BAT, International Society on Thrombosis and Haemostasis Bleeding Assessment Tool; OR, odds ratio.
[a]$P < .05$.
[b]In reference to type 1.

definitions of sexual dysfunction, inadequate descriptions of populations, and a predominant focus on male sexual dysfunction [34–37]. One of the strengths of our study is that we focused on differences between men and women and on women-specific bleeding symptoms.

The study also has limitations. Despite the fact that the questions on sexuality used in the WiN-Pro questionnaire were also used in a large cohort study in persons with hemophilia (Hemophilia in the Netherlands 6), this questionnaire has not been validated in other cohorts [10]. Nevertheless, additional studies should be performed using validated questionnaires pertaining to sexuality, such as the Female Sexual Function Index, the International Index of Erectile Function, or the Female Sexual Distress Scale, also validated for men [18,19,38,39].

From our findings, we conclude that the percentage of patients reporting sexual restrictions is higher in women than in men. The physical and mental domain scores for the women were lower than the mean of the Dutch general population (PCS: 49.7, MCS: 52.1) [25]. Since the majority of VWD patients are women and >85% experience HMB, the impact of VWD on sexual functioning is expected to be large [40–42].

We also found that the percentage of reported sexual restrictions is higher for premenopausal patients than for nonmenstruating patients. Logistic regression analysis revealed that the ISTH-BAT item for menstrual bleeding emerged as the most important determinant of reporting sexual restriction, even after accounting for the confounding effects of age at inclusion. The effects of age may partly be explained by a known increase in VWF levels with age in type 1 VWD patients, which may influence the bleeding phenotype and consequently lead to effects on sexuality [43]. A more elaborate analysis is warranted to assess the influence of age-related factors on sexuality, such as physiological changes as a result of menopause in women. Unfortunately, analyses performed on subgroups of nonmenstruating patients (after hysterectomy or postmenopausal) were unfortunately underpowered due to low patient numbers.

Multiple studies demonstrated improved QoL and better sexual health following hysterectomy or endometrial ablation in women with HMB in the general population [12,13]. In our logistic regression model, hysterectomy appeared to lower sexual restrictions, but the result was not statistically significant. Iron supplementation to treat anemia and iron deficiency resulting from HMB has been shown to improve sexual function by reducing anxiety and fatigue, which can lower sexual desire [44]. HMB should, therefore, be treated with, eg, hormonal therapy, intrauterine devices, tranexamic acid, desmopressin, or VWF-containing factor concentrates to increase the QoL and sexual functioning [42,45,46].

Notably, one-third of all participating women in the study reported bleeding during sexual activity, a considerably higher prevalence compared with the 0.7% to 9.0% range observed for postcoital bleeding in the general Dutch population [47]. This increased rate may be linked to the heightened bleeding tendency in VWD, making blood loss more noticeable in these patients. Psychological factors, such as anxiety from past bleeding episodes or reduced self-confidence, could also play a role by lowering sexual arousal and causing inadequate lubrication [48,49]. This may increase the risk of postcoital bleeding and pain during intercourse, potentially creating a vicious cycle [50,51]. Given the multiple risk factors and treatment options for dyspareunia and postcoital bleeding, a comprehensive sexual health evaluation is essential for effective treatment [52].

Unfortunately, our results indicate that sexuality is not a topic that is regularly discussed by hemophilia physicians or nurses during outpatient visits of VWD patients. This was also observed in earlier studies in persons with hemophilia [10]. In addition, our data and that of similar studies in persons with hemophilia reflect that patients may not disclose possibly concerning symptoms, such as hematospermia, resulting in underreported cases [10]. Although many participants were indifferent to discussing sexuality in the outpatient clinic, only one-third reported unwillingness to discuss this topic. Additionally, the proportion of patients willing to discuss sexuality is much larger in the group of patients who reported sexual restrictions, also shown before in hemophilia patients [10].

Previous studies show that patients are more comfortable discussing sexuality when the initiative is taken by healthcare professionals, which may also be true for the patients who reported being indifferent to the topic of sexuality [16]. However, our data reflect that our patient groups exhibit a wide range of preferences regarding the discussion of sexuality, suggesting the necessity of a personalized approach. The professionals, in turn, acknowledge the topic of sexuality and disease but require adequate information and training [53,54]. Therefore, it is important to perform future studies on sexual health and bleeding and the way it evolves over time in order to generate evidence-based tools and training for healthcare professionals treating these patients.

In conclusion, women experience more sexual restrictions due to VWD than men, and they report significantly more postcoital bleeding than the general population. Premenopausal patients report sexual restrictions more often than nonmenstruating patients, particularly due to HMB. Our findings highlight the need for health care providers to address sexual health during routine consultations and to adequately treat HMB to improve overall care for VWD patients.

APPENDIX

List of the members of the WiN-Pro study

University Medical Centre, Amsterdam, the Netherlands: K. Fijnvandraat, M. Coppens. The Netherlands Haemophilia Society, the Netherlands: J. de Meris. University Medical Centre Groningen, Groningen, the Netherlands: K. Meijer, R.Y.J. Tamminga. HagaZiekenhuis, The Hague, the Netherlands: P.F. Ypma. Leiden University Medical Centre, Leiden, the Netherlands: H.C.J. Eikenboom, J.G. van der Bom, F.J.W. Smiers. Maastricht University Medical Centre, Maastricht, the Netherlands: F.C.J.I. Heubel-Moenen, A. van der Veer. Radboud University Medical Centre, Nijmegen, the Netherlands: S.E.M. Schols. Erasmus University Medical Centre, Rotterdam, the Netherlands: F.W.G. Leebeek (principal investigator), M.H. Cnossen, F. Atiq, C.B. van Kwawegen. Van Creveldkliniek, University Medical Centre Utrecht, Utrecht, the Netherlands: E.P. Mauser-Bunschoten, K.P.M. van Galen.

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AUTHOR CONTRIBUTIONS

C.B.v.K. designed the study. C.B.v.K. and F.A. collected the data. C.B.v.K. performed statistical analyses, interpreted the data, and wrote the manuscript. F.W.G.L. conceived and designed the study, interpreted data, and critically revised the manuscript. All authors critically revised and gave their consent to the final version of the manuscript.

RELATIONSHIP DISCLOSURE

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DATA AVAILABILITY

Upon reasonable request, original data can be reviewed by sending an email to the corresponding author.

ORCID

Calvin B. van Kwawegen https://orcid.org/0000-0002-3822-1496
Frank W. G. Leebeek https://orcid.org/0000-0001-5677-1371

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SUPPLEMENTARY MATERIAL

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