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Living With Factor VII Deficiency—A Mixed Methods Study

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ABSTRACT

Background: Factor VII deficiency (FVIID) is a rare autosomal recessive disorder, resulting in potentially unpredictable and life-threatening bleeding. The prevalence of symptomatic patients is 1 in 300,000. Treatment is mostly given following bleeding, but those with the lowest levels may be offered prophylaxis.

Objectives: We aimed to explore the real-life impact of FVIID on individuals and their families, focusing on psychosocial wellbeing and quality of life (QoL).

Methods: The study used a quantitative survey, including validated QoL tools, and qualitative one-to-one interviews to enable deeper exploration of the quantitative findings.

Results: One hundred people with FVIID (74 adults; 26 caregivers of children) completed the survey; 24 (18 adults; 6 caregivers) were interviewed. A significant gender-based disparity was observed: males were diagnosed at a median age of 4 years, versus 17 years in females ($p < 0.001$). 56% of respondents reported a mean of 1.25 bleeds per week; significantly higher in women than men (mean 1.65 vs. 0.53/week, respectively; $p < 0.01$). QoL scores decreased with increased bleeding measured by the self-BAT ($p < 0.001$). Bleeding was associated with significant social impact: missed physical activity (64%), avoidance of social engagements (53%) and lost education (50%). Interviews yielded six core themes associated with unmet need.

Conclusion: FVIID causes significant challenges, disproportionately borne by women and compounded by gaps in management, especially treatment. Current treatments are burdensome and fail to prevent breakthrough bleeds. People with FVIID have unmet needs that require therapeutic innovation, improved diagnosis and management strategies, and data collection to improve their QoL and outcomes.

1 | Introduction

In recent decades, prophylaxis has transformed haemophilia care with >80% of patients in high-income countries receiving prophylaxis. Extended half-life factor concentrates, subcutaneous treatments, and gene therapy have reduced treatment burden while improving bleeding control. Congenital Factor VII deficiency (FVIID) has not followed this trajectory.

FVIID is an autosomal recessive disorder with an estimated prevalence of 1 in 300,000 [1, 2]. It exhibits a wide spectrum of bleeding, ranging from bruising and mucosal bleeding to life-threatening intracranial haemorrhage (ICH) [3]. Women with FVIID commonly report heavy menstrual bleeding (HMB) which significantly impacts quality of life (QoL) [4, 5]. The correlation between FVII level and bleeding symptoms is weak. While those with severe FVIID (<5 IU/dL) have an elevated risk of major bleeds, not all experience frequent bleeds [6, 7].

Management of FVIID is based on bleeding severity; treatment is principally with plasma-derived FVII concentrates or recombinant activated FVII (rFVIIa), usually given reactively. Individuals

with a severe bleeding history may be treated prophylactically, but prophylaxis is not widespread. FVII and rFVIIa have short half-lives, necessitating frequent dosing, creating a high treatment burden; additionally, reimbursement for prophylactic use is inconsistent [8, 9].

The lived experience and impact of FVIID are poorly understood. This natural history study explored the real-life impact of FVIID on affected individuals and their families, focusing on psychosocial wellbeing and health-related quality of life (HRQoL).

2 | Methods

This mixed methods study utilised a quantitative survey and qualitative interviews enabling deeper exploration. Individuals and caregivers of those with a FVIID were eligible. Recruitment was via social media, word of mouth and patient groups. Survey participation was incentivised by a prize draw. Interviewees were compensated for their time.

2.1 | Study Measures

Self-reported demographic data including bleed site and frequency and quantitative data were collected following tick box consent (which was necessary to proceed) via an online survey incorporating validated patient-reported outcome measures:

- Bleeding assessment: modified ISTH self-BAT [10] adapted to use lay language rather than medical (e.g., nosebleed not epistaxis), estimated weekly bleed rate, treatment history, Menstrual Impact Questionnaire (MIQ) [11]
- HRQoL: EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) [12], using country-specific value sets
- Psychosocial impacts: Patient Health Questionnaire (PHQ-8) for depression [13], Generalized Anxiety Disorder-7 (GAD-7) [14], Rosenberg's self-esteem score [15], Self-Efficacy to Manage Chronic Disease Scale [16].

Following written informed consent, in-depth, semi-structured interviews were conducted by experienced researchers (SF, KK), using an online platform and interview guide focused on QoL, family knowledge of FVIID, education/career impacts, and societal/cultural issues. Field notes were written after each interview.

2.2 | Statistical Analysis

Sociodemographic and clinical data are summarised using descriptive statistics. Data are presented as number and frequency for categorical variables or mean (with SD or SE) for continuous variables. Associations between clinical data and psychosocial variables were explored using Student's t-test, Mann-Whitney U-test, or ANOVA. Mean data were compared using Wilcoxon rank sum test with continuity correction. $P < 0.05$ was considered significant.

Interviews were transcribed, thematically analysed and coded using NVivo (v12). Themes were identified and synthesised into a descriptive framework [17]. Emergent themes were reviewed and refined following each interview to enable further exploration. This iterative process was continued until data saturation.

3 | Quantitative Results

3.1 | Participant Demographics

One hundred participants completed the survey: 74 people with FVIID (PwFVIID) (mean age 36 years, range 16–81, 67% female) and 26 carers of PwFVIID (mean age 14 years, range 1–30, 54% female) (Table 1). Over half (53%) reported a family history of FVIID. Most (81%) knew their FVII level; 37% had severe disease (FVII <5 IU/dL).

Age at diagnosis (mean 14 years, range 0–55) correlated with age when symptoms emerged (mean 11 years, range 0–50) (Figure 1). Significant gender disparity in diagnosis was observed: male diagnosis was median 4 years, versus 17 years in females ($p < 0.001$). This finding was driven by diagnostic delays >10 years among 18 women (mean age 43 years, range 25–71).

3.2 | Bleeding Experience

Over half of respondents (56%) reported at least one bleed per week (mean 1.25/week, all bleeding as reported by the participant was deemed a 'bleeding episode'. The rate was significantly higher in women than men (mean 1.65 vs. 0.53/week; $p < 0.01$; Table 2). Mean modified self-BAT score was 16.17 (median 14; range 0–47; SD 10.80) and non-significantly higher for women. Correlation between FVII level and BAT score was not statistically significant.

Epistaxis was common (men 92%, women 84%; Figure 2) and significantly more frequent among those with severe (<5 IU/dL) and moderate FVIID (6–10 IU/dL) ($p < 0.01$). Nearly all women (97%) reported HMB; 17/64 (26%) had experienced post-partum haemorrhage (PPH). Unexplained bruising was reported by 61% of men and 90% of women. Muscle haematomas (50%) and joint bleeds (35%) were significantly more frequent in participants with lower FVII levels: 52% reporting muscle haematomas had severe FVIID ($p < 0.001$), 63% reporting joint bleeds had moderate FVIID ($p < 0.01$).

Clinical burden of bleeds resulted in significant use of medical care in the month before survey completion. Around one-third (32%) experienced at least one bleed ($n = 44$) requiring contact with a medical provider; 23% had at least one bleed ($n = 37$) requiring an in-person visit. During the previous year, 21% required hospitalisation for a bleed, with 96 separate admissions.

3.3 | Treatment Experience

Despite frequent bleeding, 41% reported not currently taking any treatment; 10% reported never having preventive treatment. Tranexamic acid and FVII concentrate were the most widely used treatments. FVII was used prophylactically by 24 participants (19

TABLE 1 | Demographic characteristics of the study population.

Demographic	People with FVIID [$n = 74$]	Carers of People with FVIID [$n = 26$]	
Sex, n (%)			
Male	24 (32.4%)	12 (46%)	
Female	50 (67.5%)	14 (54%)	
Age			
Mean (median, range) years	36.1 (33.5, 16–81) years	14 (13, 1–30) years	
Ethnicity, n (%)			
White	45 (60.8%)	12 (46%)	
Asian	15 (20.2%)	8 (30.7%)	
Arab	5 (6.7%)	1 (3.8%)	
Black/African Caribbean	3 (4.0%)	2 (7.6%)	
Mixed / Multiple ethnic	3 (4.0%)	2 (7.6%)	
Other ethnic background	2 (2.7%)	1 (3.8%)	
Black American	1 (1.3%)		
Country of residence, n (%)			
United Kingdom	28 (37.8%)	13 (50.0%)	
United States/Canada	18 (24.3%)	5 (19.2%)	
Europe	21 (28.3%)	6 (23.0%)	
Middle East	4 (5.4%)	1 (3.8%)	
Asia	3 (4.0%)	1 (3.8%)	
Age at diagnosis	**Males [$n = 36$]**	**Females [$n = 64$]**	***p* value**
Mean (median, range in years)	6 (4, 0–32)	18.71 (17, 0–55)	<.001
Age at symptomatic impact			
Mean (median, range in years)	7.16 (5, 0–32)	13.65 (12) 0–50	<.01

Note: Wilcoxon rank sum test with continuity correction.

TABLE 2 | Self-reported estimates of weekly bleeds and bleed scores.

Age	Mean	Median	Range	SD	SE	*p* value
Self-reported estimates of number of bleeds/week						
Men [$n = 36$]	0.527	0	0–3	0.69	0.11	<.01
Women [$n = 64$]	1.65	1	0–20	2.87	0.35	
Modified self-BAT score						
Men [$n = 36$]	13.69	12	0–38	10.84	1.80	n.s.
Women [$n = 64$]	17.56	15	0–47	10.62	1.32	

Note: Wilcoxon rank sum test with continuity correction.

severe FVIID); administration schedules varied widely, between once a month 'tailored prophylaxis' and daily. Those on 'regular' prophylaxis given at least three times per week had significantly higher self-BAT scores and weekly bleed rates ($p < 0.001$; Table 3).

Among women reporting HMB, 79% (49/62) had consulted a doctor; 39% had not received treatment. A combination of oral contraceptives and iron was the most frequently reported treatment (47%).

3.4 | Social and Psychological Impact

Bleeding was associated with significant social impacts including missing education (50%), physical activity (64%) and avoiding social engagements (53%). Of 45% reporting missed work, over one-third (35%) were on prophylaxis.

The physical burden of bleeding impacted mental health, social isolation and relationships. Although most participants had

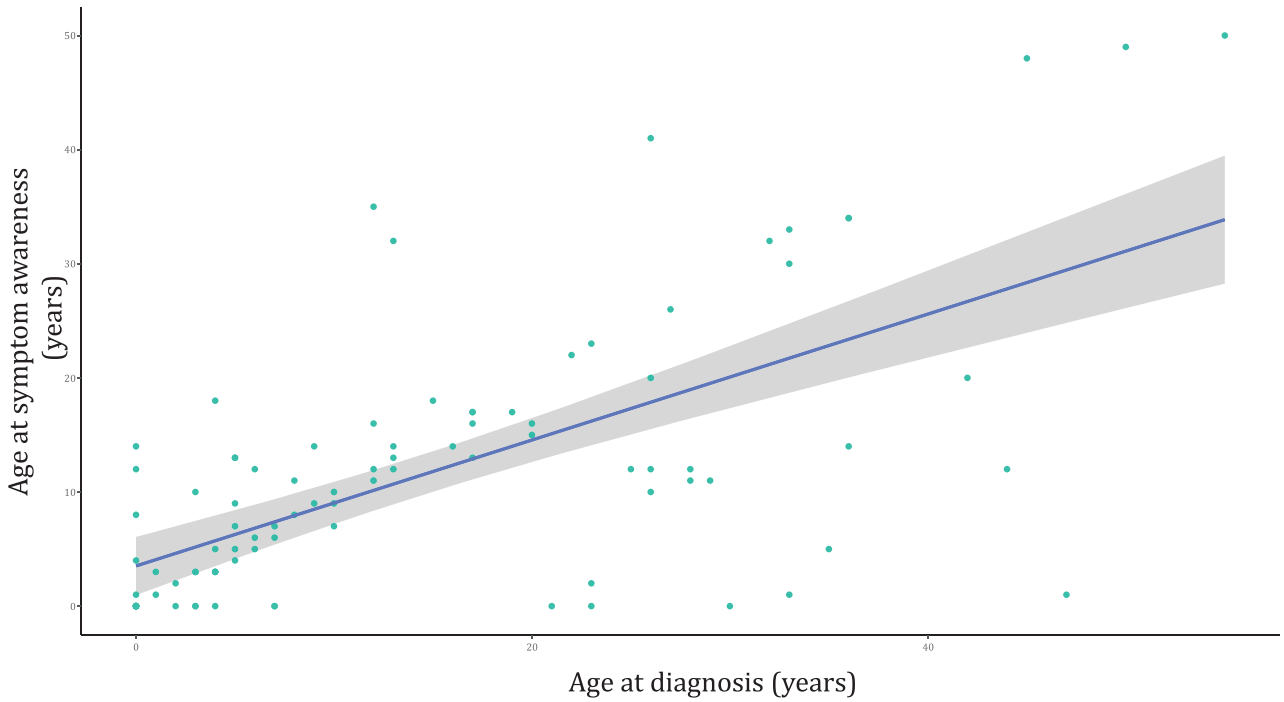

FIGURE 1 | Age at diagnosis correlated with awareness of symptoms ($p \leq 0.001$, Spearman's rank correlation rho).

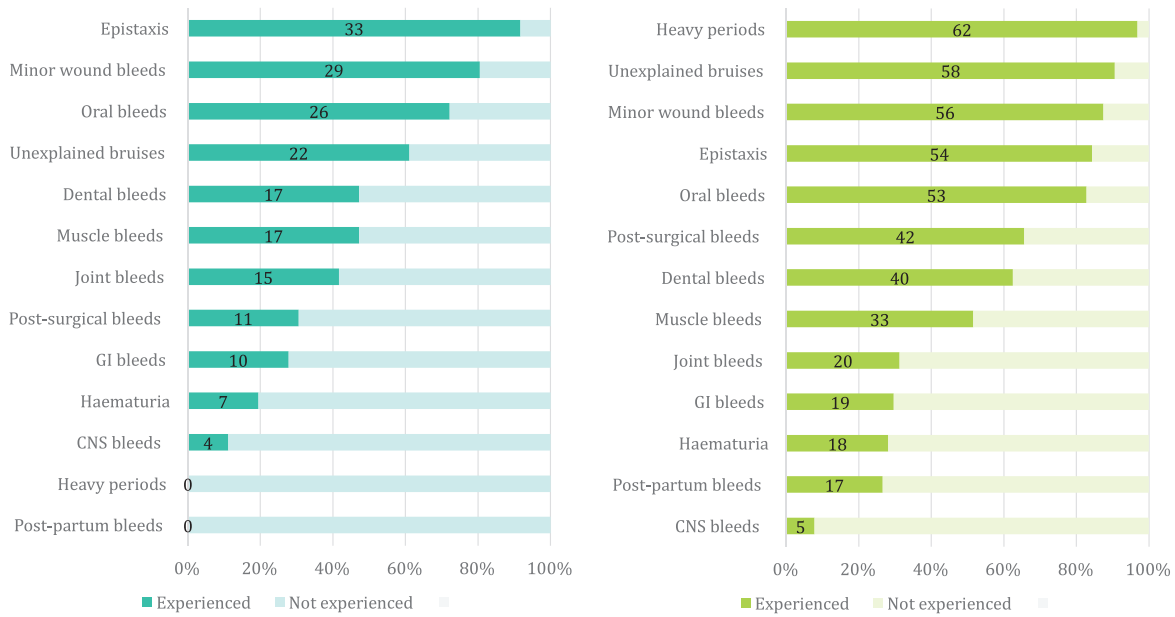

FIGURE 2 | Bleeds reported by men [left, $n = 36$] and women [right, $n = 64$] in the study population.

depression and anxiety scores in the normal range, PHQ-8 and GAD-7 (Figures 3 and 4) scores showed positive correlations with self-BAT scores ($p < 0.01$), suggesting that psychological distress increases with bleeding severity.

Psychosocial impacts were greater among women than men.

3.5 | QoL

There was significant correlation between declining QoL scores (EQ-5D-5L) and increasing bleeding severity (self-BAT) ($p < 0.001$) (Figure 5). Diminished QoL was evident in disruption around work, education, physical and social activities, and mental health impacts. Most respondents identified effective prophylaxis (82%) and less frequent bleeding (77%) as most important for improving QoL.

4 | Qualitative Results

Eighteen PwFVIID (mean age 35 years; 16 female) and 6 carers of 9 PwFVIID (mean age 21 years; 6 female) were purposively

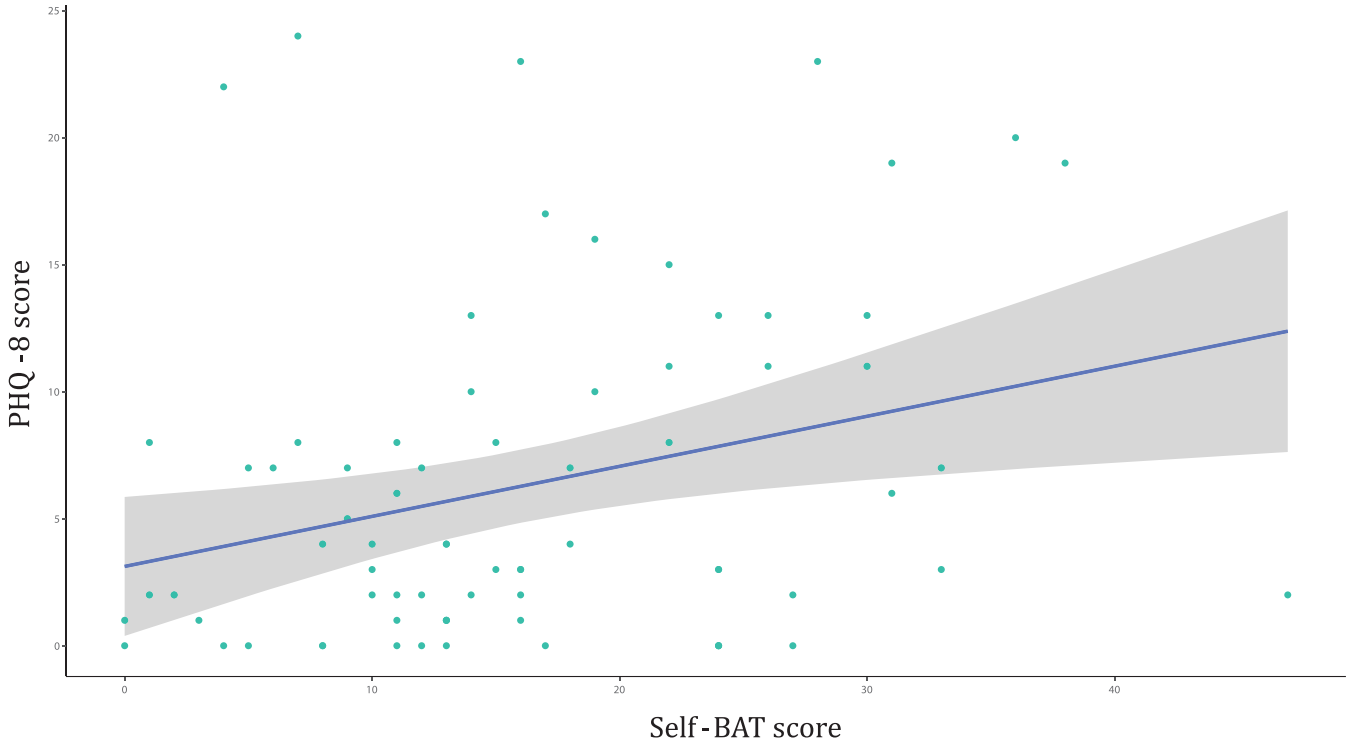

FIGURE 3 | PHQ-8 score correlated with self-BAT score ($p < 0.01$, Spearman's rank correlation rho).

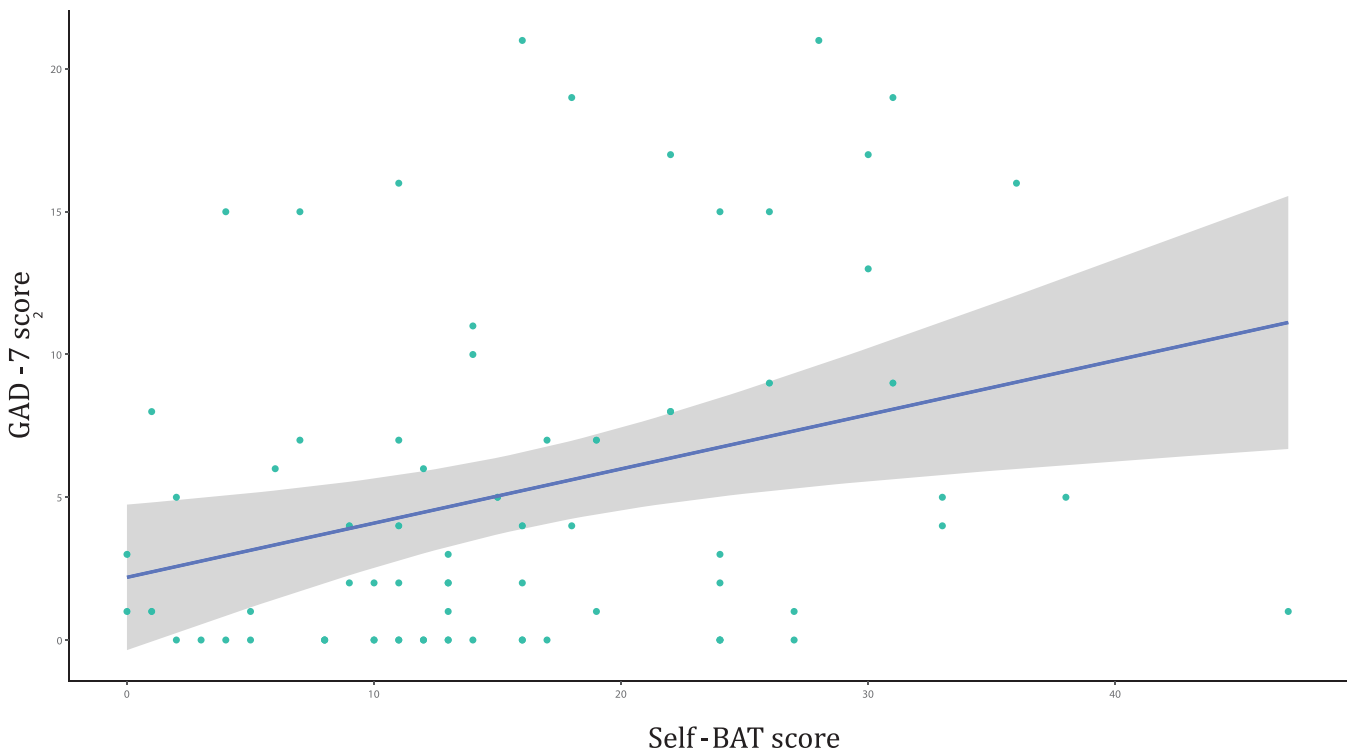

FIGURE 4 | GAD-7 score correlated with self-BAT score ($p < 0.01$, Spearman's rank correlation rho).

TABLE 3 | Impact of use of Factor VII on self-BAT score rate among the whole population and those with FVII levels below 5%.

Response	n	Mean	Median	Range	Std Dev	SEM	*p*
All participants							
Not currently on Factor VII	76	12.40	12	0–31	7.84	0.89	<.001
Currently on Factor VII	24	28.08	26.5	12–47	10.35	2.11	
Participants with factor VII levels <5%							
Not currently on Factor VII	18	15.05	16.5	1–31	9.48	2.23	<.001
Currently on Factor VII	19	29.15	27	12–47	10.88	2.49	

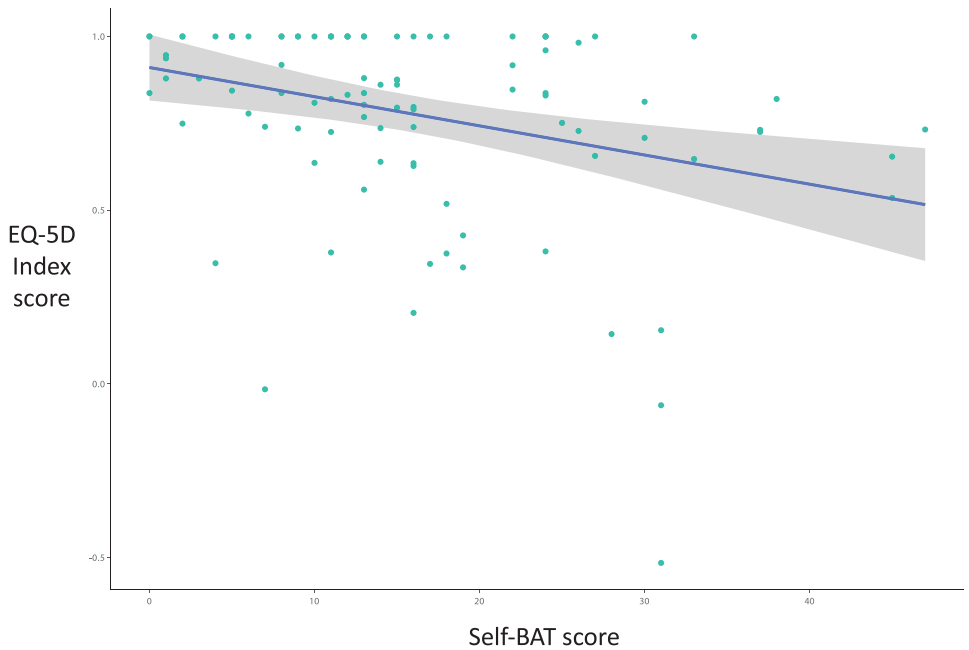

FIGURE 5 | EQ-5D Index Score correlated with self-BAT score ($p < 0.001$, Spearman's rank correlation rho).

selected for qualitative interviews. Interviews lasted 26.75 min on average (range 20–29). Following data saturation, analysis yielded six core themes associated with unmet needs. Additional supporting quotes are provided (Table 4).

4.1 | Bleeding

All interviewees referred to frequent bruising, with social impacts including suggestions of non-accidental injury.

> "My parents had to deal with that when I was younger because they would drop me off at daycare with bruises all over my body … if you're not familiar with the disease, your mind goes to the obvious." (Female, 62)

Many reported being uncomfortable with their bruises being seen, some taking measures to hide them.

> "I had my graduation coming up and I was wearing a dress. I thought, I've got to put some tights on to try and cover it up." (Female, 35)

Mucosal bleeding was common; interviewees described frequent and often persistent epistaxis, sometimes lasting hours. One described waking up with a pillow "*completely covered in blood*" *(Female, 40)*.

Bruising and mouth bleeds frequently occurred due to minor injury or routine procedures, sometimes leading to severe bleeding. Eating crisps resulted in gum bleeding for one interviewee (*Female, 22)*; another described prolonged bleeding after dental work, "*still the following day spitting blood everywhere*", and her leg becoming "*black and blue from top to bottom*" following a knee examination *(Female, 62)*.

Fourteen interviewees reported recurrent joint bleeds. One described her ankle as her "*main target joint*" since childhood (*Female, 40*). Another summarised physical impacts of bleeds

TABLE 4 | Quotes supporting the core themes identified in interviews.

Theme	Subthemes	Quotes
Bleeding	Clumsiness Fatigue—Anaemia Fear of injury Frequency Normalised Sites—Bruising, CNS bleed, Conjunctival, Epistaxis, Gastrointestinal, Haematoma, Haematuria, Joints, Mobility, Muscles, Oral-mucosal, Skin Spontaneous Surgery Trauma Treatment—Burden, Clinical trials, FEIBA, Frequency, FVIIA (Access, Inhibitor, Port-a-cath, Prophylaxis, Self-treatment, Thrombosis), Plasma, Tranexamic acid	'I had lots of bruises on the legs for example, when bashing into stuff. I also, I woke up with a black eye once' (Female, 35) 'I've always bruised, but I've kind of just accepted that' (Female, 35) 'Mostly nosebleeds, that's really my main issue' (Female, 22) 'They could be 15 min, or … I've had nosebleeds upwards of five hours' (Male, 20) '[My son] gets the odd nosebleed but they're quite bad. With my daughter, she tends to get nosebleeds. When I was younger, I'd get quite a few nosebleeds. My brother still gets nosebleeds' (Female, 35) 'I have [had joint bleeds] but no one knows why. I have always had joint problems, in my lower extremities pain and I can't walk, but the doctors told my mother that it's rheumatoid [arthritis]' (Female, 33) 'For the last 15 years since I've been flying from place to place, even though I have my meds with me I realise something always happens and I end up with a subconjunctival haemorrhage in my eyes' (Female, 52) "Prophylaxis … they want me to have three a week, but I just can't get it into the vein. I'm still getting bleeds every now and again, because it's such a short half-life." (Female, 40) 'Your survey made me realise that well I have bleeds quite often actually, and it's just so normalised. The questions made me realise how often I still have bleeds, and it was really interesting' (FVII-R006, Female aged 35)
Diagnosis	Age Attitudes—Family, Personal, Societal Comorbidities—Blood clots, Depression, Family history, Genetics Journey—Length of time, Misdiagnosis, Relief, Levels, Non-accidental injury, Psychosomatic, Restrictions Understanding—Family, Medical, Personal	'I'd had quite a few instances I think of bleeds before 12' (Female, 40) 'She'd bruised very easily from being a very unsettled baby, but nobody knew why. Then about the age of 2 she stopped using either her arm or her leg, for several days, was always covered in bruises. We kept getting sent to the rheumatologist, having x-rays, and them saying, no, she hasn't broken anything' (Mother of child, 16) 'I was going to have a procedure and was told it was not safe to do it because my blood was too thin. This was the first time I got a sense that there was something wrong' (Male, 25) 'I was diagnosed when I was pregnant. My blood pressure went up, so they did a blood test, and in that blood test was my clotting factors and that's how they found out' (Female, 46) 'I was diagnosed within one or two days of being born. I was throwing up blood, and my heel prick wouldn't stop bleeding' (Female, 22) 'I think my mother told me the back of my hand was swollen, and they knew that I hadn't fallen off somewhere or anything like that, so they went to the hospital, and I was diagnosed' (Female, 35) 'No-one in my family knew anything about it' (Female, 22) 'Those early years [were] harder for them as parents, because they were constantly saying there was something wrong, and no-one knew what it was' (Female, 40)

(Continues)

TABLE 4 | (Continued)

Theme	Subthemes	Quotes
Isolation	Abuse Coping—Acceptance, Normality, Denial, Doubt, Over-protection, Taking control Difference Disability—Ableism Disclosure Discrimination—Labelling Feelings—Anger, Embarrassment, Hopelessness, Why me? Pain—Fasciitis, Joint pain, Pain relief, Relationships, Self-harm Support—Advocacy, Lack of information Travel Uncertainty Work	'My mum and dad like live close-by so they help me quite a bit. They've always kind of been part of my care bubble with my kids … if I'm in hospital with one my mum helps with the other two' (Mother of children with FVIID, 13 and 24) 'It'd be quite nice to talk to somebody else that says, I've got to do that as well' (Female, 46) 'I did feel that because the name of the organisation was haemophilia I was not a part of it. They changed their name … its better because I feel like everybody with bleeding disorders is being addressed' (Female, 44) 'I know the society is quite inclusive of all bleeding disorders, but the conversations can be very focused on things that sometimes aren't as relevant to me' (Female, 22) 'Sometimes I think he tries to ignore it or pretend that it's not there because he wants to do things like other kids' (Mother of children with FVIID, 13 and 24). 'It affects every part of your development and your life. It's not the conversation that you generally have with anybody ordinarily, certainly not with a potential new boyfriend' (Female, 52) 'I was watched over a bit more than my siblings, but I didn't really have an awareness of it until I was about 8 or 10' (Female, 22) 'Yes, I'd say I'm a lot more careful, but it's been like a learning experience, I've had good doctors around me that have taught me how to do all the stuff to treat my disease, but it's been kind of a burden having it, not being able to do a lot of the activities that other people do' (Male, 20)

(Continues)

TABLE 4 | (Continued)

Theme	Subthemes	Quotes
Menstruation	Limiting activity Menarche Not discussed (taboo) Symptoms—Clots, Cramps, Flooding, Heavy, Prolonged, Worse with age Treatment—Hormonal, Life changing Under-reporting—Normalisation	'I was looked at as kind of the weird girl, you know, like even when the little girls did their little parties on the weekends, not going to the game Friday night, not helping with the parade, not being able to go to the summer dance unless I strategically planned it' (Female, 52) 'Just recently she started her period. They are pretty heavy, and they're about nine days each. She was referred to a paediatric gynaecologist who was able to prescribe her tranexamic acid, that she can use on days that it's just really bad' (Mother of a child with FVIID, 24) 'As a child I would wear the thickest pad and it would go the full course, you know, the 7 days. But during my 30s that's when I noticed that it was extremely heavy. I had the coil fitted twice and twice it was washed out by my period. I'm increasingly having to kind of double up with all the padding and everything as I'm getting older because I leak otherwise' (Female, 50) 'As I've got older they've got heavier,' (Female, 46) 'I always thought my periods were normal, but it turns out that they are quite heavy because I've again gone through a series of questions about how often I change my pad and my tampon' (Female, 36) 'It was in the family but the terminology given to it was free bleeders, and the heavy, crazy, abnormal menses that where you pass these clots, that became the normal' (Female, 52) 'I didn't know that other people didn't bleed like this' (Female, 46) 'It's shortened them, and either they'll be longer but a lot lighter, or they'll be shorter and heavier days' (Female, 16) 'I'm in a job now where I see the public all the time and I can't even contemplate the thought of being sat there and feeling something running down my leg, I just, no. I'd rather leave my job, a job that I absolutely love than have to think about that' (Female,46) 'Even with the tranexamic acid and the hormonal therapy sometimes I think maybe one day I will have hysterectomy' (Female, 33)

(Continues)

TABLE 4 | (Continued)

Theme	Subthemes	Quotes
Pregnancy	Birth—Negative experience Caesarean section Fear—Stopping hormonal therapies, Menstruation, PPH Hysterectomy Miscarriages Post-partum	'We had miscarriages, and we really struggled, I mean we took, I think we took six years. 'In the end we'd had an injection every day at the first, and even then I still had some bleeding' (Female, 40) 'I was referred to it by my gynaecologist/surgeon, when I had, after I had my C section and then delayed postpartum haemorrhage' (Female, 36) 'I had quite a bit of blood loss. A normal caesarean is about 300–500 mL, so I had almost three times that so, but I didn't have a transfusion' (Female, 45) 'Yeah, I just don't want, I mean, it's just that I don't want to deal with periods. There's been occasions when I've had to stop it, so before I was diagnosed and if I was due to have an operation, I was told to stop it up to 6 weeks before, and then, so I did get it coming back and it was not pleasant' (Female, 35)
The future	Aspirations Fears Treatments Menopause Next generation	'I think it would be something where I wouldn't need my veins to inject, so maybe a pill, that I had to take every day, that would be I think the best that could happen' (Female, 35) 'Well, obviously, the gene patch would be the ideal solution, and not to have it at all, but yeah, that would be the second thing. It would just be not to have to do the veins anymore' (Female, 33) 'I've heard people talk about gene therapy, and I've always been interested in that, so I would definitely check that out' (Male, 20) *"There is less people who have it, so there's going to be less research towards it." (Male, 20)*

affecting elbows, knees and ankles, noting swollen joints, limited range of motion, and "*just the pain of it all*" (*Female, 52*).

Other bleeds described included subconjunctival haemorrhage and potentially life-threatening bleeding events. Four reported ICH, including neonatal ICH resulting in developmental delay. Five reported gastrointestinal bleeds.

Over half of interviewees (16/27) had received rFVIIa at some stage; only seven were on prophylaxis. Two reported bleeding despite prophylaxis:

> "I tend to have four injections a week, roughly, because I'll always bleed even if I am on top of the prophylaxis." (Female, 22)

4.2 | Diagnosis

Three interviewees were diagnosed within the first year of life. For many, diagnosis came later, often following significant bleeding events.

> "After I got in a car wreck [an ER doctor] couldn't stop me bleeding… Without this doctor I would never have known I had a diagnosis of FVII deficiency." (Female, 35)

> "After my C-section and delayed postpartum haemorrhage, I woke up and was asked by various specialists if I had a bleeding disorder." (Female, 36)

For some women, diagnosis followed menarche; normalisation of HMB contributed to the delay.

> "I didn't know that other people didn't bleed like this." (Female, 46)

4.3 | Isolation

Although keen to connect with others with FVIID, interviewees recognised that its rarity made this difficult, leaving them feeling isolated.

Those able to access bleeding disorder support groups frequently felt their needs were not met due to a focus on disorders such as haemophilia.

> "You feel as though you're the only person out there." (Female, 62)

Most found support from extended family; however, some expressed unwillingness to disclose their FVIID due to not wanting to be perceived as 'different'.

> "I don't talk about it, unless I've known the person for like a few years. School kind of instilled this thing in me to not appear any more different than I already did." (Female, 22)

Even in healthcare settings, participants described being perceived as 'rare' or 'different'.

> "You feel a bit of a spectacle sometimes. On one occasion the nurse came to give [my treatment] and all the other nurses on the ward were hovering around to see." (Female, 35)

Those diagnosed early in life were often prevented from participating in 'normal' activities by overprotective parents. Some described internalising this cautiousness, impacting work and social life.

> "I've picked a job that I work from home … actually I've done a lot of my life based on my condition … I wanted to go into certain things, and then you think well no I can't really do that." (Female, 40)

4.4 | Menstruation

HMB-related constraints led to gender-specific isolation, resulting in missed school or work, and impacting activities freely enjoyed by peers.

> "I was looked at as kind of the weird girl, you know, like… not being able to go to the summer dance unless I strategically planned it." (Female, 52)

They described prolonged bleeding (nine days to two weeks) with heavy flow, large clots, sometimes resulting in hospitalisation or blood transfusions. Some had undergone invasive surgical interventions (endometrial ablation, curettage, hysterectomy) to manage bleeding.

Coping strategies included layering sanitary products, carrying spare clothing, and having excuses to leave ready. However, the potential for 'bleeding through' remained a barrier.

> "I used to have to carry, literally, a suitcase around with me for a change of clothes, I wouldn't go and stay at people's houses because I'd bleed onto the beds." (Female, 46)

The prospect of hysterectomy to control bleeding when other treatments fail was a fear for some. Fear and anxiety about the future, including perimenopause, was also reported.

> "[It] absolutely petrifies me… because if it all starts again, I don't know how I'll cope I'd rather leave my job, a job that I absolutely love than have to think about that." (Female, 46)

4.5 | Pregnancy

While many women were impacted by HMB from menarche, some reported menstrual problems beginning after pregnancy.

> "They were terrible at the beginning, and then when I had [my son] I was alright for a bit. But recently, I've been having terrible problems, and I had a period nonstop for two years." (Female, 40)

Several reported significant pregnancy-related bleeding, which was not always controlled despite intensive prenatal management, including regular FVII infusions. Multiple miscarriages were reported. Childbirth was a period of high risk and PPH was reported by many.

> "[I] bled and bled and bled and got readmitted to the hospital and bled some more with both of them." (Female, 52)

The physical and emotional burden of managing FVIID led some women to reconsider whether to have children. Stopping contraception was a primary concern, due to the likely return of uncontrolled HMB.

> "We went completely off and I'm just like 'Oh my goodness, I remember why I went on the birth control'. I've kind of questioned recently is it worthwhile to start a family." (Female, 28)

4.6 | The Future

Interviewees expressed a strong desire for improved treatments, some noting that the FVIID treatment landscape lags behind other bleeding disorders.

> "Haemophilia's got treatment that could last 24 h, or 48 h, and then we're still stuck on like two-to-four-hour lifespans." (Male, 20)

Their hopes included longer-acting, less invasive therapies that reduce treatment burden:

> "Something that maybe you could give like that would last 3 to 4 days or even a week… That would be ideal." (Mother of child, 8)

Awareness of haemophilia gene therapy led some to wonder if it might be a possibility for FVIID. However, there was pessimism around whether companies would invest in such a rare indication, and a common feeling that FVIID is overlooked.

5 | Discussion

The Rare Coagulation Disorders Registry (www.rarecoagulationdisorders.org) collects international data on clinical information of people with FVIID and report that bleeding in FVIID occurs from a young age [18]. Our study, of patient reported data revealed more than one bleed (any bleeding described by the participant) each week, a substantially higher rate than would be considered acceptable in haemophilia care. This may reflect recruitment methodology with participation of the most affected patients, conversely these may be those with the most unmet need.

Consistent with earlier reports, epistaxis, bruising and mucosal bleeds were most commonly experienced [3, 19]. Though rare, muscle bleeds were more likely to be reported by those with severe disease. Reports of ICH and gastrointestinal bleeds highlight the serious and often life-altering nature of FVIID. Participants reported joint bleeds in higher numbers than previously recognised [20, 21]. This may be over reporting by participants as no clinical data were available or under-recognition of joint involvement in FVIID and a need for joint health strategies such as physiotherapy assessment, diagnostic investigation (ultra sound and MRI) and the possible initiation of prophylaxis aligned to haemophilia care as suggested by Siboni et al. [22] and in von Willebrands disease [23].

Most women identified HMB as their most significant and challenging symptom, reported by others as occurring in between 50%–82% of women [4, 24], reflecting its profound impact on daily life including iron deficiency anaemia [5]. Napolitano et al. [25] report that tailored prophylaxis for one or two days with menses reduced blood loss by up to 80%, this suggests a profound impact could be made on QoL of affected women. Many highlighted significant challenges related to pregnancy and childbirth, including the care involved in maintaining pregnancy. The risk of severe bleeding complications, for example, PPH, was a persistent concern causing heightened anxiety.

Many participants reported significant diagnostic delays, which appeared longer in females than males as is reported in women across all bleeding disorders [26], resulting in prolonged suffering and missed opportunities for early intervention. FVIID's rarity and the fact that clinical presentations may not always correlate with FVII levels are likely contributing factors [27, 28]. The stark gender disparity in diagnosis based upon physicians failing to elicit information on menses, bleeding recognition and management is sexism [29] and represents a critical health equity issue which profoundly impacts QoL and clinical outcomes. For women, the diagnostic journey is complicated further by widespread normalisation of HMB and may only occur after a gynaecological or obstetric crisis.

Constant fear of bleeds impacts education, work, and physical and social activities, affecting women more than men in our cohort. Many interviewees expressed a sense of loneliness due to fear of being perceived as different or vulnerable, limitations on ability to participate in activities, and lack of peer support. Alongside frequent, unpredictable bleeding, which increases healthcare utilisation (including hospital attendance and admission), this leads to a cumulative decline in HRQoL, echoing findings in other rare bleeding disorders [30–32].

Addressing these challenges and improving care for people with FVIID requires several key actions. There is a need for wider

education of healthcare professionals, particularly in primary care and gynaecology/obstetrics, to ensure timely referral to specialist centres with appropriate diagnostic facilities, to reduce diagnostic delays and improve outcomes. Expanding access to multidisciplinary care is essential to address physical and psychosocial impacts. Systematic data collection on bleeding, joint health and arthropathy is also required.

The contrast with haemophilia is informative. Developments including EHL factors, subcutaneous rebalancing agents, and gene therapies have fundamentally transformed haemophilia management; FVIID has not experienced this therapeutic revolution. In haemophilia, wider prophylaxis has significantly reduced bleeding rates, providing better standard of care and enabling affected individuals to live well. Our data suggest that current treatments and strategies fail to adequately protect people with severe FVIID who experience a significant bleeding phenotype.

Participants receiving prophylaxis reported significantly higher bleeding scores than untreated individuals due to their FVII phenotype. The paradox of a higher bleeding burden in a treated group may reflect phenotype or indicate sub-optimal pharmacokinetics of current therapies [18, 20]. The short half-life of existing FVII replacement products prevents sustained protection, which may leave patients vulnerable to breakthrough bleeds. This highlights an unmet need for longer-acting agents to improve haemostatic coverage.

6 | Limitations

Our study has some limitations. As recruitment was via social media, there may be inherent bias towards those with the worst experiences and outcomes, however these may also be the patients with most unmet need. Furthermore, data are based on participants' self-report, and were not be confirmed from clinical case notes, thus the results may not be generalisable. However, the frequency of bleeds requiring medical assessment or treatment reveals the impact on daily-life and highlights the profound burden posed by FVIID suggesting substantial underappreciation of the severity and impact of bleeding for affected individuals and their families.

7 | Conclusion

People with FVIID experience significant challenges, including diagnostic delays, limited treatments and isolation. The burden of FVIID is disproportionately borne by women, who endure often debilitating HMB which, frequently normalised, contributes to diagnostic delays and greatly diminished QoL. Pregnancy-related issues add to the physical and psychological toll. All of this is compounded by gaps in current management, not least in relation to treatment.

Currently available treatments fail to prevent breakthrough bleeds for those with the worst bleeding phenotype who are treated prophylactically and impose a significant treatment burden. Reported bleeding rates in FVIID exceed those considered acceptable in haemophilia care. Joint involvement appears under-recognised, suggesting a need for additional joint health monitoring strategies.

These findings underscore unmet needs requiring therapeutic innovation, improved diagnostic and management strategies, and systematic data collection to improve QoL and outcomes for PwFVIID.

Author Contributions

Study design: Kate Khair, Matthew Boyton, Sam Bristow, Simon Fletcher. Interviews: Kate Khair, Simon Fletcher. Survey analysis: Matthew Boyton, Kate Khair. All authors drafted, edited and agreed on the final manuscript.

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Generative AI Statement

AI was not used in this study or manuscript production.

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Ethics Statement

The study was deemed to not need full ethical approval using the Medical Research Council/National Health Service Health Research Authority research tool (http://www.hra-decisiontools.org.uk/research/). This was because the study was non-interventional, not randomised, treatment was not changed for patients involved, and study findings were not generalisable. Consent was implied by tick box for survey completion; written consent was obtained before interviews. Data were collected between September 2023 and October 2024.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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