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ORIGINAL ARTICLE

Clinical haemophilia

Pain, depression and anxiety in people with haemophilia from three Nordic countries: Cross-sectional survey data from the MIND study

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Abstract

Introduction: People with haemophilia (PwH) may experience symptoms of haemophilia-related pain, depression or anxiety, which can negatively impact health-related quality of life.

Aim: To obtain the perspective of PwH and treaters from Sweden, Finland and Denmark on the management of haemophilia-related pain, depression and anxiety using cross-sectional survey data from the MIND study (NCT03276130).

Methods: PwH or their caregivers completed a survey about experiences of pain, depression and anxiety related to haemophilia, and the standard EQ-5D-5L instrument. Five investigators at haemophilia treatment centres (HTC) were sent a complementary survey containing questions about the management of pain and depression/anxiety.

Results: There were 343 PwH (mild: 103; moderate: 53; severe: 180; seven lacking severity information) and 71 caregiver responses. Experience of pain in the last

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6 months was reported by 50% of PwH respondents and 46% of caregiver respondents. Anxiety/depression was reported by 28% of PwH respondents. Reporting of pain and anxiety/depression was associated with disease severity. Whilst 62% of PwH who had experienced pain at any time point ($n = 242$) felt this was adequately addressed and treated at their HTC, only 24% of those who had experienced depression/anxiety ($n = 127$) felt this was adequately addressed. Disease severity was negatively associated with EQ-5D-5L utility value ($p < .001$). In the HTC survey, 4/5 and 2/5 agreed that pain and depression/anxiety, respectively, are adequately addressed.

Conclusions: Pain and depression/anxiety occur more frequently with increasing haemophilia severity, with negative impacts on health-related quality of life. PwH with depression/anxiety or unaddressed pain could benefit from improved management strategies.

KEYWORDS

haemophilia A, haemophilia B, mental health, pain, quality of life, surveys and questionnaires

1 | INTRODUCTION

People with haemophilia (PwH) commonly experience acute and chronic pain associated with bleeds and haemophilic arthropathy.^{1–4} The Nordic Haemophilia Guidelines recommend that pain should be managed with paracetamol, COX-2 inhibitors or opiates, alongside non-pharmacological approaches.⁵ Depression and anxiety are also prevalent among PwH.^{6–8} Given the negative impact of pain, depression and anxiety on the health-related quality of life (HRQoL) of PwH,^{1,4,9} both physical and psychosocial health are promoted in guidelines for comprehensive care in haemophilia.¹⁰ However, data describing how pain, depression and anxiety are managed, and whether PwH feel that their needs are adequately addressed, are limited.¹¹

MIND is a two-part study conducted in Sweden, Denmark, Finland, and Norway.¹² These countries are defined as high-income by the World Bank,¹³ and have specialist haemophilia treatment centres (HTCs) for the care of PwH. Part A investigated patterns of prescribed medication in PwH using retrospective registry data. Part B investigated the management of pain, depression and anxiety in PwH using cross-sectional survey data from Sweden, Denmark and Finland, as reported here.

The objective was to obtain the perspective of PwH and healthcare professionals on the management of haemophilia-related pain, depression and anxiety in clinical practice and daily life, including satisfaction with disease management and impact on quality of life.

2 | METHODS

2.1 | Participants and study design

A survey was developed by the MIND (NCT03276130) study team, partially based on the Haemophilia Experiences, Results and Oppor-

tunities questionnaire.¹⁴ The survey included 33 questions on: demographics and haemophilia characteristics; experiences of haemophilia-related pain, depression and anxiety and respondents perceptions of their management, including the use of medications (five broad types of pain medication, and three types of medication for depression and anxiety); and the standard EQ-5D instrument.¹⁵

The study was performed in adherence to each country's practice for surveys in the healthcare sector, including age cut-offs. Invitations were distributed between October 2018 and July 2019, with two reminders. The PwH surveys were sent to PwH aged ≥ 16 (Sweden) or ≥ 18 (Finland and Denmark) years. A modified survey was developed for children with haemophilia aged 5–15 (Sweden), 6–17 (Finland), or 5–17 (Denmark) years; modifications included rephrasing of questions, and fewer questions about symptom management. Caregivers completed the survey based on their perceptions of their child's experience. Informed consent was required from all survey participants. Both male and female PwH (adults and children) were eligible to participate but the sex of respondents was not recorded. As participation was voluntary, data were not collected on non-respondents. The full data collection process is outlined in the Supplementary Appendix.

2.2 | HTC survey

Five investigators in Sweden (3/3 HTCs), Finland (1/1 HTC), and Denmark (1/2 HTCs) received a paper-based survey developed by the MIND study team. Investigators could collaborate with co-workers at the HTC and seek information from available resources at their own discretion. The survey contained questions about the management of HRQoL impairment for PwH, with the aim of capturing pharmacological and non-pharmacological aspects of management of pain, depression and anxiety from the treaters' perspective.

TABLE 1 Statistical analyses

Comparison	Type of analysis	Statistical test	Relevant figures
Disease severity, question response and EQ-5D dimensions	Test for independence	Pearson's chi square	Figures 1, 2A, 4, 5C,D, Supplementary Figures S2–S5
Disease severity and question response	Pairwise comparison	Equality of proportions	In-text only
Disease severity and EQ-5D utility values/VAS scores	Comparison between groups	Kruskal Wallis equality of populations rank	Figure 5A,B

Abbreviation: EQ-5D, EuroQol 5-Dimension. VAS, Visual Analogue Scale.

2.3 | Data analysis

Responses to the surveys were summarised using descriptive statistics. Results were aggregated across close response alternatives or not presented when there were <5 responses, following research practices in Sweden. PwH survey answers were stratified by haemophilia severity and tests used for statistical analysis are described in Table 1. EQ-5D-5L scores were transformed to utility values and presented alongside visual analogue scale (EQ VAS).¹⁶

3 | RESULTS

3.1 | Baseline demographics and characteristics

Of 996 PwH invited to participate, 343 (34%) responded. Of these, 336 reported disease severity (seven answered do not know/prefer not to answer), 103 (31%) with mild, 53 (16%) with moderate, and 180 (54%) with severe haemophilia (Table 2). There was good representation of PwH overall. Respondents were well distributed by age category, and 60%–83% of PwH in each category of severity had haemophilia A. Fewer than 15% of PwH had a history of inhibitors.

Of 236 caregivers invited to participate, there were responses from 71 (30%) caregivers of children with haemophilia, including 15 (21%) with mild, 17 (24%) with moderate and 39 (55%) with severe haemophilia (Table 3). The children were well distributed by age category, 80% had haemophilia A, and 25% had a history of inhibitors.

3.2 | Management of pain

172/343 (50%) PwH reported that their haemophilia caused them pain in the last 6 months. Stratified by severity ($n = 336$), pain in the last 6 months was reported by a significantly higher proportion of PwH with severe (122/180 [68%]; $p < .001$) or moderate (23/53 [43%]; $p = .014$) disease, compared with mild disease (25/103 [24%]) (Figure 1A). Among people with severe haemophilia, a slightly higher proportion of those who reported current or previous inhibitors reported experience of pain in the last 6 months (28/37 [76%]) than those who reported no history of inhibitors (85/130 [65%]). For all

severities, $\geq 55\%$ of PwH who reported pain in the last 6 months had pain “daily” or “once or a few times per week” (Figure 1B). 33/71 (46%) caregivers reported that their child’s haemophilia had caused their child pain in the last 6 months (Figure 1A), which did not differ between those with (9/18 [50%]) versus without (24/48 [50%]) current or previous inhibitors. Most children with pain in the last 6 months experienced pain less than once per week (Figure 1B).

Among PwH with haemophilia-related pain in the last 6 months or earlier (i.e., who had ever experienced haemophilia-related pain), 87/242 (36%) reported using treatment against haemophilia-related pain in the last 14 days. Stratified by severity ($n = 239$), compared with mild disease (6/33 [18%]), the proportion of PwH who reported using treatment in the last 14 days was higher, though not significantly, for those with moderate disease (15/42 [36%]; $p = .093$) and was significantly higher for those with severe disease (66/164 [40%]; $p = .016$) (Figure 2A). A higher proportion with mild disease (6/33 [18%]) reported that they had not used treatment, but they felt a need for it, compared with severe (8/164 [5%]) or moderate (<5/42 [<12%]) disease (not tested for significance). Among caregivers who reported that their child had ever experienced haemophilia-related pain, 8/48 (17%) reported that their child used treatment against pain related to haemophilia in the last 14 days (Figure 2A). Responses were similar for the subset of respondents in both surveys who reported pain in the last 6 months (Supplementary Figure S1).

In both surveys, over-the-counter (OTC) medication was reported to be the most frequently used treatment for haemophilia-related pain (Figure 2B). Each response alternative had a pop-up box listing all relevant medications in the drug category. Paracetamol was listed under OTC, although it may be prescribed and then subsidised for the patient/family.

Among PwH with severity data and caregivers, who reported that they/their child had ever experienced haemophilia-related pain ($n = 239$ and $n = 48$, respectively), $\geq 64\%$ reported that they had discussed their or their child’s pain problems at the HTC (Figure 3A), most frequently with a haematologist or haemophilia physician. Outside the HTC, pain was most frequently discussed with family or friends (Figure 3B). Among all PwH who had ever experienced haemophilia-related pain ($n = 242$), 149 (62%) felt that their pain was adequately addressed and treated at their HTC, but 37 (15%) did not (Supplementary Figure S2A). Among all respondents, $\leq 11\%$ felt that they or their

TABLE 2 Baseline demographics and characteristics (PwH survey)

Characteristic, n (%)	PwH by haemophilia severity			
	Mild n = 103	Moderate n = 53	Severe n = 180	Total N = 343 ^a
Age category				
16–19	9 (9)	6 (11)	17 (9)	32 (9)
20–29	13 (13)	5 (9)	24 (13)	45 (13)
30–39	19 (18)	7 (13)	44 (24)	71 (21)
40–49	11 (11)	11 (21)	28 (16)	50 (15)
50–59	18 (17)	10 (19)	36 (20)	67 (20)
60–69	15 (15)	9 (17)	16 (9)	40 (12)
70+	18 (17)	5 (9)	15 (8)	38 (11)
Type of haemophilia				
A	78 (76)	32 (60)	149 (83)	264 (77)
B	25 (24)	21 (40)	31 (17)	79 (23)
Inhibitors				
Currently has inhibitors	8 (5) ^{b,c}		10 (6)	15 (4)
Previously had inhibitors			27 (15)	30 (9)
Never had inhibitors	55 (53)	36 (68)	130 (72)	223 (65)
No answer ^d	44 (43)	13 (25)	13 (7)	75 (22)
Have you ever used factor concentrates to treat a bleed or in order to prevent a bleed from occurring?				
Yes	84 (82)	52 (98)	174 (97)	316 (92)
No	15 (15)	5 (2) ^b		20 (6)
No answer ^d	6 (2) ^b			7 (2)
If answering “yes” to the above: Do you or have you had regular preventive treatment (prophylaxis) to reduce the risk of bleeding?				
Currently and since early childhood	14 (17) ^c	9 (17)	82 (47)	92 (29)
Currently but not always		17 (33)	79 (45)	99 (31)
Earlier but not currently		8 (15)	10 (6) ^c	25 (8)
No	69 (82)	16 (31)		93 (29)
No answer ^d	6 (2) ^b			7 (2)

Note: Respondents were from Sweden, Denmark, and Finland. Haemophilia severity was self-reported and defined as mild: >5%–<40% basal factor; moderate: 1%–5% basal factor; severe: <1% basal factor. Percentages may not sum to 100% due to rounding.

^aAn additional seven respondents marked “Don’t know/prefer not to answer” on severity of haemophilia.

^bCategories merged since there were <5 respondents per subgroup.

^cResponse categories merged since there were <5 responses for one or more options.

^dSurvey response “Don’t know/prefer not to answer.” PwH, people with haemophilia.

child needed more painkillers than their doctor prescribed (Supplementary Figure S2B).

3.3 | Management of depression and anxiety

Depression or anxiety due to their haemophilia was reported by 28% (96/343) of PwH. This was more common in people with severe (63/180 [35%]) or moderate (14/53 [26%]) disease, compared with people with mild disease (16/103 [16%]) (Figure 4). Overall, there was a significant association ($p < .001$) between disease severity and experiences of depression and anxiety. Depression or anxiety was reported in 76/172 (44%) PwH with haemophilia-related pain in the last 6 months,

which was similar across disease severities (mild: 12/25 [48%]; moderate: 10/23 [43%]; severe: 52/122 [43%]).

Among PwH with haemophilia-related depression or anxiety currently or in the past (i.e., who had ever experienced depression or anxiety; $n = 127$), 19 (15%) had used treatment or counselling in the last 6 months, and an additional 16 (13%) felt a need for it; 31 (24%) felt their depression/anxiety was adequately addressed and treated at their HTC, but 42 (33%) did not. Few (<5/71 [$<7\%$]) caregivers reported that their child was using or had in the last 6 months used treatment and/or counselling due to depression or anxiety, but 9/71 (13%) thought their child had a need for it. Most PwH and children of caregivers did not feel very anxious about having a bleed or depressed about their haemophilia (Supplementary Figure S3).

TABLE 3 Baseline demographics and characteristics (caregiver survey)

Characteristic, n (%)	Children with haemophilia (N = 71)
Age category	
5–9	32 (45)
10–17	39 (55)
Type of haemophilia	
A	57 (80)
B	14 (20)
Haemophilia severity	
Mild	15 (21)
Moderate	17 (24)
Severe	39 (55)
Inhibitors	
Currently has inhibitors	6 (8)
Previously had inhibitors	12 (17)
Never had inhibitors	48 (68)
No answer ^a	5 (7)
Has your child ever used factor concentrates to treat a bleed or in order to prevent a bleed from occurring?	
Yes	65 (92)
No	6 (8) ^b
No answer ^a	
If answering “yes” to the above: Has your child at any time for at least a year had regular preventive treatment (prophylaxis) to reduce the risk of bleeding?	
Yes, currently	51 (78) ^b
Yes, earlier	
No	14 (22) ^b
No answer ^a	

Respondents were from Sweden, Denmark, and Finland. Haemophilia severity was caregiver-reported and defined as mild: >5%–<40% basal factor; moderate: 1%–5% basal factor; severe: <1% basal factor.

^aSurvey response “Don’t know/prefer not to answer.”

^bResponse categories merged since there were <5 responses for one or more options.

When analysing the patient and caregiver responses regarding pain, anxiety and depression, according to age groups, we found no unambiguous differences (data not shown).

3.4 | Health-related quality of life

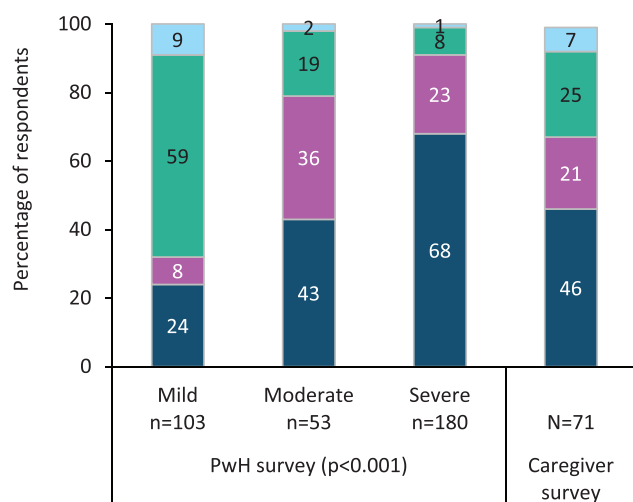
Overall, agreement was $\geq 72\%$ for statements asking if PwH or caregivers’ children coped well with their haemophilia, if their treatment functioned well, and if they liked visiting their HTC or clinic (Supplementary Figure S4). Respondents generally felt that current treatment allows them or their child to work or study, but some reported impacts on their social life and leisure activities (46% and 48%, respectively, for people with severe haemophilia [$n = 180$]). Impacts on work/study, leisure activities, social activities and social life increased with haemophilia severity, and there was a significant association ($p < .001$) between disease severity and answers to these questions

(Supplementary Figure S5A). Some PwH also expressed concern about the impact of their haemophilia on other members of their family (42% of people with severe haemophilia; Supplementary Figure S5A).

3.5 | EuroQol 5-dimension instrument

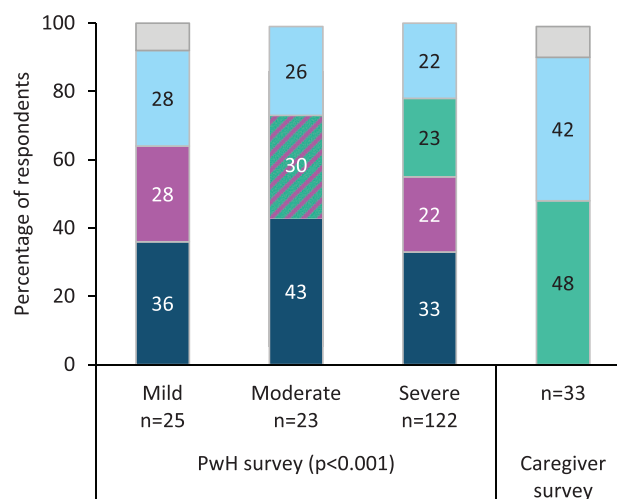
Among PwH, EQ-5D utility values decreased with increasing disease severity (Figure 5A), with a statistically significant difference between disease severities ($p < .001$). EQ VAS score showed a similar pattern across disease severities, although this was not statistically significant ($p = .094$; Figure 5B). There was a statistically significant negative association between disease severity and the pain dimension ($p < .001$), but not the anxiety dimension ($p = .201$), of the EQ-5D (Figure 5C,D). Mean total EQ-5D utility value and EQ VAS score among children with haemophilia ($n = 71$), according to their caregivers, were .81 (SD = .28) and 87 (SD = 13.1), respectively (Figure 5A,B).

(A) Has your/your child's haemophilia caused you/ him/her pain in the last 6 months?



■ Don't know/prefer not to answer
■ No, never
■ No, but I have/my child has had problems with pain before
■ Yes

(B) How often have you/has your child had pain because of your/his/her haemophilia in the last 6 months? (Respondents with pain in the last 6 months)^{a,b}



■ Daily
■ Once or a few times per week
■ Once or a few times per month
■ Less often than once per month
■ Data not shown (n<5)

FIGURE 1 Questions on experience of pain. (A) Has your/your child's haemophilia caused you/him/her pain in the last 6 months? (B) How often have you/has your child had pain because of your/his/her haemophilia in the last 6 months? (Respondents with pain in the last 6 months).^{a,b} Respondents were from Sweden, Denmark and Finland. Seven respondents in the PwH survey marked "Don't know/prefer not to answer" on severity of haemophilia. Numbers may not sum to 100% due to rounding. ^aIn the PwH survey, there were <5 (20%) respondents to "Once or a few times per month" for mild disease, so these data are not shown; answers "Once or a few times per week" and "Once or a few times per month" were merged for moderate disease, since each was answered by <5 (<22%) respondents. ^bIn the caregiver survey, there were <5 (<15%) respondents to "Daily" and "Once or a few times per week" for moderate disease, even after merging, so these are not shown. PwH, people with haemophilia

3.6 | HTC survey

Most HTCs reported that they refer to the Nordic Guidelines for treatment of pain in PwH, address pain as part of regular visits and encourage PwH to contact the HTC if they experience pain in between planned visits. All 5 reported using team-based management of pain, all including a physician and physiotherapist, with 3/5 also including a nurse. Furthermore, 4/5 reported that they refer PwH with chronic pain syndrome to a specialist. Pain medications were reported to be broadly prescribed by HTCs, varying by haemophilia severity, but there was a broad range of perceptions with respect to how pain is managed in PwH. Overall, 4/5 agreed that patients' pain is adequately treated at the HTC.

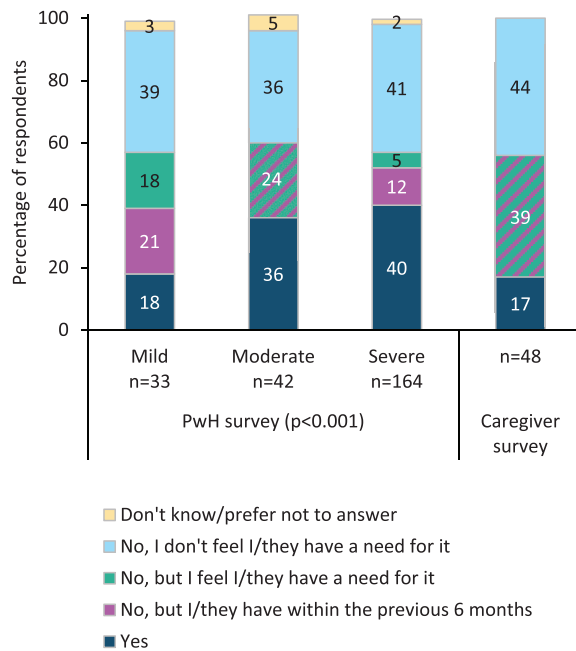
All HTCs reported that they apply an opportunistic approach toward the management of depression and anxiety. However, only 2/5 encourage PwH to contact the HTC if they experience these symptoms between planned visits. All HTCs reported involving multiple professions in the treatment of depression and anxiety, but inclusion of psychologists or psychotherapists, and collaboration with primary care,

was reported by 2/5 and 1/5 HTCs, respectively. HTCs reported that ≤10% of patients ask for medical treatment or use psychosocial therapy for depression and/or anxiety. Overall, only 2 HTCs agreed that their patients' depression/anxiety is adequately treated at the HTC. However, 4/5 agreed slightly that depression and/or anxiety are more common among patients with severe haemophilia, and 3/5 agreed that these symptoms result in lower adherence in haemophilia treatment.

4 | DISCUSSION

PwH and caregivers who responded to the MIND survey reported pain, depression or anxiety related to haemophilia. Symptoms occurred more frequently with increasing haemophilia severity and may contribute to reported negative effects on quality of life. Overall, answers indicated that PwH, caregivers and HTCs generally felt that the management of pain related to haemophilia was satisfactory, but depression and anxiety may not be as satisfactorily addressed in clinical practice.

(A) Within the last 14 days, have you/your child used any treatment against pain related to haemophilia? (Respondents with pain in the last 6 months or earlier)^{a,b}



(B) Have you/your child used any of the following medical treatments against pain due to haemophilia? (PwH with pain in the last 6 months or earlier/caregivers indicating treatment against pain in the last 6 months)^{c-e}

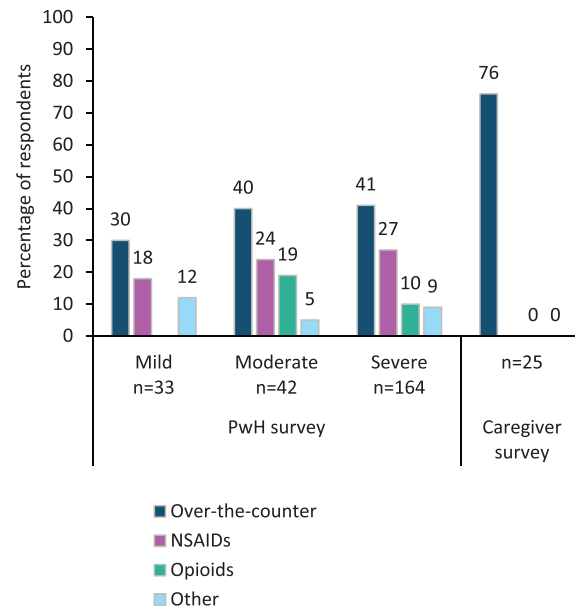


FIGURE 2 Questions on treatment of pain. (A) Within the last 14 days, have you/your child used any treatment against pain related to haemophilia? (Respondents with pain in the last 6 months or earlier).^{a,b} (B) Have you/your child used any of the following medical treatments against pain due to haemophilia? (PwH with pain in the last 6 months or earlier/caregivers indicating treatment against pain in the last 6 months).^{c-e} Respondents were from Sweden, Denmark and Finland. Seven respondents in the PwH survey marked “Don’t know/prefer not to answer” on severity of haemophilia. Numbers may not sum to 100% due to rounding. The full list of medical treatment options given in each country are available on request. ^aIn the PwH survey, there were <5 (<12%) respondents to “No, but I feel I have a need for it” for moderate disease, so it was merged with “No, but I have within the previous 6 months”; ^bIn the caregiver survey, there were <5 (<10%) respondents to “No, but I feel they have a need for it,” so it was merged with “No, but they have within the last 6 months”; ^cRespondents could tick all applicable options; “Steroids” was included in the list of options, but was not answered by ≥ 5 respondents in any category. ^dIn the PwH survey, “Opioids” is not shown for mild disease, since it was answered by <5 (<15%) respondents. ^eIn the caregiver survey, “NSAIDs” is not shown, since it was answered by <5 (<20%) respondents. NSAID, non-steroidal anti-inflammatory drug. PwH, people with haemophilia

Of the PwH survey respondents, around 50% reported experiencing pain in the last 6 months, the majority of whom had pain at least once a week. Nevertheless, over 60% of PwH were satisfied with the management of their pain overall and results were similar in the caregiver survey. Similar pain management satisfaction rates were found in a previous study evaluating the experience of chronic pain patients.¹⁷ This contrasts with a similar survey carried out in Italian PwH, in which pain was found to be unsatisfactorily addressed.¹⁸ OTC medication was the most frequently reported pharmaceutical intervention, followed by non-steroidal anti-inflammatory drugs (NSAIDs). OTC medications, for example paracetamol, may also be prescribed by haemophilia treaters with full or partial reimbursement; this is likely to be the case for most PwH with regular HTC contact. It is not clear whether respondents were referring to medications they are prescribed that are also available OTC, or whether they supplement medication provided by HTCs between visits. Overall, there was alignment between the three surveys, indicating that haemophilia-related pain is generally managed

well, in line with Nordic Haemophilia Guidelines,⁵ with a small proportion of PwH reporting that their pain is not adequately addressed.

There may be an unmet need in the management of haemophilia-related pain among people with mild haemophilia, since a higher proportion of people with mild (compared with moderate or severe) haemophilia who had experienced pain reported that they felt a need for treatment. This result was unexpected and may be due to potential selection bias in the survey. However, the impact of mild and moderate disease and best standards of care have been identified as an important gap in haemophilia research.¹⁹⁻²¹

Symptoms of depression or anxiety were less frequent than pain among PwH and caregivers overall but were more common among PwH who experienced pain. Depression and anxiety have been linked to previous urgent hospital visits, bleeding episodes, pain and perceived quality of life.⁸ This may explain the association between disease severity and depression or anxiety, as well as the higher frequency of these symptoms among PwH who reported experiencing

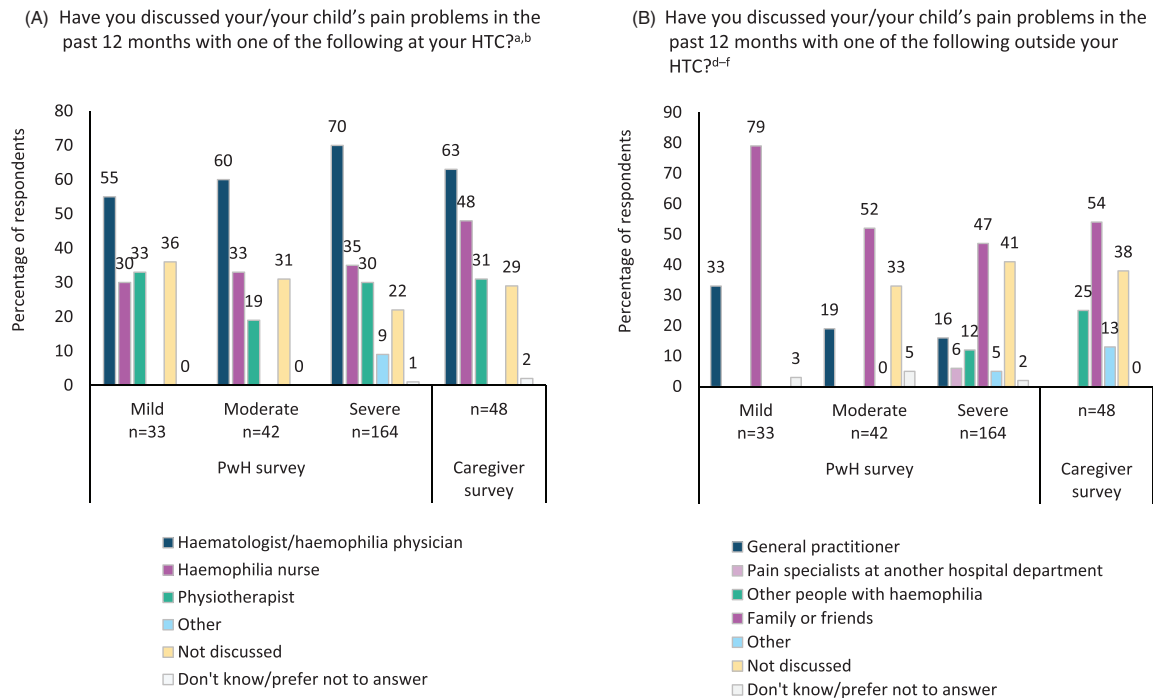
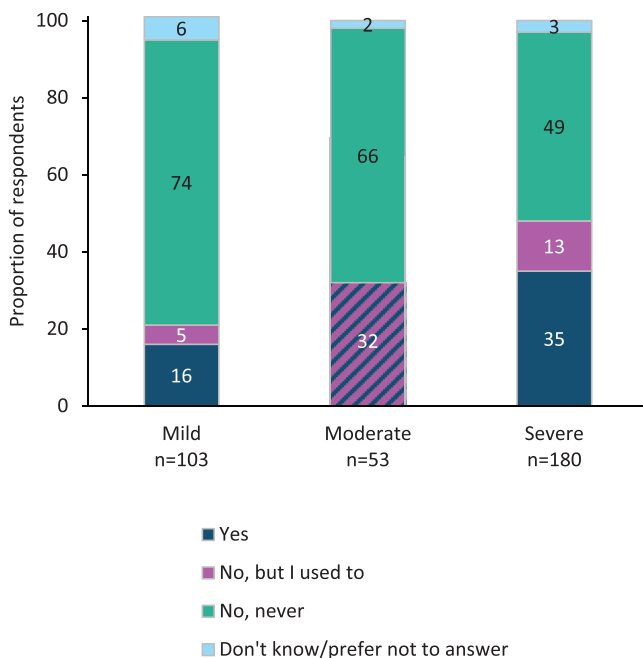


FIGURE 3 Questions on discussing pain problems (respondents with pain in the last 6 months or earlier). (A) Have you discussed your/your child's pain problems in the past 12 months with one of the following at your HTC?^{a,b} (B) Have you discussed your/your child's pain problems in the past 12 months with one of the following outside your HTC?^{d-f} Respondents were from Sweden, Denmark and Finland. Seven respondents in the PwH survey marked "Don't know/prefer not to answer" on severity of haemophilia. ^a Respondents could tick all applicable options; "Psychotherapists" was included in the list of options, but was not answered by ≥ 5 respondents in any category. ^b In the PwH survey, "Other" is not shown for mild or moderate disease, since it was answered by < 5 ($< 15\%$ and $< 12\%$, respectively) respondents. ^c In the caregiver survey, "Other" is not shown since this was answered by < 5 ($< 10\%$) respondents. ^d Respondents could tick all applicable options; "Online chat groups/social networking" was included in the list of options, but was not answered by ≥ 5 respondents in any category. ^e In the PwH survey, "Pain specialists at another hospital department," "Other people with haemophilia," "Other" and "None" are not shown for mild disease, and "Pain specialists at another hospital department" and "Other people with haemophilia" are not shown for moderate disease, since each was answered by < 5 ($< 15\%$ and $< 12\%$, respectively) respondents. ^f In the caregiver survey, "General practitioner," "Pain specialists at another hospital department" and "Online chat groups/social networking" are not shown since each was answered by < 5 ($< 10\%$) respondents. HTC, haemophilia treatment centre; PwH, people with haemophilia



pain in the last 6 months compared with those who did not. Both the PwH and HTC survey results indicated that depression or anxiety were not managed as well as pain. A third of PwH respondents reported that depression or anxiety was not adequately addressed by their HTC. This finding is concerning, since some HTCs agreed that depression or anxiety result in lower adherence to haemophilia treatment, which is supported by recent cross-sectional survey data in the US.²² This supports the need for improved guidelines with a more proactive and structured approach for the identification and management of

FIGURE 4 Questions on feelings of depression or anxiety: Have you experienced feelings of depression or anxiety because of your haemophilia? (PwH survey only) Respondents were from Sweden, Denmark and Finland. Pearson's chi-square test of independence showed a significant association between disease severity and response ($p < .001$). There were < 5 ($< 9\%$) respondents to "No, but I used to" for moderate disease, so this was merged with "Yes." Seven respondents marked "Don't know/prefer not to answer" on severity of haemophilia. Numbers may not sum to 100% due to rounding. PwH, people with haemophilia

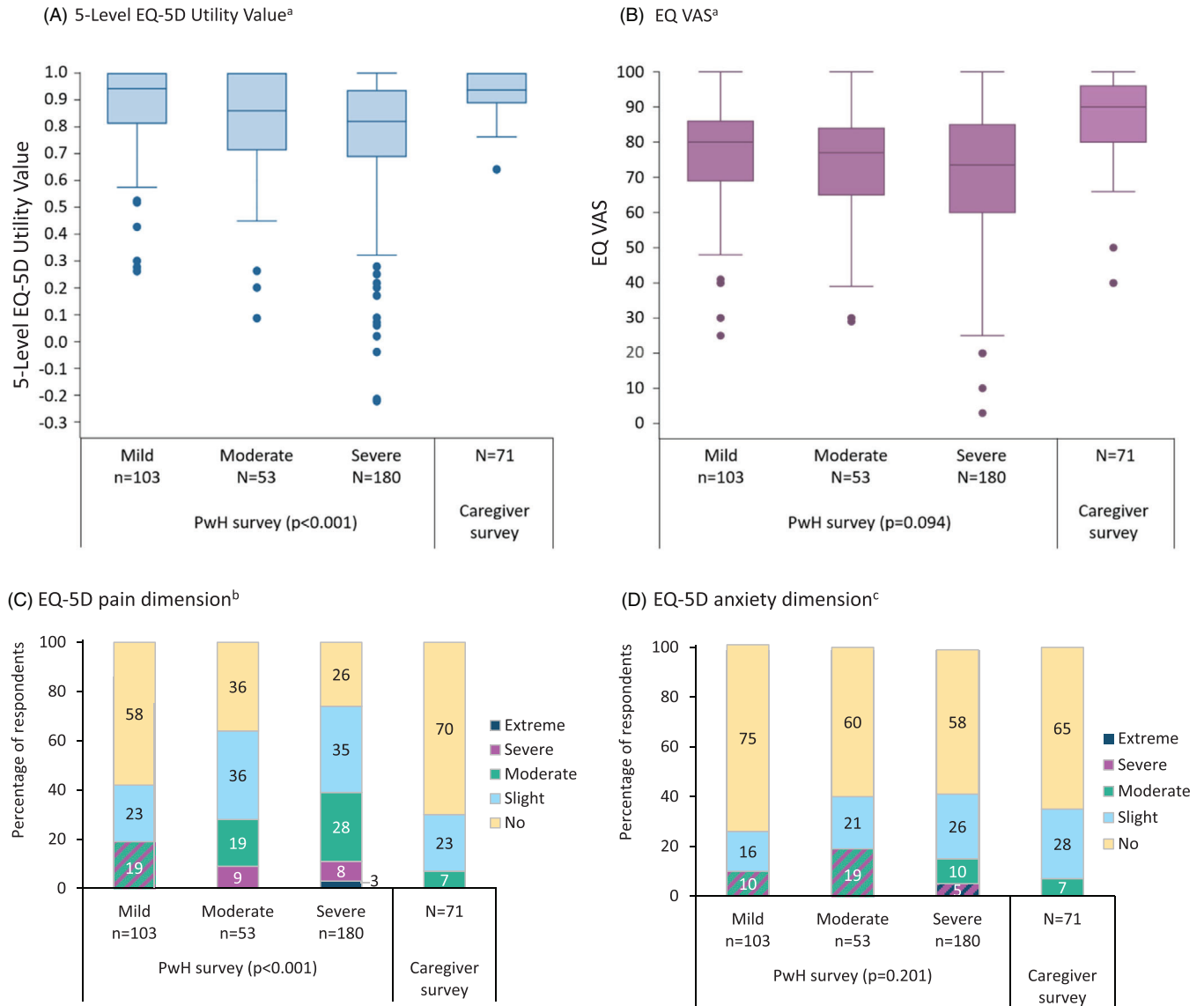


FIGURE 5 Quality of life measured using the EQ-5D instrument. (A) 5-Level EQ-5D Utility Value^a (B) EQ VAS^a (C) EQ-5D pain dimension^b (D) EQ-5D anxiety dimension.^c Respondents were from Sweden, Denmark and Finland. Seven respondents in the PwH survey marked “Don’t know/prefer to not answer” on severity of haemophilia. Numbers may not sum to 100% due to rounding. ^aBox plots show median with surrounding quartiles 1 and 3 (the box), adjacent values representing highest/lowest observation within 1.5 times interquartile range, and outliers. ^bIn the PwH survey, there were <5 (<5%) respondents to “Severe” for mild disease, so this was merged with “Moderate”. ^cIn the PwH survey, there were <5 (<5%, 9%) respondents to “Severe” for mild and moderate disease, respectively, so this was merged with “Moderate”; and there were <5 (<9%) respondents to “Extreme” for severe disease, so this was merged with “Severe.” EQ-5D, EuroQol 5-Dimension; PwH, people with haemophilia; VAS, visual analogue scale

depression and anxiety symptoms, including counselling and individualised interventions.⁶

The impact of haemophilia on HRQoL is well documented.^{1,9,23} In questions about daily life, almost 50% of people with severe haemophilia felt that their haemophilia had an impact on their social life or leisure activities. Although the median EQ VAS score in PwH with mild disease was only marginally lower than population norms for Sweden and Denmark (83.3 and 83.7, respectively²⁴), for moderate or severe disease there was a greater difference in median VAS score compared with these norms. Pain, as measured by EQ-5D, was also

more frequent in severe haemophilia compared with moderate and mild haemophilia. Therefore, despite the wide availability of clotting factor replacements,²⁵ PwH—especially those with severe disease—were less likely to enjoy a quality of life comparable to people without haemophilia.

A strength of the study was the wide reach of the surveys within Nordic countries. PwH in Sweden are treated at one of three HTC, all of which were represented in the surveys, whilst 39% of PwH in Finland are treated at a single HTC,²⁶ which was also represented in the surveys. Additionally, the HTC survey was distributed to

investigators at each of the countries' HTC, except for one of the two HTCs in Denmark. Moreover, all participants were managed under the Nordic Haemophilia Guidelines, which should minimise differences in care between study participants in different countries.⁵

There are some limitations to the study, including the subjective relationship between haemophilia and experiences of depression and anxiety. Biases may have been introduced that make it less representative, especially as around two-thirds of invited PwH did not respond (although this is a similar response rate to that reported in other surveys of PwH^{7,27,28}) and reasons for non-participation were not collected as part of this study. For instance, mild haemophilia has been less widely explored,¹⁹ so people with mild disease may have been especially interested in the opportunity to discuss their experiences. PwH who experience pain, depression or anxiety may also be more likely to participate in a survey about these symptoms. The wider reach of the Swedish survey compared to the other countries may also have introduced a bias. Furthermore, results are likely to be generalisable only to countries with similarly high resource availability. The study was performed before or soon after the extended half-life products had been launched in the Nordic countries. Therefore, patient experiences were mainly based on therapies with standard half-life factor products.

5 | CONCLUSIONS

Results from the MIND surveys indicate that PwH are frequently affected by haemophilia related pain as well as depression and anxiety, though to a somewhat lesser extent. This is observed also in mild haemophilia and the frequency of these conditions and their impact on quality of life increases with disease severity. PwH and HTCs recognise that pain is generally managed well, although there might be an unmet need for people with mild haemophilia. Management of depression and anxiety is not always satisfactory and additional guidelines in this area may be beneficial; this shortcoming is already recognised by clinicians at Nordic HTCs. Implementation of standardised procedures to further address the needs of PwH may result in improvements in their quality of life.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Substantial contributions to study conception and design: Katarina Steen Carlsson, Bent Winding, Sofia Bergenstråle, Stefan Lethagen; substantial contributions to analysis and interpretation of the data: Katarina Steen Carlsson, Bent Winding, Jan Astermark, Fariba Baghaei, Elisabeth Brodin, Eva Funding, Margareta Holmström, Klaus Österholm, Sofia Bergenstråle, Emelie Andersson, Stefan Lethagen; drafting the article or revising it critically for important intellectual content: Katarina Steen Carlsson, Bent Winding, Jan Astermark, Fariba Baghaei, Elisabeth Brodin, Eva Funding, Margareta Holmström, Klaus Österholm, Sofia Bergenstråle, Emelie Andersson, Stefan Lethagen; final approval of the version of the article to be published: Katarina Steen Carlsson, Bent Winding, Jan Astermark, Fariba Baghaei, Elisabeth Brodin, Eva Funding, Margareta Holmström, Klaus Österholm, Sofia Bergenstråle, Emelie Andersson, Stefan Lethagen.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study were collected and analysed by the Swedish Institute for Health Economics. Ethical approval was obtained for a limited number of named persons to access data. The aggregated summary data in the current study are available from the corresponding author, on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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