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Joint health and treatment modalities in Nordic patients with moderate haemophilia A and B – The MoHem study

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Abstract

Introduction: The prevalence of arthropathy in moderate haemophilia A (MHA) and B (MHB) is not well known.

Aim: We evaluated joint health in Nordic patients in relation to their treatment modality.

Methods: A cross-sectional, multicentre study covering MHA and MHB in Sweden, Finland and Norway. Arthropathy was evaluated by ultrasound (HEAD-US) and Haemophilia Joint Health Score (HJHS).

Results: We report on 145 patients: median age 28 years (IQR 13-52) and 61% MHA. Baseline factor VIII/factor IX activity (FVIII/FIX:C) was 2 IU/dL (median) (IQR 2-4): lower for MHB (2 IU/dL, IQR 1-2) than MHA (3 IU/dL, IQR 2-4) ($P < .01$). Eighty-five per cent of MHA and 73% MHB had a history of haemarthrosis ($P = .07$). Age at first joint bleed was lower for MHA (5 years [median], IQR 3-7) than MHB (7 years, IQR 5-12) ($P = .01$). Thirty-eight per cent received prophylaxis, started at median 10 years of age (IQR 4-24). Median joint bleeds and serious other bleeds during the last 12 months were both zero (IQR 0-1). Total HEAD-US captured 0/48 points (median) (IQR 0-2) and HJHS 4/120 points (IQR 1-10) with strong correlation between them ($r = .72$). FVIII/FIX:C ≤ 3 IU/dL was associated with higher HJHS ($P = .04$). Fifteen per cent had undergone orthopaedic surgery.

Conclusion: The current joint health in Nordic moderate haemophilia patients was rather good, but a subgroup had severe arthropathy. FVIII/FIX:C ≤ 3 IU/dL and MHA were associated with a more severe bleeding phenotype. We suggest primary prophylaxis to all patients with FVIII/FIX:C ≤ 3 IU/dL.

KEYWORDS

arthropathy, joint score, moderate haemophilia A, moderate haemophilia B, prophylaxis, ultrasound

1 | INTRODUCTION

Arthropathy is the main long-term complication for patients with haemophilia. Prophylactic replacement therapy has significantly reduced the prevalence in severe haemophilia,[1-3] and regular prophylaxis is now the standard of care. This has not been implemented in moderate haemophilia, and previous publications have suggested that these patients are undertreated. In a systematic review, Di Minno et al[4] reported that 15%-77% of patients with moderate haemophilia had arthropathy. Based on observations in a Dutch study, den Uijl et al[5] proposed that patients with moderate haemophilia and residual factor level <3 IU/dL should receive prophylaxis after their first joint bleed, if this occurred within 5 years of age. More recently, the THUNDER study reported high bleeding rates among patients with moderate haemophilia A in the UK.[6] Haemophilia A and B have usually been considered as indistinguishable diagnoses, but there are data suggesting that patients with severe haemophilia B have a less severe bleeding phenotype.[7,8] Data comparing the clinical phenotypes in moderate haemophilia A (MHA) and B (MHB), however, are scarce with no clear difference between them.[8,9]

The Nordic countries have long traditions of prophylaxis in haemophilia, pioneered by Sweden.[1] Our study aimed to evaluate the joint health in Nordic patients with MHA and MHB in relation to their treatment modality.

2 | MATERIALS AND METHODS

The MoHem study is a cross-sectional, multicentre study that covers MHA and MHB (factor VIII/factor IX activity [FVIII/FIX:C] 1-5 IU/dL)[10] of all ages from Sweden, Finland and Norway. There were no exclusion criteria. The study received approval by national ethical committees in all three countries and was performed in accordance with the Helsinki Declaration.[11] All participants signed informed consents, parents on behalf of the children. The Nordic haemophilia care is organized through Haemophilia Comprehensive Care Centres (HCCC) approved by the European Association for Haemophilia and Allied Disorders. The enrolment took place at the HCCCs in Oslo, Malmö, Gothenburg, Stockholm and Helsinki between January 2017 and October 2019. In Sweden and Norway, these centres manage all patients with haemophilia. In Finland, there are four Haemophilia Treatment Centres across the country, while approximately 60% of the patients are managed at the HCCC in Helsinki. Study participants were recruited consecutively as part of their regular follow-up and from national registries.

Data on treatment and medical history were self-reported and obtained from clinical records. Definitions of "joint bleed" and "on-demand" vs "prophylactic" treatment were according to recommendations from the Scientific and Standardization Committee (SCC) of the International Society on Thrombosis and Haemostasis (ISTH),[10] and bleeds were recorded if they had required clotting factor replacement therapy. The ISTH-SSC bleeding assessment tool (ISTH-BAT)[12] was used to register the patients' lifelong cumulative bleeding history.

Arthropathy in index joints (elbows, knees and ankles) was evaluated by Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)[13] and Haemophilia Joint Health Score (HJHS)[14] 2.1 for patients above 5 years of age. HEAD-US contains a score of 0-8 points for each examined joint. HJHS 2.1 contains 0-20 points per joint, reaching a total score of 120 points, gait score excluded. In order to compare results assessed by HEAD-US and HJHS, we used both scores as cumulative adding the points from all six examined joints. Joints that had undergone arthroplasties or arthrodesis were excluded on HEAD-US, and these patients are therefore missing from the total score. HJHS was scored in a regular way in all joints. Physicians or physiotherapists who had attended HEAD-US preceptorship courses performed ultrasound, and physiotherapists affiliated to the HCCCs performed HJHS. For most patients, HEAD-US and HJHS were done at enrolment. For practical reasons, examinations performed within 1 year were accepted. Either one or two persons, according to access of qualified performers at the HCCC, performed HEAD-US and HJHS.

The results were analysed together as a Nordic study group and subdivided in four groups according to age (<15, 15-34, 35-54 and ≥55 years). Patients on prophylaxis were compared with those treated on-demand, and MHA was compared with MHB. The results were also compared across residual FVIII/FIX:C based on historical values analysed locally at each study centre. For patients with several measurements, the lowest available value was used for classification. These baseline FVIII/FIX:C had been analysed both by one-stage and chromogenic assays.

2.1 | Statistical analyses

Statistical analyses used were mainly descriptive. Most parameters had a skewed distribution. Continuous data are summarized as medians and interquartile ranges (IQR), and categorical data are presented as numbers and percentages. We used Mann-Whitney *U* test and Spearman's correlation for comparison between continuous variables with skewed distribution. Student's *t* test was used for normally distributed data. For comparison between categorical data, we used chi-square test. A *P*-value < .05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 26.

3 | RESULTS

We enrolled 145 patients with MHA (n = 89) and MHB (n = 56), representing 63% of the population of patients with moderate haemophilia attending the five HCCCs. Median age was 28 years (IQR 13-52) and 89 (61%) had MHA (Table 1). The patients not attending the study were older (41 years, IQR 27-56) (*P* < .01), but the prevalence of MHA (48 [57%]) was similar to the study group (*P* = .53). Non-enrolment was mainly due to practical reasons, such as long journey to the HCCC.

TABLE 1 Patient characteristics for the MoHem study

	All patients (N = 145)
Age at enrolment (y)	28 (13-52)
Haemophilia A	89 (61%)
Baseline FVIII or FIX activity (IU/dL)	2 (2-4)
Family history of haemophilia	102 (70%)
Age at diagnosis (y)	2 (0-5)
History of haemarthrosis	117 (81%)
Age at first joint bleed[a] (y)	5 (3-8)
Currently on prophylaxis	55 (38%)
Age at start of prophylaxis (y)	10 (4-24)
FVIII/FIX prophylactic dose (IU/kg/wk)	55 (42-82)
History of inhibitor	3 (2%)
HCV-positive (Ab+/PCR+)	8 (6%)
HIV-positive	2 (1%)

Note: Numbers (%) or medians (interquartile range).

Abbreviations: FVIII, factor VIII; FIX, factor IX; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

The number of patients (n) is noted if it deviates from the total number: [a]n = 111/117.

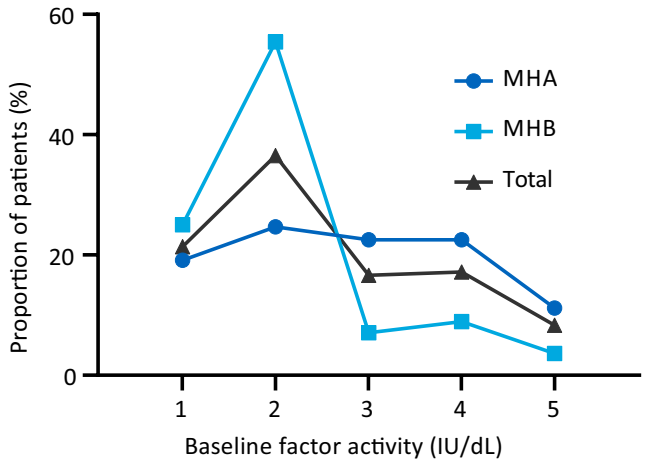

FIGURE 1 Baseline factor activity levels in the MoHem study (N = 145). The proportions of patients with moderate haemophilia A (MHA) and B (MHB) according to baseline factor activity (1-5 IU/dL) are presented as separate curves

Overall, the baseline FVIII/FIX:C was 2 IU/dL (median) (IQR 2-4) (Figure 1, Table 1). However, MHB had lower levels than MHA ($P < .01$) (Table 2). One hundred and four patients (72%) had FVIII/FIX:C ≤ 3 IU/dL, 55 (53%) of these had MHA. Age at diagnosis was 2 years (median) (IQR 0-5) and lower for patients with a family history of haemophilia than others (1 year, IQR 0-4 vs 2 years, IQR 1-7) ($P < .01$).

3.1 | Treatment and bleeding history

Fifty-five patients (38%) were receiving prophylactic replacement therapy (Table 1). Age at start of prophylaxis was 10 years (median) (IQR 4-24) and correlated strongly with age at enrolment ($r = .87$, $P < .001$) (Figure 2). Nine patients (16%) initiated prophylaxis <3 years of age, seven of whom were in the youngest age group (<15 years). The use of prophylaxis was equally distributed between MHA and MHB, and not related to baseline FVIII/FIX:C (Table 2). The median prophylactic dose was 55 IU/kg/wk (IQR 42-82) (Table 1). The annual factor consumption was higher among patients on prophylaxis (2924 IU/kg/y [median], IQR 2094-4203) compared with those treated on-demand (27 IU/kg/y, IQR 0-130) ($P < .001$). Overall, the annual factor consumption was equal between MHA and MHB (Table 2). However, among those with FVIII/FIX:C ≤ 3 IU/dL, the consumption was lower for MHB (83 IU/kg/y [median], IQR 0-2055) than MHA (653 IU/kg/y, IQR 99-3524) ($P = .02$). The annual prophylactic consumption was equal between MHA and MHB. During the last 12 months, 34 patients (25%) did not use any replacement therapy. This was irrespective of diagnosis ($P = .32$) and FVIII/FIX:C ($P = .78$). Furthermore, during the same period, 64 patients (44%) used tranexamic acid and four patients (5% among MHA) used desmopressin.

One hundred and seventeen patients (81%) had a history of haemarthrosis (Table 1): 76 (85%) with MHA and 41 (73%) with MHB ($P = .07$) (Table 2). For patients with FVIII/FIX:C ≤ 3 IU/dL, this difference between MHA and MHB was statistically significant (51 [93%] vs 37 [76%]) ($P = .02$). Median age at first joint bleed was 5 years (IQR 3-8) for the whole study group (Table 1). However, patients with MHA ($P = .01$) and those with FVIII/FIX:C ≤ 3 IU/dL ($P = .03$) experienced their first joint bleed at a younger age (Table 2). Overall, age at first joint bleed did not depend on mode of treatment ($P = .16$). Among the youngest patients (<15 years), however, prophylaxis was associated with a younger age at first joint bleed (3 years (median), IQR 1-4 vs 5 years, IQR 4-7) ($P < .01$).

Bleeding frequency was low: median number of joint bleeds and serious other bleeds during the last 12 months were both zero (IQR 0-1). There were more joint bleeds among MHA than MHB ($P = .02$) (Table 2). The number of joint bleeds did not depend on mode of treatment ($P = .57$). Ninety-nine patients (68%) had zero joint bleeds during the last 12 months: more commonly among MHB (44 [79%]) than MHA (55 [62%]) ($P = .04$). ISTH-BAT score was 14 points (median) (IQR 8-19) for the whole study group. There were no differences between type of haemophilia, treatment modality or baseline FVIII/FIX:C.

3.2 | Arthropathy

One hundred and eighteen patients were evaluated by HEAD-US, and 135 were evaluated by HJHS. Total HEAD-US (n = 109) captured 0 points (median) (IQR 0-2) and total HJHS 4 points (IQR 1-10). Patients with FVIII/FIX:C ≤ 3 IU/dL had higher HJHS than those with levels > 3 IU/dL ($P = .04$) (Table 2). This was not observed with HEAD-US. Both HEAD-US and HJHS were equal between MHA and MHB and irrespective of mode of treatment. Sixty-one patients (56%) had zero points on HEAD-US, and 76 (70%) had 0-1

TABLE 2 Outcome in moderate haemophilia A (MHA) vs B (MHB) and according to baseline factor VIII/factor IX activity (≤3 vs >3 IU/dL)

	MHA (n = 89)	MHB (n = 56)	*P*-value	≤3 IU/dL (n = 104)	>3 IU/dL (n = 41)	*P*-value
Age at enrolment (y)	27 (12-51)	28 (15-57)	.48	27 (13-50)	30 (13-59)	.40
Baseline factor activity (IU/dL)	3 (2-4)	2 (1-2)	<.01	-	-	-
Haemophilia A	-	-	-	55 (53%)	34 (83%)	<.01
History of haemarthrosis	76 (85%)	41 (73%)	.07	88 (85%)	29 (71%)	.06
Age at first joint bleed[a] (y)	5 (3-7)	7 (5-12)	.01	5 (3-7)	7 (4-10)	.03
Currently on prophylaxis	34 (38%)	21 (38%)	.93	43 (41%)	12 (29%)	.18
Age at start of prophylaxis (y)	10 (4-22)	10 (6-37)	.65	9 (4-23)	17 (9-47)	.11
Annual factor consumption[b] (IU/kg/y)	333 (18-2600)	88 (0-2109)	.14	344 (15-2670)	82 (0-2179)	.78
Joint bleeds during the last 12 mo	0 (0-1)	0 (0-0)	.02	0 (0-1)	0 (0-0)	.09
Other bleeds during the last 12 mo	0 (0-1)	0 (0-0)	.81	0 (0-1)	0 (0-1)	.90
ISTH-BAT	14 (8-20)	13 (8-18)	.32	13 (8-19)	14 (8-18)	.98
HEAD-US total[c] (0-48 points)	0 (0-2)	0 (0-2)	.58	0 (0-2)	0 (0-2)	.88
HJHS total[d] (0-120 points)	2 (0-10)	4 (1-9)	.30	4 (1-10)	1 (0-9)	.04
Orthopaedic surgery	16 (18%)	6 (11%)	.37	16 (15%)	6 (15%)	.93

Note: Numbers (%) or medians (interquartile range).

Abbreviations: HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound; HJHS, Haemophilia Joint Health Score; ISTH-BAT, International Society on Thrombosis and Haemostasis bleeding assessment tool.

The number of patients (n) is noted if it deviates from the total number: [a]n = 72/76 (MHA), 39/41 (MHB), 84/88 (≤3 IU/dL) and 27/29 (>3 IU/dL); [b]n = 83/89 (MHA), 55/56 (MHB), 100/104 (≤3 IU/dL) and 38/41 (>3 IU/dL); [c]n = 66/89 (MHA), 43/56 (MHB), 76/104 (≤3 IU/dL) and 33/41 (>3 IU/dL); [d]n = 82/89 (MHA), 53/56 (MHB), 98/104 (≤3 IU/dL) and 37/41 (>3 IU/dL).

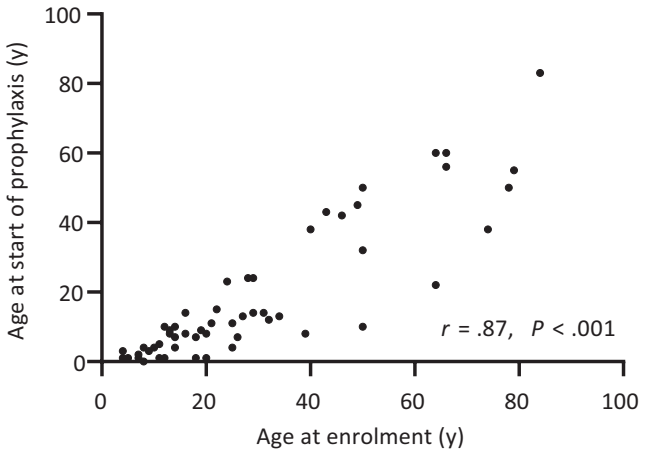

FIGURE 2 Scatter plot demonstrating Spearman's correlation (*r*) between age at start of prophylaxis and age at enrolment (n = 55)

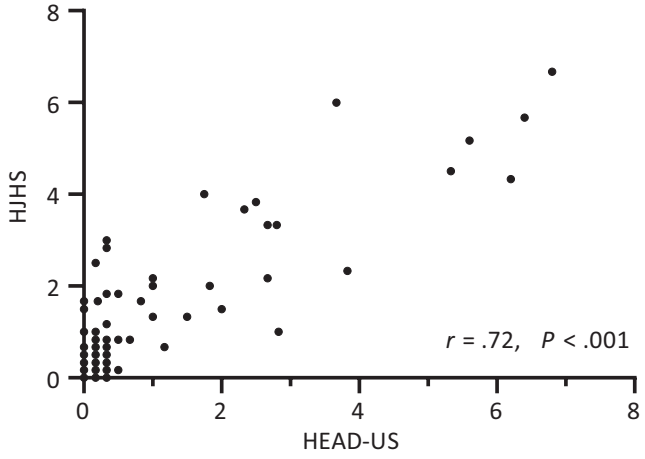

FIGURE 3 Scatter plot demonstrating Spearman's correlation (*r*) between mean joint scores assessed by Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and Haemophilia Joint Health Score (HJHS) (n = 118)

point. Sixty-seven patients (50%) had HJHS 0-3 points, and 101 (75%) had <10/120 points. Correlation between mean joint scores assessed by HEAD-US and HJHS was strong (r = .72, P < .001) (Figure 3), and 52 patients (79%) among those with 0-3 points on HJHS had zero points on HEAD-US. Both HEAD-US and HJHS increased by age (HEAD-US: r = .69, P < .001 and HJHS: r = .72, P < .001). When divided in age groups, HJHS was higher among patients on prophylaxis compared with those treated on-demand (Figure 4). Such comparison was difficult to capture in HEAD-US due to low numbers.

Twenty-two patients (15%) had undergone orthopaedic surgery due to arthropathy, equally distributed between MHA and MHB, baseline FVIII/FIX:C (Table 2), and mode of treatment. Subclassification according to age was difficult due to low numbers. However, orthopaedic surgery was more frequent in the prophylaxis group (75% [6/8] vs 17% [3/18]) (P < .01) in the age group 35-54 years. Ten patients had undergone surgery in more than one joint. Knee arthroplasties were most frequent and accounted for 18

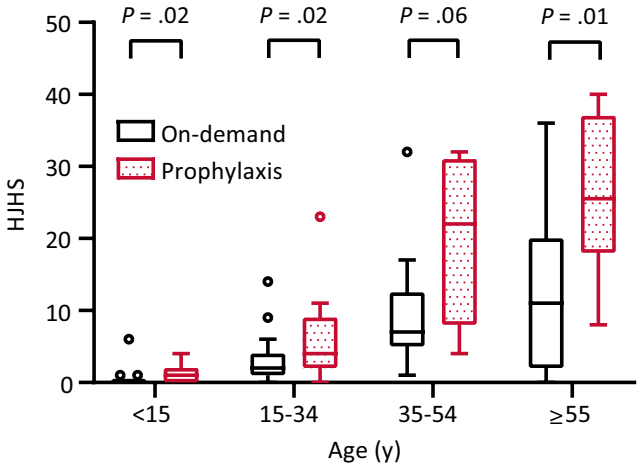

FIGURE 4 Box plot of Haemophilia Joint Health Score (HJHS) according to treatment method and age groups (n = 135). The lines represent median values, the boxes are interquartile ranges (IQR), and the whiskers are the lowest or highest observations still within 1.5 IQR of the lower or higher quartiles. Outliers are plotted as individual points. HJHS was higher among patients on prophylaxis vs on-demand

joints in 14 patients, followed by ankle arthrodesis in 12 joints in 11 patients.

4 | DISCUSSION

The MoHem study addresses joint health and treatment modalities in Nordic patients with MHA and MHB. We found an overall low score for HEAD-US and HJHS, and 38% were currently on prophylaxis. Baseline FVIII/FIX:C ≤ 3 IU/dL and MHA were associated with a more severe bleeding phenotype.

Through a Nordic collaboration, we have collected data on almost twofold as many patients as the Dutch study by den Uijl et al.[5] Our participants were slightly younger (median 28 vs 37 years of age) and baseline FVIII/FIX:C was a bit lower (median 2 vs 3 IU/dL). Median age at first joint bleed was 5 years in both studies. We report a higher prevalence of prophylaxis (38%) than among the Dutch patients (23%). In both studies, however, there was a gap of several years between age at first joint bleed and start of prophylaxis. In severe haemophilia, age at start of prophylaxis has been found as an independent predictor for development of arthropathy.[15] The annual prophylactic factor consumption was three times higher among the Nordic patients (median 2924 vs 939 IU/kg/y). This is in accordance with the different treatment traditions between the Dutch intermediate-dose and the Nordic high-dose regimens.[16] Patients treated on-demand had four times higher factor consumption in the Dutch study (median 112 vs 27 IU/kg/y). Bleeding frequency was low in both studies with a median of zero annual joint bleeds. In the Dutch study, 82% achieved HJHS <10/128 points, considered as a good joint function. We report 75% with a corresponding HJHS. A lower baseline FVIII/FIX:C may accord with this difference. We also included all available patients, even if they had a history of inhibitor (three patients), and regardless of the access to haemophilia care during childhood. Geographically, there are long distances within the Nordic countries. Combined with centralized haemophilia care, this may have contributed to a limited follow-up for some patients, especially among the elderly. The prevalence of orthopaedic surgery was equal in both studies.

Compared with the THUNDER study from the UK,[6] we report a lower prevalence of prophylaxis than among their subgroup with MHA (38% vs 69%). Still, their bleeding frequency was high with median two (prophylaxis) and five annual joint bleeds (on-demand). In our study, the annual number was zero in both treatment groups. Their low baseline FVIII:C (median 1 IU/dL) may explain this difference. In accordance with their results, we found a progressive increase in HJHS and HEAD-US with age. This suggests progression of haemophilic arthropathy due to inadequate treatment regimens in past decades and emphasizes the need of early start of prophylaxis.[15] When divided in age groups, our study showed a higher HJHS among patients on prophylaxis compared with those treated on-demand, reflecting a more severe phenotype in the prophylaxis group. The gap between age at first joint bleed (median 5 years) and age at start of prophylaxis (median 10 years) may further explain the deterioration of joint health among patients on prophylaxis.

It may also be of interest to compare our results with a former Swedish cohort of severe haemophilia on full-time prophylaxis.[16] Our patients with moderate haemophilia achieved HJHS ≥ 10 points approximately twice as often (25% vs 11%). Orthopaedic surgery was also more frequent among our patients (15% vs 8%). Although we had a slightly higher age in our study (median 28 vs 23 years), the most important difference is the widespread use and early age at start of prophylaxis in the severe haemophilia cohort. This indicates an unmet need in the treatment of patients with moderate haemophilia.

4.1 | MHA and MHB

The MoHem study contains a high proportion of patients with MHB (39%), and we may therefore compare outcomes between MHA and MHB. Prophylaxis started at 10 years (median) in both groups. Thus, we may observe a more natural course of the bleeding phenotypes than in the PedNet/RODIN cohorts of children by Clausen et al,[9] who started prophylaxis <3 years of age. In both studies, the prevalence of prophylaxis was equal between MHA and MHB. However, we detected differences regarding history of haemarthrosis and age at first joint bleed pointing towards a milder phenotype in MHB. This was even more pronounced among those with FVIII/FIX:C ≤ 3 IU/dL, which represented most (88%) of our patients with MHB. Besides, in this subgroup, the total factor consumption during the last 12 months was lower for MHB than for MHA. The number of joint bleeds was also lower among MHB. Schulman et al,[8] who studied a Swedish adult cohort of haemophilia A and B in all severities, found

a difference in total severity score and annual factor consumption between severe haemophilia A and B, but not among moderate patients. We did not find any difference between MHA and MHB with respect to arthropathy.

4.2 | Baseline factor activity level

Our study showed a more severe clinical phenotype among patients with FVIII/FIX:C ≤ 3 IU/dL with respect to younger age at first joint bleed and higher HJHS. This is in accordance with den Uijl et al,[17] who found a sharp bend in the haemophilia 'early milestone' curves towards a more severe clinical phenotype below FVIII:C of 3 IU/dL. However, in the study on moderate haemophilia,[5] they reported similar bleeding rates and HJHS across factor activity levels as opposed to our study, which might be explained by our larger cohort.

4.3 | HEAD-US and HJHS

We found a strong correlation between HEAD-US and HJHS. This is in accordance with previous publications[18,19] and support that both these tools are valuable for joint assessment. However, as HJHS contains both structural and functional items, HEAD-US only assesses the joint structure. Thus, there would naturally be some discrepancy between them. Half of our patients had 0-3 points on HJHS. Dependant on the HJHS items involved, and if the total score represents findings in a single or more joints, these low scores do not necessarily represent intraarticular pathology.[20] In our study, most of these patients (79%) captured zero points at HEAD-US, which support classifying them as within 'normal range'.

4.4 | Strengths and limitations

The MoHem study reports clinical outcome in a high number of patients with MHA and MHB. Arthropathy was broadly evaluated using both HEAD-US and HJHS. Due to a centralized follow-up, we have reached a high degree of participation among Nordic patients with moderate haemophilia. The study participants represented a younger age group than those not enrolled; thus, our results do not assess the elderly patients. The centralized care provides uniform treatment and follow-up. Even though there were different treatment traditions in previous times,[21] the Nordic countries today follow common Nordic treatment guidelines in accordance with international recommendations. The multicentre design may give rise to inter-individual and inter-centre variability, even if we have struggled to provide uniform instructions to all persons involved. There might be misclassification of baseline FVIII/FIX:C, because these analyses have been performed at several laboratories at different time points and with different methods. However, we standardized the classification by using the lowest available value for all participants. Our data on bleeding history were collected retrospectively. Especially among the elderly, the documentation in medical records could be sparse. Although we used validated scores to classify haemophilic arthropathy,[13,14] there might be some variability when several performers are involved.[22] However, HEAD-US reliability has previously been classified as good.[23,24]

5 | CONCLUSION

The current joint health among Nordic moderate haemophilia patients was rather good, but a subgroup had severe arthropathy. Baseline FVIII/FIX:C ≤ 3 IU/dL was associated with a younger age at first joint bleed and higher HJHS. One third experienced joint bleeds during the last 12 months. Differences in bleeding history between MHA and MHB pointed towards a milder phenotype in MHB. Orthopaedic surgery, however, was equally performed in both diagnoses and irrespective of FVIII/FIX:C. Altogether, the MoHem study indicates a need for a more extended use of prophylaxis among patients with moderate haemophilia from early ages, prior to the onset of joint disease. We suggest primary prophylaxis to all patients with baseline FVIII/FIX:C ≤ 3 IU/dL according to similar guidelines as those for severe haemophilia.

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DISCLOSURES

EB has acted as paid consultant to Bayer, Octapharma, Sobi, Takeda, CSL Behring including lectures and medical advice, and received research grants from Bayer and Shire/Takeda. JA has received research grant from SOBI, Shire/Takeda, Bayer, Octapharma and CSL Behring and acted as consultant/speaker for SOBI, Shire/Takeda, Bayer, Octapharma, Pfizer and Novo Nordisk. PAH has acted as a paid consultant to Bayer, Shire, Novo Nordisk, Octapharma, CSL Behring, Pfizer and Sobi including lectures. RJM, AO, MB, TF, VN, RL and GET stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

EB, PAH and RJM designed the study. RJM, JA, AO, MB, TF and VN collected the clinical data. RJM analysed the data and drafted the manuscript. RJM, PAH, EB and GET interpreted the data. All authors contributed to critically revision of the manuscript and gave approval of the final version.

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