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ORIGINAL ARTICLE

Musculoskeletal

Long-term joint outcomes in adolescents with moderate or severe haemophilia A

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Abstract

Introduction: Favourable joint outcomes are expected with modern haemophilia A (HA) management. Evaluation of long-term treatment outcomes is hampered by the delay between bleeding episodes during childhood and resulting joint outcomes in adulthood.

Aim: To measure the long-term joint health of adolescents with moderate and severe HA, according to severity and inhibitor status.

Methods: Pilot cross-sectional study of five European PedNet centres in moderate and severe HA patients aged 10–19 years. Structured assessment of joint status by physical examination (HJHS) and ultrasound (HEAD-US).

Results: In total, 141 HA patients were evaluable, 100 without inhibitors (81 severe, 19 moderate HA), and 41 severe HA with current/past inhibitors. On physical examination, 12/81 (15%) of severe HA without inhibitors, 3/19 (16%) of moderate HA, and 13/41 (32%) of severe HA patients with inhibitors exhibited joint abnormalities. Inhibitor persistence, longer inhibitor duration, and a high peak inhibitor level were associated with impaired joint health. Ultrasound showed joint damage (bone or cartilage) in 13/49 (27%) of severe HA without inhibitors, 1/12 (8%) of moderate HA, and 10/28 (36%) of severe HA patients with inhibitors. A discordant ankle evaluation by ultrasound versus physical examination was present in 53/169 joints (31%).

Conclusions: Most adolescents with severe or moderate HA show favourable joint health. Future research with combined ultrasound and/or MRI is needed to better understand joint outcomes in the remaining patients. Patents with inhibitors showed a two-fold increased proportion with joint deterioration. Ultrasound paired with physical examination increases sensitivity for detection of joint damage.

KEYWORDS
adolescent, arthropathy, haemophilia A, paediatrics, ultrasonography

1 | INTRODUCTION

In haemophilia A (HA), the deficiency of coagulation factor VIII (FVIII) (severe, < .01 IU/ml; moderate, .01–.05 IU/ml) is associated with characteristic joint and muscle bleeding. In developed countries, primary prophylaxis with FVIII concentrates is the standard of care for severe HA and aims to prevent bleeding events and subsequent joint damage.[1] In ~30% of children the treatment is complicated by the development of inhibitory alloantibodies to exogenous FVIII, rendering prophylaxis with FVIII concentrate ineffective. Moreover, despite prophylaxis, patients may experience traumatic bleeds. Patients with moderate HA often start with on-demand treatment, that is, treatment only with bleeding episodes or trauma. A subset of moderate HA patients shows a more severe bleeding phenotype with onset of bleeding at a young age, more frequent bleeding episodes, impaired long-term joint health; this subset may benefit from prophylaxis.[2–4]

Due to the delay between bleeding episodes in childhood and impaired joint function in adulthood, the long-term outcomes of current prophylactic regimens are difficult to assess. A substantial proportion (up to 20%) of adolescents and young adults with severe HA show signs of arthropathy, despite prophylaxis.[5,6] In a more recent cohort, 50% of patients with haemophilia showed signs of deterioration of joint health (Haemophilia Joint Health Score ≥ 5) by a mean age of 11 years.[7] Taken together, despite prophylaxis, maintaining joint health and quality of life remains a key challenge for haemophilia care.

New long-acting FVIII concentrates are emerging, and novel non-replacement prophylactic treatments such as emicizumab are available in many countries. Thus, there is a need to assess modern treatment regimens and describe the long-term outcomes to provide a benchmark and identify key areas for potential improvement.

In this study, we describe the joint health of adolescents with HA in a pilot study from five PedNet centres using structured outcome assessment. The primary aim was to investigate the robustness of the different joint assessment tools to discriminate HA severity and patients with FVIII inhibitors. First, we compared the joint health of patients with severe and moderate HA. Secondly, we compared the joint health of patients with severe HA with a history of inhibitory FVIII antibodies to patients without inhibitors (and continuous prophylaxis).

2 | METHODS

2.1 | Study design and ethical considerations

The PedNet Registry is a multicentre unselected birth cohort with prospectively collected data on patients with haemophilia A or B (baseline factor level ≤.25 IU/ml; www.pednet.eu).[8] Children treated at one of the participating haemophilia treatment centres (HTC) with complete records of bleeds and treatment with coagulation factor concentrates are eligible for participation. Data is collected through web-based case report forms by trained research nurses, investigators or data managers and contains basic characteristics, detailed information on the first 50–75 exposure days (EDs), development of inhibitors and annual follow-up data. The collected data is evaluated using logical checks as well as random source validation (≥10% monitored), and inconsistencies are resolved using queries to the HTC. The PedNet registry and studies (ClinicalTrials.gov at NCT02979119) have been approved by the ethical review board of each participating country and written informed consent is obtained.

All patients with severe or moderate HA, registered in the PedNet Registry in one of the five HTC with available structured outcome assessment (Athens, Birmingham, Malmö, Stockholm, Utrecht) and born between January 1, 2000 and December 31, 2008 (aged ≥12 years) with at least one registered HJHS examination at ≥10 years of age were included. Patients with moderate HA and FVIII inhibitors were not analysed because of small sample size.

2.2 | Clinical outcomes and definitions

The primary study outcome was the joint status measured by Haemophilia Joint Health Score (HJHS). Data on patients' demographics, severity and treatment of haemophilia, inhibitor status, follow-up data on long-term outcome including HJHS and Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) were retrieved from the PedNet registry.

The HJHS 2.1 is a structured 8-item physical examination assessment tool of clinical joint status of the elbows, knees, ankles, as well as gait, and is optimized for detecting early arthropathy in children.[9–11] In addition to gait assessment, scored key items include swelling, muscle atrophy, presence of crepitus, extension or flexion loss, strength and pain. The optimum score is 0 and the maximum score is 124. The range in healthy young men is 0–3 points,[12] and for this study a cumulative HJHS score ≥ 4 was classified as being abnormal, with HJHS ≤3 as normal. Of note, there may be observer bias especially for low HJHS values. Ultrasound of the joints was performed using the HEAD-US protocol[13,14] that scores synovial hypertrophy and damage to cartilage and bone structures of ankles, knees and elbows. The optimum score is 0 and the maximum score is 48. As synovial hypertrophy may be a reversible joint abnormality, it was reported separately from bone and cartilage damage, which are considered irreversible. Synovial hypertrophy was assessed but not synovitis (clinical symptoms and a positive Doppler sign). Joint status by HEAD-US or HJHS is registered in a 'steady state' situation, that is, patients with acute symptoms or recent bleeds were not included, and the data reflect chronic joint changes. Data on HEAD-US was only included if evaluated within 1 year of the HJHS assessment; most of the data was obtained at same clinic visit.

The start of prophylaxis was defined as regular administration of FVIII concentrate at least once weekly for a consecutive period of at least 8 weeks and was adjudicated by review of bleeding events and treatment schemes. Details on prophylactic treatment regimens (frequency or dose) during follow-up in the birth cohort were not available.

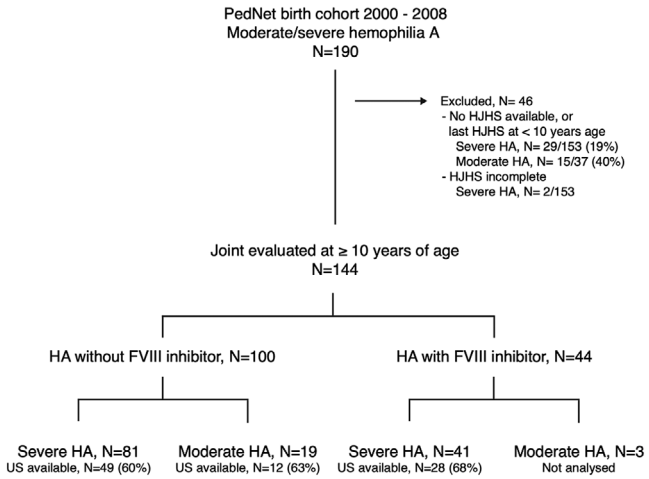

FIGURE 1 Study flow chart. HA, haemophilia A; HJHS, Haemophilia Joint Health Score; US, ultrasound

2.3 | Statistical analysis

Analyses were performed in R version 4.3 (R Core Team). Data were analysed descriptively. Statistical testing was solely performed for the pre-defined comparison of joint health (HJHS) for severe versus moderate HA, and severe HA with versus without inhibitors. Groups were compared with a non-parametric Wilcoxon-rank sum test. Correlation was assessed by Spearman's rank coefficient. Confidence intervals for proportions were calculated using Wilson's method.[15] The data that support the findings of this study are available from the corresponding author upon reasonable request.

3 | RESULTS

Of the 190 registered patients with severe or moderate HA, 141 patients were evaluable, 122 with severe HA (including 41 with current or history of inhibitors) and 19 moderate HA without inhibitors (Figure 1; details per centre in Supplementary Table). Moderate HA patients with and without available HJHS showed the same distribution of baseline FVIII levels (data not shown); one third (7/19) had a FVIII baseline activity below .03 IU/ml. Patient characteristics according to haemophilia severity and inhibitor status are shown in Table 1. The median age at joint evaluation was 15 years (Table 1). Among patients with severe HA without inhibitors ($N = 81$), prophylaxis was administered to 99% of patients for 91% of their lifetime, until the last follow-up. Prophylaxis was started before the age of 2 years in 50/79 (63%), and in 91% of patients within the first 50 exposure days to FVIII concentrate. Of the patients with moderate HA, 81% were treated with prophylaxis (13/16), and prophylaxis was generally started later than in severe HA patients, that is, after the age of 2 years in 85% (11/13; Table 1). The patients with inhibitors were classified as high-titre (27/41, 66%) and low-titre (14/41, 34%). Four patients (4/41, 10%) had current inhibitors (table 1).

TABLE 1 Participant characteristics according to haemophilia severity and inhibitor status

	Severe HA	Moderate HA	SHA with past or current inhibitors
N	81	19	41
Baseline FVIII activity, IU/ml	.00 [.00, .00]	.03 [.02, .04]	.00 [.00, .00]
Age at joint exam, years	15.1 [12.8, 17.5]	15.3 [13.1, 16.6]	15.6 [12.6, 17.2]
Age at joint ultrasound, years[a]	15.4 [13.5, 17.7]	13.4 [12.9, 15.4]	15.6 [12.8, 17.3]
Age at first joint bleed, years	1.6 [1.0, 2.2]	4.1 [3.0, 6.7]	*Na*
Age at start prophylaxis, years	1.5 [1.3, 2.3]	5.3 [3.9, 8.6]	
Prophylaxis	79/80 (98)	13/19 (68)	
Started at < 24 months age	50/79 (63)	2/13 (15)	
≥ 2 months after 1st bleed	20/30 (67)	1/2 (50)	
Prophylaxis start before 51 ED	74/80 (91)	10/17 (58)	
Proportion of life on prophylaxis, %	91 [84, 93]	61 [40, 77]	
Age at first inhibitor, years			1.4 [1.2, 1.7]
Peak inhibitor level, BU			18.9 [3.4, 162.0]
Duration of inhibitor, months			10 [5, 34]
Low titre inhibitor (≤ 5 BU)			14/41 (34)
High titer inhibitor (> 5 BU)			27/41 (66)
Inhibitor eradicated			37/41 (90)

Data are median [IQR] or number *n/N* (%), unless otherwise indicated. Start of prophylaxis was defined as the administration of factor concentrate at least once per week for a period of at least 8 weeks. First bleed was defined as a major joint or other bleed, minor bleeds were not counted.
Abbreviations: ED, exposure days; BU, Bethesda units.
[a]Ultrasound available for subset of patients, see Results.

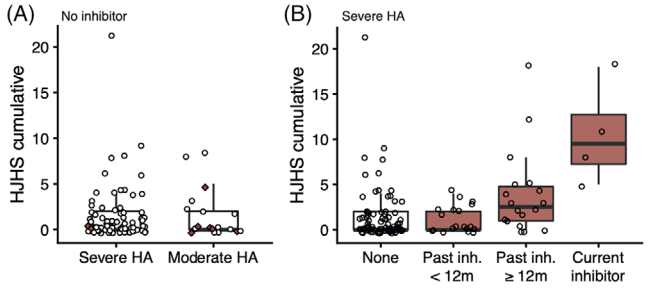

FIGURE 2 Functional joint health and gait in adolescents with haemophilia A, using structured outcome assessment. (A) Physical examination of joint health between severe and moderate haemophilia A without inhibitors. Red diamonds indicate patients with no prophylaxis or unknown status. (B) Comparison of joint health of patients with severe haemophilia A by inhibitor status. HA, haemophilia A; HJHS, Haemophilia Joint Health Score; Inh, inhibitor; m, months

3.1 | Structured assessment of functional joint health and gait

On physical examination, 12/81 severe HA patients without a history of inhibitors (15%; 95% confidence interval [CI], 8%–24%) showed joint impairment (cumulative HJHS score ≥ 4; Figure 2A; Table 2). The most affected joints were the knees, closely followed by the ankles, with the elbows least affected (Table 2 for individual data; Table 3 for joint data). Of note, all individual knee scores were < 2 points. For patients with moderate HA, the HJHS results were comparable to severe HA patients without inhibitors, 3/19 patients (16%; 95% CI, 6%–36%) displayed a HJHS score of ≥ 4. The six moderate HA patients with on-demand treatment showed similar scores as those who had prophylaxis (Figure 2A).

Patients with severe HA and current/past inhibitors showed a ~2-fold increased proportion of joint damage versus those without a history of inhibitors. An abnormal HJHS score was observed in 13/41 patients (32%; 95% CI, 20%–47%) with current/past inhibitors, compared to the 15% mentioned above. When only patients with eradicated inhibitors were analysed, the proportion of patients with an HJHS ≥ 4 was 24% (95% CI, 13%–40%; Figure 2B). In more detail, severe HA patients with past inhibitors of < 12 months duration ($N = 19$) showed no differences in HJHS compared to severe HA without history of inhibitors, whereas patients with inhibitors ≥ 12 months duration exhibited more joint damage ($N = 18$; Figure 2B). The small group of four patients with persistent inhibitors all showed signs of joint damage (HJHS ≥ 4).

3.2 | Determinants of joint health in severe HA patients with and without a history of inhibitors

For severe HA patients without a history of inhibitors, given the general good joint status in this population, we found no association of the HJHS score with the age at the joint evaluation (Figure 3A), the time between the first major bleeding event (joint or other) and start of regular prophylaxis (Spearman rho = .11), the age at the first joint bleed (rho = -.07), or the age at start of prophylaxis (rho = -.14). Of patients with severe HA and current/past FVIII inhibitors ($N = 41$), there was a moderate correlation between inhibitor duration and HJHS scores in adolescence (rho = .50; Figure 3B). There was also a weak correlation of the peak inhibitor level with HJHS scores in adolescence (rho = .35). Of note, the peak inhibitor levels showed a positive correlation with

TABLE 2 Physical examination (HJHS) and ultrasound evaluation (HEAD-US) according to severity and inhibitor history

	Severe HA without inhibitors	Moderate HA	SHA with past or current inhibitors
HJHS			
HJHS cumulative	0 [0, 2]	0 [0, 2]	2 [0, 4]
HJHS abnormal gait	7/81 (9)	2/19 (11)	6/41 (15)
HJHS ≥ 4	12/81 (15)	3/19 (16)	13/41 (32)
Affected Elbows, number of joints	11	1	15
Affected Knees, number of joints	25	8	29
Affected Ankle, number of joints	22	9	22
HEAD-US			
Synovial changes present	26/49 (53)	4/12 (33)	14/28 (50)
Cartilage changes present	12/49 (24)	1/12 (8)	9/28 (32)
Bone changes present	4/49 (8)	0/12 (0)	5/28 (18)
Cartilage or bone changes present	13/49 (27)	1/12 (8)	10/28 (36)
Pristine joints	33/49 (67)	9/12 (75)	16/28 (57)

Data are median [IQR] or number *n*/*N* (%).
Abbreviations: HJHS, Haemophilia Joint Health Score; HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound.
Synovial, cartilage and bone changes by HEAD-US protocol was only available for a subset of patients. Pristine joints were defined as HJHS < 4 and absence of bone or cartilage damage.

TABLE 3 Physical examination (HJHS) and ultrasound evaluation (HEAD-US) of individual joints

	Ankle	Knee	Elbow
HJHS (N = 141)			
HJHS available	282	282	282
HJHS non-zero	53/282 (19)	62/282 (22)	27/282 (10)
HEAD-US (N = 89)			
Joints with available US	169/178 (95)	151/178 (85)	136/178 (76)
Synovial changes present	42/169 (25)	22/151 (15)	11/136 (8)
Cartilage changes present	14/169 (8)	7/151 (5)	11/136 (8)
Bone changes present	7/169 (4)	2/151 (1)	5/136 (4)
Cartilage or bone changes present	16/169 (10)	7/151 (5)	11/136 (8)

Data arenumber *n/N* (%).
Abbreviations: HJHS, Haemophilia Joint Health Score; HEAD-US, Haemophilia Early Arthropathy Detection with Ultrasound.
Synovial, cartilage and bone changes by HEAD-US protocol. A total of 23/89 patients had incomplete HEAD-US data based on selective assessment of joints (Results, Discussion).

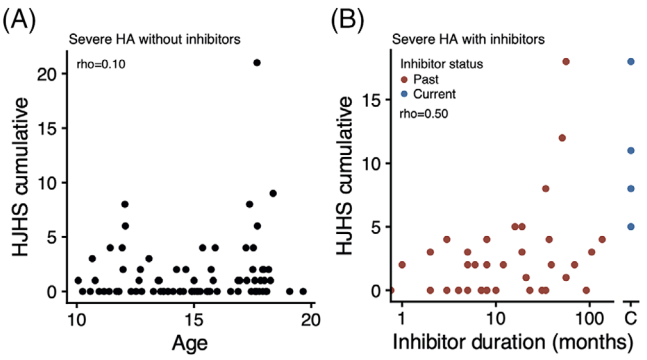

FIGURE 3 Determinants of joint health in adolescents with severe haemophilia A. (A) Age at the evaluation was not associated with the joint health and gait (severe haemophilia A without inhibitors). Older children showed no worse joint function than younger children. (B) Duration of a FVIII inhibitor presence and cumulative HJHS score (severe haemophilia A with inhibitors).
C, Current; HA, haemophilia A; HJHS, Haemophilia Joint Health Score; BU, Bethesda units; rho, Spearman's rank correlation coefficient

the inhibitor duration (rho = .69); thus, these three variables are all related.

3.3 | Structured assessment of joint health by ultrasound

Assessment of joint health by ultrasound was performed using the HEAD-US protocol (Figure 4) among 49/81 (60%) severe HA patients, 12/19 (63%) moderate HA patients, and 28/41 (68%) severe HA patients with current or past inhibitors. In 23/89 (26%) of these patients not all joints were assessed (Table 3). Among the severe HA patients without a history of inhibitors, ultrasound showed a healthy joint status (zero HEAD-US) in 19/49 patients (39%). Moreover, 13 patients exhibited either cartilage or bone damage in at least one joint (27%; 95% CI, 16%–40%; Table 2), indicative of irreversible joint damage, and 26 displayed synovial hypertrophy (53%; 95% CI, 39%–66%), which may be reversible. Patients with moderate HA showed fewer ultrasound abnormalities than those with severe HA (Figure 4A), 1/12 (8%; 95% CI, 0%–35%) patient exhibited both cartilage damage and synovial hypertrophy, and 3/12 (25%; 95% CI, 9%–53%) showed synovial hypertrophy. For severe HA patients with eradicated inhibitors, we observed similar ultrasound findings as in severe HA without inhibitors (Figure 4B). Bone or cartilage damage was present in 10/28 patients (36%; 95% CI, 21%–54%), and synovitis in 14/28 (50%; 95% CI, 33%–67%). All four severe HA patients with persistent inhibitors showed ultrasound abnormalities (Figure 4B). For severe HA patients with past inhibitors and inhibitor duration < 12 months ($N = 13$) or ≥ 12 months ($N = 12$), HEAD-US results were similar (data not shown). Across all patients, the most affected joints on ultrasound examination were the ankles (synovial hypertrophy in 42/169, 25%; Table 3) and knees (22/151, 15%).

3.4 | Paired assessment of joint health by physical examination and ultrasound

We finally evaluated the paired assessment of patients by physical examination (HJHS) and ultrasound (HEAD-US) in 89 patients. Pristine joints, defined as a normal joint assessment (HJHS < 4) and absence of bone or cartilage damage in all assessed joints, were observed in 67% of severe HA without inhibitors (95% CI, 53%–79%), 57% of severe HA with past or current inhibitors (95% CI, 39%–73%), and 75% of moderate HA (95% CI, 47%–91%).

Ultrasound and physical examination showed conflicting results in some patients. Focusing on the ankles ($N = 169$), 36/169 (21%) ankles with a HJHS between 0 and 1 displayed synovial changes on ultrasound (Figure 4C). Similarly, 11/169 (7%) and 3/169 (2%) of joints with cartilage or bone damage showed HJHS of 0–1. Of the ankles with a normal HEAD-US (score 0), 19/122 (16%) had a HJHS score above

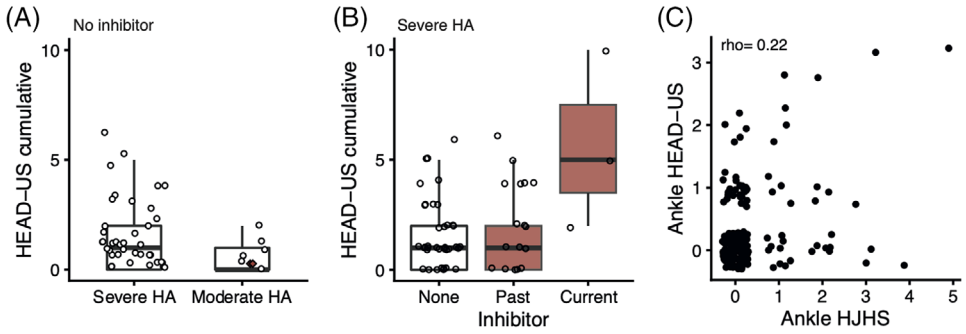

FIGURE 4 Ultrasound to identify early signs of joint arthropathy, and synergistic use together with physical examination. (A) Comparison of ultrasound evaluation between moderate and severe haemophilia A without inhibitors. Red diamonds indicate patients with no prophylaxis or unknown status. (B) Comparison of ultrasound joint health between patients with severe haemophilia A and inhibitors, by inhibitor status. (C) Correlation between HEAD-US and HJHS scores. Correlation is given for the Spearman rank coefficient rho. HA, haemophilia A; HEAD-US, Haemophilia Early Arthropathy Detection by Ultrasound score

zero. Overall, 116/169 (69%) ankles had concordant results by ultrasound versus physical examination, whereas a discordant evaluation was present in 53/169 joints (31%) considering HJHS 0–1 as normal. More strictly, when a HJHS of zero was considered abnormal, the number of discordant joints did not change (51/169, 30%).

4 | DISCUSSION

In this study we described the long-term joint health in adolescents with severe or moderate haemophilia A of five centres, representing a pilot for long-term outcome assessment within PedNet. The key finding is that 85% of severe and moderate HA patients without inhibitors and 68% of severe HA with past/current inhibitors had healthy joints on physical examination in adolescence. More combined research is needed with ultrasound and/or magnetic resonance imaging (MRI) to draw conclusions on the patients with affected joints. An important secondary finding of our study is the benefit of complementary joint assessment by both physical examination and ultrasound, where some abnormal findings of each evaluation are not covered by the other, with ultrasound possibly providing better sensitivity for early, subclinical joint changes.[16]

4.1 | Strengths and limitations

A strength of our study is the prospective collection of key data elements in the PedNet birth cohort, and the use of standardized protocols for joint evaluation, allowing five centres in four countries to contribute data. A limitation of our study was that we did not collect detailed data on findings included in the HJHS exam (e.g., if impairment was due to pain, limited range of motion, or crepitus); lifetime dose of prophylaxis was also not available, nor any measure of adherence to prophylaxis or bleeding rate. A total of 40% registered moderate HA patients had to be excluded due to missing HJHS (Figure 1). We observed no difference in FVIII activity of included and excluded moderate HA patients (Results), but the proportion who received prophylaxis (68%) was high and this might represent selection bias, where patients with more bleeds and prophylaxis were more frequently assessed by HJHS.

Regarding ultrasound, results were only available for 63% of the full cohort, and 26% patients had an incomplete (selective) assessment of joints. We suspected from clinical practice that assessed joints were the ones with bleeds or symptoms. Consequently, the number of patients with pristine joints in the total PedNet cohort may be underestimated. Moreover, particularly for this multicentre study, inter-rater variability may contribute to variance in HJHS and HEAD-US scores. MRI can be considered the golden standard for joint assessment. However, as it is not a regular follow-up method in haemophilia, we could not compare our finding to MRI images. Finally, still longer follow-up might be required to reveal differences on joint outcomes,[17] and we may have missed small effects due to insufficient power. Our data are observational and did not consider other factors which may affect joint health, such as bleeding rate, sports participation, or accidents.

4.2 | Comparison with other publications

Several historic studies assessed joint status of ankles, knees and elbows in adolescents with haemophilia.[5–7] In a Swedish cohort of 121 patients with severe haemophilia A or B without inhibitors, born 1963–96, by 10 years of age, 76/90 (84%) had a World Federation of Haemophilia (WFH) orthopaedic score of zero, and by 15–18 years of age this was 27/50 (54%).[5] Patients were treated with on-demand or prophylactic therapy from the first year of life. Notably, the WFH score is less sensitive for mild arthropathy than HJHS.[10] Similarly, a Dutch cohort of 76 adolescents and young adults with severe haemophilia A or B without inhibitors born 1965–1985 showed a median WFH orthopaedic score 0 (IQR 0–6) at a median age 19 years (IQR 15–25).[6] The use of prophylaxis increased from 44% to 95% during the study period. X-ray examination of the same patients showed 28% had a zero Pettersson score (median 7, IQR 0–17).[6] Finally, a more recent multicentre cohort of 226 patients with severe, moderate, and mild haemophilia A or B (24% inhibitors) showed a median HJHS of 5 (IQR

0–12) at a mean age of 11 years (range, 4–16).[7] Here, 38% were on primary prophylaxis, 28% on secondary prophylaxis, and 35% treated on-demand. The direct comparison of our results with these studies is not feasible by use of different radiological and clinical assessments, treatment regimens, as well as clinical heterogeneity of the cohorts. Nonetheless, some inferences can be made. In our study, 85% patients with severe HA without inhibitors had a normal joint and gait examination and might have better joint health than the historic cohorts. Moreover, the distribution of HJHS in our study (median and IQR) of severe and moderate HA as well as severe HA with past inhibitors is significantly better than the previously reported median score of 5 (IQR, 0–12).[7] Altogether, the included PedNet population of the five participating centres can be considered to have very good outcomes.

Our results suggest that the included patients with moderate HA could have minor joint abnormalities to a similar degree than severe HA patients, which is in agreement with previous results.[5–7] As discussed above, there was potential for selection bias, and the results should be interpreted cautiously. Furthermore, consistent with previous literature, patients with FVIII inhibitors showed the most severely affected joint function and health[18,19]; and the change was of a similar order of magnitude compared to patients without inhibitors.[18] Moreover, in contrast to previous data and our ultrasound findings, we observed more affected knees than ankles in HJHS. As the individual knee scores were low, this finding is rather indicative of the generally good clinical joint health in the whole population.

4.3 | Clinical implications

Most patients have favourable joint outcomes with pristine joints. Affected joints might be related to (lack of) adherence, breakthrough/traumatic or subclinical bleeds, or different treatment regimens. More research is needed enabling imaging with ultrasound/MRI to draw conclusions on the patients with affected joints. As expected, patients with long-time FVIII inhibitors showed the most severely affected joint function and health, emphasizing the importance of inhibitor eradication by immune tolerance induction, and/or use of prophylactic treatment. Finally, the paired assessment with ultrasound and physical examination provides information on different dimensions, and joints that appear healthy with one structured evaluation may show abnormalities in the other modality. Thus, ultrasound could help unmask reversible and irreversible subclinical alterations in otherwise functionally normal joints.[20] This could help physicians to prevent further deterioration of joints in the future, implementing a closer follow-up of patients and monitoring of their adherence to treatment.

5 | CONCLUSIONS

In severe HA, 85% patients without inhibitors had a healthy joint examination in adolescence. Patients with severe HA and past/current inhibitors showed a 2-fold increased proportion with affected joint health. More data is needed to accurately assess joint outcomes in moderate HA. Paired physical examination and ultrasound should be used to evaluate joints.

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CONFLICTS OF INTEREST

Susanna Ranta is an investigator in clinical trials sponsored by SOBI, Roche, Novo Nordisk, received grants for research from the Childhood Cancer Foundation and Stockholm County Council, and participated in Steering Committee for Roche. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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