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Monitoring joint health in haemophilia: Factors associated with deterioration

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Introduction: Joint bleeds in patients with haemophilia may result in haemophilic arthropathy. Monitoring joint health is essential for identifying early signs of deterioration and allows timely adjustment of treatment.

Aim: The aim was to describe changes in joint health over 5-10 years follow-up and identify factors associated with joint health deterioration in patients with haemophilia.

Methods: A post hoc analysis was performed from previous cohort studies in patients with moderate/severe haemophilia, ≥16 years. Joint health of ankles, knees and elbows was measured with the Haemophilia Joint Health Score (HJHS) from 2006-2008 (T0) to 2011-2016 (T1). Analyses were performed on patient level (ΔHJHS-total) and joint level (ΔHJHS-joint). Deterioration was defined as ΔHJHS-total ≥4 and ΔHJHS-joint ≥2.

Results: Sixty-two patients (median age 25, 73% severe haemophilia, median [interquartile range] 0.0 [0.0;2.0] joint bleeds between T0 to T1) were included. After median 8 years, HJHS-total deteriorated in 37% and HJHS-joint in 17%. Ankle joints (31%) showed deterioration more often than elbows (19%) and knees (3%). Deterioration of HJHS-total was only associated with severe haemophilia. Deterioration of HJHS-joint was weakly associated with a lower HJHS at baseline and more self-reported limitations in activities, and strongly with more joint bleeds between T0 and T1 and presence of synovitis.

Conclusion: In 37% of patients with moderate/severe haemophilia and low joint bleeding rates, joint health deteriorated over 5-10 years. Ankle and elbow joints showed deterioration most frequently. Factors found in this study help to identify which joints need frequent monitoring in patients with haemophilia with access to early prophylaxis.

KEYWORDS

haemophilia A, haemophilia arthropathy, haemophilia B, Haemophilia Joint Health Score, outcome measure, physical examination

1 | INTRODUCTION

Persons with haemophilia (PWH) experience intra-articular and intramuscular bleeding; eventually joint bleeds may result in haemophilic arthropathy (HA).[1] The mechanism of HA is multifactorial; joint bleeds affect cartilage directly, as well as indirectly through synovial inflammation.[2] HA leads to pain, loss of range of motion and muscle atrophy resulting in loss of activities and restrictions

in participation.[1,3] In the Netherlands prophylactic clotting factor replacement therapy was introduced in 1968. This medical treatment is proven to be effective: it prevents bleeds and subsequent arthropathy.[4,5]

Monitoring joint health is essential for identifying early signs of deterioration as it enables adjustments in clotting factor replacement therapy, physical therapy, use of walking aids or prescription of braces to limit further decline. Previous studies detected no or minimal changes in joint health over the years measured with the radiologic Pettersson score and World Federation of Hemophilia (WFH) physical examination score in patients treated with prophylaxis.[6,7] However, early joint alterations remain undetected on the Pettersson score as X-ray only shows osteochondral changes.[8] Furthermore, in a paediatric population, the WFH physical examination score is less sensitive than the Haemophilia Joint Health Score (HJHS), which was developed more recently[9] and is the recommended tool for routine patient follow-up assessments of joint health.[10] The WFH guidelines recommend annual use of the HJHS during regular evaluations,[1] although assessment must be performed by a trained physiotherapist and is time consuming. Data on the occurrence and rate of deterioration in HJHS scores in adults with low bleeding rates are lacking. Identifying patients and/or joints at risk for deterioration may help individualize monitoring schedules and promote efficiency without jeopardizing the quality of care.

Known factors related to joint health in haemophilia are severity of disease, use of prophylactic clotting factor replacement, number of joint bleeds, radiological status, synovitis and Body Mass Index (BMI).[1,2,4,11] In addition, limitations in activities could predict joint health deterioration, as demonstrated in patients with osteoarthritis.[12]

The aim of this study was to describe changes in joint health over a 5- to 10-year follow-up and identify factors associated with joint health deterioration in adult patients with moderate or severe haemophilia.

2 | MATERIALS AND METHODS

2.1 | Study design and study population

This study was a post hoc analysis using HJHS data collected for previous cohort studies and data from medical files. Studies used for our post hoc analysis reported the HJHS in patients with moderate (1-5 IU/dL factor VIII/IX activity) or severe (<1 IU/dL factor VIII/IX activity) haemophilia treated at the Van Creveldkliniek in Utrecht. In this study, we included data of subjects with 2 HJHS measurements with an interval of at least 5 years. For each subject, the last available HJHS score was selected to get the follow-up period as long as possible. Patients aged <16 years at first measurement were excluded.

Regardless of study participation, all patients visited the clinic at least annually, including evaluation and documentation of treatment and bleeding. The HJHS at T0 was derived from the studies by Den Uijl et al and Fischer et al.[13-15] For the follow-up measurement (T1), the HJHS was derived from the studies by Nijdam et al[16] and routine measurements documented in medical files. This resulted in a data collection period from January 2006-August 2008 (T0) to November 2011-May 2016 (T1). These previous studies were approved by the Medical research ethics committee (MREC) of the University Medical Centre Utrecht (06-248, 06-002, 11-442) and informed consent included permission for subsequent analyses of joint outcome data.

The potential factors self-reported limitations in activities (Haemophilia Activity List [HAL]) and radiological status were obtained from Den Uijl et al and Fischer et al.[13-15] In addition, patient characteristics, severity of disease, number of joint bleeds, use of prophylaxis, presence of synovitis and BMI were extracted from patient logs and medical files.

2.2 | Measurements

2.2.1 | Outcome

The primary outcome was joint health of elbows, knees and ankles measured with the HJHS 2.1, which consists of 8 item scores on joint level and a global gait score. Scores range from 0 to 20 per joint and the global gait score ranges from 0 to 4, resulting in a HJHS-total score (0 to 124). A higher score indicates worse joint health.[17] In this study, the HJHS-total score and the HJHS-joint scores of the HJHS version 2.1 were reported. Scores of T0 were measured with HJHS 1.0 and were converted to HJHS 2.1 by recoding of original range of motion data according to the manual.

Since this tool was developed for detection of early joint changes, the manual of the HJHS does not prescribe how items have to be scored in case of joint replacement or arthrodesis.[17] It was decided to score joints after joint replacement or arthrodesis similar to joints without joint replacement or arthrodesis, and to correct for a history of surgery in the statistical analyses.

2.2.2 | Factors associated with joint health deterioration

Disease severity and medication use

Severity of disease was reported as moderate or severe. The use of prophylactic clotting factor between T0 and T1 was reported in 4 categories: (i) no prophylaxis, (ii) continuous prophylaxis, (iii) non-compliant use of prophylaxis (according to the notes in the medical file) and (iv) change from prophylactic clotting factors to on-demand use or vice versa.

Joint bleeds

The number of joint bleeds between T0 and T1 was reported per joint for elbows, knees and ankles. Joint bleeds were defined as any complaint in elbows, knees or ankles requiring treatment with clotting factor concentrate.

Joint status

Joint health at baseline (T0) was measured with the HJHS 2.1.[17] The radiological status of the joints at baseline (T0) was scored by means

of the Pettersson score.[18] Knees, elbows and ankles were evaluated with a maximum score of 13 points per joint. Higher scores reflect more severe arthropathy.[18] Pettersson scores available within 2.5 years of T0 measurement of the HJHS were included. For consistency, all Pettersson scores were performed by 2 radiologists. The presence of synovitis between T0 to T1 was reported per joint. Synovitis was considered present when documented in the patient file and treated according to the local synovitis protocol in which synovitis is defined as a painless swelling and warmth of the joint on clinical exam.

Age, BMI and limitations in activities

Age in years was reported at baseline. BMI (kg/m^2) was calculated with the height and weight. Self-reported limitations in activities at baseline (T0) were measured with the HAL.[19,20] The HAL is a validated 42-item haemophilia-specific self-administered questionnaire assessing self-reported limitations in activities in 8 domains. Normalized scores range from 0 to 100, where 100 represents no limitations in activities.[20]

2.2.3 | Patient characteristics

Type of disease (haemophilia A or B), regimen of prophylaxis, presence of Hepatitis C Virus and/or Human immunodeficiency virus and history of surgery (joint replacement or arthrodesis) were reported as patient characteristics.

2.3 | Statistical analyses

Descriptive results were presented as proportions or medians (interquartile ranges [IQR]). Analyses were conducted on patient level (HJHS-total) and joint level (HJHS-joint). To account for correlation of joint scores within patients, all analyses on joint level were performed using multilevel models.[21] Change (Δ) scores between T0 and T1 were calculated for the HJHS-total score, HJHS-joint score and for the elbow, knee and ankle joints separately (*ΔHJHS = HJHS T1-HJHS T0*). Cut-off points for clinical relevant changes were ≥|4| for the HJHS-total score and ≥|2| on joint level. Cut-off points were based on expert opinion (KF, MT) and a published range of 0-3 points on the HJHS-total score in young adults without haemophilia.[22] Differences in HJHS-total scores between T0 and T1 were tested by the non-parametric Wilcoxon signed-rank test. At joint level, differences in HJHS scores were tested with a univariate three-level regression including the level measurement point, patient and joint.

Individual factors associated with ΔHJHS-total score were determined with univariate linear regression analyses. Multicollinearity between the determinants was checked. Subsequently, to determine factors associated with the ΔHJHS-total score, a multivariate linear regression analysis was performed. Determinants were selected stepwise backward. Variables were removed if $P > .10$.

Factors associated with ΔHJHS-joint score were determined with univariate and multivariate two-level regression analyses, including adjustment for joint type (elbow, knee or ankle). The best fitting model was chosen based on the lowest Akaike Information Criterium (AIC) value.[21] All analyses for determining factors associated with ΔHJHS were adjusted for time between HJHS measurement at T0 and T1 and history of joint surgery. Unstandardized β with 95% confidence intervals (95%-CI) were presented.

Sensitivity analyses were done with other cut-off scores (ΔHJHS-joint ≥|3|, ΔHJHS-total ≥|6|) for HJHS changes. In addition, the multivariate two-level regression was performed excluding the joints with a history of surgery.

Multiple imputations were used to impute missing data in this study.[23] Ten imputed data sets were created, which were analysed separately. The results of the 10 analyses were combined with the Rubin's rules.[23]

SPSS version 22 (IBM Corp., Armonk, New York, USA) was used for the statistical analyses.

TABLE 1 Patient characteristics

Patient characteristics (n = 62)	Median (IQR), n (%)
Age (y)	25.1 (20.8; 33.4)
BMI (kg/m^2)	24.0 (22.3; 27.4)
Haemophilia A	56 (90.3)
Severe haemophilia	45 (72.6)
Clotting factor	
No prophylaxis	17 (27.4)
Continuous prophylaxis	23 (37.1)
Non-compliant use of prophylaxis	14 (22.6)
Change prophylaxis to on demand or vice versa	8 (12.9)
Frequency of prophylaxis per week	3.0 (2.3; 3.0)
Dose of prophylaxis, IU	1000 (1000; 1000)
HCV-positive	12 (19.4)
HIV-positive	4 (6.5)
History of joint surgery	6 (9.7)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; HJHS, Haemophilia Joint Health Score; BMI, body mass index; IQR, interquartile ranges.

3 | RESULTS

3.1 | Patients and joint characteristics

Sixty-two patients were included in this post hoc analysis. Tables 1 and 2 show the patient and joint characteristics. Median age at baseline was 25.1 (mean age 28.4), ranging from 16 to 58 years. Forty-five patients had severe haemophilia. The follow-up period varied from 5.1 to 10.1 years, with a median of 8.0 years. A total of 372 joints were measured, including 9 joints after total joint replacement or arthrodesis. About half of the joints (47.8%) had ≥1 joint bleed between T0 and T1. The percentage of joints with ≥1 joint bleed and the median number of joint bleeds was highest for the ankle joints. Pettersson

TABLE 2 Joint characteristics at baseline and during follow-up

	Median (IQR), %			
	Elbow (n = 124)	Knee (n = 124)	Ankle (n = 124)	Total (n = 372)
Baseline characteristics				
HJHS	0.0 (0.0; 2.0)	0.0 (0.0; 1.0)	1.0 (0.0; 3.0)	0.0 (0.0; 2.0)
HJHS-joint level score ≥2	27.4	15.3	38.7	17.5
During follow-up (T0-T1)				
Joint bleeds	0.0 (0.0; 2.0)	0.0 (0.0; 1.0)	1.0 (0.0; 3.0)	0.0 (0.0; 2.0)
≥1 joint bleed	45.2	41.9	56.5	47.8
Synovitis	4.0	2.4	3.2	3.2
Before and during follow-up period				
History of joint surgery	0.8	1.6	4.8	2.4

HJHS, Haemophilia Joint Health Score; IQR, interquartile ranges.

scores and HAL scores were missing for, respectively, 45.2% (n = 28) and 22.6% (n = 14) of the patients. Joint bleeds of the elbows and knees were missing in 3.2% (n = 2) and of the ankles in 4.8% (n = 3) of the patients. Missing data were Missing at Random (MAR).

3.2 | Change in HJHS

Changes in HJHS-total scores (ΔHJHS ≥|4|) and HJHS-joint scores (ΔHJHS ≥|2|) are shown in Figure 1. HJHS-total score increased significantly ($P < .001$) from a median of 8.5 (IQR 3.8;14.8) at T0 to 11.0 (IQR 4.0;19.0) at T1. In 37.1% (n = 23) of the patients, the HJHS-total score increased by a minimum 4 points over time. HJHS-joint score remained stable with median scores of 0.0 (IQR 0.0;2.0) at T0 to 0.0 (IQR 0.0;3.0) at T1. In 17.5% (n = 65) of the joints, the HJHS-joint score deteriorated by a minimum of 2 points. Ankle joints (30.6%) showed deterioration more often than the elbows (18.5%) and knees (3.2%). The HJHS scores for knee joints did not change significantly from T0 to T1 (3.2% deterioration, $P = .060$). Improvement of joint health was found in a small proportion of the patients and joints (9.7% and 8.3%, respectively). Sensitivity analyses with higher cut-off scores (ΔHJHS-total ≥|6| and ΔHJHS-joint ≥|3|) showed higher rates of joints which stayed constant during follow-up (HJHS-total 66.1%, elbow 86.3%, knee 92.7% and ankle 71.8%). Ankle and elbow joints deteriorated more often.

In addition, a flow chart (Figure 2) was made to show the follow-up of joints without joint impairment at baseline. Of the joints without impairment (HJHS-joint ≤1) at baseline, with ≤1 joint bleed and no synovitis during follow-up, 91.9% of the joints maintained HJHS-joint scores ≤1 at T1.

3.3 | Factors associated with joint health deterioration

Multicollinearity was found between radiological status and joint health at baseline. Since joint health is more often available in daily care, joint health at baseline was included in the multivariate analyses. Use of prophylaxis correlated with severity of disease. Because use of prophylaxis correlated most with the other factors, this factor was not included in the multivariate analyses.

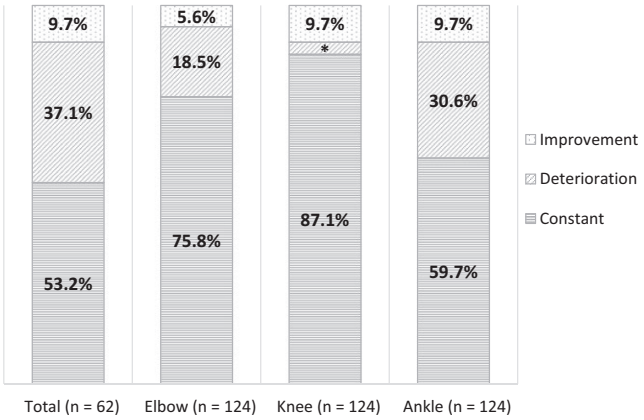

FIGURE 1 Change in Haemophilia Joint Health Score (HJHS)-total score and joint scores. ΔHJHS-total score deterioration ≥4; improvement ≥−4; constant from −3 to 3. ΔHJHS-joint score deterioration ≥2; improvement ≥−2; constant from −1 to 1. * = 3.2%

3.3.1 | Factors associated with overall change in joint health over time

Univariate linear regression analyses resulted in 2 factors significantly associated with ΔHJHS; severity of disease and total number of joint bleeds between T0 and T1. In the multivariate linear regression model severe haemophilia was the only factor associated with joint health deterioration (β [95%-CI]: 4.60 [1.07;8.13], $P = .011$). The univariate and multivariate linear regression models studying the potential factors associated with ΔHJHS-total score are presented in the Appendix S1.

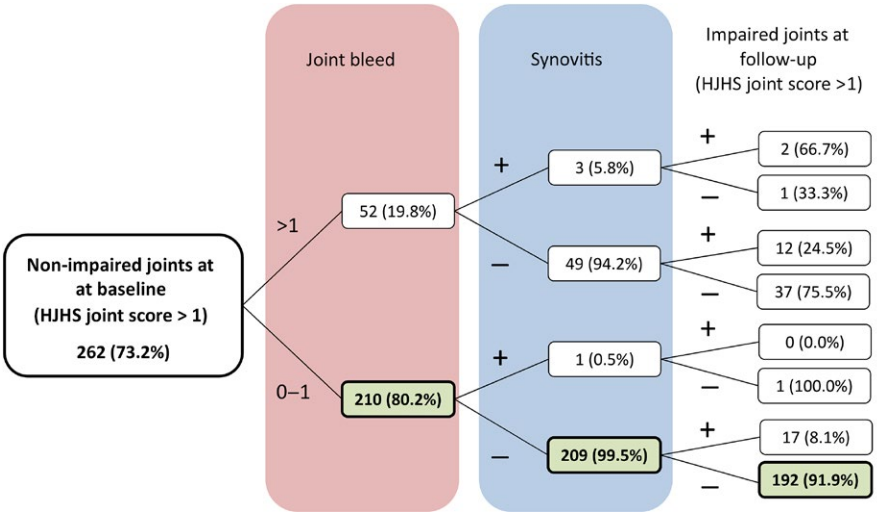

FIGURE 2 Observed development of HJHS-joint scores in non-impaired joints, stratified by reported joint bleeds (>1) and presence of synovitis during a 5- to 10-year follow-up. + present; − absent. Complete case analysis for joints. HJHS, Haemophilia Joint Health Score [Colour figure can be viewed at wileyonlinelibrary.com]

3.3.2 | Factors associated with change in joint health on joint level over time

The multivariate two-level regression models of factors associated with ΔHJHS-joint score are presented in Table 3, data on the univariate two-level regression models are shown in Appendix S1. Univariate two-level regression analyses resulted in 6 factors significantly associated with ΔHJHS; severity of disease, joint health at baseline, limitations in activities, joint type, number of joint bleeds and presence of synovitis. In the multivariate two-level regression analyses, 6 factors were independently associated with deterioration of HJHS-joint; better joint health at baseline, lower BMI, more limitations in activities, joint type, higher number of joint bleeds and presence of synovitis. The association between ΔHJHS and time between T0 and T1 was not significant ($P = .179$), signifying that follow-up times of 5 or 10 years did not influence the HJHS scores. Random slopes for the variables number of joint bleeds and joint health at baseline were added, which improved the model fit.

The sensitivity analysis of the multivariate two-level regression model excluding the joints with a history of joint surgery yielded similar results.

TABLE 3 Multivariate two-level regression model for Δ Haemophilia Joint Health Score (HJHS) at joint level

Potential factors	β (95%-CI)	*P*-value
Baseline characteristics		
Severe haemophilia (compared to moderate)	—	—
Joint health (per point)	−0.31 (−0.45; −0.18)	<.001
Age (y)	—	—
BMI (kg/m^2)	−0.05 (−0.11; +0.01)	.093
Limitations in activities (HAL, point)	−0.04 (−0.07; −0.02)	<.001
Joint type (knee = reference)		
Elbow	0.54 (+0.12; +0.97)	.012
Ankle	1.23 (+0.79; +1.66)	<.001
During follow-up (T0-T1)		
Joint bleeds (bleed)	0.21 (+0.10; +0.33)	<.001
Presence of synovitis	1.78 (+0.54; +3.01)	.005
Parameters used for adjustment of the model		
Time between HJHS measurement (y)	−0.13 (−0.28; +0.03)	.112
History of joint surgery	1.19 (−0.54; +2.91)	.179

HAL, Haemophilia Activity List.
Interpretation: after median 8.0 years, the HJHS-joint score increases by 1.05 points after 5 joint bleeds; 1.78 points in case of presence of synovitis; 0.54 and 1.23 points in elbow and ankle joints, respectively, compared to knee joints. The HJHS-joint score deteriorated less when patients had more joint impairment at baseline: ie 0.93 points less when the HJHS at T0 was 3 points higher. In addition, the HJHS deteriorated only 1 point when body mass index (BMI) was 20 kg/m^2 higher and 1 point when the HAL was 25 points higher.

4 | DISCUSSION

This study describes changes in joint health in PWH over a 5- to 10-year period as measured by the HJHS. After a median of 8.0 years, HJHS scores decreased in 37.1% of patients (≥4 points) and in 17.5% of joints (≥2 points). Deterioration was most prevalent in ankle joints (30.6%). The majority (91.9%) of joints without impairment at baseline, with ≤1 joint bleed and no synovitis during follow-up showed no deterioration during 5- to 10-year follow-up.

Both HJHS-total and HJHS-joint level factors associated with change in joint health were identified. Patients with severe haemophilia were more likely to show deterioration on the HJHS-total score than patients with moderate haemophilia. No other factors were associated with deterioration of the HJHS-total score. At joint level, the presence of synovitis, joint type and increased joint bleeds were the most important factors associated with deterioration. This information may be used to determine which joints need more frequent monitoring.

4.1 | Internal and external validity

Results of this study depend on both the population included and psychometric properties of the HJHS, which have not been widely investigated for adult PWH. The majority of the study population had very limited joint changes and low bleeding rates (median number of joint bleeds 0.0/joint [IQR 0.0;2.0] during follow-up of median 8 years) due to access to early prophylaxis. This is the population that the HJHS was designed for, but limits representativeness of these findings in settings with more prevalent arthropathy and/or higher bleeding rates.

In this study, several patients had undergone joint surgery. Currently, the HJHS manual does not give directions on how to score joints after surgery. Since the HJHS is recommended for adult patients nowadays, agreement among health professionals and researchers about scoring of joints in patients after joint surgery is needed. Given the uncertainty of how to score these joint, we performed a sensitivity analysis, which showed similar results.

For this longitudinal study with limited change rates adequate responsiveness of the HJHS is essential. Currently, information on responsiveness is still insufficient but the evidence regarding responsiveness is emerging. The HJHS was able to measure improvement in joint status 3 months after radiosynovectomy[24] and was able to distinguish between severe and non-severe haemophilia and different treatment groups.[9,13,16,25] In this study, sensitivity analysis of the cut-off scores for changes of the HJHS showed that higher cut-off scores resulted in more joints which are indicated as stable joints.

Finally, in this study, HJHS assessments were performed by 2 physical therapists who were experienced with the HJHS and trained together to calibrate HJHS assessment.

While most studies analyse joint health at patient level, we focused on both patient and joint level. Since most joints were unaffected, HJHS sum scores were low. Analyses at joint level gave more specific information about joint conditions. The more direct association of joint-specific factors on joint health may explain why at total and joint level different factors were associated with HJHS changes.

4.2 | Comparison with other studies

In this study, most patients showed minimal HJHS changes over time. This is in line with the minimal changes in joint health measured with the WFH physical examination score and radiologic Pettersson score in previous reports on young adults in Sweden and the Netherlands, who also have access to early prophylaxis.[6,7]

The observation that the ankle was the most affected joint in this study is in accordance with earlier observations.[26] It is hypothesized that physical abilities and activity levels of PWH increased after the institution of early prophylactic replacement therapy. The increased participation in sports and activities could have resulted in higher impact on ankle joints and thus a higher bleeding frequency in ankles compared to knees and elbows.[26] The number of bleeds at joint level during 8 years of follow-up was very low and only ankles, knees and elbows were considered. Overall joint bleed rates were not calculated and cannot be compared with other studies.

4.3 | Clinical implications and future research

Results suggest that not all patients need high frequent monitoring of all 6 joints by means of a complete HJHS. Time was not associated with joint health deterioration during a follow-up of 5 to 10 years. This implicates that monitoring all 6 joints every 5 years in PWH on long-term prophylaxis with low bleeding rates seems to be a safe interval when there are no reported bleeds or synovitis. However, less frequent monitoring of joints will only be safe in the presence of reliable and timely bleeding reporting. Particularly, joints suffering from repeated bleeding and/or synovitis are at risk for deterioration and should be closely and frequently monitored. The 3 factors 'better joint health at baseline', 'lower BMI' and 'more self-reported limitations in activities' were of minor interest for clinical practice because of small coefficients. In the absence of data on the optimum interval for monitoring joint health following synovitis and/or frequent bleeding, we suggest to follow the WFH guidelines and recommend monitoring these joints at least annually. Less frequent monitoring of joints without bleeding/synovitis saves time that can be used for efficient care in acute situations in PWH, especially by physical therapists. For more exact determination of the optimum interval, we suggest a study including more frequent measurements in this patient group. Although systematic and repeated joint health assessment by a trained physiotherapist does not directly improve joint health, it allows for early detection of changes and therefore adaptation of prophylactic treatment initiation of physiotherapy treatment. Moreover, confronting PWH with joint changes may promote adherence to prophylaxis.[27]

5 | CONCLUSION

Joint health deteriorated over 5-10 years in 37.1% of the patients with moderate or severe haemophilia and low joint bleeding rates. Ankle and elbow joints showed deterioration most frequently. Deterioration in joint health was associated with joint type, increased joint bleeding and presence of synovitis. Joints without impairment that suffered ≤1 joint bleed and no synovitis during follow-up remained healthy during 5- to 10-year follow-ups. Monitoring all 6 joints every 5 years seems to be a safe interval when there are no reported bleeds or synovitis in PWH with access to early prophylaxis.

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All authors contributed to the design of the study, IK and MT performed the statistical analyses, IK wrote the first draft of the paper, all authors contributed to interpretation of the data, modification of statistical analyses and the writing of the manuscript.

DISCLOURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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