Received: 13 September 2023 | Revised: 13 January 2024 | Accepted: 9 February 2024

https://doi.org/10.1016/j.rpth.2024.102355

ORIGINAL ARTICLE

Arthropathy on X-rays in 363 persons with hemophilia: long-term development, and impact of birth cohort and inhibitor status

Dayna A. M. van Heel[1] | Wouter Foppen[2] | Kathelijn Fischer[1]

[1]Center of Expertise for Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

[2]Department of Radiology and Nuclear Medicine, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

Correspondence
Kathelijn Fischer, Center of Expertise for Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, Heidelberglaan 100, Utrecht, 3508 GA, the Netherlands.
Email: K.Fischer@umcutrecht.nl

Handling Editor: Dr Michael Makris

Abstract

Background: Arthropathy following repeated bleeding is common in persons with hemophilia. Since the introduction of prophylaxis, treatment has intensified and joint health has improved. However, data on the long-term development of arthropathy are still scant.

Objectives: To evaluate long-term arthropathy development since the introduction of prophylaxis according to birth cohort, hemophilia severity, and inhibitor status.

Methods: This single-center historic cohort study included persons with severe and moderate hemophilia A and hemophilia B born between 1935 and 2005. Arthropathy on X-rays was evaluated using the Pettersson score. Patient and joint characteristics were studied per birth cohort (<1970, 1970-1980, 1981-1990, and >1990) and compared according to hemophilia severity. The distribution of affected joints and cumulative incidence of arthropathy were analyzed. The association of Pettersson score with birth cohort and inhibitor characteristics was explored using multivariable regression analyses adjusted for age at evaluation.

Results: In total, 1064 X-rays of 363 patients were analyzed. Of persons with severe hemophilia (n = 317, 87.3%), 244 (77.0%) developed arthropathy. Prophylaxis was started at younger ages over time, from a median of 18 to 2.1 years, and concomitantly, arthropathy decreased in consecutive birth cohorts. Ankles were most commonly affected in 188 of 258 (72.9%) patients. Persons with moderate hemophilia (n = 46, 12.7%) had a lower risk of arthropathy (27/46 [58.7%]), but a reduction over time was less pronounced. In the multivariable analyses, birth cohort and age at evaluation were predictors for the development of arthropathy, while inhibitor status showed no association.

Conclusion: The development and severity of arthropathy have decreased over the past decades. However, patients have remained at risk for developing arthropathy, especially in their ankles.

KEYWORDS
birth cohort, cohort studies, hemophilia A, hemophilia B, joint diseases, X-rays

Essentials

- Joint damage due to bleeds is common in persons with hemophilia, impairing quality of life.
- Long-term joint damage development and its predictors were studied in 1064 X-rays of 363 patients.
- Birth cohort and age at X-ray evaluation were independent determinants of joint damage.
- Ankles remained most susceptible to joint damage in the youngest birth cohorts.

1 | INTRODUCTION

Hemophilia is a rare hereditary X-linked recessive genetic disorder characterized by impaired blood coagulation due to a lack of functional clotting factor (F)VIII in hemophilia A or FIX in hemophilia B [1]. In the Netherlands, the prevalences of hemophilia A and B are estimated to be 17 and 2 per 100,000 males, respectively [2,3]. The severity of hemophilia is determined based on residual clotting factor levels and is classified as severe (<0.01 IU/mL), moderate (0.01-0.05 IU/mL), or mild (0.05-0.40 IU/mL). Persons with severe hemophilia have the highest risk of spontaneous bleeds, while persons with moderate and mild hemophilia often have a milder bleeding phenotype [1].

Arthropathy following repeated joint bleedings (hemarthrosis) is a common comorbidity in persons with hemophilia. Intra-articular blood leads to a multifactorial process of blood-induced joint destruction [4]. Previous research showed that health-related quality of life in persons with hemophilia is often impaired and strongly related to the frequency of joint bleeds and the extent of hemophilic arthropathy [5–7].

In order to prevent (joint) bleeds and subsequent arthropathy, prophylaxis with clotting factor replacement treatment was introduced in the 1970s. Over the past decades, as clotting factor products became more widely available, prophylaxis has been started earlier, and concomitantly, the number of accepted joint bleeds per year decreased and joint health improved [8–13]. Another factor affecting the efficacy of prophylaxis and bleeding control is the development of neutralizing antibodies (inhibitors) against FVIII or FIX. The development of inhibitors occurs in approximately 30% of persons with hemophilia A [14] and 10% of persons with hemophilia B [15]. For ±66% of persons with hemophilia A, inhibitors can be eradicated by immune tolerance induction. However, hemophilia B inhibitor eradication is generally more difficult [16]. The development of inhibitors is a serious complication and leads to an increased bleeding risk [17].

Studies on treatment intensity and long-term arthropathy have been limited due to short follow-up and low patient numbers. Especially, data on patients with past or present inhibitors are lacking. Therefore, the primary objective was to evaluate the long-term development of arthropathy according to birth cohort since the introduction of prophylaxis in persons with severe hemophilia. The secondary objectives were to evaluate the distribution of arthropathy per joint and compare arthropathy according to hemophilia severity and inhibitor status.

2 | METHODS

2.1 | Study design, subjects, and setting

In this single-center retrospective cohort study, persons with severe and moderate hemophilia A and hemophilia B (FVIII and FIX activity <0.01 IU/mL and 0.01-0.05 IU/mL, respectively) born between 1935 and 2005 with information on long-term treatment and at least 1 X-ray evaluation of elbows, knees, and ankles available were included. Patients were treated and had routine X-ray evaluations performed at the Van Creveldkliniek, University Medical Centre Utrecht, Utrecht, the Netherlands. Ethical approval was obtained from the Medical Ethics Committee of the Utrecht Medical Centre Utrecht (number 22-725).

2.2 | Data collection and X-ray scoring

Patient and treatment characteristics were independently extracted from preexisting research databases [18–21] and combined. Extracted characteristics included the severity of hemophilia, year of birth, age at X-ray evaluation, age at the start of prophylaxis, age at inhibitors, and duration of inhibitors. Data were anonymized before analysis.

The primary outcome measure of the study was presence and severity of arthropathy quantified using the validated radiologic Pettersson score (PS) [22] on X-rays of elbows, knees, and ankles, taken at ±5-year intervals during usual care. The PS classifies hemophilic arthropathy according to 8 radiologic parameters for osteochondral joint changes on a 0 to 1 or 0 to 2 point scale. Each elbow, knee, and ankle is scored from 0 to 13, resulting in a total PS ranging from 0 to 78 points. An abnormal total PS at patient level was defined as ≥3. An abnormal score at joint level was defined as ≥1 [23]. After joint replacement surgery/arthrodesis, joints were scored as 13 on joint level. PSs were assessed by 2 trained radiologists.

2.3 | Data analysis

Data were analyzed using R version 4.2.0 and IBM SPSS Statistics 27. Missing data were handled using pairwise deletion. Categorical variables were reported as frequencies and percentages. For continuous

variables, the normality of distribution was assessed using visual inspection and Shapiro–Wilk test for normality. Continuous variables were reported with appropriate measures of central tendency and dispersion. When multiple PSs were available per patient, the last registered score was used unless specified otherwise. *P* values of ≤0.05 were considered statistically significant.

2.3.1 | Development of hemophilic arthropathy

As hemophilia treatment became more widely available over the past decades, arthropathy development was studied according to the following birth cohorts: <1970, 1970-1980, 1981-1990, and >1990 [13,18]. These birth cohorts are described in the Box. Persons with severe hemophilia were divided into the aforementioned birth cohorts, and characteristics were analyzed accordingly.

Total PS at patient level was visualized per birth cohort using graphs. Every PS per patient was taken into account and clustered into age categories according to age at X-ray evaluation (<20, 20-30, 31-40, and >40 years). These age categories were made pragmatically to evaluate the trend of arthropathy at group level at 10-year intervals. One minus survival analyses were performed to estimate the cumulative incidence of an abnormal PS at patient and joint levels for patients in birth cohorts 1981-1990 and >1990 to evaluate the differences between birth cohorts.

Distribution of hemophilic arthropathy: The prevalence of arthropathy per joint was studied per birth cohort based on the presence of minimally one abnormal joint score per bilateral elbows, knees, and ankles.

Arthropathy in moderate hemophilia: Patient and treatment characteristics and development of arthropathy of persons with moderate hemophilia were compared with persons with severe hemophilia. Categorical variables were analyzed using the chi-squared test, and continuous variables were analyzed using the Mann–Whitney U-test. Total PS at patient level was visualized similarly as described for persons with severe hemophilia.

2.3.2 | Predictors of hemophilic arthropathy

Treatment characteristics: To evaluate the association between birth cohort and arthropathy independently of other determinants, regression analysis based on generalized linear modeling (GLM) was performed. Due to an excessive number of 0 values and the right-skewed distribution of the PS, regression analysis was divided into 2 parts. First, a binary logistic regression model was used to assess the association between birth cohort and the presence of arthropathy (defined as abnormal total PS at patient level). Second, for the patients with arthropathy, a GLM (gamma distribution with log-link) was used to further investigate the effect of birth cohort on the severity of arthropathy.

Inhibitor development: The independent effects of inhibitor development (defined as age at inhibitors and duration of inhibitors) on the presence and severity of arthropathy were studied using the same regression models.

BOX. Treatment according to birth cohort [13,18].

Birth cohort	Treatment
<1970	No access to early clotting factor replacement therapy
1970-1980	Clotting factor replacement therapy (on-demand/prophylaxis) became available for patients in their childhood
1981-1990	Prophylaxis became standard of care
>1990	Primary prophylaxis. Prophylaxis was gradually started at a younger age, and fewer bleeds were accepted

Univariable analyses were performed, and determinants were selected for the multivariable model when the threshold of *P* value of ≤.1 was met. If both birth cohort and age at the start of prophylaxis were eligible for inclusion in the multivariable model, only birth cohort was included as both determinants are highly correlated. Multivariable analyses were adjusted for age at the last X-ray evaluation.

3 | RESULTS

In this study, a total of 363 patients were included. Patients were born between 1935 and 2005. Radiologic data were collected between 1975 and 2022. The youngest patient was aged 7.1 years at the first X-ray evaluation; the oldest was aged 79.1 years at the last evaluation. A total PS was available for all X-ray evaluations. PSs at joint level were available for 304 of 363 (83.7%) patients.

3.1 | Patient characteristics

Of the 363 included patients, 317 (87.3%) had severe hemophilia and 46 (12.7%) had moderate hemophilia. Patient and joint characteristics of persons with severe hemophilia are presented per birth cohort in Table 1. Of 317 persons with severe hemophilia, 299 (94.3%) received prophylaxis. The proportion of severe patients receiving prophylaxis at one point during their treatment remained relatively constant between birth cohorts and varied between 90.2% and 98.3%. However, age at the start of prophylaxis became earlier over time, from a median of 18 years (IQR, 13.1-30.6) <1970 to 2.1 years (IQR, 1.4-3.8) >1990.

3.2 | Development of hemophilic arthropathy

In persons with severe hemophilia, the development of arthropathy reduced over time in consecutive birth cohorts. As depicted in Figure 1A, patients born <1970 had the most arthropathy for all age

TABLE 1 Characteristics of persons with severe hemophilia per birth cohort.

Birth cohort	<1970	1970-1980	1981-1990	>1990
Patients	136 (42.9)	70 (22.1)	60 (18.9)	51 (16.1)
X-rays	356 (35.5)	325 (32.4)	218 (21.8)	103 (10.3)
Age at last evaluation	45.6 (36.7-51.3)	38.5 (31.3-41.8)	26.6 (20.6-30.6)	17.5 (14.6-21.6)
Treatment history				
Received prophylaxis	127/136 (93.4)	67/70 (95.7)	59/60 (98.3)	46/51 (90.2)
Age at the start of prophylaxis	18.0 (13.0-31.3)	5.8 (4.0-9.0)	4.2 (2.6-5.9)	2.1 (1.3-3.8)
Inhibitors				
History of inhibitors	13/136 (9.6)	10/70 (14.3)	8/60 (13.3)	6/51 (11.8)
Age at inhibitors	17.4 (7.2-32.6)	4.0 (2.0-17.5)	2.6 (1.7-4.9)	1.5 (0.8-1.8)
Duration of inhibitors	6.0 (0.6-13.3)	5.0 (0.9-10.3)	0.8 (0.4-4.4)	0.7 (0.4-2.1)
History of long-standing inhibitors (≥1 y)	5/8 (62.5)	5/7 (71.4)	3/8 (37.5)	2/5 (40.0)
Outcome				
Total PS (0-78)	45.5 (32.0-59.0)	19.0 (8.5-26.5)	4.5 (1.0-12.5)	0 (0-2.0)
Abnormal total PS (≥3)	132/136 (97.1)	63/70 (90.0)	38/60 (63.3)	11/51 (21.6)
PS elbow (0-26)	17 (8-24.25)	3 (0-9)	0 (0-5)	0 (0-0)
Abnormal PS elbow (≥1)	82/90 (91.1)	39/63 (61.9)	22/54 (40.7)	7/51 (13.7)
PS knee (0-26)	16.50 (6-26)	2 (0-5)	0 (0-1)	0 (0-0)
Abnormal PS knee (≥1)	78/90 (86.7)	35/63 (55.6)	15/54 (27.8)	2/51 (3.9)
PS ankle (0-26)	21 (14-26)	11 (4-16)	2 (0-6.5)	0 (0-0)
Abnormal PS ankle (≥1)	88/90 (97.8)	56/63 (88.9)	32/54 (59.3)	12/51 (23.5)

Data are presented as *n* (%), *n/N* (%) or median (IQR, P25-P75). Age and duration are reported in years. Abnormal PS at joint level is noted as an abnormal score for minimally 1 joint.

PS, Pettersson score.

categories. Patients born in the birth cohorts after 1970 showed both a gradual reduction in arthropathy severity per age category as well as a less pronounced increase in arthropathy with age.

Figure 2 shows the cumulative incidence of the development of arthropathy in birth cohorts 1981-1990 and >1990. The proportion of patients with an abnormal total PS was lower for

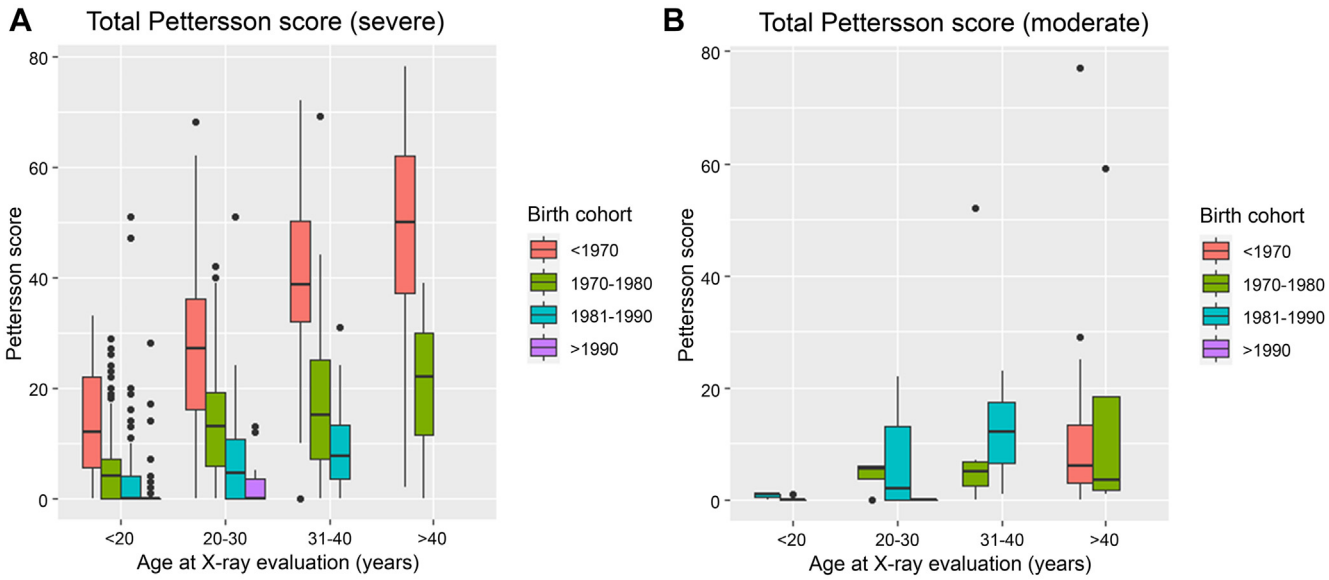

FIGURE 1 Comparison per birth cohort of the total Pettersson score according to the age at X-ray evaluation of (A) persons with severe hemophilia and (B) persons with moderate hemophilia. All available X-ray evaluations were taken into account (total 1064).

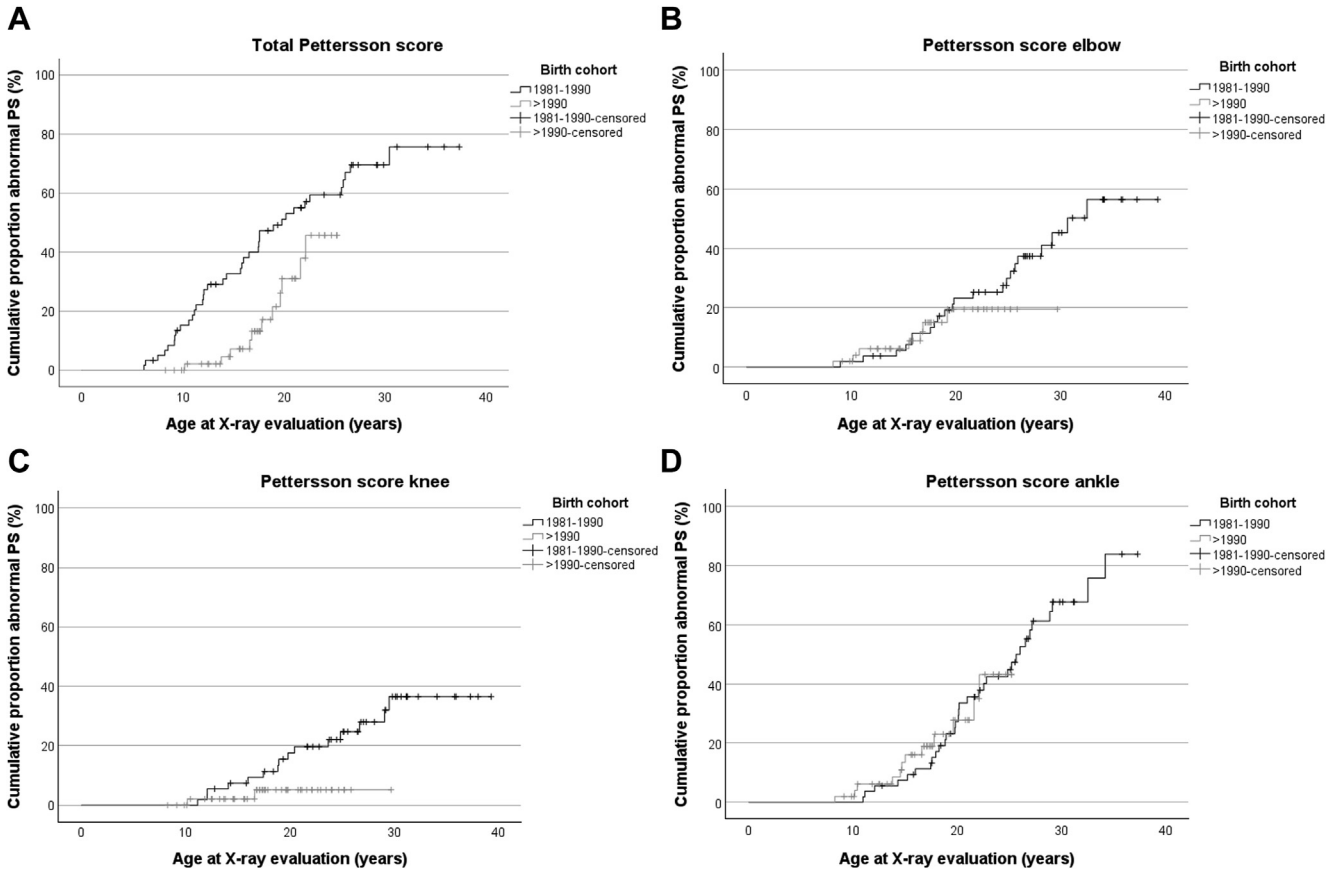

FIGURE 2 One minus survival plot estimate for the cumulative incidence of arthropathy according to age at X-ray evaluation, comparing birth cohorts 1981-1990 and >1990. (A) All joints, (B) elbows, (C) knees, and (D) ankles. PS, Pettersson score.

patients born >1990 than for patients born between 1981 and 1990 over the whole follow-up period (Figure 2A). A similar pattern could be observed for knees (Figure 2C), while for elbows and ankles, the cumulative incidence remained relatively stable (Figure 2B, D).

3.2.1 | Distribution of hemophilic arthropathy

PSs at joint level were available for 258 of 317 (81.4%) persons with severe hemophilia and are presented in Table 1. Ankles were most affected by arthropathy among all birth cohorts, with 88/90 (97.8%) patients born <1970 and 12/51 (23.5%) patients born >1990 having minimally 1 affected ankle. Among all birth cohorts, knees were affected the least, with the proportion of patients with arthropathy ranging from 78/90 (86.7%) born <1970 to 2/51 (3.9%) born >1990. Moreover, between birth cohorts, the proportion of patients with arthropathy in their knees decreased most strongly by 82.8% between <1970 and >1990. For elbows and ankles, the proportion of patients with arthropathy decreased by 77.4% and 74.3%, respectively.

3.2.2 | Arthropathy in moderate hemophilia

Patient and joint characteristics of persons with severe and moderate hemophilia are presented in Supplementary Table S1. Similar to persons with severe hemophilia, prophylaxis for persons with moderate hemophilia was started progressively earlier, as visualized in the Supplementary Figure. Nevertheless, persons with moderate hemophilia received prophylaxis less often compared with persons with severe hemophilia (12/46 [26.1%] vs 299/317 [94.3%], respectively). Moreover, persons with moderate hemophilia started prophylaxis only at a median age of 13.8 years (IQR, 7.9-49.1 years) compared with 8.4 years (IQR, 3.9-17.2 years) in those with severe hemophilia.

As shown in Figure 1B, persons with moderate hemophilia had a lower chance of developing arthropathy. However, a decrease in arthropathy in consecutive birth cohorts was less pronounced. Knees were most affected by arthropathy, with 24/46 (52.2%) patients having an abnormal PS at the joint level. Elbows and ankles were both affected in 19/46 (41.3%) patients. When persons with severe and moderate hemophilia were compared, as shown in Supplementary Table S1, elbows and ankles were more frequently

TABLE 2 Univariable and multivariable logistic regression for presence of arthropathy and gamma regression for severity of arthropathy analysis for determinants of total Pettersson score in persons with severe hemophilia.

Determinant	Univariable Exp(B) (95% CI)	Multivariable Exp(B) (95% CI)
Presence of arthropathy		
Birth cohort		
<1970	1	1
1970-1980	0.26 (0.07-0.93)	0.40 (0.11-1.49)
1981-1990	0.05 (0.02-0.16)	0.17 (0.05-0.60)
>1990	0.01 (0.00-0.03)	0.05 (0.01-0.20)
Age at the last evaluation	1.16 (1.12-1.20)	1.08 (1.03-1.13)
Treatment history		
Age at the start of prophylaxis	1.29 (1.19-1.40)	-
Inhibitors		
Age at inhibitors	1.09 (0.94-1.27)	-
Duration of inhibitors	1.19 (0.89-1.59)	-
Severity of arthropathy		
Birth cohort		
<1970	1	1
1970-1980	0.44 (0.37-0.53)	0.49 (0.41-0.59)
1981-1990	0.27 (0.22-0.34)	0.36 (0.28-0.47)
>1990	0.19 (0.14-0.28)	0.28 (0.18-0.41)
Age at last evaluation	1.04 (1.03-1.04)	1.01 (1.01-1.02)
Treatment history		
Age at the start of prophylaxis	1.02 (1.01-1.03)	-
Inhibitors		
Age at inhibitors	1.01 (0.98-1.03)	-
Duration of inhibitors	1.02 (0.97-1.07)	-

Exp(B) from the logistic regression analyses for the presence of arthropathy are presented as odds ratios, and Exp(B) from the gamma regression analyses for the severity of arthropathy as incidence rate ratios. Multivariable regression analyses included birth cohort, adjusted for age at the last evaluation. *Interpretation gamma regression:* coefficients were interpreted as multiplicative effects. For example, the incidence of arthropathy (total Pettersson score at patient level ≥3) among patients in birth cohort 1970-1980 (Exp[B] = 0.49) is 49% of the incidence of arthropathy among patients born <1970.

and severely affected in the former, while no difference in knees was found.

3.3 | Predictors of hemophilic arthropathy

3.3.1 | Treatment characteristics

The results of the regression analyses are presented in Table 2. Univariable regression analyses showed that birth cohort, age at the last X-ray evaluation, and age at the start of prophylaxis were associated with both the presence and severity of arthropathy.

To predict the presence of arthropathy with the multivariable binary logistic analysis, birth cohort and age at the last X-ray evaluation were included in the model and remained independent predictors, as shown in Table 2. Patients born between 1981 and 1990 and >1990 showed lower odds of having an abnormal PS, independent of the age at the last X-ray evaluation (0.17 [95% CI, 0.05-0.60] and 0.05 [95% CI, 0.01-0.20], respectively). Patients born between 1970 and 1980 showed comparable odds of an abnormal PS compared with patients born <1970 (0.40 [95% CI, 0.11-1.49]; P = .17). Age at the last X-ray evaluation showed a factor of 1.08 (95% CI, 1.03-1.13) higher odds of an abnormal PS per year of age as a result of age-related joint deterioration. In Supplementary Table S2, patient and treatment characteristics are summarized for persons with severe hemophilia divided by normal and abnormal total PS.

Results of the multivariable GLM analysis regarding determinants of the severity of arthropathy are shown in Table 2. Birth cohort and age at the last X-ray evaluation were included in the model and remained independent predictors. PSs were highest for patients born <1970 and decreased steadily in consecutive birth cohorts independent of the age at the last X-ray evaluation. Compared with patients born <1970, patients born between 1970 and 1980 and 1981 and 1990 showed an improvement in joint health (lower PS) due to the intensification of the prophylactic treatment (factor 0.49 [95% CI, 0.41-0.59] and 0.36 [95% CI, 0.28-0.47], respectively). Patients born >1990 showed the largest improvement in joint health of factor 0.28 (95% CI, 0.18-0.41). Birth cohort was adjusted for age at the last X-ray evaluation, which showed a factor 1.01 (95% CI, 1.01-1.02) increase in PS per year of age due to age-related joint deterioration.

3.3.2 | Inhibitor status

Due to the data extraction from a combination of preexisting databases, which excluded long-term inhibitors, only 37 (11.7%) of the 317 included persons with severe hemophilia had inhibitors at one point during their prophylactic treatment (Table 1). The proportion of severe patients per birth cohort with inhibitors remained relatively constant, ranging from 9.6% to 14.3%. As inhibitors mostly develop in the first 50 exposure days, in accordance with age at the start of prophylaxis, the age at inhibitors also became progressively earlier in consecutive birth cohorts: from a median of 17.4 years (IQR, 8.2-28.1) (<1970) to 1.5 years (IQR, 0.8-1.6) (>1990). A decrease in the duration of inhibitors included was most pronounced between the birth cohorts 1970-1980 and 1981-1990, from a median duration of 5 years (IQR, 1.0-9.0) in 1970-1980 to 0.8 years (IQR, 0.4-3.3) in 1981-1990. Inhibitor status was not associated with the presence of joint abnormalities on X-ray.

Univariable regression analysis for age at inhibitors and duration of inhibitors was performed for persons with severe hemophilia (see Table 2). In this cohort, neither age at inhibitors nor duration of

inhibitors was associated with either the presence or severity of arthropathy. Therefore, the age at inhibitor development and duration of inhibitors were not included in the final multivariable regression models.

4 | DISCUSSION

4.1 | Principal findings

This cohort study aimed to investigate the long-term development of arthropathy and its predictors in persons with hemophilia A and hemophilia B born between 1935 and 2005. The development of arthropathy decreased for persons with severe hemophilia born after 1970 when clotting factor replacement therapy—first as on-demand treatment and later as prophylaxis—became more widely available. Ankles were the most commonly affected joint, followed by elbows and knees. In comparison, persons with moderate hemophilia showed less arthropathy, but a decrease in arthropathy development over time was less pronounced. In multivariable analysis, birth cohort and age at the last X-ray evaluation were the strongest predictors for the development of arthropathy. Age at inhibitors and duration of inhibitors showed no association with long-term arthropathy development.

4.2 | Strengths and limitations

One of the strengths of this study is the long-term follow-up and inclusion of patients born before 1970 when prophylactic therapy was not yet widely available. A large number of persons with severe hemophilia were included, which allowed us to study them in predefined birth cohorts. Additionally, persons with moderate hemophilia were studied. Despite the limited number of persons with moderate hemophilia, these results support evidence of the differences in phenotype between severity levels. Further, X-rays were evaluated by 2 trained radiologists. Therefore, the risk of interobserver bias was minimalized.

Some limitations need to be addressed as well. The present study combined preexisting databases to evaluate the long-term arthropathy development since the introduction of prophylaxis, which excluded long-term inhibitors in most studies [18–20], except one that included patients with long-term inhibitors [21]. This has probably led to an underestimation of the predictive value of inhibitor development on arthropathy in the present data. Due to the retrospective design of the cohort study and the use of data collected over an extended period of time, there were some missing data. Nevertheless, overall, only a small proportion of patients (18/363 [5%]) had missing data in 1 or more of the determinants of interest. However, one minus survival analyses could not be performed for the older birth cohorts (<1970 and 1970-1980), as these results would have been biased due to an older age at the first X-ray evaluation. Furthermore, no information was available on race and ethnicity of the included patients, which made it not possible to assess their potential effects on treatment characteristics and arthropathy development. Moreover, information on joint bleeds before the start of prophylaxis was not available for all patients. However, as the number of accepted joint bleeds before the initiation of prophylaxis decreased over the past decades, the comparison between birth cohorts indirectly took bleeds into account. Therefore, the results suggest the cumulative effect of joint bleeds and the improvement of clotting factor replacement therapy over time. Lastly, due to the excess number of 0 values and the right-skewed distribution of the PS, it was not feasible to study all patients in a single regression model. Nevertheless, despite this challenge, the use of 2 regression models allowed us to gather more information on both the presence and severity of arthropathy development.

4.3 | Comparison with previous publications

4.3.1 | Development of hemophilic arthropathy

In this cohort, the development of arthropathy decreased over time and started to show up later on X-ray evaluation in consecutive birth cohorts. Ankles were most commonly affected by arthropathy, followed by elbows and knees. It is suggested that the availability of prophylaxis enabled patients to participate in sports and other high-impact activities, making ankles the most vulnerable joints [24].

Persons with moderate hemophilia experienced less arthropathy than persons with severe hemophilia despite receiving prophylaxis less often and starting at an older age. These results are in accordance with those of Schmidt et al. [25], who studied 141 adolescents with severe and moderate hemophilia aged a median of 15 years. Persons with moderate hemophilia received prophylaxis in 61% vs 91% in severe hemophilia and were older at the start (median, 5.3 years [IQR, 3.9-8.6 years] vs 1.5 years [IQR, 1.3-2.3 years]) but showed fewer joint changes than those with severe hemophilia using the Haemophilia Early Arthropathy Detection with Ultrasound score [25].

4.3.2 | Predictors of hemophilic arthropathy

The development of arthropathy was best predicted by birth cohort and age at the last X-ray evaluation. Nijdam et al. [8] predicted long-term PSs in 124 persons with severe hemophilia born since 1965, with a median age of 22 years (IQR, 15.6-29.5). In patients starting prophylaxis at ≥6 years of age, the highest PS and greatest age-related increase were found, while patients starting at <3 years of age had the lowest scores [8]. These findings were consistent with results found by Khawaji et al. [26] in 81 persons with severe hemophilia born between 1932 and 1992. They found that patients who started prophylaxis at ≤3 years of age had better joint outcomes using the Hemophilia Joint Health Score than those of patients starting at >3 years of age (median, 3 years [range, 0-19 years] vs 40 years [range, 0-64 years]; $P < .001$). Further, in patients who started at >3 years of age,

age at the start of prophylaxis and age at evaluation were correlated with the joint outcome score (r = 0.69; $P < .001$ and r = 0.60; $P < .001$, respectively) [26]. This is in line with the current findings, as age at the start of prophylaxis became gradually younger in consecutive birth cohorts, and long-term arthropathy development decreased accordingly.

Despite the finding that patients with an abnormal PS were diagnosed with inhibitors at an older age and were positive for a longer duration, no associations between arthropathy development and inhibitors were found in regression analyses. This is in contrast to prior studies suggesting worse joint outcomes for patients with inhibitors. Morfini et al. [27] performed a case-control study and included 87 persons with severe hemophilia aged 14 to 35 years, of whom 38 (43.7%) had an inhibitor. They found higher PSs for patients with permanent/long-term (>5 years) inhibitors of 22.9 (SD, 14.3) than patients with no/past inhibitors of 8.0 (SD, 10.2), (95% CI, 8.25-24.10; $P < .05$) [27]. Schmidt et al. [25] found a 2-fold increased proportion of joint damage for adolescents (median, 15 years) with severe hemophilia and current/past inhibitors and a moderate correlation (Spearman's rho = 0.50) between the duration of inhibitors and Hemophilia Joint Health Score. This difference might be due to inadequate statistical power in the present study since only a small proportion (37/317 [11.7%]) of patients had inhibitors, with missing data on age at development of inhibitors and duration of inhibitors in 7 of 37 (18.9%) and 9 of 37 (24.3%) patients, respectively.

4.4 | Future perspectives

Over time, arthropathy on X-rays appeared later in life. However, despite improvements, persons with hemophilia remain at risk for developing arthropathy as not all joint bleeds can be prevented. In the youngest birth cohort evaluated (>1990), the majority of patients aged <20 years did not show arthropathy on X-rays of elbows, knees, or ankles. However, prior research showed that both magnetic resonance imaging (MRI) and ultrasound were able to detect soft-tissue and osteochondral changes in patients without signs of arthropathy on X-rays [28]. It was found that soft-tissue changes on MRI could predict joint bleeding risk and arthropathy development after 5 years [29]. Further, MRI could detect signs of subclinical bleeds in joints without a bleeding history [30]. This indicates that, despite adequate prophylactic treatment, (subclinical) joint bleeds and changes may occur. Early identification of these changes may help clinicians to further tailor prophylactic treatment to the patients' individual needs. New treatment strategies for hemophilia, like nonfactor replacement therapies and gene therapy, may reduce the risk of joint bleeds even further [31,32]. As X-rays are not sensitive to detect early blood-induced joint changes, ultrasound and MRI are of interest for the evaluation of these new treatment strategies. Routine use of X-rays therefore contributes less to the evaluation of joint status in patients aged <20 years with access to early prophylaxis and/or new treatments for hemophilia. Nevertheless, X-rays remain a commonly used method for the radiologic evaluation of joints [33–35] and of value for long-term follow-up when initial joint changes have occurred.

5 | CONCLUSIONS

Decreased levels of arthropathy development were seen in consecutive birth cohorts. Over time, ankles remained the most affected, while knees were affected least and showed the strongest decrease in arthropathy development. Persons with moderate hemophilia had a lower chance of arthropathy, but the development was less affected by birth cohort. Birth cohort and age at the last X-ray evaluation showed to be the best predictors for arthropathy development, while inhibitor development showed no association with joint status in this cohort due to the exclusion of long-term inhibitors in the databases used. However, despite improvements in treatment, persons with hemophilia remain susceptible to developing arthropathy. Future research is needed to investigate the impact of interventions on early soft-tissue and osteochondral changes on long-term joint health.

FUNDING

This research received no external funding.

ETHICS STATEMENT

Ethical approval was obtained from the Medical Ethics Committee of the Utrecht Medical Centre Utrecht (number 22-725), individual patient informed consent was waivered.

AUTHOR CONTRIBUTIONS

D.A.M.v.H. conducted analysis and visualization and wrote the final manuscript. W.F. and K.F. conceptualized the study, interpreted the data, critically reviewed and edited the manuscript, and supervised the conduct of the study.

RELATIONSHIP DISCLOSURE

D.A.M.v.H. has no competing interests. W.F. has received research grants from Novo Nordisk and Pfizer and performed consultancy activities for Pfizer. K.F. has acted as a consultant and participated in expert groups for Bayer, Biogen, CSL Behring, Novo Nordisk, and SOBI; has received research grants from Bayer, Novo Nordisk, Pfizer; has given invited educational lectures for Bayer, Novo Nordisk, and Pfizer; and has received travel support from SOBI and Bayer.

REFERENCES

[1] Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26:1–158.

[2] Stonebraker JS, Bolton-Maggs PHB, Michael Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia*. 2010;16:20–32.

[3] Stonebraker JS, Bolton-Maggs PHB, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia B prevalence

around the world. *Haemophilia*. 2012;18:e91–4. https://doi.org/10.1111/j.1365-2516.2011.02588.x

[4] Pulles AE, Mastbergen SC, Schutgens REG, Lafeber FPJG, van Vulpen LFD. Pathophysiology of hemophilic arthropathy and potential targets for therapy. *Pharmacol Res*. 2017;115:192–9.

[5] Zhang H, Huang J, Kong X, Ma G, Fang Y. Health-related quality of life in children with haemophilia in China: a 4-year follow-up prospective cohort study. *Health Qual Life Outcomes*. 2019;17:28. https://doi.org/10.1186/s12955-019-1083-3

[6] Niu J, Ning L, Zhang Q, Liu Z, Ma Y, Xu X, et al. Health-related quality of life of patients with haemophilia: a cross-sectional survey in the Northeast of China. *BMJ Open*. 2022;12:e056668. https://doi.org/10.1136/bmjopen-2021-056668

[7] Fischer K, Bom JG, Mauser-Bunschoten EP, Roosendaal G, Berg HM. Effects of haemophilic arthropathy on health-related quality of life and socio-economic parameters. *Haemophilia*. 2005;11:43–8.

[8] Nijdam A, Foppen W, van der Schouw YT, Mauser-Bunschoten EP, Schutgens REG, Fischer K. Long-term effects of joint bleeding before starting prophylaxis in severe haemophilia. *Haemophilia*. 2016;22:852–8.

[9] Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, de Kleijn P, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. *Blood*. 2002;99:2337–41.

[10] Fischer K, de Kleijn P, Negrier C, Mauser-Bunschoten EP, van der Valk PR, van Galen KPM, et al. The association of haemophilic arthropathy with health-related quality of life: a post hoc analysis. *Haemophilia*. 2016;22:833–40.

[11] van den Berg HM, Fischer K, Mauser-Bunschoten EP, Beek FJ, Roosendaal G, van der Bom JG, et al. Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol*. 2001;112:561–5.

[12] Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients - a long-term follow-up. *J Intern Med*. 1997;241:395–400.

[13] Nijdam A, Altisent C, Carcao MD, Cid AR, Claeyssens-Donadel S, Kurnik K, et al. Bleeding before prophylaxis in severe hemophilia: paradigm shift over two decades. *Haematologica*. 2015;100:e84–6.

[14] Berntorp E, Shapiro A, Astermark J, Blanchette VS, Collins PW, Dimichele D, et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. *Haemophilia*. 2006;12(Suppl 6):1–7.

[15] Male C, Andersson NG, Rafowicz A, Liesner R, Kurnik K, Fischer K, et al. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: a PedNet study. *Haematologica*. 2021;106:123–9.

[16] Ljung R, Auerswald G, Benson G, Dolan G, Duffy A, Hermans C, et al. Inhibitors in haemophilia A and B: management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients. *Eur J Haematol*. 2019;102:111–22.

[17] Abdel-Messih IY, Mohamed Habashy DM, Moftah SG, El-Alfy M. Persistent factor VIII inhibitors and orthopaedic complications in children with severe haemophilia A. *Haemophilia*. 2011;17:490–3.

[18] Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE, et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia*. 2001;7:446–52.

[19] Nijdam A, Foppen W, De Kleijn P, Mauser-Bunschoten EP, Roosendaal G, van Galen KPM, et al. Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates. *Thromb Haemost*. 2016;115:931–8.

[20] van Bergen EDP, van Leeuwen FHP, Foppen W, Timmer MA, Schutgens REG, Mastbergen SC, et al. Subclinical synovial proliferation in patients with severe haemophilia A: advocating ultrasound screening. *Haemophilia*. 2023;29:1580–8.

[21] van Vulpen LFD, Mastbergen SC, Foppen W, Fischer K, Lafeber FPJG, Schutgens REG. Towards personalized treatment in haemophilia: the role of genetic factors in iron and heme control to identify patients at risk for haemophilic arthropathy. *J Pers Med*. 2024;14:145.

[22] Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res*. 1980;149:153–9.

[23] Foppen W, van der Schaaf IC, Beek FJA, Verkooijen HM, Fischer K. Scoring haemophilic arthropathy on X-rays: improving inter- and intra-observer reliability and agreement using a consensus atlas. *Eur Radiol*. 2016;26:1963–70.

[24] Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011;1:51–9.

[25] Schmidt DE, Michalopoulou A, Fischer K, Motwani J, Andersson NG, Pergantou H, et al. Long-term joint outcomes in adolescents with moderate or severe haemophilia A. *Haemophilia*. 2022;28:1054–61.

[26] Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. *Eur J Haematol*. 2012;88:329–35.

[27] Morfini M, Haya S, Tagariello G, Pollmann H, Quintana M, Siegmund B, et al. European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia*. 2007;13:606–12.

[28] Poonnoose PM, Hilliard P, Doria AS, Keshava SN, Gibikote S, Kavitha ML, et al. Correlating clinical and radiological assessment of joints in haemophilia: results of a cross sectional study. *Haemophilia*. 2016;22:925–33.

[29] Foppen W, van der Schaaf IC, Beek FJA, Mali WPTM, Fischer K. MRI predicts 5-year joint bleeding and development of arthropathy on radiographs in hemophilia. *Blood Adv*. 2020;4:113–21.

[30] van Leeuwen FHP, van Bergen EDP, Timmer MA, van Vulpen LFD, Schutgens REG, de Jong PA, et al. Magnetic resonance imaging evidence for subclinical joint bleeding in a Dutch population of people with severe hemophilia on prophylaxis. *J Thromb Haemost*. 2023;21:1156–63.

[31] Kiialainen A, Niggli M, Kempton CL, Castaman G, Chang T, Paz-Priel I, et al. Effect of emicizumab prophylaxis on bone and joint health markers in people with haemophilia A without factor VIII inhibitors in the HAVEN 3 study. *Haemophilia*. 2022;28:1033–43.

[32] Yamaguti-Hayakawa GG, Ozelo MC. Gene therapy for hemophilia: looking beyond factor expression. *Exp Biol Med (Maywood)*. 2022;247:2223–32.

[33] Gomber S, Singhal G, Dewan P, Upreti L, Sikka M. Twice weekly vs. thrice weekly low-dose prophylactic factor VIII therapy in children with hemophilia A: an open label randomized trial. *J Trop Pediatr*. 2022;68:530–7.

[34] Mabrouk AG, Abbas MAEB, Ezzat DA, Sayed MT, Ali FM. Hemophilia Joint Health Score, Functional Independence Score in Hemophilia, and Pettersson Score in pediatric patients with severe hemophilia A. *J Pediatr Hematol Oncol*. 2023;45:344–8.

[35] Daffunchio C, Landro ME, Galatro G, Neme D, Cambiaggi G, Moretti N, et al. How mild is mild haemophilia? *Haemophilia*. 2023;29:530–7.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102355.