Sports participation and physical activity in adult Dutch and Swedish patients with severe haemophilia: A comparison between intermediate- and high-dose prophylaxis

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Funding information
Data collection and analysis were performed with two independent, unrestricted grants from Bayer.

Abstract

Introduction: Differences in treatment and outcome have been reported for persons with haemophilia (PWH) on intermediate-dose (Dutch) and high-dose (Swedish) prophylaxis, but the potential influence of sports participation has not been considered.

Aim: To compare sports participation and clinical outcome between adult Dutch and Swedish PWH.

Methods: Self-reported sports participation (type and frequency per week), physical functioning (SF-36PF: 100-0), joint status (HJHS: 0-144), perceived limitations (HALsum: 100-0) and physical activity (IPAQ) were recorded. Sports were classified according to National Haemophilia Foundation classification (5 categories, highest two were classified as high-risk sports). Sports participation and clinical outcome were compared according to country and age (18-22, 23-29, 30-40 years) using non-parametric tests and Spearman correlations (rho).

Results: Seventy-one adult PWH (NL: 43, SWE: 28) completed sports questionnaires (mean age: 26 years). All participants engaged in sports, including 59.2% in high-risk sports (33.9% twice weekly). Dutch PWH showed a significant age-related decline in (high-risk) sports participation (7x/wk in PWH 18-22 years to 2x/wk in PWH 30-40 years, P < 0.05), joint health (HJHS: median 2-15.5, P < 0.01) and physical functioning (SF-36PF: median 100 to 77.5, P < 0.01), while Swedish did not. Sports participation was not associated with bleeding (Spearman’s rho = −0.119).

Conclusion: All participants reported sports participation, including 59.2% in high-risk sports. Dutch PWH treated with intermediate-dose prophylaxis showed an age-related decline in sports participation, joint status and physical functioning, whereas Swedish PWH on high-dose prophylaxis did not. Sports participation was not associated with bleeding.

Keywords
factor consumption, haemarthrosis, prophylaxis, sports participation, treatment strategies
INTRODUCTION

Sports participation and an active lifestyle are important aspects of daily life for persons with haemophilia (PWH).¹ The increased availability of recombinant clotting factor (FVIII/IX) and the introduction of prophylactic replacement therapy have promoted sports participation and an active lifestyle for PWH. In fact, several studies have reported that PWH are just as physically active as the general population.²,³ With the increased sports participation in PWH, sports participation and physical activity (PA) seem to have become relevant outcome parameters for PWH. However, most studies assessing sports participation in PWH showed conflicting results⁴ and reported on children and adolescents only.²,⁴,⁵

In a previous study, Fischer et al (2013) compared costs and outcome of intermediate-dose prophylaxis in the Netherlands (46 IU/kg/wk) and high-dose prophylaxis in Sweden (88 IU/kg/wk).⁶ Besides differences on factor dosage, costs and clinical outcome (joint function), this study reported a non-significant trend towards higher PA in Dutch PWH. However, no detailed overview of sports participation data or its association with outcome was provided. Sports participation, especially high-risk sports, may be associated with bleeding and/or treatment strategy. Perceived differences in bleeding risk according to different types of sports are reflected in the risk categories that were formulated by the National Hemophilia Foundation (NHF).⁷ These categories run from 1 (safe) via 1.5 (safe to moderate), 2 (moderate risk), 2.5 (moderate to dangerous) to 3 (dangerous). The first category contains low impact sports with a low collision risk like walking and swimming, while sports in category 2.5 (eg soccer) and category 3 (eg boxing and rugby) are considered to be high-risk sports. This current analysis explored age-related differences in sports participation and high-risk sports between adult PWH and age-matched peers in two countries with different treatment strategies. Furthermore, associations between PA and perceived limitations, physical functioning, joint status, treatment and bleeding data were investigated.

METHODS

2.1 Design and setting

The data analysed in this study were collected as a prespecified part of a prospective observational study comparing cost and outcome of intermediate-dose vs high-dose prophylaxis.⁵ Details of study design and methods have been reported elsewhere.⁵ The study was performed at the haemophilia treatment centres of the University Medical Centre Utrecht, the Netherlands (Van Creveldkliniek); the Karolinska University Hospital in Stockholm, Sweden; and the Skåne University Hospital in Malmö, Sweden. Dutch and Swedish PWH were selected based on comparable socioeconomic, demographic⁶,⁹ and cultural aspects.¹⁰,¹¹

2.2 Participants

The participants in the original study consisted of two birth cohorts of PWH with severe haemophilia A and B (FVIII/IX, <1 IU/dL) without a history of inhibitors from the age of 12 onwards. Because the aim of this study was to assess sports participation in adult PWH, only adult PWH who completed the sports questionnaires were included in the current analysis. The participants were divided into three age groups of approximately equal size: 18-22 (‘youngest’), 23-29 (‘intermediate’) and 30-40 (‘oldest’). Data and questionnaires were collected during regular outpatient consultations. All participants provided written informed consent before being included in this study. To be able to compare patients’ sports participation with a group of healthy, age-matched peers, all participating PWH were requested to ask two male friends, colleagues or neighbours (maximum age difference: 3 years) to complete the same sports questionnaire. Not all adult participants included in the original study completed the sports questionnaire. To assess potential selection bias, responders and non-responders were compared with regard to clinical and self-reported scores and bleeding data.

2.3 Data collected

Sports participation, bleeding and treatment history, clinical and self-reported outcomes were collected for participating PWH. Bleeding and treatment data were collected from medical files, patient logs and hospital records. This included the total number of (joint) bleeds, treatment regimen and annual clotting factor for the last 3 years.

All participants completed a specifically developed sports questionnaire, listing 23 sports (see Table 1), on which they marked what sports they had been performing during the last 12 months. Furthermore, they were asked to indicate how often they would perform this sport during a typical week in May. This month was chosen because the European weather in May is generally optimal for performing sports outdoors. Comparisons in sports participation...
had to be made at country level, as most popular sports were different according to country. Joint health was assessed by performing the Haemophilia Joint Health Scale (HJHS, optimum score 0, worst score 144). Self-reported limitations in activities were forming the Haemophilia Joint Health Scale (HJHS). Risk sports and bleeding (risk), sports were classified into risk categories according to the NHF classification. The outcomes for HALsum and SF-36 have a score range of 0-100, with a higher score indicating different according to country. Joint health was assessed by per-

### TABLE 1 Sports included in the sports questionnaire with the injury risk category used

| Sport            | NHF risk category |
|------------------|-------------------|
| 1. Swimming      | 1                 |
| 2. Walking       | 1                 |
| 3. Cycling       | 1.5               |
| 4. Aerobics<sup>a</sup> | 2         |
| 5. Fitness<sup>a</sup> | 1.5            |
| 6. Billiards<sup>a</sup> | 1         |
| 7. Bowling       | 2                 |
| 8. Golf          | 1                 |
| 9. Football      | 2.5               |
| 10. Indoor Football<sup>a</sup> | 2.5         |
| 11. Tennis       | 2                 |
| 12. Squash<sup>a</sup> | 2         |
| 13. Jogging/Running | 2             |
| 14. Ice hockey   | 3                 |
| 15. Field hockey | 3                 |
| 16. Indoor hockey| 3                 |
| 17. Table tennis<sup>a</sup> | 1         |
| 18. Basketball   | 2.5               |
| 19. Volleyball   | 2.5               |
| 20. Skiing (downhill) | 2.5        |
| 21. Skiing (cross country) | 2          |
| 22. Ice skating  | 2.5               |
| 23. Skateboarding| 2.5               |

<sup>a</sup>Not included in the NHF classification. These sports were classified according to their impact and collision risk.

### 2.4 Statistics

The primary aim of this study was to compare sports participation according to treatment strategy and age in Dutch and Swedish PWH. This was done by assessing and comparing age-related sports participation based on country of origin for PWH. All age-related comparisons were made for three age groups based on approximately equal size: 18-22 ("youngest"), 23-29 ("intermediate") and 30-40 years ("oldest"). For sports participation, the weekly number of different sports, frequency and high-risk sports were assessed. Participation in high-risk sports was compared by means of chi-square testing. Secondary outcome parameters included physical activity (IPAQ), bleeding data, joint health status, limitations in activities (HALsum) and health-related quality of life (SF-36). To be able to present clinical outcomes in a similar fashion, data from HAL and SF-36 are presented as the relative deviation from the optimal score (100%-test result). Differences between PWH and peers according to country and age categories were analysed using Mann-Whitney U test or Kruskal-Wallis tests. Associations between sports participation and bleeding characteristics, treatment history and clinical data were analysed with Spearman's rank correlation testing. Correlation coefficients were regarded small (rho = 0.1), medium (rho = 0.3) or large (rho = 0.5).

All results are being presented as median and interquartile range (IQR). Significance levels were set at 5% (P < 0.05). Statistical analyses were performed using SPSS statistical software (version 22; IBM Corp., Armonk, NY).

### 3 RESULTS

#### 3.1 Participants

Figure 1 shows an overview of the participants (patients and peers) and the outcome parameters available. The original study sample included 103 adult PWH, of which 71 (68.9%), 43/62 Dutch (69.4%) and 28/41 Swedish (68.3%), completed the sports questionnaire. Dutch PWH provided 46 healthy peers, while 27 Swedish provided 27 peers who completed the sports questionnaire. These numbers combined into a total number of 144 participants.
A comparison of adult PWH who did (n = 71; 68.9%) and did not (n = 32; 31.1%) complete sports questionnaires showed similar treatment, joint status and self-reported outcome (HAL, IPAQ, SF-36), but increased bleeding: non-responders had significantly more soft tissue bleeds (median 1 [IQR: 1.0–2.3] vs 0 [IQR: 0–2.0]; P < 0.05), joint bleeds (2.0 [IQR: 0.8–3.0] vs 1.0 [IQR: 0–2.0]; P < 0.05) and 5-year joint bleeds (15.5 [IQR: 4.5–21.3] vs 9.8 [IQR: 1.0–15.0]; P < 0.05) than responders.

3.2 Participant characteristics and treatment

Table 2 shows participant characteristics and treatment data of the PWH in this study. The average age for all participants was 26 years (IQR 23–30, range: 18–40), in both Dutch and Swedish participants, and included 62 (87%) with severe haemophilia A and 9 (13%) with severe haemophilia B. Similar to the original study, <10% of PWH in both cohorts was HIV positive while the proportion of PWH with HCV was significantly higher in Dutch PWH (53.5% vs 25.0%). Treatment was significantly less intensive in the Netherlands: prophylaxis was started later (at median age 5.0 in Dutch vs median 1.7 years in Swedish PWH) and current weekly prophylactic dosing was lower at 41 vs 82 IU/kg/wk. Clinical outcome showed more joint damage in Dutch PWH (HJHS 9.0 vs 4.5), more limitations in activities (HAL: sum 94 vs 99) and lower quality of life scores (SF-36: 95 vs 100).

3.3 Clinical and self-reported outcome according to age

Treatment and outcome according to age and country are shown in Table 3. Consistent with the previous publication, treatment was significantly less intensive for Dutch PWH in all age groups. Dutch PWH reported more joint bleeds than Swedish PWH in all age categories. Concomitantly, Dutch PWH showed an age-related increase in HJHS score (median 2 [IQR: 1.0–12.3] to 15.5 [8.8–22.5], P for trend: <0.01), indicating a trend of decreasing joint health and physical functioning (SF-36: median 100 [90–100] to 77.5 [42.5–95.0], P for trend: <0.01) with age, while Swedish PWH (100 [91.3–100] vs 97.5 [IQR 95.0–100], P = 0.767) remained stable (see Figure 2). As in the original study, Dutch PWH reported more limitations (HAL: sum)
than Swedish PWH, although this difference was not statistically significant \((P = 0.223)\).

### 3.4 | Sports participation according to country

All 71 PWH who completed the sports questionnaire indicated to be active in some kind of sports. 59.2% of PWH was engaged in high-risk sports \((\text{NHF} > 2)\), of which 33.9% \((\text{NL}: 27.9\%; \text{SWE}: 42.9\%; P < 0.05)\) at least twice weekly. Dutch and Swedish PWH showed different 10 most frequently reported sports. In both countries, the 10 most frequently reported sports in PWH \((\text{Dutch PWH}: \text{cycling, swimming, walking, fitness, bowling, billiards, ice skating, football and jogging}; \text{Swedish PWH}: \text{cycling, swimming, walking, fitness, jogging, bowling, skiing, football and skating})\) were similar to their peers \(\text{(data available on request)}\).

### 3.5 | Sports participation according to age

Sports participation according to age and country is shown in Table 4. A clear decrease in sports participation \(\text{(number of sports, frequency per week and high-risk sports per week)}\) according to age was observed in Dutch PWH but not in Swedish PWH. An age-related decline in the proportion of PWH engaged in high-risk sports \((\text{NHF} > 2)\) in Dutch PWH was observed: from 73% \((18-22\text{ years old})\) and 86% \((23-29\text{ years old})\) in the youngest groups to 28% for 30- to 40-year-old PWH. Proportionally, more Swedish PWH aged 30-40 \((75\%)\) were engaged in high-risk sports than Dutch PWH \((28\%)\) aged 30-40.

### 3.6 | Sports participation in relation to clinical outcome

Spearman rank correlation showed a negative correlation between joint status \((\text{HJHS})\), number of sports \((\rho = -0.46; P < 0.01)\) and number of sports per week \((\rho = -0.36; P < 0.05)\) for Dutch PWH. However, due to the low correlation coefficients \((\rho > -0.5)\), these correlations do not seem to be clinically relevant.

### 3.7 | Treatment and bleeding parameters

Because of the assumed increased bleeding risk associated with engaging in high-risk sports, the potential association between performing high-risk sports and joint bleeding \(\text{(annual and 5-year joint bleeding)}\) was analysed. Spearman rank correlation coefficient testing showed no associations \((\rho < 0.5)\) between high-risk sports participation per week and bleeding data \(\text{(NL}: \rho = -0.25, P = 0.27; \text{SWE}: \rho = 0.08, P = 0.76)\) in Dutch or Swedish PWH.
DISCUSSION

This is the first study to report on sports participation according to age for two groups of adult PWH under different treatment strategies. All participants indicated to be active in some kind of sports, with 59.2% of PWH engaged in high-risk sports. A similar proportion was participating in high-risk sports in the Netherlands and Sweden. The main difference identified was a trend towards significantly worse joint status combined with less (high-risk) sports participation in Dutch PWH aged 30-40, but not in Swedish. Dutch PWH aged 30-40 reported more limitations than Swedish. Sports participation was not associated with bleeding.

4.1 Internal and external validity

This analysis included a Dutch and Swedish birth cohort (1970-1991). These groups were chosen because of similar socio-economic status, cultural norms, and lifetime differences in treatment, enabling to explore potential associations between treatment intensity and sports participation. The current data may represent an overestimation of sports participation in PWH. The questionnaire was not completed by 31% of PWH. Analysis showed that non-responders had significantly more joint bleeds. Data on bleeds were retrieved from hospital records and are based on patient reports. Even if this would result in underestimation of bleeding events, this potential bias occurred...
both in Swedish and Dutch patients and is therefore unlikely to affect the comparison between both groups. The data collected with the sports questionnaire were limited to type and frequency of sports, without considering duration or intensity and without any objective confirmation. This could potentially lead to overestimation of total PA.25,26 All participating PWH were asked to invite two healthy, age-matched peers to complete the sports questionnaire. This procedure may induce selection bias, as peers are more likely to perform similar sports/activities. The sample size in this study was limited, especially in the Swedish sample, limiting the power to address age-related trends. Due to a lack of a valid, standardized tool, data on sports participation were collected by means of a self-devised, non-validated questionnaire. Recently, the Modifiable Activity Questionnaire (MAQ) was validated for adults.27,28 This questionnaire can be used in prospective studies to document sports participation and exposure. Recently, the HEP test Questionnaire was developed and validated in adults and children with haemophilia.29,30 This instrument assesses self-reported physical activity and fitness including four domains: physical status, mobility, strength and coordination, and endurance and body perception.

4.2 Comparison with other studies

The key observation of the present study was a significant reduction in sports participation for 30- to 40-year-old Dutch PWH, which was not observed in Swedish PWH. A similar trend has been reported in the general population: sports participation seems to decline with increasing age in both the Dutch13 and the Swedish12 general population. The high sports participation observed is corroborated by previous publications reporting that PWH were just as active as healthy subjects.2,3,31-36 However, of these studies only the studies by Heijnen et al (2001) and Khawaji et al (2011) involved adult PWH.3,33

4.3 Clinical relevance and future research

This study showed a trend towards an age-related decrease in sports participation and clinical and functional outcomes in Dutch PWH, but not in Swedish PWH. This suggests that differences in outcome only become apparent in the fourth decade of life and may be associated with changes in sports participation. However, it is yet unknown whether this decrease is related to differences in treatment strategy.

To enable use of the present results on sports participation in clinical counselling, more details on duration, frequency and intensity of sports performed are needed. More information is needed regarding the balance between benefits and burdens of PA in PWH, particularly regarding injuries and bleeding risk. The present study did not find an association between sports participation and bleeding risk, but this may have been affected by selection bias, as the participants showed a potential overrepresentation of low sports participation and a low number of bleeds.

Ideally, assessment of sports participation should include information on frequency, duration and intensity of physical activity; the MAQ27,28 and the use of accelerometers are potential, validated tools for this purpose. Furthermore, assessment of sports participation should be accompanied by assessment of sports-related injuries, with sufficient follow-up to include seasonal differences. To combine information on sports-related injury risk with treatment intensity, data on sports injuries should be combined with information on FVIII/IX levels at the time of injury similar to the study by Broderick et al24. This information is especially valuable in the context of extended half-life FVIII/IX concentrates, which result in more time with lower FVIII/IX activity levels.38

5 Conclusion

In conclusion, all Dutch and Swedish PWH in this study were actively engaged in sports, the majority including high-risk sports. The main finding of this study is an age-related decrease in (high-risk) sports participation and joint health and a decrease in physical functioning in Dutch patients, who received less intensive treatment. No associations were observed between bleeding data and sports participation. To support counselling on sports participation, future research should focus on prospective studies for sports participation, exposure and should include sports injuries.

Disclosures

OV has reported no interests which might be perceived as posing a conflict or bias. EB has reported no interests which might be perceived as posing a conflict or bias. PP has been a paid consultant to Baxter/Shire, Bayer, Sobi and Roche. RL has during the last 5 years received speakers’ or consultancy fees from Baxter/Shire, CSL Behring, Novo Nordisk, Octapharma, Pfizer—however not related to this paper. JA has served as a consultant for Shire, CSL Behring, Bayer, Novo Nordisk, Sobi, Pfizer, Spark Therapeutics, Unique, Octapharma and has research grants from Bayer, Shire and CSL Behring. None of these is considered to compete with this paper’s content and message. MH has reported no interests which might be perceived as posing a conflict or bias. PK has reported no interests which might be perceived as posing a conflict or bias. KF has received speaker’s fees from Bayer, Baxter/Shire, Biotest, CSL Behring, Octapharma, Pfizer, Novo Nordisk; performed consultancy for Bayer, Baxter/Shire, Biogen, CSL Behring, FreeLine, Novo Nordisk, Pfizer, Roche and SOBI; and has received research support from Bayer, Pfizer, Baxter/Shire and Novo Nordisk.

Author Contribution

EB, PP, RL, JA, MH, PK and KF designed and performed the study. OV and KF analysed the data and wrote the paper. All authors reviewed and approved the final version of the paper.

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How to cite this article: Versloot O, Berntorp E, Petriní P, et al. Sports participation and physical activity in adult Dutch and Swedish patients with severe haemophilia: A comparison between intermediate- and high-dose prophylaxis. Haemophilia. 2019;25:244–251. https://doi.org/10.1111/hae.13683