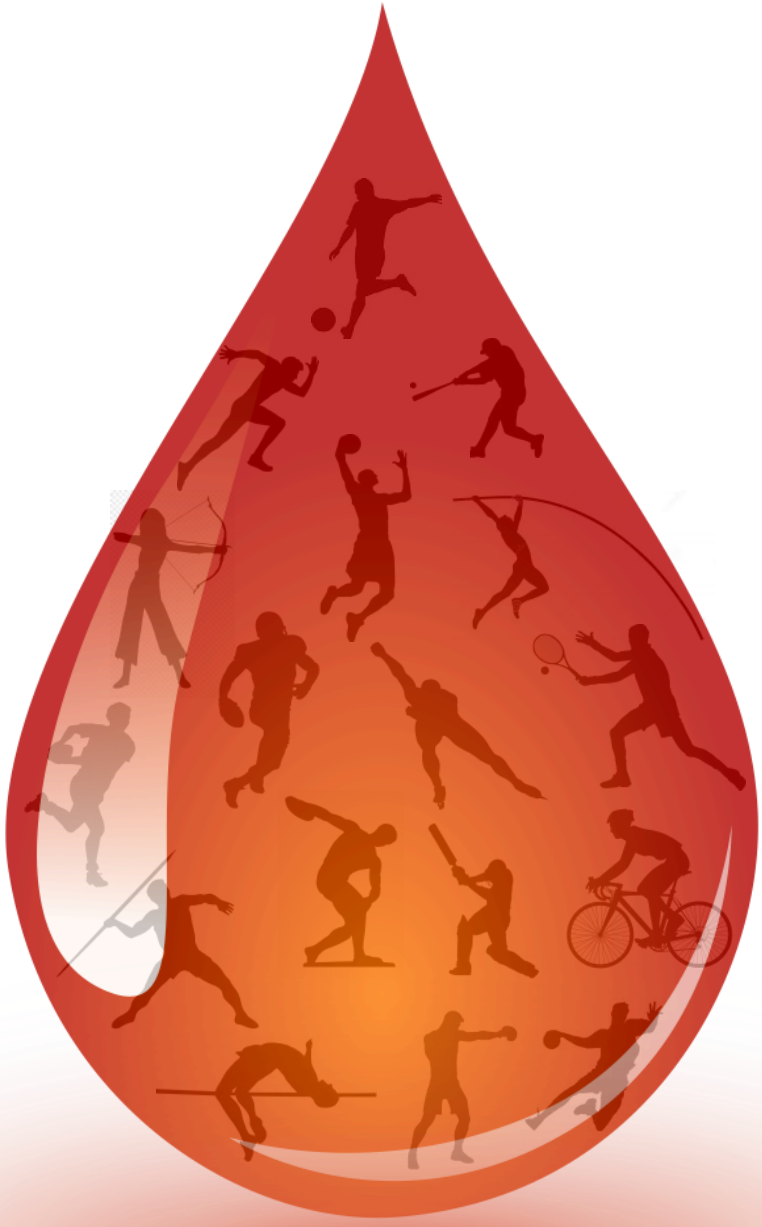
Sports Participation, Injuries and Bleeds in People with Haemophilia



Olav Versloot

Sports Participation, Injuries and Bleeds in People with Haemophilia

Olav Versloot

Sports participation, Injuries and Bleeds in People with Haemophilia
PhD Thesis, Utrecht University, the Netherlands

ISBN/EAN: 9789464197051

Cover Design and lay-out: Olav Versloot
Printing: Gildeprint Enschede, www.gildeprint.nl
Foto achterzijde: Roos Koole Fotografie

Sports Participation, Injuries and Bleeds in People with Haemophilia

Sportdeelname, blessures en bloedingen bij mensen met hemofilie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
donderdag 23 maart 2023 des middags te 12:15

door

OLAV VERSLOOT
geboren op 2 augustus 1975
te Hoorn

Promotor:
Prof. dr. R.E.G. Schutgens

Copromotoren:
Dr. K. Fischer
Dr. J. van der Net

Beoordelingscommissie:
Prof. dr. C. Veenhof
Prof. dr. L.J. Bont
Prof. dr. J.W. Gorter
Prof. dr. C.J. Fijnvandraat
Dr. M.H. Cnossen

The research presented in this thesis was financially supported by an unrestricted grant from Bayer. Additionally, Sobi financially contributed to the research described in chapter 12. The printing of this thesis was financially supported by the Scientific College Physical Therapy of the Royal Dutch Society for Physical Therapy (KNGF)

I can... make it happen, if I want to.
Make it happen, if I try.

(Plague of Ghosts - Fish, 1999)

Voor Tom, Nina en Sara
Omdat het altijd om de toekomst gaat

Table of Contents

CHAPTER 1

General Introduction

Haemophilia

Haemophilia is an congenital blood clotting disorder that affects approximately 1:500 new-born boys worldwide[1]. There are currently approximately 1,700 people with haemophilia in The Netherlands[2]. People with haemophilia have absent or reduced levels of clotting factor VIII (FVIII; haemophilia A) or factor IX (FIX, haemophilia B), leading to impaired clotting function, causing prolonged bleeding. People with severe haemophilia (<1% FVIII/FIX) suffer from spontaneous bleeds, whereas people with moderate haemophilia (1-5%) mainly suffer from prolonged bleeds after minor trauma and surgery. People with mild haemophilia (5-40%) only experience bleeds after major trauma or surgery[3,4]. Most bleeds occur in joints (70-80%) and muscles (10-15%)[4]. Joint bleeds occur most frequently (70-80%) in large, synovial joints (e.g. knee, elbow, ankle), potentially leading to haemophilic arthropathy. In the absence of a definite cure, current treatment for haemophilia consists of regular prophylactic intravenous infusions with the deficient clotting factor (replacement therapy). Even with prophylactic infusions, patients with severe haemophilia still report 1-2 bleeding episodes per year[5].

Sports participation

The current body of knowledge suggests regular physical activity and exercise in people with haemophilia might assist in improving proprioception[6,7] and strength[6,8], increase range of motion[9] and potentially prevent joint trauma and bleeding[10].

To date, sports participation studies in people with haemophilia have been limited to studies with children[11–13]. Data from adults with haemophilia and data according to severity and patient characteristics remain limited.

Sports injuries and sports-induced bleeds

People with haemophilia were traditionally discouraged from (contact) sports participation due to the anticipated increased risk of bleeds and the concomitant risk of development of haemophilic arthropathy[14–16]. However, the association between sports-induced bleeds and factor activity is currently unknown and needs to be established to enable adequate counselling.

In order to establish safe sports participation for people with haemophilia, risk factors for sports injuries and sports-induced bleeds need to be identified. Studies in the general population have identified (older) age[17], obesity[18], previous injury[19,20], strength imbalances[21], poor conditioning[22] and poor motor performance[23] as risk factors for sports injuries. However, specific risk factors for sports injuries and (particularly) sports-induced bleeds in people with haemophilia have not been assessed so far.

Pharmacokinetics

The aim of current haemophilia treatment is to increase factor levels from "severe" to "moderate"[5]. However, debate remains how high trough levels should be and how bleeds are associated with baseline factor levels[24]. Terminal half-life partially defines infusion frequency and is associated with protection from spontaneous bleeding. Extended half-life (EHL) concentrates have been developed recently, among others to decrease the infusion frequency while maintaining sufficient factor levels. Although claims have been made that half-life could increase 1.5-2 fold in FVIII and 4 to 6 fold in FIX EHL products[26,27], these claims have not been studied in clinical data or on an individual level in large study populations.

In conclusion, the aim of this thesis is to answer the following questions:

- How do sports participation and injuries in PWH compare to the general population?
- Are sports-induced bleeds associated with factor levels during sports?
- Can tests of balance, strength, speed & agility and endurance predict sports injuries and sports-induced bleeds in people with haemophilia?
- Can we establish reference values for terminal half-life for FVIII/FIX extended half-life concentrates?
- Can we identify determinants of a clinically relevant terminal half-life extension in people with severe haemophilia?

Outline of this thesis

Part I – Participation

Sports participation has increased in PWH in recent years. However, an exact overview of sports activities in Dutch PWH is currently lacking. **Chapter 2** presents sports participation in Dutch people with haemophilia in relation to age and severity and compares this to the general population. **Chapter 3** compares sports participation in Dutch and Swedish PWH on different treatment protocols. **Chapter 4** provides a retrospective overview of sports participation and injuries in Dutch boys with haemophilia and compares this to the general population. **Chapter 5** provides an overview of sports participation in PWH during the COVID-19 pandemic and the association between (high-risk) sports participation and therapeutic adherence.

Part II – Injuries

The aim of part II is to identify potential risk factors for sports injuries and sports-induced bleeds from a motor proficiency perspective. **Chapter 6** describes the testing protocol. **Chapter 7** compares sports injuries in PWH and the Dutch general population

and assesses the association between factor VIII and IX levels and sports-induced bleeds, while **chapter 8** describes and evaluates a motor proficiency and exercise testing protocol aiming to predict sports injuries and sports-induced bleeds. **Chapter 9** aims to assess associations between sports participation, factor VIII levels and bleeding in persons with hemophilia A.

Part III - Pharmacokinetics

Part III aims to assess half-life in standard and extended half-life concentrates. **Chapter 10** assesses the increase in terminal half-life after changing to EHL concentrates according to age, body composition and treatment parameters. The aim of **Chapter 11** is to assess and predict individual increases in terminal half-life after switching to EHL concentrates. Finally, **chapter 12** shows that therapeutic adherence was not associated with (high-risk) sports participation.

References

1. Stonebraker JS, Bolton-Maggs PHB, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia*. 2010;16(1):20-32. doi:10.1111/j.1365-2516.2009.02127.x
2. Leebeek FWG, Fischer K. Quality of haemophilia care in the Netherlands: New standards for optimal care. *Blood Transfus*. 2014;12(SUPPL. 3):501-504. doi:10.2450/2014.0041-14s
3. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672
4. Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;(May):1-158. doi:10.1111/hae.14046
5. Den Uijl IEM, Biesma DH, Grobbee DE, Fischer K. Turning severe into moderate haemophilia by prophylaxis: Are we reaching our goal? *Blood Transfus*. 2013;11(3):364-369. doi:10.2450/2012.0092-12
6. Hilberg T, Herbsleb M, Puta C, Gabriel HHW, Schramm W. Physical training increases isometric muscular strength and proprioceptive performance in hemophilic subjects. *Haemophilia*. 2003;9(2):86-93. doi:679 [pii]
7. Hilberg T, Herbsleb M, Gabriel HHW, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. *Haemophilia*. 2001;7(6):582-588. doi:10.1046/j.1365-2516.2001.00563.x
8. Tiktinsky R, Falk B, Heim M, Martinovitz U. The effect of resistance training on the frequency of bleeding in haemophilia patients: A pilot study. *Haemophilia*. 2002;8(1):22-27. doi:10.1046/j.1365-2516.2002.00575.x
9. Harris S, Boggio LN. Exercise may decrease further destruction in the adult haemophilic joint. *Haemophilia*. 2006;12(3):237-240. doi:10.1111/j.1365-2516.2006.01214.x
10. Pierstorff K, Seuser A, Weinspach S, Laws HJ. Physiotherapy home exercise program for haemophiliacs. *Klin Padiatr*. 2011;223(3):189-192. doi:10.1055/s-0031-1275337
11. Heijnen L, Mauser-Bunschoten EP, Roosendaal G. Participation in sports by Dutch persons with haemophilia. *Haemophilia*. 2000;6(5):537-546. doi:10.1046/j.1365-2516.2000.00422.x
12. Köiter J, Van Genderen FR, Brons PPT, Nijhuis-van Der Sanden MWG. Participation and risk-taking behaviour in sports in children with haemophilia. *Haemophilia*. 2009;15(3):686-694. doi:10.1111/j.1365-2516.2009.02006.x
13. Groen WG, Takken T, van der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. *Haemophilia*. 2011;17(5):906-912. doi:10.1111/j.1365-2516.2011.02555.x
14. Patel DR, Yamasaki A, Brown K. Epidemiology of sports-related musculoskeletal injuries in young athletes in United States. *Transl Pediatr*. 2017;6(3):160-166. doi:10.21037/tp.2017.04.08
15. Schmikli SL, de Vries WR, Inklaar H, Backx FJG. Injury prevention target groups in soccer: Injury characteristics and incidence rates in male junior and senior players. *J Sci Med Sport*. 2011;14(3):199-203. doi:10.1016/j.jsams.2010.10.688
16. Seuser A, Boehm P, Kurme A, Schumpe G, Kurnik K. Orthopaedic issues in sports for persons with haemophilia. *Haemophilia*. 2007;13(SUPPL. 2):47-52. doi:10.1111/j.1365-2516.2007.01507.x
17. Ryan J, DeBurca N, Mc Creesh K. Risk factors for groin/hip injuries in field-based sports: A systematic review. *Br J Sports Med*. 2014;48(14):1089-1096. doi:10.1136/bjsports-2013-092263
18. Jespersen E, Verhagen EALM, Holst R, et al. Total body fat percentage and body mass index and the association with lower extremity injuries in children: A 2.5-year longitudinal study. *Br J Sports Med*. 2014;48(20):1497-1501. doi:10.1136/bjsports-2013-092790
19. Murphy DF, Connolly DAJ, Beynnon BD. Risk factors for lower extremity injury: A review of the literature. *Br J Sports Med*. 2003;37(1):13-29. doi:10.1136/bjsm.37.1.13
20. Toohey LA, Drew MK, Cook JL, Finch CF, Gaida JE. Is subsequent lower limb injury associated with previous injury? A systematic review and meta-analysis. *Br J Sports Med*. 2017;51(23):1670-1678. doi:10.1136/bjsports-2017-097500
21. Croisier JL, Ganteaume S, Binet J, Genty M, Ferret JM. Strength imbalances and prevention of hamstring injury in professional soccer players: A prospective study. *Am J Sports Med*. 2008;36(8):1469-1475. doi:10.1177/0363546508316764

22. Watson A, Brindle J, Brickson S, Allee T, Sanfilippo J. Preseason Aerobic Capacity Is an Independent Predictor of In-Season Injury in Collegiate Soccer Players. *Clin J Sport Med*. 2016;0(3):1-6. doi:10.1097/JSM.0000000000000331

23. Larsen LR, Kristensen PL, Junge T, Møller SF, Juul-Kristensen B, Wedderkopp N. Motor Performance as Risk Factor for Lower Extremity Injuries in Children. *Med Sci Sport Exerc*. 2016;48(6):1136-1143. doi:10.1249/MSS.0000000000000877

24. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: The association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17(1):41-44. doi:10.1111/j.1365-2516.2010.02383.x

25. Kumar R, Dunn A, Carcao M. Changing Paradigm of Hemophilia Management: Extended Half-Life Factor Concentrates and Gene Therapy. *Semin Thromb Hemost*. 2016;42(1):18-29. doi:10.1055/s-0035-1568877

26. Graf L. Extended Half-Life Factor VIII and Factor IX Preparations. *Transfus Med Hemotherapy*. 2018;45(2):86-91. doi:10.1159/000488060

27. Mancuso M, Santagostino E. Outcome of Clinical Trials with New Extended Half-Life FVIII/IX Concentrates. *J Clin Med*. 2017;6(4):39. doi:10.3390/jcm6040039

Part I - Sports Participation

CHAPTER 2

Sports Participation in Dutch patients with haemophilia is similar to the general population. Results from the nationwide Haemophilia in the Netherlands Study

O. Versloot[1,2], E.C. van Balen[3], S. Hassan[3], S.E.M. Schols[4,5], F.W.G. Leebeek[6], H.C.J. Eikenboom[7], M. Coppens[8], L.F.D. van Vulpen[1], C. Smit[3], M.H.E. Driessens[9] J. van der Net[10], S.C. Gouw[3,11,], K. Fischer[1]. *On behalf of the Haemophilia in the Netherlands 6 steering committee*

[1] Van Creveldkliniek, University Medical Center Utrecht, Utrecht, the Netherlands.

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

[4] Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands.

[5] Hemophilia Treatment Center Nijmegen-Eindhoven-Maastricht, The Netherlands.

[6] Department of Hematology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

[7] Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands.

[8] Department of Vascular Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

[9] Netherlands Haemophilia Patient Society (NVHP), Nijkerk, The Netherlands.

[10] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, University Medical Center, Utrecht, The Netherlands.

[11] Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands.

Haemophilia, 2021 Sep; 27(5): 876-885, doi: 10.1111/hae.14366. Epub 2021 Jun 19.

Bullet Points

What is already known:

- Sports participation is an important aspect of social participation
- Detailed data on sports participation in Dutch adults with haemophilia is lacking.

What this study adds:

- Sports participation among 760 adults and children with haemophilia was high and similar to the general population;
- As in the general population, older patients with haemophilia were less involved in sports.
- Sports participation was negatively associated with haemophilia severity in adults with haemophilia, but not in children.
- Children with haemophilia were more likely to participate in high-risk sports than adults.

Abstract

Introduction: Although sports participation is advocated in people with haemophilia (PWH), detailed data concerning sports participation in Dutch PWH is lacking.

Aim: to assess sports participation in Dutch PWH (6-65 years) compared to the Dutch general population (GP).

Methods: Data from a nationwide, cross-sectional study in PWH were analysed. Sports participation (type, duration, frequency) was assessed by the Modifiable Activities Questionnaire (MAQ), limitations in activities using the (Paediatric) Haemophilia Activities List ((Ped)HAL). Sports in the two highest categories according to the National Hemophilia Foundation classification were considered high-risk sports. Groups were compared using Chi-square testing.

Results: 524 Adult PWH (median age: 45 (IQR: 30-55); 37% severe) and 126 paediatric PWH (median age: 11 (IQR: 8-14); 52% severe) were included. Sports participation was higher in adults (70%) than the GP (58%) and similar to the GP in children (PWH: 68%, GP: 72%). High-risk sports participation decreased with age in PWH: from 65% (6-12 yrs) to 17% (50-65 yrs), which was also observed in the GP. Sports participation in children was independent of severity (non-severe: 67% vs. severe: 65%; $p=0.97$), but not in adults (non-severe: 75%, severe: 62%; $p<0.01$). Non-severe PWH played more high-risk sports than severe PWH: children at 65% vs. 48% ($p=0.05$), adults at 25% vs. 15% ($p=0.07$).

Discussion: These results suggest that sports participation in PWH was comparable to the GP. Sports participation was dependent of haemophilia severity in adults. Children were more involved in high-risk sports than adults. More studies on sports-related injury-risk are needed for adequate counselling.

Introduction

Haemophilia is an inherited haematological condition, causing clotting factor VIII (FVIII) of IX (FIX) deficiency[1]. Patients with low levels of clotting factor experience spontaneous or traumatic bleeds, particularly in joints and muscles leading to haemophilic arthropathy[2]. Until recently, treatment consisted of regular intravenous replacement of the missing clotting factor (prophylaxis). Novel non-replacement therapies have recently been introduced[3,4].

Physical activity is part of a healthy lifestyle and promotes general well-being, and is recommended by the World Health Organization (WHO)[5]. Sports are a fundamental element of physical activity. Among other domains (strength, balance and flexibility), the WHO recommends at least 60 minutes of moderate to vigorous activity per day in children and 150-300 minutes per week for adults to maintain or improve general health. Besides this, the WHO recommends strength (≥2 days/wk) and balance (≥3 days/wk) exercises for adults[5]. In addition, regular physical exercise is especially recommended for patients with haemophilia (PWH) to increase muscle strength and proprioception[6], and potentially reduce bleeding risk[7]. Traditionally, PWH were advised to only participate in low-impact sports like swimming and cycling[8] and to avoid (contact) sports like soccer or basketball. The introduction of prophylaxis[9] has drastically improved the opportunities to participate in sports for PWH, making sports participation a patient relevant outcome.

Most studies on sports participation in PWH have reported on children[10–13], data of adult PWH are limited[14]. The majority of these studies have reported on the proportion of PWH engaged in sports and type of sports[15], without considering self-reported limitations in activities.

The primary aim of this current study was to describe sports participation in Dutch PWH according to age and severity and compared to the general population (GP), including an assessment of high-risk sports according to age and severity. A secondary aim was to assess, the association between sports participation and self-reported limitations in activities.

Methods

Design and setting

This study was part of the 6th nationwide cross-sectional "Haemophilia in the Netherlands" (HiN6) study[16]. The HiN6 survey aimed to include all Dutch PWH or their parents. The data of the HiN6 survey were collected between May 2018 and August 2019. Participants were asked to complete a series of questionnaires covering multiple aspects of haemophilia (disease characteristics, treatment, employment, limitations, etc.). All questionnaires were either completed online or on paper. Sports participation was one aspect that was addressed in the HiN6 study. The study was approved by the Institutional Review Board of the Leiden University Medical Centre (NL59114.058.17). Participants (or their parents in those under 16) who completed the questionnaire were considered as having consented to participate (opt-in inclusion).

Participants

Eligible patients were contacted by their haemophilia treatment centre to consider participation. Male patients with haemophilia A or B with endogenous clotting factor activity levels <0.40 IU/ml who are registered at one the haemophilia treatment centres in the Netherlands were eligible. The present analysis included all PWH aged between 6 and 65 who completed the sports questionnaires of the HiN6 study. This age group was selected because persons between the age of 6 and 65 are most likely to be participating in organized sports in the Netherlands.

Data Collected

Data were collected on patient characteristics (age, height, weight, comorbidities), diagnosis (type, severity, comorbidities) and treatment (use of prophylaxis, treatment frequency, dose). Clinical characteristics were collected from electronic patient records, to improve reliability over self-reported data. The HiN6 included separate questionnaire-sets for children (younger than 12), adolescents (12-17) and adults (18 and older). The questionnaires for children were completed by their parents.

Patients completed validated questionnaires on sports participation (Modifiable Activities Questionnaire [MAQ][17]), physical performance (HEP-Test-Q)[18] and limitations in activities (Haemophilia Activities List [HAL][19] or Paediatric Haemophilia Activities List [PedHAL][20]. Table 1 shows detailed information about the questionnaires used in this analysis.

Sports participation was defined as being actively engaged in sports at least 10 times in the last 12 months[17] (as defined in the EU Sports Charter[21]). Daily physical activities as walking or cycling to work or school or PE classes were not considered.

The MAQ[19] was validated in Dutch[23] and assesses type of sports and weekly sports exposure (frequency x duration) using free-text. Outcome consists of type of sports and weekly exposure, which can be used to calculate energy expenditure.

The HAL (49 questions) and PedHAL (53 questions) assess limitations in activities, and yields a total score (HALsum). HALsum scores are normalized to 0-100, with higher scores indicating fewer limitations.

The HEP-Test-Q[18] questionnaire assesses physical state, mobility, strength & coordination, endurance and body perception. The HEP-Test-Q was not analysed, but only used to classify participants who failed to complete the MAQ but did complete the HEP-Test-Q as sporting or not playing sports.

Sports injury risk was categorized according to the classification of the American National Hemophilia Foundation (NHF; see supplemental tables S1, S2 and S3)[24]. These categories run from 1 (low risk; e.g.: swimming) via 1.5 (low to moderate risk; e.g.: rowing), 2 (moderate risk; e.g.: tennis), 2.5 (moderate to high risk; e.g.: soccer) to 3 (high risk; e.g.: field hockey). Sports in category 2.5 and category 3 were considered high-risk sports[24]. In case of a reported range in the NHF categorization (e.g.: baseball: 1.5-2.5), the median value was used.

General population data

Sports participation data from the male GP were collected by the Dutch central bureau of statistics (CBS) and downloaded on October 17, 2018. These data were collected by means of a self-devised questionnaire by the CBS. The questionnaire was applied either online or on paper. Participants were asked in which sports they participated, including weekly frequency and duration. Both the MAQ and the CBS questionnaire included a question asking which sports were performed (answered in free text) and had a recall period of one month.

Statistics

Limitations in activities were categorized into “no limitations” (HAL>89 or pedHAL>95) and “with limitations” (HAL≤89 or pedHAL≤95), based on the smallest detectable change in the HAL of 10.9 points[25]. For the present analysis, the results of children (6-11 years of age) and adolescents (12-17) and were combined to one group (“children”).

Table 1: Overview of used questionnaires with domains, content, validated age categories and outcome

	Year of publication	Domains	Number of questions	Validated age categories	Outcome
MAQ	1993	- Leisure time - Professional and domestic activities	11	12-16[39]; adults[23]	Free text, energy expenditure
HAL	2004	- Lying, sitting, kneeling, standing - Functions of the legs - Functions of the arms - use of transportation - Self-care - Household tasks - Leisure activities and sports - Adaptations and using an aid	49	18-76[40]	Standardized score (0-100), higher scores indicate fewer limitations
PedHAL	2010	- Sitting, kneeling, standing - Functions of the legs - Functions of the arms - Use of transportation - Self-care - Household tasks, - Leisure activities and sports - Adaptations and using an aid	53	<8[20], 8-17[20] (<8: completed by parents)	Standardized score (0-100), higher scores indicate fewer limitations
HEP-Test-Q	2010	- Physical status - Mobility - Strength & coordination - Endurance - Body perception	25	6-17[41]; 24-64[18]	Standardized score (0-100), high scores indicate better subjective physical performance

Sports participation was compared according to haemophilia severity (severe, moderate, mild), age categories (6-12, 13-18, 19-29, 30-49, 50-65 years) and self-reported limitations (absent (PedHAL>95[20] or HAL>89[25]) or present). For the analysis of the association of high-risk sports, age and self-reported limitations in activities, patients were classified according to the highest reported sports-risk category.

Differences between sports participation and severity and age subgroups were assessed by Pearson's Chi Square testing.

All results were presented as median values with interquartile range (P25-P75, IQR) and / or proportions with 95% confidence intervals (CI) where appropriate.

Statistical significance levels were set at 5% ($p<0.05$). The statistical analysis was performed using SPSS statistical software, version 25 (IBM corp., Armonk, NY).

Results

Participants

The HiN6 study had an overall response rate of 46% (1009/2191), including 771 participants aged 6-65. The sports questionnaires (MAQ and HEP-Test-Q) were completed by 650 participants (524 adults, 126 children).

Patient characteristics for adults and children are presented in Table 2. Median age for adults was 47 years (IQR: 31-56) and 11 (8-14) for children. Haemophilia A was most prevalent in both adults and children (87%). In adults, 37% had severe haemophilia and in children 52% had severe haemophilia. Prophylaxis, consisting of infusions mostly 1-3 times/wk, was used by 164 (86%) adults and 62 (94%) children with severe haemophilia. BMI was classified as underweight (<18,5 kg/m^2), normal weight (18,5-25), overweight (25-30) or obese (>30) for adults. For children, BMI was classified according to age using normal values for Dutch boys. The prevalence of being overweight was similar to the GP in both adults (51% vs 50.1%) and children (16.8% vs 16.4%)[26,27]. Adults reported more limitations in activities (median HALsum adults: 95.7 (74-100), 49% below 89) than children (99.6 (95.4-100), 21% below 95).

Sports Participation

Participation - general

The MAQ was completed by 408 adults (78%) and 126 children (100%). In addition, 116 adults completed the HEP-Test-Q but not the MAQ and were included and classified as non-sporting, resulting in a total of 524 adults and 126 children available for analysis. Table 3 reports detailed sports participation for children and adults. Compared to adults, children reported a similar sports participation (68% (CI: 59-76) vs. 70% (66-74); p=0.66) and significantly more HR-sports participation (55% (CI: 46-64) vs. 22% (CI: 19-26); p<0.01). The most reported risk category in children was 2.5 (moderate to high risk). This was mainly due to high involvement in soccer (60%). Adults predominantly reported category 1 (low risk), especially swimming (28%).

Children reported a median weekly frequency of 4.2 (IQR: 2.1-6.5) times and a weekly exposure of 4.2 (2.7-6.7) hours of sports. Adults reported a median weekly frequency of 3.0 (1.4-5.6) times and 3.3 (1.9-6.0) hours of sports.

Participation compared to the general population

Sports participation was higher than the GP in adults (PWH: 70% vs. GP: 58%; p<0,01) and similar to the GP in children (68% vs. 72%; p=0.33)[28]. Table 4 shows differences in favourite sports between both adults and children with haemophilia and the GP. Soccer was most popular in both children with haemophilia and the GP (see supplemental table S3 for all reported sports), but the subsequent sports in the top-5 were different.

Participation according to age

Sports participation in PWH was compared to the GP in age groups (6-11; 12-17;18-29;30-49; 50-65). This selection was made to enable the comparison with GP data as these data were analysed according to these groups. Figure 1 shows that sports participation was relatively stable in PWH around 70% for all age groups, although some fluctuation can be observed, particularly during adolescence and young adulthood. Sports participation in the GP showed an age-related decline in adults (18-29: 67% to 50-65: 48%). For high-risk sports however, participation showed a sharp age-related decline in both children (from 65% in 6-12 yrs to 40% in 13-17 yrs; Chi Square: p=0.01) and adults with haemophilia (from 35% in 18-29 yrs to 19% in 30-49 and 17% in 50-65 yrs; p<0.01). This is most likely due to the age-related decrease in soccer, which was the most popular sport in children but was rarely reported by adults (table 4).

Participation according to haemophilia severity and age

Sports participation according to age and severity is shown in table 3. Sports participation was not associated with severity in children (severe: 65% moderate: 67% and mild 67%; Chi square: p=0.97) haemophilia. In contrast, sports participation was associated with severity in adults with haemophilia: patients with severe haemophilia (62%), were less involved in sports than those with mild (75%; p<0.01) and moderate (77%; p<0.01) haemophilia. High-risk sports participation was lower in those with severe haemophilia for both children (severe: 48% vs. mild: 65%; p=0.05) and adults (15% vs. 25%; p=0.06).

Weekly frequency was independent of severity in children (mild: median 3.7 (IQR: 2.8-5.9) vs. severe: 4.5 (1.9-7.3); p=0.35) and adults (3.7 (1.9-6.1) vs. 2.7 (1.2-5.7) times/wk; p=0.55). Total weekly duration was independent of severity in children (3.7 (2.1-7.0) vs. 3.7 (1.9-6.0) hrs/wk; p=0.30) and adults (3.8 (1.9-7.0) vs. 2.9 (1.4-5.6) hrs/wk; p=0.86) as well.

Table 2: Patient and treatment characteristics (n=650)

	Adults				Children			
	Overall	**Severe**	**Moderate**	**Mild**	**Overall**	**Severe**	**Moderate**	**Mild**
	Median (IQR) or number (%)							
number of participants	524	192 (37%)	64 (12%)	264 (50%)	126	66 (52%)	12 (10%)	48 (38%)
Age (yrs)	47 (31-56)	44 (30-54)	39 (28-53)	48 (34-57)	11 (8-14)	12 (8-14)	9 (8-13)	10 (9-13)
	Disease and treatment (n=650)							
Haemophilia A	455 (87%)	168 (88%)	55 (86%)	229 (87%)	107 (87%)	53 (82%)	12 (100%)	41 (85%)
Full time prophylaxis	177 (35%)	164 (86)	7 (11%)	6 (2%)	69 (55%)	62/66 (94%)	5 (42%)	2 (4%)
Prophylaxis dose (IU/kg/infusion)	14.3 (11.9-22.0)	14.5 (11.9-22.1)	11.4 (4.8-19.7)	12.0 (0.0-20.5)	24.1 (17.7-32.1)	23.5 (17.5-32.5)	27.8 (21.1-34.7)	-
Prophylaxis Frequency (times/week)	3 (2-3.5)	3 (2-4)	3 (1 -3)	-	3 (2-3)	3 (2-3)	3 (2-3)	-
	Body composition (n=648)							
Height (cm)	183 (178-187)	182 (178-186)	183 (179-189)	183 (179-188)	150 (140-170)	153 (140-172)	143 (133-172)	150 (140-168)
Weight (kg)	85 (77-95)	83 (74-92)	87 (80-94)	86 (77-95)	40 (30.9-56.6)	42 (32-60)	40 (27-62)	40 (31-54)
% overweight	51%	46%	51%	55%	16.8%	10%	5%	6%
	Comorbidities (n=650)							
HCV ever	170 (32%)	108 (56%)	20 (31%)	42 (16%)	-	-	-	-
HIV present	17 (3.2%)	17	0	0	-	-	-	-
	Functional scores (n=634)							
Self-reported limitations (HAL; 0-100)	95.7 (74.4-100)	74.5 (49.5-92.8)	95.3 (82.9-99.6)	99.5 (94.4-100)	99.6 (95-100)	99.6 (95.3-100)	99.6 (87.0-100)	99.4 (96.6-100)
HAL<89/PedHAL<95	257 (49%)	151 (80%)	33 (52%)	72 (27%)	26 (21%)	14 (21%)	4 (33.3%)	8 (17%)

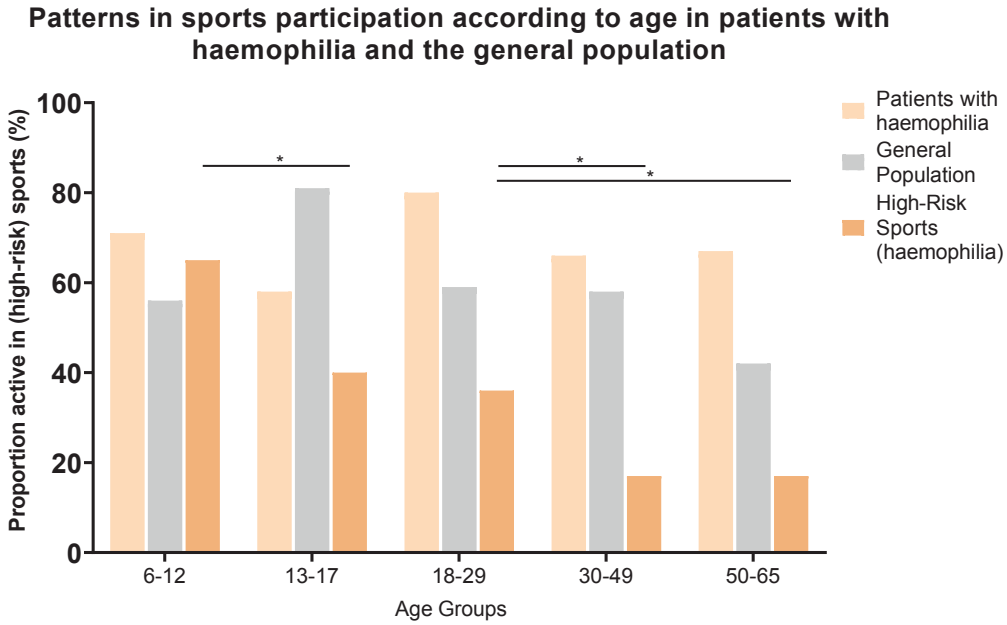


Figure 1: Dutch PWH show consistent sports participation and an age-related decrease in high-risk sports. Adults in the GP showed an age-related decline in sports participation. Dark grey columns represent PWH, grey columns represent the male Dutch GP (data source: gezondheidsmonitor [health monitor])[42]. Dotted columns represent high-risk sports participation in PWH, as the proportion of sporting participants that plays high-risk sports. Sports participation was defined as being actively engaged in sports (as defined in the EU Sports Charter[21]) at least 10 times in the last 12 months[17]. *: Participation in high-risk sports declined with age (p<0,01).

Self-reported limitations and sports participation

Children playing sports reported similar limitations in activities as those not playing sports in the overall score (PedHALsum: median 100 (97-100) vs. 100 (91-100); p=0.44). Likewise, PedHALsum scores were similar between children playing high risk sports and those playing other sports.

For adults however, those playing sports reported significantly fewer limitations in overall activities than those who did not (HALsum: 97 (83-100) vs. 66 (43-96); p<0.01).

For those playing sports, the association between type of sports and self-reported limitations in activities was small. Those playing high risk sports had slightly higher HAL scores than those playing other sports: HALsum score was 99 (93-100) vs. 95 (75-100) (p<0.01). However, although this difference was statistically significant, the difference was below the smallest detectable change for the HAL (11 points), suggesting limited clinical relevance.

Table 3: Sports participation according to age and severity

	children				adults				GP	
	overall	severe	moderate	mild	overall	severe	moderate	mild	Children	Adults
	Number (% [95%CI]) or median (IQR)									
Participants	126	65	12	49	524	192	64	264	2587	9978
Playing sports	68% (59-76)	65% (52-75)	67% (39-86)	67% (52-75)	70% (66-74)	62% (55-69)*	77% (65-85)	75% (69-79)	68%	54%
Playing high risk sports	55% (46-64)	48% (36-60)	58% (32-81)	65% (50-77)	22% (19-36)	15% (11-21)	31% (21-43)	25% (21-31)	-[a]	-[a]
Frequency (times/week)	4.2 (2.1-6.5)	4.6 (1.9-6.7)	2.1 (1.6-6.5)	3.7 (2.8-5.6)	3 (1.4-5.6)	3 (1.4-5.3)	3 (1.9-5.8)	3.3 (1.4-5.8)	-[a]	-[a]
Exposure (hours/wk)	4.2 (2.7-6.7)	3.7 (2.6-6.1)	2.5 (1.6-5.6)	4.3 (2.9-9.4)	3.3 (1.9-6.5)	3.4 (1.6-6.2)	3.2 (2.1-7)	3.2 (1.9-6.4)	-[a]	-[a]

*: sports participation was lower in adult patients with severe haemophilia compared to non-severe haemophilia.
[a]: not assessed in the questionnaire used by the Dutch central bureau of statistics

Table 4: Top 5 most popular sports in children and adults with haemophilia, compared to the male general population

Children (<12)		Children (12-17)		Adults (18+)	
PWH	GP	PWH	GP	PWH	GP
Soccer (21%)	Soccer (41%)	Soccer (15%)	Soccer (34%)	Cycling (22%)	Fitness (26%)
Swimming (19%)	Tennis (7%)	Running (8%)	Fitness (14%)	Fitness (20%)	Running (14%)
Cycling (7%)	Judo (7%)	Cycling (7%)	Hockey (6%)	Walking (14%)	Soccer (9%)
Gymnastics (7%)	Swimming (4%)	Fitness (7%)	Running (4%)	Running (9%)	Swimming (6%)
Judo (4%)	Hockey (4%)	Swimming (5%)	Tennis (4%)	Swimming (7%)	Tennis (5%)

Discussion

Principle findings

This first nationwide study on sports participation in Dutch PWH showed that sports participation across all age groups was high and similar to the GP. Both children and adults with haemophilia reported high sports participation, which was relatively stable from the age of 13 years onwards. Children reported fewer limitations than adults, while adults with haemophilia who were active in sports and high-risk sports reported fewer limitations than those not involved in sports. This may be a cause or a consequence. Adults playing high-risk sports reported fewer limitations than those not playing high-risk sports. Prospective, longitudinal follow-up studies are necessary to elucidate this association.

Internal and external validity

The overall response rate of the entire HiN6 study was 46%, but it is unlikely that (non-) participation was associated with sports participation and the study size is still considerable. A comparison between responders and non-responders was not possible as no data from the non-responders was collected. The MAQ was not completed by all participants. To reduce bias and overestimation of actual sports participation, participants who completed the HEP-Test-Q but not the MAQ were considered as not playing sports. Although we acknowledge that the use of two questionnaires is an indirect method of identifying patients who did not play sports, we believe this method to be superior to classifying non-responders based solely on the MAQ response. Without using this method, the percentage of sporting adult participants would be 89% (367/408) instead of 70% (367/524). This is much higher than the Dutch GP, suggesting selection bias. By including the HEP-Test-Q data, we were able to reduce selection bias and overestimation. Patient and treatment characteristics in the analysed data and the entire dataset were similar, giving no indication for the presence of selection bias.

Sports participation and self-reported limitations were assessed with standardized questionnaires (MAQ[17] and HAL/PedHAL[19,20], respectively) which have been extensively used in haemophilia research[10,11,29,30]. Both the data collected in the HiN6 and the GP data were self-reported, assessing sports participation over recent months[28]. Self-reported assessments often lead to an overestimation of sports participation . Particularly duration of sports is notoriously difficult to estimate for participants, leading to overestimation of sports participation and physical activity[31,32]. Prospectively collecting physical activity data with an objective tool, such as an accelerometer[33], is expected to result in more reliable study results. In this study, we have limited ourselves to sports participation, rather than physical activity in general because of the ongoing debate about

the benefits and limitations of sports participation for people with haemophilia among patients, caregivers and healthcare professionals.

Comparison with other studies

This was the first study that assessed sports participation in both children and adults with haemophilia on a national level over the same time period. In addition, the number of respondents (n=760) is much higher than in previous studies, allowing for more detailed analyses with smaller error margins.

For adult persons with haemophilia, previous studies are scarce. Von Mackensen et al. (2016) reported high sports participation (64%; 2 times/wk, 4 hrs/wk) in adult PWH (n=50; age: 35-44; 56% severe)[34]. In contrast with the present study, more participants with severe haemophilia than those with mild haemophilia were active in sports (78.6 vs. 45.5%). The results of the current study were corroborated by studies in Dutch, Swedish and Irish adults with haemophilia[14,29,35]. All these studies assessed sports participation using questionnaires (self-devised, MAQ, International Physical Activity Questionnaire). These studies reported similar high sports participation (57-100%). Sherlock et al. reported 66% of Irish PWH (n=46; age: 16-63; 49% severe haemophilia) participating in sports, with an age-related decline in sports participation. As in the current study, this study reported less sports participation in adults with severe haemophilia than in mild haemophilia and a negative association with limitations in acitivities[35].

For children with haemophilia, most studies focused on sports injuries[13,36–38], rather than participation. A British cross-sectional study was the only study collecting similar data to this current study (n=84, age: 6-18). As in the current study, this study reported high sports participation with 90.5% playing sports (2x/wk; 4.9 hours/wk), without comparison with the GP[38]. A retrospective study in Dutch boys with haemophilia (n=102; age: 6-18) reported similar sports participation to the GP in (77%; 3x/wk)[13]. As in this study, the MAQ was used in studies with Dutch and Australian boys with haemophilia. Both studies reported higher weekly sports exposure in children with haemophilia (8.6 and 7.9 hrs/wk, respectively) than the current study (4.2 hrs/wk). However, the groups in these studies were smaller (n=36 (age: 8-18; 45% severe; cross-sectional) and n=104 (4-18; 82.7% severe), respectively) than the current study[10,11]. Besides a patient-reported measure for physical activity, the Australian study included prospectively recorded activity and injuries during a one year follow-up as well.

Perspective and clinical inference

Sports participation as well as other physically demanding activities (e.g.: labour) are an interesting and novel research area in PWH as it represents both physical status and

societal participation. Although sports participation was high across the age groups, differences still exist. The source for the differences between adults and children is unknown. Potential sources are bleeding and treatment history, poorer joint status in adults and/or a more restrictive policy towards sports participation in the earlier years of older PWH. Increased sports participation comes with a concomitant increase in injury risk. Therefore, studies need to collect injury data as well. Future research should focus on life span prospective studies assessing both sports participation and sports injuries, and compare this with GP data for correct interpretation.

Conclusion

The results of this study suggested high sports participation that was consistent with age in both children and adults with haemophilia, which was similar to the GP in both groups, although the GP showed an age-related decrease in sports participation. Adults with severe haemophilia were less involved in sports than those with non-severe haemophilia. This was not reported in children. Patients active in (high-risk) sports reported fewer limitations than those not involved in (high-risk) sports. This may be cause or consequence. The objective of haemophilia treatment is to guide patients towards a healthy (older) adulthood. In this respect, adequate counselling with regards to physical activity and sports is an important aspect of clinical care. Therefore, prospective information on type and intensity of sports performed as well as on injuries remains a necessity.

References

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672
2. Pulles AE, Mastbergen SC, Schutgens REG, Lafeber FPJG, van Vulpen LFD. Pathophysiology of hemophilic arthropathy and potential targets for therapy. *Pharmacol Res*. 2017;115:192-199. doi:10.1016/j.phrs.2016.11.032
3. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia : from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;6736(20):1-11. doi:10.1016/S0140-6736(20)32722-7
4. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. *N Engl J Med*. 2018;379(9):811-822. doi:10.1056/nejmoa1803550
5. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour.*; 2020. https://apps.who.int/iris/bitstream/handle/10665/325147/WHO-NMH-PND-2019.4-eng.pdf?sequence=1&isAllowed=y%0Ahttp://www.who.int/iris/handle/10665/311664%0Ahttps://apps.who.int/iris/handle/10665/325147
6. Hilberg T, Herbsleb M, Puta C, Gabriel HHW, Schramm W. Physical training increases isometric muscular strength and proprioceptive performance in hemophilic subjects. *Haemophilia*. 2003;9(2):86-93. doi:679 [pii]
7. Tiktinsky R, Falk B, Heim M, Martinovitz U. The effect of resistance training on the frequency of bleeding in haemophilia patients: A pilot study. *Haemophilia*. 2002;8(1):22-27. doi:10.1046/j.1365-2516.2002.00575.x
8. McLain LG, Heldrich FT. Hemophilia and Sports. *Phys Sportsmed*. 1990;18(11):73-80. doi:10.1080/00913847.1990.11710175
9. Nilsson IM, Hedner U, Ahlberg A. Haemophilia Prophylaxis in Sweden. *Acta Paediatr Scand*. 1976;65:129-135.
10. Groen WG, Takken T, van der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. *Haemophilia*. 2011;17(5):906-912. doi:10.1111/j.1365-2516.2011.02555.x
11. Broderick CR, Herbert RD, Latimer J, van Doorn N. Patterns of physical activity in children with haemophilia. *Haemophilia*. 2013;19(1):59-64. doi:10.1111/j.1365-2516.2012.02904.x
12. Köiter J, Van Genderen FR, Brons PPT, Nijhuis-van Der Sanden MWG. Participation and risk-taking behaviour in sports in children with haemophilia. *Haemophilia*. 2009;15(3):686-694. doi:10.1111/j.1365-2516.2009.02006.x
13. Versloot O, Timmer MA, de Kleijn P, et al. Sports participation and sports injuries in Dutch boys with haemophilia. *Scand J Med Sci Sports*. 2020;30(7):1256-1264. doi:10.1111/sms.13666
14. Versloot O, Berntorp E, Petrini 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(2). doi:10.1111/hae.13683
15. Heijnen L, Mauser-Bunschoten EP, Roosendaal G. Participation in sports by Dutch persons with haemophilia. *Haemophilia*. 2000;6(5):537-546. doi:10.1046/j.1365-2516.2000.00422.x
16. Plug I, Van Der Bom JG, Peters M, et al. Thirty years of hemophilia treatment in the Netherlands, 1972-2001. *Blood*. 2004;104(12):3494-3500. doi:10.1182/blood-2004-05-2008
17. Aaron DJ, Kriska AM, Dearwater SR, Cauley JA, Metz KF, LaPorte RE. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. *Am J Epidemiol*. 1995;142(2):191-201. http://www.ncbi.nlm.nih.gov/pubmed/7598119
18. von Mackensen S, Czepa D, Herbsleb M, Hilberg T. Development and validation of a new questionnaire for the assessment of subjective physical performance in adult patients with haemophilia--the HEP-Test-Q. *Haemophilia*. 2010;16(1):170-178. doi:10.1111/j.1365-2516.2009.02112.x
19. Van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: Validation of the Haemophilia Activities List. *Haemophilia*. 2006;12(1):36-46. doi:10.1111/j.1365-2516.2006.01186.x
20. Groen WG, van der Net J, Helders PJM, Fischer K. Development and preliminary testing of a Paediatric Version of the Haemophilia Activities List (pedhal). *Haemophilia*. 2010;16(2):281-289. doi:10.1111/j.1365-2516.2009.02136.x
21. The European Sports Charter. *Counc Eur*. Published online 1992:1-10.

22. Aaron DJ, Kriska AM, Dearwater SR, Cauley JA, Metz KF, LaPorte RE. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. *Am J Epidemiol*. 1995;142(2):191-201. doi:10.1093/oxfordjournals.aje.a117618

23. Tonoli C, Heyman E, Roelands B, Georges B, Berthoin S, Meeusen R. Validation and reliability of the Dutch language version of the Modifiable Activity Questionnaire in healthy subjects. *Sport Sci Health*. 2013;9(3):139-144. doi:10.1007/s11332-013-0160-y

24. Anderson A, Forsyth A. *Playing It Safe: Bleeding Disorders, Sports and Exercise*. National Hemophilia Foundation; 2017. doi:10.1136/jech.2007.061960

25. Kuijlaars IAR, van Emst M, van der Net J, Timmer MA, Fischer K. Assessing the test – retest reliability and smallest detectable change of the Haemophilia Activities List. *Haemophilia*. 2020;(September):1-5. doi:10.1111/hae.14226

26. Central Bureau of Statistics - Overweight in Dutch adults. 2Volksgezondheid en zorg. Published 2020. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie#node-overgewicht-volwassenen

27. Central Bureau of Statistics - Overweight in Dutch children. Volksgezondheid en zorg. Published 2020. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie#node-overgewicht-kinderen

28. Tiessen-Raaphorst (ed.) A, Tiessen-Raaphorst A. *Rapportage Sport 2014.*; 2015. https://www.scp.nl/Publicaties/Alle_publicaties/Publicaties_2015/Rapportage_Sport_2014

29. Khawaji M, Astermark J, Akesson K, Berntorp E. Physical activity and joint function in adults with severe haemophilia on long-term prophylaxis. *Blood Coagul Fibrinolysis*. 2011;22(1):50-55. doi:10.1097/MBC.0b013e32834128c6

30. Timmer MA, Gouw SC, Feldman BM, et al. Measuring activities and participation in persons with haemophilia: A systematic review of commonly used instruments. *Haemophilia*. 2018;24(2):e33-e49. doi:10.1111/hae.13367

31. Nusser SM, Beyler NK, Welk GJ, Carriquiry AL, Fuller WA, King BM. Modeling errors in physical activity recall data. *J Phys Act Heal*. 2012;9 Suppl 1(Suppl 1):S56-67. http://www.ncbi.nlm.nih.gov/pubmed/22287449

32. Chinapaw MJM, Mokkink LB, van Poppel MNM, van Mechelen W, Terwee CB. Physical activity questionnaires for youth: A systematic review of measurement properties. *Sport Med*. 2010;40(7):539-563. doi:10.2165/11530770-000000000-00000

33. Timmer MA, Pisters MF, de Kleijn P, de Bie RA, Schutgens REG, Veenhof C. Movement behaviour in adults with haemophilia compared to healthy adults. *Haemophilia*. 2018;(January):1-7. doi:10.1111/hae.13441

34. von Mackensen S, Harrington C, Tuddenham E, et al. The impact of sport on health status, psychological well-being and physical performance of adults with haemophilia. *Haemophilia*. 2016;22(4):521-530. doi:10.1111/hae.12912

35. Sherlock E, O'Donnell JS, White B, Blake C. Physical activity levels and participation in sport in Irish people with haemophilia. *Haemophilia*. 2010;16(1):202-209. doi:10.1111/j.1365-2516.2009.02111.x

36. McGee S, Raffini L, Witmer CM. Organized sports participation and the association with injury in paediatric patients with haemophilia. *Haemophilia*. 2015;21(4):538-542. doi:10.1111/hae.12696

37. Ross C, Goldenberg N, Hund D, Manco-Johnson MJ. Athletic participation in severe hemophilia: bleeding and joint outcomes in children on prophylaxis. *Pediatrics*. 2009;124(5):1267-1272. doi:10.1542/peds.2009-0072

38. Khair K, Littley A, Will A, von Mackensen S. The impact of sport on children with haemophilia. *Haemophilia*. 2012;18(6):898-905. doi:10.1111/j.1365-2516.2012.02857.x

39. Aaron DJ, Kriska AM, Dearwater SR, et al. The epidemiology of leisure physical activity in an adolescent population. *Med Sci Sports Exerc*. 1993;25(7):847-853.

40. van Genderen FR, van Meeteren NLU, van der Bom JG, et al. Functional consequences of haemophilia in adults: The development of the Haemophilia Activities List. *Haemophilia*. 2004;10(5):565-571. doi:10.1111/j.1365-2516.2004.01016.x

41. Von Mackensen S, Hilberg T, Valentino LA, Kurnik K, Khair K. Validation of the Haemophilia & Exercise Project-Test-Questionnaire (HEP-Test-Q) - An instrument for the assessment of subjective physical functioning in children with haemophilia. *Haemophilia*. 2018;24:888-895. doi:10.1111/hae.13533

42. RIVM (National Institute for Public Health and the Environment). Leeftstijlmonitor [Life Style Monitor, in Dutch]. Leefstijlmonitor 2019. Published 2019. Accessed February 3, 2021. https://www.sportenbewegenincijfers.nl/kernindicatoren/sportdeelname-wekelijks

Supplemental material

Supplemental Table S1: NHF risk categories with example sports

	NHF Category				
	1	**1,5**	**2**	**2,5**	**3**
Risk	Low risk	Low to moderate risk	Moderate risk	Moderate to high risk	High risk
Example	swimming	fitness	tennis	soccer	(field) hockey

NHF: National Hemophilia Foundation

Supplemental Table S2: Sports and their concomitant injury risk category according to the US NHF[24]

Activity	categories	Activity	categories
aquatics	1	power lifting	3
archery	1	racquetball	2,5
baseball	1,5-2,5	river rafting	2
basketball	1,5-2,5	rock climbing, indoor	1,5-2
bicycling	1,5-3	rock climbing, outdoor	2,3
BMX racing	3	rodeo	3
body sculpture class	1,5	rowing	1,5
boot camp workout class	2	rowing machine	1,5
bounce houses	2,5-3	rugby	3
bowling	2	running/jogging	2
boxing	3	scooters, motorized	2-2,5
canoeing	1,5-2,5	scooters, non-motorized	1,5-2,5
cardio kickboxing class	2	scuba diving	2-2,5
cheerleading	1,5-2,5	skateboarding	1,5-2,5
circuit training	1,5	skating, ice	1,5-2,5
dance	1-3	skating, inline and roller	1,5-2,5
diving, competitive	2-3	skiing, cross-country	2
diving, recreational	2	skiing, downhill	2,5
elliptical machine	1	skiing, water	2-2,5
fishing	1-2	ski machine	1,5
soccer, flag or touch	2	snorkelling	1
soccer, tackle	3	snowboarding	2,5
frisbee	1-1,5	snowmobiling	3
frisbee, golf	1,5-2	soccer	2-3
frisbee, ultimate	2-2,5	softball	1,5-2,5
golf	1	stationary bike	1
gymnastics	2-3	stepper	1-1,5
high intensity functional training class	2-3	strength training, weight lifting	1,5
hiking	1-1,5	surfing	2-2,5
hockey, field/ice/street	2,5-3	swimming	1
horseback riding	1,5-2,5	tee-ball	1,5
indoor cycling class	1,5-2	tennis	2
jet-ski (personal watercraft, PWC)	2-3	track and field	2-2,5
jumping rope kayaking	2	trampoline	2,5-3
kayaking	1,5-2,5	treadmill	1,5
lacrosse	3	volleyball	2-2,5
martial arts, tai chi	1	walking	1
martial arts, traditional and mixed	2-3	water polo	2,5
motorcycle/motocross (ATV, dirt bikes)	3	wrestling	3
mountain biking	2,5	yoga	1,5-2
pilates	1,5-2	zumba class	1,5-2

Supplemental Table S3: All reported sports by participants with haemophilia in the HiN6 study

Adults				Children			
	NHF	N	%		NHF	N	%
(Kick)Boxing	3	3	0,4%	(Kick)Boxing	3	1	0,5%
(Roller)skating	1.5-2.5	1	0,1%	Aerobics	1.5	1	0,5%
Archery	1	2	0,3%	Badminton	2	2	1,1%
Badminton	2	6	0,8%	Balance bike	1.5-2.5	1	0,5%
Basketball	1.5-2.5	1	0,1%	Base-/softball	1.5-2.5	1	0,5%
Billiards	1	9	1,2%	Basketball	1.5-2.5	3	1,6%
BMX	3	1	0,1%	Bouldering	3	1	0,5%
Boot camp	2	2	0,3%	Canoe	1.5-2.5	1	0,5%
Bouldering	3	1	0,1%	Circus	2-3	1	0,5%
Bowling	2	1	0,1%	Cycling	1.5	14	7,5%
Brisk walking	1.5	1	0,1%	Dancing/ballet	1-3	1	0,5%
Canoeing	1.5-2.5	1	0,1%	Fitness	2	7	3,7%
Chess	1	1	0,1%	Gymnastics	2-3	14	7,5%
Circus	2-3	1	0,1%	Handball	2-3	3	1,6%
Cycle cross	2.5	1	0,1%	Hockey (field)	3	2	1,1%
Cycling	1.5	158	20,8%	Ice skating	1.5-2.5	1	0,5%
Dancing/Ballet	1-3	4	0,5%	Judo	2	7	3,7%
Darts	1.5	4	0,5%	Korfball	1.5-2.5	4	2,1%
Dog training	2	1	0,1%	Mountain biking	2.5	1	0,5%
Fitness	2	148	19,5%	Physical Education	2	21	11,2%
Frisbee	1-1.5	1	0,1%	Running	3	5	2,7%
Futsal	2-3	7	0,9%	Sailing	1.5	1	0,5%
Golf	1	12	1,6%	Scouting	2-3	4	2,1%
Gymnastics	2-3	1	0,1%	Skiing	2-2.5	4	2,1%
Hockey (field)	2.5-3	5	0,7%	Snorkelling	1	1	0,5%
Hockey (indoor)	2.5-3	1	0,1%	Soccer	2-3	36	19,3%
Horseback riding	1.5-2.5	2	0,3%	Surfing	2-2.5	1	0,5%
Hydro therapy	1	1	0,1%	Swimming	1	30	16,0%
Ice skating	1.5-2.5	4	0,5%	Table Tennis	2	4	2,1%
Jiu Jitsu	2-3	1	0,1%	Taekwondo	2-3	1	0,5%
Jogging	2	4	0,5%	Tennis	2	4	2,1%
Karate	2-3	1	0,1%	Track and Field	2-2.5	2	1,1%
Kite surfing	2-3	1	0,1%	Trampoline	3	2	1,1%
Korfball	1.5-2.5	3	0,4%	Volleyball	2-2.5	2	1,1%
Motor cross	3	3	0,4%	Walking	1	2	1,1%
Motor cycling	3	1	0,1%	Wheelchair hockey	2-3	1	0,5%
Mountain hiking	1.5-2	7	0,9%				
Mountain biking	2.5	12	1,6%				
Padel	2	2	0,3%				
Physical Education	2	1	0,1%				

Pole dancing	2	1	0,1%
Refereeing	1.5	3	0,4%
Rowing	1.5	5	0,7%
Rugby	3	1	0,1%
Running	2	70	9,2%
Sailing	1.5	9	1,2%
Scuba diving	2-2.5	2	0,3%
Shooting	1	1	0,1%
Skateboarding	1.5-2.5	3	0,4%
Skiing	2-2.5	15	2,0%
soccer	2-3	27	3,6%
Squash	2-3	3	0,4%
Surfing	2-2.5	3	0,4%
Swimming	1	51	6,7%
Table tennis	2	6	0,8%
Tennis	2	31	4,1%
Track and Field	2-2.5	1	0,1%
Volleyball	2-2.5	3	0,4%
Volplane	2-3	1	0,1%
Walking	1	99	13,1%
Waterpolo	2.5	2	0,3%
Wind surfing	2-2.5	2	0,3%
Yoga	1.5-2	2	0,3%

CHAPTER 3

Sports participation in adult patients with severe haemophilia: a comparison between intermediate and high-dose prophylaxis

O. Versloot[1,2], E. Berntorp[3,7], P. Petrini[4], R. Ljung[5], J. Astermark[6], M. Holmström[7,8], P. de Kleijn[1], K. Fischer[1]

[1] Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Clinical Coagulation Research Unit, Lund University, Skåne University Hospital, Malmö, Sweden

[4] Department of Pediatrics, Clinic of Coagulation Disorders, Karolinska Hospital, Stockholm, Sweden

[5] Clinical Coagulation Research Unit, Lund University and Malmö Centre for Thrombosis and Haemostasis, Skåne University Hospital, Malmö, Sweden

[6] Centre for Thrombosis and Haemostasis, Skåne University Hospital, Lund University, Malmö, Sweden.

[7] Department of Translational Sciences, Faculty of Medicine, Lund University, Malmö, Sweden.

[8] Coagulation Unit, Karolinska University Hospital, Stockholm, Sweden

Haemophilia, 2019 Mar; 25(2): 244-251

Bullet Points

What is already known:

- With modern treatment strategies, sports participation is part of daily life for PWH.
- PWH on a high-dose regimen report fewer bleeds than PWH on intermediate-dose, but similar quality of life.
- Data on sports participation and physical activity in adults with severe haemophilia are lacking

What this study adds:

- All participants were active in sports, including high-risk sports.
- An age-related decline in sports participation, joint status and HRQoL was observed in Dutch PWH, but not in Swedish PWH.
- No associations between sports participation and bleeding or clotting factor consumption were observed.

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 ($SF\text{-}36_{PF}$: 100-0), joint status (HJHS: 0-144) perceived limitations (HAL_{sum}: 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: 71 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/week in PWH 18-22 years to 2x/week in PWH 30-40 years, $p<0.05$), joint health (HJHS: median 2 to 15.5, $p<0.01$) and physical functioning ($SF\text{-}36_{PF}$: 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.

Introduction

Sports participation and an active life style 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 life style 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 results[4] 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 (e.g. soccer) and category 3 (e.g. 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

Design and setting

The data analysed in this study were collected as a pre-specified part of a prospective observational study comparing cost and outcome of intermediate-dose vs. high-dose prophylaxis[6]. Details of study design and methods have been reported elsewhere[6]. 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, demographic [8,9] and cultural aspects[10,11].

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 regards to clinical and self-reported scores and bleeding data.

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 three years.

All participants completed a specifically developed sports questionnaire, listing 23 sports (see table 1), on which they marked the 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[12,13]. Joint health was assessed by performing the Haemophilia Joint Health Scale ($HJHS_{1.0}$, optimum score 0, worst score 144)[14,15]. Self-reported limitations in activities were assessed using the Hemophilia Activities Lists (HAL sum score)[16–18]. Additionally, physical functioning was assessed by means of the SF-36 (domain: physical functioning: $SF\text{-}36_{PF}$)[19–21]. Both the HAL and the SF-36 have a score range of 0-100, with a higher score indicating less limitations or better physical functioning.

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*	2
5.	Fitness*	1.5
6.	Billiards*	1
7.	Bowling	2
8.	Golf	1
9.	Football	2.5
10.	Indoor Football*	2.5
11.	Tennis	2
12.	Squash*	2
13.	Jogging/Running	2
14.	Ice Hockey	3
15.	Field Hockey	3
16.	Indoor Hockey	3
17.	Table Tennis*	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

To facilitate the comparison of HJHS, HAL_{sum} and $SF\text{-}36_{PF}$ scores, the outcomes for HAL_{sum} and $SF\text{-}36_{PF}$ scores are presented as the proportional deviation from the optimal score (100). A HJHS score of 10 was used as a cut-off value to be able to distinguish between patients with significant joint damage (HJHS≥10) and patients without significant joint damage (HJHS<10)[6].

To assess potential associations between participation in high-risk sports and bleeding (risk), sports were classified into risk categories according to the NHF classification[7]. This classification runs from 1 (safe) via 1.5 (safe to moderate), 2 (moderate risk), 2.5 (moderate to dangerous) to 3 (dangerous). The injury risk for several sports was classified over a range of risk categories (e.g.: soccer 2 [moderate] – 3 [dangerous])[7]. In these cases the median value of the indicated range was applied in the analysis. Sports that were not included in the NHF classification were classified according to their estimated impact and collision risk. Throughout the text, whenever "football" is mentioned, this refers "soccer", not American football. Sports in categories 2.5 (e.g.: soccer, skiing) and

3 (e.g.: boxing, rugby) are considered to be high-risk sports. The highest risk category in which participants were engaged at least twice per week was determined to assess how often participants were exposed to high-risk sports. PA was assessed with the International Physical Activity Questionnaire (IPAQ), which was converted into, and expressed as Metabolic Equivalent of Task (METs)[22]

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 (HAL_{sum}) and health related quality of life ($SF\text{-}36_{PF}$). 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)[23]

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).

Results

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 Dutch (69.4%), 28 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.

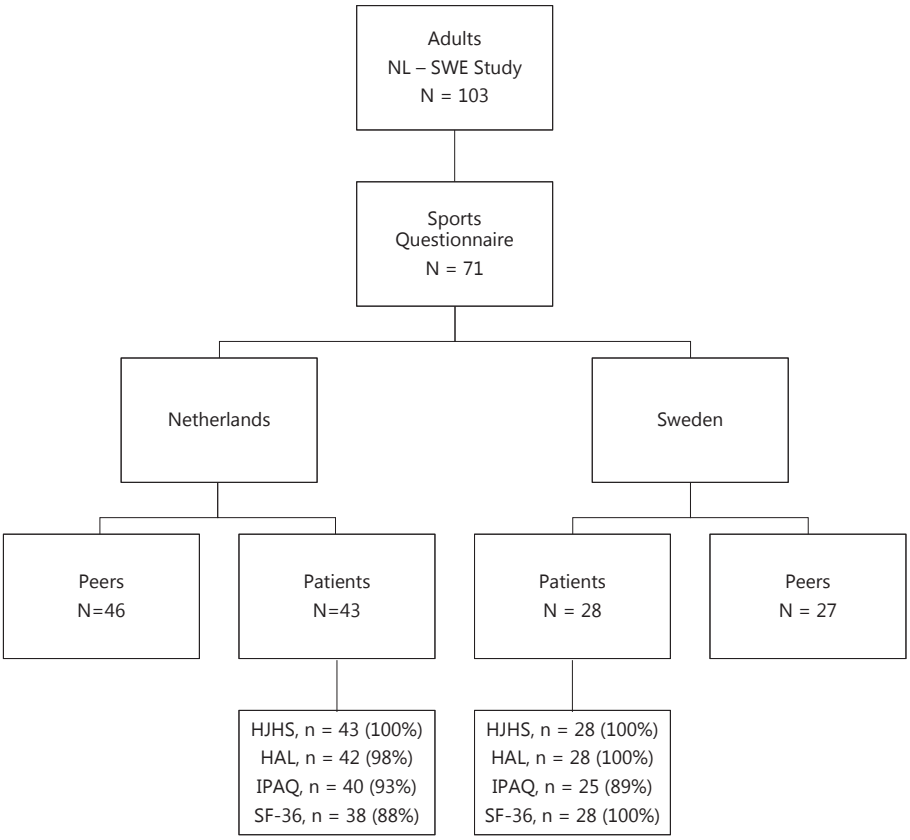


Figure 1: overview of available participants and data response.

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, less than 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 ($SF36_{PF}$: 95 vs. 100).

Table 2: Patient characteristics and treatment history

	Dutch PWH	Swedish PWH
N	**43**	**28**
	Median (IQR) or number (%)	
Age (y)	27.3 (22 - 30)	25 (22 - 31)
Haem Type A (%)	37 (86%)	25 (89%)
HIV+ (%)	4 (9.3%)	1 (3.6%)
HCV+ (%)	23‡ (53.5%)	7 (25.0%)
Age start prophylaxis (y)	5.0* (3.3 - 5.6)	1.7 (1.3 - 3.0)
Weekly Dose (IU/kg)	41* (31 - 51)	82 (59 - 96)
Joint health (HJHS, 0-144)	9* (2 - 18)	4.5 (2.3 - 7)
Limitations (HAL, 100-0)	94* (82 - 98)	99 (94 - 100)
Physical functioning (SF-36PF, 100-0)	95‡ (75 - 100)	100 (95 - 100)

Dutch PWH score significantly higher than Swedish PWH with regard to treatment history ($p<0.01$), joint health ($p<0.01$), self-reported limitations ($p<0.01$) and physical functioning ($p<0.05$), but have lower weekly treatment dose ($p<0.01$).

Clinical and self-reported outcome according to age

Treatment and outcome according to age and country is shown in Table 3. Consistent with the previous publication, treatment was significantly less intensive for Dutch PWH in all age groups[6]. 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 ($SF\text{-}36_{PF}$: 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[6], Dutch PWH reported more limitations (HAL_{sum}) than Swedish PWH, although this difference was not statistically significant ($p = 0.223$)

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 (NHF>2), of which 33.9% (NL: 27.9%; 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 (Dutch PWH: cycling, swimming, walking, fitness, bowling, skiing, billiards, ice skating, football and jogging; Swedish PWH: cycling, swimming, walking, fitness, jogging, bowling, skiing, football, billiards and skating) were similar to their peers (data available on request).

Sports participation according to age

Sports participation according to age and country is shown in Table 4. A clear decrease in sports participation (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 (NHF>2) in Dutch PWH was observed: from 73% (18-22 years old) and 86% (23-29 years old) in the youngest groups to 28% for 30-40 year old PWH. Proportionally more Swedish PWH aged 30-40 (75%) were engaged in high-risk sports than Dutch PWH (28%) aged 30-40.

Sports participation in relation to clinical outcome.

Spearman rank correlation showed a negative correlation between joint status (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)[23], these correlations do not seem to be clinically relevant.

Table 3: Treatment and outcome according to age and country

	Dutch Patients			Swedish Patients		
Age group	**18-22 years**	**23-29 years**	**30-40 years**	**18-22 years**	**23-29 years**	**30-40 years**
N	**11**	**14**	**18**	**8**	**12**	**8**
			Median (IQR) or number (%)			
Age start prophylaxis (y)	4.3 (3.4 - 5.1)	3.6 (2.1 - 5.9)	5.3 (4.4 - 8.4)*	1.4 (1.2 - 1.7)	1.5 (1.2 - 5.1)	2.7 (2.0 - 4.2)
Weekly dose (IU/kg)	50 (38.5 - 64.4)	42.9 (24.1 - 53.8)	35.7 (29.4 - 47.1)	91 (81.9 - 108.5)	63.0 (51.4 - 106.0)	81 (52.7 - 92.0)
Annual number of joint bleeds	1 (1 - 2)	1 (0.8 - 2)	2 (1 - 3.5)	0.3 (0.0 - 1.0)	0 (0.0 - 1.0)	0 (0.0 - 2.5)
Total number of joint bleeds (during 5 year follow up)	8 (4 - 15)	11 (3 - 17)*	10.5 (6.5 - 21.3)	1.5 (0.3 - 7.8)	1 (0.0 - 5.5)	0.5 (0.0 - 19.3)
Joint health (HJHS, 0-144)	2.0 (1 - 12.3)	6.5 (1.8 - 11.8)	15.5 (8.8 - 22.5)‡	3.0 (3.0 - 6.8)	4.5 (3.0 - 6.0)	6.5 (1.3 - 18.5)
HJHS ≥10 (N[%])	3 (27.3)	4 (28.6)	11 (61.1)	1 (12.5)	1 (8.3)	2 (25)
Limitations (HAL_{sum}, 100-0)	95 (76 - 98)	92 (82 - 100)	94 (87 - 98)	98.5 (91 - 100)	100 (93 - 100)	99.5 (96 - 100)
Physical functioning ($SF\text{-}36_{PF}$, 100-0)	100 (90 - 100)	100 (91.3 - 100)	77.5 (42.5 - 95)*‡	100 (92.5 - 100)	100 (91.3 - 100)	97.5 (95 - 100)
Physical Activity (x1000 METS/week)	5.8 (1.1 - 15.1)	5.0 (0.7 - 14.9)	2.6 (1.1 - 12.1)	3.5 (1.2 - 7.9)	4.5 (1.3 - 12.0)	1.8 (0.5 - 12.6)

Dutch PWH started using prophylaxis later than Swedish PWH and use lower weekly doses ($p<0.001$). Dutch PWH report more (annual) joint bleeds than Swedish PWH in all age categories. Dutch PWH show an age-related decline in joint health (*p for trend* <0.01). Joint health could not be assessed independently from age for Swedish PWH due to a lack of variation. Dutch 30-40 year old PWH show an age-related decrease in physical functioning and report more limitations and lower physical functioning than Swedish PWH. Dutch PWH show a trend towards more PA than Swedish in all age groups.

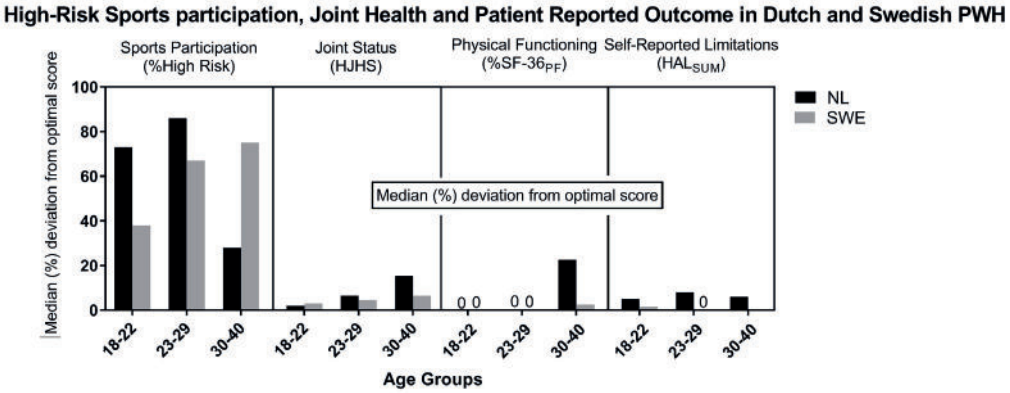


Figure 2: High-risk sports participation and relative deviations from optimal score for joint status, physical functioning and self-reported limitations in Dutch and Swedish PWH. Patient reported outcomes are presented as median deviation (%) from the optimal score. Dutch PWH aged 30-40 showed less high-risk sports participation and worse outcome than younger Dutch PWH and Swedish PWH of all age categories.

Table 4: Sports participation according to age and country

	Dutch PWH			Swedish PWH		
	18-22	23-29	30-40	18-22	23-29	30-40
N	11	14	18	8	12	8
	Median (IQR)					
Sports participation: - Number of sports	5.0 (2.0 - 8.0)	4.0 (1.8 - 8.0)	3.0° (1.0 - 3.0)	3.0 (2.0 - 5.8)	4.5 (2.0 - 7.0)	4.0 (1.0 - 5.8)
Sports participation: - Times/week	3.0 (2.0 - 5.8)	7.0 (3.0 – 13.0)	2.0 (1.0 - 6.5)	5.5 (3.5 - 6.5)	6.0 (2.0 – 11.0)	5.0 (2.0 – 14.0)
Sports participation High-risk Sports - Times/week	1.5 (1.0 – 4.3)	3.0 (1.0 – 8.0)	0 (0.0 - 6.5)	3.5 (0.5 - 7.3)	5.0 (3.0 – 6.0)	2.0 (1.8 - 3.8)
	Number of participants involved in HR-sports (n[%])					
High-Risk Sports (NHF>2)	8	12	5	3	8	6
	73%	86%	28%*	38%	67%	75%†

Dutch PWH show an age-related decrease in sports participation and high-risk sports participation. High-risk sports were defined as sports in categories 2.5 (moderate risk to dangerous) or 3 (dangerous) of the NHF classification. Participants in HR sports are those active in one of these sports at least once per week.

*: 30-40 year old Dutch PWH are proportionally less involved in HR sports (*)than young Dutch PWH (18-22 and 23-29 year old) and proportionally more involved in safe than in (moderately) dangerous sports (§).

†:Swedish 30-40 year old PWH are proportionally more involved in HR sports than 30-40 year old Dutch PWH

Treatment and bleeding parameters.

Because of the assumed increased bleeding risk associated with engaging in high-risk sports[24], the potential association between performing high-risk sports and joint bleeding (annual and 5 year joint bleeding) was analysed. Spearman rank correlation coefficient testing showed no associations (rho<0.5)[23] between high-risk sports participation per week and bleeding data (NL: rho= -0.25, p=0.27, 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.

Internal and external validity

This analysis included a Dutch and Swedish birth cohort (1970-1991). These groups were chosen because of similar socioeconomic status[8], cultural norms[10,11] 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 was 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 was 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 was 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, endurance and body perception.

Comparison with other studies

The key observation of the present study was a significant reduction in sports participation for 30-40 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 Dutch[13] and the Swedish[12] 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].

Clinical relevance and future research

This study showed a trend toward 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 MAQ[27,28] and the use of accelerometers[37] 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 al[24]. 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].

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.

References

1 Von Mackensen S. Quality of life and sports activities in patients with haemophilia. Haemophilia *2007*; **13:** 38–43.

2 Groen WG, Takken T, Van Der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. Haemophilia *2011*; **17:** 906–12.

3 Heijnen L, Mauser-Bunschoten EP, Roosendaal G. Participation in sports by Dutch persons with haemophilia. Haemophilia *2000*; **6:** 537–46.

4 Broderick CR, Herbert RD, Latimer J, van Doorn N. Patterns of physical activity in children with haemophilia. Haemophilia *2013*; **19:** 59–64.

5 Fromme A, Dreeskamp K, Pollmann H, et al. Participation in sports and physical activity of haemophilia patients. Haemophilia *2007*; **13:** 323–7.

6 Fischer K, Steen Carlsson K, Petrini P, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: Comparing outcome and costs since the 1970s. Blood *2013*; **122:** 1129–36.

7 Anderson A, Forsyth A. Playing it safe: Bleeding Disorders, Sports and Exercise. New York, NY.: National Hemophilia Foundation; *2017*.

8 EuroStat. Quality of Life - Facts and Views. *2015*.I

9 United States Census Bureau (27 june 2011), International Database. Retrieved September 6, 2018, from https://www.census.gov/data-tools/demo/idb/region.php?N= Results &T=13&A=separate&RT=0&Y=2018&R=-1&C=NL,SW

10 Wilson TC. The Paradox of Social Class and Sports Involvement. The Roles of Cultural and Economic Capital. Int Rev Sociol Sport *2002*; **37:** 5–16.

11 van Tuyckom C, Scheerder J, Bracke P. Gender and age inequalities in regular sports participation: A cross-national study of 25 European countries. J Sports Sci *2010*; **28:** 1077–84.

12 Norberg JR. Statens stöd till idrotten. *2014*.

13 Tiessen-Raaphorst (ed.) A. Rapportage Sport 2014. *2015*.

14 Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. Haemophilia *2006*; **12:** 518–25.

15 Feldman BM, Funk SM, Bergstrom BM, et al. Validation of a new pediatric joint scoring system from the international hemophilia prophylaxis study group: Validity of the hemophilia joint health score. Arthritis Care Res *2011*; **63:** 223–30.

16 van Genderen FR, van Meeteren NLU, van der Bom JG, et al. Functional consequences of haemophilia in adults: The development of the Haemophilia Activities List. Haemophilia *2004*; **10:** 565–71.

17 Van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: Validation of the Haemophilia Activities List. Haemophilia *2006*; **12:** 36–46.

18 Brodin E, Baghaei F, Elfvinger P, Lindvall K, Sunnerhagen KS. The Swedish version of the Haemophilia Activity List. Haemophilia *2011*; **17:** 662–8.

19 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36) 1. Conceptual framework and item selection. Med Care *1992*; **30:** 473–83.

20 McHorney C a, Ware JE, Raczek a E. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care *1993*; **31:** 247–63.

21 Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ *1992*; **305:** 160–4.

22 Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc *2003*; **35:** 1381–95.

23 Cohen J. A power primer. Psychol Bull *1992*; **112:** 155–9.

24 Broderick CR, Herbert RD, Latimer J, et al. Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia. JAMA J Am Med Assoc *2012*; **308:** 1452–9.

25 Klesges R, Eck L, Mellon M, et al. The accuracy of self-reports of physical activity. Med Sci Sports Exerc *1990*; **22:** 690–7.

26 Nusser SM, Beyler NK, Welk GJ, et al. Modeling errors in physical activity recall data. J Phys Act Heal *2012*; **9 suppl 1:** S56-67.

27 Momenan AA, Delshad M, Sarbazi N, et al. Reliability and validity of the modifiable activity questionnaire (MAQ) in an Iranian urban adult population. Arch Iran Med *2012*; **15:** 279–82.

28 Tonoli C, Heyman E, Roelands B, et al. Validation and reliability of the Dutch language version of the Modifiable Activity Questionnaire in healthy subjects. Sport Sci Health *2013*; **9:** 139–44.

29 von Mackensen S, Czepa D, Herbsleb M, Hilberg T. Development and validation of a new questionnaire for the assessment of subjective physical performance in adult patients with haemophilia--the HEP-Test-Q. Haemophilia *2010*; **16:** 170–8.

30 Khair K, Littley A, Will A, von Mackensen S. The impact of sport on children with haemophilia. Haemophilia *2012*; **18:** 898–905.

31 Köiter J, Van Genderen FR, Brons PPT, Nijhuis-van Der Sanden MWG. Participation and risk-taking behaviour in sports in children with haemophilia. Haemophilia *2009*; **15:** 686–94.

32 Buxbaum NP, Ponce M, Saidi P, Michaels LA. Psychosocial correlates of physical activity in adolescents with haemophilia. Haemophilia *2010*; **16:** 656–61.

33 Khawaji M, Astermark J, Akesson K, Berntorp E. Physical activity and joint function in adults with severe haemophilia on long-term prophylaxis. Blood Coagul Fibrinolysis *2011*; **22:** 50–5.

34 Cuesta-Barriuso R, Torres-Ortuño A, Pérez-Alenda SSS, et al. Sporting Activities and Quality of Life in Children With Hemophilia. Pediatr Phys Ther *2016*; **28:** 453–9.

35 González LM, Peiró-Velert C, Devís-Devís J, et al. Comparison of physical activity and sedentary behaviours between young haemophilia A patients and healthy adolescents. Haemophilia *2011*; **17:** 676–82.

36 Schoenmakers MAGC, Gulmans VAM, Helders PJM, Van Den Berg HM. Motor performance and disability in Dutch children with haemophilia: A comparison with their healthy peers. Haemophilia *2001*; **7:** 293–8.

37 Westerterp KR. Reliable assessment of physical activity in disease: An update on activity monitors. Curr Opin Clin Nutr Metab Care *2014*; **17:** 401–6.

38 Collins PW, Fischer K, Morfini M, Blanchette VS, Björkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. Haemophilia *2011*; **17:** 2–10.

CHAPTER 4

Sports participation and sports injuries in Dutch boys with haemophilia

O. Versloot[1,2], M.A. Timmer[1], P. de Kleijn[1], M. Schuuring[3], C.F. van Koppenhagen[4], J. van der Net[3], K. Fischer[1]

[1] Van Creveldkliniek, University Medical Center Utrecht, Utrecht, The Netherlands.

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, University Medical Center, Utrecht, The Netherlands.

[4] Physical Medicine and Rehabilitation, University Medical Centre, Utrecht, the Netherlands.

Scandinavian Journal of Medicine and Science in Sports, 2020 Jul; 30(7): 1256-1264

Bullet Points

What is already known:

- Sports participation in children with haemophilia is generally considered to be associated with increased injury risk, which is generally considered highest in severe haemophilia.
- Knowledge about injury risk associated with sports participation (in these children) is needed for adequate counselling.

What this study adds:

- Overall sports participation (~77%) was similar for severe and non-severe haemophilia, and similar to the general population.
- Injury rate was similar in severe and non-severe haemophilia.
- Dutch boys with haemophilia did not report more sports injuries than age-matched children in the general population.
- Type and weekly frequency of sports participation were not associated with bleeds or injuries.

Abstract

Introduction: Sports participation in children with haemophilia is generally considered to be associated with increased injury risk, which is generally considered highest in severe haemophilia.

Aim: To assess sports participation according to age and severity in children with haemophilia and its association with sports injuries.

Methods: In a retrospective single centre study, sports participation, injuries and bleeding data from three consecutive annual clinic visits were collected for young patients with haemophilia (PWH, aged 6-18). Sports in categories 2.5 and 3 of 3 according to the National Hemophilia Foundation classification were considered high-risk. Groups were compared using Chi-square testing.

Results: 105 PWH (median age: 13(IQR 10-14); 53% severe; bleeding rate: 1/year) were identified; three were unable to perform sports and were excluded. The majority of PWH (77%) played sports weekly, of which 80% high-risk sports. Sports participation (median 3.0x/week), and the proportion of injured PWH was similar in severe (42%) and non-severe (33%) PWH. Sports injuries were rare (65% no injuries in 3 yrs, median 0/year (IQR 0-1)). Annually, PWH did not report more injuries (15%) than age-matched boys (28%). Sports injuries were not associated with frequency and type of sports.

Discussion: This retrospective study showed high sports participation (including high-risk sports) and low injury rates. Sports participation was similar across severities and injury rates were not higher than among the general population. Injuries were not associated with frequency or type of sports. A prospective study with objective assessment of sports participation and injuries is warranted to confirm these findings and avoid recall bias.

Introduction

Haemophilia is an inherited, chronic haematological disease in which patients have decreased levels of clotting factor VIII (haemophilia A, FVIII) or IX (haemophilia B, FIX). At this moment, there is no cure. Haemophilia severity is classified as severe (<1% FVIII/FIX), moderate (1-5%) or mild (5-40%)[2]. Low clotting factor levels can cause spontaneous or traumatic bleeds, including joint bleeds. These joint bleads can lead to haemophilic arthropathy if not managed appropriately[7]. Accordingly, patients with haemophilia (PWH) are at an increased risk of reduced social participation (work, education, sports). PWH were traditionally discouraged to participate in sports because of the assumed increased bleeding risk due to body contact or joint trauma. The introduction of prophylactic therapy[4] has drastically improved the opportunity to participate in sports for PWH, making it a patient relevant outcome.

Participation in sports is essential for children[116], both with and without haemophilia. As in other chronic health conditions (e.g. rheumatoid arthritis, cerebral palsy, cystic fibrosis)[117–120], participating in sports has been associated with numerous positive effects in children with haemophilia: improved endurance, increased strength and proprioception[14,16,66], conservation of muscle mass and bone density[66,68,121], reduced bleeding risk[16,69], as well as improved health related quality of life[92], social development[110] and physical literacy[122]. However, independent of haemophilia, sports participation, especially in high-risk (HR) sports, increases the risk of injuries or bleeds[71,123,124]. Due to this increased injury risk, parents and care-givers may still be reluctant towards sports participation, potentially limiting children with haemophilia in achieving an active lifestyle[88,113].

Previous studies have reported that Dutch children with haemophilia are just as active as their peers[24,26,113], but information on type and intensity of sports participation and the associated injury risk with regard to age or severity remains limited.

Two American studies with one year follow-up failed to show an association between participation in (high-impact) sports and an increased injury risk in children with haemophilia[31,91]. A detailed Australian study showed a transient increase in bleeding risk in children and adolescents with moderate and severe haemophilia after vigorous physical activity but the absolute increase in bleeding risk was small[33]. A nationwide cross-sectional study in Finland reported higher sports injury risk in adolescents with a chronic health condition (e.g. asthma, diabetes, joint pain) than in the general population[125].

The primary aim of this study was to assess sports participation according to age and severity in Dutch children with haemophilia over a 3 year period. As a secondary aim, the association between sports participation and the number of sports injuries was assessed.

Methods

Design and setting

This single-centre, retrospective study was performed at the van Creveldkliniek (University Medical Center (UMC) Utrecht) in 2018. At our clinic, patients are assessed annually in a structured multi-disciplinary clinic (e.g.: physician, physiotherapist), including routine assessment of sports participation, bleeds and injuries. Sports participation (regular planned sports) and, injuries were self-reported; bleeds were extracted from the infusion logs and hospital files. Injury data were cross-checked with hospital files. All data were entered in the patient file during the annual multidisciplinary clinic visit. Data from the three most recent annual multidisciplinary visits were extracted anonymously from electronic patient files. The study was approved by the IRB of UMC Utrecht (approval number: 18-265). Informed consent was waived because the data was collected anonymously.

Participants

The participants of this study were children with haemophilia A or B who were 6-18 years during their three most recent annual clinic visits (range: 2011-2018). Patients with current inhibitors or neurological disability were excluded. Due to the low number of patients with moderate haemophilia, patients with moderate and mild haemophilia were grouped as “non-severe”.

Data collected

Sports participation characteristics (active in organised sports at least once weekly (yes/no), active in HR-sports at least once weekly (yes/no), number and type of sports, weekly frequency), number of bleeds and number of sports injuries were collected from the three most recent annual clinic visits. Infusion logs included bleeding data and were completed mostly by parents.. Sports was defined as “all forms of physical activity which, through casual or organized participation aim at expressing or improving physical fitness and mental well-being, forming social relationships or obtaining results in competition at all levels.”[78]. Participation in school physical education classes was not considered. Sports injuries were defined as any injury as a result of participation in sport resulting in the need for any form of medical treatment, including infusion of clotting

factor concentrate with or without concomitant treatment such as physiotherapy, taping, braces, crutches etc. Joint bleeds were defined as any complaint located in peripheral synovial joints (ankles, knees, elbows, shoulders, hips or wrists) requiring treatment with clotting factor concentrate. A muscle bleed was defined as "an episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and loss of movement over baseline"[2].Bleeds reported included both bleeds related as well as unrelated to sports. Weekly sports frequency (times/week) was recorded. Sports were categorized into five risk categories according to the classification of the US National Hemophilia Foundation (NHF)[32]. A selection of sports and their risk categories are displayed in supplemental table S1. These categories run from 1 (safe) via 1.5 (safe to moderate risk), 2 (moderate risk), 2.5 (moderate risk to high risk) to 3 (high risk). Category 1 contains low impact sports with a low collision risk like walking and swimming, while sports in category 2.5 (e.g. football) and category 3 (e.g. rugby) are considered to be HR-sports[32]. Sports categorised across multiple categories were classified as the average risk category (e.g. 2.5 for football). The highest category in which participants were involved in was used to test the association of sports participation with injuries and/or bleeds. In case of participation in sports of different risk categories, patients were classified into the highest risk category. Sports participation was collected for each annual clinic visit and was analysed and presented per year.

The collected data of PWH was compared to the sports participation and sports injury data of Dutch general population (GP)[80,126]. These data are collected bi-annually by a standardized Dutch questionnaire and were collected online or by phone. Participants were asked to provide a maximum of 4 sports they performed. In order to compare these groups, similar age groups were created: 6-12 and 12-18 years. Data on injuries in the GP was collected from a nationwide injury registry[127].

Statistics

Sports participation and HR-sports participation according to age and haemophilia severity (severe vs. non-severe) were tested by means of Pearson's Chi Square tests. Age groups of 6-11 and 12-18 years were created in order to compare results to the Dutch general population[126]. Associations between haemophilia severity and HR-sports and between sports participation and the number of sports injuries were tested using Pearson's Chi Square tests.

All results were presented as median values with interquartile range (IQR) with 95% confidence intervals (CI) where appropriate. Statistical significance levels were set at 5% ($p<0.05$). The statistical analysis was performed using SPSS statistical software, version 25 (IBM corp., Armonk, NY).

Results

Participants

Originally, 105 patients with haemophilia (PWH) were identified. Three patients were excluded due to epilepsy, cerebral palsy or a current inhibitor, leaving 102 eligible patients. Patient characteristics are shown in Table 1. In total, 86% had haemophilia A, and 53% had severe, 5% moderate and 42% mild haemophilia. Because of the low number of patients with moderate haemophilia (n=5), patients with moderate and mild haemophilia were grouped as "non-severe" to be able to assess differences in PWH with no clotting factor activity and PWH with some, but insufficient factor activity[53]. Median age of the participants was 13 years (IQR 11-15). Continuous prophylaxis was used by all severe and 2 moderate patients. A total number of 187 bleeds were reported during follow up. These bleeds were reported by 69 (68%) patients, with 33 PWH (32%) not reporting any bleeds during follow-up. The median bleeding rate was 1 bleed/3 years (range: 0-8). PWH with bleeds reported a median of 2.7 bleeds/3 years (range: 1-8).

Table 1: Patient and treatment characteristics

	Median (IQR) or number (%)	Range
Number of patients	102	-
Age at first visit (years)	13 (10-14)	6-17
Haemophilia type A	88/102 (86%)	-
Severe	54/102 (53%)	-
Follow up (years)	3 (3-3)	1-3
Treatment		
Full time prophylaxis	56 (55%, severe: 100%)	-
Treatment dose (IU/kg/infusion)	17.5 (14-28.2)	7.1-83.3
Frequency (times/week)	3 (3-3,5)	2-7
Bleeds		
Total number of reported bleeds	187	-
Number of patients with bleeds	69 (68%)	-
Number of bleeds/patient during follow-up	1 (0-3)	0-8
Annual number of bleeds	0 (0-1)	0-6

During a median follow-up of 3 years (year 1: 100%; year 2: 99%; year 3: 93%) a total of 287 person-years were collected. Due to shifting age distributions, the number of patients aged 6-18 varied during the three years of data collection. Due to these reasons, group sizes varied for each year: n=102, n=98, and n=89, respectively). All participants routinely visited the clinic at least once during the studied period; 99% had data from two clinic visits, while 92% had data from all three visits during the study period.

Sports participation

Participation

Sports participation and injuries according to year and severity is shown in figure 1. Overall, 87/102 (85%) of PWH played sports at any time during the follow-up period. Due to switching between sports and overlapping activities within PWH, sports participation was presented per year (1; 2; 3).

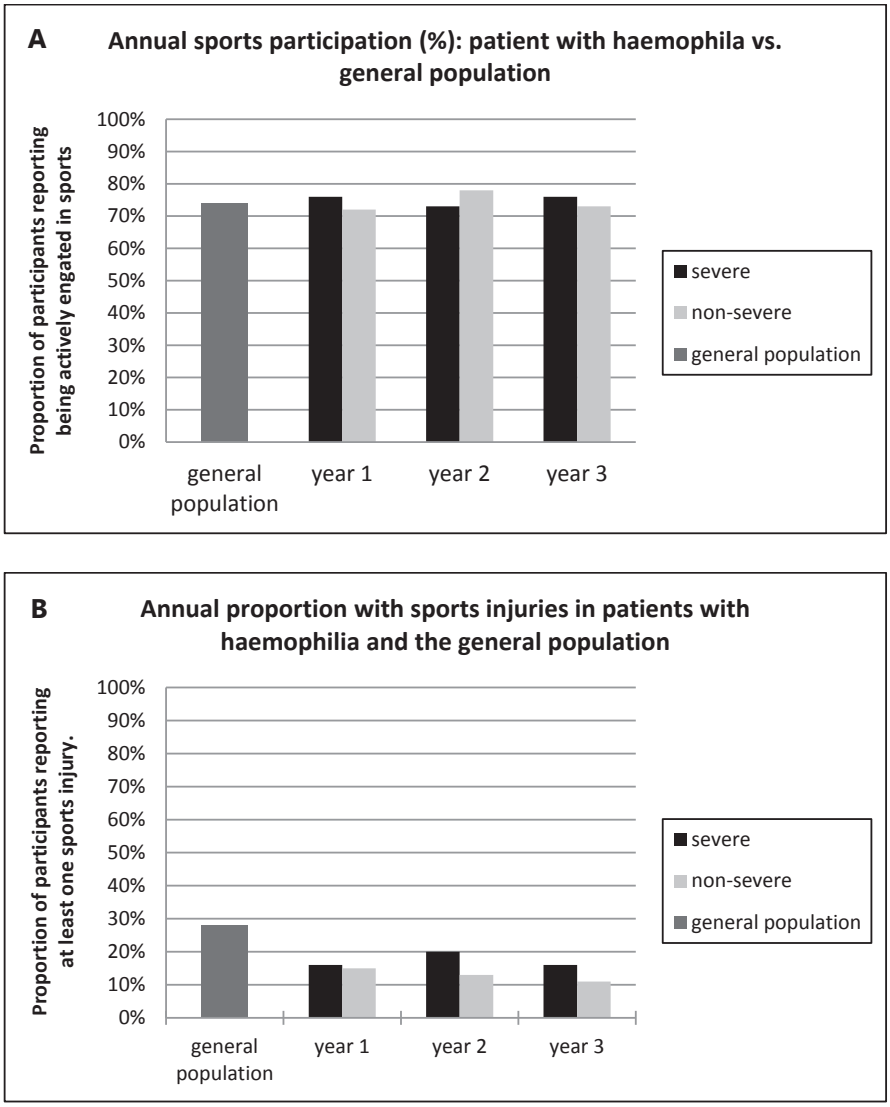


Figure 1: Sports participation (1A) and sports injuries (1B) in the general population and in young Dutch PWH.

Per year, 77% of PWH participated in a total number of 37 different sports at some time during the study, including 70/87 (80%) participating in HR-sports. Sports participation remained consistent during the three year follow-up (year 1: 73/102 (72%), year 2: 76/98 (78%), year 3: 74/89 (83%); p=0.65). The majority (59%) played one sport, 13% played two sports and 1% three sports. A median weekly frequency of 3 (IQR 2-3) was reported.

Within the risk categories, "moderate risk to high risk" (NHF 2.5) was the most frequently reported category (75%). This seems to be particularly based on the high number of participants (49%) playing football.

Sports participation according to age

Average annual sports participation (6-11yrs.: 94% (CI 83-98) vs. 12-18yrs.: 84% (CI 71-91); p=0.13) and HR-sports participation (81% (CI 72-88%) vs. 76% (CI 66- 83%), p=0.91) were similar between age groups for the entire follow-up period (see supplemental material: table S2). The highest reported risk category was similar in both age groups (median 2.5 (IQR 2.5-2.5) vs. 2.5 (IQR 2.5-2.5), p=0.39).

Sports participation compared to the general population

Sports participation was similar for Dutch boys with haemophilia and their healthy peers. An average of 77%, (CI 72-82%) of PWH played sports, compared to 74% (CI 73-75%) in the age matched GP[80]. Participation in HR sports was similar as well, at 74% (CI 68-80%) in PWH, compared to 64.5% (CI 60-69%) in GP. Sports participation according to age was similar as well (6-11yrs.: 75% PWH vs. 65% GP; 12-18yrs.; 74% PWH vs. 76% GP)[128].

Type of sports chosen according to age is shown in Table 2. Boys with haemophilia and age-matched healthy children preferred different sports, as did different age groups. Football was the most popular sport in both PWH and the general population in both age groups. In addition, the top three included swimming and judo among PWH, and fitness and field hockey in the general population[128].

Table 2: Top 5 most popular sports in Dutch children with haemophilia and the Dutch general population according to age (%)

Dutch boys with haemophilia		Dutch general population32	
<12	12-18	<12	12-18
Football (45%)	Football (35%)	Football (41%)	Football (34%)
Swimming (8%)	Basketball (5%)	Tennis (7%)	Fitness (14%)
Judo (5%)	Field Hockey (5%)	Judo (7%)	Field Hockey (6%)
Golf (5%)	Judo (3%)	Swimming (4%)	Running (4%)
Various (3%)	Mountain biking (3%)	Field Hockey (4%)	Tennis (4%)

p<0.05 for comparisons between PWH aged 6-11 and 12-18 years; p<0.05 for comparisons between the PWH and the GP"[32].

Sports participation according to haemophilia severity

Sports participation, bleeding, and injuries during follow-up according to haemophilia severity is shown in Table 3. Sports participation was similar in patients with severe and non-severe haemophilia (severe vs. non-severe: 76% vs. 72% (p=0.64) for year 1, 73% vs. 78% (p=0.55) for year 2, and 76% vs. 73% (p=0.56) for year 3, respectively). HR-sports participation was similar for patients with severe and non-severe haemophilia (72% vs. 82% (p=0.57), 68% vs. 83% (p=0.12), 77% vs. 79% (p=0.59), respectively). Weekly sports frequency was similar for patients with severe and non-severe haemophilia (median 3.0 times/week (IQR 2.0-3.8) vs. 3.0 (IQR 3.0-3.0), p=0.30) and remained stable throughout

Table 3: Sports participation, bleeds and injuries according to severity and year

	Severe			Non-Severe		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
	Number (%) or median (P25-P75)					
Participants (n)	53	49	51	49	49	38
Age	13 (10-14)	13 (10-15)	14 (11-16)	12 (10-14)	13 (11-16)	15 (11-16)
Playing sports	39 (74)	39 (80)	42 (82)	34 (69)	37 (76)	32 (84)
Playing HR sports	30 (77)	25 (64)	29 (69)	28 (82)	30 (81)	24 (75)
Freq. /week (med, IQR)	2 (2-3)	3 (2-3)	3 (2-3)	3 (2.5-3)	3 (2-3)	3 (2-3)
Injuries	11	14	9	10	6	6
Participants with injuries	16%	20%	16%	15%	13%	11%
Injuries/participant	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
Bleeds	64	45	30	18	22	13
Participants with bleeds	55%*	49%*	39%	26%	39%	21%
Bleeds/participant	1 [0-2]	0 [0-1,75]	0 [0-1]	0 [0-1]	0 [0-1]	0 [0-1]

p>0.05 for sports participation, high-risk sports participation and sports injuries throughout follow-up and for patients with severe and non-severe haemophilia. *: P<0.05 (year 1 and year 2) for bleeds between patients with severe haemophilia and patients with non-severe haemophilia.

the follow-up. Patients with severe and non-severe haemophilia reported similar highest NHF categories (median 2.5 (IQR 2.0-2.5) vs. 2.5 (IQR 2.5-2.5); p=0.12). This could be due to the high overall number of patients playing football (NHF=2.5; severe: 44% (CI 31-57%), non-severe: 56% (CI 42-69%); p=0.21) in both groups.

Sports injuries

Sports injuries were rare: 56 sports injuries were reported by 33 (38%) PWH, resulting in a median of 1.7 injury/PWH in three years and 0 (IQR 0-1; range: 0-7) injuries/year. Although the majority of injuries (34/56) was reported by patients with severe haemophilia, injury rates were not associated with severity: both the number of patients with injuries (severe: 20/48 (42%) vs. non-severe: 13/39 (33%) and the number sports injuries per PWH (median 0 (IQR 0-1) vs. 0 (IQR 0-1); p=0.63) were similar in severe and non-severe patients. The proportion of PWH reporting was not higher than the GP (14.9% vs. 28.0%).

Haemophilia severity, increased training frequency, higher risk category, nor age differences were associated with an increase in sports injuries. Playing football was not associated with increased injury risk. In PWH playing football, injury risk was not associated with haemophilia severity (data available in supplemental material: tables S2, S3, S4).

Bleeds were reported more frequently than sports injuries. The results of the study show that even with prophylactic treatment, more PWH with severe haemophilia reported bleeds than PWH with non-severe haemophilia (year 1: 55 vs. 26%; year 2: 49 vs. 39%; year 3: 39 vs. 21% bleeds), reaching statistical significance in year 1 and 2 ($p< 0.05$) only (table 3). The proportion of PWH reporting bleeds was similar in those actively involved and those not involved in both sports (39% vs. 37%) and HR-sports (38% vs. 43%)

Discussion

Principal findings

PWH reported high sports participation (77%), of which 74% participated in HR-sports. Sports participation was similar to the general population and across haemophilia severity. Dutch boys with haemophilia preferred different sports than children in the general population.

Sports injuries were rare (38% of PWH during 3 year follow-up, median 0 (IQR 0-1) injury/year), and were not associated with haemophilia severity, (high-risk) sports participation, weekly frequency, risk category or age**.** PWH did not report more sports injuries than the GP.

Strengths and limitations

This was a retrospective study which analysed data routinely provided by children with haemophilia and their parents over their last three clinic visits. The lack of a standardised collection method could have led to information bias in the data and potential overestimation of sports participation and underestimation of sports injuries[86,129]. Although no gold standard for self-reporting of sports participation exists, using a standardised questionnaire as the Modifiable Activities Questionnaire (MAQ)[74,130] might be one way of improving sports participation assessment. The MAQ was recently validated in a Dutch population[83] and has been used in studies with PWH before[26,71].

Duration of sports activities was not included in this study, as this is known to be difficult to estimate by participants[85]. Collecting data prospectively with an objective tool, such as accelerometers[86,87], is expected to result in less variation and more reliable estimates of duration and intensity of PA. The analysis of sports injuries was limited to the number of sports injuries during the studied period. Data on severity, location and injury mechanism of the injury were unavailable in the current data set and confirms the need for prospective studies with regards to injury studies[131].

Comparison with other studies

This study showed high sports participation by young Dutch PWH, similar to the general Dutch general population[127]. Previous studies in Dutch[24,26], British[92], Australian[71], Irish[90] and Israeli[132] PWH already reported high participation in PWH. These were cross-sectional studies, most of them[24,26,71,90,132] only reporting being active in sports or not. Maximal follow-up was three months[132]. The current study included weekly sports frequency as exposure measure and a three year follow-up. The study by Khair et al.[92] included weekly sports frequency (79% at least twice weekly). Median weekly frequency was calculated from published data and seemed to be slightly lower (median 2 (IQR 2-3)) than in the current study, with 79% sporting at least twice weekly [92].

This study had a three year follow-up, which allowed for a more reliable assessment of sports participation and explore the association with age. Only four studies[31,33,91,132] assessed the association between sports participation and sports injuries. Tiktinsky et al. excluded patients under prophylaxis[132]. This hampers a comparison with the current study. Ross et al.[91], McGee et al.[31] and Broderick et al.[33] studied sports and injuries and/or bleeds. Ross et al. and McGee et al. reported similar bleeding rates during 1 and 3 year follow-up. Ross et al. reported no association between the impact of sports and injuries in 37 boys with severe haemophilia receiving prophylaxis during a one year follow-up[91]. McGee et al. included all severities and showed no association between sports injuries and being engaged in organised sports[31]. Broderick et al. included 104 boys with moderate

and severe haemophilia. They reported more bleeds (median 3/year) and an transient, increased relative bleeding risk (OR: 3) after PA with a follow-up of up to 1 year[33].

This study was the first to assess self-reported sports injuries in Dutch PWH. In comparison, Schmikli et al. performed a nationwide cross-sectional sports injury study in the Netherlands[127]. With a 3-month recall-period, 28% of boys below 18 reported at least one injury. No follow-up was involved in this study. Although frequently assumed, PWH in the present study did not report a higher injury rate than age-matched Dutch boys. The exact reason for this difference cannot easily be given: PWH might be more cautious when playing sports, but recall bias could have underestimated the number of reported injuries as well.

Perspective

Individualising haemophilia treatment includes counselling on (the risks of) sports injuries. Although studies in the general population have reported that sports injury risk is associated with type of sports[133–136] and intensity[33,123,124], this was not observed in the present cohort. Even a low number of joint injuries could lead to significant joint damage[7]. Both data from the present study and previous studies suggest that playing sports is relatively safe in young PWH. However, we were unable to identify any studies containing data on adult PWH. Injury risk is expected to be higher in young adults[127], especially for contact sports such as football. In addition, injury risk may depend on physical fitness, physical literacy and/or motor proficiency as well. Ideally, these factors should be assessed and taken into account when performing sports counselling, but first their impact needs to be addressed in future studies.

Conclusion

This study assessed sports participation with regard to age and severity and the association with sports injuries in PWH. Sports participation among PWH (77%) was similar to the general population). Sports injuries were reported by 38% of patients in a 3 year-period. Neither sports participation nor the number of sports injuries was associated with disease severity or age. Active involvement in sports or HR-sports was not associated with a higher proportion of bleeds. In addition, the association between clotting factor activity levels, sports injuries and bleeds should be considered. To be able to address clinical issues and provide adequate counselling at patient level, more detailed data on sports injury risk factors is needed. For this purpose, future studies should rely on objective, prospective data, instead of patient reported retrospective outcome.

References

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672
2. Pulles AE, Mastbergen SC, Schutgens REG, Lafeber FPJG, van Vulpen LFD. Pathophysiology of hemophilic arthropathy and potential targets for therapy. *Pharmacol Res*. 2017;115:192-199. doi:10.1016/j.phrs.2016.11.032
3. Nilsson IM, Hedner U, Ahlberg A. Haemophilia Prophylaxis in Sweden. *Acta Paediatr Scand*. 1976;65:129-135.
4. Young and unfit? *Lancet*. 1992;340(8810):19-20.
5. Verhoeven F, Tordi N, Prati C, Demougeot C, Mougin F, Wendling D. Physical activity and rheumatoid arthritis. *Rev du Rhum (Edition Fr*. 2016;83(2):99-104. doi:10.1016/j.jbspin.2015.10.002
6. van Brussel M, van der Net J, Hulzebos E, Helders PJM, Takken T. The Utrecht Approach to Exercise in Chronic Childhood Conditions. *Pediatr Phys Ther*. 2011;23(1):2-14. doi:10.1097/PEP.0b013e318208cb22
7. Morris PJ. Physical activity recommendations for children and adolescents with chronic disease. *Curr Sports Med Rep*. 2008;7(6):353-358. doi:10.1249/JSR.0b013e31818f0795
8. Philpott JF, Houghton K, Luke A. Physical activity recommendations for children with specific chronic health conditions: Juvenile idiopathic arthritis, Hemophilia, Asthma, and Cystic fibrosis. *Clin J Sport Med*. 2010;20(3):167-172. doi:http://dx.doi.org/10.1097/JSM.0b013e3181d2eddd
9. Hilberg T, Herbsleb M, Puta C, Gabriel HHW, Schramm W. Physical training increases isometric muscular strength and proprioceptive performance in hemophilic subjects. *Haemophilia*. 2003;9(2):86-93. doi:679 [pii]
10. Tiktinsky R, Falk B, Heim M, Martinovitz U. The effect of resistance training on the frequency of bleeding in haemophilia patients: A pilot study. *Haemophilia*. 2002;8(1):22-27. doi:10.1046/j.1365-2516.2002.00575.x
11. Eid MA, Ibrahim MM, Aly SM. Effect of resistance and aerobic exercises on bone mineral density, muscle strength and functional ability in children with hemophilia. *Egypt J Med Hum Genet*. 2014;15(2):139-147. doi:10.1016/j.ejmhg.2013.12.002
12. Parhampour B, Torkaman G, Hoorfar H, Hedayati M, Ravanbod R. Effects of short-term resistance training and pulsed electromagnetic fields on bone metabolism and joint function in severe haemophilia A patients with osteoporosis: a randomized controlled trial. *Clin Rehabil*. 2014;28:440-450. doi:10.1177/0269215513505299
13. Querol F, Gallach JE, Toca-Herrera JL, Gomis M, Gonzalez L-M. Surface electrical stimulation of the quadriceps femoris in patients affected by haemophilia A. *Haemophilia*. 2006;12(6):629-632. doi:10.1111/j.1365-2516.2006.01356.x
14. Gomis M, Querol F, Gallach JE, Gonzalez LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: A systematic review. *Haemophilia*. 2009;15(1):43-54. doi:10.1111/j.1365-2516.2008.01867.x
15. Khair K, Littley A, Will A, von Mackensen S. The impact of sport on children with haemophilia. *Haemophilia*. 2012;18(6):898-905. doi:10.1111/j.1365-2516.2012.02857.x
16. Buxbaum NP, Ponce M, Saidi P, Michaels LA. Psychosocial correlates of physical activity in adolescents with haemophilia. *Haemophilia*. 2010;16(4):656-661. doi:10.1111/j.1365-2516.2010.02217.x
17. Lang JJ, Chaput J, Longmuir PE, et al. Cardiorespiratory fitness is associated with physical literacy in a large sample of Canadian children aged 8 to 12 years. *BMC Public Health*. 2018;18(Suppl 2: 1041):90-111. doi:10.1186/s12889-018-5896-5
18. van Mechelen W, Hlobil H, Kemper HCG. Incidence, Severity, Aetiology and Prevention of Sports Injuries: A Review of Concepts. *Sport Med*. 1992;14(2):82-99. doi:10.2165/00007256-199214020-00002
19. Broderick CR, Herbert RD, Latimer J, van Doorn N. Patterns of physical activity in children with haemophilia. *Haemophilia*. 2013;19(1):59-64. doi:10.1111/j.1365-2516.2012.02904.x
20. Emery CA. Risk Factors for Injury in Child and Adolescent Sport: A Systematic Review of the Literature. *Clin J Sport Med*. 2003;13(4):256-268. doi:10.1136/bjsports-2014-094372
21. Schoenmakers MAGC, Gulmans VAM, Helders PJM, Van Den Berg HM. Motor performance and disability in Dutch children with haemophilia: A comparison with their healthy peers. *Haemophilia*. 2001;7(3):293-298. doi:10.1046/j.1365-2516.2001.00504.x

22. von Mackensen S, Harrington C, Tuddenham E, et al. The impact of sport on health status, psychological well-being and physical performance of adults with haemophilia. *Haemophilia*. 2016;22(4):521-530. doi:10.1111/hae.12912

23. Heijnen L, Mauser-Bunschoten EP, Roosendaal G. Participation in sports by Dutch persons with haemophilia. *Haemophilia*. 2000;6(5):537-546. doi:10.1046/j.1365-2516.2000.00422.x

24. Groen WG, Takken T, van der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. *Haemophilia*. 2011;17(5):906-912. doi:10.1111/j.1365-2516.2011.02555.x

25. McGee S, Raffini L, Witmer C. Organized sports participation and the association with injury in paediatric patients with haemophilia. *Haemophilia*. 2015;21(4):538-542. doi:10.1111/hae.12696

26. Ross C, Goldenberg N, Hund D, Manco-Johnson MJ. Athletic participation in severe hemophilia: bleeding and joint outcomes in children on prophylaxis. *Pediatrics*. 2009;124(5):1267-1272. doi:10.1542/peds.2009-0072

27. Broderick CR, Herbert RD, Latimer J, et al. Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia. *JAMA J Am Med Assoc*. 2012;308(14):1452-1459. doi:10.1001/jama.2012.12727. eTable

28. Ng KW, Tynjälä J, Rintala P, Kokko S, Kannas L. Do adolescents with long-term illnesses and disabilities have increased risks of sports related injuries? *Inj Epidemiol*. 2017;4(1). doi:10.1186/s40621-017-0112-0

29. The European Sports Charter. *Counc Eur*. 1992:1-10.

30. Anderson A, Forsyth A. *Playing It Safe: Bleeding Disorders, Sports and Exercise*. New York, NY.: National Hemophilia Foundation; 2017. doi:10.1136/jech.2007.061960

31. Tiessen-Raaphorst (ed.) A, Tiessen-Raaphorst A. *Rapportage Sport 2014*. The Hague; 2015. https://www.scp.nl/Publicaties/Alle_publicaties/Publicaties_2015/Rapportage_Sport_2014.

32. RIVM (National Institute for Public Health and the Environment). Leefstijlmonitor [Life Style Monitor, in Dutch]. Leefstijlmonitor 2016. https://www.volksgezondheidenzorg.info/onderwerp/sport-en-bewegen/cijfers-context/huidige-situatie#node-sportdeelname-wekelijks-naar-leeftijd-en-geslacht. Published 2016. Accessed October 17, 2018.

33. Schmikli SL, Backx FJG, Kemler HJ, van Mechelen W. National survey on sports injuries in the Netherlands: target populations for sports injury prevention programs. *Clin J Sport Med*. 2009;19(2):101-106. doi:10.1097/JSM.0b013e31819b9ca3

34. den Uijl IEM, Fischer K, van der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Clinical outcome of moderate haemophilia compared with severe and mild haemophilia. *Haemophilia*. 2009;15(1):83-90. doi:10.1111/j.1365-2516.2008.01837.x

35. Tiessen-Raaphorst A, Verbeek D, Haan J de, Breedveld K. *Sport: Een Leven Lang, Sportrapportage 2010*. Den Haag / 's Hertogenbosch; 2010. http://www.scp.nl.

36. Hagströmer M, Oja P, Sjöström M. Physical activity and inactivity in an adult population assessed by accelerometry. *Med Sci Sports Exerc*. 2007;39(9):1502-1508. doi:10.1249/mss.0b013e3180a76de5

37. Sprengeler O, Wirsik N, Hebestreit A, Herrmann D, Ahrens W. Domain-specific self-reported and objectively measured physical activity in children. *Int J Environ Res Public Health*. 2017;14(3):1-12. doi:10.3390/ijerph14030242

38. Aaron DJ, Kriska AM, Dearwater SR, Cauley JA, Metz KF, LaPorte RE. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. *Am J Epidemiol*. 1995;142(2):191-201. doi:10.1093/oxfordjournals.aje.a117618

39. Aaron DJ, Kriska AM, Dearwater SR, et al. The epidemiology of leisure physical activity in an adolescent population. *Med Sci Sports Exerc*. 1993;25(7):847-853.

40. Tonoli C, Heyman E, Roelands B, Georges B, Berthoin S, Meeusen R. Validation and reliability of the Dutch language version of the Modifiable Activity Questionnaire in healthy subjects. *Sport Sci Health*. 2013;9(3):139-144. doi:10.1007/s11332-013-0160-y

41. Klesges R, Eck L, Mellon M, Fulliton W, Somes G, Hanson C. The accuracy of self-reports of physical activity. *Med Sci Sports Exerc*. 1990;22(5):690-697.

42. Timmer MA, Pisters MF, de Kleijn P, de Bie RA, Schutgens REG, Veenhof C. Movement behaviour in adults with haemophilia compared to healthy adults. *Haemophilia*. 2018;(January):1-7. doi:10.1111/hae.13441

43. Bahr R, Holme I. Risk factors for sports injuries, a methodological approach. *Br J Sports Med*. 2003;37:384-392.

44. Sherlock E, O'Donnell JS, White B, Blake C. Physical activity levels and participation in sport in Irish people with haemophilia. *Haemophilia*. 2010;16(1):202-209. doi:10.1111/j.1365-2516.2009.02111.x

45. Tiktinsky R, Kenet G, Dvir Z, et al. Physical activity participation and bleeding characteristics in young patients with severe haemophilia. *Haemophilia*. 2009;15(3):695-700. doi:10.1111/j.1365-2516.2009.01990.x

46. Dehaven KE, Lintner DM. Athletic injuries: Comparison by age, sport, and gender. *Am J Sports Med*. 1986;14(3):218-224. doi:10.1177/036354658601400307

47. Bloemers F, Collard D, Paw MC., Van Mechelen W, Twisk J, Verhagen EALM. Physical inactivity is a risk factor for physical activity-related injuries in children. *Br J Sports Med*. 2012;46(9):669-674. doi:10.1136/bjsports-2011-090546

48. Nauta J, Martin-Diener E, Martin BW, van Mechelen W, Verhagen E. Injury Risk During Different Physical Activity Behaviours in Children: A Systematic Review with Bias Assessment. *Sport Med*. 2015;45(3):327-336. doi:10.1007/s40279-014-0289-0

49. Carter EA, Westerman BJ, Hunting KL. Risk of injury in basketball, football, and soccer players, ages 15 years and older, 2003-2007. *J Athl Train*. 2011;46(5):484-488. doi:10.4085/1062-6050-46.5.484

Supplemental Material

Table S1: Sports and their concomitant injury risk category according to the US NHF[30]

Activity	categories	Activity	categories
aquatics	1	power lifting	3
archery	1	racquetball	2,5
baseball	1,5-2,5	river rafting	2
basketball	1,5-2,5	rock climbing, indoor	1,5-2
bicycling	1,5-3	rock climbing, outdoor	2,3
BMX racing	3	rodeo	3
body sculpture class	1,5	rowing	1,5
boot camp workout class	2	rowing machine	1,5
bounce houses	2,5-3	rugby	3
bowling	2	running/jogging	2
boxing	3	scooters, motorized	2-2,5
canoeing	1,5-2,5	scooters, non-motorized	1,5-2,5
cardio kickboxing class	2	scuba diving	2-2,5
cheerleading	1,5-2,5	skateboarding	1,5-2,5
circuit training	1,5	skating, ice	1,5-2,5
dance	1-3	skating, inline and roller	1,5-2,5
diving, competitive	2-3	skiing, cross-country	2
diving, recreational	2	skiing, downhill	2,5
elliptical machine	1	skiing, water	2-2,5
fishing	1-2	ski machine	1,5
football, flag or touch	2	snorkelling	1
football, tackle	3	snowboarding	2,5
frisbee	1-1,5	snowmobiling	3
frisbee, golf	1,5-2	soccer	2-3
frisbee, ultimate	2-2,5	softball	1,5-2,5
golf	1	stationary bike	1
Gymnastics	2-3	stepper	1-1,5
high intensity functional training	2-3	strength training	1,5
hiking	1-1,5	surfing	2-2,5
hockey, field/ice/street	2,5-3	swimming	1
horseback riding	1,5-2,5	tee-ball	1,5
indoor cycling class	1,5-2	tennis	2
jet-ski (personal watercraft, PWC)	2-3	track and field	2-2,5
jumping rope kayaking	2	trampoline	2,5-3
kayaking	1,5-2,5	treadmill	1,5
lacrosse	3	volleyball	2-2,5
martial arts, tai chi	1	walking	1
martial arts, traditional and mixed	2-3	water polo	2,5
motorcycle/motocross (ATV, dirt bikes)	3	wrestling	3
mountain biking	2,5	yoga	1,5-2
Pilates	1,5-2	zumba class	1,5-2

Supplemental Table S2: Sports participation in PWH per year with regards to age groups (n(%)).

	year 1	year 2	year 3
6-11	36/48 (75%)	37/42 (88%)	19/24 (79%)
12-18	37/50 (74%)	39/58 (67%)	51/65 (78%)
High Risk Sports Participation			
6-11	28/36 (78%)	26/37 (70%)	15/19 (79%)
12-18	30/37 (81%)	29/39 (74%)	38/50 (76%)

p>0.05 for difference between age groups and study years

Supplemental Table S3: Number of injuries (median (IQR)) according to weekly sports frequency, risk category and age group.

	Overall	Severe	Non-severe
N	**87**	**48**	**39**
Number of sports injuries in three years according to weekly frequency			
Untrained (<1x/wk)	0 (0-1)	0 (0-1)	0 (0-0)
Recreationally trained (1-2x/wk)	0 (0-0.25)	0 (0-1)	0 (0-0)
Trained (3x/wk)	0.5 (0-1.25)	1 (0-2)	0 (0-1)
Well Trained (4-5x/wk)	0 (0-1)	0 (0-0)	0 (0-0)
Professional (>5x/wk)	1 (0-2)	0 (0-0)	2 (2-2)
Number of sports injuries according to risk category			
NHF 1: safe	0 (0-0)	0 (0-0)	0 (0-0)
NHF 1.5: safe to moderate risk	1 (0-1)	1 (0-1)	-
NHF 2: moderate risk	0 (0-0,75)	0 (0-0,25)	0.5 (0-)
NHF2.5: moderate risk to high risk	0 (0-1)	0 (0-1)	0 (0-1)
NHF 3: high risk	1 (0-2)	1,5 (1)	0 (0-0)
Number of sports injuries according to age group			
6-11	0 (0-0)	0 (0-0)	0 (0-0)
12-18	0 (0-0)	0 (0-0)	0 (0-0)

p>0.05 for differences in sports injuries between patients with severe and non-severe haemophilia with increasing weekly training frequency, risk category of age.

Supplemental Table S4: Annual proportion of injured PWH according to haemophilia severity, stratified for playing football or not.

		severe			non-severe		
		year 1	year 2	year 3	year 1	year 2	year 3
football	yes	5/32 (15,6%)	5/18 (27,8%)	4/18 (22,2%)	5/20 (25%)	4/21 (19,1%)	3/16 (18,8%)
	no	3/19 (15,8%)	5/33 (15,2%)	4/33 (12,1%)	2/27 (7,4%)	1/26 (3,9%)	2/31 (6,5%)
	p	**0,709**	**0,555**	**0,341**	**0,146**	**0,05**	**0,432**

p>0.05 for injuries in PWH playing football vs. PWH not playing football.

CHAPTER 5

Sports participation of patients with haemophilia in the COVID-19 era: the Dutch experience

O. Versloot[1,2], J. van der Net[2], K. Fischer[1]

[1] Van Creveldkliniek, University Medical Center Utrecht, Utrecht, The Netherlands.

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, University Medical Center, Utrecht, The Netherlands.

Haemophilia, 2021 May; 27(3): e402-e405

Bullet points

What is already known:

- COVID-19 restrictions have negatively affected sports participation in the Dutch general population
- Sports participation in people with haemophilia is similar to the general population

What this study adds:

- Sports participation in people with haemophilia during COVID-19 showed a more pronounced decrease than in the general population.
- General population recommendations to maintain fitness and health benefits from physical activity during the COVID-19 pandemic should be applied to people with haemophilia as well.

Introduction

Physical activity (PA) in general and sports participation in particular have been promoted for years for their positive effects on human health[1]. This applies to both healthy persons as well as persons with congenital, chronic diseases, such as haemophilia[2]. Because of these positive health effects, physical activity and sports participation have been advocated by haemophilia physicians since the introduction of prophylactic infusions in the 1970s and 1980s. In recent years, sports participation in Dutch patients with haemophilia (PWH) has been comparable to the general population (GP), especially in children [3,4].

The recent COVID-19 pandemic has forced governments worldwide to take drastic actions. Although Dutch society has not been in complete lock-down, sports facilities were closed, (outdoor) gatherings of more than 3 persons were forbidden and social distancing of 1.5 meters was mandatory. These measures were in effect from the 12th of March until the first of July 2020. Obviously, this has had dramatic effects on the possibilities for sports participation in the Netherlands, both for PWH and for the GP. This letter aims to assess the impact of these measures on sports participation in Dutch PWH and compared to the Dutch GP.

Methods

The data for Dutch PWH were collected as part of an ongoing study on sports participation in PWH. Patients (6-49 years) playing sports at least once weekly were included in this study with a one year follow-up for injuries. In addition, type of sports, risk category according to the National Hemophilia Foundation (NHF) classification[6], weekly frequency and weekly duration were collected. All patients in follow-up were asked about their weekly sports participation (type of sports, weekly frequency and duration) since the implementation of the COVID-19 restrictions in a telephone interview by means of the Modifiable Activities Questionnaire (MAQ)[5], which is used in the ongoing study as well. Within the NHF classification for risk categories, sports in the two highest categories (2.5 and 3: moderate to high risk and high risk) were considered high-risk (HR) sports[6]. General population data were collected from a nationwide, study, reporting standardized telephone interviews with 1020 Dutch adults about their sports participation and behaviour before and after the COVID-19 limitations were imposed[7]. Although different questionnaire were used, the results were considered comparable as the relevant questions showed assessed the same aspects of sports participation before and during COVID-19 restrictions (e.g.: weekly duration). Data on weekly frequency of sports was not collected for the GP.

Data was checked for normality using the Kolmogorov-Smirnoff test and is presented as median (IQR) or as proportion where appropriate. Groups were compared using non-parametric testing. Statistical analysis was performed with SPSS (v.25.0.0.2, IBM corp., Armonk, NY). This study was part of a larger study into sports participation in PWH, which was approved by the IRB of the UMC Utrecht (approval number: 18-141).

Results

A total of 82 PWH (median age 23.6 (IQR: 16.8-33.3)) provided data about their sports participation since the COVID-19 restrictions. Details about patient, disease and sports participation are provided in table 1.

Table 1 Patient, disease and sports participation characteristics

n=82		Median (IQR), n(%)	
Age		23,6 (16,8-33,3)	
Adults		60 (73,2%)	
Type A		75 (92%)	
Severe		27 (33%)	
		Sports participation	
	Before COVD-19	Since COVD-19	p
%sport [n(%)]	82 (100%)	51 (62%)	<0,01
Duration (hrs/wk)	4,2 (2,3-6,4)	2,1 (0-4,9)	<0,01
Frequency (times/week)	3,3 (2,1-4,3)	3,9 (2,5-6,5)	0,02
HR sports [n(%)]	71 (59%)	6 (5%)	<0,01

Fewer PWH reported to be playing sports since the social restrictions were imposed due to the COVID-19 outbreak. Total time per week spent sporting was nearly halved, while weekly frequency increased slightly. The number of PWH playing high-risk sports decreased dramatically. These results show that sports participation in PWH decreased in number, duration and risk taken.

Table 1 shows an overall decrease in sports participation in PWH of 38% (100 to 62%; p<0.01), and a reduction of sports activities by 1.4 hours/week. However, median weekly sports frequency increased slightly (3.3 (IQR: 2.3-4.5) to 3.9 (2.5-6.5) times per week; p=0.03). Participation in HR sports decreased from 59% (95%CI: 50-67%) to 5.0% (2.0-10.6; p<0.01), indicating that although PWH were active more often, their bouts of

activity were also shorter and HR (team) sports were almost completely avoided. These differences were independent of disease severity.

Children and adults with haemophilia showed a similar change in sports participation. All PWH played sports before the COVID-19 era, but this decreased after these restrictions were imposed: 56% (95%CI: 45-77) reduction in adults and 54% (39-68) in children. Weekly duration (adults: median 3.7 (1.9-1.1) to 2.4 (1.1-4.8) hrs/wk; p<0.01; children: 4.6 (3.4-7.8) to 1.3 (0-5.9) hrs/wk; p<0.01) decreased in both groups, while weekly frequency increased in both groups (adults: median 2.9 (IQR: 1.9-4.2) to 3.8 (2.5-5.6); p=0.03; children: 3.7 (2.8-5.5) to 6.0 (2.0-7.0); p=0.33). Both groups showed a significant reduction in HR sports participation (adults: from 45% (19.8-42.6) to 5.0% (0.0-11.0); p<0.01; children: from 85%(67-96) to 5% (0-17); p<0.01).

The data for the GP included 508 men. Age was only provided in groups, but at a median of 45-54 yrs, the GP was substantially older than PWH in our study (23.6 yrs).

Team sports and gymnasium activities were no longer possible due to the imposed social restriction. This led to a shift in participation from organised sports (e.g. tennis) to individual sports (e.g. running) and from high risk sports (e.g. football) to low risk sports (e.g. walking) in both PWH and the GP.

The reduction in sports participation in the GP was significant (from 81% (77-84) to 74% (70-78; p<0.01)), but less pronounced than in adult PWH (100% (95-101) to 56% (45-77); p<0.01). There was a shift towards not sporting at all, particularly in PWH reporting low sports participation at baseline (<2hrs/wk). This seems to indicate that persons already moderately to highly active in sports remained active at a similar level, whereas people sporting on a low level would be more prone to stop. Both groups showed an increase in proportion of persons playing less than 1 hour per week (PWH: 8% to 23%; GP: 21% to 33%), while intermediate (1-2 hrs/wk; PWH: 23% to 18%; p=0.53); GP: 20% to 23%; p=0.25) and intensive sports participation (>4 hrs/wk; PWH: 46% to 38%; GP: 29% to 21%)) remained relatively similar in both groups.

Discussion

This is the first study comparing sports participation in PWH before and after social distancing rules were imposed to prevent infections with COVID-19 in the Netherlands. These data show a decrease in sports participation in both GP and PWH, both in number

of people playing sports as well as in the total time people play sports per week: less people play sports in less time per week and in safe, individual, unorganized outdoor sports.

Both studies relied on participant reported outcomes, potentially introducing bias due to socially desirable answers (leading to potential overestimation of sports participation). Furthermore, a potential selection bias may have been present in PWH: only PWH who played sports at least once weekly were included in the original study, while this was not the case in the GP sample, who were generally older. This might lead to an overestimation of the sports participation reduction in PWH.

Sports participation is just one of life's aspects severely affected during the COVID-19 pandemic. Despite an abundancy of literature regarding exercise strategies during, and return to sports after the COVID-19 pandemic, we were only able to identify three studies on the effects of the social restrictions on sports. Hemphill et al. (2020) reported a decrease of 21-24% in PA since restrictions were imposed in 109 Canadian children (9-16, 58% male) with congenital heart disease[8]. Shalash et al. (2020) reported a decrease in PA compared to pre-lockdown in 38 Egyptian adults with Parkinson's disease (mean age 55.6±10.0; 76% male)[9]. Pietrobelli et al. (2020) reported a mean decrease from 3.6 (±4.3) to 1.3 (±1.4) hours of sports per week in 41 obese Italian children (22 male, mean age 13.3 (±3.0))[10]. Despite different conditions and measurement methods, and potential differences in government regulations, these results seem to indicate a decrease in PA or sports participation is a common feature in all these chronic conditions. None of these studies compared their data to the GP. Despite changing medical and social circumstances. Physicians and other healthcare workers need to keep stimulating their patients to remain physically active while restrictions last. Patients with chronic conditions should ideally be provided with guidelines on PA under changing circumstances.

In conclusion, Dutch PWH and the GP both showed a decrease in sports participation since the COVID-19 restrictions came into effect. However, the decrease in PWH was more pronounced. The reason for this is unclear. Selection bias at baseline might be involved as only PWH already engaged in sports were included. This study's findings suggest that the recommendations and actions to maintain fitness and positive health effects from PA during the COVID-19 pandemic that apply to the GP should be applied to PWH as well.

References

1. World Health Organization. *Global Recommendations on Physical Activity for Health*.; 2010. doi:10.1080/11026480410034349
2. Philpott JF, Houghton K, Luke A. Physical activity recommendations for children with specific chronic health conditions: Juvenile idiopathic arthritis, Hemophilia, Asthma, and Cystic fibrosis. *Clin J Sport Med*. 2010;20(3):167-172. doi:http://dx.doi.org/10.1097/JSM.0b013e3181d2eddd
3. Groen WG, Takken T, van der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. *Haemophilia*. 2011;17(5):906-912. doi:10.1111/j.1365-2516.2011.02555.x
4. Versloot O, Timmer MA, de Kleijn P, et al. Sports participation and sports injuries in Dutch boys with haemophilia. *Scand J Med Sci Sports*. 2020;e-publicat(april 2020). doi:10.1111/sms.13666
5. Aaron DJ, Kriska AM, Dearwater SR, Cauley JA, Metz KF, LaPorte RE. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. *Am J Epidemiol*. 1995;142(2):191-201. doi:10.1093/oxfordjournals.aje.a117618
6. Anderson A, Forsyth A. *Playing It Safe: Bleeding Disorders, Sports and Exercise*. National Hemophilia Foundation; 2017. doi:10.1136/jech.2007.061960
7. van den Dool R. *Sport En Bewegen in Tijden van Covid-19*.; 2020. https://www.kennisbanksportenbewegen.nl/?file=9994&m=1588764274&action=file.download
8. Hemphill NM, Kuan MTY, Harris KC. Reduced Physical Activity During COVID-19 Pandemic in Children with Congenital Heart Disease. *Can J Cardiol*. 2020;Epub ahead(april 2020).
9. Shalash A, Roushdy T, Essam M, et al. Mental health, physical activity and quality of life in Parkinson's disease during COVID-19 pandemic. *Mov Disord*. 2020;Epub ahead. doi:10.1002/mds.28134
10. Pietrobelli A, Pecoraro L, Ferruzzi A, et al. Effects of COVID-19 Lockdown on Lifestyle Behaviors in Children with Obesity Living in Verona, Italy: A Longitudinal Study. *Obesity*. Published online 2020:0-3. doi:10.1002/oby.22861

Part II – Injuries and Bleeds

CHAPTER 6

Sports Participation and Injuries in Dutch Patients with Haemophilia: the SPRAIN Study. A Prospective Observational Study Protocol.

O. Versloot[1,2], C.F. van Koppenhagen[3,4], J. van der Net[5], K. Fischer[1]

[1] Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Physical Medicine and Rehabilitation, University Medical Centre, Utrecht, the Netherlands.

[4] Basalt Rehabilitation, The Hague, The Netherlands

[5] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, University Medical Center, Utrecht, The Netherlands

Abstract

Background: Traditionally, people with haemophilia (PWH) were advised to limit their physical activity (PA) to low-impact sports (swimming, walking). However, in current settings of intensive treatment most PWH are involved in many different sports, including high-risk sports, such as soccer. Although data on sports participation are increasing, data on associated bleeding risk and sports injuries is currently lacking, particularly in adults. Patients and caregivers can benefit from this study by creating a better understanding of the association between haemophilia, sports participation, physical fitness and sports injuries.

Methods: This observational study will assess sports participation, limitations in activities, anthropometry, motor proficiency and physical fitness, followed by a 12-month prospective assessment of PA, sports injuries and sport-induced bleeds. Patients aged 6-49 with severe, moderate or mild haemophilia A and B (FVIII/FIX: 0-30%) engaged in sports at least once per week are eligible for this study. At baseline, sports participation will be assessed by the Modifiable Activities Questionnaire, limitations in activities by the HAL or pedHAL. Anthropometry measures will include height, weight, BMI and fat percentage and will be measured by bio impedance. Motor proficiency will be assessed by selected items of the Bruinings-Orezetsky Test of Motor Proficiency, while physical fitness will be assessed with a steep ramp test. During a 12-month follow-up, PA will be recorded by wearing an accelerometer for 1 week during the 4 annual seasons (4x1 week), while simultaneously recording sports activity in a training diary. Sports injuries will be recorded during follow-up on a two-weekly basis by the investigator. Data about disease and treatment (history), treatment regimen (dose and frequency) factor consumption and joint status will be extracted from medical files and will be updated during regular clinic visits. Injury and bleeding data will be analysed according to motor proficiency, physical activity, and type of sports. Individual bleeding risk according to clotting factor activity level will be modelled by repeated-time-to-event analysis.

Discussion: The results of this study are expected to assist in providing more structured and individualized advice towards sports participation of PWH.

Trial Registration: This trial is registered in the Dutch trial register (www.trialregister.nl) under trial ID NTR6769.

Background

Haemophilia is an X-related inherited bleeding disorder caused by deficiencies in coagulation factor VIII (FVIII, haemophilia A) or IX (FIX, haemophilia B)(1) that currently has no cure. Haemophilia is characterized clinically by an increased bleeding tendency, primarily in joints and soft tissue. The most common locations for joint bleeds include the ankles, knees and elbows(2). These bleeds can occur either spontaneously or due to trauma or surgery. Severity of haemophilia A and B is classified into three levels: severe (FVIII/IX<1%), moderate (FVIII/FIX: 1-5%) and mild (FVIII/FIX: 5-40%)(3). Recurrent joint bleeds eventually lead to destruction of cartilage, synovium and subchondral bone due to exposure to iron in the blood(4) . This haemophilic arthropathy, causes chronic pain, functional limitations, and loss of health related quality of life for patients.

Physical activity is part of a healthy lifestyle and promotes general well-being(5). In addition, regular physical exercise is especially recommended for people with haemophilia (6,7) to increase muscle strength, maintain muscle mass and bone density, and potentially reduce bleeding risk(6). As overexertion, high impact sports and collision risk are considered to increase the risk of (joint) bleeds, people with haemophilia have traditionally been advised to limit their sports participation to low-impact sports like swimming and cycling(8).

In the setting of intensive treatment, it has been reported that up to 71% of both young and adult people with severe haemophilia in the Netherlands are engaged in many different sports, including contact sports that are considered to increase bleeding risk, such as soccer(9). Although data on participation in sports are increasing, data on associated bleeding risk are lacking. So far, the best data are from a 1-year study in 104 boys with moderate and severe haemophilia A and B suggesting that the risk of bleeding due to sports participation was relatively mild and transient(10). Additional reports on bleeding and sports participation were limited in size (37-44 pts) and age range (6-25 years)(11,12).

Therefore, the Sports Participation and Injuries in patients with haemophilia (SPRAIN) study aims to assess whether an association between sports participation and sports injuries or bleeds exists for both children and adults with haemophilia. This association will be evaluated according to age, patient characteristics, motor proficiency(13), physical fitness(14) and current treatment.

Rather than generating data on the relative risk of sports participation in individual patients, the present project will generate information on the association of sports

injuries and injury induced bleeding and compare injury rates to the general population. These data can be used for counselling patients on sports participation.

Information obtained on bleeding according to factor levels and physical activities may help to identify the importance of peak and trough levels in prophylactic dosing. In the current era of introduction of longer-acting clotting factor concentrates, the association of clotting factor levels with bleeding during sports is another topic of special interest. Longer-acting concentrates may be administered with longer intervals(15). Such a dosing schedule will result in extended periods with relatively low clotting factor activity levels and less frequent peak levels, which may increase susceptibility to injuries(16). In addition, non-replacement therapy with more constant correction of coagulation potential have been introduced(17,18).

Since the study includes patients with moderate haemophilia (only 25% on prophylaxis) (19) and severe haemophilia treated with intermediate dose prophylaxis (3x10-15 IU/kg per week)(20) it is expected to yield important information on lower FVIII/IX levels.

Analyses on the association of clotting factor levels with bleeding and injuries will be adjusted for the other (potential) determinants of injuries and bleeding, such as age, sports exposure (weekly frequency x duration), injury risk and previous injuries. These results may help identify optimum dosing schedules on longer-acting clotting factor concentrates.

Methods

Aim

The aim of this study is to assess sports participation as well as bleeding and/or injuries associated with sports participation, including a comparison to the general population and association with clotting factor levels.

Hypotheses

This study will focus on a number of hypotheses related to sports participation and injuries in people with haemophilia:

- Sports participation in people with haemophilia is dependent on age, joint status, self-reported limitations in activities, and disease severity;
- Sports participation in people with haemophilia is lower than in age-matched, healthy peers;

- Sport injuries occur more frequently in people with haemophilia than in age-matched, peers without haemophilia;
- FVIII/FIX levels at the time of sports participation are associated with sports injury risk;
- Sports-induced bleeding is similar between severe patients on prophylaxis and non-severe haemophilia patients treated on demand;
- Joint health status, physical fitness and motor proficiency are associated with the occurrence of sports injuries.

Study design

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) were followed to describe the design of this study (see figure 1 and Additional file 1: SPIRIT Checklist)(21,22). This will be a prospective, observational study aimed at assessing active sports participation, sports injuries and sports-induced bleeding. Participants who indicated being actively engaged in sports at least once per week will be asked to participate. This study will start with administration of the Modifiable Activities Questionnaire (MAQ)(23–25) and the Haemophilia Activities List (HAL)(26,27) or Paediatric HAL (PedHAL)(28), depending on age. In addition, there will be a baseline assessment in which anthropometrics, motor proficiency and physical fitness of the participants will be tested. During a one-year follow-up, participants will be asked to wear a triaxial accelerometer for 1 week during each season (4x1 week) to objectively assess PA. This will be combined with recording training data in a training/sports diary. This assessment will be repeated each annual season to account for seasonal variation in sports participation(29). During this one-year follow-up, participants will be contacted (through their preferred method: email, phone or text messaging) by the investigator every two weeks to assess the occurrence of sports injuries and/or bleeds. In case an injury occurred in the previous 2 weeks, the investigator will record the injury in a detailed way by using a standardized form. Data about disease and treatment history, treatment regimen and joint status (e.g. Hemophilia Joint Health Score; HJHS) will be extracted from medical files or will be assessed during regular clinic visits. In case no recent (≤1 year) evaluation of joint status has been performed, this will be done before the baseline assessment.

The design of the proposed study is in accordance with the recommendations of the Declaration of Helsinki(30), and was approved by the Institutional Review Board of the University Medical Center Utrecht under approval number 18-141. The trial has been registered at the Dutch trial register (https://www.trialregister.nl) under trial ID NTR6769.

Figure 1: Spirit table for the SPRAIN study

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT	**t<0**	**t = 0**	**Season 1**	**Season 2**	**Season 3**	**Season 4**
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Assessments:						
Patient Characteristics	X					
Disease Characteristics	X					
Pharmacokinetic Characteristics	X					
Baseline:						
Sports Participation		X				
Joint Health Status		X				
Self-reported limitations		X				
Anthropometrics		X				
Motor Proficiency		X				
Physical Fitness		X				
Outcome:						
Sports Participation			X	X	X	X
Accelerometer data			X	X	X	X
Injury data			●	———	———	●

Population

All patients with haemophilia A or B (severe, moderate or mild; factor VIII/IX levels of 0-30%), 6 to 47 years (born between 01-01-1970 and 31-12-2011), who are engaged in sports at least once per week (N=±200) are eligible.

Participant recruitment

Participants will be recruited at the Van Creveldkliniek of the University Medical Center (UMC) Utrecht. The Van Creveldkliniek is a specialized clinic for the treatment of bleeding disorders, among which haemophilia.

Eligible patients will be informed by physicians and/or physiotherapists of the Van Creveldkliniek 3-4 weeks prior to their during regular visits or telephone consults about the purpose and the content of the study. Patients who agree to receive information will then receive the study information and informed consent form by email. The investigator

will contact them after one week to answer any remaining questions. Patients who agree to participate will sign informed consent at the next clinic visit, followed by completing questionnaires and baseline testing for anthropometric parameters, motor proficiency and physical fitness. The assessments will be performed at the time of clinic visits to limit the burden to participants as much as possible. No participants will be included without prior written informed consent.

Inclusion criteria

Patients with haemophilia A or B with FVIII/FIX levels between 0-30% born between 01-01-1970 and 31-12-2011 who participate in sports at least once per week will be included in this study.

Exclusion criteria

Patients refusing to participate or provide informed consent, patients with a current presence of FVIII or FIX antibodies and patients who received an arthroplasty or arthrodesis in the last 12 months will be excluded from participating in this study.

Outcome measures

Primary outcome measures

Primary outcome measures include sports participation, sports injuries and sports induced bleeds.

Sport was defined as "all forms of physical activity which, through casual or organized participation, aim at expressing or improving physical fitness and mental well-being, forming social relationships or obtaining results in competitions at all levels"(31).

Data on *sport participation* will include type of sport and exposure (duration x frequency), Type of sport, frequency and duration will be registered by completing the MAQ and by completing a training log and wearing an accelerometer during the follow-up.

The *sports risk category* will be classified according to the NHF classification (1: low risk, 1.5: low to moderate risk, 2: moderate risk, 2.5: moderate to high risk, 3: high risk). Sports in the highest two categories are considered high-risk sports (e.g.: soccer, rugby)(32).

A *sports injury* is defined as "any injury as a result of participation in sport with one or more of the following consequences: (a) a reduction in the amount or level of sports activity; (b) a need for (medical) advice or treatment; or (c) adverse social or economic

effects"(33). In this specific case, 'medical treatment' is most likely indicating extra infusion(s) of clotting factor concentrate.

Sports injury characteristics (anatomical location, type of sport, risk category, severity/ time loss(34), time since last infusion and injury mechanism) will be recorded using a standardized form. Participants will be contacted by the investigator every two weeks to evaluate the occurrence of sports injuries by their preferred method (phone, email, text message). The investigator will complete the standardized form.

Sports-induced bleed: A bleed is considered a sports-induced bleed when the bleed occurred during (or immediately after) a sports action, had identical symptoms to a (joint/muscle/soft tissue) bleed and required (immediate) extra treatment with clotting factor concentrate or consultation with a haemophilia consultant.

Secondary outcome measures

Secondary outcome measures include bleeding data: bleed, joint bleed, soft-tissue/ muscle bleed, re-bleed. These bleeds are defined according to Blanchette et al. (2014) (1). A joint bleed is defined as "an unusual sensation 'aura' in the joint, in combination with any of the following: (a) increasing swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline". A soft-tissue/muscle bleed is defined as "an episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and loss of movement over baseline" A re-bleed (both joint and soft-tissue) is defined as "a bleed occurring within 72 hours after stopping treatment for the original bleed for which treatment was initiated)". All other bleeds will be considered new bleeds.

Determinants

Determinants include patient characteristics, disease characteristics, assessment outcomes, physical activity level, and pharmacokinetic characteristics

Patient characteristics:

Age will be recorded from the participants' medical record. Height, weight and fat percentage will be measured for all participants, BMI will be calculated from height and weight data. Fat percentage will be measured using a bio impedance device (Bodystat Quadscan 4000, Bodystat, Douglas, UK).

Disease characteristics

Haemophilia severity (severe, moderate, mild), inhibitor history and the presence of target joints will be recorded from medical records. A positive inhibitor history is defined as having had a FVIII/FIX alloantibody level of >0.6 Bethesda units/ml measured on two occasions within 1-4 weeks(1). Participants with a current positive inhibitor cannot participate in the study. A target joint is defined as three or more spontaneous bleeds into a single joint within a consecutive 6-month period(1))

Assessment outcomes:

Sports participation will be assessed with the validated Dutch Modifiable Activities Questionnaire (MAQ)(23,25,35). Participants are asked to provide the sports they participate in with the monthly frequency and duration. Adults and children older than 11 will complete the MAQ themselves, while parents will complete the MAQ for children younger than 11. Energy expenditure is calculated from MAQ data according to the instructions by Aaron et al.(23).

Self-reported limitations in activities will be assessed by completing the Haemophilia Activities List (HAL)(26,27) for adults or Paediatric Haemophilia Activities List (PedHAL) (28) for children. Adults and children older than 8 will complete the (Ped)HAL themselves. Parents or caregivers will be asked to complete the parent form of the PedHAL for participants under the age of 8. The (Ped)HAL records physical abilities of participants in several domains (e.g. upper extremity, walking, leisure time). Besides an overall score (HALsum), each domain has an individual score. The maximal overall score of the (Ped) HAL is 100 points, with 100 points indicating no self-reported limitations in activities. Adult participants with a HALsum≤89 and children with a HALsum≤95 were scored as being limited in activities (36).

Joint health status will be assessed with the Hemophilia Joint Health Score (HJHS)(37,38). The HJHS assesses range of motion, crepitus, pain, swelling, strength and atrophy for both ankles, knees and elbows, including a separate score for gait. The total score is 124, with a lower score indicating a better joint status. This score is obtained routinely by a trained physiotherapist in patients with severe and moderate haemophilia, annually until age 18 and every 5 years in adults. Joint health will be assessed both on patient and joint level. A joint with a score of 4 or higher at joint level is considered to be a joint with arthropathy(39,40).

Motor proficiency will be assessed by performing selected items of the Bruinings-Orezetsky Test of Motor Proficiency (BOT-2®)(41), which is a validated test with normative values for the general population. The selected items include balance

(subtest 5), running speed and agility (subtest 6) and strength (subtest 8). These items were selected based on their feasibility in the current group of participants. Tests are performed in a hierarchal order. If a particular test cannot be performed due to pain or inability, then the following test is not performed.

Balance is assessed by standing on one leg, standing on one leg on a balance beam and standing heel-to-toe on a balance beam. All tests are performed with eyes open first, and then repeated with eyes closed. Maximum duration for each test is 60 seconds. Participants get two opportunities for each test.

Running Speed and Agility consists of one-legged stationary hop, one-legged side hop and two-legged side hop. In all assessments, participants are instructed to achieve as many repetitions as possible within 15 seconds.

Strength is assessed by standing long jump, (knee) push-ups, sit-ups and wall sit. Participants get two opportunities for a maximal score on each test. For the standing long jump, the participant is instructed to jump as far as possible, with both feet setting off and landing simultaneously. The distance is measured to the nearest millimetre. In both push-ups and sit-ups, the participant has 30 seconds to achieve as many repetitions as possible. Participants younger than 12 are allowed to perform the push-ups on their knees. With the wall sit, participants are instructed to sit against the wall with their knees flexed to 90° and maintain this as long as possible (maximal 60 seconds).

Physical fitness will be assessed by performing a steep ramp test on a stationary bike (Lode Corival, Lode BV, Groningen, The Netherlands) (42,43). This is a validated test in which peak power (W_{peak}) is assessed, from which maximal oxygen uptake (VO_2-max) can be estimated(44). After adjusting the stationary bike to the participant, the participant is instructed to cycle for 3 minutes with a load of 25W at a frequency between 60 and 80 rpm to customize themselves with the bike. Heart rate is monitored throughout the test with an electronic heart rate monitoring device (Polar A5, Polar Oy, Kempele, Finland). After 3 minutes, the load is automatically increased by 20W/10s for adults(42) and 10W/10s for children(45). The participant is instructed to continue cycling until exhaustion, indicated by no longer being able to continue cycling at 60 rpm despite strong verbal encouragement. Peak workload (W_{peak}), peak heart rate (HR_{peak}) and rate of perceived exertion (RPE) are recorded at the end of the test. Wpeak is defined as the work rate (watts) at peak exercise, the point at which the participant's pedalling frequency definitely dropped below 60 rpm. HR_{peak} is defined as the highest value achieved during the last 30 seconds before test termination. RPE is recorded before and directly after the test, using a 10-point visual analogue scale indicating their level of fatigue(46).

Physical activity level

An objective assessment of physical activity will be made by collecting physical activity data from accelerometry and training diaries. Data collected from the accelerometry will include daily physical activity, energy expenditure and sedentary time. Energy expenditure will be expressed in Metabolic Equivalents of Task (MET)-minutes/week. 1 MET is the equivalent of an oxygen uptake of 3,5 ml/kg/min. Standardized MET values per activity are available for adults(47) and children(48). For the conversion to MET-minutes per week, the activity specific MET value is multiplied by the total number of minutes per week the participant is engaged in that particular activity (e.g. MET x minutes)(49). Sedentary activities are defined as activities involving an energy expenditure of 1-1.5 METs(50).

Pharmacokinetic characteristics

FVIII/FIX treatment regimen (dose, frequency/wk) and half-life data will be either extracted from medical records (treatment) or be estimated for each patient based on available pharmacokinetic assessments. Half-life of FVIII/FIX will be estimated for patients treated with prophylaxis based on population based calculations using the WAPPS software(51,52).

Sample size calculation

Data from the general population were used for the power-calculation of this study. The reported sports participation (at least once per week) in the general Dutch male population is 58%(53), resulting in 5 million males participating in sports. The annual number of sports injuries reported was 1.5 million for both men and women(54). Assuming that 1 million injuries incurred in men, the incidence rate of sports injuries in the male general population is 26% (95%CI: 25.96-26.04%) per year(54).

However, injury incidence is dependent on age: incidence was higher in adults (18-37) than in children (4-17)(54). Based on these data, the weighted incidence rate of annual sports injuries for men aged 4-46 was calculated at 26%/year.

Power calculations are based on all people with haemophilia (severe, moderate and mild), born between 01-01-1970 and 31-12-2011 (n=±450). At an estimated sports participation in patients with severe and moderate haemophilia of 71%(55) (and similar in those with mild haemophilia based on our pilot study(56)) and study participation of 50%, the minimal number of eligible patients is 0.71x 0.5 x 450 = 164 patients. With 164 participants and existing cohort of 2.700.000 controls(54), an absolute increase of 11% in the incidence of injuries (from 26 to 37%) can be detected (one sided testing, Chi-square test, power 0,80, p=0,025)(57). However, we are aiming to include 200 participants.

With 200 participants and the same existing cohort, an absolute increase of 10% in the incidence of injuries (from 26% to 36%) can be detected.

Severe and non-severe children with haemophilia showed similar annual injury rates in a paediatric pilot study(56). In a cohort of 98 children with haemophilia (6-18 years), 39% of children with severe haemophilia reported sports injuries, while 28% children with non-severe reported sports injuries (p>0,05). The annual number of sports injuries was similar in severe (median 0 (IQR: 0-1)) and non-severe (0 (0-1); p=0,49) patients.

The overall bleed rate in patients with severe haemophilia on prophylaxis at the Van Creveldkliniek is about 3-4 bleeds per year, including a median of 1.3 joint bleeds(10,20). Patients with moderate (0 [0-6]) or mild (0 [0-0]) haemophilia report fewer bleeds per year(58). Within the total of 200 participants, we aim to include at least 100 patients with severe haemophilia. The number of expected bleeds will be about 3 x 100 = ±300 (including ±103 joint bleeds), allowing ample power to study the effects of FVIII/IX level, age, existing joint damage (clinically affected yes/no), sports participation, last years' Annual Joint Bleeding Rate (AJBR), and trauma using multivariable regression analysis (n=6 determinants). For the analysis of sports related bleeds, the number of bleeds due to injuries is expected to be higher than 19% (38 injuries), and will therefore be sufficient to study the independent effects of the three main determinants: FVIII/IX level, age (per year) and existing joint damage (clinically affected: yes/no). Higher participation rates and/or higher injury rates will allow for the analysis of the independent effects of different sports in the multivariable analysis.

Statistical analysis

Descriptive analyses will include mean and standard deviation, median and interquartile range (IQR), range and/or proportions with 95% confidence intervals. Data will be tested for normality, which will form the basis for decisions regarding following parametric or nonparametric analysis. All comparisons across categories will be made using (non-) parametrical tests as appropriate. Test results, bleeds and injuries will be assessed according severity. For this purpose, severity is grouped in severe and non-severe because of the low number of participants with moderate haemophilia.

Descriptive analysis of motor proficiency and physical fitness (VO_2-max, W_{peak}) according to haemophilia severity (severe and non-severe), age (6-11; 12-17; 18-30; 31-49) and joint status, with separate analyses according to age, joint status, haemophilia severity, sports participation and type of sports. Multivariable logistic regression analysis will be used to assess the associations of sports injuries with physical fitness and motor proficiency

independent of age, severity, joint status, intensity of sports participation (hrs/week) and/or risk category of sports.

Descriptive analysis of sports-related injuries will be performed with separate analyses of the types of sports, risk categories as classified by the NHF (1: safe; 1,5: safe to moderate risk; 2: moderate risk; 2,5: moderate to dangerous; 3: dangerous)(59), age, joint status, haemophilia severity, self-reported limitations in activities and motor proficiency. At patient level, the association between bleeds and sports participation/injuries during follow-up will be calculated and reported according to age, joint health status, haemophilia severity and regular treatment. Analyses will be performed using multivariable regression (linear with negative binomial distribution and log link, or Cox proportional hazards analyses).

Occurrence of sports injuries will be compared to the general male Dutch population as well(60). This will be done for the overall sports injuries and according to type of sports (risk category), age, haemophilia severity and regular treatment parameters (weekly treatment dose and frequency).

For all bleeding events (it is expected that almost all sports injuries will be associated with bleeding), the effects of FVIII/IX activity level at the time of bleeding (baseline levels for patients treated on demand, and projected FVIII/IX levels based on pharmacokinetic (PK) data for patients on prophylaxis independent of age, presence of arthropathy, last years' AJBR, physical fitness, sports participation, and trauma will be analysed using multivariable regression with a negative binomial distribution and a log link(61). Recent data on sports participation and injuries from the Dutch general male population are available from the Dutch bureau of statistics(60).

The use of Repeated Time-To-Event (RTTE)(62) modelling will be explored, combining exposure information including pharmacokinetic data (population PK), patient characteristics, dose and dose frequency with the likelihood to bleed around sporting/physical activities. RTTE combines trough information derived from population PK modelling and the likelihood of bleeding events, and can also include other influences like sporting/physical activities and adherence (RTTE modelling utilizes data from the individual patient history prior to the bleeding episode). To assess the potential underestimation of joint bleeding due to the exclusion of re-bleeding, we will repeat the analysis while counting re-bleeds as separate bleeds. The NONMEM software package (ICON Development Solutions, Ellicott City, MD, USA) (63) will be used to perform the RTTE analysis.

The proportion of missing data is expected to be low, as most parameters will be measured prospectively. In case of 10% or more missing values, multiple imputations will be applied to complete the dataset before analysis. Data in this study will be analysed with SPSS (version 26; IBM Corp., Armonk, NY) and R (RStudio, PBC, Boston, MA, v1.3.1093) (64). A p-value<0.05 will be considered statistically significant.

After completing 8 months of follow-up in 60% of patients, an interim analysis will be performed to assess if the number of bleeds/injuries observed, and assessment of PA (both objective and subjective) are sufficient to perform the planned analysis. Patient responsiveness and commitment to completing the diaries and wearing the accelerometers will be evaluated. If the expected number is lower than 30, we will ask patients and IRB for an extension of the follow-up period. At this analysis, statistical methods will be used as described above for all parameters.

Incidence of (S)AE

An adverse event (AE) is defined as an undesirable medical event in a patient or subject that does not necessarily has a causal relationship with the treatment. In case the outcome of this AE is fatal, life threating, necessitates hospitalization, leads to permanent disability or might lead to any of these, the AE is defined as a serious adverse event (SAE). All AE and SAE occurring during this study will be documented in detail by means of standardized forms and any SAE will be reported to the relevant Institutional Review Board within 7 days.

Quality assurance

This protocol was devised and reviewed by experts on haemophilia and physical activity and approved by the Institutional Review Board of the UMC Utrecht. Quality will be assured by independent monitoring of the study. During this monitoring, all relevant documentation related to the case report forms will be evaluated against standards of good clinical practice. Monitoring will be executed by trained staff of the Julius Center of the UMC Utrecht.

Confidentiality and data management

Data will be handled confidentially in accordance with the Dutch Personal Data Protection Act. Subject identification codes will consist of a study code and serial number. Subject identification codes will be ascribed on arrival and these codes will be used throughout the study. The key to the identification code will be safeguarded by the principal investigator. Access to the data is limited to direct involved investigators and the monitor. Subject privacy will be protected by only assigning study codes and serial

numbers to their data. These codes and numbers will not include personal, traceable data (e.g. date of birth, initials, etcetera).

Data will be stored in protected files on personal computers according to Standard Operating Procedures of the Department of Internal Medicine and Dermatology of the UMC Utrecht. Both standard of care and study-specific data will be initially documented in the patient's electronic medical record system (source data). A study team member will then enter the data in the eCRF (CASTOR). CASTOR is compliant with the Good Clinical Data Management Practices guideline. Research data will be kept until publication of the study results and stored for 15 years at the investigational site where the data was collected.

Ethical considerations

The institutional review board of the UMC Utrecht has approved the protocol of this study under number 18-141. Participants and their parents will be fully informed by the investigators about the purpose, risks and benefits of this study before approving to participate in this study. All participants have to provide written informed consent before being allowed to participate. In case of minor aged participants, both parents have to provide written informed consent. No participants will be included without written informed consent. Participants were not compensated for their participation in this study, except for travel expenses in case they had to visit the clinic extra for the baseline tests.

Discussion

Haemophilia is a rare bleeding disorder which potentially leads to serious joint pathology. To maintain proper joint function while under intensive treatment with coagulation factor VIII or IX improving and maintaining coordination, strength and physical fitness are critical. The optimal way to achieve this is by being physically active. However, being physically active may be associated with an increased risk of injuries and (joint) bleeds, especially when engaging in (high-risk) sports. So far, there is limited data available about this, especially in adults, making any predictions or comparisons difficult. This proposed study is the first study to include both adults and children to assess physical activity and the associated injury and bleeding data, with regards to haemophilia severity, age, joint function, self-reported limitations, motor proficiency and physical fitness. These data will be compared to healthy, age-matched peers.

This proposed study relies in part on self-reported data by the participants. This is a potential source for recall bias. With regards to physical activity and injuries, this will be accounted for in two ways. First of all, physical activity will be recorded with accelerometers, creating more objective, standardized results. This will create an opportunity to compare these objective results to the subjective, self-reported data to assess reliability of this method. For injury and bleeding data, recall bias is limited by actively contacting the participants every two weeks instead of having the participants record their injuries in any form (online, app or in a diary) or using a longer recollection period.

The proposed study is expected to assist in providing more structured and more individualized advice regarding sports participation and prevention of sports injuries in people with haemophilia. In addition, it will serve as a basis for further research, aiming at an intervention or patient consultation programme.

Dissemination policy

The results of this study will be published in peer-reviewed journals and presented at international congresses during the study and after its completion.

References

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. J Thromb Haemost. 2014;12(11):1935–9.
2. Stephensen D, Tait R, Brodie N, Collins P, Cheal R, Keeling D, et al. Changing patterns of bleeding in patients with severe haemophilia A. Haemophilia. 2009;15(6):1210–4.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1–47.
4. Pulles AE, Mastbergen SC, Schutgens REG, Lafeber FPJG, van Vulpen LFD. Pathophysiology of hemophilic arthropathy and potential targets for therapy. Pharmacol Res [Internet]. 2017;115:192–9. Available from: http://dx.doi.org/10.1016/j.phrs.2016.11.032
5. Young and unfit? Lancet. 1992;340(8810):19–20.
6. Gomis M, Querol F, Gallach JE, Gonzalez LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: A systematic review. Haemophilia. 2009;15(1):43–54.
7. Querol F, Pérez-alenda S, Enrique J, Devís-devís J, Valencia-Peris A, Millán L, et al. Haemophilia : exercise and sport. Apunt Med Esport. 2011;46(169):29–39.
8. McLain LG, Heldrich FT. Hemophilia and Sports. Phys Sportsmed [Internet]. 1990;18(11):73–80. Available from: http://www.tandfonline.com/doi/full/10.1080/00913847.1990.11710175
9. Groen WG, Takken T, van der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. Haemophilia. 2011;17(5):906–12.
10. Broderick CR, Herbert RD, Latimer J, Barnes C, Curtin JA, Mathieu E, et al. Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia. JAMA J Am Med Assoc [Internet]. 2012;308(14):1452–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23047359
11. Ross C, Goldenberg N, Hund D, Manco-Johnson MJ. Athletic participation in severe hemophilia: bleeding and joint outcomes in children on prophylaxis. Pediatrics. 2009;124(5):1267–72.
12. Tiktinsky R, Kenet G, Dvir Z, Falk B, Heim M, Martinowitz U, et al. Physical activity participation and bleeding characteristics in young patients with severe haemophilia. Haemophilia. 2009;15(3):695–700.
13. Larsen LR, Kristensen PL, Junge T, Møller SF, Juul-Kristensen B, Wedderkopp N. Motor Performance as Risk Factor for Lower Extremity Injuries in Children. Med Sci Sport Exerc [Internet]. 2016;48(6):1136–43. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005768-201606000-00020
14. Watson A, Brindle J, Brickson S, Allee T, Sanfilippo J. Preseason Aerobic Capacity Is an Independent Predictor of In-Season Injury in Collegiate Soccer Players. Clin J Sport Med. 2016;0(3):1–6.
15. Ragni MV. New and Emerging Agents for the Treatment of Hemophilia: Focus on Extended Half-Life Recombinant Clotting Proteins. Drugs. 2015;75(14):1587–600.
16. Collins PW, Fischer K, Morfini M, Blanchette VS, Björkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. Haemophilia. 2011;17(1):2–10.
17. Lenting PJ, Denis C V., Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: How does it actually compare to factor VIII? Blood. 2017;130(23):2463–8.
18. Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, et al. Factor VIII–Mimetic Function of Humanized Bispecific Antibody in Hemophilia A. N Engl J Med. 2016;374(21):2044–53.
19. Den Uijl IEM, Biesma DH, Grobbee DE, Fischer K. Turning severe into moderate haemophilia by prophylaxis: Are we reaching our goal? Blood Transfus. 2013;11(3):364–9.
20. Fischer K, Steen Carlsson K, Petrini P, Holmström M, Ljung R, Van Den Berg HM, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: Comparing outcome and costs since the 1970s. Blood. 2013;122(7):1129–36.
21. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, et al. SPIRIT 2012 Explanation and Elaboration: Guidance for protocols of clinical trials. Br Med J. 2012;In press:1–42.
22. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K. Research and Reporting Methods Annals of Internal Medicine SPIRIT 2013 Statement : Defining Standard Protocol Items for Clinical Trials. Ann Intern Med [Internet]. 2013;158(3):200–7. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-158-3-201302050-00583

23. Aaron DJ, Kriska AM, Dearwater SR, Cauley JA, Metz KF, LaPorte RE. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. Am J Epidemiol [Internet]. 1995;142(2):191–201. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7598119

24. Aaron DJ, Kriska AM, Dearwater SR, Anderson RL, Olsen TL, Cauley JA, et al. The epidemiology of leisure physical activity in an adolescent population. Vol. 25, Medicine and science in sports and exercise. 1993. p. 847–53.

25. Tonoli C, Heyman E, Roelands B, Georges B, Berthoin S, Meeusen R. Validation and reliability of the Dutch language version of the Modifiable Activity Questionnaire in healthy subjects. Sport Sci Health. 2013;9(3):139–44.

26. Van Genderen FR, Westers P, Heijnen L, De Kleijn P, Van Den Berg HM, Helders PJM, et al. Measuring patients' perceptions on their functional abilities: Validation of the Haemophilia Activities List. Haemophilia. 2006;12(1):36–46.

27. van Genderen FR, van Meeteren NLU, van der Bom JG, Heijnen L, de Kleijn P, van den Berg HM, et al. Functional consequences of haemophilia in adults: The development of the Haemophilia Activities List. Haemophilia. 2004;10(5):565–71.

28. Groen WG, van der Net J, Helders PJM, Fischer K. Development and preliminary testing of a Paediatric Version of the Haemophilia Activities List (pedhal). Haemophilia. 2010;16(2):281–9.

29. Uitenbroek DG. Seasonal variation in leisure time physical activity. Med Sci Sports Exerc. 1993;25(6):755–60.

30. World Health Organisation. Declaration of Helsinki World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. J Am Med Assoc. 2013;310(20):2191–4.

31. The European Sports Charter. Council of Europe. 1992. p. 1–10.

32. Anderson A, Forsyth A. Playing it safe: Bleeding Disorders, Sports and Exercise. New York, NY.: National Hemophilia Foundation; 2017.

33. van Vulpen AV. Sport for all: sports injuries and their prevention. Oosterbeek: Council of Europe, Nationaal instituut voor Sportgezondheidszorg; 1989.

34. van Mechelen W, Hlobil H, Kemper HCG. Incidence, Severity, Aetiology and Prevention of Sports Injuries: A Review of Concepts. Sport Med. 1992;14(2):82–99.

35. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. Diabetes Care. 1990;13(4):401–11.

36. Kuijlaars IAR, van Emst M, van der Net J, Timmer MA, Fischer K. Assessing the test – retest reliability and smallest detectable change of the Haemophilia Activities List. Haemophilia. 2020;(September):1–5.

37. Fischer K, de Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: Exploring reliability and validity. Haemophilia. 2013;19(6):944–50.

38. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, van der Net J, et al. Validation of a new pediatric joint scoring system from the international hemophilia prophylaxis study group: Validity of the hemophilia joint health score. Arthritis Care Res. 2011;63(2):223–30.

39. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. Clin Orthop Relat Res [Internet]. 1980;(149):153–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7408294

40. Sluiter D, Foppen W, de Kleijn P, Fischer K. Haemophilia joint health score in healthy adults playing sports. Haemophilia. 2014;20(2):282–6.

41. Deitz JC, Kartin D, Kopp K. Review of the Bruininks-Oseretsky test of motor proficiency, second edition (BOT-2). Phys Occup Therepy Pediatr. 2007;27(4):87–102.

42. Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Lehmann M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure- application to exercise training. Eur Heart J. 1996;17(7):1040–7.

43. Bongers BC, De Vries SI, Helders PJM, Takken T. The steep ramp test in healthy children and adolescents: Reliability and validity. Med Sci Sports Exerc. 2013;45(2):366–71.

44. Stuiver MM, Kampshoff CS, Persoon S, Groen WG, van Mechelen W, Chinapaw MJM, et al. Validation and Refinement of Prediction Models to Estimate Exercise Capacity in Cancer Survivors Using the Steep Ramp Test. Arch Phys Med Rehabil. 2017;98(11):2167–73.

45. Bongers BC, Takken T. The paediatric version of the steep ramp test. J Physiother [Internet]. 2014;60(2):113. Available from: http://dx.doi.org/10.1016/j.jphys.2014.03.002

46. Foster C, Florhaug J a, Franklin J, Gottschall L, Hrovatin L a, Parker S, et al. A new approach to monitoring exercise training. J strength Cond Res. 2001;15(1):109–15.

47. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 compendium of physical activities: A second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575–81.

48. Butte NF, Watson KB, Ridley K, Zakeri IF, McMurray RG, Pfeiffer KA, et al. A Youth Compendium of Physical Activities. Vol. 50, Medicine & Science in Sports & Exercise. 2017. 246–256 p.

49. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334–59.

50. Pate RR, O'Neill JR, Lobelo F. The Evolving Definition of "Sedentary." Exerc Sport Sci Rev [Internet]. 2008;36(4):173–8. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003677-200810000-00002

51. Iorio A, Keepanasseril A, Foster G, Navarro-Ruan T, McEneny-King A, Edginton AN, et al. Development of a Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Study Protocol. JMIR Res Protoc [Internet]. 2016;5(4):e239. Available from: http://www.researchprotocols.org/2016/4/e239/

52. McEneny-King A, Foster G, Iorio A, Edginton AN. Data Analysis Protocol for the Development and Evaluation of Population Pharmacokinetic Models for Incorporation Into the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo). JMIR Res Protoc [Internet]. 2016;5(4):e232. Available from: http://www.researchprotocols.org/2016/4/e232/

53. Tiessen-Raaphorst (ed.) A, Tiessen-Raaphorst A. Rapportage Sport 2014 [Internet]. The Hague; 2015. Available from: https://www.scp.nl/Publicaties/Alle_publicaties/Publicaties_2015/Rapportage_Sport_2014

54. Schmikli SL, Backx FJG, Kemler HJ, van Mechelen W. National survey on sports injuries in the Netherlands: target populations for sports injury prevention programs. Clin J Sport Med. 2009;19(2):101–6.

55. Heijnen L, Mauser-Bunschoten EP, Roosendaal G. Participation in sports by Dutch persons with haemophilia. Haemophilia. 2000;6(5):537–46.

56. Versloot O, Timmer MA, Schuuring M, de Kleijn P, van Koppenhagen CF, van der Net J, et al. Sports participation and sports injuries in boys with haemophilia. Press.

57. Lenth R. Java Applets for Power and Sample Size [Computer software]. 2009. p. Retrieved 13-10-2017, from http://www.stat.uiowa.e.

58. den Uijl IEM, Fischer K, van der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Clinical outcome of moderate haemophilia compared with severe and mild haemophilia. Haemophilia [Internet]. 2009 Jan;15(1):83–90. Available from: http://doi.wiley.com/10.1111/j.1365-2516.2008.01837.x

59. Anderson A, Forsyth A. Playing It Safe. 2005;1–45.

60. Veiligheid.nl. Sportblessures in Nederland - cijfers 2019 [Internet]. Veiligheid NL. 2020. Available from: https://www.veiligheid.nl/.ibmmodres/domino/OpenAttachment/veiligheid/website.nsf/8AB1F5320A6EEB1BC1258640005808F4/asset/Cijferrapportage Sportblessures 2019.pdf

61. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: The association of joint bleeds according to baseline FVIII activity levels. Haemophilia. 2011;17(1):41–4.

62. Guo Z, Gill TM, Allore HG. Modeling repeated time-to-event health conditions with discontinuous risk intervals: an example of a longitudinal study of functional disability among older persons. Methods Inf Med2. 2008;47(2):107–16.

63. ICON. NONMEM [Internet]. [cited 2021 Apr 9]. Available from: https://www.iconplc.com/innovation/nonmem/

64. Team Rs. RStudio [Internet]. Boston, MA.: RStudio: Integrated Development for R. RStudio, Inc.; 2015. Available from: www.rstudio.com

List of abbreviations and relevant definitions.

FVIII:	coagulation factor VIII;
FIX:	coagulation factor IX;
AJBR:	Annual Joint Bleeding Rate;
BOT-2:	Bruinings-Orezetsky Test of Motor Proficiency;
HAL:	Haemophilia Activities List;
HJHS:	Hemophilia Joint Health Score;
IQR:	Interquartile Range;
MAQ:	Modifiable Activity Questionnaire;
METs:	Metabolic Equivalents of Task;
PedHAL:	Paediatric Haemophilia Activities List;
RTTE:	Repeated Time-To-Event;
SPIRIT:	Standard Protocol Items: Recommendations for Intervention Trials;
SPRAIN:	Sports Participation and Injuries in patients with haemophilia;
VO_2-max:	Maximal Oxygen Uptake;
W_{peak}:	Peak Work Load.

Additional file 1

SPIRIT 2013 checklist : Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	1-13
Protocol version	3	Date and version identifier	All pages
Funding	4	Sources and types of financial, material, and other support	30
Roles and responsi-bilities	5a	Names, affiliations, and roles of protocol contributors	1, 30
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	30
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
	6b	Explanation for choice of comparators	7-9
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	10

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8, fig. 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-18
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	15-18
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	31
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Figure 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CHAPTER 7

Clotting factor activity levels and bleeding risk in people with hemophilia playing sports

O. Versloot[1,2], E. Kemler[3], J. Blokzijl[1], M.A. Timmer[1], M.D. Schuuring[4], K.P.M. van Galen[1], I.C.L. Kremer Hovinga[1], P.R. van der Valk[1], L.F.D. van Vulpen[1], R.E.G. Schutgens[1], C.F. van Koppenhagen[5], J. van der Net[4] and K. Fischer[1]

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

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Dutch Consumer Safety Institute, Amsterdam, the Netherlands.

[4] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, University Medical Center, Utrecht University, The Netherlands.

[5] Rehabilitation Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Currently under review for Haemophilia

Bullet points

What was already known:

- Sports participation in Dutch people with haemophilia is high, but no data on injuries have been reported to date.
- Sports injury studies in children have shown low sports injury rates with a limited association with sports intensity

What this study adds:

- Sports-induced bleeds were rare: only 26 sports-induced bleeds were reported in 15,999 sports exposures
- Clotting factor activity level was the main determinant of bleeding after sports injury, while severity was not.
- Participants with less than 10% factor levels at time of injury had a twofold risk of a sports-induced bleed.
- Most injuries and bleeds were not sustained during sports activities.

Abstract

Improved treatment options for people with hemophilia (PWH) have increased the possibilities for sports participation, but the risk of sports-induced bleeding (SIB) is still considered considerable by many. The aim of this study was to firstly assess sports injury bleeding risk in PWH and subsequently to assess clotting levels associated with safe sports participation. Sports injuries and SIBs were prospectively collected for 12 months in PWH aged 6-49 without inhibitors playing sports at least once weekly. Injuries were compared according to factor levels, severity, joint health, high-risk , or high-intensity sports. Factor activity at the time of injury was estimated using a pharmacokinetic model. 125 participants aged 6-49 (41 children, 90% hemophilia A; 48% severe, 95% severe on prophylaxis) were included. Sports injuries were reported by 51 participants (41%). Most participants (62%) reported no bleeds at all and only 16% reported SIBs. SIBs were associated with factor levels at time of injury (OR: 0.93 (CI 0.88-0.99); p=0.02), but not with hemophilia severity (OR: 0.62 (CI 0.20-1.89); p=0.40), joint health, sports risk category or sports intensity. PWH with less than 10% factor levels during sports injury had a bleeding risk of 41% vs. 20% in those with higher (>10%) factor levels.. The results of this study emphasize the importance of clotting factor levels in prevention of bleeds. This information is vital for patient counselling and tailoring prophylactic treatment with clotting factors and non-replacement therapy.

Introduction

Hemophilia is a congenital hematological condition, characterized by decreased or absent activity of coagulation factor VIII (FVIII; hemophilia A) or IX (FIX; hemophilia B)[1]. People with hemophilia (PWH) are at an increased risk of spontaneous musculoskeletal bleeds and subsequent impaired joint function[2]. Current treatment consists of regular intravenous self-infusions of coagulation factor concentrate.

Physical activity and sports are universally accepted as beneficial[3]. Despite generic health benefits, hemophilia specific risks (e.g. joint or intracranial bleeds)[2] are being debated among caregivers, PWH and peers. With the improved treatment options for PWH, the possibilities for sports participation have increased significantly. Although the World Federation for Hemophilia (WFH) still encourages low-risk sports[1], PWH receiving prophylaxis are currently as active in sports as the general population (GP), including high-risk (HR) sports[4] such as soccer[5–7]. Moreover, the WFH recommendation for sports participation is primarily based on expert opinion, as data on sports related injury and bleeding risks are scant and sports-specific data have not been reported.

In general, sports participation is positively associated with injuries[8,9]. So far only Broderick et al. (2012) performed a prospective study of the association between sports participation and bleeding risk in PWH. They reported a transient increased bleeding risk after sports and a negative association between factor levels and bleeds in 104 boys with hemophilia. Moreover, the majority of bleeds were not associated with physical activity[10]. Two retrospective studies in American boys with hemophilia reported no association between sports participation and injuries[11,12]. In case of PWH, sports-induced bleeds (SIB) might be a more clinically relevant outcome than sports injuries. Assessment and quantification of injury- and bleeding risks is needed to enable adequate counselling.

The aim of this study was firstly to assess injury- and bleeding risk in Dutch PWH and subsequently to assess target clotting factor levels associated with safe sports participation.

Methods

Methods and setting

This analysis was part of the "Sports Participation and Injuries in People with Hemophilia" (SPRAIN) study. This was a single-center prospective study assessing sports injuries in PWH treated at the Van Creveldkliniek of the University Medical Center Utrecht, the

Netherlands. Inclusion of participants started in October 2018 and was discontinued prematurely at the start of the COVID-19 lockdown in March 2020. Each participant was followed for 12 months, all participants had a complete follow-up. The study was approved by the Institutional Review Board of the UMC Utrecht (IRB number: 181-41). This study was registered in the Dutch trial register (www.trialregister.nl) under trial ID NTR6769.

Participants

PWH aged 6-49 years without a current inhibitor who played sports at least once weekly were eligible for inclusion in the study. Exclusion criteria were the presence of FVIII/FIX antibodies, an arthroplasty or arthrodesis within the last 12 months or refusal or inability to provide informed consent. All participants provided written informed consent prior to being included in the study. Parents provided informed consent in case of participants younger than 16 years.

Data collected

Participant (age, height, weight), disease (type of hemophilia, severity, factor activity, annual bleeding rate (ABR), annual joint bleeding rate (AJBR)) and treatment characteristics (use of prophylaxis, treatment frequency, dose, pharmacokinetics) of all participants were collected from electronic hospital records.

Sports participation was assessed by the validated Dutch version of the Modifiable Activities Questionnaire (MAQ)[13–15]. It assesses type of sports and weekly sports exposure (frequency x duration) using free-text input. Physical education classes in children were not considered.

Joint health status was assessed using the Hemophilia Joint Health Score 2.1(HJHS)[16,17]. The HJHS assesses range of motion, crepitus, pain, swelling, strength and atrophy for both ankles, knees and elbows, plus a global gait score. The total score is 124, with a score of zero considered optimal and scores of 4 or higher considered abnormal[18,19].

Sports associated injury risk was categorized according to the National Hemophilia Foundation (NHF) classification (1: safe; 1,5: safe to moderate risk; 2: moderate risk; 2,5: moderate to dangerous; 3: dangerous). Sports in the two highest categories were classified as HR sports (e.g.: soccer)[4].

Sports intensity was assessed by means of an Activ8® accelerometer, a validated tool to assess physical activity[20]. The Activ8® is worn on the thigh and can distinguish various activities, both in time and energy expenditure (Metabolic Equivalent of Task; METs)[21].

Energy expenditure (EE) >6 METs is considered vigorous physical activity[22]. Participants scoring >75th percentile of time in high-intensity (HI) sports were classified as (predominantly) participating in HI sports.

A *sports injury* was defined as "any injury as a result of participation in sports with one or more of the following consequences: (a) a reduction in the amount or level of sports activity; (b) a need for (medical) advice or treatment; or (c) adverse social or economic effects"[23]. Sports injury data were collected by contacting the participants every two weeks by their preferred method (phone, email or text message). In case of an injury, they were contacted by phone to record injury details (e.g. mechanism, sports injury, bleed) as well as the time of the last infusion of clotting factor concentrate for those using prophylaxis (see supplemental table S1). Sports injuries were presented as the number of injuries/1000hrs of exposure[24]. Based on the patient interviews, the etiology of sports injuries was identified as resulting from a single trauma or from prolonged, repetitive overuse.

Bleeds were classified according to Blanchette et al. (2014)[25], with definitions shown in supplemental table S2. In the absence of a formal definition, a *sports-induced bleed* was defined as a bleed that occurred as a result of a sports injury, when the patient experienced identical symptoms to a (joint/muscle/soft tissue) bleed and required (immediate) extra treatment with clotting factor concentrate or consultation with a hemophilia consultant.

Baseline factor activity levels were extracted from hospital records. Participant with non-severe hemophilia who were not on prophylactic treatment (n=65; 51%) were assumed to have stable factor levels. For participants using prophylaxis with known trough levels (35/61; 56%), PK data was estimated based on individual concentrate-specific pharmacokinetics and through levels. For the remaining 26 (44%) participants without recent measurements available baseline factor level was estimated based on concentrate, age and weight specific data using the WAPPS database.

Clotting factor activity at the time of injury in 60 participants using prophylaxis was estimated by combining information on the timing of the last prophylactic infusion before the injury with pre-study individual pharmacokinetics.

General population data

GP data were collected by the National Institute for Public Health and the Environment (RIVM) and the Dutch Consumer Safety Institute (VeiligheidNL) in collaboration with Statistics Netherlands. GP data were extracted from the 2019 'additional module

physical activity and accidents/Lifestyle monitor'[26,27]. This is an ongoing large population-based retrospective cross-sectional study, drawing a sample of persons from the Basic Registration of Persons at monthly intervals. The questionnaire is carried out in a "mixed-mode" design. Annually, around 10.000 persons are questioned online, by telephone or a face-to-face interview. Respondents could report a maximum of four sports. For each sport, annual hours of participation were calculated. Sporting participants were asked to report the number of sports injuries they have had in the past 3 months. Detailed information about the two most recent injuries was collected (injury type, body location, onset of the injury, cause of the injury, medical treatment of the injury, sports absence, etc.). To be able to compare data from PWH with the GP, a sub-analysis was made in which the GP data on male sports participants aged between 6 and 50 were compared with the number of injuries sustained by PWH during the first 3 months of follow-up.

Statistics

Injury data were summarized as medians and interquartile ranges (IQR) and/or proportions with 95% confidence intervals (CI), as appropriate. Data were analyzed with non-parametric techniques. Injuries and bleeds were assessed according to hemophilia severity.–factor levels, age, joint health status, high-risk and high-intensity sport. and injury risk category..

Sports injuries and SIBs were analyzed according to factor VIII and IX levels at time of injury, type of sports (HR sports: yes/no; HI sports: yes/no), age and joint status. For this purpose, disease severity, joint health status and injury risk were grouped. Severity was grouped into severe and non-severe (participants with moderate and mild hemophilia) due to the low number of participants with moderate hemophilia. Joint health status was categorized as "unaffected" (HJHS≤4) or "affected" (HJHS>4)[19].

Sports injuries characteristics (e.g. prevalence, location, duration) were compared to the general male Dutch population. The association between factor levels at time of injury and the probability of an SIB was assessed by means of a backward, logistic regression analysis that adjusted for age, joint status (affected vs. unaffected), HR sports (yes/no), HI sports (yes/no), total annual sports exposure (hours) and hemophilia severity (severe/non-severe). Potential predictors were selected based on univariable analysis, with $p<0.10$ as an inclusion criterion. As HR sports participation decreased as a result of COVID-19 restrictions in the Netherlands[28], an additional sensitivity analysis was performed in which the number of SIB due to HR sports before and after COVID-19 restriction were compared.

The online electronic data capturing tool CASTOR was used to collect, record and store all data. The statistical analysis was performed using SPSS statistical software, version 26 (IBM corp., Armonk, NY) and R (RStudio, PBC, Boston, MA, v1.3.1093)[29]. A p-value<0.05 was considered statistically significant.

Data sharing statement

External parties can have access to the anonymized data upon reasonable written request to the investigators.

Results

Participants

Injury and bleeding data of 125 participants (41 children, 84 adults) were included in this study. Table 1 shows participant-, disease- and treatment characteristics according to severity. Most participants had hemophilia A (90%). Nearly half the participants had severe hemophilia (48%), participants with non-severe hemophilia had a median FVIII/IX activity level of 15 IU/dl (IQR 8-16); distribution in Supplemental figure S1). All but

Table 1: Patient characteristics and sports exposure according to hemophilia severity

N=125	overall	severe	non-severe
	N (%), or median (IQR)		
Number	125	60 (48%)	65 (52%)
Age (yrs)	23.1 (15.9-33.7)	23.0 (15.8-34.1)	23.8 (16.1-33.1)
Hemophilia A	112 (90%)	54 (92%)	58 (88%)
Baseline factor activity (IU/dl)	2 (0-15)	0 (0-0)	14.5 (7.5-17.0)
Prophylactic treatment	61 (49%)	57 (95%)	4 (6%)
Prophylactic dose/kg/week[a]	42 (36-55)	42 (35-55)	52 (39-74)
Factor levels after infusion	42 (35-52)	42 (36-52)	32 (25-48)
Positive inhibitor history	17 (14%)	14 (82%)	3 (18%)
ABR	0 (0-0)	0 (0-1)	0 (0-0)
	Sports Participation		
Annual sports exposure (hrs/yr)	144 (53-224)	120 (50-222)	153 (65-248)
Energy Expenditure (METs-hrs/wk)	19.4 (8.1-34.6)	16.6 (7.9-34.6)	21.7 (8.1-34.6)
High-risk sports	74 (59%)	41 (69%)	33 (50%)
High-intensity sports	25 (20%)	12 (20%)	13 (20%)
	Joint health		
AJBR	0 (0-0)	0 (0-0)	0 (0-0)
HJHS	0 (0-3)	1 (0-7)	0 (0-1)
HJHS≥4	28 (22%)	22 (79%)	6 (21%)

[a]: median weekly treatment dose for participants undergoing prophylactic treatment. ABR: annual bleeding rate; AJBR: Annual Joint Bleeding Rate; HJHS: Hemophilia Joint Health Score

three participants with severe hemophilia used prophylactic treatment (95%), with a median weekly dose of 42.3 IU/kg (A: 41.7; B: 53.6 IU/kg), leading to median factor levels of 42 (IQR 35-52) IU/dl immediately after infusion. Median energy expenditure during sports was similar for severe and non-severe hemophilia (16.6 MET-h/wk (IQR 7.9-34.6) vs. 21.7 (IQR 8.2-34.6); p=0.44). A median ABR and AJBR of 0 (IQR 0-0) was observed. GP data were collected from 2072 male participants (645 children, 1427 adults) aged 6-50 (supplemental table S3).

All participants with hemophilia played sports at least once weekly. A total of 15.999 (2.5x/participant/week) sports exposures were reported throughout the follow-up. Total sports participation in PWH was high and similar to the GP (144 (IQR 53-224) vs. 160 (IQR 80-278) hrs/yr). Children mostly played soccer (40%), fitness (7%) and gymnastics (4%), while adults mostly practiced fitness (29%), running (16%) and soccer (8%). Many participants (59%) practiced at least one HR sport, children more than adults (85% (CI: 71-93) vs. 46% (36-57); p<0.01).

Injuries and bleeds: general characteristics

The infographic in figure 1 shows an overview of all reported injuries, sports injuries, bleeds and SIBs. A total of 184 injuries were reported, of which 87/187 (47%) were sports-related. One third of the participants (43/125; 34%) reported no injuries at all while 51/125 (41%) participants reported sports injuries. Supplemental table S5 shows that most sports injuries were muscle (42%) and joint (35%) injuries, mostly in the upper leg (30%) and ankle (23%).

A total of 80 bleeds were reported, of which 26 (33%) occurred after a sports-induced trauma, 49/80 (61%) were not sports-related and five (6%) occurred spontaneously. Most participants (78/125; 62%) reported no bleeds at all during follow-up, and only 20 (16%) participants reported SIBs.

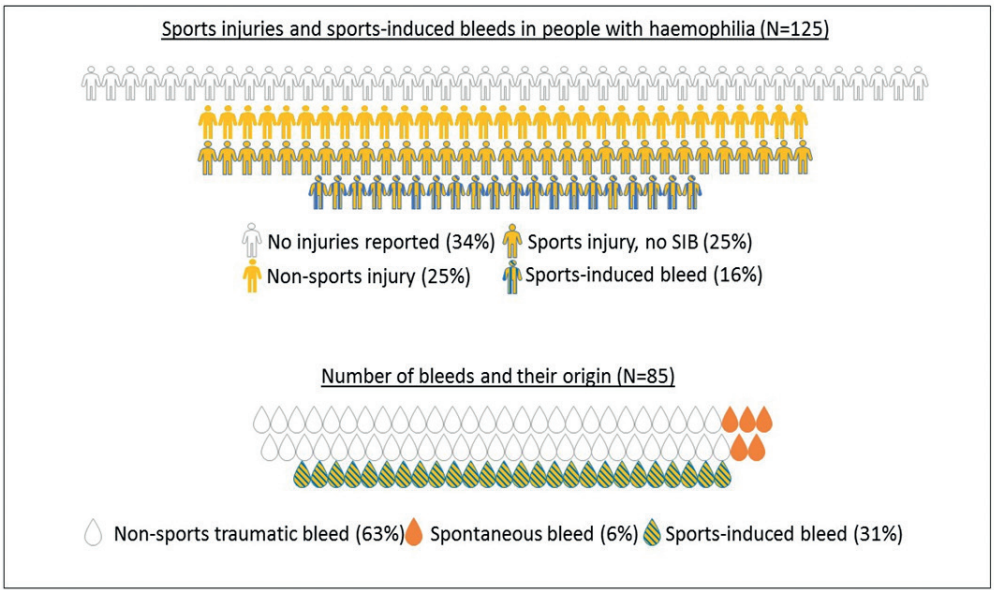


Figure 1: Infographic showing the number of participants reporting no injuries, non-sports injuries, sports injuries, bleeds and SIBs and the origin of all reported bleeds during the 12 month' follow-up of the SPRAIN study. Most injuries and SIBs were not sports-related.

Sports injuries and sports-induced bleeds according to severity

Table 2 shows sports injuries and SIBs according to hemophilia severity. Sports injuries were reported by 41% (n=51) of participants. Despite similar annual sports exposure, more participants with severe hemophilia reported sports injuries than non-severe participants (53% vs. 29%; p<0.01). The median number of injuries/participant was higher in participants with severe hemophilia (1 (IQR 0-2) vs. 0 (IQR 0-1); p<0.01). Participants with severe hemophilia reported a higher incidence rate (median 5 (IQR 0-15) vs. 0 (IQR 0-5) inj/1000hrs exposure; p<0.01), most likely due to the small group reporting injuries in people with non-severe hemophilia (n=19). Participants with severe hemophilia reported shorter median time-loss (7 (3-19) vs. 14 (7-25) days; p=0.05). 59% Of injuries occurred during HR sports, while 29% occurred during HI sports. Participants with severe hemophilia reported more injuries in both HR (67 vs. 33%; p<0.01) and HI sports (84 vs. 16%; p=0.04).

Table 2: Sports injuries and bleeds according to hemophilia severity

Median (IQR) or N (%)				
	PWH	**Severe**	**Non-severe**	**p**
N	**125**	**60**	**65**	
Total Annual Sports Exposure (hrs/yr)	144 (53-224)	120 (50-222)	153 (65-248)	0.35
Injuries and Bleeds				
Total number of reported injuries	179	118/179 (67%)	61/179 (33%)	**<0.01**
Total number of reported bleeds	80	54/80 (68%)	26/80 (32 %)	**<0.01**
Spontaneous bleeds	5	5	0	-
Participants with no bleeds during follow-up	78/125 (62%)	29/60 (48%)	49/65 (75%)	**<0.01**
Sports injuries				
Sports injuries	87	60	27	
Participants with sports injury	51/125 (41%)	32/60 (53%)	19/65 (29%)	**<0.01**
Within first three months	22/125 (18%)	13/60 (32%)	9/65 (14%)	0.15
Sports injuries/participant	0 (0-1)	1 (0-2)	0 (0-1)	**<0.01**
Range	0-7	0-7	0-3	-
Sports injuries/1000hrs exposure	0 (0-10)	5 (0-15)	0 (0-5)	**<0.01**
Range	0-231	0-91	0-231	**-**
Time loss (days)	7 (4-21)	7 (3-19)	14 (7-25)	**0.04**
During high-risk sports[a]	51/87 (59%)	34/51 (67%)	17/51 (33%)	<0.01
During high-intensity sports[b]	25/87 (29%)	21/25 (84%)	4/25 (16%)	**0.04**
Sports-Induced Bleeds (SIB)				
Sports-induced bleed	26	18	8	
Participants with SIB	20/125 (16%)	14/60 (23%)	6/65 (9%)	**0.03**
SIB/sports injury	26/87 (30%)	18/60 (30%)	8/27 (30%)	0.97
SIB/participant	0 (0-0)	0 (0-0)	0 (0-0)	0.03
Range	0-4	0-4	0-2	-
SIBs/1000hrs exposure	0 (0-0)	0 (0-0)	0 (0-0)	**0.0**
Range	0-71	0-71	0-42	-
Time loss after SIB (days)	11 (4-21)	7 (4-19)	19 (9-37)	0.13
During high-risk sports[a]	14/26 (54%)	8/14 (57%)	6/14 (43%)	0.15
During high-intensity sports[b]	6/26 (23%)	4/6 (67%)	2/6 (33%)	0.88

Bold numbers indicate a significant difference between participants with severe and non-severe hemophilia. The denominators are shown because of the variety in groups and group sizes. [1]:high-risk sports: categories 2.5 and 3 according to the NHF classification[a]. [b]: high-intensity sports: participants who predominantly perform sports with >6METs energy expenditure. SIB: sports-induced bleed.

Sports injuries: people with hemophilia vs. general population

Table 3 shows similar injury incidence in PWH and the GP (18% (CI 12-25%)) vs. 16% (CI 14-18%)) over a 3-month' period. Injury rates were stable across seasons (see supplemental table S4a and S4b). Median time loss (7 (IQR 4-21) vs. 10 (IQR 5-28) days) and the proportion of injuries during HR sports (59% (CI 48-68) vs. 57% (CI 53-61)) were similar.

The overall mean incidence rate was higher than in the GP (11.0 vs. 3.1 inj/1000hrs) which may be attributable to repeated injuries in PWH as the incidence rate is similar (3.2 vs. 3.1 inj/1000hrs) when excluding repeated injuries in PWH.

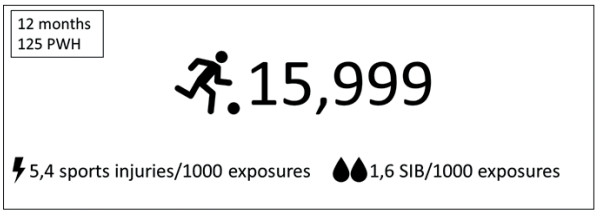


Figure 2: sports injuries and SIBs were rare when the total sports exposure over the 12-month follow-up was considered. The vast majority of sports exposures did not cause an injury or SIB. On a total of 15,999 sports exposures, only 87 sports injuries were reported (0.5%), while only 26 SIBs were reported (0.16%).

Sports-induced bleeds in people with hemophilia

Figure 2 shows that on a total of 15,999 sports exposures, only 0.16% resulted in an SIB. Only a minority of all sports injuries (26/87; 30%) resulted in an SIB. The proportion of SIBs after a sports injury was similar in severe and non-severe hemophilia (18/60 (30%) vs. 8/27 (30%); p=0.97). SIBs were reported by 20 (16%) participants, with 2 participants reporting more than 1 SIB. Median interruption of sports participation after an SIB was 11 (IQR 4-21) days. Most SIBs (14/26; 54%) were sustained during HR sports. As in sports injuries, SIBS were stable across seasons (supplemental table S4a and S4b).

Soccer was played by 39 participants (31%) and was associated with 26 sports injuries and 4 SIBs. Soccer-specific injury incidence (13%) was similar to the entire group (18%), but the majority of injuries (73%) and all SIBs in soccer were sustained by participants with severe hemophilia.

Sixteen percent of all participants reported an SIB, with more SIBs in participants with severe hemophilia (14/60 (23%) vs. 6/65 (9%)). Although the median number of SIBs/participant was 0 (0-0) for both severe and non-severe hemophilia, the variation was larger in severe hemophilia (range: 0-4 vs. 0-2; p=0.03). This was also observed for the median SIBs/1000hrs with a median of 0/1000hrs (range 0-71) for severe, and 0/1000hrs (range 0-42) for non-severe participants (p=0.04). Participants with severe hemophilia reported a trend towards shorter interruption from sports participation following an SIB (median 7 (IQR 4-19) vs. 19 (IQR 9-37) days; p=0.13). While about half of the SIBs occurred during HR sports (59%), only one quarter (23%) occurred during HI sports.

Table 3: Sports injuries in people with hemophilia and the general population (over 3 months)

	N (%) or median (IQR)	
	GP	**PWH**
n	2072	125
Total Annual Sports Exposure (hrs/yr)	160 (80-278)	144 (53-224)
Sports injuries		
Sports injuries	486	87
Participants with sports injury	-	51 (41%)
Within first three months	330 (16%)	22 (18%)
Sports injuries/participant	1 (1-2)	2 (1-3)
Time loss (days)	10 (5-28)	7 (4-21)
During high-risk sports[1]	277 (57%)	51 (59%)
Injuries/1000hrs exposure	3.1	11.0

Sports injuries were similar in PWH and GP. The number of injuries according to exposure (inj/1000 hr) was higher in PWH. a: high-risk sports: categories 2.5 and 3 according to the NHF classification[4]

An additional sensitivity analysis showed similar proportions of SIBs due to HR sports before and after COVID restrictions (26% (CI: 14-41%) vs. 31% (12-58%); p=0.72). The flow chart in figure 4 shows the number of SIBs/participant according to factor levels.

Sports induced bleeds according factor levels

Table 4 shows the characteristics of sports injuries who developed into an SIB and those who did not. Participants with an SIB reported lower median factor levels at time of injury (6.0 (IQR 2.8-14.0) vs. 12.3 (IQR 5.4-22.3) IU/dl; p=0.03, see figure 3). Most participants on prophylaxis who developed an SIB (71%) had their last infusion more than 12 hours before their sports activity and thus had not adhered to the recommendation to infuse prophylaxis shortly before sports participation.

Table 4: Participant and disease characteristics according to bleeding (SIB) following a sports injury

	Median (IQR) or n(%)		
	SIB (n=26)	**no SIB (n=61)**	**p**
Age (yrs)	19.8 (14.3-33.5)	17.7 (15.5-27.4)	0.52
Severe hemophilia	69%	69%	0.97
Factor level @time of injury (IU/dl)	6.0 (2.8-14.0)	12.3 (5.4-22.3)	0.03
ABR	1 (0-4)	0 (0-4)	0.64
AJBR	0 (0-2)	0 (0-1)	0.47
Last prophylactic infusion >12hrs[a]	72%	41%	0.02
Last prophylactic infusion >24hrs[a]	54%	51%	0.80
HJHS ≥4	31%	15%	0.09
Total Annual Sports Exposure (hours/year)	148 (68-241)	168 (81-271)	0.62
Injury during HR Sports[b]	54%	61%	0.56
Injury during high-intensity sports	23%	33%	0.37

Factor levels at time of injury were lower in participants sustaining an SIB following a sports injury. Participants using prophylactic infusions who had their last infusion within 12 hours before their sports injury had a lower risk of an SIB. Bold numbers indicate a significant difference between participants with or without an SIB. [a]: only for participants under prophylactic treatment. [b]: high-risk sports: according to the NHF classification[4]

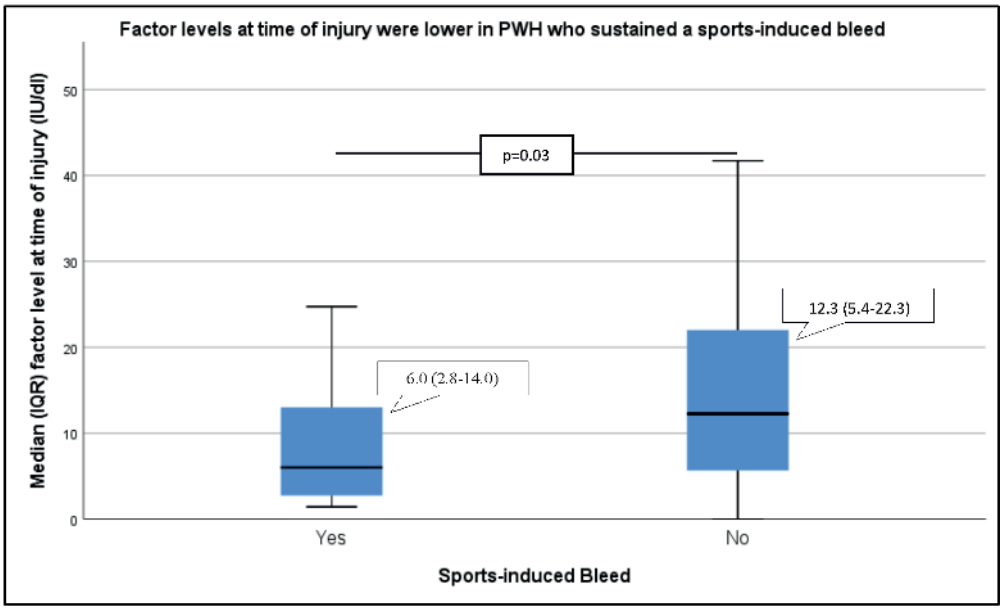


Figure 3: factor levels at time of injury were lower in people with hemophilia who developed an SIB than those who did not develop an SIB.

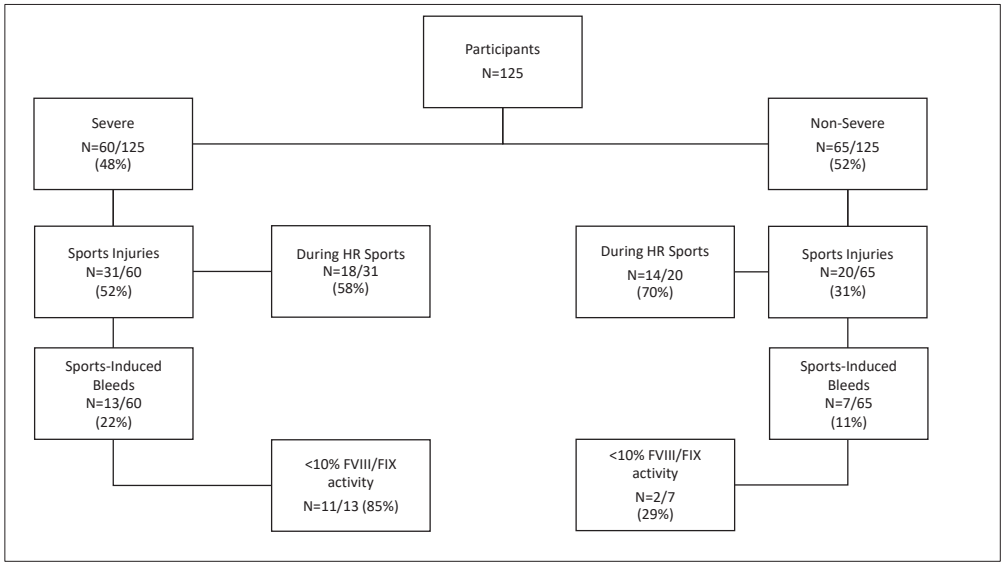


Figure 4: number and proportion of participants sustaining an SIB following a sports injury according to severity during the 12 month' follow up. Participants with severe hemophilia and factor levels below 10% at the time of injury reported most SIBs.

Figure 5 shows predicted SIB probability according to clotting factor activity levels at the time of sports injury: participants with higher factor levels at time of injury were less likely to develop an SIB following a sports injury. Logistic regression showed that SIBs were associated with factor levels at time of injury (OR: 0.93/ %FVIII/FIX (CI 0.88-0.99); p=0.02; independent of age, joint health, HR sports, HI sports, total annual exposure and hemophilia severity supplemental table S6). For example, twice as many participants with factor level <10% at time of injury reported an SIB (41% vs. 20%) compared to those with higher factor levels, resulting in a negative predictive value of 80%.

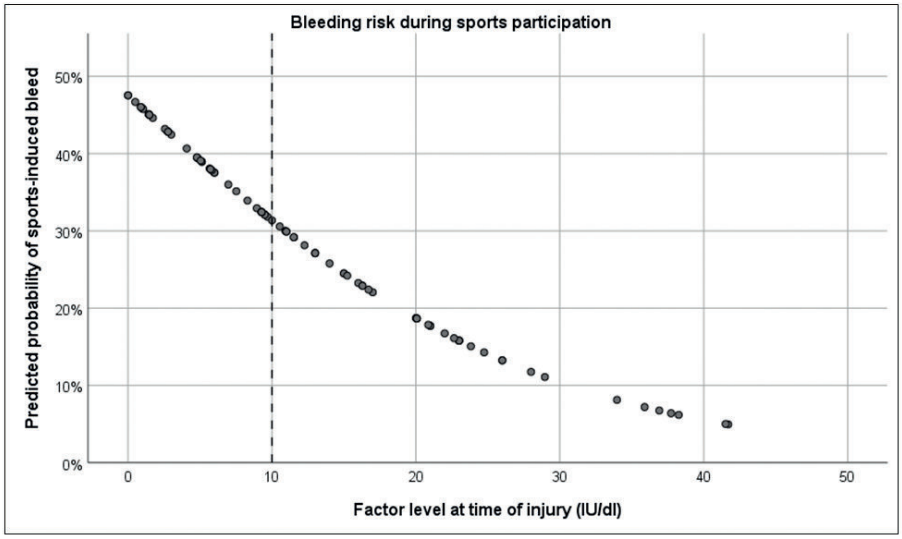


Figure 5: The predicted probability of SIBs after sustaining a sports injury was higher with lower factor levels at the time of injury. Multivariable regression analysis identified a factor level >10% factor level at the time of injury as a relevant predictor (OR: 0.93 (95%CI: 0.88-0.98); p=0.02). The dashed line indicates 10% factor level at the time of injury, the solid line and grey area represent median peak levels after prophylactic infusion with interquartile range (median: 42 (IQR: 35-52) IU/dl)

Discussion

Principal findings

We present a large prospective study on sports injuries and SIBs including both children and adults with hemophilia. A total of 87 sports injuries and 26 SIBs were reported during 15,999 exposures. 25% of all injuries and 16% of all bleeds were sports related. The results showed that participants with severe hemophilia sustained more sports injuries and SIBs than those with non-severe hemophilia, both in an absolute sense as well as according to exposure. SIBs were negatively associated with factor levels at time of injury: participants with lower factor levels reported more SIBs. Participants with factor levels ≤10 IU/dl at the time of injury had twice the risk of developing an SIB following a sports injury (41% vs 20%). PWH and the GP reported similar annual sports participation and a similar proportion reported sports injuries. In addition, the low injury rates and the low number of SIBs in PWH suggest that sports participation for PWH seems safe while at sufficient factor levels.

Strengths and limitations

This was a 12-month' prospective follow-up study, in which participants were contacted on a biweekly basis to record their sports injuries and SIBs.

The inclusion of participants aged 6-49, covering the age group with the highest sports participation, increases the external validity of the present study in comparison to previous studies covering the age range of 4-21)[7,10–12]. All participants played sports at least once weekly. This may have led to an overestimation of (sports) injuries and bleeds when compared to all Dutch PWH. The risk of Selection bias is considered low as 68% of Dutch PWH play sports[6].

Sports participation and injury data were compared to the Dutch male GP (aged 6-50y)[26]. These data were collected with a 3-month recall period, increasing the risk of recall bias[30], potentially causing an underestimation of the number of sports injuries and the increased difference between PWH and GP in the mean number of sports injuries according to exposure. Due to the nature of the GP data, data were only matched for sex and age (range 6-49) while matching for sports characteristics was impossible. Although people without bleeding disorders do suffer from bleeds with sports injuries, bleeding data was unavailable for the GP and could not be compared[26,27].With the outbreak of the COVID-19 pandemic, inclusion of participants was prematurely halted in March 2020. Combined with the low number of injuries and bleeds, this has limited the power of the present study, especially regarding the issue of bleeding risk following HR sports. But we can recommend to ensure that clotting factor levels are >10% during sports to minimize bleeding risk. The imposed restrictions by the Dutch government in March 2020 led to a change in sports participation, especially in HR sports[28], and a decrease in the number of sports injuries and SIBs. As most sports injuries and SIBs occurred during HR sports, this could have led to an underestimation of the true number of sports injuries during this period of restricted sports participation. However, a sensitivity analysis showed similar proportions of SIBs and SIBs/1000hrs due to HR sports before and after COVID restrictions.

In absence of a formal definition, an SIB was defined as a bleed occurring during or immediately after a sports injury with similar symptoms as a regular bleed and the need for extra clotting factor substitution. Participants were asked to interpret their complaints and assess whether this was an SIB or not, the hemophilia treatment center was only consulted in a minority (31%) of sports injuries. PWH have shown to regularly misinterpret musculoskeletal complaints as (sports) injuries or (joint) bleeds[31], potentially leading to over reporting of sports injuries and SIBs, which could explain the higher injury rate in people with severe hemophilia. Given the lack of direction in this misinterpretation, this could be either an over- or underestimation[31].

Comparison with other studies

To date, a limited number of studies has been published about sports injuries in people with hemophilia up to 20 years[7,10–12]. The only prospective study to date reported a transient increased bleeding rate in the first 8 hours after vigorous exercise in 104 Australian boys with moderate or severe hemophilia (aged 4-18; 86% on prophylaxis). As in the present study, these authors stated that most bleeds were not associated with physical activity, although without providing details[10]. In addition, two retrospective studies in American boys with hemophilia (N=48 and N=37) failed to identify an association between (high-intensity) sports participation and bleeding risk[11,12].. A previous, retrospective study in 102 Dutch boys (aged 6-18; 55% on prophylaxis) reported similar injury rates across hemophilia severity, which was similar to the GP as well[7]. Our data corroborate those of a recent nationwide study reporting overall and HR sports participation in Dutch PWH (n=650) and the GP (N=12565)[6].

Regarding optimum protective factor levels during sports, The findings of this study seem to corroborate a previous study, who concluded that bleeds were rare in PWH with factor levels of at least 10-15%[32], and recommended factor levels over 15 IU/dl for sports activities[33].

Clinical relevance and future directions

Although sports participation in PWH has increased with improved treatment options, the debate around sports participation and bleeding risk in PWH remains. This study contributes to this debate by showing that only 31% of bleeds were sustained during sports and 16% of participants sustained an SIB during follow-up. Most importantly, the multivariable regression identified factor levels at the time of injury as the most important determinant of developing a SIB/bleed: with an OR of 0.93, the risk of an SIB decreased by 7% for every 1% increase in FVIII/FIX level activity. From a clinical perspective, factor levels are unlikely to explain all observations. However, they remain the primary candidate for intervention. The finding that factor levels over 10% were associated with a 50% lower bleeding risk could potentially be extrapolated to future treatment options such as non-replacement therapy (e.g. emicizumab®)[34]. We have no direct observations of emicizumab, as all participants used replacement therapy, and *only* one switched to emicizumab® after 11 months of follow-up, making a comparison impossible.

Regarding prophylactic replacement therapy, it is important to note that PWH reached considerable factor levels (35-52 IU/dl) after prophylactic infusion, suggesting that adequate timing of prophylaxis is sufficient to cover sports participation. Future studies may focus on bleeding during high-risk sports, and non-replacement therapy.

Until then, the present results do suggest significant protection reached at minimum FVIII activity levels of 10%, suggesting limited benefits of infusing FVIII before sports in patients using emicizumab. A more precise analysis of bleeding risk according to FVIII/IX level during sports should include the varying factor levels during prophylaxis, with repeated assessment of each sports exposure and clotting factor level at the time of sports exposure. For this purpose, an RTTE analysis is currently being performed[35].

Conclusions

This first-time study assessed sports injuries and SIBs in children and adults with hemophilia and compared this to sports injuries in the GP. Participants with hemophilia did not report more sports injuries than the GP. Higher factor levels at the time of injury were associated with a lower risk of SIBs. Clinicians and PWH can use this result to aim for appropriate factor levels during sports and to inform patients, caregivers and other peers about the risks and benefits of sports participation, in particular in those using prophylaxis.

References

1. Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;(May):1-158. doi:10.1111/hae.14046
2. Pulles AE, Mastbergen SC, Schutgens REG, Lafeber FPJG, van Vulpen LFD. Pathophysiology of hemophilic arthropathy and potential targets for therapy. *Pharmacol Res*. 2017;115:192-199. doi:10.1016/j.phrs.2016.11.032
3. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour.*; 2020. https://apps.who.int/iris/bitstream/handle/10665/325147/WHO-NMH-PND-2019.4-eng.pdf?sequence=1&isAllowed=y%0Ahttp://www.who.int/iris/handle/10665/311664%0Ahttps://apps.who.int/iris/handle/10665/325147
4. Anderson A, Forsyth A. *Playing It Safe: Bleeding Disorders, Sports and Exercise*. National Hemophilia Foundation; 2017. doi:10.1136/jech.2007.061960
5. Groen WG, Takken T, van der Net J, Helders PJM, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. *Haemophilia*. 2011;17(5):906-912. doi:10.1111/j.1365-2516.2011.02555.x
6. Versloot O, van Balen EC, Hassan S, et al. Similar sports participation as the general population in Dutch persons with haemophilia; results from a nationwide study. *Haemophilia*. 2021;27:876-855. doi:10.1111/hae.14366
7. Versloot O, Timmer MA, de Kleijn P, et al. Sports participation and sports injuries in Dutch boys with haemophilia. *Scand J Med Sci Sports*. 2020;30(7):1256-1264. doi:10.1111/sms.13666
8. van Mechelen W, Hlobil H, Kemper HCG. Incidence, Severity, Aetiology and Prevention of Sports Injuries: A Review of Concepts. *Sport Med*. 1992;14(2):82-99. doi:10.2165/00007256-199214020-00002
9. Emery CA. Risk Factors for Injury in Child and Adolescent Sport: A Systematic Review of the Literature. *Clin J Sport Med*. 2003;13(4):256-268. doi:10.1136/bjsports-2014-094372
10. Broderick CR, Herbert RD, Latimer J, et al. Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia. *JAMA J Am Med Assoc*. 2012;308(14):1452-1459. doi:10.1001/jama.2012.12727. eTable
11. McGee S, Raffini L, Witmer CM. Organized sports participation and the association with injury in paediatric patients with haemophilia. *Haemophilia*. 2015;21(4):538-542. doi:10.1111/hae.12696
12. Ross C, Goldenberg N, Hund D, Manco-Johnson MJ. Athletic participation in severe hemophilia: bleeding and joint outcomes in children on prophylaxis. *Pediatrics*. 2009;124(5):1267-1272. doi:10.1542/peds.2009-0072
13. Aaron DJ, Kriska AM, Dearwater SR, et al. The epidemiology of leisure physical activity in an adolescent population. *Med Sci Sports Exerc*. 1993;25(7):847-853.
14. Kriska AM, Knowler WC, LaPorte RE, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. *Diabetes Care*. 1990;13(4):401-411. doi:10.2337/diacare.13.4.401
15. Tonoli C, Heyman E, Roelands B, Georges B, Berthoin S, Meeusen R. Validation and reliability of the Dutch language version of the Modifiable Activity Questionnaire in healthy subjects. *Sport Sci Health*. 2013;9(3):139-144. doi:10.1007/s11332-013-0160-y
16. Fischer K, de Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: Exploring reliability and validity. *Haemophilia*. 2013;19(6):944-950. doi:10.1111/hae.12197
17. Feldman BM, Funk SM, Bergstrom BM, et al. Validation of a new pediatric joint scoring system from the international hemophilia prophylaxis study group: Validity of the hemophilia joint health score. *Arthritis Care Res*. 2011;63(2):223-230. doi:10.1002/acr.20353
18. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res*. 1980;(149):153-159. http://www.ncbi.nlm.nih.gov/pubmed/7408294
19. Sluiter D, Foppen W, de Kleijn P, Fischer K. Haemophilia joint health score in healthy adults playing sports. *Haemophilia*. 2014;20(2):282-286. doi:10.1111/hae.12290
20. Timmer MA, Veenhof C, de Kleijn P, de Bie RA, Schutgens REG, Pisters MF. Movement behaviour patterns in adults with haemophilia. *Ther Adv Hematol Adv Hematol*. 2020;11:1-9. doi:10.1177/https
21. Valkenet K, Veenhof C. Validity of three accelerometers to investigate lying, sitting, standing and walking. *PLoS One*. 2019;14(5):1-9. doi:10.1371/journal.pone.0217545

22. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 compendium of physical activities: A second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581. doi:10.1249/MSS.0b013e31821ece12

23. van Vulpen AV. *Sport for All: Sports Injuries and Their Prevention.* Council of Europe, Nationaal instituut voor Sportgezondheidszorg; 1989.

24. Phillips L. Sports injury incidence. *Br J Sports Med*. 2000;34:133-136. doi:10.1136/bjsm.34.2.133

25. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672

26. National Institute for Public Health and the Environment (RIVM), Dutch Consumer Safety Institute (VeiligheidNL) in collaboration with Statistics Netherlands. *Additional Module Physical Activity and Accidents/Lifestyle Monitor.* 2019. https://www.rivm.nl/leefstijlmonitor/onderzoeksbeschrijvingen-lsm/a-bewegenenongevallen

27. Stam C, Valkenberg H. *Sportblessures in Nederland - Cijfers 2019.*; 2020. https://www.veiligheid.nl/.ibmmodres/domino/OpenAttachment/veiligheid/website.nsf/8AB1F5320A6EEB1BC1258640005808F4/asset/Cijferrapportage Sportblessures 2019.pdf

28. Versloot O, van der Net J, Fischer K. Sports participation of patients with haemophilia in the COVID-19 era: The Dutch experience. *Haemophilia*. 2021;27(2):e295-e297. doi:10.1111/hae.14189

29. RStudio Team. RStudio: Integrated Development for R. Published online 2020. www.rstudio.com

30. Clarke PM, Fiebig DG, Gerdtham UG. Optimal recall length in survey design. *J Health Econ*. 2008;27(5):1275-1284. doi:10.1016/j.jhealeco.2008.05.012

31. Ceponis A, Wong-Sefidan I, Glass CSS, von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. *Haemophilia*. 2013;19(5):790-798. doi:10.1111/hae.12175

32. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: The association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17(1):41-44. doi:10.1111/j.1365-2516.2010.02383.x

33. Seuser A, Boehm P, Kurme A, Schumpe G, Kurnik K. Orthopaedic issues in sports for persons with haemophilia. *Haemophilia*. 2007;13(SUPPL. 2):47-52. doi:10.1111/j.1365-2516.2007.01507.x

34. Kizilocak H, Marquez-Casas E, Malvar J, Carmona R, Young G. Determining the approximate factor VIII level of patients with severe haemophilia A on emicizumab using in vivo global haemostasis assays. *Haemophilia*. 2021;27(5):730-735. doi:10.1111/hae.14359

35. Guo Z, Gill TMM, Allore HGHG. Modeling repeated time-to-event health conditions with discontinuous risk intervals: An example of a longitudinal study of functional disability among older persons. *Methods Inf Med.* 2008;47(2):107-116. doi:10.3414/ME0478

Supplemental Material

Supplemental table S1: Collected data in case of injuries or bleeds.

Patient number	Study ID
Severity	Severe, moderate, mild
Date injury	Date and time
Days after inclusion	Calculated
Age at injury	Calculated
Location	Anatomical location
Side	Left / right
Structure	Bone / ligament / muscle / joint / skin / tendon / other
Specific diagnosis	Free text
Mechanism	Distortion / fall from height / fall after jump / other fall / bump / hit by object / bodily contact / overuse / fatigue / other / unknown
Origin?	Acute / chronic
During Sports?	Yes / no
Which sports?	Free text
NHF category	1 / 1,5 / 2 / 2,5 / 3
During game or training?	Game / training
Bleed?	Yes / no
Sports-Induced Bleed?	Yes / no
Timing last prophylaxis	Date and time
Number of days since last prophylaxis	Calculated
Number of hours since last prophylaxis	Calculated
Medical assistance?	Yes / no
Treatment	None / extra prophylaxis / physiotherapy / rest / surgery / immobilisation / other
Contact with HTC?*	Yes / no
Recurring injury?	Yes / no
When last injury?	Date
Date recovered	Date
Time loss	Number of days since injury

*: HTC = Hemophilia Treatment Centre

Supplemental table S2: Definitions and characteristics of various bleeds in people with hemophilia25

Joint Bleed	An unusual sensation 'aura' in the joint, in combination with any of the following: (a) increasing swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline.
Soft-tissue/Muscle Bleed	An episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and loss of movement over baseline.
Re-bleed	A bleed occurring within 72 hours after stopping treatment for the original bleed for which treatment was initiated.
Sports-induced Bleed	A bleed occurred during (or immediately after) a sports action, with identical symptoms to a (joint/muscle/soft tissue) bleed that required (immediate) extra treatment with clotting factor concentrate or consultation with a hemophilia consultant.

Supplemental Table S3: Participant characteristics of a sub selection of the general population (male sports participants aged between 6 and 50)[26]

	Overall	Children	Adults
Number	**2072**	**645**	**1427**
		Median (IQR)	
Age (yrs)	26 (15-38)	12 (8-14)	33 (25-42)
Height (cm)	174 (170-186)	154 (138-174)	183 (178-187)
Weight (kg)	75 (60-86)	42 (30-60)	81 (74-90)
BMI (kg/m^2)	22.9 (19.6-25.5)	17.8 (15.8-20.1)	24.3 (22.3-26.6)
Overweight	658 (32%)	73 (12%)	585 (41%)

Supplemental table S4a: Sports injury incidence in people with hemophilia during each 3-month' period of the 12-month' follow-up.

	Number of sports injuries	% (CI)	Number of SIB	% (CI)
First 3-month' period of follow-up	22	18% (12-25)	8	6% (3-12)
Second 3-month' period of follow-up	15	12% (7-19)	4	3% (1-8)
Third 3-month' period of follow-up	20	16% (11-24)	8	6% (3-12)
Fourth 3-month' period of follow-up	16	13% (8-20)	6	5% (2-10)

PWH showed similar distribution in sports injuries (p=0.77) and SIBs (p=0.55) over 3-month' period

Supplemental table S4b: Sports injury incidence in people with hemophilia during annual season of the 12-month' follow-up.

	Between-season comparison			
	Number of sports injuries	% (CI)	Number of SIBs	% (CI)
Winter (21/12 – 20/3)	22	25% (17-35)	7	27% (13-46)
Spring (21/3 – 20/6)	20	23% (15-33)	7	27% (13-46)
Summer (21/6 – 20/9)	23	26% (18-37)	7	27% (13-46)
Fall (21/9- 20/21)	22	25% (17-35)	5	19% (8-38)

PWH reported no seasonal effect of sports injuries (p=0.25) and SIBs (p=0.84) during follow-up.

Table S5: Most frequently reported sports injury locations in people with hemophilia and the general population.

	GP	PWH	Severe	Non-severe	p[1]
n	**2072**	**125**	**59**	**66**	
Upper and lower leg	58 (14%)	26 (30%)	17 (28%)	9 (33%)	0.42*
Ankle	55 (13%)	20 (23%)	14 (23%)	6 (22%)	
Knee	85 (20%)	11 (13%)	7 (12%)	4 (15%)	
Foot	42 (10%)	7 (8%)	6 (10%)	1 (4%)	

*: the overall distribution of injury locations was similar in participants with severe and non-severe hemophilia.

Supplemental table S6: Risk factors for sports-induced bleeds following a sports injury: results of a logistic regression model

	Odds Ratio	Confidence interval	p
Age (yrs)	1.01	0.95-1.06	0.84
Hemophilia Severity	0.62	0.20-1.89	0.40
Estimated factor level at time of injury	0.93	0.88-0.98	**0.02**
HJHS≥4	1.63	0.51-5.29	0.41
Injury during HR sports	1.49	0.50-4.42	0.47
Injury during high-intensity sports	0.57	0.21-1.56	0.27
Total annual sports exposure	1.00	0.99-1.00	0.82

Estimated factor level at time of injury was the online significant determinant for developing an SIB following a sports injury.

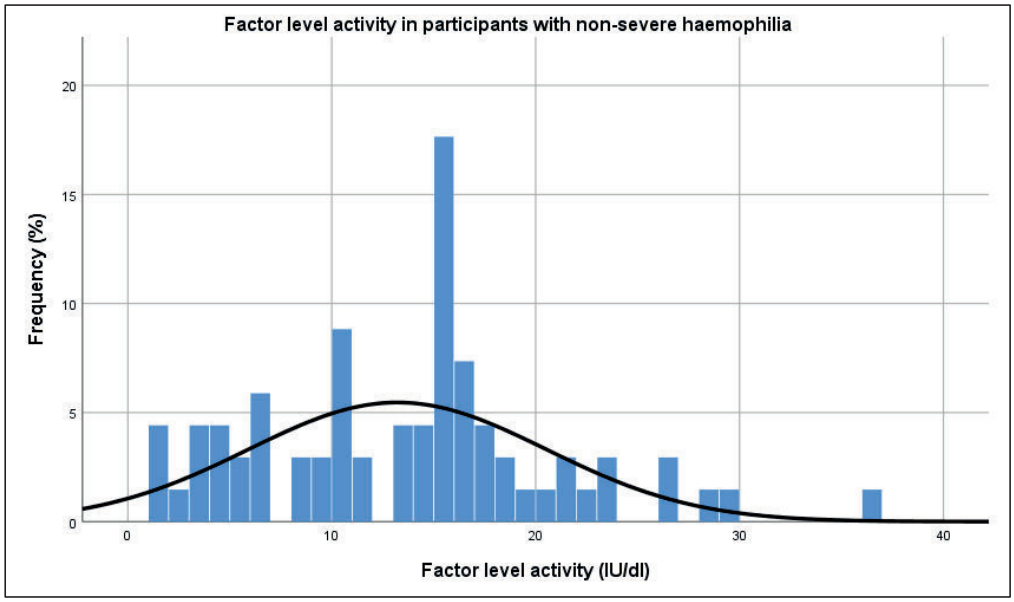


Figure S1: distribution of factor level activity in participants with non-severe hemophilia. Median factor level was 15 IU/dl (IQR 8-16).

CHAPTER 8

Can motor proficiency testing predict sports injuries and sports-induced bleeds in people with haemophilia?

O. Versloot[1,2], J. Blokzijl[1], M.A. Timmer[1], M.D. Schuuring[3], K.P.M. van Galen[1], I.C.L. Kremer Hovinga[1], P.R. van der Valk[1], L.F.D. van Vulpen[1], R.E.G. Schutgens[1], C.F. van Koppenhagen[4], J. van der Net[3] and K. Fischer[1]

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

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science, Utrecht, the Netherlands

[3] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, University Medical Center, Utrecht, The Netherlands.

[4] Erasmus Medical Center, Rotterdam, The Netherlands

Currently under review for Haemophilia

Bullet Points

What is already known:

- Independent of haemophilia, increased sports participation is associated with increased injury risk.
- Balance, strength and speed tests are widely used in sports to identify participants at risk for injuries.

What this study adds:

- Few (15%) of 125 participants playing sports had poor results on motor proficiency and endurance testing.
- 41% of participants reported sports injuries and 16% reported sports-induced bleeds
- Tests of Running Speed & Agility, Balance, Strength and Endurance could not predict sports injuries or sports-induced bleeds in active people with haemophilia.

Abstract

Introduction: Predicting the risk of sports injuries and sports-induced bleeds (SIBs) in people with haemophilia (PWH) may support clinical counselling.

Aim: assess the association between motor proficiency testing and sports injuries and SIBs and to identify a specific set of tests for predicting injury risk in PWH.

Methods: In a single centre, prospective study male PWH aged 6-49 playing sports ≥1x/week were tested for Running Speed & Agility, Balance, Strength and Endurance. Test results below -2Z were considered poor. Sports injuries and SIBs were collected for 12 months while 7 days of physical activity (PA) for each season was registered with accelerometers. Injury risk was analysed according to test results and type of physical activity (%time walking, cycling, running). Predictive values for sports injuries and SIBs were determined.

Results: Data from 125 PWH (mean (±SD) age: 25 (±12), 90% haemophilia A; 48% severe, 95% on prophylaxis, median factor level: 2.5 (IQR 0-15)IU/dl) were included. Few participants (n=19, 15%) had poor scores. Eighty-seven sports injuries and 26 SIBs were reported. Poor scoring participants reported 11/87 sports injuries and 5/26 SIBs. The current tests were poor predictors of sports injuries (range PPV: 0-40%,) or SIBs (0-20%). PA type was not associated with season (seasonal p values >0.20) and type of PA was not associated with sports injuries or SIBs (Spearman's rho<0.15).

Conclusion: These motor proficiency- and endurance tests were unable to predict sports injuries or SIBs in PWH, potentially due to few PWH with poor results and low numbers of sports injuries and SIBs.

Introduction

Haemophilia is an inherited haematological condition with impaired coagulation caused by a lack of clotting factor VIII (haemophilia A) or IX (haemophilia B)[1]. People with haemophilia (PWH) specifically suffer from bleeding in muscles and joints, leading to joint destruction in the absence of proper treatment[2]. Current treatment consists of regularly self-infusing clotting factor concentrate to prevent and/or treat bleeding, although non-replacement therapy has recently been introduced[3].

Regular physical activity is promoted by the World Health Organization for both healthy people and people with chronic conditions, such as haemophilia[4,5]. Despite established health benefits, sports participation in PWH has been discouraged for decades to minimize bleeding risk. Recently, awareness about the importance of exercise on joint stability and prevention of joint bleeds has increased. Nowadays, PWH under adequate prophylactic treatment have become as active in sports as the general population, including contact sports such as soccer or field hockey [6,7]. Independent of haemophilia, an increased sports participation leads to a higher injury risk[8,9], with a risk of SIB being of particular concern in PWH as well as the long term effects of (joint) bleeds[2]. In order to prevent sports injuries and SIBs, identifying risk factors is clinically important. PWH may benefit from a sports injury prevention approach including prophylaxis and careful examination of the patients' physical fitness and physical activity levels[10].

A proposed model of injury causation for sports injuries specific for PWH (including joint status, adherence and factor levels at time of injury) is shown in Figure 1 [11,12]. This model includes modifiable internal and external risk factors. Especially internal risk factors may be modified by haemophilia treatment and/or specific preventive training. Most existing test protocols and prevention programmes (such as the FIFA 11+ in soccer) focus on reducing the internal risk factors for sports injuries by improving balance, strength, power, range of motion (ROM) and endurance [9,13–20]. However, such sports injury risk test protocols have not been established for PWH so far.

Before implementing a sports injury assessment protocol, its clinical relevance should be determined by assessing the predictive value of selected tests in the desired population. In a population of PWH, predicting sports-induced bleeds (SIBs) is of particular interest.

Therefore, the aim of this study was to assess the clinical relevance of motor proficiency, endurance tests and type of physical activity to predict sports injuries and SIBs in a cohort of PWH actively involved in physical activity and sports.

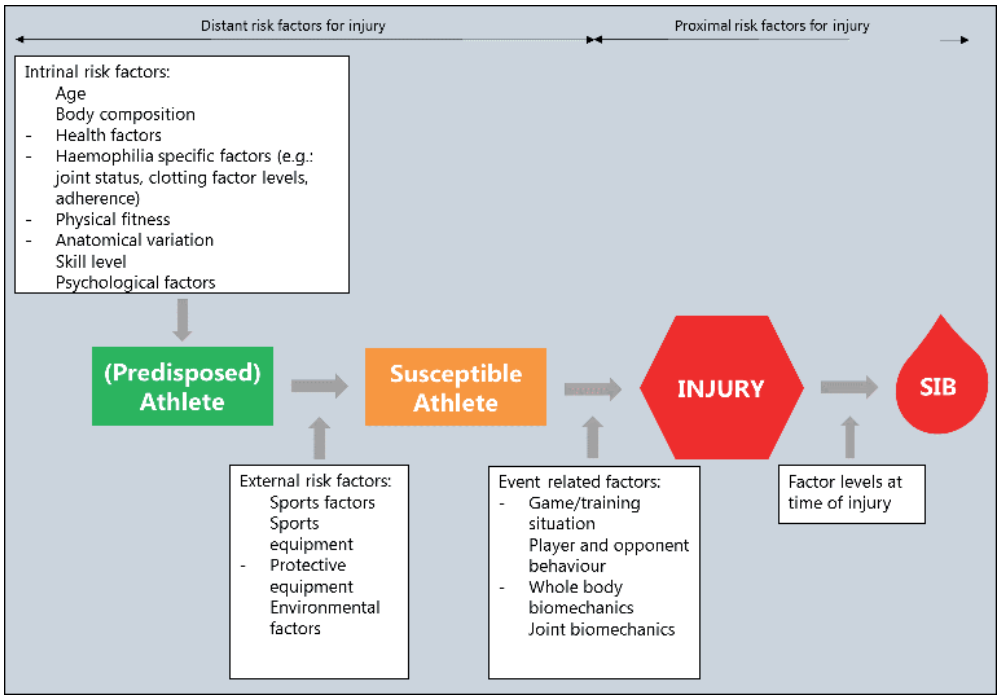


Figure 1: an example of a comprehensive model for injury causation showing potential internal and external risk factors for the occurrence of sports injuries and sports-induced bleeds. Adapted specifically for people with haemophilia from Bahr & Krosshaug (2005) to include haemophilia specific risk factors[12]

Methods

Methods and setting

This study was performed as part of the "Sports Participation and Injuries in People with Haemophilia" (SPRAIN) study, a single-centre, prospective longitudinal study and was performed at the Van Creveldkliniek of the UMC Utrecht.

The study was approved by the Internal Review Board of the UMC Utrecht (approval number: 18-141). All participants signed informed consent prior to participating in the study. In case of children, both parents or caregivers provided informed consent.

All participants were included between October 2018 and March 2020, when inclusion was discontinued prematurely due to the COVID-19 lockdown. Follow-up was 12 months. After baseline testing, participants were contacted every two weeks to record injuries

and bleeds. The study was registered in the Dutch trial register (www.trialregister.nl) under trial ID NTR6769.

Participants

PWH aged 6-49 at inclusion, who participated in sports at least once weekly were invited to participate in the study. The presence of FVIII/FIX antibodies, an arthrodesis or arthroplasty within the last 12 months or neurological disabilities were exclusion criteria for participation. All haemophilia severities were included.

Data collected

Baseline testing consisted of motor proficiency and endurance tests. Motor proficiency was assessed by means of selected domains of the Bruininks-Oseretsky Test 2 (BOT-2®)[21,22]. The BOT-2 was developed to assess motor proficiency in children and has been validated in various populations[23–25]. It consists of 8 domains: fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance, running speed&-agility, upper-limb coordination and strength. A composite score can be calculated when all domains of the BOT-2 are tested. However, not all domains were considered clinically relevant to assess sports injury risk, especially in a population active in contact sports. The domains balance (single-leg stance, single-leg stance on balance beam, heel-to-toe stance on balance beam), strength (push-ups, sit-ups, wall sit) and running speed & agility (standing long jump, single leg hop, single leg side hop, two legged side hop) were selected for this study based on their expected clinical relevance. Running speed & agility was used as a proxy for lower extremity power (fast/explosive development of speed). The tests were conducted according to protocol of the BOT-2® test[26]. The other domains were excluded as these were not considered relevant for prediction of sports injuries and SIBs. The results of the tests in the various domains ('balance', 'running speed & agility' and 'strength') were grouped. If a participant had a 'poor' score on one of the individual tests of the domain, the entire domain was classified as 'poor'. Predictive performance of the motor proficiency tests was evaluated by means of the positive and negative predictive values (PPV and NPV, respectively) for the motor proficiency tests. A positive predictive value is calculated as the proportion of participants with a sports injury or SIB divided by the number of participants with poor test results. A negative predictive value is calculated as the number of participants with no sports injury or SIB divided by the number of participants with a poor test result. PPV and NPV were calculated separately for sports injuries and SIBs and for poor and average-to-good results.

Based on its performance in both children and adults with chronic conditions, endurance was assessed by the steep-ramp test[27–31]. The test was performed according to the

protocol described previously for adults[30] and children[31]. The test ended when a participant was no longer able to maintain the required pedalling frequency despite strong verbal encouragements, or due to any physical complaints from the participant (nausea, dizziness, etc.). Peak work load and peak heart rate were recorded. Peak work load was defined as the resistance at the moment pedalling frequency dropped below 60 rpm. Peak heart rate was defined as the maximal attained heart rate during the test. An effort was considered to be maximal when participants showed subjective signs of intense effort (e.g., unsteady biking, sweating, facial flushing, clear unwillingness to continue despite strong verbal encouragement)[31].

Following inclusion and baseline testing, Injuries and bleeds were prospectively collected during a 12-months' follow-up. Participants were contacted by the researcher every two weeks by their preferred method to check if any injuries had occurred during the previous two weeks. In case of an injury or bleed, the researcher would call the participant to record the details of the injury on a standardized form (see supplemental table S1 for details).

A *sports injury* was defined as "any injury as a result of participation in sport with one or more of the following consequences: (a) a reduction in the amount or level of sports activity; (b) a need for (medical) advice or treatment; or (c) adverse social or economic effects"[32].

Bleeds were classified according to the ISTH definition [33]. Definitions are shown in Supplemental table S2. A bleed was considered a *sports-induced bleed* when the bleed occurred as a result of a sports injury, had identical symptoms to a bleed and required extra infusion of clotting factor concentrate or consultation with a haemophilia consultant.

Sports injury risk was classified according to the National Hemophilia Federation (NHF) classification. The NHF used 5 categories to classify injury risk in sports (1: safe; 1.5: safe to moderate risk; 2: moderate risk; 2.5: moderate to high risk; 3: high risk). Sports in the highest two categories (e.g.: soccer, hockey) were considered high-risk sports. Sports injury mechanisms were subdivided in "intrinsic"(physical fitness, limited skills), "extrinsic" (equipment, protective equipment, environment) and "other" to enable analysing the source of the injury or SIB[12].

Physical activity was measured using an Activ8® (Activ8, Valkenswaard, The Netherlands) 3-axial accelerometer (30x32x10 mm; 20 gram) for 24 hours per day for 7 days, with a minimum of 4 consecutive days containing data days to be included for analysis. Data

are presented as proportion of 24 hours. The Activ8 is a valid, accurate tool to assess physical activity[34–36] and has been used in a wide array of medical conditions, including people with haemophilia [37]. The Activ8 is worn on the thigh and can distinguish lying, sitting, standing, walking, running and cycling, both in time and energy expenditure. Participants were asked to wear the Activ8 continuously for 7 days. For this purpose, the Activ8 was attached to the right upper thigh with a waterproof, transparent Tegaderm® self-adhesive plaster (see supplemental figure 1). Time spent lying, sitting, standing and walking were reported in hours/day, running and cycling were reported in minutes/day. Time spent lying, sitting and standing was classified as "passive activities". Walking, running and cycling were classified as "dynamic activities".

An interim analysis on complete data (4 weeks of ≥4 days of data) of 15 participants showed similar types of physical activity between the various seasons for all activities as measured by the Activ8 (Lying: p=0.55 Sitting: p=0.20; Standing: p=0.29; Walking: p=0.85; Cycling: p=0.63; Running: p=0.46). In order to minimize demands of the participants, data was only collected for one week in subsequent participants.

Statistics

Descriptive injury data were presented as medians and interquartile ranges (IQR) and/or proportions with 95% confidence intervals (95%CI), as appropriate. Z-scores were computed for each domain tested. A score of Z<-2 was considered a 'poor' score, a score of Z>2 was considered a 'good' score. Scores between -2 and 2 were considered 'average'. Data were analysed with (non-)parametric techniques, depending on the distribution of the data. This was done for separately for children and adults. Participants with moderate and mild haemophilia were grouped as "non-severe" due to the low number of participants with moderate haemophilia in this study.

Outcomes were compared with non-parametric Spearman, Chi Square and Mann-Whitney tests, as appropriate. A p-value<0.05 was considered statistically significant. Sports participation changed as a result of COVID-19 restrictions in the Netherlands, especially from high-risk team sports (e.g.: soccer) to low-risk individual sports (running and walking) [38]. Therefore, an additional analysis was performed in which the number of sports injuries and SIBs as well as predictive test results before and during COVID-19 restrictions were compared. An additional analysis was performed to assess the predictive values in soccer, as this was the most frequently reported sports.

The online electronic data capturing tool CASTOR was used to collect, record and store patient characteristics, injury data and test results[39]. The statistical analysis was performed using SPSS statistical software, version 26 (IBM corp., Armonk, NY).

Data sharing statement

External parties can have access to the data upon reasonable written request to the investigators.

Results

Participants

Test results, injury- and bleeding data from 125 participants (41 children (median age: 13 (IQR 10-16), 84 adults (30 (IQR 23-39)) were collected for this study. Table 1 shows participant and treatment characteristics. Most participants had haemophilia A (90%) and almost half had severe haemophilia (47%). Nearly all participants with severe haemophilia (95%) received prophylactic replacement therapy at a median weekly treatment dose of 42 (A: 42; B: 52) IU/kg. All participants had a complete, 12 months' follow-up. Sports participation decreased during the COVID-19 pandemic, and shifted from high-risk team sports (e.g. soccer) to low-risk individual sports (e.g.: running and fitness) [38]. Only a minority (39/125; 31%) contacted the haemophilia treatment centre in case of a suspected sports injury or bleed.

Table 1: Participant, disease, treatment characteristics and joint health of participants with haemophilia

N=125	overall	severe	non-severe
	N (%), or median (IQR)		
Number	125	60	65
Age (yrs)	23,1 (15,9-33,7)	23,0 (15,8-34,1)	23,8 (16,1-33,1)
Haemophilia A	112 (90%)	54 (92%)	58 (88%)
Baseline factor activity (%IU)	2 (0-15)	0 (0-0)	14,5 (8,3-16,8)
Severe haemophilia	59 (47%)	-	-
Prophylactic treatment	61 (49%)	56 (95%)	5 (8%)
Prophylactic dose IU/kg/week	42,3 (35,8-55,1)	42,0 (35,2-55,1)	52,0 (39,1-73,7)
History of anti FIVIII/IX antibodies*	17 (14%)	14 (82%)	3 (18%)
	Sports Participation		
Annual sports exposure (hrs/yr)	146 (65-227)	156 (77-250)	144 (64-220)
High-risk sports	74 (59%)	41 (69%)	33 (50%)
Energy Expenditure (METs-hrs/wk)	19.4 (8.1-34.6)	16.6 (7.9-34.6)	21.7 (8.1-34.6)
High-intensity sports	25 (20%)	12 (20%)	13 (20%)
Follow-up before COVID	27 (22%)	22 (81%)	5 (19%)
Follow-up during COVID	98 (78%)	38 (39%)	60 (61%)

*: People with haemophilia under prophylactic treatment sometimes develop antibodies against FVIII/FIX concentrates.

Sports participation, sports injuries and sports-induced bleeds

All participants were involved in sports at least once weekly (median annual exposure: 146 (IQR 65-227) hrs), an overview of all reported sports is shown in supplemental table S3. Participants were engaged in 43 sports, including 74/125 (59%) in high-risk sports (see supplemental figure 2 for the distribution of NHF risk categories). Adults were mostly engaged in fitness (29%), running (16%) and soccer (8%); children mostly played soccer (40%), fitness (7%) and gymnastics (4%). A total of 87 sports injuries were reported by 51 (41%) participants, of which 26 (20 participants; 16%) resulted in SIBs, indicating a very low risk for SIBs during sports. During COVID-19 restrictions, Participants reported more injuries (median 1 (IQR 1-2) vs. 0 (IQR 0-1); p<0.01) but similar SIBs (0 (IQR 0-0) vs. 0 (IQR 0-1); p=0.09).

Testing

Motor proficiency levels

Figure 2 and supplemental table S4 show the distribution of the standardised individual test results. Only a minority of the participants reported poor motor proficiency scores (below -2Z): over 90% (mean: 96%±1.6) of participants had average-to-good scores (all score higher than -2Z) on all tests. Standing on 1 leg with eyes open most frequently scored as 'poor' (7%).

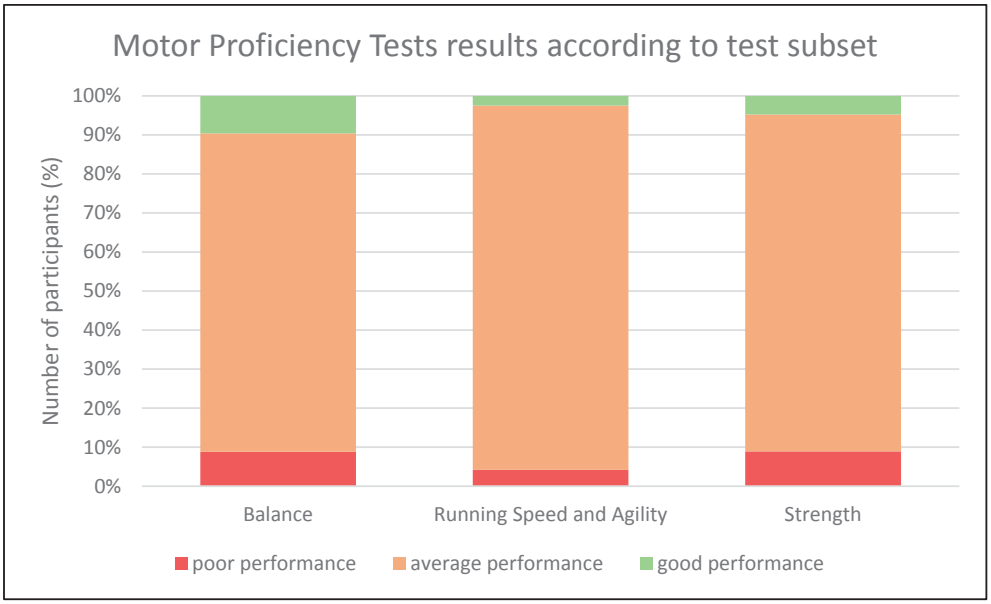


Figure 2: Motor proficiency test results according to BOT-2® subset. The majority of participants showed an average score on the composite test groups 'balance', 'running speed & agility' and 'strength'. Only a minority (2.5%) had a poor performance.

Endurance

A total of 123 participants completed the Steep Ramp Test for endurance. One participant was unable to perform the test due to limited range of motion in the knee, the other had an unusually high heart rate before starting the test. This test was subsequently cancelled. Median maximal workload was similar in children and adults (children: 4.9 W/kg (IQR 4.3-5.6); adults: 4.9 W/kg (IQR 4.3-6.0)), corresponding to an estimated median VO_2-max of 2.2 (IQR 1.5-3.0) in children and 3.0 (IQR 2.9-3.4) in adults. Only 2 participants (1.6%) scored "poor" on the endurance test. These participants reported no sports injuries or SIBs.

Sports injuries according to motor proficiency and endurance results

Table 2 shows the positive and negative predictive value (PPV and NPV, respectively) of the motor proficiency tests. Missing data were caused by physical impairments of the participants (limited ROM or painful joint). None of the tests could identify risk factors for sports injuries or SIBs. The PPV for sports injuries was below 50% for all domains (Balance: 36% (CI 15-68%); Running Speed & Agility: 40% (CI 12-77%); Strength: 27% (CI 9-57%); Endurance: 0% (CI 0-71%)), and SIBs (Balance: 9% (CI 0-40%); Running Speed & Agility: 20% (CI 2-64%); Strength: 18% (CI 4-49%); Endurance: 0% (CI 0-71%); see supplemental table S5). The wide confidence intervals reflect the low number of participants with low scores and the few reported sports injuries and SIBs. Injury mechanism was similar across PWH with poor scores (intrinsic: 8/19 vs. extrinsic: 8/19; 3/19 no injury; p=0.10). An intrinsic source had a limited PPV (sports injury: 38%; SIB: 25%). Although PPV during COVID-restrictions were higher than before COVID, they remained below 50% for all tests with very wide confidence intervals (see supplemental table S7).

Table 2: Predictive values for sports injuries and sports-induced bleeds according to motor proficiency and endurance

		Predictive value	
N=125	**n**	**Sports injuries**	**Sports-induced bleeds**
Balance			
Poor	11	PPV: 36%	PPV: 9%
Average-to-good	114	NPV: 59%	NPV: 83%
Running Speed & Agility			
Poor	5	PPV: 40%	PPV: 20%
Average-to-good	114	NPV: 59%	NPV: 85%
Strength			
Poor	11	PPV: 27%	PPV: 18%
Average-to-good	113	NPV: 58%	NPV: 84%
Endurance			
Poor	2	PPV: 0%	PPV: 0%
Average-to-good	120	NPV: 59%	NPV: 84%

PPV: positive predictive value, the number of participants who sustained a sports injury or sports-induced bleed with a poor test result (e.g.: 4 sports injuries in 11 poor results on balance tests: 4/11 = 0.36). NPV: negative predictive value, the number of participants who did not sustain a sports injury or sports-induced bleed after an average-to-good test result (e.g.: 47 sports injuries in 114 "average-to-good" scores on balance tests: NPV = (114-47)/114 = 0.59).

The large variation in sports (N=43, see supplemental table S3) and the range in test results, may have contributed to the low PPV of the various tests. Because soccer was the most frequently performed sport (n=39; high-risk sport), a subgroup analysis was conducted to determine the PPV and NPV for the tests in soccer players. Despite high PPV values for the motor proficiency tests in the soccer group (Balance: 67% (CI 20-94%); Speed & Agility: 100% (CI 29-105%)), the numbers of PWH with poor results and the number of reported sports injuries and SIBs were too low to provide a clinically relevant prediction, as reflected by the wide confidence intervals.

Physical activity

101 participants (81%) had sufficient physical activity data collected with an Activ8® activity tracker. Missing data was caused by malfunctioning equipment (n=22) or skin irritation from the device (n=2). Figure 3 shows the overall distribution of physical activity/24 hours and the distribution according to season and shows that no seasonal variation in physical activities was observed (Lying: p=0.55 Sitting: p=0.20; Standing: p=0.29; Walking: p=0.85; Cycling: p=0.63; Running: p=0.46).

Participants spent the majority of time sitting (51.5%) and only limited time in high-intensity activities (cycling and running combined: 1%). Overall, participants spent 90% (~22.5 hrs/day) in passive activities, of which median 23% (IQR 19-29%) lying (including

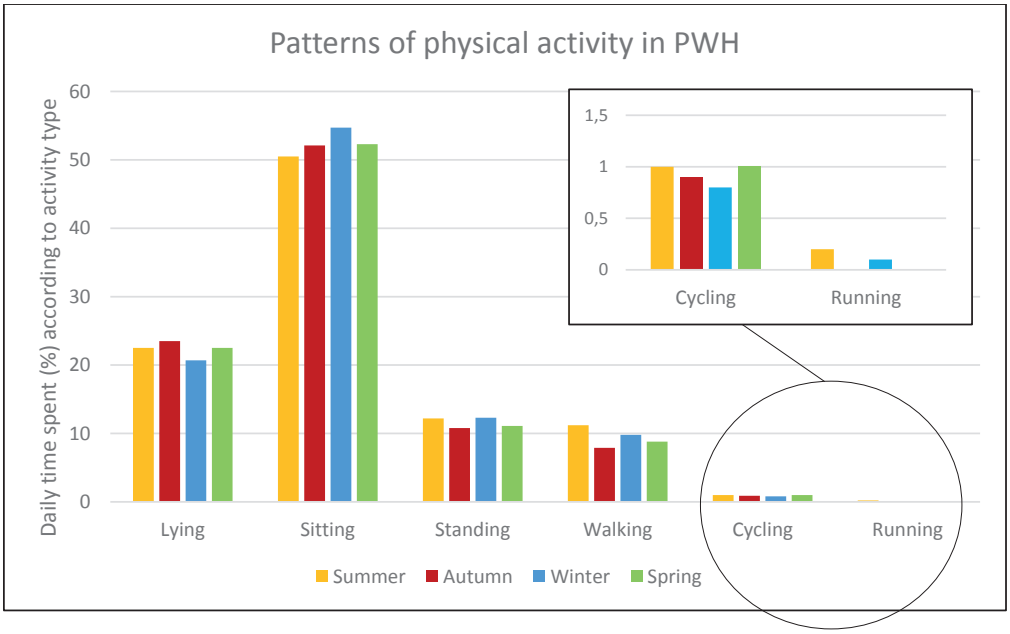


Figure 3: patterns of physical activity in people with haemophilia. No seasonal variation was observed in types of physical activity.

sleep) and only 10% in dynamic activities. Dynamic activities were similar in children and adults (median 12% (IQR: 10-16) vs. 10% (8-13); p=0.07), but children spent more time in high-intensity physical activity (cycling (1.6 vs. 0.6%; p<0.01) and running (0.3% vs. 0.08%; p<0.01) than adults.

Injuries and SIB according to physical activity

Sports injuries and SIBs were not associated with types of physical activity. Table 3 shows that the proportion of time spent in dynamic activity was similar in participants with sports injuries and those without sports injuries (10% (6-14) vs. 11% (8-14); p=0.21) and those with and without SIBs (9% (6-14) vs. 11% (9-14); p=0.25)). Neither was time spent in dynamic activities associated with the number sports injuries (Spearman's rho: 0.11; p=0.28) or SIBs (rho: 0.04; p=0.73).

Table 3: Sports injuries and sports-induced bleeds according to physical activity pattern as measured by Activ8® accelerometers

	Overall (median proportion (IQR))					
	Sports injury	**No sports injury**	**p**	**Sports-induced bleed**	**No sports-induced bleed**	**p**
Time spent in dynamic activities	10% (6-14%)	11% (9-14%)	0.21	9% (6-14%)	11% (9-14%)	0.25
	Children (median proportion (IQR))					
Time spent in dynamic activities	11% (7-16%)	13% (11-16%)	0.23	15% (8-18%)	12% (9-16%)	0.40
	Adults (median proportion (IQR))					
Time spent in dynamic activities	9% (6-14%)	10% (8-13%)	0.43	8% (5-11%)	11% (8-14%)	0.06

Discussion

Principal findings

This was the first study aiming to identify internal, physical risk factors (see figure 1) for sports injuries and sports-induced bleeds in PWH. The selected physical tests included tests of motor proficiency, endurance, and type of physical activity. Very few participants (n=19; 15%) had poor scores and/or sports injuries (n=51; 41%) or SIBs (n=20; 16%). In the current dataset motor proficiency testing, endurance and physical activity were unable to identify PWH with an increased risk of sports injuries or SIBs. Furthermore, the results indicated that types of physical activity levels showed no variation throughout the annual seasons.

Strengths and limitations

This was a 12-month prospective study assessing injury risk based on motor proficiency testing in PWH. As this study focused on sports injuries, only PWH active in sports were included. This makes the generalizability limited to active PWH and those aspiring to become active, which is the population at risk for sports injuries. Potential selection bias seemed limited as the majority (~70%) of Dutch PWH is active in sports[6,7].

The tests for this study were performed between October 2018 and March 2020, with a 12-month follow-up until March 2021. The COVID-19 pandemic and restrictions imposed in March 2020 caused a shift in sports behaviour in Dutch PWH, particularly from high-risk team sports (NHF categories 2.5 and 3) to low-risk individual sports (NHF 1, 1.5 and 2)[38,40]. This has potentially caused an underestimation of the true number of injuries, making it difficult to assess the predictive value of motor proficiency testing.

However, an additional analysis showed that although participants reported more injuries but similar SIBs after COVID-19 restrictions were imposed, the PPV remained similar for all tests.

Sports injuries and SIBs were self-reported. Only 31% of suspected SIBs were evaluated by a haemophilia physician. Although specific data is lacking, this was in line with clinical practice: most patients are on home treatment and only contact the treatment centre in serious situations.

The intense monitoring of injuries and bleeds might have increased the risk of over reporting of sports injuries and SIBs, potentially leading to an actual overestimation of the PPV of the test results. For bleeding episodes, it has been established that both physicians and PWH regularly misinterpret musculoskeletal complaints as (joint) bleeds and vice versa[41]. This is in line with clinical practice, and all SIBs presented here were treated as a true bleed.

Although both the PPV and NPV were calculated to evaluate the test results, the PPV seems to be more clinically relevant in this case. Unfortunately, clinical inference and interpretation are hampered by the wide confidence intervals on the PPV.

Comparison with other studies

No other studies were identified that used motor proficiency testing to predict sports injuries and SIBs in PWH. As this was a highly active population with an injury prevalence comparable to the general population[6,7], the outcome of the current study was compared to studies assessing injury risk with different tools in the general population.

The present study used specific components of the BOT-2 (Balance, Running Speed & Agility and Strength) to assess balance, power and strength. These data could be compared to those of previous studies assessing specific physical risk factors with similar constructs as the BOT-2 domains such as the Functional Movement Screen (FMS; balance, strength)[42,43], Star Excursion Balance Test (SEBT; balance)[44] or the Drop Jump Screening Test (DJST; balance, running speed & agility)[45].

In contrast to the present study, studies in the general population identified limited balance[17,46,47], poor strength[48], and poor endurance[20] as risk factors for sports injuries. This discrepancy could be due to the size and heterogeneity of our population in comparison with larger, more homogeneous groups (e.g. athletes in the same sports, soldiers) in other studies. In addition to increased statistical power based on study size, these populations potentially had a higher sports exposure with a concomitant higher

injury risk. Furthermore, differences in the tests used may have contributed to discrepancies in results.

Single leg stance was used as a proxy for balance. In contrast to the current study, it was identified as a risk factor in three previous studies involving young athletes and students (basketball (n=210; mean age 16 yrs)[46], and Australian football (n=210, aged 22 yrs)[47] and students (n=230; aged 18 yrs)[17]. Differences in results might be due to younger participants, higher baseline risk and higher exposure to high-risk sports (basketball, Australian football).

The systematic review identifying upper body strength as a predictor for sports injuries evaluated push-ups and sit-ups to predict injuries in adults (18-65 yrs). Push-ups (n=16968) were identified as predictors in 15/22 studies, while sit-ups (n=16605) were identified in 5/24 studies[48]. In both cases, study protocols were similar to the current study.

For assessment of endurance, the steep ramp test was unable to predict injuries. This is in contrast with a systematic review (49 studies; 171,318 adults) that reported an association between poor endurance and musculoskeletal injuries in 34/49 studies in soldiers and athletes. However, all these tests assessed endurance with running tests[20], potentially explaining the different conclusions. No studies were identified in which cycling tests were used to predict injuries.

Running Speed & Agility test were unable to identify lower extremity power as risk factor. This was corroborated by a recent systematic review showing that 9 out 11 selected studies (3257 participants; age: 18-65) reported no association between lower body power and musculoskeletal injuries[49]. Two other studies involving 71 collegiate basketball players (age 20.2±1.9 yrs) and 127 Swedish soccer players (aged 16-36) both failed to establish an association between lower extremity power and sports injuries as well[50,51].

Clinical relevance and future directions

The current study was unable to identify risk factors for sports injuries and SIBs from motor proficiency test or physical activity. This might be based on low statistical power due to a small proportion of participants with poor scores who reported sports injuries or SIBs or a selection of irrelevant tests for PWH, although these tests were chosen based on previous studies in athletic populations[9,13–19]. Sports injuries and SIBs are generally the result of a complex interaction between internal, external and event-related risk factors[12]. This study focused on selected internal risk factors, resulting in a limited

approach from an environmental perspective. Both internal and external risk factors (e.g.: sport specific risk factors, motivation behaviour during sports and equipment) in sports should at least be considered to create a more complete overview of sports injury risk in individual PWH. The lack of seasonal variance showed that seasonal recording of physical activity did not provide an additional value in this cohort. This suggests that a single assessment is sufficient to assess physical activity, which would decrease the participant burden of future studies.

Conclusions

This was the first study attempting to identify internal, physical risk factors for sports injury and SIBs in PWH. The majority of participants who reached "average" (from -2Z to +2Z) results in the current selection of tests showed no association with sports injuries or SIBs. This is likely due to few participants with poor test results and few reported sports injuries and SIBs during the 12-month' follow-up. This study focused on internal, physical risk factors, while injury risk is dependent on internal, external and event-related risk factors. Thus, focusing on internal, physical risk factors reflects a limited approach on injury prediction. When counselling PWH regarding sports participation, a complete individualized assessment of internal (e.g. clotting factor activity levels), external (e.g. surface and (protective) equipment) and event-related factors (NHF category, playing level, behaviour) should be made to enable proper advice PWH on reducing sports injury risk.

References

1 Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia *2020* 1–158.

2 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.

3 Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia : from standard half-life clotting factor concentrates to gene editing. Lancet *2021*; **6736:** 1–11.

4 World Health Organization. WHO Guidelines on physical activity and sedentary behaviour. *2020*.

5 De la Corte-Rodriguez H, Rodriguez-Merchan EC, Alvarez-Roman MT, Jiménez-Yuste V. Applying World Health Organization 2020 guidelines on physical activity and sedentary behavior to people with hemophilia. Expert Rev Hematol *2021*; **14:** 429–36.

6 Versloot O, van Balen EC, Hassan S, et al. Similar sports participation as the general population in Dutch persons with haemophilia; results from a nationwide study. Haemophilia *2021*; **27:** 876–855.

7 Versloot O, Timmer MA, de Kleijn P, et al. Sports participation and sports injuries in Dutch boys with haemophilia. Scand J Med Sci Sports *2020*; **30:** 1256–64.

8 van Mechelen W, Hlobil H, Kemper HCG. Incidence, Severity, Aetiology and Prevention of Sports Injuries: A Review of Concepts. Sport Med *1992*; **14:** 82–99.

9 Emery CA. Risk Factors for Injury in Child and Adolescent Sport: A Systematic Review of the Literature. Clincal J Sport Med *2003*; **13:** 256–68.

10 Seuser A, Boehm P, Kurme A, Schumpe G, Kurnik K. Orthopaedic issues in sports for persons with haemophilia. Haemophilia *2007*; **13:** 47–52.

11 Meeuwisse WH. Assessing Causation in Sport Injury: a Multifactorial Model. J Clin Sport Med *1994*; **4:** 166–70.

12 Bahr R, Krosshaug T. Understanding injury mechanisms: A key component of preventing injuries in sport. Br J Sports Med *2005*; **39:** 324–9.

13 Willems TM, Witvrouw E, Delbaere K, et al. Intrinsic risk factors for inversion ankle sprains in male subjects: A prospective study. Am J Sports Med *2005*; **33:** 415–23.

14 Butler RJ, Lehr ME, Fink ML, Kiesel KB, Plisky PJ. Dynamic Balance Performance and Noncontact Lower Extremity Injury in College Football Players: An Initial Study. Sports Health *2013*; **5:** 417–22.

15 Larsen LR, Kristensen PL, Junge T, et al. Motor Performance as Risk Factor for Lower Extremity Injuries in Children. Med Sci Sport Exerc *2016*; **48:** 1136–43.

16 Fousekis K, Tsepis E, Vagenas G. Intrinsic risk factors of noncontact ankle sprains in soccer: A prospective study on 100 professional players. Am J Sports Med *2012*; **40:** 1842–50.

17 Trojian TH, McKeag DB. Single leg balance test to identify risk of ankle sprains. Br J Sports Med *2006*; **40:** 610–3.

18 Read PJ, Jimenez P, Oliver JL, Lloyd RS. Injury prevention in male youth soccer: Current practices and perceptions of practitioners working at elite English academies. J Sports Sci *2018*; **36:** 1423–31.

19 Bizzini M, Dvorak J. FIFA 11+: An effective programme to prevent football injuries in various player groups worldwide - A narrative review. Br J Sports Med *2015*; **49:** 577–9.

20 Lisman PJ, De La Motte SJ, Gribbin TC, et al. A Systematic Review of the Association Between Physical Fitness and Musculoskeletal Inury Risk: Part 1 - Cardiorespiratory Endurance. J Strenght Cond Res *2017*; **31:** 1744–57.

21 Bruininks V., Bruininks RH. Motor Proficiency of Learning Disabled and Nondisabled Students. Percept Mot Skills *1977*; **44:** 1131–7.

22 Deitz JC, Kartin D, Kopp K. Review of the Bruininks-Oseretsky test of motor proficiency, second edition (BOT-2). Phys Occup Therepy Pediatr *2007*; **27:** 87–102.

23 Vinçon S, Green D, Blank R, Jenetzky E. Ecological validity of the German Bruininks-Oseretsky Test of Motor Proficiency - 2nd Edition. Hum Mov Sci *2016*; **53:** 45–54.

24 Hassan MM. Validity and reliability for the Bruininks-Oseretsky test for motor proficiency-short form as applied in the United Arab Emirates culture. Percept Mot Skills *2001*; **92:** 157–66.

25 Kambas A, Aggeloussis N. Construct validity of then Bruininks-Oseretsky test of motor proficiency-short from for a sample of Greek preschool and primary school children. Percept Mot Skills *2006*; **102:** 65–72.

26 Bruininks RH, Bruininks DB. Bruininks-Oseretsky Test of Motor Proficiency, 2nd ed. 2005. Minneapolis, MN: Pearson Assessment. 2nd ed. Mineapolis: Pearson Publishing; *2005*.

27 Meyer K, Samek L, Schwaibold M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure- application to exercise training. Eur Heart J *1996*; **17:** 1040–7.

28 Bongers BC, Takken T. The paediatric version of the steep ramp test. J Physiother *2014*; **60:** 113.

29 Rozenberg R, Bussmann JBJJ, Lesaffre E, Stam HJ, Praet SFE. A steep ramp test is valid for estimating maximal power and oxygen uptake during a standard ramp test in type 2 diabetes. Scand J Med Sci Sport *2015*; **25:** 595–602.

30 De Backer IC, Schep G, Hoogeveen A, et al. Exercise Testing and Training in a Cancer Rehabilitation Program: The Advantage of the Steep Ramp Test. Arch Phys Med Rehabil *2007*; **88:** 610–6.

31 Bongers BC, De Vries SI, Helders PJM, Takken T. The steep ramp test in healthy children and adolescents: Reliability and validity. Med Sci Sports Exerc *2013*; **45:** 366–71.

32 van Vulpen AV. Sport for all: sports injuries and their prevention. Oosterbeek: Council of Europe, Nationaal instituut voor Sportgezondheidszorg; *1989*.

33 Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: Communication from the SSC of the ISTH. J Thromb Haemost *2014*; **12:** 1935–9.

34 Bussmann. Validation of the Active8 Activity Monitor : detection of body postures and movements. Erasmus MC Univ Med Cent Rotterdam *2013* 18.

35 Fanchamps MHJ, Horemans HLD, Ribbers GM, Stam HJ, Bussmann JBJ. The accuracy of the detection of body postures and movements using a physical activity monitor in people after a stroke. Sensors (Switzerland) *2018*; **18:**.

36 Valkenet K, Veenhof C. Validity of three accelerometers to investigate lying, sitting, standing and walking. PLoS One *2019*; **14:** 1–9.

37 Timmer MA, Veenhof C, de Kleijn P, et al. Movement behaviour patterns in adults with haemophilia. Ther Adv Hematol Adv Hematol *2020*; **11:** 1–9.

38 Versloot O, van der Net J, Fischer K. Sports participation of patients with haemophilia in the COVID-19 era: The Dutch experience. Haemophilia *2021*; **27:** e295–7.

39 Castor EDC. (2019). Castor Electronic Data Capture. [online]brui *2019*.

40 Anderson A, Forsyth A. Playing it safe: Bleeding Disorders, Sports and Exercise. New York, NY.: National Hemophilia Foundation; *2017*.

41 Ceponis A, Wong-Sefidan I, Glass CSS, von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. Haemophilia *2013*; **19:** 790–8.

42 Cook G, Burton L, Hoogenboom B. Pre-participation screening: the use of fundamental movements as an assessment of function. Part 2. N Am J Sports Phys Ther *2006*; **1:** 132–9.

43 Cook G, Burton L, Hoogenboom B. Pre-participation screening: the use of fundamental movements as an assessment of function - part 2. N Am J Sports Phys Ther *2006*; **1:** 132–9.

44 Kinzey SJ, Armstrong CW. The reliability of the star-excursion test in assessing dynamic balance. J Orthop Sports Phys Ther *1998*; **27:** 356–60.

45 Noyes FR, Barber-Westin SD, Fleckenstein C, Walsh C, West J. The drop-jump screening test: Difference in lower limb control by gender and effect of neuromuscular training in female athletes. Am J Sports Med *2005*; **33:** 197–207.

46 McGuine TA, Greene JJ, Best T, Leverson G. Balance as a predictor of ankle injuries in high school basketball players. Clin J Sport Med *2000*; **10:** 239–44.

47 Hrysomallis C, McLaughlin P, Goodman C. Balance and injury in elite Australian footballers. Int J Sports Med *2007*; **28:** 844–7.

48 De La Motte SJ, Gribbin TC, Lisman P, Murphy K, Deuster PA. Systematic Review of the Association Between Physical Fitness and Musculoskeletal Injury Risk: Part 2 - Muscular Endurance and Muscular Strength. J Strenght Cond Res *2017*; **31:** 3218–34.

49 De La Motte SJ, Lisman P, Gribbin TC, Murphy K, Deuster PA. Systematic Review of the Association Between Physical Fitness and Musculoskeletal Injury Risk: Part 3 - Flexibility, Power, Speed, Balance, and Agility. J Strenght Cond Res *2019*; **33:** 1723–35.

50 Brumitt J, Engilis A, Isaak D, Briggs A, Mattocks A. Preseason Jump and Hop Measures in Male Collegiate Basketball Players: an Epidemiologic Report. Int J Sports Phys Ther *2016*; **11:** 954–61.

51 Svensson K, Alricsson M, Olausson M, Werner S. Physical performance tests - A relationship of risk factors for muscle injuries in elite level male football players. J Exerc Rehabil *2018*; **14:** 282–8.

Supplemental Material

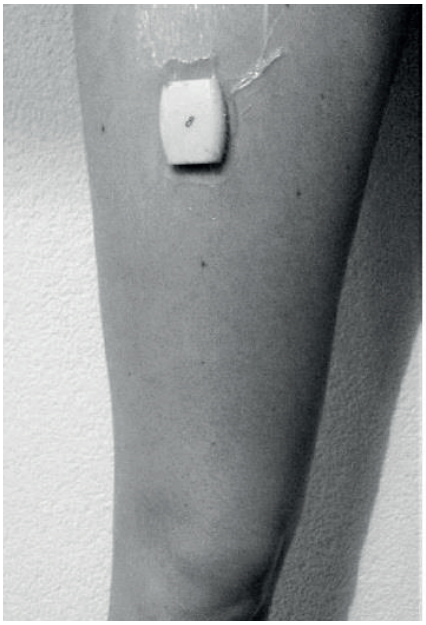
Supplemental table S1: Collected data in case of injuries or bleeds.

Patient number	Study ID
Severity	Severe, moderate, mild
Date injury	Date and time
Days after inclusion	Calculated
Age at injury	Calculated
Location	Anatomical location
Side	Left / right
Structure	Bone / ligament / muscle / joint / skin / tendon / other
Specific diagnosis	Free text
Mechanism	Distortion / fall from height / fall after jump / other fall / bump / hit by object / bodily contact / overuse / fatigue / other / unknown
Origin?	Acute / chronic
During Sports?	Yes / no
Which sports?	Free text
NHF category	1 / 1,5 / 2 / 2,5 / 3
During game or training?	Game / training
Bleed?	Yes / no
Sports-Induced Bleed?	Yes / no
Timing last prophylaxis	Date and time
Number of days since last prophylaxis	Calculated
Number of hours since last prophylaxis	Calculated
Medical assistance?	Yes / no
Treatment	None / extra prophylaxis / physiotherapy / rest / surgery / immobilisation / other
Contact with HTC?*	Yes / no
Recurring injury?	Yes / no
When last injury?	Date
Date recovered	Date
Time loss	Number of days since injury

*: HTC = Haemophilia Treatment Centre

Supplemental table S2: Definitions and characteristics of various bleeds in people with haemophilia[33]

Joint Bleed	An unusual sensation 'aura' in the joint, in combination with any of the following: (a) increasing swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline.
Soft-tissue/Muscle Bleed	An episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and loss of movement over baseline.
Re-bleed	A bleed occurring within 72 hours after stopping treatment for the original bleed for which treatment was initiated.
Sports-induced Bleed	A bleed occurred during (or immediately after) a sports action, with identical symptoms to a (joint/muscle/soft tissue) bleed that required (immediate) extra treatment with clotting factor concentrate or consultation with a haemophilia consultant.

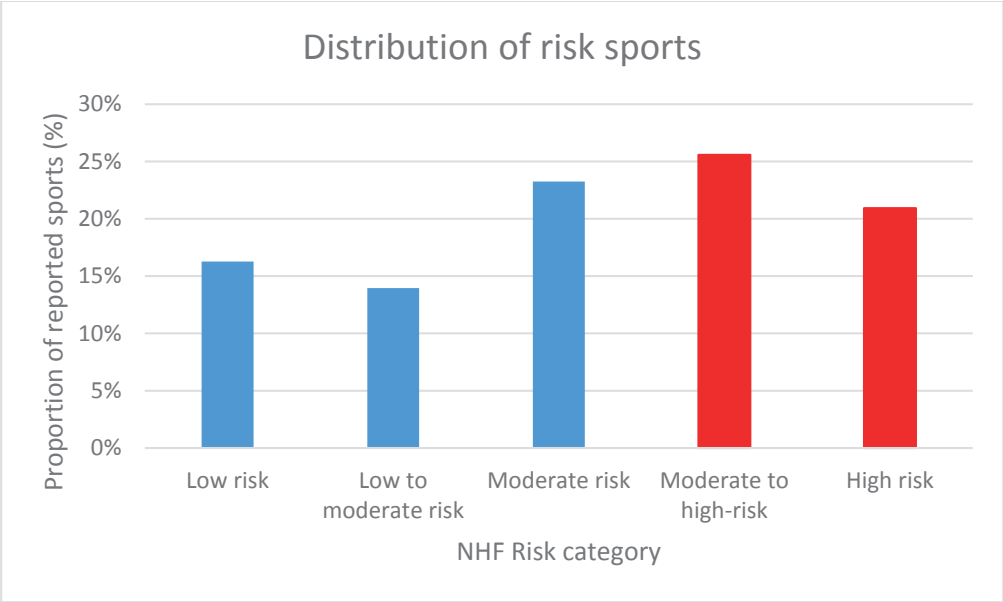


Supplemental figure 1: Positioning of the Activ8 activity sensor on the upper thigh.

Supplemental table S3: Sports reported by participants of the SPRAIN study

N=125	NHF	N	%
Aikido	3	1	0,5%
Badminton	1.5	1	0,5%
Basketball	2	4	1,9%
Boxing	3	2	1,0%
Circus	2.5	1	0,5%
CrossFit	1.5	1	0,5%
Eurhythmia		1	0,5%
Cycling	1.5	11	5,2%
Fitness	1.5	48	22,9%
Golf	1	2	1,0%
General exercises	2.5	2	1,0%
Running	2	19	9,0%
Field hockey	3	3	1,4%
Jogging	2	1	0,5%
Judo	2.5	2	1,0%
Kickboxing	3	2	1,0%
Korfball	2	2	1,0%
Krav Maga	3	1	0,5%
Motor cross	3	1	0,5%
Mountain biking	2.5	3	1,4%
Rescue swimming	2.5	1	0,5%
Rowing	1.5	1	0,5%
Ice skating	2	1	0,5%
Scouting	2	2	1,0%
Skiing	2.5	2	1,0%
Snow boarding	3	2	1,0%
Squash	2	3	1,4%
Table tennis	2	4	1,9%
Tennis	2	9	4,3%
Gymnastics	2.5	1	0,5%
Fishing	1.5	1	0,5%
Soccer	2.5	37	17,6%
Volleyball	2.5	1	0,5%
Walking	1	11	5,2%
Water scouts	2	1	0,5%
Cycling (racing)	3	6	2,9%
Wind surfing	2.5	1	0,5%
Indoor hockey	3	1	0,5%
Indoor soccer	2.5	1	0,5%
Sailing	1	2	1,0%
Swimming lessons	1	1	0,5%
Teaching swimming	1	1	0,5%
Swimming	1	12	5,7%

NHF: injury risk category according to the NHF classification (1: low risk - 3: high risk)[40]



Supplemental figure 2: distribution of injury risk according to the NHF classification. Sports in red categories (moderate to high risk and high risk) are considered high-risk sports[40].

Supplemental Table S4: Motor proficiency test results.

N=125	Poor (<-2SD)	Average (-2SD – +2SD)	Good (>2SD)
Individual Tests			
Balance – 1 Leg – Eyes open	7.0%	93.0%	0.0%
Balance – 1 Leg – Eyes closed	1.6%	98.4%	0.0%
Balance – 1 Leg – Balance Beam – Eyes open	4.0%	96.0%	0.0%
Balance – 1 Leg – Balance Beam – Eyes closed	3.2%	96.8%	0.0%
Balance – Heel-toe – Balance Beam – eyes open	0.0%	99.2%	0.8%
Balance – Heel-toe – Balance Beam – eyes closed	0.0%	94.2%	5.8%
Running Speed & agility – Single Leg Hop (stationary)	2.5%	95.8%	1.7%
Running Speed & agility – Single Leg Side Hop	2.5%	96.6%	0.8%
Running Speed & agility – Two legged side hop	1.7%	95.0%	3.4%
Running Speed & agility – Standing Long Jump	2.5%	96.7%	0.8%
Strength – Push ups	1.7%	95.8%	2.5%
Strength – Sit ups	0.8%	95.9%	3.3%
Strength – Wall sit	5.6%	94.4%	0.0%
Grouped test			
Balance	8.8%	81.6%	9.6%
Running Speed & agility	4.2%	93.2%	2.5%
Strength	8.9%	86.3%	4.8%

Supplemental table S5: Predictive values for sports injuries and sports-induced bleeds according to motor proficiency and endurance

		Sports injuries				Sports-induced bleeds			
	n	n	Predictive value	95% Confidence Interval	p	n	Predictive value	95% Confidence Interval	p
Balance									
Poor	11	4	PPV: 36%	15-68%	0,75	1	PPV: 9%	0-40%	0,51
Average-to-Good	114	47	NPV: 59%	50-70%		19	NPV: 83%	75-89%	
Running Speed & Agility									
Poor	5	2	PPV: 40%	12-77%	0,96	1	PPV: 20%	2-64%	0,76
Average-to-Good	114	47	NPV: 59%	50-70%		17	NPV: 85%	77-91%	
Strength									
Poor	11	3	PPV: 27%	9-57%	0,33	2	PPV: 18%	4-49%	0,85
Average-to-Good	113	48	NPV: 58%	48-66%		18	NPV: 84%	76-90%	
Endurance									
Poor	2	0	PPV: 0%	0-71%	0,24	0	PPV: 0%	0-71%	0,54
Average-to-Good	120	49	NPV: 59%	50-68%		19	NPV: 84%	77-90%	

PPV: positive predictive value, the number of participants who sustained a sports injury or sports-induced bleed with a poor test result (e.g.: 4 sports injuries in 11 poor results on balance tests: 4/11 = 0.36). NPV: negative predictive value, the number of participants who did not sustain a sports injury or sports-induced bleed after an average-to-good test result (e.g.: 47 sports injuries in 114 "average-to-good" scores on balance tests: NPV = (114-47)/114 = 0.59).

Table S6: Predictive values for sports injuries and sports-induced bleeds according to motor proficiency and endurance in participants playing soccer

		Predictive value	
N=39	**n**	**Sports injuries**	**Sports-induced bleeds**
Balance			
Poor	3	PPV: 67%	PPV: 33%
Average-to-good	36	NPV: 59%	NPV: 92%
Running Speed & Agility			
Poor	2	PPV: 100%	PPV: 50%
Average-to-good	37	NPV: 59%	NPV: 92%
Strength			
Poor	3	PPV: 33%	PPV: 0%
Average-to-good	36	NPV: 56%	NPV: 89%
Endurance			
Poor	0	PPV: 0%	PPV: 0%
Average-to-good	39	NPV: 59%	NPV: 89%

PPV: positive predictive value, the number of participants who sustained a sports injury or sports-induced bleed with a poor test result (e.g.: 2 sports injuries in 3 participants with poor results on balance tests: 2/3 = 0.67). NPV: negative predictive value, the number of participants who did not sustain a sports injury or sports-induced bleed after an average-to-good test result (e.g.: 15 sports injuries in 36 "average-to-good" scores on balance tests: NPV = (36-15)/36 = 0.59).

Table S7: Sports injuries and sports-induced bleeds according to motor proficiency and endurance according to follow-up during COVID restrictions

	Predictive value - Pre COVID			Predictive value - COVID		
	n	Sports injuries	Sports-induced bleeds	n	Sports injuries	Sports-induced bleeds
Balance						
Poor	3	PPV: 0%	PPV: 0%	8	PPV: 50%	PPV: 13%
Average to Good	24	NPV: 42%	NPV: 71%	90	NPV: 63%	NPV: 87%
Running Speed & Agility						
Poor	1	PPV: 0%	PPV: 0%	4	PPV: 50%	PPV: 25%
Average to Good	24	NPV: 46%	NPV: 75%	90	NPV: 62%	NPV: 88%
Strength						
Poor	3	PPV: 33%	PPV: 33%	8	PPV: 25%	PPV: 13%
Average to Good	24	NPV: 54%	NPV: 75%	36	NPV: 61%	NPV: 87%
Endurance						
Poor	2	PPV: 0%	NPV: 0%	0	PPV: 0%	PPV: 0%
Average to Good	25	NPV: 44%	NPV: 72%	95	NPV: 63%	NPV: 87%

PPV: positive predictive value, the number of participants who sustained a sports injury or sports-induced bleed with a poor test result (e.g.: 4 sports injuries in 8participants with poor results on balance tests: 4/8 = 0.50). NPV: negative predictive value, the number of participants who did not sustain a sports injury or sports-induced bleed after an average-to-good test result (e.g.: 15 sports injuries in 36 "average-to-good" scores on balance tests: NPV = (90-33)/90 = 0.63

CHAPTER 9

Association between sports participation, factor VIII levels and bleeding in hemophilia A

Laura H. Bukkems[1], Olav Versloot[2,3], Marjon H. Cnossen[4], Siv Jönsson[5], Mats O. Karlsson[5], Ron A.A. Mathôt[1], Kathelijn Fischer[2]

[1] Hospital Pharmacy-Clinical Pharmacology, Amsterdam University Medical Center, the Netherlands;

[2] Center for Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands;

[3] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science, Utrecht, the Netherlands;

[4] Department of Pediatric Hematology and Oncology, Erasmus University Medical Center - Sophia Children's Hospital Rotterdam, Rotterdam, the Netherlands;

[5] Department of Pharmacy, Uppsala University, Uppsala, Sweden

Accepted for Thrombosis and Haemostasis

Bullet Points

What is already known:

- Uncertainty remains regarding bleeding risk during sports activities in people with haemophilia

What this study adds:

- FVIII levels, presence of arthropathy and previous annual bleeding rate are determinants for the bleeding hazard, while sports frequency, participation in high-risk sports and sports participation were not.
- In people with severe hemophilia a higher bleeding hazard was observed than in non-severe at similar FVIII levels, suggesting that time spent at lower trough levels presents additional bleeding risk.

Abstract

Background: Little is known how sports participation affects bleeding risk in hemophilia. This study aimed to examine associations between sports participation, factor VIII (FVIII) levels and bleeding in persons with hemophilia A.

Methods: In this observational, prospective, single-center study, persons with hemophilia A who regularly participated in sports were followed for 12 months. The association of patient characteristics, FVIII levels, and type/frequency of sports participation with bleeding were analyzed by repeated time-to-event (RTTE) modelling.

Results: One hundred twelve persons (median age 24 years [IQR:16 – 34], 49% severe, 49% on prophylaxis) were included. During follow-up, 70 bleeds of which 20 sports-induced were observed. FVIII levels were inversely correlated with the bleeding hazard; a 50% reduction of the baseline bleeding hazard was observed at FVIII levels of 3.1 and a 90% reduction at 28.0 IU/dL. The bleeding hazard did not correlate with sports participation. In addition, severe hemophilia, pre-study annual bleeding rate and presence of arthropathy showed a positive association with the bleeding hazard.

Conclusions: This analysis showed that FVIII levels were an important determinant of the bleeding hazard, but sports participation was not. This observation most likely reflects the presence of adequate FVIII levels during sports participation in our study. Persons with severe hemophilia A exhibited a higher bleeding hazard at a similar FVIII levels than non-severe, suggesting that the time spent at lower FVIII levels impacts overall bleeding hazard. These data may be used to counsel persons with hemophilia regarding sports participation and the necessity of adequate prophylaxis.

Introduction

Persons with hemophilia A suffer from factor VIII (FVIII) deficiency and impaired hemostasis, resulting in spontaneous and/or trauma-related bleeding. Bleeding characteristically occurs in joints and muscles and eventually results in hemophilic arthropathy. Most severe and some moderate persons with hemophilia A are treated prophylactically with FVIII replacement therapy. For mild and most moderately affected persons, on demand treatment is usually used. Recently, also non-replacement therapies have been introduced.[1]thereby restoring hemostasis. In a phase 3, multicenter trial, we investigated its use as prophylaxis in persons who have hemophilia A without factor VIII inhibitors. METHODS We randomly assigned, in a 2:2:1 ratio, participants 12 years of age or older who had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A

Historically, only low impact sports were recommended for persons with hemophilia due to a perceived increased bleeding risk when engaging in high-risk sports activities.[2] This advice has contributed to poor exercise performance and impaired muscle strength in persons with hemophilia as reported in early studies.[3–5] The widespread availability of factor concentrates in well-resourced countries and the introduction of prophylaxis has however enhanced the ability for sports participation for all persons with hemophilia. This is of importance as adequate physical activity overall reduces risk of chronic diseases and all-cause mortality.[6,7] Later studies conducted in settings in which adequate prophylaxis and on demand treatment were available have demonstrated similar sports participation, physical fitness and muscle strength in persons with hemophilia in comparison to the general population.[8–10] However, whether similar sports participation in persons with hemophilia as in the general population leads to a higher bleeding risk remains unanswered. Presumably, the risk of bleeding during sports participation is dependent on the achieved factor level.

Only a few studies have assessed the relationship between bleeding risk and physical activity.[11,12] Ross et al[11] observed no impact of athletic participation on joint outcomes. Tiktinsky et al[12] reported a higher bleeding rate during vigorous exercise in persons with severe hemophilia who were treated on demand. Only Broderick et al[13] examined the effect of factor levels and sports participation on bleeding risk and reported a moderate relative increase in bleeding risk for vigorous physical activities together with a reduction of bleeding at increasing FVIII levels. This study included only children with severe and moderate hemophilia, leaving a knowledge gap for both adult and mild hemophilia patients.

The association between sports participation, FVIII levels and bleeding hazard can be modeled with a parametric repeated time-to-event (RTTE) model. This technique can characterize the occurrence of repetitive events (bleeding) over time and can be used to examine the association of various patient factors with the bleeding hazard.[14–16] The aim of this study was to examine the influence of sports participation and FVIII levels on the bleeding hazard in persons with hemophilia A in the current treatment setting in the Netherlands using an RTTE analysis.

Methods

A detailed method description is presented in the supplementary material.

Data

In this observational, prospective, single-center study from University Medical Center Utrecht, persons with hemophilia who regularly participated in sports were followed for 12 months (SPRAIN study). Sports participation was defined as active engagement in sports at least ten times per year.[17] Participants were contacted bi-weekly to enquire about bleeds and injuries, including information on nature, mechanism, involvement of sports participation and details of last factor concentrate administration. Data on prophylactic treatment regimen, body mass index (BMI), presence of arthropathy and pre-study annual bleeding rate (ABR) were extracted from electronic patient files. Physical activity was assessed using a one-week training diary. The sports described were assumed to be constant during the entire study period, with exception of summer and winter recess.

The study was registered in the Dutch Trial register under NTR6769 (www.trialregister.nl). The Medical Ethical Committee approved the study (IRB number: 181-41). Informed consent was obtained from all study participants and data was collected in accordance with the declaration of Helsinki.

Development of repeated-time-to-event (RTTE) model

The modelling process is visualized in figure 1. The probability of bleeding over time was analyzed using an RTTE model, which is a parametric survival method.[14,15] In the RTTE model, the bleeding probability over time is estimated by the parametric hazard function. Exponential, Gompertz and Weibull hazard functions were evaluated to describe how the hazard varied over time. Inter-individual variability on the overall bleeding hazard was considered.

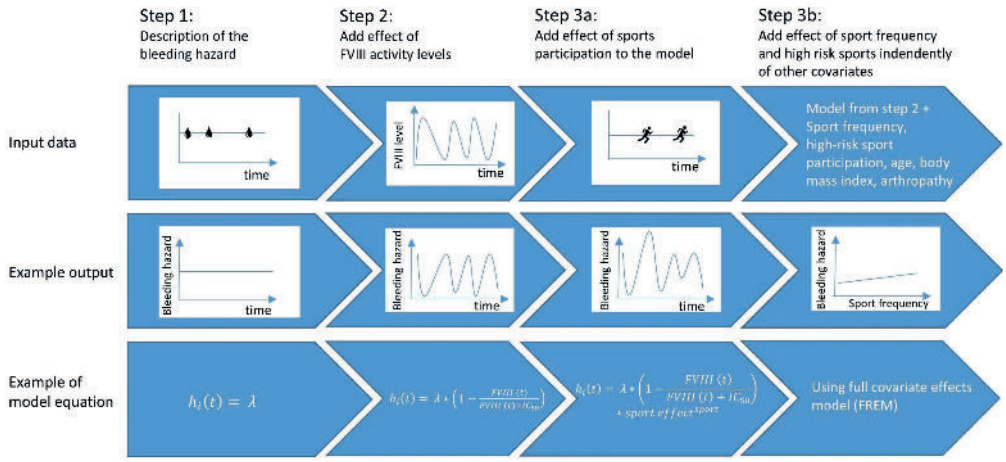


Figure 1: Visual description of the workflow to develop the repeated time-to-event (RTTE) model to evaluate the association between sports participation, FVIII levels and bleeding. In the example equations, hi(t) describes the individual bleeding hazard at time t, λ the baseline bleeding hazard, FVIII, FVIII activity level at time t, IC50 the FVIII activity level at which 50% of the maximum inhibition on the bleeding hazard occurs, 'sport effect' describes the change in bleeding hazard during sports and 'sport' is equal to 1 during a sports exposure and zero when not participating in sports.

The effect of FVIII levels on the bleeding hazard was assessed by a maximum inhibition (Imax) model (Step 2 in figure 1). FVIII level was assumed to be constant for persons treated on demand, and was described by the lowest measured endogenous FVIII level. For persons treated prophylactically with data on FVIII levels available, individual PK parameters were estimated with the Web Accessible Population Pharmacokinetic Service (WAPPS) online tool using Bayesian forecasting.[18–20] For people lacking information on FVIII levels, individual PK parameters were estimated based on FVIII concentrate, age, bodyweight and blood group using the population PK models applied by WAPPS.[18]

The association between bleeding and sports participation was evaluated using two different methods. Firstly, sports participation was incorporated as a time-varying covariate (set to 1 or 0 depending on exposure or not) in the data set, and the effect of sports participation on the bleeding hazard was evaluated (Step 3a in figure 1).

Secondly, a full random effects model (FREM) was used (Step 3b in figure 1). The FREM characterizes the correlation between the bleeding hazard and all covariates of interest independently.[21]described by mean and variance. The method captures the covariate effects in estimated covariances between individual parameters and covariates. This

approach is robust against issues that may cause reduced performance in methods based on estimating fixed effects (e.g., correlated covariates where the effects cannot be simultaneously identified in fixed-effects methods Examined covariates in the FREM were: BMI, ABR, presence of arthropathy, endogenous FVIII level, sports frequency per month and participation in high-risk sports.[22]

Model development and assessment

Model building was performed using non-linear mixed effect modelling in NONMEM v7.4.1.[23] Model evaluation was performed based on comparison of the observed and model-simulated Kaplan Meier curves, scientific plausibility of the parameter estimates, their standard error and the objective function value (OFV) via the likelihood ratio test.

Results

Data

Patient and treatment characteristics are presented in Table 1. One hundred and twelve persons with hemophilia A of which 13 children <12 years were included. Fifty-five had severe- (endogenous FVIII <1 IU/dL), 8 moderate- (endogenous FVIII ≥1 and ≤5 IU/dL) and 49 had mild hemophilia (endogenous FVIII >5 IU/dL). In total, around half of the study population (49%) was treated prophylactically with FVIII concentrate, while the others used on demand treatment. One person with moderate hemophilia was treated with prophylaxis and one person with severe hemophilia was treated on demand. FVIII levels were available for 23 (42%) persons on prophylaxis, for the other 32 persons on prophylaxis FVIII levels were not available. Sports activities were performed a median of 13 times per month (range: 2 - 33) and 59% participated in high-risk sports. During the follow up period, 167 injuries and 70 bleeds were reported, of which 35 (50%) were joint bleeds and 20 (29%) were sports-induced bleeds. Bleeds were mostly self-diagnosed by study participants, but 25 bleeds (36%) were evaluated by a medical professional.

Table 1: Participant, disease, treatment and bleeding characteristics

Characteristic	Number (percentage) or median [IQR] (range)
Patients	112
Age (years)	24.1 [16.0 – 33.7] (7.2 - 49.6)
Weight (kg)	77.0 [62.8- 85.3] (24.0 - 135.0)
Body mass index (kg/m^2)	22.5 [19.5 – 25.1] (14.2 – 38.5)
Hemophilia Severity	
Severe (FVIII<1 IU/dL)	55 (49%)
Moderate (FVIII≥1 and ≤5 IU/dL)	8 (7%)
Mild (FVIII>5 IU/dL)	49 (44%)
Endogenous FVIII level non-severe (IU/dL)	15 [10 – 17] (2 – 29.0)
Sports frequency (per month)	13 [9 – 17] (2 – 33)
Participation in high-risk sports	66 (59%)
Follow up (days)	365 [365 – 365] (365 – 365)
Hemophilia joint health score	0 [0 – 3] (0 – 44)
Pre-existing arthopathy	22 (20%)
Treatment specifications	
Prophylaxis	55 (98% of severe patients)
Median FVIII dose (IU/kg/week)	43.1 [36.0 – 53.9] (11.7 – 89.5)
Factor concentrate	
Standard half-life FVIII*	40 (73%)
Extended half-life FVIII**	15 (27%)
Bleeding specifications	
Bleeds (n observed)	70
Joint bleeds	35 (50%)
Sports-induced bleed	20 (29%)
ABR before study inclusion	0 [0 – 1] (0 – 9)
AJBR before study inclusion	0 [0 – 0] (0 – 4)
ABR during study	0 [0 – 1] (0 – 5)

FVIII: Factor VIII, ABR: annual bleeding rate, AJBR: annual joint bleed rate, *Advate, Kogenate and Novoeight, ** Elocta. ABR describes the number of bleeds observed within 365 days.

Development of repeated-time-to-event (RTTE) model

An exponential hazard function described the bleeding data best, indicating a constant bleeding hazard over time. For 18 bleeds (26%, all not sports-induced) the exact time of bleed was unknown therefore interval censoring over the day was applied. The effect of FVIII level on the bleeding hazard was statistically significant ($p<0.001$) and was described with an Imax model, showing a higher bleeding hazard at lower FVIII levels (Supplement figure 1). The final individual hazard function was described by Equation 1.

$$h_i(t) = \lambda\left(1 - \frac{FVIII\,(t)}{FVIII\,(t) + IC_{50}}\right) e^{\eta i} \qquad (1)$$

in which $h_i(t)$ describes the individual bleeding hazard at time t, λ the bleeding hazard in absence of FVIII, FVIII the FVIII level at time t, IC_{50} the FVIII level at which 50% of the maximum inhibition on the bleeding hazard occurs and η is a random effect describing the inter individual variability in bleeding hazard.

The parameter estimates of the model are presented in Table 2. The estimated bleeding hazards can be interpreted as the estimated annual bleeding rate when a person has a constant FVIII level. As a result, a median person with a constant FVIII level of 0, 1, 10 or 20 IU/dL will experience 1.5, 1.1, 0.4 or 0.2 bleeds per year, respectively. The estimated bleeding hazards for other FVIII levels are visualized in figure 2.

Compared to persons with severe hemophilia and no measurable FVIII level, the annual bleeding rate was reduced by 50% at a FVIII level of 3.1 IU/dL, by 75% at a FVIII level of 9.3 IU/dL and by 90% at a FVIII level of 28.0 IU/dL. The inter-individual variability of bleeding hazard was high (coefficient of variation of 92.4%), demonstrating that people with similar FVIII levels presented with a varying number of bleeds. For instance, ABR for persons with a constant FVIII level of 1 IU/dL is median 1.1 per year but the 95% prediction interval was 0.2 – 5.3 per year.

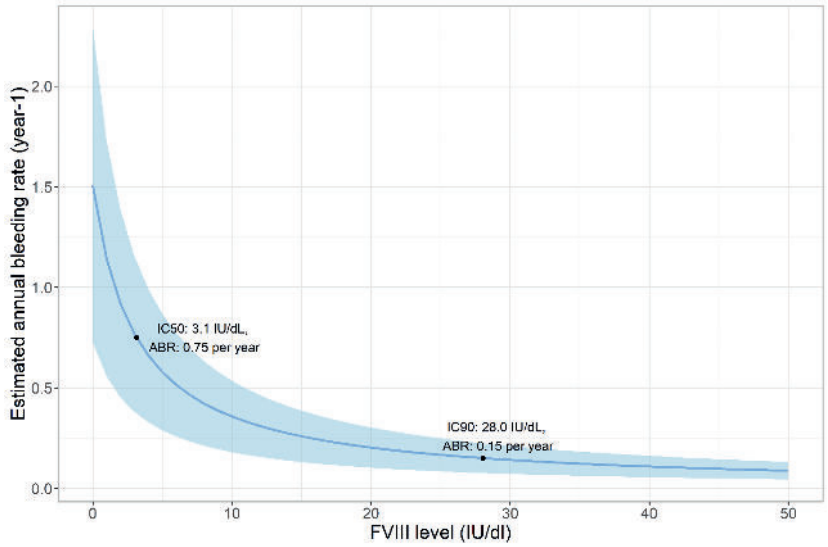


Figure 2: Relationship between factor VIII (FVIII) level and estimated annual bleeding rate (ABR). The solid blue line gives the median relation (based on the estimated model parameters) and the shaded area the 95% confidence interval (based on the relative standard errors of the parameter estimates). The IC50 and IC90 depict the FVIII level at which 50% or 90% of the maximal protective effect occur, respectively. A median patient in this dataset with a constant FVIII level of 3.1 IU/dL will experience 0.75 bleeds per year.

Table 2: Parameter estimates of the final repeated time-to-event (RTTE) model

Parameter	Estimate	95% CI
Bleeding hazard at FVIII 0 IU/dL(derived) (year^{-1})	1.50	-
Bleeding hazard at FVIII 1 IU/dL (year^{-1})	1.14	0.56 – 1.72
Bleeding hazard at FVIII 10 IU/dL (derived) (year^{-1})	0.36	-
Bleeding hazard at FVIII 20 IU/dL (year^{-1})	0.20	0.10 – 0.30
IC50 (derived) (IU/dL)	3.12	-
IC90 (derived) (IU/dL)	28.0	-
Inter-individual variability of bleeding hazard (CV%)	92.4	48.9 – 135.9

IC50: FVIII activity level resulting in 50% reduction of the baseline bleeding hazard at a FVIII level of 0 IU/dL, IC90: FVIII activity level resulting in 90% reduction of the baseline bleeding hazard at a FVIII level of 0 IU/dL, CI: confidence interval, CV: coefficient of variation calculated as $\sqrt{e^{\omega^2} - 1}$, shrinkage of inter-individual variability of bleeding hazard was 50%. The estimated bleeding hazards at 0, 1, 20 and 20 IU/dL can be interpreted as the median estimated annual bleeding rate when a patient has the respective constant FVIII level. A FVIII level of 3.12 IU/dL was found to reduce the median baseline annual bleeding rate of 1.50 year^{-1} to 0.75 year^{-1}.

In supplement figure 2, the observed Kaplan Meier curves of the first, second and third bleed combined 2.5th and 97.5th percentile of the model simulated Kaplan Meier curves are presented. The simulated shaded areas cover the observed Kaplan Meier curves, demonstrating that the model describes the bleeding probability observed in our data adequately. As described in the method section, we used two different strategies to estimate the individual PK parameters since FVIII levels were not available every person. To analyze if these different strategies affected the estimates of the RTTE model, we developed RTTE models including only the prophylaxis patients with FVIII levels or only the prophylaxis patients without FVIII levels. The results showed similar parameters estimates, indicating that these different methods did not affect the results (Supplement Table 1).

Sports participation

During the study, 20 sports-induced bleeds occurred during 14,162 sport exposures. On average subjects presented with a 21% higher FVIII level during sports than their average FVIII levels. The median estimated FVIII level during sports-induced bleeds was 5.9 IU/dL (range: 0 – 20 IU/dL) while these were 11.0 IU/dL (range: 0 - 95 IU/dL) during sports activities without occurrence of bleeding. When the median FVIII levels between sports-induced bleeds and during sport activities were compared for severe, moderate and mild hemophilia patients seperately, the difference was larger for persons with severe hemophilia (4.5 IU/dL during sport induced bleeds and 8.6 IU/dL during sports activities without bleeding) than for for mild hemophilia (14.0 IU/dL during sport induced bleeds and 15.0 IU/dL during sports activities without bleeding).

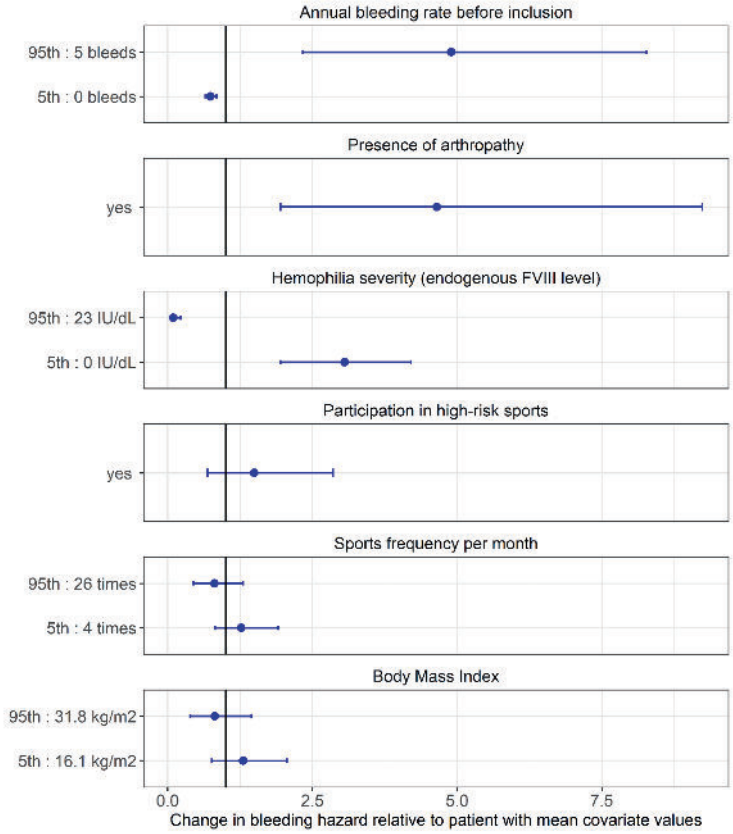


Figure 3: Effect of the examined patient characteristics (covariates) on the bleeding hazard. The change in bleeding hazard (dots, point estimate) relative to a patient with mean covariate values is described for the 5th and 95th percentiles of the distribution of the examined covariates. The error bars present the uncertainty around the 5th and 95th percentiles point estimates, given by the 90% confidence interval. The solid line at 1.0 indicates no change in the bleeding hazard relative to a patient with mean covariate values. The mean study patient presented with an annual bleeding rate of 0.8 per year, experienced no arthropathy, had an endogenous FVIII level of 7.1 IU/dL, did not participate in high-risk sports, played sports 13.6 times per month and had a body mass index of 22.9 kg/m^2. Covariates are ranked from covariates with the strongest correlation with bleeding hazard on top (based on point estimates) to no correlation with the bleeding hazard on the bottom.

In the first covariate analysis, sports participation was related to the bleeding hazard. Results showed that during sports participation the bleeding hazard did not change statistically significantly, as inclusion of this covariate did not improve the goodness-of-fit ($p>0.05$).

The results of the second covariate analysis using the FREM methodology, estimated weak, statistically non-significant, correlations between bleeding hazard and both i) sports frequency per month, and, ii) participation in high-risk sports, as illustrated in figure 3. In this figure, the 90% confidence interval whiskers cross the solid reference line of a mean participant, indicating that when sports frequency per month and participation in high-risk sports differ from this mean, there is no strong association with the bleeding hazard. Covariates that showed strong correlations with bleeding hazard and indicated an increased bleeding hazard were: high ABR, presence of arthropathy and severe hemophilia. For instance, pre-existing arthropathy resulted in a median 4.6 times higher bleeding hazard when compared to persons without pre-existing arthropathy. Consequently, persons with pre-existing arthropathy required a 4.6 times higher FVIII level to achieve a similar ABR as persons without pre-existing arthropathy.

Discussion

This study is the first to evaluate the association of sports participation and FVIII levels with bleeding hazard in both severe and non-severe hemophilia A in a wide age range. Bleeding hazard was predominantly determined by FVIII levels. A FVIII level of 3.1 IU/dL was found to reduce the ABR in absence of FVIII by 50%, while a FVIII level of 28.0 IU/dL reduced this baseline ABR by 90%. No association between sports participation and bleeding hazard was observed in our study population, as neither frequency nor intensity of sports participation (low versus high-risk) showed an independent association with bleeding hazard. Other covariates independently associated with the bleeding hazard were: ABR before study inclusion, presence of arthropathy and hemophilia severity.

Possible explanations for observed results

How can we explain the lack of association between sports participation and bleeding hazard? We presume two main reasons may play a role. Firstly, prophylactic treatment is personalized according to an individual's sports schedule and other physical activities, consciously targeting higher FVIII levels during sports. The median estimated FVIII levels during sports-induced bleeds were lower than the median FVIII levels observed during sports activities in which no bleeding occurred (5.9 vs 11.0 IU/dL), which suggests that higher FVIII levels protected against bleeding during sports activities. Secondly, as our study population regularly participated in sports, increased muscle mass and strength may also have protected against sports-induced bleeds, as physical fitness and muscle strength resulting from regular sports participation may help prevent bleeding.[24,-25]several studies have been done in this patient population and have found no increased risk. In addition, there are many other benefits to participation including improvement

in physical fitness status, better health outcomes, improvement in quality of life, and the development of increased flexibility, gait coordination, and muscular strength, which may actually reduce the risk of subsequent injury. With adequate pre-participation preparation and surveillance, patients with hemophilia have few restrictions in their choice of activity. In the United States, the National Hemophilia Foundation (NHF

In the covariate analysis, additional covariates showed independent associations with the bleeding hazard. As expected, a higher ABR before study inclusion and presence of arthropathy predicted a higher bleeding hazard. Hemophilia severity and thus endogenous FVIII levels were negatively associated with bleeding hazard, indicated a higher bleeding hazard for persons with lower endogenous FVIII levels. This suggests that persons with severe hemophilia have a higher bleeding hazard than persons with non-severe hemophilia when similar FVIII levels are achieved. For example, when a person with severe hemophilia reaches a FVIII level of 20 IU/dL with the use of prophylaxis, his bleeding hazard will be higher at this time point than when a person with mild hemophilia has a FVIII level of 20 IU/dL. This finding seems to contradict the general view that prophylaxis is able to convert severe hemophilia into moderate hemophilia.[26] However, this study observation may be explained by the fact that persons with non-severe hemophilia solely treated on demand in majority have stable endogenous FVIII levels. Contrastingly, persons with severe hemophilia on prophylaxis experience fluctuating FVIII levels, often returning to FVIII levels under or around 1 IU/dl, not seen in persons with non-severe hemophilia A. These repetitive low FVIII trough levels, seen before administration of prophylaxis could increase the overall bleeding hazard. This observation is in accordance with the observation of Collins et al., which observed that increased time periods spent with FVIII levels <1 IU/dL were associated with an overall higher bleeding risk, and emphasizes the importance of FVIII trough levels and/or time spent under a certain FVIII level during prophylactic treatment.[27]

Study strengths and limitations

Strengths of this study include the bi-weekly contact with participants to gather information on bleeding and injuries, minimizing recall bias. Furthermore for this analysis, RTTE modelling was used, which is a powerful method to describe time-varying events such as bleeding over time and its association with FVIII levels.

Importantly, we underline that study results cannot be directly extrapolated to all persons with hemophilia A, as this study only included persons who regularly participated in sports. This may have introduced selection bias, as persons experiencing many and severe bleeds due to sports participation may have ended sports activities and could therefore not be included in this study. On the other hand, it has been established

that the majority (±70%) of Dutch adults and Dutch children with hemophilia play sports. [10]detailed data concerning sports participation in Dutch PWH is lacking. Aim: to assess sports participation in Dutch PWH (6-65 years Furthermore, in settings in which FVIII prophylaxis regimens are not consciously adjusted to sports schedules, an association between sports participation, factor levels and bleeding may be easier identified. Our findings may also be limited due to incomplete data on exact FVIII timing and doses, as well as sports activities during the follow up period as the training diary was only completed for a one-week period due to practical considerations, which may be too short and less representative. Importantly, exact details of the last FVIII dose and details of sports participation were recorded for each bleed. During other periods standard FVIII dosing and sports regimens were presumed. Lastly, bleeds were generally self-reported by study participants and only 36% of the bleeds were evaluated by a medical specialist.

Comparison to other studies

In our study, the bleeding hazard for a constant FVIII level of 0.5 IU/dL was estimated to give 1.3 bleeds per year (95%CI: 0.5 – 2.1), which is lower than the 2.8 bleeds per year with a constant FVII level of 0.5 IU/dL estimated by Abrantes et al[16]but the relationship between exposure (factor VIII activity in a RTTE analysis of the BAY 81-8973 clinical trial data in severe hemophilia. Concomitantly, the IC50 estimate in this current study of 3.1 IU/dL was also lower than the IC50 value of 10.2 IU/dL reported by Abrantes. These differences may be due to the lower overall number of bleeds observed in our study population, caused by differences in intensity of treatment, different evaluations of bleeding events as well as the inclusion of persons with non-severe hemophilia. Importantly, the study of Abrantes et al[16]but the relationship between exposure (factor VIII activity did not include sports participation as a covariate in the analysis.

Broderick et al.[13] examined sports participation and bleeding in 104 boys with severe hemophilia and observed a moderate relative increase in the bleeding risk immediately following vigorous physical activities, while we were not able to identify an association between participation in high-risk sports and bleeding hazard. Possibly, this is caused by the differences in statistical power (436 vs. 70 bleeds), population (children versus all ages), different statistical methods and/or a different FVIII treatment regimen.

Conclusions and clinical implications

We conclude that in this study, FVIII levels are an important determinant for the bleeding hazard, while sports frequency, participation in high-risk sports and sports participation were not associated with the bleeding hazard. The low number of sports-induced bleeds, complicated analyses of the association between FVIII levels and bleeding, during sports participation. However, based on the association between FVIII levels

and bleeding during the entire study, it could be derived that FVIII levels above 28.0 IU/dL decrease the ABR by at least 90% compared to when no FVIII level is measureable. Furthermore, a higher bleeding hazard was observed for persons with a high ABR or persons with pre-existing arthropathy, suggesting the need for higher FVIII levels. Moreover, in persons with severe hemophilia a higher bleeding hazard was observed than in non-severe hemophilia at similar FVIII levels. Importantly, this finding suggests that lower FVIII levels in between prophylactic infusions impact the overall bleeding hazard. These data provide important information for counselling regarding sports participation and underline the need for adequate prophylaxis as well as adequate targets for replacement and non-replacement therapy.

References

1. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia a without inhibitors. N Engl J Med 2018;379:811-822
2. McLain LG, Heldrich FT. Hemophilia and Sports. Phys Sportsmed 1990;18:73-80
3. Koch B, Galioto jr FM, Kelleher J, Goldstein D. Physical fitness in children with hemophilia. Arch Phys Med Rehabil 1984;65:324-326
4. Falk B, Portal S, Tiktinsky R, Weinstein Y, Constantini N, Martinowitz U. Anaerobic power and muscle strength in young hemophilia patients. Med Sci Sports Exerc 2000;32:52-57
5. Hilberg T, Herbsleb M, Gabriel HHW, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. Haemophilia 2001;7:582-588
6. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: Systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol 2011;40:1382-1400
7. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. Lancet 2012;380:219-229
8. Broderick CR, Herbert RD, Latimer J, Curtin JA. Fitness and quality of life in children with haemophilia. Haemophilia 2010;16:118-123
9. Douma-van Riet DCM, Engelbert RHH, van Genderen FR, ter Horst-de Ronde MTM, de Goede-Bolder A, Hartman A. Physical fitness in children with haemophilia and the effect of overweight. Haemophilia 2009;15:519-527
10. Versloot O, van Balen EC, Hassan S, et al. Similar sports participation as the general population in Dutch persons with haemophilia; results from a nationwide study. Haemophilia 2021;27:876-885
11. Ross C, Goldenberg NA, Hund D, Manco-Johnson MJ. Athletic participation in severe hemophilia: Bleeding and joint outcomes in children on prophylaxis. Pediatrics 2009;124:1267-1272
12. Tiktinsky R, Kenet G, Dvir Z, et al. Physical activity participation and bleeding characteristics in young patients with severe haemophilia. Haemophilia 2009;15:695-700
13. Broderick CR, Herbert RD, Latimer J, et al. Association between physical activity and risk of bleeding in children with hemophilia. JAMA 2012;308:1452-1459
14. Holford N. A time to event tutorial for pharmacometricians. CPT Pharmacometrics Syst Pharmacol 2013;2:e43
15. Cox EH, Veyrat-Follet C, Beal SL, Fuseau E, Kenkare S, Sheiner LB. A population pharmacokinetic-pharmacodynamic analysis of repeated measures time-to-event pharmacodynamic responses: The antiemetic effect of ondansetron. J Pharmacokinet Biopharm 1999;27:625-644
16. Abrantes JA, Solms A, Garmann D, Nielsen EI, Jönsson S, Karlsson MO. Relationship between factor VIII activity, bleeds and individual characteristics in severe hemophilia A patients. Haematologica 2020;105:1443-1453
17. The European Sports Charter. Counc Eur 1992:1-10
18. Hajducek D, Chelle P, Hermans C, et al. Development and evaluation of the population pharmacokinetic models for FVIII and FIX concentrates of the WAPPS-Hemo project. Haemophilia 2020;26:384-400
19. Iorio A, Keepanasseril A, Foster G, et al. Development of a Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Study Protocol. JMIR Res Protoc 2016;5:e239
20. McEneny-King A, Foster G, Iorio A, Edginton AN. Data Analysis Protocol for the Development and Evaluation of Population Pharmacokinetic Models for Incorporation Into the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo). JMIR Res Protoc 2016;5:e232
21. Yngman G, Bjugård Nyberg H, Nyberg J, Jonsson EN, Karlsson MO. An introduction to the full random effects model. CPT Pharmacometrics Syst Pharmacol 2022;11:149-160
22. Anderson A, Forsyth A. Playing it safe: Bleeding Disorders, Sports and Exercise. Natl Hemoph Found 2017:1-72
23. Beal S, Sheiner L, Boeckmann A, Bauer R, Editors. NONMEM 7.4 Users Guides. https://nonmem.iconplc.com/nonmem741.
24. Howell C, Scott K, Patel DR. Sports participation recommendations for patients with bleeding disorders. Transl Pediatr 2017;6:174-180

25. Heijnen L. The role of rehabilitation and sports in haemophilia patients with inhibitors. Haemophilia 2008;14:45-51

26. Ahlberg A. Haemophilia in Sweden VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. Acta Orthop Scand Suppl 1965;Suppl 77:3-132

27. Collins PW, Blanchette VS, Fischer K, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. J Thromb Haemost 2009;7:413-420

Supplementary Methods

Data

In this observational, prospective, single-center Sports Participation and Injuries in people with hemophilia (SPRAIN) study from University Medical Center Utrecht (The Netherlands), persons with hemophilia who regularly participated in sports were followed for one year. For the present analysis, data from 13 people with hemophilia B were excluded, as the exposure-effect relation of factor VIII (FVIII) and factor IX concentrates could be different. Injuries and bleeds were assessed proactively, i.e. participants were contacted bi-weekly, and information about nature, involvement of sports participation, mechanism of injury leading to a bleed and, in case of prophylactic treatment, last factor concentrate dose and timing of dosing and event were recorded. Bleeding was defined according to the ISTH definitions.[1] A bleed was classified as occurring during sports, when the bleed developed following a sports injury and required treatment with factor concentrates with or without a consultation with the hemophilia treatment center. Participation in high-risk sports was based on a National Hemophilia Foundation (NHF) score >2.[2] The hemophilia joint health score (HJHS) was assessed at study initiation.[3,4]

Repeated time-to-event model (RTTE)

An RTTE model is able to characterize the occurrence of time-varying events (bleeding over time) together with event predictors (e.g. factor activity levels and sports activities). In an RTTE model, the bleeding probability over time is described by the hazard function. First, a median bleeding hazard was estimated which describes the bleeding hazard for a median person using data from the whole population simultaneously. Differences in bleeding hazard between persons were evaluated by inclusion of the inter-individual variability on the hazard (IIV).

Exponential (equation 1), Gompetz (equation 2) and Weibull (equation 3) hazard functions were tested to describe the distribution of time to bleeding. An exponential hazard function describes a constant hazard over time, while Gompertz and Weibull hazard functions can describe increasing or decreasing bleeding hazards over time.[5] The final individual hazard function was described by equation 4.

$$h(t) = \lambda \quad (1)$$

$$h(t) = \lambda\, e^{\gamma t} \quad (2)$$

$$h(t) = \lambda\gamma\,(\lambda t)^{\gamma-1} \quad (3)$$

$$h_i(t) = \lambda\left(1 - \frac{FVIII\ (t)}{FVIII\ (t) + IC_{50}}\right) e^{\eta i} \qquad (4)$$

in which the bleeding hazard of the i^{th} patient at time t is described by $h_i(t)$. λ describes the scale, γ the shape, FVIII the FVIII activity level at time t, IC_{50} the FVIII activity level at which 50% of the maximal inhibition on the bleeding hazard occurs and ηi the inter individual variability in bleeding hazard with mean 0 and variance ω^2.

For persons not receiving a FVIII dose on the day of study initiation, FVIII levels at start of study were calculated based on the previous dose administered prior to study inclusion.

The λ and IC50 were parameterized to describe the bleeding hazard for a FVIII level of 0.5 and 20 IU/dL following equation 5 and 6.[6]but the relationship between exposure (factor VIII activity

$$\lambda = \frac{\lambda_{0.5}\ \lambda_{20}\ (0.5 - 20)}{(\lambda_{0.5}\ 0.5 - \lambda_{20}\ 20)} \qquad (5)$$

$$IC50 = \frac{(\lambda_{0.5}\ 0.5 - \lambda_{20}\ 20)}{(\lambda_{0.5} - \lambda_{20})} \qquad (6)$$

The survival function describes the probability of not having a bleed within a specific time interval. By taking the integral of the hazard the cumulative hazard can be calculated, which is used to calculate the survival function (equation 7).

$$S_i(t) = e^{-\int_0^t h_i(t)\ dt} \qquad (7)$$

in which the survival function of the i^{th} patient within the time interval 0 to t_j is described by $S_i(t)$. In this example 0 is taken as start of the time interval and t_j as end of the time interval, $h_i(t)$ is the individual bleeding hazard.

For some bleeds only the day of the bleeding was known, but not the exact time of the bleeding event. Interval censoring was applied for these bleeds. The probability that these bleeds occurred can be described by the probability that the event occurred between t_j and t_j +24h, following equation 8.

$$P\left(t_j < t < t_j + 24\right) = \left(e^{-\int_0^t h_i(t)\ dt}\right) * \left(1 - e^{-\int_{t_j}^{t+24} h_i(t)\ dt}\right) \qquad (8)$$

Covariate analysis

A full random effects model (FREM) was used to identify covariates with an effect on individual bleeding hazard.[7]described by mean and variance. The method captures the covariate effects in estimated covariances between individual parameters and covariates.

This approach is robust against issues that may cause reduced performance in methods based on estimating fixed effects (e.g., correlated covariates where the effects cannot be simultaneously identified in fixed-effects methods This covariate analysis method can characterize the correlation between model parameters - such as the bleeding hazard - and all patient characteristics of interest simultaneously. Herewith, the correlation between the bleeding hazard (including the effect of FVIII levels) and sports activities can be evaluated independently of other patient factors.

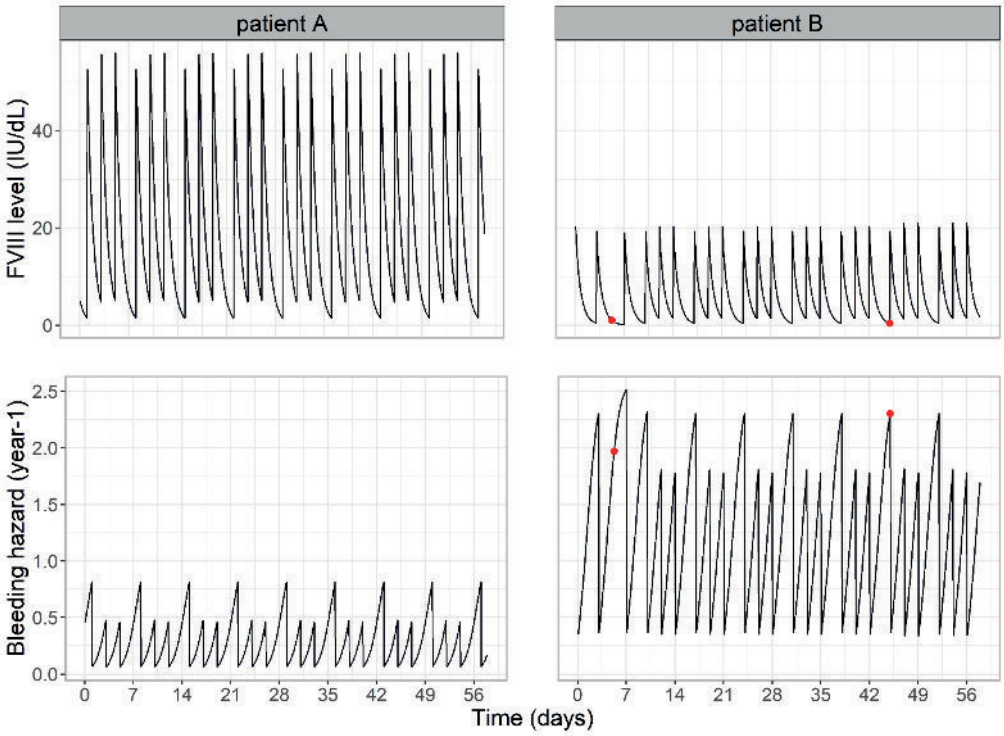
Furthermore, problems with correlations between covariates and multiplicity are avoided with this method. Covariates are described by the mean and variance, handled as observations into the dataset. The mean is included as fixed effect and the variance as a random effect. The FREM model estimates the random effects of the parameters and covariates and the covariance between those two in a full covariance matrix. The covariance between the parameter and covariates describes the covariate effect. An exponential covariate parameter relationship was used.

During model development we did not evaluate injuries as a covariate, as all bleeds except for 4 spontaneous bleeds, were related to an injury. Furthermore, when an injury occurred without a bleed, the timing of the last concentrate dose was not explicitly recorded.

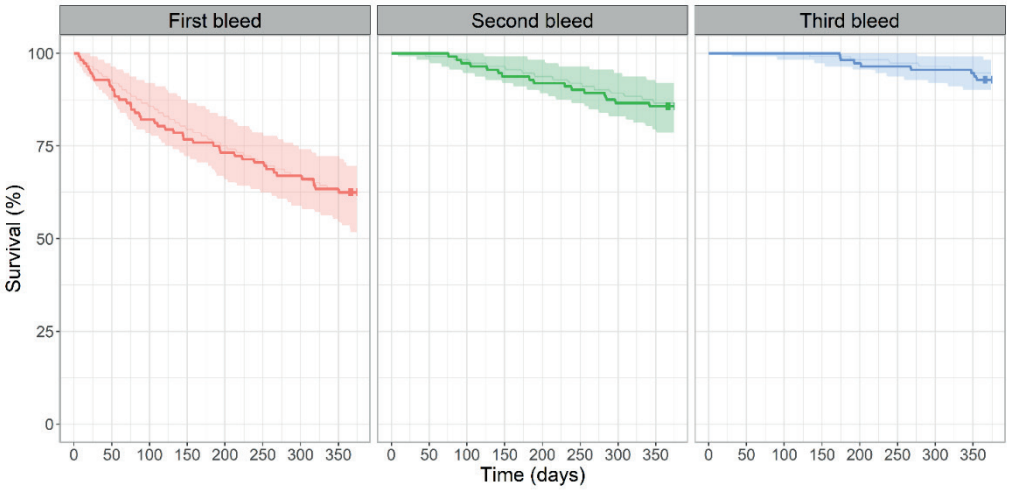
Model development and assessment

The repeated-time to event model was developed in NONMEM (v7.4.1, Icon Development Solutions, Gaithersburg, Maryland, United States). The model was estimated with the Monte Carlo importance sampling assisted by mode a posteriori (IMPMAP) method. R v4.1.1, Pirana v2.9.9. and PsN v5.2.6 were used for data handling, visualization, model management and evaluation.

Supplementary Figures



Supplement Figure 1: Illustration of relationship between factor VIII (FVIII) levels and bleeding hazard for two individuals from the dataset. In the top panels, individual FVIII level over time is plotted, while the bottom panels show the corresponding model predicted individual bleeding hazard. Patient A (10 years, 33 kg, treated with 3x per week 750 IU Elocta) did not experience any bleeds, while patient B (34 years, 73 kg, treated with 3x per week 1000 IU Novoeight) experienced two bleeds (red dots). The bleeding hazard is inversely related to the FVIII levels and is in general higher for patients that experience more bleeds.

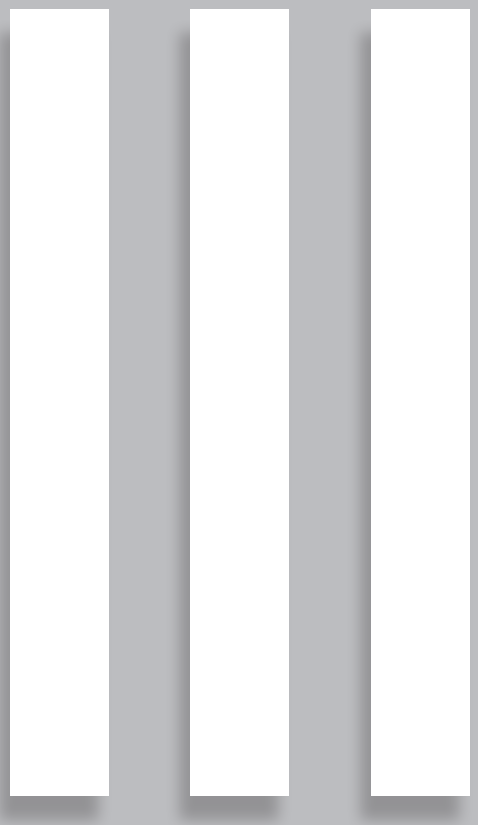


Supplement Figure 2: Kaplan Meier curves of the first, second and third bleed (solid lines) combined with 2.5th and 97.5th percentile of the model-predicted model predicted Kaplan Meier curves (shaded area, n=500 simulations). The shaded areas cover the Kaplan Meier curves of observed bleeds, demonstrating that the developed model describes the bleeding probability in our data adequately.

References

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. J Thromb Haemost. 2014;12:1935-1939
2. Anderson A, Forsyth A. Playing it safe: Bleeding Disorders, Sports and Exercise. Natl Hemoph Found. 2017:1-72
3. Feldman BM, Funk S, Lundin B, Doria AS, Ljung R, Blanchette V. Musculoskeletal measurement tools from the International Prophylaxis Study Group (IPSG). Haemophilia. 2008;14:162-169
4. Feldman BM, Funk SM, Bergstrom BM, et al. Validation of a new pediatric joint scoring system from the international hemophilia prophylaxis study group: Validity of the hemophilia joint health score. Arthritis Care Res. 2011;63:223-230
5. Holford N. A time to event tutorial for pharmacometricians. CPT Pharmacometrics Syst Pharmacol. 2013;2:e43
6. Abrantes JA, Solms A, Garmann D, Nielsen EI, Jönsson S, Karlsson MO. Relationship between factor VIII activity, bleeds and individual characteristics in severe hemophilia A patients. Haematologica. 2020;105:1443-1453
7. Yngman G, Bjugård Nyberg H, Nyberg J, Jonsson EN, Karlsson MO. An introduction to the full random effects model. CPT Pharmacometrics Syst Pharmacol. 2022;11:149-160

Part II – Pharmacokinetics



CHAPTER 10

Terminal half-life of FVIII and FIX according to age, blood group and concentrate type: data from the WAPPS database

Olav Versloot[1,2], Emma Iserman[3], Pierre Chelle[4], Federico Germini[3,5], Andrea N. Edginton[4], Roger E.G. Schutgens[1], Alfonso Iorio[3,5,6], Kathelijn Fischer[1] on behalf of the Pharmacokinetic (PK) Expert Working Group of the International Prophylaxis Study Group (IPSG).

[1] Van Creveldkliniek, University Medical Centre Utrecht, Utrecht, The Netherlands.

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada.

[4] School of Pharmacy, University of Waterloo, Waterloo, ON, Canada.

[5] Department of Medicine, McMaster University, Hamilton, ON, Canada.

[6] McMaster-Bayer Endowed Research Chair in Clinical Epidemiology of Congenital bleeding Disorders, Department of Medicine, McMaster, Hamilton, ON, Canada.

Journal of Thrombosis and Haemostasis, 2021 Aug; 19(8): 1896-1906

Bullet Points

What is already known:

- Trough levels during prophylactic treatment are dependent on dose, frequency and pharmacokinetics
- Data on terminal half-life are based on limited data, especially data on children is lacking
- Terminal half-life is associated with age in FVIII

What this study adds:

- Real-life pharmacokinetic data of FVIII/IX concentrates in large cohorts are currently lacking
- FVIII/IX reference values according to patient characteristics were created in a large dataset
- Terminal half-life increases linearly for age across the entire life-span for FVIII concentrates
- Terminal half-life increase increases up to age 30 years for FIX and remains constant afterwards

Abstract

Background: Real-life data on pharmacokinetics of FVIII/IX concentrates, especially extended half-life (EHL), concentrates in large cohorts of persons with hemophilia are currently lacking.

Objectives: This cross-sectional study aimed to establish reference values for terminal half-life (THL) for FVIII/IX concentrates according to concentrate type, age, blood group and inhibitor history.

Patients/Methods: Data were extracted from the Web-Accessible Population Pharmacokinetics Service (WAPPS) database. Groups were compared by non-parametric tests. THL was modelled according to patient characteristics and concentrate type.

Results: Infusion data (n=8022) were collected from 4832 subjects (including 2222 children) with severe hemophilia (age: 1 month–85 years; 89% hemophilia A; 34% using EHL concentrates, 9.8% with history of inhibitors). THL of FVIII-EHL was longer than of FVIII-Standard half-life (SHL; median 15.1 vs. 11.1 hours). FVIII-THL was dependent on age, concentrate type, blood group, and inhibitor history. THL of FIX-EHL was longer than of FIX-SHL (median 106.9 vs. 36.5 hours). FIX-THL increased with age until 30 years and remained stable thereafter. FVIII-THL was shorter in subjects with blood group O. THL was decreased by 1.3 hours for FVIII and 22 hours for FIX in subjects with a positive inhibitor history.

Conclusions: We established reference values for FVIII/IX concentrates according to patient characteristics and concentrate type in a large database of hemophilia patients. These reference values may inform clinical practice (e.g. assessment of immune tolerance success), economic implications of procurement processes and value attribution of novel treatments (e.g. mimetics or gene therapy).

Introduction

Severe hemophilia is a congenital disorder characterized by absence of coagulation factor VIII (FVIII, hemophilia A) or IX (FIX, hemophilia B). Intravenous replacement therapy has been the standard of care to prevent bleeding and its long-term consequences since its introduction. This has recently been complemented with non-replacement therapy. [1].

Terminal half-life (THL) for coagulation concentrates is relatively short: 9-15 hours for FVIII[2–4] and 17-33 hours for FIX[5–9]. Consequently, frequent infusions are required to maintain minimum trough levels needed for effective prophylaxis[10]. These regular infusions pose a burden for persons with hemophilia. This may lead to poor adherence and less favorable treatment results [11]. To facilitate decreased infusion frequency and/or higher trough levels, longer acting clotting factor concentrates have been developed in recent years. These concentrates are referred to as Extended Half-Life concentrates (EHL), as opposed to the traditional, largely unmodified Standard Half-life (SHL) concentrates. Mahlangu et al.[12] defined EHL concentrates as a product that was designed to, and has an increase in area under the curve (AUC) of at least 25% and a THL increase of at least 30%. Phase III studies with limited (range: 7-118 subjects) sample size have reported 1.5-2 fold increased terminal half-life values in FVIII EHL concentrates and 4 to 6 fold in FIX EHL concentrates[10,13–16]. However, these data need to be confirmed in clinical practice, both at group and individual level.

Persons with hemophilia show a high interpatient variability in dosing and THL of FVIII and FIX to sustain desired trough levels[9,17]. Individual pharmacokinetics (PK) are relevant in the choice and design of prophylactic treatment regimens and perioperative management. Pharmacokinetics are dependent on age and anthropometric values[1,18–22] and , since the introduction of EHL concentrates, on type of concentrate too[23–26]. Anthropometric assessments include several constructs [e.g.: body weight, body mass index (BMI), body surface area (BSA), fat free mass (FFM)][27]. It remains unclear which of these constructs is the optimal predictor in PK.

The aim of this study was to estimate THL for various FVIII/IX concentrates and establish reference values according to concentrate type, age, blood group and inhibitor status.

Methods

Design and Setting

This multi-center analysis was performed in collaboration between the University Medical Centre Utrecht (Utrecht, the Netherlands), McMaster University (Hamilton, Ontario, Canada) and the University of Waterloo (Waterloo, Ontario, Canada) on behalf of the Pharmacokinetic Expert Working Group of the International Prophylaxis Study Group (IPSG). The data were collected as part of the Web Accessible Population Pharmacokinetic Service (WAPPS) project and consisted of PK data collected between September 2016 and March 2020 (downloaded: 03/03/2020). The WAPPS project aims to assemble a database of patients' PK data for all existing factor concentrates, develop and validate population PK models, and integrate these models within a Web-based calculator for individualized pharmacokinetic estimation in patients at participating treatment centres[25,28,29]. The data included patient characteristics, treatment specific data, and calculated pharmacokinetic parameters. The WAPPS project was approved by the Institutional Review Board of McMaster University (#14-601-D) and University of Waterloo (#31977). The approval included the use of the collected data for modelling purposes and for investigating the determinants of factor concentrates pharmacokinetic variability, thus covering the analysis of the present study. All data were anonymized and did not include information on hemophilia treatment centers or date of assessment.

Data Collected

Infusion data from persons with severe hemophilia that were included in the WAPPS database until March 3rd, 2020 were included in this study. At that time, 298 treatment centers in 47 countries were participating in WAPPS. Patient data was were included in the WAPPS database when the treating physician wanted to estimate PK values for this patient. There was no targeted selection. Patients had to provide informed consent to have their data entered in the WAPPS database.

Patient characteristics (age, disease type and severity, weight, height, blood group, inhibitor status), treatment specific data (concentrate, dose administered, timing of laboratory samples), and calculated THL were collected. THL, calculated by the WAPPS Bayesian engine from the PK data, was the main outcome measure. THL was defined as the time required for the plasma concentration of concentrate to decrease by 50% after pseudo-equilibrium of distribution has been reached[30]. Inhibitor status was entered as formerly, currently, or never positive. This dataset contained inhibitor negative patients only, including those with a history of inhibitors. Blood group was collected as a proxy for von Willebrand Factor antigen (vWF:Ag), as vWF:Ag is lower in blood group O, and blood group is not an acute phase protein[31–33]. Blood group status was classified as O

or non-O. Clotting factor concentrates were grouped as SHL or EHL concentrates (see supplemental table S1).

Individual THL was derived from the PK parameters obtained from a Bayesian estimation model using concentrate specific models and according to concentrate types[28]. SHL Factor concentrates were subdivided into plasma derived (PD) or recombinant (Rc) concentrates. All EHL concentrates are recombinant products. These were subdivided according to their chemical binding structure with FVIII or FIX, being Fc bound (Fc), Albumin bound (Alb) or glycoPEGylated (PEG). FVIII concentrates are limited to Fc and PEG, all three recombinant types exist in FIX. THL was assessed according to this subdivision as well by means of non-parametric testing.

Statistics

Distribution of data were checked and outliers were removed to avoid overestimation in THL due to biased data. An outlier was defined as a value larger than the third quartile (Q3)+(1.5 x interquartile range (IQR)) or smaller than the first quartile (Q1)-(1.5 x IQR). Any value beyond these limits was discarded. Data are presented as median (IQR: P25-P75), mean (SD) or proportion (95% confidence interval (CI)) as appropriate.

Between group differences in THL were compared by means of parametric and non-parametric testing, as appropriate. The data from each subset (age, type of concentrate, inhibitor history) were checked for normality by means of Kolmogorov-Smirnoff testing. Parametric (ANOVA) or non-parametric (Mann-Whitney, Wilcoxon) methods were used for analysis, as appropriate.

Anthropometric measures (BMI, body surface area (BSA)[34], ideal body weight (IBW) and fat free mass (FFM)[35,36]) were calculated from height, weight and age (see appendix A). The association between anthropometric variables and THL was determined by separate univariable regression analyses for FVIII and FIX.

Age (children (<18) vs. adults (≥18)), BMI (underweight (BMI<18,5), normal weight (18,5-24), overweight (25-29), obese (30-40) were treated as categorical variables. A univariable analysis of THL as a function of selected parameters (age, inhibitor status, anthropometric measures, concentrate type) was performed for FVIII and FIX separately in order to select variables for a multivariable regression model. Parameters with a (borderline) significant association (p value <0,10) in the univariable analysis were included in the multivariable regression model.

Multivariable regression models were created for FVIII and FIX. A stepwise backwards

linear regression model was used to predict estimated THL (inclusion criterion: p<0,05; exclusion criterion: p>0,10). A univariable regression analysis of THL in FIX showed an age-related increase in THL for subjects until the age of 30, while THL remained stable from the age of 30 onwards (see results for details). Based on this, the models for the prediction of THL consisted of two separate formulas: one for persons younger than 30 and one for persons older than 30 years. The models were checked for collinearity by evaluating the variance inflation factor (VIF); collinearity was considered to be present when VIF was equal to 4 or more. Based on the regression coefficients, a formula was derived to allow estimation of THL based on patient characteristics.

Statistical significance levels were set at 5% (p<0,05). The statistical analysis was performed using SPSS statistical software, version 25 (IBM corp., Armonk. NY) and R (version 3.5.1.) and Rstudio (version 1.1.456)[37].

Data Sharing Statement

Original data can be accessed upon request from the original authors. Please contact wappshemo@mcmasterhkr.com.

Results

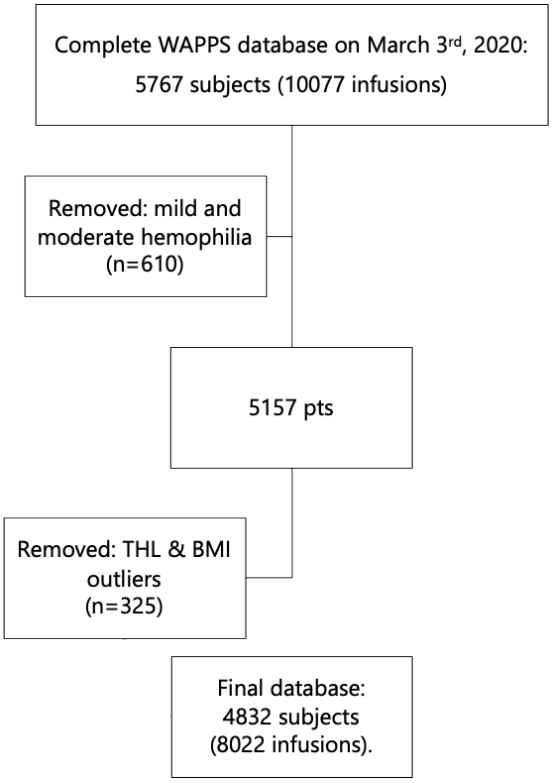


Figure 1: overview of available subjects and selection process of final database. Elimination of subjects with moderate and mild hemophilia reduced the number of included subjects (n=610). Subsequent elimination of outliers in BMI and THL reduced the total number of 4832 subjects with 8022 infusions.

Subjects and infusions

The selection process is shown in figure 1. Data from 100077 infusions (5767 participants) were available. After removal of persons with non-severe (moderate and mild: FVIII/FIX>0.01 IU/ml) hemophilia (n=610) and outliers on BMI (n=200) and THL (n=125), data from 4832 subjects with severe hemophilia (2222 children, 2610 adults) were included in the analysis. These subjects received 8022 infusions. Patient, disease and treatment characteristics for children and adults are shown in Table 1. Median age was 8 years (IQR: 5-12) for children, including 13.7% younger than 6 years (4.5% younger than 2 years). Median age for adults was 33 (25-45) years. The median BMI was 17.4 (15.6; 20.2) for children and 24.7 (22.3; 27.7) for adults, indicating that nearly half of the adults in

this study were overweight (BMI≥25), 13.5% were obese (BMI≥30). The majority (89%) of subjects had hemophilia A. EHL concentrates were used by 1619 subjects (34%). Table 2 shows patient characteristics according to diagnosis, age group and concentrate type (SHL and EHL). Subject characteristics for adults and children were similar. However, more children reported a positive inhibitor history (13.5%; 95%CI: 12.1-14.9), as compared to adults (6.7% (5.8-7.7); p<0.01).

Table 1: Subject, disease and treatment characteristics

	Overall		Children (0-17)		Adults (18-85)	
N	**4832**		**2222**		**2610**	
	n(%) or median (IQR)	**Range**	**n(%) or median (IQR)**	**Range**	**n(%) or median (IQR)**	**Range**
Age (years)	19 (9-35)	0-85	8 (5-12)	0-17	33 (25-45)	18-85
<2 year	205 (4,5%)		205 (4,5%)			
<6 year	625 (13,7%)		625 (13,7%)			
Weight (kg)	63 (32-78)	4-146	30 (19-49)	4-103	76 (67-86)	29-146
BMI (kg/m^2)	22 (18-26)	8-36	17 (16-21)	8-29	25 (22-28)	15-36
Blood group O	1233 (26%)		578 (26%)		655 (25%)	
Blood group missing	2063 (43%)		973 (44%)		1090 (42%)	
Positive inhibitor history	473 (9,8%)		298 (13%)		175 (7%)	
Disease and infusion characteristics						
Hemophilia A	4316 (89%)		2026 (91%)		2290 (88%)	
Extended half-life concentrate	1619 (34%)		683 (31%)		936 (36%)	
Infusions (n)	8022		3365 (42%)		4657 (58%)	
Infusions/patient	1,7		1,4		1,8	

IQR: Interquartile range (25th – 75th percentile); BMI: Body Mass Index

Terminal half-life according to concentrate type in FVIII and FIX

In total, 37 FVIII-SHL concentrates were included in the data set (including 10 recombinant and 27 plasma derived concentrates) and 13 FIX-SHL concentrates (including 2 recombinant and 11 plasma derived concentrates). Supplemental table S-1 shows the number of EHL and SHL concentrates for FVIII and FIX and their respective frequencies.

For SHL concentrates, THL was similar for FVIII-PD (n=1103) and FVIII-Rc (4177) concentrates (median 11.0 (IQR: 8.7; 13.8) vs. 11.0 (8.8; 13.7) hours; p=0.86). THL was longer for FIX-Rc (n=155) than FIX-PD concentrates (n=75): median 38.3 (32.3-42.9) vs. 33.7 (29.3-41.8) hours; p=0.02.

Table 2: Infusion (n=8022) characteristics according to diagnosis, age group and concentrate type

	FVIII				FIX			
N=8022	**Children (0-17)**		**Adults (18-85)**		**Children (0-17)**		**Adults (18-85)**	
	SHL	**EHL**	**SHL**	**EHL**	**SHL**	**EHL**	**SHL**	**EHL**
	n (%) or median (IQR)							
n	2134	941	3146	1152	106	184	124	235
Age (years; median (IQR))	8.6 (5.4-12.6)	10.6 (6.6-14.0)	35.9 (27.5-46.3)	35.5 (26.8-47.1)	9.7 (5.7-13.8)	9.0 (5.3-13.4)	34.2 (23.7-49.3)	37.4 (27.4-52.2)
Weight (kg; median (IQR))	29.5 (20.0-45.7)	37.0 (22.7-56.2)	75.0 (67.0-85.0)	77.0 (66.0-86.0)	36.4 (23.5-51.0)	30.3 (19.5-51.9)	77.0 (66.0-86.8)	80.0 (69.0-90.0)
BMI (kg/m^2; median (IQR))	17.3 (15.5-20.2)	18.2 (15.921.3)	24.3 (22.0-27.3)	24.5 (22.1-27.7)	18.5 (16.0-20.8)	17.5 (15.6-20.5)	25.8 (22.6-29.0)	25.3 (23.1-28.0)
Positive inhibitor history (N(%))	304 (14.2)	113 (12.0)	237 (7.5)	96 (8.3)	16 (15.1)	13 (7.1)	5 (4.0)	2 (0.9)
Blood group O (N(%))	639 (29.9)	234 (24.9)	945 (30)	296 (25.7)	31 (29.2)	31 (16.8)	28 (22.6)	42 (17.9)
THL (hours; median (IQR))	9.3 (7.7-11.3)	13.3 (10.9-16.4)	12.2 (10.0-14.9)	16.7 (13.4-20.2)	34.1 (29.3-39.0)	87.7 (66.2-111.7)	39.6 (33.4-44.1)	127.1 (99.0-153.0)

THL was similar for both types of FVIII-EHL concentrates (PEG: median (15.0 (IQR: 12.1; 18.4) vs. Fc: 15.0 (12.0-18.9) hours; p=0.41), whereas THL was shorter for FIX-Fc (90.0 (71.0-116.0) hours) than for FIX-Alb (128.3 (106.8-157.0) hours; p<0.01) and FIX-PEG (150.8 (138.8-164.8) hours; p<0.01). THL was similar in FIX-Alb (128.3 (106.8-157.0)) and FIX-PEG (150.8 (138.8-164.8); p=0.76). Despite a large absolute difference (~22 hrs; 15%), no significance was reached. This was likely due to a lack of statistical power (FIX-PEG: n=21; FIX-Alb: 149; FIX-Fc: 249). Therefore, THL was modelled separately for FIX-Fc and FIX-Alb/PEG.

Median THL for FVIII was 1.4 times longer for EHL concentrates (from 10.9 (8.7-13.6) to 15.1 (12.0-19.0) hours; p<0.01). The same accounts for FIX: median THL was 2.9 times longer for EHL concentrates (from 36.5 (31.2; 42.6) to 106.9 (81.1; 134.2) hours; p<0.01).

Terminal half-life according to age

Table 3A shows the results of the multivariable regression analysis of THL. THL increased 0,9 (95%CI: 0.8-0.9) hours in 10 years for FVIII and 12 hours/10 years (8-17) for FIX in subjects younger than 30. THL was not associated with age in FIX in subjects older than 30.

Figure 2A shows the association between age and THL in FVIII for SHL and EHL concentrates. THL showed a steady, linear increase with age in both SHL and EHL FVIII concentrates across the entire age rage (0-85 yrs). THL increased consistently by 1.0 hour/10 years (regression coefficient: 0.10 (CI: 0.09-0.10) for FVIII-SHL and by 1.2 hours/10 years (0.12 (0.10-0.13) for FVIII-EHL across all ages. Table 3B shows the results of an additional analysis with age as a categorical variable in children (age groups: 0-5; 6-11; 12-17 with the youngest age group as reference group). This showed the increase in THL with age was indeed linear in children (increase: 1,07 yr/age group). Figure 2B shows the association between age and THL in FIX. THL increased by 2.5 hours/10 years for subjects younger than 30 in FIX-SHL (0.25 (CI: 0.07-0.42) and 22 hours/10 years in FIX-EHL (2.2 (CI: 1.7-2.7)), showing an additional 2 hours/year increase compared to those on FIX-SHL. THL remained stable from age 30 onwards.

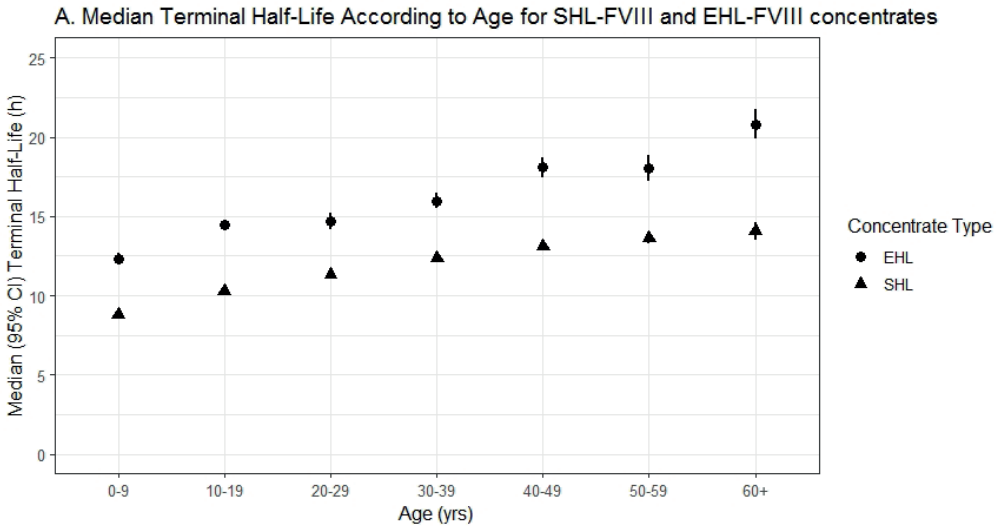
Table 3A: Regression coefficients (with 95% Confidence Interval) for multivariable regression analysis of terminal half-life

	FVIII (all ages)	FIX (<30)	FIX (≥30)
Constant	9.9 (9.4 - 10.1)	15.8 (0.03 - 31.6)	43.4 (4.9 – 82.0)
Age (per year)	0.09 (0.08 - 0.09)	1.2 (0.8 - 1.7)	n.s.
Extended Half Life (reference = SHL)	4.4 (4.2 - 4.5)	65.7 (60.2 - 71.2)	91.4 (83.1 - 99.6)
Positive inhibitor history	-0.9 (-1.2 – -0.7)	n.s.	n.s.
Blood group (O=1; non-O=0)	-1.4 (-1.6; -1.3)	-	-

Regression coefficients from a multivariate linear regression of THL for FVIII and FIX (<30 and ≥30). Only statistically significant parameters are specified. Age, Dose, Weight and BMI were included as continuous variable. Concentrate type, Positive inhibitor history, Child/adult and Blood group were included as dummy variables, with SHL, no history, child and blood group O as reference values. N.s.: non-significant

Table 3B: Regression coefficients (with 95% Confidence Interval) for multivariable regression analysis of THL in children with age as a categorical variable, corrected for inhibitor history, concentrate type and blood group.

	FVIII (children)
Age: 0-5 (reference category)	0
Age: 6-11	1,07 (0,78; 1,35)
Age: 12-17	2,14 (1,84; 2,44)



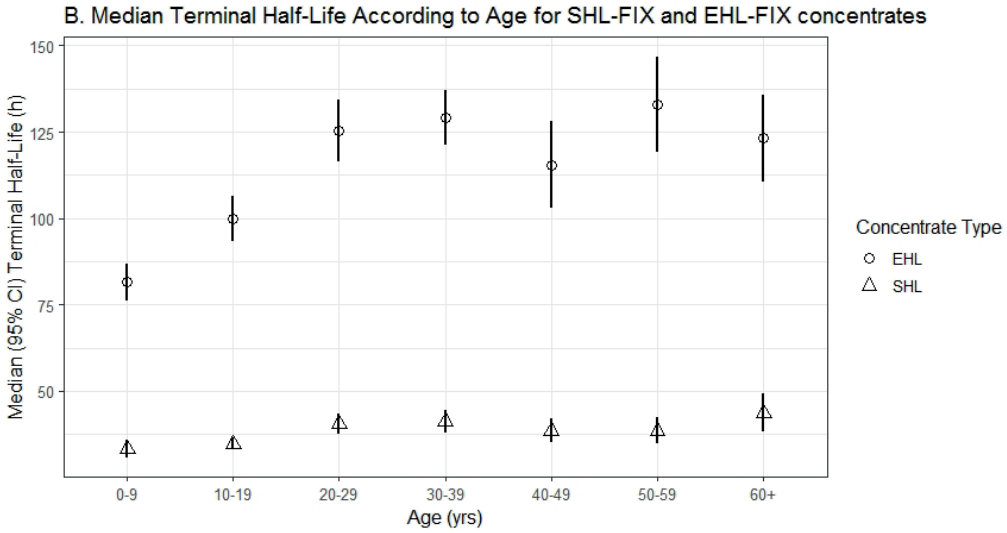


Figure 2: THL was associated with age in both FVIII and FIX. Figure 2A shows the association between THL and age for FVIII-SHL (solid triangles) and FVIII-EHL (solid circles). Figure 2B shows the association between THL and for FIX-SHL (open triangles) and FIX-EHL (open circles). Displayed error bars represent 95% confidence intervals.

Terminal half-life according to blood group

Figure 3A (SHL) and 3B (EHL) show the association between age and THL in FVIII for subjects with blood groups O or non-O. Only infusions with blood group data (5331 infusions (62%) in 2769 subjects (57%)) were included in this analysis. Overall median THL was ~2 hours shorter for hemophilia A subjects with blood group O compared to non-O (10,7 (8,5-13,8) vs. 13,0 (10,4-16,4) hours; p<0,01). This was observed for both FVIII-SHL and FVIII-EHL concentrates. FVIII-THL was shorter in subjects with blood group O using SHL concentrates (fig. 3A): median 9.8 (8.0-12.2) vs. 11,9 (9,6-14,5) hours in subjects with non-O; p<0,01), and in subjects using FVIII-EHL (median 13,6 (11,3-17,2) for blood group O vs. 17,6 (13,9-21,3) hours for those with blood group non-O; p<0,01). For FIX, THL was not associated with blood group (Spearman's rho: 0,31; p=0,20).

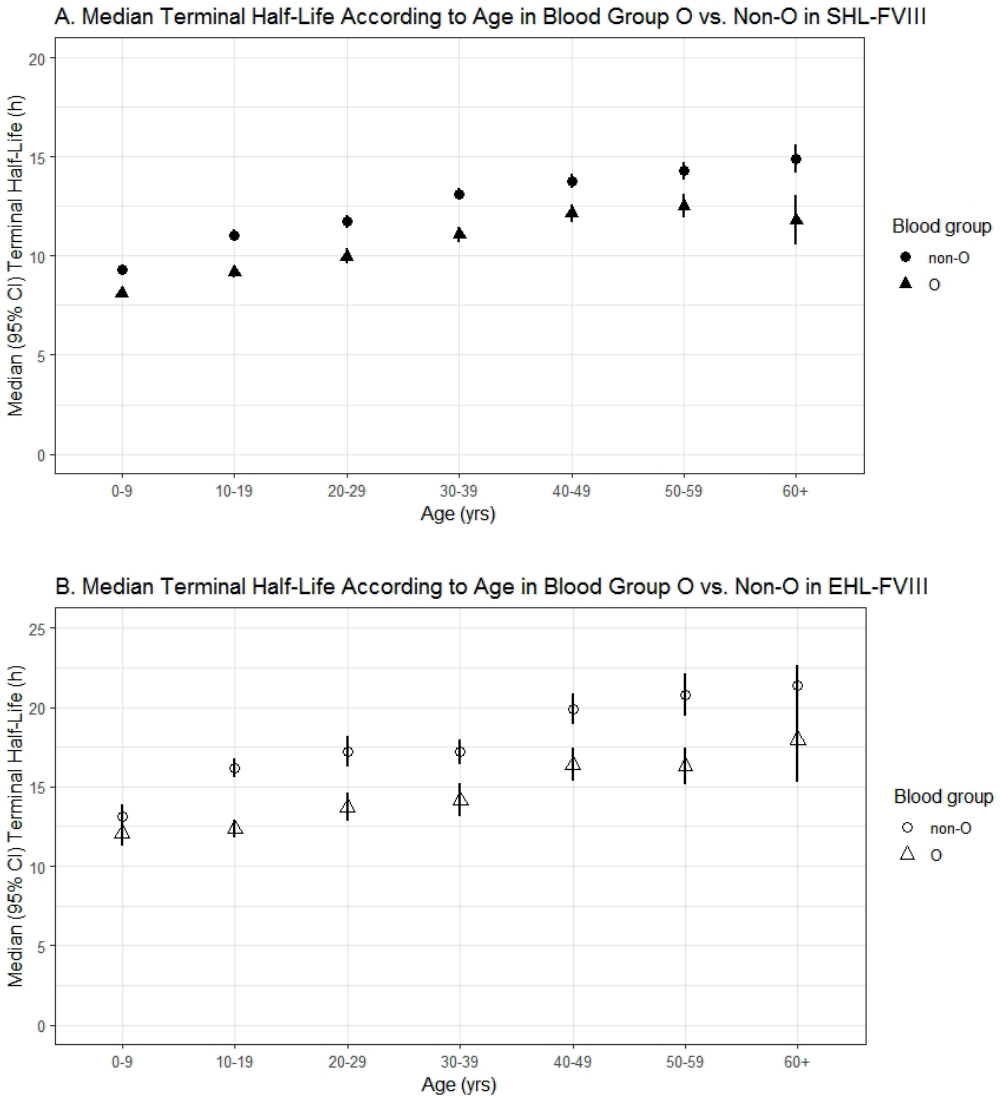


Figure 3: Terminal half-life (THL) in subjects with blood group O was lower than those with blood group non-O for both FVIII-SHL and FVIII-EHL concentrates. Figure 3A shows THL for FVIII-SHL in blood group O (solid triangles) and non-O (solid circles). Figure 3B shows median THL for blood group O (open triangles) and non-O (open circles) Displayed error bars represent 95% confidence intervals.

Terminal half-life according to body composition

To determine which parameter of body composition should be included in the estimation of THL, we compared the variance explained (adjusted R^2) by weight, BMI, BSA, and FFM in univariable regression models for THL of FVIII and FIX. The individual results are presented in table A-1 in appendix A. For FVIII, all parameters had similar R^2 values. Therefore, the parameter 'weight' was chosen for its ease of application. For FIX, weight turned out to be the poorest predictor of THL. Adjusted R^2 was similar for BMI, BSA and FFM. Therefore, BMI was chosen as the body composition parameter for FIX for the ease of practical application.

Terminal half-life according to inhibitor history

A positive inhibitor history was reported for 473 (9.8%; FVIII: 454 (10.5%); FIX: 19 (3.7%)) subjects, who underwent a total of 893 (10.4%) PK assessments. Subjects with a positive inhibitor history reported a shorter median THL for both FVIII (10.4 (8.1-13.3) hours for ex-inhibitor subjects vs. 12.1 (9.5-15.6) for others) and FIX (median 38.6 (30.1-72.5) vs. 81.1 (41.1-121.2) hours). Subjects with a positive inhibitor history were younger in both users of FVIII (15.4 (7.6-29.0) vs. 24.3 (11.3-39.8)) and FIX (13.7 (7.3-16.0) vs. 22.0 (10.0-41.1)). Multivariable regression analysis showed that a history of inhibitors was independently associated with a shorter THL (regression coefficient: -0,9 (95%CI: -1,2 to-0,6) for FVIII, but not for FIX (-0.15 (-10 to +9); p=0.98). Although there was a shorter THL in subjects with a positive history of FIX inhibitors, the number of observations was limited (n=19) and significance was not reached due to a lack of statistical power.

Table 4: Regression formulas for THL (in hours) for FVIII and FIX

		THL formula (in hours)
FVIII	All ages	= 9,9 + 0,09 x age (years) + 4,4 (if on EHL) -0,9 (if positive inhibitor history) -1,4 (if blood group O)
FIX	<30 years	= 15,8 + 1,2x age (years) +65,7 (if on FIX-Fc) +98,7(If on FIX-Alb)
	≥30 years	= 43,4 +91,4 (if on FIX-Fc) +109,6(if on FIX-Alb)

Regression formulas for the prediction of THL in FVIII and FIX. Calculation example: for a 14-old boy with hemophilia A on SHL, with a positive inhibitor history and blood group A, THL would become 10,3 hours. When the same boy is using EHL, THL will be 11,3 hours. These reference values, including 95% confidence intervals, can be determined using the new calculator on the WAPPS website (www,wapps.hemo.org).

Establishing reference values

Reference values according to patient characteristics were based on multivariable regression analyses. For FVIII, these analyses showed that THL was independently associated with age, body weight, concentrate type, a positive inhibitor history and blood group. However, due to the limited independent significance of body weight (+0.2 hours/10 kg), body weight was not included in the final model for FVIII. This limited clinical significance is likely caused by the correlation between body weight and age. The proposed final formula for FVIII-THL estimation according to patient characteristics is shown in Table 4. FVIII-THL could be estimated by age (+1 hour/10 years), blood group (-1.4 hours for blood group O), history of inhibitors (-0.9 hours when positive), and concentrate type (+4.4 hours when on EHL).

FIX-THL was increased with age until the age of 30, and was modelled according to two age-categories to promote interpretation of regression analyses. For subjects younger than 30 years FIX-THL could be predicted by age (+12 hours/10 years) and concentrate type, with an added THL for FIX-Fc (+65.7 hours) and FIX-Alb (+98.7 hours), while from age 30 onwards, THL remained stable and was only predicted by concentrate type, i.e. FIX-Fc (+91.4 hours) or FIX-Alb (≥30 years: +109.6 hours). Although BMI showed a significant association with FIX-THL, it was not identified as a significant predictor in the multivariable model for FIX-THL. A positive inhibitor history did not contribute significantly to the model in FIX, despite the significant decrease in THL for subjects with a positive inhibitor history in the univariable analysis.

Discussion

Principal findings

This study of 8022 infusions in 4832 subjects represents the largest series of pharmacokinetic assessments in persons with hemophilia to date. It is the first study to include over 600 children younger than 6 years. It is the first to show that THL increases linearly with age across the entire age span for FVIII concentrates and increased up to age 30 years for FIX concentrates. The prolongation of THL for extended half-life FVIII/IX concentrates was confirmed and quantified in this study. THL of FVIII was dependent on age, weight, blood group, inhibitor status and concentrate type. THL of FIX concentrates was dependent on age and concentrate type.

By demonstrating the linear effect of age on PK, this study may allow simplifying the design and conduct of future studies in the field by releasing the specific sampling of children in the age bands 0-6, 6-12, and 12-18. Indeed, PK data can be confidently pooled

across all ages increasing the power of analysis while simplifying enrollment, usually difficult to achieve for a rare disease like hemophilia. By providing reference values for THL for FVIII and FIX, this study promotes effective treatment decision making in hemophilia.

Strengths and limitations

This study analyzed THL and its determinants in the largest multicenter, multinational database currently available (WAPPS) so far. All data were collected and recorded in a standardized way and FVIII/IX activity levels were measured according to local laboratory standards. As the database includes data from 298 centers, its data are subject to inter-laboratory variation. the model was not corrected for individual centers as these real-world data are representative of a large proportion of users of factor concentrates globally, thus increasing the external validity of our results.

Classical PK assessments are very demanding, which is why most previous studies addressing PK in hemophilia have relied on adults or children over six years. Population based Bayesian PK models can provide estimates based on a limited number of samples, making PK assessment much more accessible[18,28,29,38–42]. This is well illustrated in the WAPPS database [24,25,43–45]. As a result, this study included subjects of all ages (13,7% below 6), including very young children (4,5% below 2) as well. This large number of young children adds to the existing data and allows for assessment of the effects of age on THL.

Blood group was missing in a substantial proportion (43%) of the subjects in this study. However, the distribution of the remaining blood group data was similar to the global distribution, suggesting absence of bias. The analysis of those with blood group data indicate that blood group is an important covariate, particularly in persons with hemophilia A. The remaining dataset however, was sufficiently large to generate reliable results.

Comparison with other studies

This study confirmed the reported 1,4-fold prolongation of THL for FVIII-EHL concentrates and 3-fold (range: 2.4 (Fc)-4.0 (PEG)) prolongation of THL for FIX-EHL as reported in previous studies[15,16,46]. However, these previous studies were generally smaller in size (<100 subjects). Data on FIX-Fc concentrates and FIX-Albumin concentrates were considered individually. Fc-fusion concentrates accounted for an additional prolongation of 65,7 hours in subjects below 30 years and 98,7 hours in subjects over 30 years while Albumin-fusion concentrates accounted for extensions of 91,4 and 109,6 hours, respectively. These increases were more pronounced than those presented in a review of data in 518 subjects by Mannucci et al.[47], who reported an 82,1 hour increase in THL

for FIX-Fc (123 subjects) and 92 hours in FIX-Alb concentrate (25 subjects)[47]. However, the differences were relatively small (10% and 16%, respectively), especially given the differences in sample size.

This study showed a linear age-related increase in THL in FVIII, independent of product type over the entire age range of this study (0-85 years). The linear correlation between age and THL has the potential to simplify estimation of THL across age groups, particularly in combination with the proposed regression model for FVIII[48]. This increase in THL may be explained with a recently suggested age-related increase in vWF:Ag[49]. In contrast to earlier reports, this study showed that THL increased with age in FIX, but this increase was only observed for subjects up to 30 years. Björkman reported stable THL with increasing age in a series of 56 subjects (46 severe, aged 4-56, number of assessments not reported)[20].

This study reported a 2-hour reduction of THL of FVIII in subjects with blood group O in a subgroup of 2769 subjects (5331 infusions). This was a confirmation of previous studies performed in small groups of <40 subjects/assessments. Vlot et al.[33] (n=32, age range: 13-63) and Fischer et al.[50] (n=38; mean age: 28±10) reported THL being 4.4 and 2.8 hours shorter in subjects with blood group O compared to blood group non-O, respectively. Two other studies Tiede et al.[22] (n=35; mean age: 37±10) and Carcao et al. (n=25, age range: 12-18) reported shorter THL in subjects with blood group O as well without specifying the magnitude of the difference[22,51].

Although we could not identify any published reports, many clinicians have suggested that subjects with a positive inhibitor history show a shorter THL in both FVIII and FIX, which was confirmed in this study. Although the proportion of subjects with a history of inhibitors in the present study was relatively small (FVIII: 454 (10,5%); FIX: 19 (3,7%)) compared to other studies[52,53], it represents the largest dataset available to study the association between inhibitor history and THL. The proportion of subjects with a positive history of inhibitors was about one third of the 30% reported cumulative inhibitor incidence for severe hemophilia A[52] and the 10% reported for severe hemophilia B.[53] A selection bias or information bias cannot be excluded due to the low number of subjects with a history of inhibitors and/or the fact that these subjects were generally younger. Multivariable regression showed the independent effect of inhibitor history on THL of FVIII, but not on FIX-THL, probably due to lack of statistical power.

Body composition parameters have been under discussion in PK research. This study suggested that body weight (FVIII) and BMI (FIX) seem sufficient for the modelling of THL. Although FFM might be performing better in modelling[24,26], body weight or BMI seem

to be sufficient for clinical purposes as well as more practical for clinicians. However, several studies indicated the importance of other body composition parameters (e.g.: BMI, FFM, BSA) with regards to PK[22,27,54]. Henrard et al.[55] showed the importance of BMI and IBW in dosing of under- and overweight in FVIII in 201 persons with hemophilia A, while Tiede et al.[22] reported that clearance and recovery were more associated with BMI than with other body composition parameters (e.g.: BSA and LBW) in 35 adult subjects (mean age 37,4; mean BMI: 28,6; 66% overweight or obese), but THL was not associated with BMI. FIX is present in extravascular tissues, whereas FVIII seems to be limited to the vascular system[56]. This could explain that PK modelling of FIX relies more on total body predictors (e.g.: BMI, BSA) than on body weight.

Clinical relevance and future research

The clinical use of EHL in hemophilia treatment is increasing, urging researchers to study the mechanisms and benefits of these concentrates. Population-based PK modelling can be a valuable tool to estimate THL in persons with hemophilia[25,39]. Particularly in the absence of measured data, or when subjects and caregivers consider switching to EHL concentrates, population-based models based on elementary patient data (e.g.: age, body weight/BMI, type of concentrate, inhibitor history, blood group)[22,27] can assist in establishing dose, choice of concentrate, and dosing intervals. In addition, results from the formula can be used to establish reference values. Reference values are especially important for setting standards around surgery and determining the return to normal THL during immune tolerance therapy in subjects with inhibitors[1]. In addition, reference values provide essential information in the assessment of the economic impact of procurement processes and value attribution of novel treatment modalities such as mimetics or gene therapy. Clinicians can determine the reference values of THL, including the 95% confidence intervals, using the new calculator provided In the WAPPS system (www.wapps-hemo.org).

This study showed that subjects with blood group O in FVIII had lower THL than those with blood group non-O, which emphasizes the need to routinely assess blood group type in persons with hemophilia A. Subjects with blood group O may require a different initial dosing when starting prophylaxis.

This study was performed at population level. Within the age of personalized medicine, individualized PK assessments seem more appropriate. Our next project will be to analyze the effects of switching from SHL to EHL in individual subjects.

Conclusions

THL increased linearly with age across the entire lifespan for FVIII concentrates. For FIX concentrates, THL increased up to age 30 years and remained stable afterwards. Furthermore, THL was shorter in subjects with a history of an inhibitor against FVIII. FVIII-THL was shorter in subjects with blood group O. The extension of THL for EHL concentrates was confirmed. FIX-THL was longer in recombinant FIX than in plasma derived FIX. These results have the potential to give clear clinical guidance to clinicians for establishing long-term treatment strategies in daily life, around surgery or when treating subjects with ITI.

References

1. Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;(May):1-158. doi:10.1111/hae.14046
2. EMA. *Product Characteristics Kogenate - Annex I*.; 2010. doi:10.1163/ej.9789004166523.i-402.43
3. EMA. *Product Characteristics Advate - Annex I*.; 2013. doi:10.1163/ej.9789004166523.i-402.43
4. EMA. *Product Characteristics Kovaltry - Annex I*.; 2016. doi:10.1163/ej.9789004166523.i-402.43
5. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B. *N Engl J Med*. 2013;369(24):2313-2323. doi:10.1056/nejmoa1305074
6. EMA. *Product Characteristics Benefix - Annex I*.; 2009. doi:10.1163/ej.9789004166523.i-402.43
7. EMA. *Product Characteristics Rixubis - Annex I*.; 2014. doi:10.1163/ej.9789004166523.i-402.43
8. FDA. Product Characteristics Mononine. Mononine. Published 2021. https://www.drugs.com/pro/mononine.html#s-34090-1
9. Collins PW, Fischer K, Morfini M, Blanchette VS, Björkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. *Haemophilia*. 2011;17(1):2-10. doi:10.1111/j.1365-2516.2010.02370.x
10. Kumar R, Dunn A, Carcao M. Changing Paradigm of Hemophilia Management: Extended Half-Life Factor Concentrates and Gene Therapy. *Semin Thromb Hemost*. 2016;42(1):18-29. doi:10.1055/s-0035-1568877
11. Hacker MR, Geraghty S, Manco-Johnson MJ. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia*. 2001;7(4):392-396. doi:10.1046/j.1365-2516.2001.00534.x
12. Mahlangu J, Young G, Hermans C, Blanchette V, Berntorp E, Santagostino E. Defining extended half-life rFVIII—A critical review of the evidence. *Haemophilia*. 2018;24(3):348-358. doi:10.1111/hae.13438
13. Graf L. Extended Half-Life Factor VIII and Factor IX Preparations. *Transfus Med Hemotherapy*. 2018;45(2):86-91. doi:10.1159/000488060
14. Mancuso M, Santagostino E. Outcome of Clinical Trials with New Extended Half-Life FVIII/IX Concentrates. *J Clin Med*. 2017;6(4):39. doi:10.3390/jcm6040039
15. Mullins ES, Stasyshyn O, Alvarez-Román MT, et al. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. *Haemophilia*. 2017;23(2):238-246. doi:10.1111/hae.13119
16. Tiede A, Abdul-Karim F, Carcao M, et al. Pharmacokinetics of a novel extended half-life glycoPEGylated factor IX, nonacog beta pegol (N9-GP) in previously treated patients with haemophilia B: results from two phase 3 clinical trials. *Haemophilia*. 2017;23(4):547-555. doi:10.1111/hae.13191
17. Collins PW, Björkman S, Fischer K, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: Influences of variance in pharmacokinetics and treatment regimens. *J Thromb Haemost*. 2010;8(2):269-275. doi:10.1111/j.1538-7836.2009.03703.x
18. Björkman S, Oh M, Spotts G, et al. Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Thromb Haemost*. 2012;119(2):612-618. doi:10.1182/blood-2011-07-360594.The
19. Dargaud Y, Delavenne X, Hart DP, Meunier S, Mismetti P. Individualized PK-based prophylaxis in severe haemophilia. *Haemophilia*. 2018;24(November 2017):3-17. doi:10.1111/hae.13397
20. Björkman S, Shapiro AD, Berntorp E. Pharmacokinetics of recombinant factor IX in relation to age of the patient: Implications for dosing in prophylaxis. *Haemophilia*. 2001;7(2):133-139. doi:10.1046/j.1365-2516.2001.00465.x
21. Aronstam A, McLellan DS, Wassef M, Mbatha PS. Effect of height and weight on the in vivo recovery of transfused factor VIII C. *J Clin Pathol*. 1982;35(3):289-291. doi:10.1136/jcp.35.3.289
22. Tiede A, Cid AR, Goldmann G, et al. Body Mass Index Best Predicts Recovery of Recombinant Factor VIII in Underweight to Obese Patients with Severe Haemophilia A. *Thromb Haemost*. 2020;120(2):277-288. doi:10.1055/s-0039-3400745
23. Collins PW, Fischer K, Morfini M, Blanchette VS, Björkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. *Haemophilia*. 2011;17(1):2-10. doi:10.1111/j.1365-2516.2010.02370.x

24. McEneny-King A, Chelle P, Foster G, Keepanasseril A, Iorio A, Edginton AN. Development and evaluation of a generic population pharmacokinetic model for standard half-life factor VIII for use in dose individualization. *J Pharmacokinet Pharmacodyn*. 2019;46(5):411-426. doi:10.1007/s10928-019-09634-7

25. Hajducek DM, Chelle P, Hermans C, et al. Development and evaluation of the population pharmacokinetic models for FVIII and FIX concentrates of the WAPPS-Hemo project. *Haemophilia*. 2020;(February):1-17. doi:10.1111/hae.13977

26. Chelle P, Yeung CHT, Croteau SE, et al. Development and Validation of a Population-Pharmacokinetic Model for Rurioctacog Alfa Pegol (Adynovate®): A Report on Behalf of the WAPPS-Hemo Investigators Ad Hoc Subgroup. *Clin Pharmacokinet*. 2020;59(2):245-256. doi:10.1007/s40262-019-00809-6

27. McEneny-King A, Chelle P, Henrard S, Hermans C, Iorio A, Edginton AN. Modeling of body weight metrics for effective and cost-efficient conventional factor VIII dosing in hemophilia a prophylaxis. *Pharmaceutics*. 2017;9(4). doi:10.3390/pharmaceutics9040047

28. Iorio A, Keepanasseril A, Foster G, et al. Development of a Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Study Protocol. *JMIR Res Protoc*. 2016;5(4):e239. doi:10.2196/resprot.6558

29. McEneny-King A, Foster G, Iorio A, Edginton AN. Data Analysis Protocol for the Development and Evaluation of Population Pharmacokinetic Models for Incorporation Into the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo). *JMIR Res Protoc*. 2016;5(4):e232. doi:10.2196/resprot.6559

30. Toutain PL, Bousquet-Mélou A. Plasma terminal half-life. *J Vet Pharmacol Ther*. 2004;27(6):427-439. doi:10.1111/j.1365-2885.2004.00600.x

31. Gill JC, Endres-Brooks J, Bauer PJ, Marks Jr. WJ, Montgomery RR. The effect of ABO Blood Group on the Diagnosis of von Willebrand Disease. *Blood*. 1987;69(6):1691-1695. doi:10.5040/9781408185094.00000006

32. Franchini M, Capra F, Targher G, Montagnana M, Lippi G. Relationship between ABO blood group and von Willebrand factor levels: from biology to clinical implications. *Thromb J*. 2007;5(14):1-5. doi:10.1186/1477-9560-5-14

33. Vlot AJ, Mauser-Bunschoten EP, Zarkova AG, et al. The half-life of infused factor VIII is shorter in hemophiliac patients with blood group O than in those with blood group A. *Thromb Haemost*. 2000;83(1):65-69. doi:10.1055/s-0037-1613759

34. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098. doi:10.1056/NEJM198710223171717

35. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet*. 2005;44(10):1051-1065. doi:10.2165/00003088-200544100-00004

36. Al-Sallami HS, Goulding A, Grant A, Taylor R, Holford N, Duffull SB. Prediction of Fat-Free Mass in Children. *Clin Pharmacokinet*. 2015;54(11):1169-1178. doi:10.1007/s40262-015-0277-z

37. Team Rs. RStudio. Published online 2015. www.rstudio.com

38. Wakefield J. The Bayesian Analysis of Population Pharmacokinetic Models. *J Am Stat Assoc*. 1996;91(433):62-75. doi:10.1080/01621459.1996.10476664

39. Björkman S. Limited blood sampling for pharmacokinetic dose tailoring of FVIII in the prophylactic treatment of haemophilia A. *Haemophilia*. 2010;16(4):597-605. doi:10.1111/j.1365-2516.2009.02191.x

40. McEneny-King A, Iorio A, Foster G, Edginton AN. The use of pharmacokinetics in dose individualization of factor VIII in the treatment of hemophilia A. *Expert Opin Drug Metab Toxicol*. 2016;12(11):1313-1321. doi:10.1080/17425255.2016.1214711

41. Björkman S, Collins P. Measurement of factor VIII pharmacokinetics in routine clinical practice. *J Thromb Haemost*. 2013;11(1):180-182. doi:10.1111/jth.12055

42. McEneny-King A, Yeung CHT, Edginton AN, Iorio A, Croteau SE. Clinical application of Web Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Patterns of blood sampling and patient characteristics among clinician users. *Haemophilia*. 2020;26(1):56-63. doi:10.1111/hae.13882

43. Brekkan A, Degerman J, Jönsson S. Model-based evaluation of low-dose factor VIII prophylaxis in haemophilia A. *Haemophilia*. 2019;25(3):408-415. doi:10.1111/hae.13753

44. Brekkan A, Berntorp E, Jensen K, Nielsen EI, Jönsson S. Population pharmacokinetics of plasma-derived factor IX: Procedures for dose individualization. *J Thromb Haemost*. 2016;14(4):724-732. doi:10.1111/jth.13271

45. Björkman S, Carlsson M, Berntorp E, Stenberg P. Pharmacokinetics of Factor VIII in Humans: Obtaining Clinically Relevant Data from Comparative Studies. *Clin Pharmacokinet*. 1992;22(5):385-395. doi:10.2165/00003088-199222050-00005

46. Young G, Mahlangu JN. Extended half-life clotting factor concentrates: results from published clinical trials. *Haemophilia*. 2016;22:25-30. doi:10.1111/hae.13028

47. Mannucci PM. Half-life extension technologies for haemostatic agents. *Thromb Haemost*. 2015;113(1):165-176. doi:10.1160/TH14-04-0332

48. Björkman S. Comparative pharmacokinetics of factor VIII and recombinant factor IX: For which coagulation factors should half-life change with age? *Haemophilia*. 2013;19(6):882-886. doi:10.1111/hae.12253

49. Biguzzi E, Castelli F, Lijfering WM, et al. Rise of levels of von Willebrand factor and factor VIII with age: Role of genetic and acquired risk factors. *Thromb Res*. 2021;197(November 2020):172-178. doi:10.1016/j.thromres.2020.11.016

50. Fischer K, Pendu R, van Schooten CJ, et al. Models for prediction of factor VIII half-life in severe haemophiliacs: Distinct approaches for blood group O and non-O patients. *PLoS One*. 2009;4(8):1-7. doi:10.1371/journal.pone.0006745

51. Carcao M, Chelle P, Clarke E, et al. Comparative pharmacokinetics of two extended half-life FVIII concentrates (Eloctate and Adynovate) in adolescents with hemophilia A: Is there a difference? *J Thromb Haemost*. 2019;17(7):1085-1096. doi:10.1111/jth.14469

52. Van Den Berg HM, Fischer K, Carcao M, et al. Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. *Blood*. 2019;134(3):317-320. doi:10.1182/blood.2019000658

53. Male C, Andersson NG, Rafowicz A, et al. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: a PedNet study. *Haematologica*. Published online 2020:haematol.2019.239160. doi:10.3324/haematol.2019.239160

54. Suzuki N, Hirakawa A, Kishimoto M, et al. Retrospective analysis of in vivo recovery and clearance during continuous infusion of recombinant factor VIII products: a single-institution study. *Haemophilia*. 2017;23(2):215-221. doi:10.1111/hae.13082

55. Henrard S, Speybroeck N, Hermans C. Impact of being underweight or overweight on factor VIII dosing in hemophilia A patients. *Haematologica*. 2013;98(9):1481-1486. doi:10.3324/haematol.2013.084038

56. Stafford DW. Extravascular FIX and coagulation. *Thromb J*. 2016;14(Suppl 1). doi:10.1186/s12959-016-0104-2

Appendix A – Body Composition Parameters

Body Mass Index (BMI, kg/m^2): $\frac{\text{weight (kg)}}{\text{height (m)}^2}$

Body Square Area (BSA; m^2)[28]: $\sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$

Ideal Body Weight (IBW, kg): $\text{height} - 100 - \left(\frac{\text{height} - 150}{4}\right)$ (Lorentz formula for men)

Fat Free Mass (FFM; kg)[29,30]: $\left[0.88 + \left(\frac{1 - 0.88}{1 + \left(\frac{\text{Age}}{13.4}\right)^{-12.7}}\right)\right] \times \frac{9720 \times \text{weight (kg)}}{6680 + (216 \times \text{BMI})}$

Table A-1: Adjusted R^2 values from univariable regression of THL as a function of body composition parameters

	Weight	BMI	BSA	FFM
FVIII	0.375	0.376	0.380	0.380
FIX - <30	0.616	0.630	0.631	0.631
FIX - ≥30	0.664	0.672	0.681	0.683

Univariable regression analysis of THL as a function of individual body composition parameters showed minimal differences between parameters in FVIII, while weight performed considerably poorer than the other parameters in FIX. For the ease of practical application, weight was chosen for FVIII, while BMI was chosen for FIX.

Supplemental Material

Table S-1a: frequency distribution of prescribed FVIII clotting factor concentrates (SHL)

Concentrate type	Product name	Recombinant (Rec) or Plasma Derived (PD)	Infusion Frequency	Percentage
SHL	Advate	Rec	1531	29
	Kogenate	Rec	890	16.9
	Kovaltry	Rec	436	8.3
	Refacto	Rec	277	5.2
	Fanhdi	PD	255	4.8
	Refacto AF	Rec	255	4.8
	Recombinate	Rec	258	4.8
	Nuwiq	Rec	229	4.3
	Octanate	PD	165	3.1
	Novoeight	Rec	139	2.6
	Green VIII	PD	125	2.4
	Kogenate Nextgen	Rec	91	1.7
	Alphanate	PD	87	1.6
	Beriate	PD	78	1.5
	Afstyla	Rec	71	1.3
	Immunate	PD	66	1.3
	Hemophil M	PD	56	1.1
	Wilate	PD	37	0.7
	Koate DVI	PD	36	0.7
	Monoclate	PD	28	0.5
	Hualan	PD	26	0.5
	Taibang-FVIII	PD	18	0.3
	Factane	PD	17	0.3
	Haemoctin Sdh	PD	17	0.3
	Emoclot	PD	14	0.3
	Amofil	PD	12	0.2
	Profilate	PD	12	0.2
	Haemate P	PD	9	0.2
	Aafact	PD	8	0.2
	GreenMono	PD	8	0.2
	Humaclot	PD	6	0.1
	Octavi	PD	6	0.1
	Biostate	PD	5	0.1
	Klott	PD	5	0.1
	Optivate	PD	4	0.1
	HemoRAAS	PD	2	0
	Faktor VIII SDH Intersero	PD	1	0

Table S-1a (continued): frequency distribution of prescribed FVIII clotting factor concentrates (EHL)

Concentrate type	Product name	Recombinant (Rec) or Plasma Derived (PD)	EHL method	Infusion Frequency	Percentage
EHL	Percentage				
	Elocta	Rec	Fc	1629	77.8
	Adynovate	Rec	PEG	433	20.7
	Jivi	Rec	PEG	27	1.3
	Esperoct	Rec	PEG	4	0.2

Table S-1b: frequency distribution of prescribed FIX clotting factor concentrates

Concentrate type	Product name	Recombinant (Rec) or Plasma Derived (PD)	EHL method	Infusion Frequency	Percentage
SHL	Benefix	Rec	-	141	61.3
	Octanine	PD	-	19	8.3
	Alphanine	PD	-	17	7.4
	Rixubis	Rec	-	14	6.1
	Aimafix	PD	-	13	5.7
	Factor IX Grifols	PD	-	9	3.9
	Immunine	PD	-	9	3.9
	Berinin	PD	-	2	0.9
	Replenine – Vf	PD	-	2	0.9
	Betafact	PD	-	1	0.4
	Mononine	PD	-	1	0.4
	Nonafact	PD	-	1	0.4
	Octafix	PD	-	1	0.4
EHL	Alprolix	Rec	Fc	249	59.4
	Idelvion	Rec	Albumin	149	35.6
	Rebinyn	Rec	PEG	21	5.0

CHAPTER 11

Predicting individual changes in terminal half-life after switching to extended half-life concentrates in patients with severe hemophilia.

Olav Versloot[1,2], Emma Iserman[3], Pierre Chelle[4], Federico Germini[3,5], Andrea N. Edginton[4], Roger E.G. Schutgens[1], Alfonso Iorio[3,5,6], Kathelijn Fischer[1] on behalf of the Pharmacokinetic (PK) Expert Working Group of the International Prophylaxis Study Group (IPSG).

[1] Van Creveldkliniek, University Medical Centre Utrecht, Utrecht, The Netherlands.

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada.

[4] School of Pharmacy, University of Waterloo, Waterloo, ON, Canada.

[5] Department of Medicine, McMaster University, Hamilton, ON, Canada.

[6] McMaster-Bayer Endowed Research Chair in Clinical Epidemiology of Congenital bleeding Disorders, Department of Medicine, McMaster, Hamilton, ON, Canada.

Hemasphere, 2022 Mar; 6(4): e694-e700

Bullet Points

What is already known:

- Hemophilia treatment requires a high self-infusion frequency of people with hemophilia
- This high infusion frequency can lead to reduced adherence because of the high burden
- Longer acting concentrates have been developed for FVIII and FIX

What this study adds:

- 40% of people with hemophilia A showed limited or no increase in terminal half-life after switching to EHL FVIII concentrates.
- Short THL on SHL concentrates and blood group non-O were identified as predictors for a relevant THL increase in people with hemophilia A.

Abstract

Predicting individual effects of switching from standard half-life (SHL) to extended half-life (EHL) FVIII/FIX concentrates is pivotal in clinical care, but large-scale individual data are scarce. The aim of this study was to assess individual changes in Terminal Half-Life (THL) after switching to EHL concentrates and identifying determinants of a clinically relevant THL extension in people with severe hemophilia. Data from participants with pharmacokinetic studies on both SHL and EHL were extracted from the Web-Accessible Population Pharmacokinetics Service (WAPPS) database and stratified according to hemophilia type and age groups (children/adults). A 30% increase in THL was considered clinically relevant. Predictors of a relevant increase were identified using logistic regression. Data from 688 persons with severe hemophilia (2174 infusions) were included: 89% hemophilia A; median age: 21.7 (IQR: 11.5-37.7); positive inhibitor history: 11.7%. THL increased by 38% (IQR: 17-67%) and 212% (139-367%) for hemophilia A and B, respectively. All EHL-FIX concentrate users showed clinically relevant THL extension. However, 40% (242/612) of people with hemophilia A showed limited extension or decrease in THL after switching. Relevant FVIII-THL extension was predicted by short baseline THL and blood group non-O in both children and adults. In conclusion, clinically relevant THL extension was observed in all 75/76 participants switching to EHL-FIX, and in 60% of 612 switching to EHL-FVIII. Short THL on SHL-FVIII and blood group non-O were identified as predictors for a relevant THL increase after switching to EHL-FVIII. individualized pharmacokinetic assessment may guide clinical decision making when switching from SHL to EHL-FVIII.

Introduction

Hemophilia is a congenital hematological condition which is characterized by lower levels or complete absence of coagulation factor VIII (FVIII, hemophilia A) or IX (FIX, hemophilia B)[1]. People with hemophilia (PWH) are at an increased risk of spontaneous (joint) bleeds and impaired joint function. Although non-replacement and gene therapy were recently introduced, the current standard treatment consists of prophylactic replacement therapy with regular self-administered intravenous infusions of FVIII or FIX[1]. Terminal half-life (THL) for naïve coagulation factor concentrates is relatively short: 8-12 hours for FVIII[2] and 17-33 hours for FIX[3–7], requiring a high infusion frequency to maintain adequate trough levels[8]. This high infusion frequency poses a burden on PWH that could lead to reduced adherence to treatment[9].

Longer acting concentrates have been developed in recent years. These concentrates are referred to as extended half-life concentrates (EHL, as opposed to conventionally defined standard half-life (SHL)). For the proposed definition of EHL, concentrates had to be designed to extend circulating biological half-life, have an increase of the area under the ROC curve (AUC) of at least 25% and a THL increase of at least 30%[10,11]. Implementing longer acting clotting factor concentrates could lead to lower infusion frequencies and/or higher trough levels while reporting at least similar annualized bleeding rate[12–15] and lower patient or caregiver burden[16].

When aiming to maintain minimum trough levels of FVIII/IX to prevent bleeding, THL is one of the parameters defining infusion frequency. Consequently, THL is an important parameter in pharmacokinetics of hemophilia treatment[17]. Previous studies have reported THL average increases of 1.5-2 fold in FVIII EHL products and 4 to 6 fold in FIX EHL products[3,13,18,19]. These data are from registration and Phase III studies (range: 7-118 subjects), and have recently been confirmed in a large, multicenter dataset spanning across all concentrates[20]. However, all these studies assessed and reported THL and its increase at group level. In the era of individualized medicine[21], the individual effects of switching to EHL concentrates seem particularly interesting from a clinical perspective. From that perspective, it is important to assess how many people benefit from switching to EHL concentrates, quantify the (relative) increase in THL and try to predict the probability of a clinically relevant increase in THL after switching to EHL concentrates.

Therefore, the primary aim of this current study was to assess individual differences in THL after switching from SHL concentrates to EHL concentrates according to hemophilia type across all factor concentrates in a real world setting. A secondary aim was to quantify predictors for a clinical relevant increase in THL.

Methods

Design and setting

This study was multi-center, collaborative project of the University Medical Centre Utrecht (Utrecht, the Netherlands), McMaster University (Hamilton, Ontario, Canada) and the University of Waterloo (Waterloo, Ontario, Canada) and was conducted as part of the activities of the Pharmacokinetics Expert Working Group of the International Prophylaxis Study Group (IPSG). Data were collected as part of the Web Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo). The WAPPS project aims to assemble a database of patient pharmacokinetic data for all existing factor concentrates, develop and validate population pharmacokinetics models, and integrate these models within a Web-based calculator for individualized pharmacokinetic estimation in patients at participating treatment centres[22–24]. The dataset included patient characteristics, treatment specific data and calculated pharmacokinetic data. The WAPPS project was approved by the Institutional Review Board of McMaster University (#14-601-D) and University of Waterloo (#31977). The approval included the use of the collected data for modelling purposes and for investigating the determinants of factor concentrates pharmacokinetic variability, thus covering the analysis of the present study. All data were anonymized and did not include information on hemophilia treatment centers or date of assessment.

Data collected

Data were downloaded on June 26th, 2020. On this date, 298 treatment centers in 47 countries were participating in WAPPS. Patient data were entered in the WAPPS database when the clinician wanted to estimate pharmacokinetic values for their patient. Data of participants with severe hemophilia A or B with at least one infusion for both SHL concentrates and EHL concentrates were included in this analysis. No inclusion criteria were formulated regarding minimum time between assessments or a minimum number of assessments. Participants had to provide consent to have their data included in the WAPPS database. "Any patient in the participating centres had an equal opportunity to be included in the WAPPS database. Information on the reason for THL assessment was not recorded. However, in case of switching concentrates, it is likely that switching itself was the reason. The distribution of THL on SHL-FVIII was similar to the distribution observed in the entire WAPPS database[20], this suggests no selection bias.

The database included data on patient and disease characteristics (age, disease type and severity, height, weight, inhibitor status, blood group), concentrate) and calculated THL.

The main outcome measure was individual THL, which was defined as the time required for the plasma/blood concentration to decrease by 50% at steady state [25]. Individual THL was derived using a Bayesian estimation method leveraging concentrate specific population pharmacokinetic models [22]. THL from SHL concentrates was classified as "baseline THL". Blood group was collected as a proxy for von Willebrand Factor antigen (vWF:Ag). Blood group was more frequently available in the WAPPS database and is not an acute phase protein, unlike vWF:Ag[26]. Clotting factor concentrates were classified as SHL or EHL products based on the proposed mechanism of the concentrate, manufacturer data and publicly available data[27]. An increase of ≥30% in THL after switching to EHL concentrates was considered clinically relevant for people with hemophilia A[10,11]. This threshold was specified before the analysis. In the absence of an established threshold for patients with hemophilia B, and given the fact that earlier studies showed much larger increases in FIX_THL than in FVIII (FIX: 4-6 fold; FVIII: 1.5-2 fold), the authors decided to use an increase in THL of at least 36 hours as clinically relevant as this is expected to lead to a meaningful decrease in infusion frequency. This would mean a doubling of the current median THL.

Statistics

Because of clinically unrealistic THL values in the original dataset, the distribution of THL data were checked and outliers were removed. An outlier in THL was defined according to Tukey's rule. THL values longer than the third quartile (Q3) + (1,5 x interquartile range (IQR: Q1-Q3)) or shorter than the first quartile (Q1) – (1,5 x IQR)[28] were considered outliers. Any values beyond these limits were discarded as they were deemed outliers, irrespective of the source of the outlier. Data are presented as median (IQR) or proportion (95% Confidence Interval (CI)) as appropriate.

Individual differences in THL were presented as the median (IQR) of the individual changes and were compared by means of paired non-parametric testing. The data from each subset (THL, differences in THL, age, weight, BMI) were checked for normality by means of Kolmogorov-Smirnoff testing. Parametric (ANOVA) or non-parametric (Mann-Whitney, Wilcoxon) methods were used for comparisons, as appropriate.

Backward logistic regression was conducted to predict the probability of at least 30% prolongation in THL after switching to EHL concentrates in people with hemophilia A. Separate models were constructed for children (younger than 18) and adults (18 and older) because of the age-related increase in THL in hemophilia A[20]. Prior to conducting the logistic regression, potential predictors were individually selected by univariable regression. Parameters with a significant result on the univariable regression ($p<0.05$) were included in/selected for the multivariable regression model. Age, baseline

THL, body weight, BMI, positive inhibitor history and blood group were included as independent variables. BMI (<25/>25 for adults, age-dependent cut-offs for overweight for children[29,30]), positive inhibitor history (yes/no), blood group (O/non-O) and baseline THL (tertiles: short, middle, long) were entered in the model as categorical variables. Baseline THL was divided into three equal groups by determining the tertiles, based on the THL distribution for children (short: <8 hours; middle: 8-10 hours; high: >10 hours) and adults (short: <10.5 hours; middle: 10.5-13.5 hours; high: >13.5 hours). Interactions between age and baseline THL, blood group and THL, and between age and body weight were included in the model. The final models were tested for accuracy by means of receiver operating characteristics (ROC) and area under the ROC curve (AUC). The AUC shows the diagnostic accuracy of the model (range: 0-1, 1 indicates a perfect accuracy). An AUC of less than 0.5 suggests no discrimination, 0.7-0.8 acceptable and 0.8-0.9 excellent and more than 0.9 outstanding[31]. Multicollinearity between individual predictors was assessed by means of the variance inflation factor (VIF). A VIF lower than 5 was considered to be indicative of moderate multicollinearity, that does not need correction[32]. The results from the logistic regression and the ROC analysis were used to construct probability tables for a clinically relevant increase in THL (≥30%)[10]. Finally, a sensitivity analysis was performed to assess the influence of the number of samples entered for the PK estimation on the occurrence of a clinically relevant THL prolongation in people with hemophilia A.

Statistical significance levels were set at 5% ($p<0.05$). The statistical analysis was performed using SPSS statistical software, version 26 (IBM corp., Armonk. NY), R (version 3.5.1.) and Rstudio (version 1.1.456)[33].

Data Sharing Statement

Original data can be accessed upon request from the original authors. Please contact wappshemo@mcmasterhkr.com.

Results

Participants

Participant demographic and biometric details are shown in table 1. Data on 688 participants (2174 infusions; SHL: 1073; EHL: 1101) from 121 hemophilia treatment centers in 43 countries were extracted from the WAPPS data base. The dataset consisted of 286 children and 402 adults, all with severe hemophilia. The majority of participants had hemophilia A (children: 91%; adults: 89%). The median age was 9.8 (IQR: 6.0-14.0) for children and 34.6 (26.0-47.5) for adults. The median weight was 36.8 kg (22.0-54.3; BMI: 19.2 (16.1-22.9)) for children and 75.6 kg (66.4-86.5; BMI: 24.6 (22.3-27.7)) for adults. Median time between the SHL and EHL assessments in participants with hemophilia A was 165 (IQR: 49-467) days and 141 (39-441) days in participants with hemophilia B. Although non-significant, median time between assessments longer in children than in adults in both hemophilia A (223 (58-428) vs. 142 (25-474) days; p=0.06) and hemophilia B (154 (63-433) vs. 126 (18-472) days; p=0.58). Blood group data was available for 65% of the participants, while inhibitor history and BMI were available for nearly all participants (95% and 96%, respectively).

Terminal Half-Life according to hemophilia type Hemophilia A

The median individual increase of the THL in people with hemophilia A (n=612) was 4.1 (range: -7 – 21) hours (from 10.6 (IQR 8.4-13.1) to 14.8 (11.9-18.5) hours; p<0.01) after switching to EHL-FVIII concentrates, indicating a median 1.4 fold (IQR: 1.2-1.7) increase. However, 242/612 (40%) people with hemophilia A showed limited to no improvement of THL after switching to EHL concentrates. THL decreased (median -1.1 (-2.4 to -0.4) hours) in 61/612 (10%) of people with hemophilia A after switching, whereas another 181/612 (30%) reported an increase less than 30%. Figure 1 shows that prolongation in participants with hemophilia A was dependent on baseline THL: the number of participants with a decrease in THL after switching was higher in participants with a longer baseline THL (short: 9; medium: 16; long: 36; p<0.01).

Table 1: Terminal Half-Life according to hemophilia type and age groups

		Children (0-17)		Adults (≥18)	
	Overall	**A**	**B**	**A**	**B**
n	688 (612 A)	259 (42%)	27 (36%)	353 (58%)	49 (64%)
Age (yrs)	21.6 (11.5-37.9)	10.0 (6.0-14.0)	9.3 (6.6-14.0)	34.5 (26.0-47.1)	35.5 (23.8-49.0)
Weight (kg)	66.0 (43.0-80.0)	37.0 (22.0-53.6)	30.1 (24.1-57.4)	75.3 (66.3-85.8)	79.0 (66.7-91.0)
BMI[1]	22.5 (18.9-25.4)[1]	17.9 (15.9-21.1)	17.8 (15.7-20.9)	24.4 (22.2-27.4)	25.0 (23.6-29.2)
Inhibitor history[1]	76 (11%)[1]	42 (16%)	3 (11.1%)	30 (8.5%)	1 (2.0%)
Blood group O[1]	204/444 (46%)	80/170 (47%)	8/13 (62%)	104/243 (43%)	12/18 (67%)
		Terminal Half-Life (median (IQR))			
SHL concentrate (hrs)	-	8.9 (7.6-10.8)*	33.6 (30.0-38.6)	11.9 (9.7-14.7)*	38.7 (32.1-42.6)
EHL concentrate (hrs)	-	13.0 (10.4-15.6)*	93.3 (71.0-118.5)†	16.9 (13.4-21.4)*	117.9 (93.2-131.8)*
Time between SHL and EHL assessments (days)	-	223 (58-428)	154 (63-433)	142 (25-474)	126 (18-472)
Absolute increase in THL (hrs)	-	3.8 (1.9-6.0)	63.9 (31.8-84.1)	4.3 (2.0-7.2)†	80.4 (58.5-99.1)†
Relative increase in THL (EHL:SHL)	-	1.4 (1.2-1.7)	2.8 (1.8-3.4)	1.4 (1.2-1.7)	3.2 (2.5-4.4)[a]

Abbreviations: IQR: Interquartile Range (Q1-Q3); yrs: years; BMI: Body Mass; hrs: hours; THL: Terminal Half-Life; EHL: Extended Half-Life; SHL: Standard Half-Life
[1]: BMI and inhibitor history were available for 95% and 96% of participants, respectively. Blood group was available for 65% of participants.
*: THL was longer for EHL concentrates than SHL concentrates in both children and adults and was longer in adults than in children in both SHL and EHL ($p<0.01$).
†: Increase in THL is larger in adults than children (A and B).
[a]: relative increase in THL is larger in adults than children (B)

Hemophilia B

In contrast to people with hemophilia A, all people with hemophilia B showed an extension of THL after switching to EHL concentrates. The median individual extension of the THL was 74.1 (range: 10-154) hours (from median 35.7 (IQR: 31.3-41.0) to 108.9 (84.1-129.3) hours; $p<0.01$) after switching to EHL concentrates, which was a median 3.1 fold (2.4-3.7) increase. The majority (65/76; 86%) of participants with hemophilia B showed an increase of more than 36 hours.

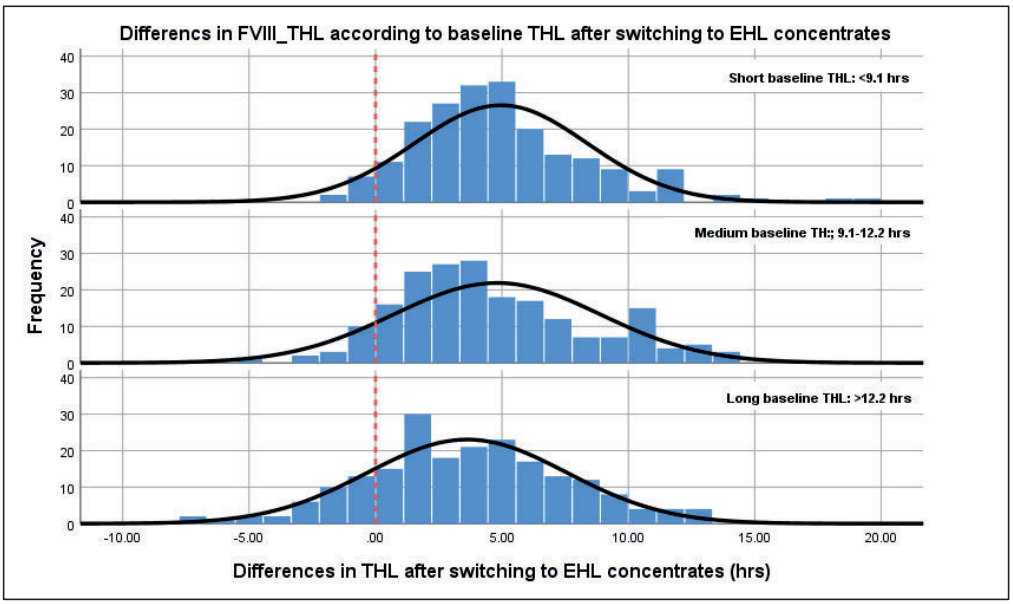


Figure 1: distribution of differences in THL after switching to EHL concentrates in participants with hemophilia A. The dotted line indicates no change in THL after switching to EHL concentrates. The number of participants with hemophilia A reporting a decrease was greater in participants with a long baseline THL (>12.2 hrs).

Individual changes in THL according to age groups

Table 1 shows changes in THL after switching from SHL concentrates to EHL concentrates for children and adults. THL in children with hemophilia A increased by a median of 3.8 (IQR: 1.9-6.0) hours after switching from SHL concentrates to EHL concentrates (from 8.9 (7.6-10.8) to 13.0 (10.4-15.6); p<0.01). THL in adults with hemophilia A increased by 4.3 (2.0-7.2) hours (from 12.0 (9.8-15.2) on SHL concentrates to 16.3 (13.4-21.4) on EHL concentrates; p<0.01). The relative increase in THL was similar in children and adults with hemophilia A, with a median 1.4 fold (1.2-1.7) increase in both children and adults.

People with hemophilia B showed an age-related increase in THL: children reported a median increase of 63.9 (31.8-84.1) hours (from median 33.6 (30.0-38.6) to 93.3 (71.0-118.5)). This was smaller than in adults, who reported a median increase of 80.4 (58.5-99.1) hours (from 38.7 (32.1-42.6) to 117.9 (93.2-131.8); p<0.01). This indicates a smaller, although non-significant, relative increase in children than in adults (median 2.8 (1.8-3.4) vs. 3.2 (2.5-4.4) fold; p=0.05).

Identifying predictors for clinically relevant prolongation of THL in hemophilia A

Not all participants with hemophilia A reported a clinically relevant increase in THL after switching to EHL concentrates. Table 2 shows the characteristics of participants according to clinically relevant FVIII-THL extension. Participants showing a clinical relevant THL prolongation (≥30%) had blood group non-O more often (60 vs. 47%; p=0.01) and a shorter baseline THL for SHL concentrates (9.5 (7.9-11.9) vs. 11.9 (9.9-14.4) hours; p<0.01) than those with a limited prolongation (<30%). Interaction terms for age and baseline THL, blood group and THL, and between age and body weight did not reach significance. Despite blood group non-O and long baseline THL being associated, no indications for multicollinearity were reported (VIF for adults: 1.13, children: 1.05).

Table 2: Participant characteristics according to relevant FVIII-THL extension after switching from SHL to EHL concentrates

	<30% increase	≥30% increase	p
	Median (IQR) or % (95%CI)		
Number	242	370	
Age (yrs)	26 (12-40)	20 (11-35)	0.06
Children (%)	39% (33-45)	45% (40-50)	0.13
BMI*	22 (20-25)	22 (18-25)	0.13
Weight (kg)	67 (46-80)	65 (40-80)	0.44
Blood Group O (%)*	53% (45-60)	40% (34-46)	0.01
Inhibitor Status (%)*	14% (10-19)	11% (8-15)	0.47
Baseline THL_SHL (hrs)	11.9 (9.9-14.4)	9.5 (7.9-11.9)	<0.01

*: BMI was available for 95% of participants with hemophilia A, blood group data for 65%, inhibitor status for 96%. Abbreviations: FVIII-THL: Terminal Half-Life for factor VIII. IQR: Interquartile Range (Q1-Q3); CI: Confidence Interval; yrs: years; BMI: Body Mass; kg: kilos; hrs: hours.

In order to identify predictors for a clinically relevant prolongation in hemophilia A, separate logistic regression models were generated for children (supplemental table S2) and adults (supplemental table S2). Baseline THL and blood group O were identified as relevant predictors in children. ROC analysis reported an AUC of 0.74 (95%CI: 0.66-0.82) for children, indicating that the model for children had an acceptable predictive value. In children, the model behaved well on correctly predicting a clinically relevant increase in THL (positive predictive value (PPV): 97%). However, the performance on predicting non-relevant prolongation of THL was poor (negative predictive value (NPV): 22%).

Adults with a short baseline THL showed higher odds of a clinically relevant THL extension. ROC analysis reported an AUC of 0.73 (95%CI: 0.66-0.79) for adults. The model

for adults behaved particularly well in predicting a clinically relevant outcome (PPV: 77%), while moderately well in predicting a non-relevant outcome (NPV: 57%).

Table 3a: Probability of more than 30% increase in THL for children (0-18) with hemophilia A

THL on SHL FVIII	Blood group	probability of a clinically relevant increase in THL on EHL_FVIII
Short (<8 hrs)	non-O	96%
	O	69%
Middle (8-10 hrs)	non-O	81%
	O	27%
Long (>10 hrs)	non-O	55%
	O	10%

Table 3a (children) and 3b (adults) show probability tables for clinical purposes. These tables show the probability of a clinically relevant increase in THL based on the patient characteristics (baseline THL and blood group in both children and adults). Although BMI was identified as a significant predictor in adults as well, the added value turned out to be limited. Adding BMI to the model did not change the final outcome. Therefore, BMI was excluded from the final clinical model.

Table 3b: Probability of a clinically relevant THL extension in FVIII for adults (>18) with hemophilia A

THL on SHL FVIII	blood group	probability of a clinically relevant increase in THL on EHL_FVIII
Short (<10.5 hrs)	non-O	96%
	O	85%
Middle (10.5-13.5 hrs)	non-O	78%
	O	49%
Long (>13.5 hrs)	non-O	35%
	O	15%

Irrespective of blood group and BMI, adult participants with a baseline THL on SHL concentrates of less than 10.5 hours had the highest probability to achieve a clinically relevant increase in THL (predicted probability: 85-98%). Participants with a baseline THL between 10.5 and 13.5 hours showed medium probabilities (63-86%), indicating that an individual approach and extensive monitoring is warranted in this group. Participants with a baseline THL of more than 13:30 hours showed the lowest probability (≤35%), indicating that the majority of participants with a high baseline THL showed no relevant pharmacokinetic benefit of switching to EHL concentrates. As in adults, children with a

short baseline THL (<8 hours) showed the highest probabilities of a clinically relevant increase in THL (69-96%). This was irrespective of type of blood group.

Extension of FVIII-THL in children with a baseline THL of 8-10 hours or more than 10 hours was highly dependent on blood group. Children with blood group non-O were mostly likely to show a clinically relevant THL increase (8-10 hours: non-O: 81% vs. O: 27%; >10 hours: non-O: 55% vs. O: 10%).

Effect of the number of samples per assessments: a sensitivity analysis

Supplemental table S3 shows the distribution of the number of samples per assessment in participants with hemophilia A. The majority of participants with hemophilia A had one or two samples available for analysis. A sensitivity analysis showed that adding "number of samples" did not significantly change the outcome (OR: 0.89 (95%CI: 0.75-1.07; p=0.21)), nor did an additional analysis only including participants with more than 3 samples per assessment (OR: 0.89 (0.52-1.54); p=0.67). Table 4 shows the descriptive results when including all participants or all participants with at least 3 samples per assessments.

Table 4: Sensitivity analysis comparing the results when including all assessments compared to all patients with at least 3 assessments for SHL and EHL

	All assessments		≥3 assessments for both SHL and EHL	
	A	B	A	B
N	612	76	129	17
Median (IQR) or N (%)				
THL_EHL	14.8 (11.9-18.5)	109 (84-129)	15.5 (12.7-18.3)	112 (96-130)
THL_difference	4.1 (1.9-6.6)	74 (53-93)	4.1 (2.0-6.5)	77 (68-93)
THL_ratio	1.4 (1.2-1.7)	3.1 (2.4-3.7)	1.4 (1.2-1.7)	3.3 (2.5-4.3)
Less than 30% progression THL	241/612 (39%)	1/76 (1.3%)	53/129 (41%)	0

Abbreviations: SHL: Standard Half-Life; EHL: Extended Half-Life; IQR: Interquartile Range (Q1-Q3); THL: Terminal Half-Life; THL_difference: absolute differences between THL_SHL and THL_EHL; THL_ratio: relative differences between THL_SHL and THL_EHL.

Discussion

Main findings

This study with 688 participating people with hemophilia represents the largest study assessing individual changes in THL after switching from SHL to EHL products so far. The majority of participants showed an extended THL after switching to EHL products, although large inter-individual differences were observed in patients with both hemophilia A and B. In addition, this study showed that 40% of participants with hemophilia A did not have a clinically relevant improvement of THL (30% no clinically relevant prolongation; 10% with reduction) after switching to EHL concentrates. The relative increase in THL was age-related in people with hemophilia B, but not in people with hemophilia A. Baseline THL and blood group were identified as predictors in both adults and children.

Strengths and limitations

The primary strength of this study is its size and its multicenter, multinational nature. In addition, it includes a substantial number of young children (10% under 6, 1% under 2), which is a valuable addition to the information on previous reports, which have mostly relied on hemophilia on adults and children over 6[10,34–36]. Especially the inclusion of young children allowed for assessment of the effects of age on individual changes in THL over the entire age range. Furthermore, the distribution of THL on SHL-FVIII was similar to the global WAPPS database, suggesting no selection bias was introduced[20].

THL and other pharmacokinetic data in this dataset were modelled using concentrate-specific population pharmacokinetic models and Bayesian methods[23,24]. Applying Bayesian methods is an established and widely used practice in population-based pharmacokinetic prediction models to limit patient and economic burdens of traditional pharmacokinetic samping[37–40]. These Bayesian models were established with existing, real-life data. All clotting factor activity assessments were performed in local laboratories , inducing inter-laboratory variation. These real-world data are representative of the large number of users of the WAPPS model. No correction for laboratories was applied in this large dataset.. In addition, the external validity of the present study is expected to be higher than in controlled studies, as many different laboratories and reagents are included in the dataset.

The definition of a clinically relevant increase in THL after switching remains subjective. Therefore, we used the international expert consensus definition for hemophilia A, stating that an increase in THL of 30% was required for a concentrate to be regarded an EHL concentrate[10,11]. This relative value was used as a cut-off for a clinically relevant

THL prolongation in this study. Although this relative increase seems most feasible to make comparisons, the increase in absolute hours is also presented to promote clinical application.

The accuracy of the modelled data is associated with the number of samples taken for PK assessment[41,42]. Estimates based on only one sample may cause bias. However, a sensitivity analysis suggests no significant effect of adding "number of samples" to the model. Still, future studies should aim to exclusively include patients with multiple assessments in order to model more accurate data and to avoid inaccurate estimation of true THL[42].

THL is known to be lower in blood group O than in non-O for patients with hemophilia A[26,43]. However, this does not directly explain why blood group non-O is a relevant predictor of a higher increase in THL. Besides this, blood group is hypothesized to be associated with vWF. However, vWF is an acute phase protein as well, making blood group potentially a better predictor than measured vWF. However, other than the short THL at baseline, neither previous publications nor pathophysiological reasoning provide an explanation for the observation that blood group O was associated with more extension of THL after switching to EHL FVIII.

Blood group data was lacking in a substantial number of participants (35%). However, the number of remaining available blood group data was sufficient to be included in the analysis. Furthermore, the fact that the distribution of the included blood group data was similar to the global distribution suggests there was no selection bias.

Comparison with other studies

In the present study, 10% (CI: 5-20%) of children younger than 6 and 12% (7-19%) of children age 6-12 reported no prolongation in THL. This is similar to the publication of Young et al reporting no individual prolongation in around 5% of children under 6 (n=19; CI 0-26%) and 12% of children aged 6-12 (n=27; CI 7-19%)[44].

Our findings are also in line with previous reports on series of intra-patient changes in THL for both hemophilia A and B. For hemophilia A, Mahlangu et al. (1.5 fold increase, n=28, aged >12) and Traets (1.4 fold increase, n= 15, 9 adults) reported similar increases in THL[13,45]. For hemophilia B, Powell et al. reported a 2.4 fold increase(n= 22) and Traets et al. reported a 2.6 fold increase, (n=15, 10 adults) in people with hemophilia B[3]. Fischer et al. (2017) reported a similar increase in THL (3.7 fold (CI: 2.6-5.5)) in 30 children, with 50% under 6 years, with hemophilia B switching from SHL to EHL concentrates[46].

Clinical relevance and future directions

This study showed that 40% of people with hemophilia A did not achieve clinically relevant THL prolongation after switching to EHL concentrates. A short baseline THL and blood group non-O were identified as possible predictors for a clinically relevant increase of THL. Predictive tables were created for adults and children to guide clinicians and patients in their decision-making concerning switching to EHL concentrates in people with hemophilia A.

This study assessed the increase in THL after switching from SHL to EHL concentrates. However, focusing on THL is a limited approach[47]. The current dataset did not assess the clinical consequences of switching (e.g.: annual bleeding rate, annual number of infusion, and through levels). These clinical consequences of switching on these parameters need to be studied as well. A prolonged THL may allow for the use of a lower prophylactic infusion frequency, potentially leading to a lower burden for patients and/or caregivers. This study showed a median increase in THL of 4 hours for FVIII and 74 hours for FIX. This means the infusion intervals are extended by 20-24 hours (±1 day) for FVIII and 300-350 hours (±12-14 days) for FIX, which may enable a reduction of infusion frequency without dose changes. Concomitantly, EHL extension results in higher trough levels when the same infusion frequency is maintained. Both seem viable options to improve bleeding protection people with hemophilia, the exact rationale for switching to EHL concentrates depends on the patient and his particular circumstances (e.g. bleeding phenotype, physical activity levels). This study represents a first step to identify predictors for a clinically relevant increase in THL after switching to EHL concentrates. Future studies should include clinical results and expand on other pharmacokinetic parameters to assess overall individual effects of switching to EHL concentrates.

Conclusions

All people with hemophilia B and 60% with hemophilia A showed a clinically relevant extension (≥30%) of THL after switching from SHL to EHL concentrates. Clinically relevant FVIII-THL extension was predicted by short baseline THL and blood group non-O. These results support the importance of individualized treatment strategies to guide clinical decision making when switching from SHL to EHL concentrates. The predictive tables created in this study, can support clinicians and patients to make an appropriate, evidence-based decision regarding the switch to EHL concentrates.

References

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672
2. McEneny-King A, Iorio A, Foster G, Edginton AN. The use of pharmacokinetics in dose individualization of factor VIII in the treatment of hemophilia A. *Expert Opin Drug Metab Toxicol*. 2016;12(11):1313-1321. doi:10.1080/17425255.2016.1214711
3. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B. *N Engl J Med*. 2013;369(24):2313-2323. doi:10.1056/nejmoa1305074
4. Collins PW, Fischer K, Morfini M, Blanchette VS, Björkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. *Haemophilia*. 2011;17(1):2-10. doi:10.1111/j.1365-2516.2010.02370.x
5. FDA. Product Characteristics Mononine. Mononine. Published 2021. https://www.drugs.com/pro/mononine.html#s-34090-1
6. EMA. *Product Characteristics Rixubis - Annex I.*; 2014. doi:10.1163/ej.9789004166523.i-402.43
7. EMA. *Product Characteristics Benefix - Annex I.*; 2009. doi:10.1163/ej.9789004166523.i-402.43
8. Kumar R, Dunn A, Carcao M. Changing Paradigm of Hemophilia Management: Extended Half-Life Factor Concentrates and Gene Therapy. *Semin Thromb Hemost*. 2016;42(1):18-29. doi:10.1055/s-0035-1568877
9. Hacker MR, Geraghty S, Manco-Johnson MJ. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia*. 2001;7(4):392-396. doi:10.1046/j.1365-2516.2001.00534.x
10. Mahlangu J, Young G, Hermans C, Blanchette V, Berntorp E, Santagostino E. Defining extended half-life rFVIII—A critical review of the evidence. *Haemophilia*. 2018;24(3):348-358. doi:10.1111/hae.13438
11. Hermans C, Mahlangu J, Booth J, et al. Pharmacokinetic modelling and validation of the half-life extension needed to reduce the burden of infusions compared with standard factor VIII. *Haemophilia*. 2018;24(3):376-384. doi:10.1111/hae.13483
12. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: Recommendations for specifying and reporting. *Implement Sci*. 2013;8(1):1-11. doi:10.1186/1748-5908-8-139
13. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123(3):317-325. doi:10.1182/blood-2013-10-529974
14. Iorio A, Krishnan S, Myrén KJ, et al. Indirect comparisons of efficacy and weekly factor consumption during continuous prophylaxis with recombinant factor VIII Fc fusion protein and conventional recombinant factor VIII products. *Haemophilia*. 2017;23(3):408-416. doi:10.1111/hae.13160
15. Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;(May):1-158. doi:10.1111/hae.14046
16. Schwartz CE, Powell VE, Su J, Zhang J, Eldar-Lissai A. The impact of extended half-life versus conventional factor product on hemophilia caregiver burden. *Qual Life Res*. 2018;27(5):1335-1345. doi:10.1007/s11136-018-1792-9
17. Benet LZ, Zia-Amirhosseini P. Basic principles of pharmacokinetics. *Toxicol Pathol*. 1995;23(2):115-123. doi:10.1177/019262339502300203
18. Graf L. Extended Half-Life Factor VIII and Factor IX Preparations. *Transfus Med Hemotherapy*. 2018;45(2):86-91. doi:10.1159/000488060
19. Mancuso M, Santagostino E. Outcome of Clinical Trials with New Extended Half-Life FVIII/IX Concentrates. *J Clin Med*. 2017;6(4):39. doi:10.3390/jcm6040039
20. Versloot O, Iserman E, Chelle P, et al. Terminal half-life of FVIII and FIX according to age, blood group and concentrate type: data from the WAPPS database. *J Thromb Haemost*. 2021;Epub ahead(February):1-11. doi:10.1111/jth.15395
21. Poon MC, Lee A. Individualized prophylaxis for optimizing hemophilia care: Can we apply this to both developed and developing nations? *Thromb J*. 2016;14(Suppl 1). doi:10.1186/s12959-016-0096-y
22. Iorio A, Keepanasseril A, Foster G, et al. Development of a Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo): Study Protocol. *JMIR Res Protoc*. 2016;5(4):e239. doi:10.2196/resprot.6558

23. Hajducek DM, Chelle P, Hermans C, et al. Development and evaluation of the population pharmacokinetic models for FVIII and FIX concentrates of the WAPPS-Hemo project. *Haemophilia*. 2020;(February):1-17. doi:10.1111/hae.13977

24. McEneny-King A, Foster G, Iorio A, Edginton AN. Data Analysis Protocol for the Development and Evaluation of Population Pharmacokinetic Models for Incorporation Into the Web-Accessible Population Pharmacokinetic Service - Hemophilia (WAPPS-Hemo). *JMIR Res Protoc*. 2016;5(4):e232. doi:10.2196/resprot.6559

25. Toutain PL, Bousquet-Mélou A. Plasma terminal half-life. *J Vet Pharmacol Ther*. 2004;27(6):427-439. doi:10.1111/j.1365-2885.2004.00600.x

26. Vlot AJ, Mauser-Bunschoten EP, Zarkova AG, et al. The half-life of infused factor VIII is shorter in hemophiliac patients with blood group O than in those with blood group A. *Thromb Haemost*. 2000;83(1):65-69. doi:10.1055/s-0037-1613759

27. Public Health - Union Register of medicinal products. European Medicinces Agency. Published 2020. Accessed April 1, 2020. https://ec.europa.eu/health/documents/community-register/html/reg_hum_act.htm?sort=a

28. Tukey JW. *Exploratory Data Analysis*. 1st ed. Addison-Wesley Publishing Company; 1977.

29. De Onis M, Lobstein T. Defining obesity risk status in the general childhood population: Which cut-offs should we use? *Int J Pediatr Obes*. 2010;5(6):458-460. doi:10.3109/17477161003615583

30. World Health Organization (WHO). Child Growth Standards. Published 2007. Accessed July 5, 2021. www.who.int/childgrowth/en

31. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. Vol 2. Wiley & Sons; 2000. https://onlinelibrary.wiley.com/doi/pdf/10.1002/0471722146

32. Marcoulides KM, Raykov T. Evaluation of Variance Inflation Factors in Regression Models Using Latent Variable Modeling Methods. *ol Educ Psychol Meas*. 2019;79(5):874-882. doi:10.1177/0013164418817803

33. RStudio Team. RStudio: Integrated Development for R. Published online 2020. www.rstudio.com

34. Powell JS, Josephson NC, Quon D, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood*. 2012;119(13):3031-3037. doi:10.1182/blood-2011-09-382846

35. Santagostino E, Negrier C, Klamroth R, et al. Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients. *Blood*. 2012;120(12):2405-2411. doi:10.1182/blood-2012-05-429688

36. Negrier C, Knobe K, Tiede A, Giangrande P, Møss J. Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: A first human dose trial in patients with hemophilia B. *Blood*. 2011;118(10):2695-2701. doi:10.1182/blood-2011-02-335596

37. McEneny-King A, Chelle P, Foster G, Keepanasseril A, Iorio A, Edginton AN. Development and evaluation of a generic population pharmacokinetic model for standard half-life factor VIII for use in dose individualization. *J Pharmacokinet Pharmacodyn*. 2019;46(5):411-426. doi:10.1007/s10928-019-09634-7

38. Brekkan A, Degerman J, Jönsson S. Model-based evaluation of low-dose factor VIII prophylaxis in haemophilia A. *Haemophilia*. 2019;25(3):408-415. doi:10.1111/hae.13753

39. Brekkan A, Berntorp E, Jensen K, Nielsen EI, Jönsson S. Population pharmacokinetics of plasma-derived factor IX: Procedures for dose individualization. *J Thromb Haemost*. 2016;14(4):724-732. doi:10.1111/jth.13271

40. Gringeri A, Wolfsegger M, Steinitz KN, Reininger AJ. Recombinant full-length factor VIII (FVIII) and extended half-life FVIII products in prophylaxis - new insight provided by pharmacokinetic modelling. *Haemophilia*. 2015;21(3):300-306. doi:10.1111/hae.12605

41. Björkman S. Limited blood sampling for pharmacokinetic dose tailoring of FVIII in the prophylactic treatment of haemophilia A. *Haemophilia*. 2010;16(4):597-605. doi:10.1111/j.1365-2516.2009.02191.x

42. Yu JK, Iorio A, Edginton AN. A comparison of methods for prediction of pharmacokinetics when switching to extended half-life products in hemophilia A patients. *Thromb Res*. 2020;196(August):550-558. doi:10.1016/j.thromres.2020.10.024

43. Fischer K, Pendu R, van Schooten CJ, et al. Models for prediction of factor VIII half-life in severe haemophiliacs: Distinct approaches for blood group O and non-O patients. *PLoS One*. 2009;4(8):1-7. doi:10.1371/journal.pone.0006745

44. Young G, Mahlangu J, Kulkarni R, et al. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *J Thromb Haemost*. 2015;13(6):967-977. doi:10.1111/jth.12911

45. Traets MJM, Fischer K, Uitslager N, et al. Real-Life Pharmacokinetics of rFVIII-Fc and rFIX-Fc. *Thromb Haemost Open*. 2020;4:362-364. doi:10.1055/s-0040-1718416

46. Fischer K, Kulkarni R, Nolan B, et al. Recombinant factor IX Fc fusion protein in children with haemophilia B (Kids B-LONG): results from a multicentre, non-randomised phase 3 study. *Lancet Haematol*. 2017;4(2):e75-e82. doi:10.1016/S2352-3026(16)30193-4

47. Ragni MV, Croteau SE, Morfini M, Cnossen MH, Iorio A. Pharmacokinetics and the transition to extended half-life factor concentrates: communication from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(7):1437-1441. doi:10.1111/jth.14153

Supplemental Data

Table S1: Regression coefficients from logistic regression: probability of a clinical relevant increase in THL (≥30%) after switching from SHL to EHL in children

Children (n=259)	Odds Ratio	95% CI for OR		P
		Lower	Upper	
Short THL on SHL FVIII (<8 hrs)	Reference			<0.01
Medium THL on SHL FVIII (8-10 hrs)	0.17	0.02	1.66	0.13
Long THL on SHL FVIII (>10 hrs)	0.05	0.01	0.40	<0.01
Blood Group (ref = non-O)	0.09	0.01	0.76	0.03

*: outcome: probability of an increase in THL of ≥30%.

Table S2: Regression coefficients from logistic regression: probability of a clinical relevant increase in THL (≥30%) after switching from SHL to EHL in adults*

Adults (n=353)	Odds Ratio	95% CI for OR		p
		Lower	Upper	
Short THL on SHL FVIII (<10 hrs)	Reference			<0.01
Medium THL on SHL FVIII (10-13:30 hrs)	0.17	0.02	1.29	0.09
Long THL on SHL FVIII (>13:30 hrs)	0.01	0.00	0.16	<0.01
BMI (ref = BMI>25)	0.57	0.31	1.03	0.06
Blood group (ref = non-O)	0.27	0.14	0.52	0.01

*: outcome: probability of an increase in THL of ≥30%.

Table S3: Number of participants with hemophilia A with >30% increase in THL according to number of samples per assessment

Number of samples	N (total)	N (>30% increase)	%
1	144	93	65
2	203	123	61
3	136	79	58
4	93	58	62
5	18	11	61
6	8	3	38
7	6	1	17
8	2	2	100
9	0	0	0
10	1	1	100

Supplemental table S4: Frequency distribution of prescribed FVIII clotting factor concentrates (SHL)

FVIII concentrates			
Product name	**Recombinant (Rec) or P lasma Derived (PD)**	**Number of participants**	**Percentage**
Advate	Rec	182	26,5%
Kogenate	Rec	104	15,1%
Refacto	Rec	83	12,1%
Kovaltry	Rec	38	5,5%
Helixate	A	48	7.0%
Nuwiq	Rec	30	4,4%
Fanhdi	PD	22	3,2%
Afstyla	Rec	19	2.8%
yntha	A	15	2,2%
Kogenate FS	Rec	13	1,9%
Factane	A	8	1,2%
Wilate	PD	7	1,0%
Aafact	PD	6	0,9%
Immunate	PD	5	0.7%
Octanate	PD	5	0,7%
Novoeight	Rec	4	0,6%
Recombinate	Rec	4	0,6%
Alphanate	PD	4	0,6%
Amofil	PD	4	0,6%
Iblias		4	0,6%
Haemoctin Sdh	PD	3	0,4%
Beriate	PD	3	0,4%
Klott	PD	3	0,4%
Hemophil M	PD	2	0,3%
Humate P		1	0,1%
Emoclot	PD	1	0,1%
Haemate P	PD	1	0,1%
HemoRAAS	PD	1	0.1%
FIX concentrates			
Benefix	Rec	54	7,8%
Factor Ix Grifols	PD	8	1,2%
Aimafix	PD	7	1,0%
Immunine	PD	5	0,7%
Octanine	PD	3	0,4%
Rixubis	Rec	2	0,3%
Replenine – Vf	PD	2	0,3%
Mononine	PD	2	0,3%
Alphanine	PD	1	0,1%
Nonafact	PD	1	0,1%
Betafact	PD	1	0,1%

Supplemental table S4 (continued): requency distribution of prescribed FVIII clotting factor concentrates (EHL)

FVIII concentrates				
Product name	**Recombinant (Rec) or Plasma Derived (PD)**	**EHL Method**	**Number of participants**	**Percentage**
Elocta	Rec	Fc	497	72,2%
Adynovate	Rec	PEG	82	12%
Jivi	Rec	PEG	13	1,9%
Esperoct	Rec	PEG	3	0,4%
FIX concentrates				
Alprolix	Rec	Fc	57	8,3%
Idelvion	Rec	Albumin	13	1,9%
Rebinyn	Rec	PEG	5	0.7%

CHAPTER 12

Sports participation is not associated with adherence to prophylaxis in Dutch patients with haemophilia

Hoefnagels, J.W.[1], Versloot, O.[1,2], Schrijvers, L.H.[1,3], van der Net, J.[4], Leebeek, F.W.G.[5], Gouw, S.C.[6], Fischer, K.[1], *on behalf of the Haemophilia in the Netherlands 6 steering group.*

[1] Van Creveldkliniek, University Medical Center Utrecht, Utrecht, The Netherlands

[2] Department of Physiotherapy, Institute of Movement Studies, University of Applied Science Utrecht, Utrecht, the Netherlands

[3] Nursing department, Utrecht University of applied sciences, Utrecht, The Netherlands

[4] Center for Child Development, Exercise and Physical Literacy, University Children's Hospital, UMC Utrecht, Utrecht, The Netherlands

[5.] Department of Hematology, Erasmus MC, University Medical Center Rotterdam , Rotterdam, The Netherlands.

[6] Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherland

Haemophilia, 2021 Mar; 27(3): e402-405

Bullet points

What is already known:

- Therapeutic adherence is generally high in people with haemophilia using prophylaxis
- Sports participation in people with haemophilia is high, including high-risk sports.

What this study adds:

- Despite our assumptions, (high-risk) sports participation was not associated with increased therapeutic adherence.

Introduction

Patients with severe haemophilia (PWH) lack clotting factor VIII or IX activity (<1 IU/dl) and are at risk for spontaneous bleeds in joints, soft tissue and muscles [1]. In the Netherlands, regular replacement therapy (prophylaxis) to prevent bleeding) and subsequent joint damage is standard treatment [1]. This replacement therapy consists of intravenously self-administered clotting factor concentrate 2-3 times/week, usually started before the age of three years [1]. In young children, parents generally perform these injections. Around the age of 12 years children are taught self-infusion and gradually take on more responsibility for their prophylaxis [2]. This treatment, requiring continuous frequent infusions for life, is very effective but demanding. Maintaining minimum levels of clotting factor activity requires continuous adherence to prophylaxis. With early prophylaxis, patients are able to lead an active life, including participation in (high risk) sports. Today, regular sports participation in young Dutch PWH is high (77%) and comparable to the general population [3]. Non-adherence of prophylaxis is associated with increased bleeding, more absence from school and work and reduced quality of life [4]. A person is considered non-adherent if he regularly deviates from the prescribed dose, takes his prophylaxis in the evenings or skips infusions. Depending on age, non-adherence in PWH is estimated around 57% [2], An active, sportive lifestyle is a deliberate choice people make. With the inherent injury- and bleeding risks of sports in mind, we hypothesized that PWH active in sports are more adherent to prophylaxis than PWH who are not active in sports The aim of the present study was to assess the association between adherence versus non-adherence to prophylaxis and sports participation in people with haemophilia on prophylaxis.

Methods

A cross-sectional questionnaire study was performed as part of the nationwide 'Haemophilia in the Netherlands 6' study (HIN-6). This is a recurring study which is conducted every 6-10 years, the current questionnaire was administered in 2019. The HIN study includes patient characteristics, treatment history and numerous patient reported outcome measures. Medical ethical approval was obtained from the Medical ethical committee Leiden, number: NL59114.058.17.

All male Dutch patients with haemophilia who are registered in one of the haemophilia treatment centres in the Netherlands were invited to participate. Participants who used prophylaxis and completed both the adherence and sports activity questionnaires were included. Adherence was evaluated using the Dutch version of the Validated Hemophilia

Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) [5]. The VERITAS-Pro (VP) consists of 24 questions with a five-point Likert scale ranging from 'always' to 'never'. The questionnaire produces a total score and six domain scores: T*ime, Dose, Plan, Remember, Skip and Communicate*. VERITAS-Pro scores were normalized into a 0-100 score with a high score indicating low adherence.

Sports and physical activity were evaluated using the Dutch 'Modifiable Activity Questionnaire' (MAQ) [6]. The MAQ assesses type of sports, frequency/month and average duration (hours), resulting in an average of the total hours of activity per week for the past year (TOT-H week). Sports injury risk was based on the National Hemophilia Foundation (NHF)[7]. The two highest risk categories (2,5 (e.g.: soccer) and 3 (e.g. field hockey) were considered high-risk (HR) sports. Sports were categorized according to joint impact and risk of falls and collisions.

Participants were divided into 3 age groups (children (0-11 years), adolescents and young adults (12-30 years ; AYA) and adults (over 30 years)). For children younger than 12, questionnaires were completed by their parents. VERITAS-Pro and MAQ results are presented as median and 25th to 75th percentiles (i.e. interquartile range: IQR) or proportion with 95% confidence intervals (95%CI) where appropriate and were analysed using descriptive statistics. Between-group differences for age groups and between sporting and non-sporting PWH were analysed using non-parametric Mann Whitney U tests and Chi squared testing. Some participants did not complete the MAQ questionnaire, while completing the previous and the next questionnaire (HEP-Test-Q). To avoid selection bias, those who completed the HEP-Test-Q but not the MAQ were classified as non-sporting. Statistical significance levels were set at 5% ($p<0,05$). The statistical analysis was performed with SPSS statistical software, version 25 (IBM corp., Armonk. NY)

Results

A total of 267 participants with haemophilia A or B who used prophylaxis completed both questionnaires and were included in the analyses. This included 222 participants who completed both MAQ and VERITAS-Pro, and 45 participants (all adults) who did not complete the MAQ but completed the HEP-Test-Q. These 45 participants were categorized as not playing sports. Table 1 shows patient and treatment characteristics. Median age was 34 years (IQR: 15-53), most participants were diagnosed with haemophilia A (87%) and had severe haemophilia (91%). The median age in the adult subgroup was 51 years,

in adolescents 20 years and in children 7 years. The overall median VERITAS-Pro total score was 17 (IQR 10-26). All groups showed high treatment adherence: adherence was higher in young children (median 10 (IQR: 9-14)) than in AYAs (21 (19-31)) and adults (20 (11-26); p<0.01). A total of 188 participants (71%) played regular sports, of which 88 (40%) played high risk sports. PWH reported different sports than the GP. The overall top 5 sports in PWH were fitness and recreational cycling (30%), walking (19%), soccer (17%), swimming (13%) and running (9%). In the general male Dutch population, the top 5 sports consisted of fitness (22%), soccer (14%), running (12%), tennis (6%) and swimming (4%). Sports participation was associated with age: children (93%) and AYAs (95%) were more involved in sports than adults (76%; p<0.01). Participation in HR sports decreased with age: from 67% in children to 45% in AYAs (p<0.01) and 20% in adults (p<0.04).

Table 1: Patient, disease and treatment characteristics, adherence outcomes and sports participation

Median (IQR) or N(%)					
	All	**Children (0-11yr)**	**AYA (12-29yr)**	**Adults (30+yr)**	**p**
n	**266**	**44**	**56**	**167**	
Age (y)	34 (15-53)	7 (5-10)	20 (15-23)	51 (41-61)	
Weight (kg)	70 (54-86)	28 (21-34)	70 (63-82)	85 (73-93)	
BMI	23 (19-26)	16 (15-17)	22 (20-24)	26 (23-28)	
Haemophilia A	194 (87)	39 (87)	49 (88)	106 (88)	
Severe	203 (91)	39 (87)	53 (95)	111 (92)	
IU/KG	17 (12-26)	33 (22-44)	18 (13-22)	19 (12-24)	
Infusion frequency	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-4)	
Patient Reported Outcome Measures					
VERITAS-Pro total score (med, IQR)[1]	17 (10-26)	10 (9-14)*	21 (19-31)	20 (11-26)	0.00
Participation in sports (N,%)	188 (71)	42 (93) †	54 (95) †	92 (55)	0.00
Participation in high risk sports (N,%)*	88 (40)	30 (67) ‡	25 (45)	33 (27)	0.04
Sports (hrs/wk)	3,3 (1,6-5,9)	2,8 (0,9-5,5)	5,2 (2,4-7,1)	2,7 (1,4-5,6)	0.09
HR sports (hrs/wk)	2,6 (1,0-4,2)	2,3 (0,8-3,3)	3,8 (0,3-5,8)	2,1 (1,2-5,7)	0.33

Type of haemophilia, severity , dose and infusion frequency were similar across all age groups.
[1]: a difference of 5 points was considered clinically relevant.
*: Children reported better adherence than AYA and adults.
†: Sports participation was similar in Children and AYA and higher than in adults (p=0,00).
‡: Children were more involved in HR sports than AYA and adults.

Adherence was similar between those who did and did not participate in sports (median score: 20 (IQR: 11-28) vs. 17 (13-25); p=0,50) or in HR sports (21 (12-28) vs. 20 (11-28); p=0,76), nor was adherence associated with sports participation across the different age categories. Figure 1 shows that treatment adherence was independent of sports participation in the different age groups (children: median VP=9 vs. 1; AYA: 19 vs. 20 ; adults: 20 vs. 17), as was HR sports participation (children median VP=10 vs. 7; AYA: 20 vs. 18; adults: 21 vs. 20). Finally, adherence was not associated with the weekly duration of sports (hours/week) in all age groups (children: rho=0,26; AYA: rho=-0,08; adults: p=-0,09).

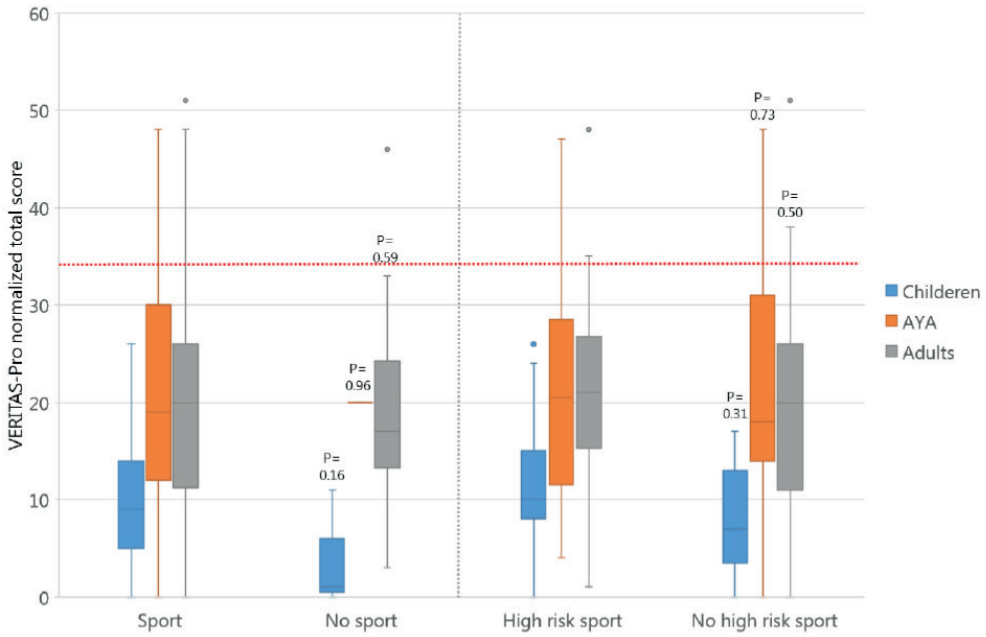


Figure 1: Treatment adherence according to (HR) sports participation and age. Values above the horizontal dotted line indicate non-adherence, p-values are indicating no statistical significant difference between 'sports vs. no sports' and 'high risk sports vs. no high risk sport'

Discussion

Previous qualitative research reported that younger patients with haemophilia who participated in sports were more motivated to follow the prescribed treatment[8]. This study shows that treatment adherence was not associated with sports participation.

There are some strengths and limitations concerning this study. As stated in the introduction, up to the age of 12 years parents are performing the infusion [2], which is a possible explanation for the high adherence in young children. This study was a nationwide study, inviting all participants with haemophilia in The Netherlands. The overall response rate of participants with severe haemophilia completing both questionnaires was low at 34%. In the Dutch haemophilia population the distribution of patients with severe haemophilia is approximately 50% [1]. This could lead to selection bias, as more adherent and more active patients are likely more prone to complete these questionnaires. The present results may therefore represent an overestimation of adherence and sports participation, both due to selection bias and due to overestimation of the patients, this may have obscured a potential association of sports and adherence.

Only one other study on the association between sports participation and treatment adherence was identified. This study was only partially comparable as the research question was contrary to the current study: Zanon et al. (2019) reported improved sports participation and physical activity in 42 adherent patients with severe haemophilia A in a prospective, multicentre study with 36 months follow-up[9]. Adherence was evaluated using empty vials of clotting factor concentrate, while physical activity was assessed by the EPIC-Norfolk questionnaire.

Although prophylaxis is very effective, non-adherence does not immediately result in increased risk of bleeding; patients with severe haemophilia who discontinued prophylaxis reported low bleeding rates, but did show accelerated progression of arthropathy [10]. It can be challenging for clinicians to motivate participants to become and remain adherent if they do not experience limitations and are able to do what they prefer [8]. This study anticipated that participants who wish to compete in (HR) sports would be more adherent to treatment, to protect themselves for the inherent injury and bleeding risks of playing sports. However, this reasoning may be too simple and participants' decision-making is likely more complex. Motivational interviewing discussing a patients' wishes, dreams, is more personalized, and specific wishes or dreams may provide more motivation for adherence. . At the time of experiencing a bleed, a PWH is limited in his daily life and sports. This may be the best time to discuss the benefits of good adherence to prophylaxis. Frequent contact among participants and clinician is needed to apply this intervention at the right time. In conclusion, our study suggests that being active in sports or even in high-risk sports does not necessarily promote adherence in this population with overall a good adherence.

References

1 Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia *2020* 1–158.

2 Schrijvers LH, Schuurmans MJ, Fischer K. Promoting self-management and adherence during prophylaxis: evidence-based recommendations for haemophilia professionals. Haemophilia *2016*; **22:** 499–506.

3 Versloot O, Timmer MA, de Kleijn P, et al. Sports participation and sports injuries in Dutch boys with haemophilia. Scand J Med Sci Sport *2020*; **30:** 1256–64.

4 Oladapo AO, Epstein JD, Williams E, et al. Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: A systematic review of results from prospective clinical trials. Haemophilia *2015*; **21:** e344–58.

5 Lock J, Raat H, Duncan N, et al. Adherence to treatment in a Western European paediatric population with haemophilia: Reliability and validity of the VERITAS-Pro scale. Haemophilia *2014*; **20:** 616–23.

6 Aaron DJ, Kriska AM, Dearwater SR, et al. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. Am J Epidemiol *1995*; **142:** 191–201.

7 Anderson A, Forsyth A. Playing it safe: Bleeding Disorders, Sports and Exercise. New York, NY.: National Hemophilia Foundation; *2017.*

8 Hoefnagels JW, Kars MC, Fischer K, Schutgens REG, Schrijvers LH. The Perspectives of Adolescents and Young Adults on Adherence to Prophylaxis in Hemophilia: A Qualitative Study. Patient Prefer Adherence *2020* 1–9.

9 Zanon E, Tagliaferri A, Pasca S, et al. Physical activity improved by adherence to prophylaxis in an Italian population of children, adolescents and adults with severe haemophilia A: the SHAPE Study. Blood Transfus *2019* 1–6.

10 Nijdam A, Foppen W, de Kleijn P, et al. Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates. Thromb Haemost *2016*; **115:** 931–8.

GENERAL DISCUSSION

General discussion and future perspectives

"Is there such a thing as a completely safe sport? Probably not.
Should people with haemophilia avoid sports and fitness activities? No."

Kathy Mulder et al. (2004)[1]

The primary aim of this thesis was to assess sports participation, sports injuries and sports-induced bleeds in people with haemophilia and to identify potential physical risk factors for these injuries and bleeds. The association between clotting factor levels and sports-induced bleeds was of particular interest in this thesis. The assessment of pharmacokinetics of extended half-life products according to concentrate and patient characteristics was a secondary topic that was discussed in this thesis.

This chapter presents the findings and interpretation of this thesis, and suggestions for clinical practice and future research.

Key findings:

Sports participation

- *Sports participation in people with haemophilia was similar to the general population across all age groups, including high-risk sports*

Sports injuries and sports-induced bleeds

- *Sports injuries were rare, sports-induced bleeds were even more rare and are associated with factor levels at time of injury.*
- *The currently selected motor proficiency tests were unable to predict sports injuries or sports-induced bleeds.*
- *Bleeding hazard was not associated with either the sporting frequency, nor with high-risk sports participation.*

Pharmacokinetics

- *Terminal half-life increases with age in people with FVIII and in young age (below 30) in FIX, but remains constant at older ages.*
- *Not all people with severe haemophilia A benefited from a switch to extended half-life products.*

Benefits of sports participation

The importance of physical activity can hardly be overestimated[2], with sports being a substantial component of physical activity. Physical activity has shown to be associated with survival in many diseases[3] and has established health benefits[4] such as weight control[5], a decreased risk on cardiovascular disease[6], type II diabetes mellitus[7], as well as prevention and survival of certain forms of cancer[8]. The number of infections, hospital admissions and mortality from COVID-19 was lower in people who are regularly physically active[9]. The World Health Organization (WHO) currently recommends 150-300 minutes of moderate-intensity exercise and 75-150 minutes of moderate-to-vigorous aerobic exercise throughout the week and strengthening exercise on at least 2 days for adults. Children are advised to perform at least 60 minutes of moderate-to-vigorous exercise per day with vigorous activity (including strengthening exercises) 3 days per week[10,11,3,12]. However, European adults and children generally do not reach these levels of physical activity[13–15], including those in the Netherlands[16,17]. In the Netherlands, roughly half (55%) the population aged 4 and older is involved in sports at least once weekly[18].

Haemophilia and sports

There is currently an increased awareness and interest in health benefits of physical activity, including in (childhood) chronic conditions. This is reflected by the WHO guidelines and the World Federation of Hemophilia (WFH) guidelines for the treatment of haemophilia: "sports" was mentioned 4 times in the second edition (2013) of the WFH treatment guidelines[19], while it is mentioned 24 times in the most recent edition of the guidelines (2020)[20]. In addition, recent athletic examples show specific policy adaptations in sports to enable people with haemophilia to enable participation in (elite) sports. The international cycling union (UCI) gave a special exemption to its' "no needle policy" to enable Alex Dowsett to participate in professional cycling while infusing FVIII concentrate to treat his severe haemophilia A[21]. Another example is from baseball in the United States, where a player with severe haemophilia A was allowed to be replaced when running bases to protect his affected ankle joint[22] in multiple innings, whereas this is normally only allowed twice per game.

Health benefits of physical activity seem to be universally applicable. However, several specific benefits have been suggested for people with haemophilia. Physical activity has been suggested to improve range of motion, endurance, strength and proprioception in people with haemophilia[23–27], as well as to conserve muscle mass and bone density[23,28,29]. Strength training in people with haemophilia has been suggested to improve joint stability and reduce the number of joint bleeds[29,30]. In addition, people with haemophilia benefit from regular physical activity and sports in improved quality of life[31,32]. As these suggestions came from studies in small groups and no specific trials have been

performed to assess the effects of physical activity on these specific health benefits in people with haemophilia to date, these remain *assumed* health benefits for now.

People with haemophilia have traditionally been discouraged to participate in sport or physical activity due to the assumed increased bleeding risk, particularly in sports with a high risk of trauma[33]. The introduction of treatment options with factor concentrates and the development of treatment with factor concentrates since the 1970s have caused a dramatic increase in the treatment opportunities for people with haemophilia. Particularly the introduction of prophylactic treatment has proven an effective strategy in decreasing the number of (joint) bleeds[34]. Currently, people with haemophilia report overall high sports participation (70%), with age-related variation[35,36].

Sports participation is high and similar to the general population[35,36]. However, a substantial proportion (30%) of people with haemophilia is still not regularly physically active. With the described health benefits in mind, promotion of physical activity seems a crucial task for all involved in clinical practice[37]. In order to achieve this, three recent papers gave directions for promoting physical activity in people with haemophilia[38–40].

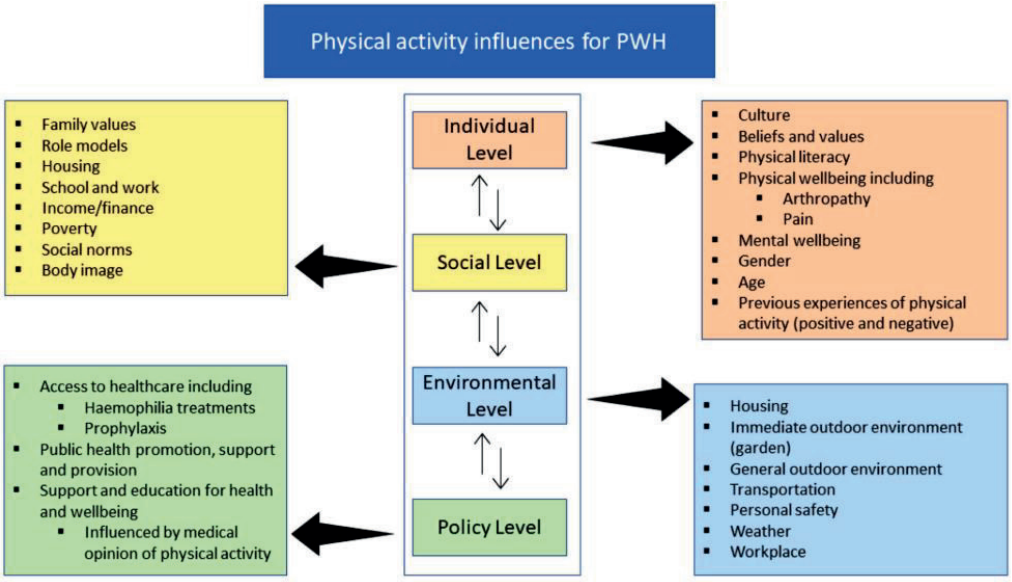


Figure 1: physical activity in people with haemophilia is influenced by different factors at various interacting levels as identified by Matlary et al[38]. Figure used with permission.

Specifically, Matlary et al. (2022) described four different levels that influence physical activity in people with haemophilia, which are shown in figure 1. The four identified levels include individual level (e.g.: pain, wellbeing, previous experiences), social level (income, role models, social norms), environmental level (outdoor environment, personal safety, weather) and policy level (access to healthcare, support). Physical activity can be promoted by acknowledging and understanding these areas for each individual[38]. All three aforementioned papers presented guidelines for physical activity in people with haemophilia and all agree that promoting physical activity is a complex process. All studies advocate an individualized approach when encouraging people with haemophilia to be physically active[38–40].

Sports injuries

Promoting physical activity is a continuous balancing act between health benefits and injury risk, both in people with haemophilia as well as in the general population. Although sports participation is widely encouraged because of health benefits[10,11,20,41,42], the price to pay is an increased injury risk[43,44]. However, in general the benefits seem to outweigh the risks[45].

Societal costs related to sports injuries are high. Total costs of sports injuries in The Netherlands amounted to €413 million in 2012, with €168 million for direct healthcare costs and 244 million in productivity loss[46]. These are costs for the general population. It seems safe to assume that costs for people with haemophilia per capita will be even higher given the high costs of haemophilia treatment and potentially longer admission times in case of hospitalization[47–50]. Besides societal costs, people with sports injuries are unable to participate in their sports, perform their daily social activities (such as walking or cycling to work, school or shops) or to meet WHO physical activity guidelines, potentially for a prolonged time.

Sports injuries and bleeds in people with haemophilia

Despite established health benefits of sports participation (e.g. weight control, cardiovascular disease) for both people with and without haemophilia, there is an ongoing debate among patients, care givers and health care providers whether safe sports participation is possible in people with haemophilia, particularly concerning participation in high-risk sports[33]. This debate was the actual motivation to the study described in this thesis.

People with haemophilia experience very specific risks in case of trauma during physical activity and sport. (e.g. joint and intracranial bleeds). In addition to this, (vigorous) physical activity was identified as a risk factor for bleeds, although the absolute increased risk seemed limited because of the transient nature of the increased risk[52,53].

SPRAIN study

The sports participation and injuries in people with haemophilia (SPRAIN) study collected sports participation data from a nationwide, cross-sectional study, while injury and bleeding data was collected in a single centre, observational study, with a total of 125 participants, where participants were contacted every two weeks to inform about any injuries or bleeds, with a specific interest in sports injuries and sports-induced bleeds. These data were compared to an ongoing, nationwide sports injury study in the general population. The intense monitoring may have caused over reporting, as participants were made more aware of any physical complaints that could be interpreted as injuries or bleeds. This could particularly explain the higher injury rates in participants with severe haemophilia.

This thesis showed that the number of reported sports-induced bleeds was limited in the current study population (chapter 7), which is particularly limited given the high number of exposure moments (15.999; 0.16% sports-induced bleeds). This seems to suggest sports participation is relatively safe for people with haemophilia. Sports injuries were similar in people with haemophilia and the general population, both in numbers (~18% reported an injury) as in injury sites: both groups reported mainly injuries to the lower extremity. Sports injuries according to exposure (number if injuries/1000hrs) was higher than in the general population, potentially attributable to repeated injuries in people with haemophilia (chapter 7).

Factor (FVIII/FIX) levels were identified as the only predictor of sports-induced bleed. Participants with factor levels ≥10IU/dl at the time of injuries had a 50% reduced risk of a sports-induced bleed compared to those with factor levels <10 IU/dl at the time of injury. This seems to indicate that high factor levels during sports may limit the risk of sustaining sport-induced bleeds (see figure 3). However, this protective role of factor levels at the time of injury has yet to be confirmed in clinical trials. In addition, timing of prophylactic treatment is important to ensure sufficiently high factor levels during sports participation in order to prevent sports-induced bleeds: participants infusing within 12 hours before their sports activity reported fewer bleeds. This shows that both pharmacokinetic characteristics and timing are important aspects in preventing sports-induced bleeds, thus turning adherence into an important aspect in prevention of sports-induced bleeds, particularly as infusing at the agreed moment is considered an important aspect of adherence as well[55]. However, as adherence was not associated with (high-risk) sports participation, this seems of minor interest[56].

COVID-19 restrictions affected the study as sports participation changed for the participants, particularly high-risk sports participation plummeted[57]. More sports injuries were

reported during the COVID-19 restrictions, but the number of sports-induced bleeds (both absolute as according to 1000 hr exposure) remained similar during the COVID pandemic (chapter 5 and 8). Although not supported by data, it is tempting to address this to altered sports behaviour during COVID-19 restrictions and therefore potentially a different training load, particularly when increasing training load too fast[58,59].

Besides, both patients and physicians with haemophilia have shown to regularly misinterpret physical complaints as injuries or (joint) bleeds, potentially leading to overestimation of the true number of injuries and bleeds[54]. This might even be reinforced by a decreased number of regular contacts that people with haemophilia have with their consultants in an era of intensive prophylaxis. Due to this, they are only sporadically confronted with their condition, which results in reduced awareness and knowledge about it, running the risk of losing health literacy competencies concerning their condition and for example how to recognize symptoms of bleeds and how to act effectively. To meet this challenge a special application ("hemo hulpje") has been developed for Dutch people with haemophilia at the Van Creveldkliniek to provide distant advice, for instance in case of suspected bleeds. People with haemophilia are provided with information regarding the use of aids, how to recognize a bleed and how to stop a bleed.

Sports injury prevention

Sports injuries, time loss in sports and the high costs of sports injuries for the injured player and society can be limited by taking adequate preventive measures. Particularly exercise-based prevention programmes have been proven effective in multiple settings[60–63]. In order to be able to design and implement an effective preventive programme, an in-depth knowledge of these injuries is vital. To quote a former colleague: "you can't prevent what you don't know". This requires knowledge about incidence, prevalence, duration, cost, impact and specific risk factors. This thesis provides these data: the incidence and prevalence, risk factors for sports injuries and sports-induced bleeds, and other details of sports injuries and sports-induced bleeds in people with haemophilia are presented and compared to the general population (chapter 7). Specific data concerning sports-induced bleeds were lacking for the general population. Therefore, bleeding data could not be compared.

Sports injuries have a complex, multifactorial origin, with an abundance of potential risk factors. In order to give an overview of the complexity and the risk factors involved in sports injuries, Bahr and Krosshaugh (2005) further developed the multifactorial model as presented by Meeuwisse (1994) for risk factors for sports injuries, in which risk factors are subdivided into internal (age, body composition, skill level), external (equipment, environment) and inciting events risk factors (surface, behaviour)[64,65].

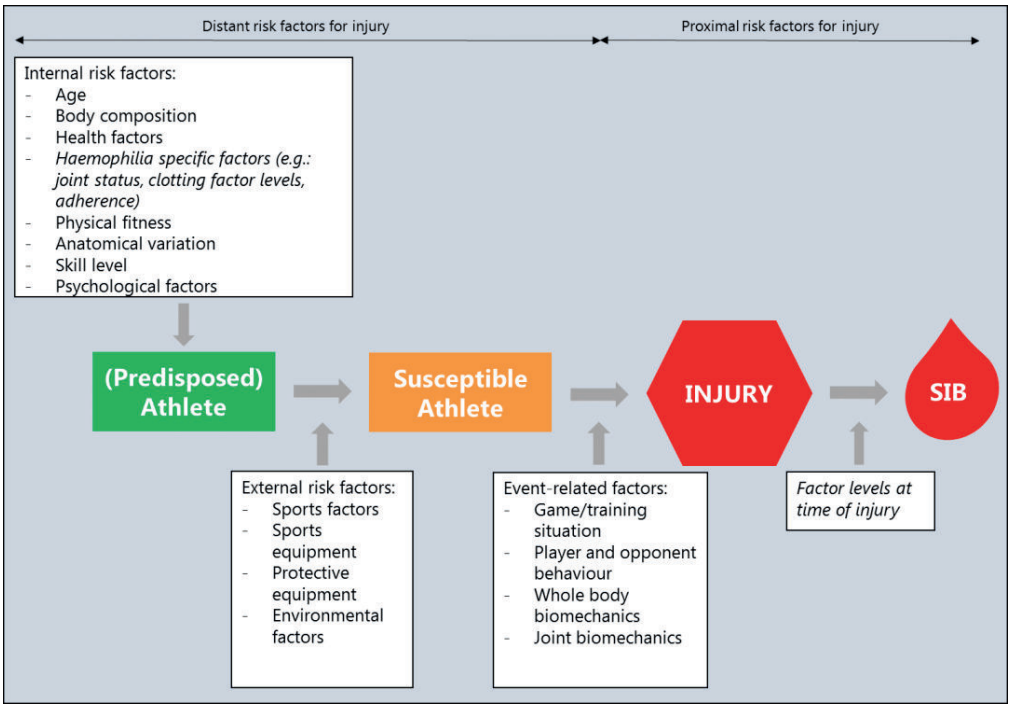


Figure 2: adjusted model for risk factors for sports injuries and sports-induced bleeds in people with haemophilia. Adapted from Bahr and Krosshaug (2005)[65]. Joint status (HJHS), clotting factor levels, adherence and factor levels at time of injury were added to make the model more specific for people with haemophilia. Added or adjusted internal risk factors are shown in Italic.

Although most risk factors apply to people with haemophilia as well, this group has its own specific risk factors. Figure 2 shows an adapted model for risk factor for sports injuries and sport-induced bleeds in people with haemophilia. Most importantly, bleeds are a relevant potential complication of a sports injury in people with haemophilia. This thesis identified coagulation factor levels at the time of injury as a strongest predictor of these bleeds (chapter 7), while aspects such as adherence and joint status seem relevant factors as well. In order to provide a full assessment of injury risk in people with haemophilia, all these aspects (and their potential interactions)[66] should be evaluated.

Identifying risk factors for sports injuries and sports-induced bleeds

Figure 2 shows that sports injury risk factors are highly multi-factorial[64–66]. This thesis focused on identifying internal physical risk factors in active people with haemophilia that are potentially modifiable. In contrast, the model shows that this is only a partial approach of a highly complex problem, requiring a multi-factorial approach when

clinicians try to predict sports injuries. This means including psychological factors (e.g.: personality traits, motivation, risk taking behaviour), external factors (e.g.: protective equipment, environmental factors) and event-related factors (e.g.: behaviour and biomechanics), as well as determining baseline factor levels and the modelling of factor levels at the time of sports participation for a full assessment of sports injuries.

Identifying risk factors for sports injuries is widely used in (elite) sports in order to minimize injury risk. However, there is currently a debate about the effectiveness of screening for sports injuries, from both a methodological[67] and a more pragmatic point of view[68]. From a methodological point of view, studies are generally too small, with often great overlap between high and low injury risk and between test results from injured and uninjured players, making it difficult to identify differences between these groups[67]. From a more pragmatic standpoint, the complexity of sports injuries is emphasized without disregarding the value of screening for injuries. These authors also stress the temporal aspect of risk factors: they vary over time[68]. A call is made to improve the methods that are applied and to test in an appropriate context to better understand the context of sports injuries[68–70].

This could be one the reasons why the tests battery used in this thesis was unable to identify lack of balance, strength, poor running speed & agility or poor endurance as risk factors for sports injuries or sports-induced bleeds. Applying individual tests to identify risk factors disregards the complexity and temporal aspects of sports injuries and ignores the context of the sports activity required to adequately assess injury risk. However, the current procedure does reflect clinical reality, as multiple tests over time seem clinically unrealistic.

Pharmacokinetics of factor levels

Figure 3 shows that multivariable regression analysis identified factor levels at time of sports injury as the only independent predictor of bleeding risk during sports in people with haemophilia. Participants with higher factor VIII/IX activity when sustaining a sports injury had a decreased risk of a sports-induced bleed compared to those with low factor levels. For example, participants with factor activity ≥10 IU/dl at the time of injury had a 50% lower risk of a sports-induced bleed compared to those below 10 IU/dl factor activity (chapter 7).

This has practical consequences for clinicians. First of all, it shows that the current policy to stimulate people with haemophilia to infuse factor concentrates on their actual sporting days, as close to training or game sessions as possible seems to be supported by the data presented in this thesis. Infusing within 12 hours of sports participation

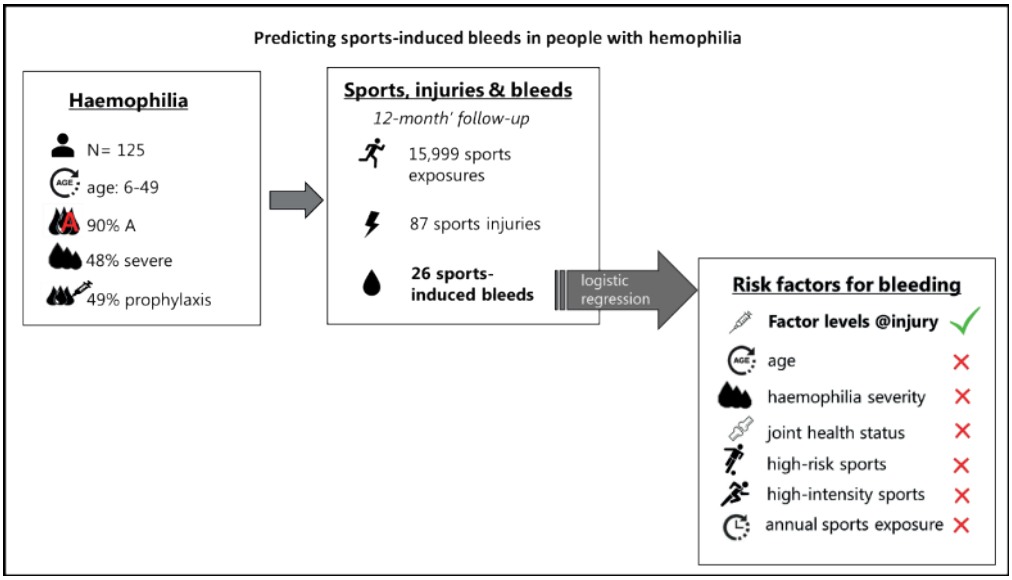


Figure 3: logistic regression shows that factor levels at the time of injury is the only relevant risk factor for developing a sports-induced bleed

showed a significant reduction in injury risk (chapter 7) and corroborates the fact that 10-15 IU/dl factor levels significantly reduce bleeding risk in people with haemophilia[34].

Secondly, the question arises what the consequences will be from switching to extended half-life concentrates or the non-replacement treatment with emicizumab. Unfortunately, no data was collected to answer this question. With the predicted 1.5-2 fold increases in half-life for extended FVIII concentrates and 4-6 fold increases for extended FIX concentrates, it seems fair to assume this will further support the protection against sports-induced bleeds[71–77]. The increased half-life when using extended half-life concentrates gives a slower decrease in factor activity in the blood. This either leads to higher factor levels when patients remain at the same infusion frequency, or a lower infusion frequency with similar factor levels. The higher factor levels in case of the same infusion frequency could potentially lead to a decreased risk on a sports-induced bleed because factor levels are higher during sports in the first 12 hours after infusion. However, the pharmacokinetic responses vary in people with severe haemophilia A and are hard to predict. (chapter 11), making it important to actually measure pharmacokinetic factors such as terminal half-life to base any decisions on existing patient data, rather than on modelled data[78]. This clearly shows once more that counselling people with haemophilia requires an individually tailored approach, in which pharmacokinetic of extended half-life products should be taken into account as well. This seems particularly important

with the increased costs of extended half-life products[79,80], although McMullen et al. (2017) reported an affordable increase in costs when using extended half-life product on a societal level[81,82].

Besides extended half-life concentrates, emicizumab was recently introduced for treatment of people with severe haemophilia A. Although the activity of emicizumab is harder to measure than conventional factor levels, indirect studies have established that treatment with emicizumab results in a coagulation activity which is equivalent to ±10 IU/dl FVIII activity [83,84]. If emicizumab activity is indeed comparable to 10 IU/dl factor VIII activity, than this could mean a similar protection against sports-induced bleeds when using emicizumab as compared to traditional replacement therapy[83,84]. None of the participants in this study used emicizumab during the course of the study (1 switched during the study). Therefore, no comparative data is available. With the anticipated increase in the use of emicizumab, this is an interesting and necessary question for follow-up studies. In short, we expect comparable results for people with haemophilia with regards to sports injuries and sports-induced bleeds, while decreasing patient burden because of less frequent subcutaneous administration.

In the current study, injury and bleeding risk due to sports participation was assessed with sports activity as a single risk exposure moment. Obviously, this is a limited approach, as each individual exposure moment (training session, game) indicates a risk to sustain an injury or bleed. These repeated risk moments should be taken into account. This was done by performing an additional analysis by means of a repeated time to event (RTTE) analysis. The outcome showed that although factor levels remained the strongest predictor of a sports-induced bleed, baseline hazard was increased by factor levels and the presence of an arthropathy as well, but not by sports participation as such (chapter 9). This study also identified factor activity as the most important; predictor for sports-induced bleeds, with a lower risk for bleeds at time of injury in participants with FVIII activity ≥3.1 IU/dl (chapter 9). The difference in outcome between these studies is likely due to the different statistical analyses used: by repeatedly including these (potential) risk factors in the RTTE, outcomes might differ from a model where each factor is only included once.

Finally, there are concerns about increased infusion frequencies or higher dosing around sports participation given the high price of factor concentrates. However, participants have factor activity of around 40 IU/dl shortly after infusing. With a terminal half-life of 6 hours, this means that factor activity would be around 28 IU/dl after 12 hours. As this is clearly over 10 IU/dl, it does not seem necessary to increase infusion frequency or higher dose before participating in (high-risk) sports, thus avoiding higher costs to be able to exercise.

Clinical implications and future research

The most important clinical implication of this thesis is that sports participation seems safe for people with haemophilia and needs to be promoted and stimulated in this group. However, injuries and bleeds will still occur, and risk factors still need to be established. This thesis has mainly identified factor levels (chapter 7), disease severity and the presence of arthropathy (chapter 9) as risk factors. However, we were unable to identify physical, sports-related risk factors (chapter 8).

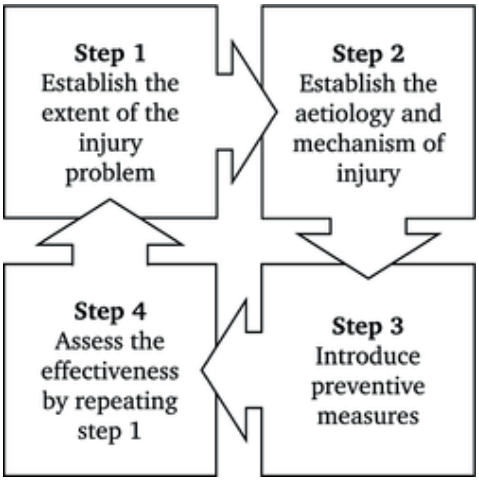


Figure 4: Injury prevention model as proposed by Mechelen et al. (1992)[43]

In order to promote sports participation in people with haemophilia, the model designed by van Mechelen et al. (1992) can be very helpful[43]. This cyclic model is shown in figure 4 and consists of 4 steps: (1) establish the extent of the problem, (2) establish aetiology and mechanisms, (3) introduce measures and (4) assess the effectiveness. This model was recently adapted to a 6-step model to include the context[70]. The current study clearly focused on steps 1 and 2, as it attempts to assess the extent of sports injuries and sports-induced bleeds in people with haemophilia and tried to identify risk factors. However, as we were unable to identify any risk factors with these tests, we should repeat the entire cycle and introduce a new strategy to identify risk factors in order to use them for prevention.

Repeating this cycle would give the opportunity to redesign the study and expand it to study risk factors in a more appropriate context. The current study focused on internal, physical risk factors, although the model in figure 2 clearly shows that this only a partial

approach when attempting to identify sports injury risk factors. Therefore, future studies assessing risk factors for sports injuries and sports-induced bleeds should include all aspects (internal, external, environmental, event) to provide a comprehensive overview of sports injury risk. Testing suspected risk factors in isolation in a laboratory-like setting as in the current study will at its best lead to partial meaningful results, as the context, complexity and temporal aspects are ignored[68–70]. One potential way to include all aspects of injury risk, including its contextual aspects, would be an observational field study in which the participants are being tested and observed in their natural (sports) environment. Since this type of research is widely used in biology, it could very well be utilized to further study injury risks during sports in haemophilia research as well. However, this methodology has its own challenges, such as time consuming, risk of bias and confounding.

Despite the fact that sports participation seems safe, this only concerns the immediate risk of injuries and sports-induced bleeds during sports. Currently, nothing is known about the long-term effects of physical activity or sports participation within people with haemophilia. For example: does prolonged exposure to (high-risk) sports lead to an increased risk of joint destruction? Besides, the potential health effects of physical activity have not been compared to a sedentary control group in a clinical trial. Studying this in a longitudinal, prospective study would lead to enormous practical and methodological challenges (sample size, commitment, measurements), making the practical execution extremely ambitious, if not impossible. A potential alternative would be to perform a retrospective cohort study in which the association between potential health markers (e.g. joint health; obesity; cardiovascular disease) and previous and current physical activity is assessed in people with haemophilia. This is despite obvious disadvantages of retrospective studies, such recall bias, the inability to control outcome or exposure and the potential need to include a large cohort.

Finally, the impact of switching to emicizumab and its consequences on sports participation, injuries and bleeds requires a thorough analysis. Although emicizumab is claimed to have activity levels similar to 10 IU/dl FVIII, the effects of this on prevalence and prevention on sports injuries and sports-induced bleeds need to be studied. With the increase in sports participation, sports and physical activity seem to become more important outcome measures in haemophilia research, including in studies on the clinical application and efficacy of emicizumab[85–90].

General conclusions

The main question this thesis tried to answer was: can people with haemophilia safely participate in sports? Based on this thesis, sports participation in people with haemo-

philia seems (relatively) safe. Besides established risk factors in the general population, factor levels during sports have a key role in people with haemophilia.

People with haemophilia using prophylactic therapy are very active in sports, while injuries and sports-induced bleeds are rare. Sports injuries were sustained, but participants did not report more than the general population. Sports injuries according to exposure showed sports-specific differences between people with haemophilia and the Dutch general population. A minority of these injuries turned into a bleed. Although the risk of developing a joint bleed was very limited, even a single joint bleed could still induce clinically meaningful joint/cartilage damage. Factor activity at the time of the injury determined bleeding risk. Unfortunately, the tests used were unable to identify risk factors or predict injuries.

References

1. Mulder K, Cassis F, Seuser A, Narayan P, Dalzell R, Poulsen W. Risks and benefits of sports and fitness activities for people with haemophilia. *Haemophilia*. 2004;10 Suppl 4:161-163. doi:10.1111/j.1365-2516.2004.01000.x
2. Warburton DER, Bredin SSD. Health benefits of physical activity: A systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541-556. doi:10.1097/HCO.0000000000000437
3. Sawalla Guseh J, Lieberman D, Baggish A. The Evidence for Exercise in Medicine — A New Review Series. *NEJM Evid*. 2022;1(3):1-8. doi:10.1056/evidra2100002
4. Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity - A systematic review of longitudinal studies. *BMC Public Health*. 2013;13(1):1-9. doi:10.1186/1471-2458-13-813
5. Oppert JM, Bellicha A, Ciangura C. Physical activity in management of persons with obesity. *Eur J Intern Med*. 2021;93(April):8-12. doi:10.1016/j.ejim.2021.04.028
6. Li J, Siegrist J. Physical Activity and Risk of Cardiovascular Disease—A Meta-Analysis of Prospective Cohort Studies. *Int J Environ Res Public Health*. 2012;9(12):391-407. doi:10.3390/ijerph9020391
7. Katzmarzyk PT, Craig CL, Gauvin L. Adiposity, physical fitness and incident diabetes: The physical activity longitudinal study. *Diabetologia*. 2007;50(3):538-544. doi:10.1007/s00125-006-0554-3
8. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Med Sci Sports Exerc*. 2019;51(6):1252-1261. doi:10.1249/MSS.0000000000001937
9. Ezzatvar Y, Ramírez-Vélez R, Izquierdo M, Garcia-Hermoso A. Physical activity and risk of infection, severity and mortality of COVID-19: a systematic review and non-linear dose–response meta-analysis of data from 1 853 610 adults. *Br J Sports Med*. Published online 2022:1-7. doi:10.1136/bjsports-2022-105733
10. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451-1462. doi:10.1136/bjsports-2020-102955
11. World Health Organization. *Guidelines on Physical Activity, Sedentary Behaviour and Sleep for Children under 5 Years of Age*.; 2019. http://www.who.int/iris/handle/10665/311664
12. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour.*; 2020.https://apps.who.int/iris/bitstream/handle/10665/325147/WHO-NMH-PND-2019.4-eng.pdf?sequence=1&isAllowed=y%0Ahttp://www.who.int/iris/handle/10665/311664%0Ahttps://apps.who.int/iris/handle/10665/325147
13. Gerovasili V, Agaku IT, Vardavas CI, Filippidis FT. Levels of physical activity among adults 18-64 years old in 28 European countries. *Prev Med (Baltim)*. 2015;81:87-91. doi:10.1016/j.ypmed.2015.08.005
14. López-Fernández J, López-Valenciano A, Mayo X, et al. No changes in adolescent's sedentary behaviour across Europe between 2002 and 2017. *BMC Public Health*. 2021;21(1):1-8. doi:10.1186/s12889-021-10860-3
15. Lera-López F, Marco R. Sports participation, physical activity, and health in the European regions. *J Sports Sci*. 2018;36(15):1784-1791. doi:10.1080/02640414.2017.1418810
16. Takken T, de Jong N, Group on behalf of the DPARCS. Results from the Netherlands' 2018 report card on physical activity for children and youth. *J Phys Act Heal*. 2018;15(Suppl 2):S388-389. doi:10.1123/jpah.2016-0299
17. Burghard M, Knitel K, Van Oost I, Tremblay MS, Takken T. Is our youth cycling to health? results from the Netherlands' 2016 report card on physical activity for children and youth. *J Phys Act Heal*. 2016;13(11):S218-S224. doi:10.1123/jpah.2016-0299
18. Duijvestijn M, Schurink T, van den Berg S, Euser S, Wendel-Vos W. *Sport En Beweeggedrag in 2020 (in Dutch).*; 2021. www.rivm.nl
19. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-e47. doi:10.1111/j.1365-2516.2012.02909.x
20. Srivastava A, Santagostino E, Dougall A, Al. E. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;(May):1-158. doi:10.1111/hae.14046
21. Reynolds T. Alex Dowsett: Haemophilia no barrier to cyclist's hour record bid. BBC. Published 2015. Accessed May 30, 2022. https://www.bbc.com/sport/get-inspired/32434988
22. Callaway K. Pinch-runner rule instituted to aid Phoenix player with hemophilia. Spectrum News 1. Published 2022. Accessed May 30, 2022. https://spectrumlocalnews.com/nys/central-ny/news/2022/05/23/pinch-runner-rule-helps-player-with-hemophilia#

23. Eid MA, Ibrahim MM, Aly SM. Effect of resistance and aerobic exercises on bone mineral density, muscle strength and functional ability in children with hemophilia. *Egypt J Med Hum Genet*. 2014;15(2):139-147. doi:10.1016/j.ejmhg.2013.12.002

24. Parhampour B, Dadgoo M, Vasaghi-Gharamaleki B, et al. The effects of six-week resistance, aerobic and combined exercises on the pro-inflammatory and anti-inflammatory markers in overweight patients with moderate haemophilia A: A randomized clinical trial. *Haemophilia*. 2019;25(4):e257-e266. doi:10.1111/hae.13764

25. Querol F, Gallach JE, Toca-Herrera JL, Gomis M, Gonzalez LM. Surface electrical stimulation of the quadriceps femoris in patients affected by haemophilia A. *Haemophilia*. 2006;12(6):629-632. doi:10.1111/j.1365-2516.2006.01356.x

26. Hilberg T, Herbsleb M, Gabriel HHW, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. *Haemophilia*. 2001;7(6):582-588. doi:10.1046/j.1365-2516.2001.00563.x

27. Harris S, Boggio LN. Exercise may decrease further destruction in the adult haemophilic joint. *Haemophilia*. 2006;12(3):237-240. doi:10.1111/j.1365-2516.2006.01214.x

28. Hilberg T, Herbsleb M, Puta C, Gabriel HHW, Schramm W. Physical training increases isometric muscular strength and proprioceptive performance in hemophilic subjects. *Haemophilia*. 2003;9(2):86-93. doi:679 [pii]

29. Tiktinsky R, Falk B, Heim M, Martinovitz U. The effect of resistance training on the frequency of bleeding in haemophilia patients: A pilot study. *Haemophilia*. 2002;8(1):22-27. doi:10.1046/j.1365-2516.2002.00575.x

30. Gomis M, Querol F, Gallach JE, Gonzalez LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: A systematic review. *Haemophilia*. 2009;15(1):43-54. doi:10.1111/j.1365-2516.2008.01867.x

31. Cuesta-Barriuso R, Torres-Ortuño A, Pérez-Alenda S, José Carrasco J, Querol F, Nieto-Munuera J. Sporting Activities and Quality of Life in Children With Hemophilia. *Pediatr Phys Ther*. 2016;28(4):453-459. doi:10.1097/PEP.0000000000000296

32. Khair K, Littley A, Will A, von Mackensen S. The impact of sport on children with haemophilia. *Haemophilia*. 2012;18(6):898-905. doi:10.1111/j.1365-2516.2012.02857.x

33. Anderson A, Forsyth A. *Playing It Safe: Bleeding Disorders, Sports and Exercise*. National Hemophilia Foundation; 2017. doi:10.1136/jech.2007.061960

34. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: The association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17(1):41-44. doi:10.1111/j.1365-2516.2010.02383.x

35. Versloot O, van Balen EC, Hassan S, et al. Similar sports participation as the general population in Dutch persons with haemophilia; results from a nationwide study. *Haemophilia*. 2021;27(5):876-885. doi:10.1111/hae.14366

36. Versloot O, Berntorp E, Petrini 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(2):244-251. doi:10.1111/hae.13683

37. Sallis R, Franklin B, Joy L, Ross R, Sabgir D, Stone J. Strategies for Promoting Physical Activity in Clinical Practice. *Prog Cardiovasc Dis*. 2015;57(4):375-386. doi:10.1016/j.pcad.2014.10.003

38. Matlary RED, Grinda N, Sayers F, Versloot O, McLaughlin P. Promoting physical activity for people with haemophilia in the age of new treatments. *Haemophilia*. 2022;(April):1-6. doi:10.1111/hae.14641

39. Biasoli C, Baldacci E, Coppola A, et al. Promoting physical activity in people with haemophilia: the MEMO (Movement for persons with haEMOphilia) expert consensus project. *Blood Transfus*. 2022;20(1):66-77. doi:10.2450/2021.0138-21

40. De la Corte-Rodriguez H, Rodriguez-Merchan EC, Alvarez-Roman MT, Jiménez-Yuste V. Applying World Health Organization 2020 guidelines on physical activity and sedentary behavior to people with hemophilia. *Expert Rev Hematol*. 2021;14(5):429-436. doi:10.1080/17474086.2021.1924054

41. American College of Sports Medicine. *Physical Activity Guidelines for Americans*.; 2018. https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf

42. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report. *Washingt DC US*. 2008;67(2):683. doi:10.1111/j.1753-4887.2008.00136.x

43. van Mechelen W, Hlobil H, Kemper HCG. Incidence, Severity, Aetiology and Prevention of Sports Injuries: A Review of Concepts. *Sport Med*. 1992;14(2):82-99. doi:10.2165/00007256-199214020-00002

44. Emery CA. Risk Factors for Injury in Child and Adolescent Sport: A Systematic Review of the Literature. *Clincal J Sport Med*. 2003;13:256-268.

45. Melzer K, Kayser B, Pichard C. Physical activity: The health benefits outweigh the risks. *Curr Opin Clin Nutr Metab Care*. 2004;7(6):641-647. doi:10.1097/00075197-200411000-00009

46. Polinder S, Haagsma J, Panneman M, Scholten A, Brugmans M, Van Beeck E. The economic burden of injury: Health care and productivity costs of injuries in the Netherlands. *Accid Anal Prev*. 2016;93:92-100. doi:10.1016/j.aap.2016.04.003

47. Feldman BM, Berger K, Bohn R, et al. Haemophilia prophylaxis: How can we justify the costs? *Haemophilia*. 2012;18(5):680-684. doi:10.1111/j.1365-2516.2012.02790.x

48. Fischer K, Van Den Berg HM, Thomas R, et al. Dose and outcome of care in haemophilia how do we define cost-effectiveness. *Haemophilia*. 2004;10(Suppl. 4):216-220. doi:10.1111/j.1365-2516.2004.01047.x

49. Heemstra HE, Zwaan T, Hemels M, et al. Cost of severe haemophilia in Toronto. *Haemophilia*. 2005;11(3):254-260. doi:10.1111/j.1365-2516.2005.01082.x

50. Lippert B, Berger K, Berntorp E, et al. Cost effectiveness of haemophilia treatment: A cross-national assessment. *Blood Coagul Fibrinolysis*. 2005;16(7):477-485. doi:10.1097/01.mbc.0000178830.39526.ff

51. Souza JC, Simoes HG, Campbell CSG, Pontes FL, Boullosa DA, Prestes J. Haemophilia and exercise. *Int J Sports Med*. 2012;33(2):83-88. doi:10.1055/s-0031-1286292

52. Germini F, Noronha N, Abraham Philip B, et al. Risk factors for bleeding in people living with hemophilia A and B treated with regular prophylaxis: A systematic review of the literature. *J Thromb Haemost*. 2022;20(6):1364-1375. doi:10.1111/jth.15723

53. Broderick CR, Herbert RD, Latimer J, et al. Association Between Physical Activity and Risk of Bleeding in Children With Hemophilia. *JAMA J Am Med Assoc*. 2012;308(14):1452-1459. doi:10.1001/jama.2012.12727. eTable

54. Ceponis A, Wong-Sefidan I, Glass CSS, von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. *Haemophilia*. 2013;19(5):790-798. doi:10.1111/hae.12175

55. Schrijvers LH, Cnossen MH, Beijlevelt-Van der Zande M, Peters M, Schuurmans MJ, Fischer K. Defining adherence to prophylaxis in haemophilia. *Haemophilia*. 2016;22(4):e311-e314. doi:10.1111/hae.12935

56. Hoefnagels JW, Versloot O, Schrijvers LH, et al. Sports participation is not associated with adherence to prophylaxis in Dutch patients with haemophilia. *Haemophilia*. 2021;27(3):online ahead of print. doi:10.1111/hae.14244

57. Versloot O, van der Net J, Fischer K. Sports participation of patients with haemophilia in the COVID-19 era: The Dutch experience. *Haemophilia*. 2021;27(2):e295-e297. doi:10.1111/hae.14189

58. Drew MK, Finch CF. The Relationship Between Training Load and Injury, Illness and Soreness: A Systematic and Literature Review. *Sport Med*. 2016;46(6):861-883. doi:10.1007/s40279-015-0459-8

59. Gabbett TJ, Hulin BT, Blanch P, Whiteley R. High training workloads alone do not cause sports injuries: How you get there is the real issue. *Br J Sports Med*. 2016;50(8):444-445. doi:10.1136/bjsports-2015-095567

60. Verhagen EALM, Van Der Beek A, Twisk JWR, Bouter L, Bahr R, Van Mechelen W. The effect of a proprioceptive balance board training program for the prevention of ankle sprains: A prospective controlled trial. *Am J Sports Med*. 2004;32(6):1385-1393. doi:10.1177/0363546503262177

61. Bizzini M, Dvorak J. FIFA 11+: An effective programme to prevent football injuries in various player groups worldwide - A narrative review. *Br J Sports Med*. 2015;49(9):577-579. doi:10.1136/bjsports-2015-094765

62. Gouttebarge V, Zwerver J, Verhagen EALM. Preventing musculoskeletal injuries among recreational adult volleyball players: Design of a randomised prospective controlled trial. *BMC Musculoskelet Disord*. 2017;18(1):1-6. doi:10.1186/s12891-017-1699-6

63. Lemes IR, Pinto RZ, Lage VN, et al. Do exercise-based prevention programmes reduce non-contact musculoskeletal injuries in football (soccer)? A systematic review and meta-analysis with 13 355 athletes and more than 1 million exposure hours. *Br J Sports Med*. 2021;55(20):1170-1178. doi:10.1136/bjsports-2020-103683

64. Meeuwisse WH. Assessing Causation in Sport Injury: a Multifactorial Model. *J Clin Sport Med*. 1994;4(3):166-170. https://journals.lww.com/cjsportsmed/Abstract/1994/07000/Assessing_Causation_in_Sport_Injury__A.4.aspx

65. Bahr R, Krosshaug T. Understanding injury mechanisms: A key component of preventing injuries in sport. *Br J Sports Med*. 2005;39(6):324-329. doi:10.1136/bjsm.2005.018341

66. Bahr R, Holme I. Risk factors for sports injuries, a methodological approach. *Br J Sports Med*. 2003;37:384-392.

67. Bahr R. Why screening tests to predict injury do not work-and probably never will.: A critical review. *Br J Sports Med*. 2016;50(13):776-780. doi:10.1136/bjsports-2016-096256

68. Verhagen EALM, van Dyk N, Clark N, Shrier I. Do not throw the baby out with the bathwater; screening can identify meaningful risk factors for sports injuries. *Br J Sports Med*. 2018;0(0):bjsports-2017-098547. doi:10.1136/bjsports-2017-098547

69. Bolling C, van Mechelen W, Pasman HR, Verhagen EALM. Context Matters: Revisiting the First Step of the 'Sequence of Prevention' of Sports Injuries. *Sport Med*. 2018;48(10):2227-2234. doi:10.1007/s40279-018-0953-x

70. Finch C. A new framework for research leading to sports injury prevention. *J Sci Med Sport*. 2006;9(1-2):3-9. doi:10.1016/j.jsams.2006.02.009

71. Kumar R, Dunn A, Carcao M. Changing Paradigm of Hemophilia Management: Extended Half-Life Factor Concentrates and Gene Therapy. *Semin Thromb Hemost*. 2016;42(1):18-29. doi:10.1055/s-0035-1568877

72. Graf L. Extended Half-Life Factor VIII and Factor IX Preparations. *Transfus Med Hemotherapy*. 2018;45(2):86-91. doi:10.1159/000488060

73. Mancuso M, Santagostino E. Outcome of Clinical Trials with New Extended Half-Life FVIII/IX Concentrates. *J Clin Med*. 2017;6(4):39. doi:10.3390/jcm6040039

74. Mullins ES, Stasyshyn O, Alvarez-Román MT, et al. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. *Haemophilia*. 2017;23(2):238-246. doi:10.1111/hae.13119

75. Tiede A, Abdul-Karim F, Carcao M, et al. Pharmacokinetics of a novel extended half-life glycoPEGylated factor IX, nonacog beta pegol (N9-GP) in previously treated patients with haemophilia B: results from two phase 3 clinical trials. *Haemophilia*. 2017;23(4):547-555. doi:10.1111/hae.13191

76. Collins PW, Björkman S, Fischer K, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: Influences of variance in pharmacokinetics and treatment regimens. *J Thromb Haemost*. 2010;8(2):269-275. doi:10.1111/j.1538-7836.2009.03703.x

77. Versloot O, Iserman E, Chelle P, et al. Terminal half-life of FVIII and FIX according to age, blood group and concentrate type: data from the WAPPS database. *J Thromb Haemost*. 2021;Epub ahead(February):1-11. doi:10.1111/jth.15395

78. Versloot O, Iserman E, Chelle P, Germini F, Edginton AN, Schutgens REG. Predicting Individual Changes in Terminal Half-Life After Switching to Extended Half-Life Concentrates in Patients With Severe Hemophilia. *Hemasphere*. Published online 2022:1-7.

79. Tortella BJ, Alvir J, McDonald M, et al. Real-world analysis of dispensed IUs of coagulation factor IX and resultant expenditures in hemophilia B patients receiving standard half-life versus extended half-life products and those switching from standard half-life to extended half-life products. *J Manag Care Spec Pharm*. 2018;24(7):643-653. doi:10.18553/jmcp.2018.17212

80. Bullement A, McMordie ST, Hatswell AJ, Li N, Wilson K. Cost-Effectiveness Analysis of Recombinant Factor VIII Fc-Fusion Protein (rFVIIIFc) for the Treatment of Severe Hemophilia A in Italy Incorporating Real-World Dosing and Joint Health Data. *PharmacoEconomics - Open*. 2020;4(1):133-142. doi:10.1007/s41669-019-0158-8

81. McMullen S, Buckley B, Hall E, Kendter J, Johnston K. Budget Impact Analysis of Prolonged Half-Life Recombinant FVIII Therapy for Hemophilia in the United States. *Value Heal*. 2017;20(1):93-99. doi:10.1016/j.jval.2016.09.2396

82. Rodriguez-Merchan EC. The cost of hemophilia treatment: the importance of minimizing it without detriment to its quality. *Expert Rev Hematol*. 2020;13(3):269-274. doi:10.1080/17474086.2020.1716726

83. Lenting PJ. Laboratory monitoring of hemophilia A treatments: New challenges. *Blood Adv*. 2020;4(9):2111-2118. doi:10.1182/bloodadvances.2019000849

84. Muto A, Yoshihashi K, Takeda M, et al. Anti-factor IXa X bispecific antibody ACE910 hemostatic potency against ongoing - Muto et al. (2013).pdf. *J Thromb Haemost*. 2013;12:206-213. doi:10.1111/jth.12474

85. Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. *Haemophilia*. 2022;28(S4):103-110. doi:10.1111/hae.14524

86. Skinner MW, Négrier C, Paz-Priel I, et al. The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without FVIII inhibitors in the HAVEN 3 and HAVEN 4 studies. *Haemophilia*. 2021;27(5):854-865. doi:10.1111/hae.14363

87. Jiménez-Yuste V, Auerswald G, Benson G, et al. Practical considerations for nonfactor-replacement therapies in the treatment of haemophilia with inhibitors. *Haemophilia*. 2020;27(3):340-350. doi:10.1111/hae.14167

88. Yada K, Nogami K. Spotlight on emicizumab in the management of hemophilia a: Patient selection and special considerations. *J Blood Med*. 2019;10:171-181. doi:10.2147/JBM.S175952

89. Kiadaliri AA, Eliasson B, Gerdtham UG. Does the choice of EQ-5D tariff matter? A comparison of the Swedish EQ-5D-3L index score with UK, US, Germany and Denmark among type 2 diabetes patients. *Health Qual Life Outcomes*. 2015;13:145. doi:10.1186/s12955-015-0344-z

90. Kiialainen A, Castaman G, Levy GG, 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;(July):1-11. doi:10.1111/hae.14642

SUMMARY

Summary

Around 1,700 men and boys in the Netherlands suffer from haemophilia, which is characterized by prolonged bleeding after trauma or surgery and an increased risk of (spontaneous) muscle and joint bleeds. In the absence of a definite cure, people with haemophilia require lifelong prophylactic treatment. Despite improved treatment options and acclaimed health benefits, people with haemophilia have traditionally been discouraged to participate in sport, particularly because of the anticipated increased bleeding risk. With the introduction of prophylactic treatment options, possibilities for sports participation have increased in people with haemophilia. Despite these improvements, the debate about the safety of sports participation among patients, peers and clinicians continues to this date. The aim of this study was to describe sports participation, sports injuries and sports-induced bleeds in people with haemophilia, with a special emphasis on the role of factor levels in the risk of sports-induced bleeds. Besides this, we tried to identify physical risk factors for sports injuries and sports-induced bleeds. As a secondary aim, we describe a prediction model to describe the increase in terminal half-life in people with haemophilia using extended half-life concentrates and the individual benefit of switching to extended half-life concentrates.

Part I – Sports participation

Sports participation in people with haemophilia is currently similar to the general population across all age groups. Although sports participation decreased in older people with haemophilia, this was less pronounced than in the general population. Sports participation was associated with severity in adults, but not in children: adults with severe haemophilia were less involved in sports than those with non-severe haemophilia (**chapter 2**). **Chapter 3** showed similar sports participation in people with haemophilia with high-dose (Sweden) and intermediate-dose (The Netherlands) treatment strategies. However, Dutch people with haemophilia showed an age-related decrease, unlike their Swedish counterparts. Furthermore, this chapter showed sports participation was not associated with (sports-induce) bleeds or clotting factor consumption. The retrospective study described in **chapter 4** showed high sports-participation (including high-risk sports) and low injury rates in 102 Dutch boys with haemophilia. Furthermore, similar injury rates in boys with severe and non-severe haemophilia were observed. Sports participation was similar to the general population and sports injuries were not higher than the general population. **Chapter 5** showed that sports participation in people with haemophilia decreased as a result of the imposed restriction during the COVID-19 pandemic, just as in the general population. The decrease in sports participation was more pronounced than in the general population and mainly showed a shift from high-risk sports to safe sports and from team sports to individual sports.

Part II – Sports injuries and sports-induced bleeds

Chapter 6 describes the measurement protocol of this prospective study. It describes the use of domains of the BOT-2® testing protocol, the steep-ramp test, recording of physical activity with Activ8® accelerometers and the follow-up procedure. The results from the 12-month' follow-up in **chapter 7** showed that sports injuries and sports-induced bleeds were rare in active people with haemophilia and that sports-induced bleeds were associated with factor levels at the time of injury, but not with severity. Factor levels ≥10 IU/dl showed a 50% reduction in bleeding risk when sustaining a sports injury. **Chapter 8** showed that the current selection of motor proficiency and endurance tests could not predict sports injuries or sports-induced bleeds, most likely due to a low number of injuries and bleeds and lack of variation in the test results. A more detailed repeated time-to-event analysis of the association between sports participation and sports-induced bleeds was presented in **chapter 9**. This analysis showed an inverse association between FVIII levels and bleeding hazard, but no association between sports participation and bleeding hazard, confirming that FVIII levels are the most important determinant for bleeding hazard. In addition, this study did show associations between haemophilia severity and joint health, and bleeding hazard.

Part III - Pharmacokinetics

Extended half-life concentrates have recently been developed to provide longer terminal half-life and limit patient burden by decreasing the infusion frequency, while maintaining sufficient factor VIII/IX levels. **Chapter 10** provides reference values for FVIII and FIX extended half-life concentrates based on patient characteristics and concentrate types. Furthermore, it showed an age-related increase in terminal half-life in both FVIII (all ages) and FIX (until 30, remaining stable in older ages) and a shorter FVIII half-life in subjects with blood group O and people with haemophilia with a positive inhibitor history. **Chapter 11** showed that not all people with haemophilia A benefited from switching to extended half-life concentrates. A clinically meaningful extension in half-life in people with haemophilia A was predicted by short half-life at baseline and blood group non-O. People with haemophilia who are active in sports are advised to infuse their prophylactic factor concentrates shortly before sports activities to prevent sports-induced bleeds. Therefore, sport participation, and in particular participation in high-risk sports was assumed to improve therapeutic adherence as we assumed that people with haemophilia make deliberate choices to participate in sports. However, **chapter 12** showed no association between (high-risk) sports participation and adherence to prophylactic treatment.

The general discussion aims to place the results into a clinical perspective and tries to formulate future research directions. This chapter first presents the results of this study, which is followed by a discussion how to implement the findings of this thesis into daily clinical practice.

ADDENDA

Nederlandse samenvatting
Acknowledgements
About the author
List of publications
Posters and Presentations
Awards

Nederlandse samenvatting (Dutch summary)

Ongeveer 1.700 mannen en jongens in Nederland lijden aan hemofilie. Deze aandoening wordt gekenmerkt door bloedingen na trauma of operatie en een verhoogd risico op (spontane) spier- en gewrichtsbloedingen. Zolang genezing niet mogelijk is, moeten mensen met hemofilie levenslang profylactisch behandeld worden. Ondanks verbeterde behandelingsopties en aangetoonde gezondheidsvoordelen wordt sporten vaak nog afgeraden aan het mensen met hemofilie, vooral vanwege het mogelijk verhoogde bloedingsrisico. Sinds profylactische behandeling mogelijk is hebben mensen met hemofilie veel meer mogelijkheden om te sporten. Ondanks deze verbeteringen gaat het debat over de veiligheid van sportdeelname onder behandelaars, patiënten en ouders/verzorgers tot op de dag van vandaag door. Het doel van deze studie was om de sportdeelname, sportblessures en sportbloedingen bij mensen met hemofilie te beschrijven, waarbij we vooral benieuwd waren naar de rol van de factorspiegels bij het risico op door sportbloedingen. Daarnaast hebben we geprobeerd om fysieke risicofactoren voor sportblessures en sportbloedingen te bepalen. Daarnaast beschrijven we een voorspellingsmodel om de toename van de halfwaardetijd bij mensen met hemofilie die langwerkende medicatie gebruiken te beschrijven en het individuele voordeel van het overschakelen naar langwerkenden medicatie.

Deel I – Sportdeelname

Mensen met hemofilie sporten in Nederland op dit moment evenveel als mensen zonder hemofilie. Dit geldt voor alle leeftijdsgroepen. Hoewel de sportdeelname bij ouderen met hemofilie afneemt, was dit minder uitgesproken dan in de rest van de bevolking. Er is een verband tussen ernst van de hemofilie en hoeveel men sport bij volwassenen, maar niet bij kinderen: volwassenen met ernstige hemofilie sportten minder dan volwassenen met niet-ernstige hemofilie (**hoofdstuk 2**). **Hoofdstuk 3** laat een vergelijkbare sportdeelname zien bij mensen met hemofilie met een high-dose behandelingsstrategieën (Zweden) en lagere doses (Nederland). Nederlanders met hemofilie vertoonden in tegenstelling tot hun Zweedse tegenhangers een leeftijdsgebonden daling bij het sporten. Verder blijkt uit dit hoofdstuk dat er geen verband lijkt te zijn tussen sportdeelname en sportbloedingen of stollingsfactorconsumptie. De retrospectieve studie die beschreven wordt in **hoofdstuk 4** laat een hoge sportdeelname (inclusief risicosporten) en weinig sportblessures bij 102 Nederlandse jongens met hemofilie zien. Er was geen verschil in het aantal blessures tussen jongens met ernstige en niet-ernstige hemofilie. De mate van sportdeelname was vergelijkbaar met de algemene bevolking en het aantal sportblessures was niet hoger dan in de algemene bevolking. Uit **hoofdstuk 5** blijkt dat de sportdeelname bij mensen met hemofilie

afnam als gevolg van de COVID-19-maatregelen, net als bij de rest van de Nederlandse bevolking. De daling van de sportdeelname bij mensen met hemofilie was echter groter dan in de rest van Nederland en liet vooral een verschuiving zien van risicosporten naar sporten met een laag risico en van teamsporten naar individuele sporten.

Deel II – Sportblessures en sportbloedingen

Hoofdstuk 6 beschrijft het meetprotocol van deze prospectieve studie. Het beschrijft het gebruik van de domeinen van het BOT-2® testprotocol, de steep ramp test, registratie van fysieke activiteit met Activ8® activiteitenmeters en de follow-up procedure van de studie. De resultaten van de follow-up van 12 maanden in **hoofdstuk 7** laat zien dat sportblessures en sportbloedingen zeldzaam waren bij sportende mensen met hemofilie en dat er een verband lijkt te bestaan tussen en factorspiegels op het moment van blessure, maar niet met de ernst van de hemofilie. Factorniveaus ≥10 IU/dl toonden een 50% lager risico op sportbloedingen bij het oplopen van een sportblessure. **Hoofdstuk 8** laat zien dat sportblessures en sportbloedingen niet voorspeld kunnen worden met de gebruikte tests (motor proficiency en uithoudingsvermogen). Dit komt hoogstwaarschijnlijk door het lage aantal blessures en bloedingen en het gebrek aan variatie in de testresultaten. Een meer gedetailleerde repeated time-to-event analyse van het verband tussen sportdeelname en door sportbloedingen is te lezen in **hoofdstuk 9**. Dit hoofdstuk laat een omgekeerd verband zien tussen FVIII-spiegels en bloedingsgevaar, maar geen verband tussen sportdeelname en bloedingsgevaar, wat bevestigt dat FVIII-spiegels de belangrijkste determinant zijn voor bloedingsgevaar bij sportblessures. Bovendien laat deze studie dat ernst van hemofilie en de gezondheid van de gewrichten een rol spelen in het risico op sportbloedingen.

Deel III - Farmacokinetiek

Langwerkende hemofilie medicatie is recent ontwikkeld om een langere halfwaardetijd te bereiken en daardoor de belasting van de patiënt beperken door de infusiefrequentie te verlagen, terwijl de FVIII en FIX-spiegels even hoog blijven. **Hoofdstuk 10** bevat referentiewaarden voor FVIII- en FIX-concentraten met verlengde halfwaardetijden op basis van patiëntkenmerk-en en concentraattypen. Bovendien laat het een leeftijdsgebonden toename van de halfwaardetijd bij zowel FVIII (alle leeftijden) als FIX (tot 30 jaar, stabiel blijvend bij oudere leeftijd) zien en een kortere FVIII-halfwaardetijd bij proefpersonen met bloedgroep O en mensen met een remmer. **Hoofdstuk 11** laat zien dat niet alle mensen met hemofilie A baat hebben bij het overschakelen naar langwerkenden medicatie. Een klinisch betekenisvolle verlenging van de halfwaardetijd bij mensen met hemofilie A werd voorspeld door een korte halfwaardetijd voor de overstap naar langwerkende medicatie en mensen die niet bloedgroep O hebben.

Mensen met hemofilie die sporten, wordt geadviseerd om hun profylaxe kort voor hun sport toe te dienen om sportbloedingen te voorkomen. Daarom werd aangenomen dat sporten de therapietrouw zou verbeteren, in het bijzonder bij deelname aan risicosporten, omdat we ervan uitgingen dat mensen met hemofilie bewuste keuzes maken om deel te nemen aan sport. **Hoofdstuk 12** toonde echter geen correlatie tussen deelname aan risicosporten en therapietrouw.

De afsluitende algemene discussie heeft tot doel de resultaten in een klinisch perspectief te plaatsen en probeert toekomstige onderzoeksrichtingen te formuleren. Dit hoofdstuk presenteert eerst de resultaten van deze studie, die wordt gevolgd door een discussie over hoe de bevindingen van dit proefschrift in de dagelijkse klinische praktijk kunnen worden geïmplementeerd.

Dankwoord

Zoals altijd begon ook dit proefschrift ooit als een blanco velletje. Nu het bijna volwassen is, is ook de tijd gekomen om iedereen te bedanken die hier belangrijk voor is geweest tijdens. Het voelt vaak alsof je het allemaal alleen doet (zeker gezien mijn 21:00-05:00 mentaliteit), maar dat is niet zo. Promoveren is teamwork pur sang en zonder de steun van iedereen om mij heen was dit proefschrift er nooit gekomen!

Allereerst de allerbelangrijkste groep: de **deelnemers** aan dit onderzoek. Dit onderzoek is voor en door jullie mogelijk gemaakt. Bedankt voor jullie deelname en dat ik jullie een jaar lang mocht lastig vallen over jullie blessures!

Roger, de van Creveldkliniek is een hele speciale plek en daar mag je trots op zijn! Ook al was je als promotor meer op de achtergrond aanwezig, je was altijd bereik- en benaderbaar. Ik wil je heel hartelijk bedanken dat je me de kans gaf om dit onderzoek te doen bij de van Creveldkliniek en dat je altijd mee wilde denken en werken. Je feedback was enorm waardevol, zeker toen we met de injury paper met z'n allen last van een klassiek gevalletje tunnelvisie bleken te hebben en jij het gelukkig wel zag.

Kathelijn, toen je me belde dat ik deze promotieplek kreeg, zei je dat je al helemaal blij was geworden toen je mijn brief kreeg. Ik ben nog steeds blij dat jij het wel zag, want ik durfde hem eigenlijk niet eens op te sturen. Ik heb je leren kennen als een ongelooflijk betrokken arts, wetenschapper en begeleider. Direct, kritisch en bevlogen, zowel voor patiënten als promovendi. Je hebt altijd tijd voor overleg. Waarschijnlijk niet meteen en zeker niet op het afgesproken tijdstip, maar verder maak je er altijd tijd voor. Overleg dat soms alle kanten op fladderde en sowieso altijd veel langer duurde dan gepland, maar altijd nieuwe ideeën opleverde. En sommige dingen zetten we op een tegeltje!

Janjaap, we hebben ooit teruggerekend dat we elkaar in 1979 al tegen hadden kunnen komen in het WKZ. Jij begon daar dat jaar als jonge fysiotherapeut en ik was daar als 4-jarig mannetje opgenomen met een nierziekte. Ik lag alleen niet op jouw afdeling, dus destijds hebben we elkaar helaas gemist. 38 jaar later kwam het er alsnog van. Jij keek vaak door net een iets andere bril naar hetzelfde, wat tot prachtige, inspirerende, maar soms onnavolgbare gesprekken met jou en Kathelijn leidde. Door die andere bril zag je altijd nog wel ergens een uitweg of een oplossing. Ik ben je ook heel erg dankbaar dat je me op de mogelijkheden wees om les te gaan geven bij klinische gezondheidswetenschappen.

De **leden van de leescommissie**: prof. dr. C. Veenhof, prof. dr. L.J. Bont, prof. dr. J.W. Gorter, prof. dr. C.J. Fijnvandraat en dr. M.H. Cnossen, **en de leden van de oppositie** dank ik hartelijk voor het beoordelen van de wetenschappelijke waarde van dit proefschrift.

A very warm thank you to all **co-authors** who shared their knowledge, expertise and feedback to produce better manuscripts!

(Oud-)collega's van de **van Creveldkliniek** en het **kinderbewegingscentrum** van het WKZ: hartelijk dank voor de oprechte interesse die jullie de afgelopen jaren in mij en mijn onderzoek getoond hebben en de praktische en morele steun die ik soms hard nodig had.

In het bijzonder **Piet:** je wilt het niet weten en al helemaal niet horen, maar zonder jou was dit onderzoek nooit van de grond gekomen. Urenlang hebben we samen in het belhok gezeten om patiënten te bellen. Dit leidde regelmatig tot hilarische, typische Pietgesprekken met patiënten die ik eigenlijk op had moeten nemen, want niemand gelooft het als ik het vertel. Door jouw hulp en enthousiasme deed uiteindelijk bijna iedereen mee, dat was me alleen nooit zo makkelijk gelukt. Ik ben er ongelooflijk trots op om je als paranymf naast me te hebben staan tijdens de verdediging.

Collega-puppy's van de van Creveldkliniek: **Anne, Annelies, Eline, Floor, Isolde, Johan, Konrad, Maaike, Marieke, Merel, Myrthe** en **Wobke**. Ik heb ongelooflijk veel steun aan jullie gehad. Of het nou ging om onbegrijpelijke statistiek, mopperen op begeleiders, reviewers die er *he-le-maal* niets van snappen of gewoon samen koffie (thee voor mij!) drinken: ik heb er van genoten, dank jullie wel! O ja, en vanaf vandaag heeft waarschijnlijk niemand het ooit nog over puppy's op de van Creveldkliniek. Iets meer aandacht voor **Isolde:** we begonnen op dezelfde dag bij de van Creveldkliniek, maar kwamen elkaar door allerlei verbouwingen pas een week of 6 later tegen. Ik vind het heel knap hoe gestructureerd jij dingen aanpakt, met 10% daarvan zou ik al heel gelukkig zijn. Ik ben dan ook heel trots dat je mij als paranymf wilt ondersteunen bij mijn verdediging.

Evelien Mauser-Bunschoten: jij kwam met het idee om naar Bunschoten-Spakenburg (what's in a name?) te gaan toen we besloten om ook mensen met milde hemofilie mee te laten doen aan de studie. Ik ben je daar nog steeds dankbaar voor!

Evelyne en **Jesse,** bedankt voor jullie hulp bij de metingen, vooral die op locatie in Spakenburg, jullie maakten daarmee mijn leven een stuk makkelijker!

Onno Jägers en collega's van **het Fysiohuis** in Bunschoten-Spakenburg: bedankt dat we gebruik mochten maken van jullie faciliteiten bij het testen.

Collega-docenten van klinische gezondheidswetenschappen en fysiotherapie van de HU: ik draai nog maar kort mee als docent, en ik merk dat ik nog heel veel van jullie kan leren. Ik verheug me daarop!

Alle **familie en vrienden**: bedankt voor de interesse die jullie afgelopen jaren interesse getoond hebben in mijn onderzoek. Vaak uit beleefdheid, dat weet ik heus wel. Zo'n promotietraject blijft voor velen toch iets onbegrijpelijks, maar ik leg het met alle plezier nog een keer uit. Een speciaal woord van dank voor de spelers van Fortuna Wormerveer (**Mark, Silver, Mike, Brett** en **Tinus**) die naar Utrecht kwamen voor de pilot metingen: jullie hebben geen idee hoe waardevol jullie rol in dit onderzoek is geweest!

Willem, Rieke en Sander, bedankt voor jullie oprechte interesse de afgelopen jaren. Ook al wonen we niet bij elkaar om de hoek, we kunnen altijd een beroep jullie doen. Dank jullie wel!

Lieve **papa** en **mama**: bedankt voor alles. Maar dan ook echt alles. Jullie maakten het voor mij mogelijk om te gaan studeren en staan altijd voor ons klaar. Voor thee en koekjes tijdens het studeren kan ik ondertussen al jaren zelf zorgen, maar in Hoorn werd de basis gelegd voor alles wat nu samenkomt in dit proefschrift.

Lieve **Tom**, **Nina** en **Sara**. Wat ben ik ongelooflijk trots op jullie en blij om jullie te kunnen zien opgroeien zoals jullie dat doen. Ik heb nogal wat van jullie gevraagd de afgelopen jaren, ik hoop dat alles nu iets rustiger wordt. Ik beloof niets. Als dank heb ik speciaal jullie sporten (mede) in de kaft verwerkt. Jullie zijn de toekomst, daarom is dit proefschrift aan jullie opgedragen.

En tenslotte, lieve **Karin**: ik heb echt geen flauw idee hoe ik jou moet bedanken zonder je ernstig tekort te doen. Jij zorgt voor de vaste grond en de structuur die ik zo hard nodig heb, ik ben daar zelf nou eenmaal niet zo goed in. Dit proefschrift had ik echt ook wel alleen kunnen schrijven, maar zonder jouw basis was verder nergens iets van terecht gekomen. Ik hou van je!

About the author

Olav Versloot was born on the 2nd of August, 1975 in Hoorn, the Netherlands. After graduating from secondary school (Openbare Scholen Gemeenschap, Hoorn) in 1993, he studied physiotherapy at the University of Applied Sciences in Amsterdam, where he obtained his BSc. in 1998. Following this, he worked as a physiotherapist in private clinics and at the Ajax youth academy.

In 2007, he obtained his MSc. in Human Movement Sciences at VU University in Amsterdam. Following this, he worked as an exercise physiologist in professional football in the Netherlands, Qatar and China before joining the Van Creveldkliniek in 2017 to start this PhD project. The project was supervised by Prof. dr. R.E.G. Schutgens, Dr. K. Fischer and Dr. J. van der Net.

During his PhD project, he completed a postgraduate Master in clinical epidemiology at Utrecht University in 2020. While working on his PhD, he worked as a lecturer at Utrecht University. He received the Sobi research award 2019 with his colleague Anne Hoefnagels for their research on sports participation and therapy adherence in people with haemophilia.

In August 2021, he started working as a lecturer at the department of physiotherapy of the University of Applied Science Utrecht, where he teaches courses in the musculoskeletal domain. He lives with his wife and children in Krommenie and tries to make time for music, running and cycling.

Over de auteur

Olav Versloot is geboren op 2 augustus 1975 in Hoorn. Na zijn VWO-diploma op de Openbare Scholen Gemeenschap West-Friesland in Hoorn (1993) studeerde hij in 1998 af als fysiotherapeut aan de Hogeschool van Amsterdam. Hierna werkte hij in enkele particuliere praktijken in de regio Amsterdam en bij de jeugdopleiding van Ajax.

In 2007 haalde hij zijn master-diploma bewegingswetenschappen aan de Vrije Universiteit in Amsterdam in de afstudeerrichting "sport, biomedisch". Hierna werkte hij als inspanningsfysioloog in het betaald voetbal in Nederland (Ajax, AZ), Qatar en China, voordat hij in 2017 bij de van Creveldkliniek aan dit promotietraject onder begeleiding van prof. dr. R.E.G. Schutgens, dr. K. Fischer en dr. J. van der Net van het kinderbewegingscentrum van het Wilhelmina kinderziekenhuis.

Tijdens zijn promotie voltooide hij in 2020 zijn master klinische epidemiologie aan de Universiteit Utrecht. Als deel van zijn promotietraject is hij in 2021 gestart als werkgroep begeleider aan de Universiteit Utrecht. In 2019 ontving hij samen met zijn collega Anne Hoefnagels de Sobi Research Award voor hun onderzoek naar sport en therapietrouw bij mensen met hemofilie.

Olav werkt sinds augustus 2021 als docent fysiotherapie aan de Hogeschool Utrecht. Hij woont met zijn vrouw en kinderen in Krommenie en probeert tijd te maken om muziek te maken, hard te lopen en te fietsen.

List of publications

1. Bukkems,' L.H., **Versloot, O.**, Cnossen, M.H., Jönsson, S., Karlsson, M.O., Mathôt, R.A.A., Fischer, K. Association between sports participation, factor VIII levels and bleeding in hemophilia A. *Accepted by Thrombosis and Haemostasis*.
2. Matlary, R.E.D., Grinda, N., Sayers, F., **Versloot, O.**, McLaughlin, P. Promoting physical activity for people with haemophilia in the age of new treatments. *Haemophilia*. 2022; (April): 1-6, doi: 10.1111/hae.14641
3. **Versloot, O.**, Iserman, E., Chelle, P., Germini, F., Edginton, A. N., & Schutgens, R. E. G. (2022), Fischer, K. on behalf of the Pharmacokinetic (PK) Expert Working Group of the International Prophylaxis Study Group (IPSG). Predicting Individual Changes in Terminal Half-Life After Switching to Extended Half-Life Concentrates in Patients With Severe Hemophilia. Hemasphere (2022), 6(4), e694, 1–7, doi: 10.1097/HS9.0000000000000694
4. **Versloot, O.**, van Balen, E.C., Hassan, S., Schols, S.E.M., Leebeek, F.W.G., Eikenboom, H.C.J., Coppens, M., van Vulpen, L.F.D., Smit, C., Driessens, M.H.E., van der Net, J., Gouw, S.C., Fischer, K., on behalf of the Haemophilia in the Netherlands steering committee. Similar sports participation as the general population in Dutch persons with haemophilia; results from a nationwide study. Haemophilia, 2021; 27(5): 876-885, doi: 10.1111/hae.14366
5. **Versloot, O.**, Iserman, E., Chelle, P., Germini, F., Edginton, A.N., Schutgens, R.E.G., Iorio, A., Fischer, K., on behalf of the Pharmacokinetic (PK) Expert Working Group of the International Prophylaxis Study Group (IPSG). Terminal half-life of FVIII and FIX according to age, blood group and concentrate type: data from the WAPPS database. Journal of Thrombosis and Haemostasis, 2021, 19(8): 1895-1906, doi: 10.1111/jth.15395
6. Hoefnagels, J.W., **Versloot, O.**, Schrijvers, L.H., van der Net J.J., Leebeek F.W.G., Gouw S.C., Fischer K., on behalf of the Haemophilia in the Netherlands steering group. Sports participation is not associated with adherence to prophylaxis in Dutch patients with haemophilia. Haemophilia, 2021, 27(3), e402-e405, doi: 10.1111/hae.14244
7. **Versloot, O.**, van der Net J., Fischer K. Sports participation of patients with haemophilia in the COVID-19 era: The Dutch experience. Haemophilia, 2020; 27(2): e295-e297, doi: 10.1111/hae.14189
8. **Versloot, O.**, Timmer, M., de Kleijn, P., Schuuring, M. van Koppenhagen, C.F., van der Net, J. and Fischer, K. (2020). Sports participation and sports injuries in Dutch boys with haemophilia. Scandinavian Journal of Medicine and Science in Sports, 2020, 30(7), 1256-1264, doi: 10.1111/sms13666.
9. **Versloot, O.**, Kremer Hovinga, I.C.L. (2019). Hockeyen met een stollingsstoornis. Faktor (48). [In Dutch]

10. **Versloot, O.**, Berntrop, E., Petrini, P., Ljung, E., Astermark, J., Holmström, M., de Kleijn, P. and Fischer, K. (2019). Sports participation and physical activity in adult Dutch and Swedish patients with severe haemophilia: A comparison between intermediate- and high-dose prophylaxis. Haemophilia, 2019 (2),24-251, doi: 10.1111/hae.13683.
11. **Versloot, O.** (2017). Kunnen hemofiliepatiënten veilig sporten? Sportgericht, 71(2), 19-21. [In Dutch]

Submitted for publication:

1. **Versloot, O.,** Kemler, E., Blokzijl, J., Timmer, M.A., Schuuring, M.D., van Galen, K.P.M., Kremer Hovinga, I.C.L., van der Valk, P.R., van Vulpen, L.F.D., Schutgens, R.E.G., van Koppenhagen, C.F., van der Net, J. K. Fischer. Clotting factor activity levels and bleeding risk in people with hemophilia playing sports. *Submitted*.
2. **Versloot, O.**, Blokzijl, J., Timmer, M.A., Schuuring, M.D., van Galen, K.P.M., Kremer Hovinga, I.C.L., van der Valk, P.R., van Vulpen, L.F.D., Schutgens, R.E.G., van Koppenhagen, C.F., van der Net, J. K. Fischer. Can motor proficiency testing predict sports injuries and sports-induced bleeds in people with haemophilia? *Submitted*.

Presentations and Posters

1. Sports Injury Risk in People with Haemophilia. International Society on Thrombosis and Haemostatis (2022, London) - presentation
2. Dutch overweight people with hemophilia report more limitations in activities, but no association with sports. International Society on Thrombosis and Haemostasis (2021, online) – E-poster
3. Soccer is popular and relatively safe for children and young adults with hemophilia: experiences from the Netherlands. International Society on Thrombosis and Haemostasis (2021, online) – E-poster
4. Sports injuries in Dutch people with hemophilia: results of a 12 months' prospective study. International Society on Thrombosis and Haemostasis (2021, online) – E-poster
5. Motivate young adults with haemophilia to be active: what makes them get off the couch? European Association of Haemophilia and Associated Disorders congress (2021, online) – presentation
6. Terminal half-life of FVIII and FIX concentrates according to age and blood group: data on 8022 assessments. American Society of Hematology conference (2020, online) – presentation
7. Individual changes in THL after switching to EHL: not all patients benefit from switching to EHL concentrates. American Society of Hematology conference (2020, online) – presentation
8. A preliminary analysis of sports injuries in Dutch patients with haemophilia: no big issue? World Federation of Haemophilia congress, Kuala Lumpur (2020, online) – E-poster
9. Physical demands and energy expenditure of labour in Dutch patients with haemophilia: no role for severity? World Federation of Haemophilia congress, Kuala Lumpur (2020, online) – E-poster
10. Football is the most popular sport in Dutch patients with haemophilia: a preliminary analysis of participation. World Federation of Haemophilia congress, Kuala Lumpur (2020, online) – E-poster
11. Physical demands of work in Dutch patients with haemophilia: no role for severity? European Association for Haemophilia and Allied Disorders congress, Den Haag (2020) – Poster
12. Trends in sports participation in young and adult Dutch patients with haemophilia. European Association for Haemophilia and Allied Disorders congress, Den Haag (2020) – Poster
13. High sports participation in Dutch children with haemophilia: what about injuries? European Paediatric Physiotherapy Congress, Utrecht (2020) – presentation

14. Sports participation and sports injuries in Dutch boys with haemophilia. European Paediatric Physiotherapy Congress, Utrecht (2019) – Poster
15. The ankle and haemophilia. International Ankle Symposium, Amsterdam (2019), symposium moderator
16. The ankle and haemophilia. International Ankle Symposium, Amsterdam (2019) – presentation
17. The Dutch experience with intermediate-dose prophylaxis: Sports participation.

EUNC advisory board, Copenhagen, DK (2019) – presentation

18. The physiotherapists' perspective: outcome assessment. EUNC advisory board, Copenhagen, DK (2019) – presentation
19. Importance of exercise in haemophilia, Nordic Coagulation Symposium, Billund, DK (2019) – presentation
20. Sportblessures. Preventie en deelname aan sport activiteiten bij hemofilie. Nederlandse Vereniging van Hemofilie Verpleegkundigen, Amsterdam (2019) – Presentation
21. Sports participation and sports injuries in relation to age and severity in young persons with haemophilia. European Association for Haemophilia and Allied Disorders congress, Prague, CZ (2019) - poster
22. Sports Participation in Adult Patients with Haemophilia: an age-related comparison between intermediate and high-dose prophylaxis. World Federation of Haemophilia congress, Glasgow, UK (2018) – poster
23. Hemofilie, enkels en preventie. Biedt de EXO-L nieuwe mogelijkheden? PhysNet hemofilie symposium, Utrecht (2017) – presentation

Awards

SOBI research award 2019: Treatment Adherence and Risky Sports Participation, with Anne Hoefnagels.

European Association of Haemophilia and Allied Disorders 2020 – Top Scoring Abstract.

Je ne sais pas où je vais, mais je suis en route

Voltaire