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ORIGINAL ARTICLE

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

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Abstract

Background: Improved treatment options for people with haemophilia (PWH) have increased the possibilities for sports participation, but the risk of sports-induced bleeding (SIB) is still considered considerable by many.

Aim: To assess sports associated injury- and bleeding risk in PWH and to assess clotting levels associated with safe sports participation.

Methods: 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, sports risk category and sports intensity. Factor activity at the time of injury was estimated using a pharmacokinetic model.

Results: 125 participants aged 6–49 (41 children, 90% haemophilia 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/%factor level (CI 0.88–0.99); $p = .02$), but not with haemophilia severity (OR: 0.62 (CI 0.20–1.89); $p = .40$), joint health, sports risk category or sports intensity. PWH with factor levels <10% during sports injury had a bleeding risk of 41% versus 20% in those with higher (>10%) factor levels.

Conclusion: 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.

KEYWORDS
haemophilia, joint bleeds, sports, sports injuries, sports-induced bleeds

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1 | INTRODUCTION

People with haemophilia (PWH) are at an increased risk of spontaneous musculoskeletal bleeds and subsequent impaired joint function.[1] In addition to (prophylactic) replacement therapy with clotting factor concentrates, PWH are counselled regarding physical activity with a (perceived) increased bleeding risk.[2]

Despite generic health benefits of sports participation,[2] haemophilia specific risks of sports participation (e.g., joint or intracranial bleeds)[1] are being debated among caregivers and PWH.[3,4] With the improved treatment options, the possibilities for sports participation for PWH have increased significantly. Although the World Federation for Haemophilia (WFH) still encourages low-risk sports,[5] PWH receiving prophylaxis are currently as active in sports as the general population (GP), including in high-risk (HR) sports[6] such as soccer.[7–9] However, 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.[10,11] One prospective study reported only a transient increased bleeding risk after sports in 104 children with haemophilia, while two retrospective studies could not.[12,13] Assessment and quantification of injury- and bleeding risks is needed to enable adequate counselling.

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

What was already known

- Sports participation in Dutch people with haemophilia is high, but injury rates are unknown.
- 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 factor levels <10% at time of injury had a twofold increased risk of a sports-induced bleed.
- Most injuries (53%) a nd bleeds (67%) were not sustained during sports activities.

2 | METHODS

2.1 | Methods and setting

The single-centre prospective study "Sports Participation and Injuries in People with Haemophilia" (SPRAIN) assessed sports participation, -injuries and -bleeds in PWH treated at the Van Creveldkliniek of the University Medical Centre Utrecht, the Netherlands. Participants were included from October 2018 until premature discontinuation in March 2020 due to COVID-19 restrictions. Following signing informed consent, each participant was followed for 12 months. The study was approved by the local Ethical Review Board (IRB number: 181-41), and registered under ID NTR6769 on www.clinicaltrialregister.nl. All data were collected in accordance with the declaration of Helsinki.[14]

2.2 | Participants

PWH aged 6–49 years who played sports at least once weekly were eligible for inclusion. Exclusion criteria were the presence of *current inhibitory* FVIII/FIX antibodies or an arthroplasty or arthrodesis within the last 12 months.

2.3 | Data collected

Participant (age, height, weight), disease (type of haemophilia, severity, factor FVIII/IX activity, annual bleeding rate (ABR), annual joint bleeding rate (AJBR)) and treatment characteristics (use of prophylaxis, treatment frequency, dose, pharmacokinetics, including individual and patient specific half-life calculated using the WAPPS database), were extracted from electronic hospital records.

2.4 | Sports participation

Sports participation was defined as being actively engaged in sports at least 10 times in the last 12 months (as defined in the EU Sports Charter).[15] Type of sports and sports exposure (frequency x duration/week) were assessed by the validated Dutch version of the Modifiable Activities Questionnaire (MAQ).[16–18] Although not specifically validated in a haemophilia population, this was not considered a limitation in using the MAQ, given the high proportion active in sports and sports participation being a universal asset in the studied age category. Physical education classes at school were not considered.

To further objectify the physical activity data collected with the MAQ, physical activity data was collected using an Activ8 (Activ8, Valkenswaard, The Netherlands) 3-axial accelerometer (30 × 32 × 10 mm; 20 g). Participants were asked to wear the accelerometer for 24 h per day for 7 consecutive days, with a minimum of 4 consecutive days containing data days to be included for analysis. Data are presented as proportion of 24 h. The Activ8 is a valid, accurate tool to assess physical activity[19–21] and has been used in a wide array of medical conditions, including people with haemophilia.[22] 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

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a waterproof, transparent Tegaderm self-adhesive plaster. Time spent lying, sitting, standing and walking were reported in hours/day, running and cycling were reported in min/day.

Joint health status was assessed using the Haemophilia Joint Health Score 2.1(HJHS),[23,24] which assesses ankles, knees and elbows, with a total score range of 0–124 (zero: optimal; ≥4: abnormal[25,26]).

Sports associated injury risk was categorized according to the National Haemophilia 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).[6]

Sports intensity was assessed by means of a validated Activ8 accelerometer,[22] which generates energy expenditure (Metabolic Equivalent of Task; METs).[21] Energy expenditure (EE) > 6 METs is considered vigorous physical activity.[27] Sports were classified as high intensity (HI) sports if >75% of time was spent at >6 METs. However, any long lasting sports activities (>60 min) that had less than 75% of time at intensities >6 METs were still recorded as 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".[28] Sports injury data were collected by contacting the participants every 2 weeks through their preferred way (email, phone or text message). In case of an injury or bleed, participants were contacted to record injury details as well as the time of the last infusion of clotting factor concentrate for those using prophylaxis (see Table S1). Based on the patient interviews, the aetiology of sports injuries was identified as resulting from a single trauma or from prolonged, repetitive overuse.

Bleeds were classified according to ISTH criteria[29] (see Table S2). A *sports-induced bleed* was defined as a bleed that occurred as a result of a sports injury, either related by time or location.

Participants with non-severe haemophilia who were not on prophylactic treatment (n = 65; 51%) were assumed to have stable factor levels. Individual half-life combined with data on the last prophylactic infusion before sports injury were used to estimate clotting factor activity at the time of injury in 60 participants using prophylaxis. For 35/61 (56%) participants using prophylaxis with recent data on trough levels available individual and concentrate specific terminal half-life had been calculated using the WAPPS system. For the remaining 26 (44%) participants on prophylaxis without recent measurements available, age, weight and concentrate specific $T^{1/2}$ was estimated based on available population data by the WAPPS team.[30,31]

2.5 | 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'.[32,33] This is an ongoing large population-based retrospective cross-sectional study, which questions around 10,000 persons/year online, by telephone or a face-to-face interview. For a maximum of four sports, annual hours of participation were calculated. Detailed information about the two most recent sports related injuries over the last 3 months 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.

2.6 | Statistics

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

Sports injuries and SIBs were presented as the number of injuries/1000 h of exposure[34] and compared 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.

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 backward, logistic regression analysis, adjusted for age, joint status (affected vs. unaffected (HJHS≤4),[26] HR sports (yes/no), HI sports (yes/no), total annual sports exposure (hours) and haemophilia severity (severe/non-severe). A sensitivity analysis was performed in which the number of SIB due to HR sports before and after COVID-19 restriction[35] were compared. Finally, a sensitivity analysis was performed including only those participants with known, recent factor levels.

Statistical analyses was performed using SPSS statistical software, version 26 (IBM corp., Armonk, NY) and R (RStudio, PBC, Boston, MA, v1.3.1093).[36] A p-value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Participants

Injury and bleeding data of 125 participants (41 children, 84 adults) were analysed. Table 1 shows participant-, disease- and treatment characteristics according to severity. Most participants had haemophilia A (90%). Nearly half the participants had severe haemophilia (48%), participants with non-severe haemophilia had a median FVIII/IX activity level of 15 IU/dL (IQR 8–16); distribution in Figure S1). 57/60 Participants with severe haemophilia used prophylactic treatment (95%), with a median weekly dose of 42.3 IU/kg (A: 41.7; B: 53.6 IU/kg), with a median peak factor level of 42 (IQR 35–52) IU/dL. Children and adults had a similar treatment frequency (3x/wk),

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TABLE 1 Patient characteristics and sports exposure according to haemophilia 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)
Haemophilia 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 (h/yr)	144 (53–224)	120 (50–222)	153 (65–248)
Energy expenditure (METs-h/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%)
Adults	39/84 (46%)	17/39 (44%)	22/45 (56%
Children	25/41 (85%)	16/20 (80%)	19/21 (76%)
High-intensity sports	25 (20%)	12 (20%)	13 (20%)
Adults	15/84 (18%)	5/39 (13%)	10/45 (22%)
Children	10/41 (24%)	10/20 (50%)	0/21 (0%)
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%)

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

with dosage being higher in children (median 20 IU/kg (IQR: 16—26 IU) vs. 13 IU/kg (IQR: 12—15) in adults). Two boys in high-level, high risk sports were on daily prophylaxis (dosage: 6–8 IU/kg). Median energy expenditure during sports was similar for severe and non-severe haemophilia (16.6 MET-h/wk vs. 21.7; $p = .44$). A median ABR and AJBR of 0 was observed. GP data were collected from 2072 male participants (645 children, 1427 adults) (Table S3).

Participants reported a total of 15.999 (2.5x/participant/week) sports exposures during follow-up. 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); $p < .01$).

3.1.1 | Injuries and bleeds: General characteristics

Figure 1 shows all reported injuries, sports injuries, bleeds and SIBs. A total of 184 injuries were reported, of which 87/184 (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. 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.

3.2 | Sports injuries and sports-induced bleeds according to severity

Table 2 and Figure 3 show sports injuries and SIBs according to haemophilia severity. Sports injuries were reported by 41% ($n = 51$) of participants. Despite similar annual sports exposure, more participants with severe haemophilia reported sports injuries than non-severe participants (53% vs. 29%; $p < .01$). The median number of injuries/participant was higher in participants with severe haemophilia (1 (IQR 0—2) vs. 0 (IQR 0—1); $p < .01$). Participants with severe haemophilia reported a higher incidence rate (median 5 (IQR 0—15) vs. 0 (IQR 0—5) inj/1000 h exposure; $p < .01$), most likely due to the

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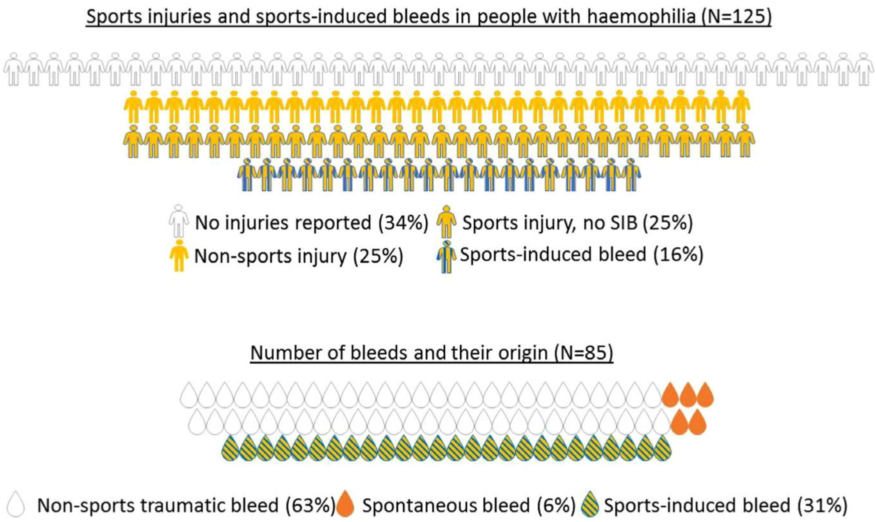

FIGURE 1 Infographic showing the number of participants reporting no injuries, non-sports injuries, sports injuries, bleeds and SIBs and the origin of all reported bleeds during the 12 month' follow-up of the SPRAIN study. Most injuries and SIBs were not sports-related.

TABLE 2 Sports injuries and bleeds according to haemophilia severity.

Median (IQR) or *N* (%)	PWH	Severe	Non-severe	*p*
N	125	60	65	
Total annual sports exposure (h/yr)	144 (53–224)	120 (50–222)	153 (65–248)	.35
Injuries and bleeds				
All reported injuries	179	118/179 (67%)	61/179 (33%)	**<.01**
All reported bleeds	80	54/60 (90%)	26/65 (40%)	**<.01**
Spontaneous bleeds	5	5	0	–
Participants with no bleeds during follow-up	78/125 (62%)	29/60 (48%)	49/65 (75%)	**<.01**
Sports injuries				
Sports injuries	87	60	27	
Participants with sports injury	51/125 (41%)	32/60 (53%)	19/65 (29%)	**<.01**
Sports injuries/participant	0 (0–1)	1 (0–2)	0 (0–1)	**<.01**
Range	0–7	0–7	0–3	–
Sports injuries/1000 h exposure	0 (0–10)	5 (0–15)	0 (0–5)	**<.01**
Range	0–231	0–91	0–231	**–**
Time loss (days)	7 (4–21)	7 (3–19)	14 (7–25)	**.04**
During high-risk sports[a]	51/87 (59%)	34/60 (57%)	17/65 (26%)	–
During high-intensity sports[b]	25/87 (29%)	21/60 (35%)	4/65 (6%)	–
Sports-Induced Bleeds (SIB)				
Sports-induced bleeds	26	18	8	
Participants with SIB	20/125 (16%)	14/60 (23%)	6/65 (9%)	**.03**
SIB/sports injury	26/87 (30%)	18/60 (30%)	8/65 (12%)	.97
SIB/participant	0 (0–0)	0 (0–0)	0 (0–0)	.03
Range	0–4	0–4	0–2	–
SIBs/1000 h exposure	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)	.13
During high-risk sports[a]	14/26 (54%)	8/60 (13%)	6/65 (9%)	.57
During high-intensity sports[b]	6/26 (23%)	4/60 (7%)	2/65 (3%)	.43

Bold numbers indicate a significant difference between participants with severe and non-severe haemophilia. The denominators are shown because of the variety in groups and group sizes.

Abbreviation: SIB, sports-induced bleed.

[a]High-risk sports: categories 2.5 and 3 according to the NHF classification.

[b]High-intensity sports: participants who predominantly perform sports with > 6METs energy expenditure.

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TABLE 3 Sports injuries in people with haemophilia and the general population (over 3 months).

N (%) or median (IQR)	GP	PWH
n	2072	125
Total annual sports exposure (h/yr)	160 (80–278)	144 (53–224)
Sports injuries		
Sports injuries	486	87
Participants with sports injury	–	51 (41%)
Within first 3 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[a]	277 (57%)	51 (59%)
Injuries/1000 h exposure	3.1	11.0

Sports injuries were similar in PWH and GP. The number of injuries according to exposure (inj/1000 h) was higher in PWH.
[a]High-risk sports: categories 2.5 and 3 according to the NHF classification.[6]

small group reporting injuries in people with non-severe haemophilia ($n = 19$). Participants with severe haemophilia reported shorter median time-loss (7 (3–19) vs. 14 (7–25) days; $p = .05$). 54% of injuries occurred during HR sports, while 23% occurred during HI sports. The number of sports injuries during HR (13 vs. 9%; $p = .57$) or HI sports (7% vs. 3%; $p = .43$) was independent of disease severity.

3.2.1 | Sports injuries: People with haemophilia versus general population

Total sports participation in PWH similar to the GP (144 (IQR 53—224) vs. 160 (IQR 80—278) h/yr). 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 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 in PWH was higher than in the GP (11.0 vs. 3.1 inj/1000 h) which may be attributable to repeated injuries in PWH as the incidence rate for first injuries was similar (3.2 vs. 3.1 inj/1000 h).

3.2.2 | Sports-induced bleeds in people with haemophilia

Figure 2 shows that only 0.16% of 15,999 sports exposures and 30% (26/87) of sports injuries resulted in an SIB. The proportion of SIBs after a sports injury was similar in severe and non-severe haemophilia (18/60 (30%) vs. 8/27 (30%); $p = .97$). SIBs were reported by 20 (16%) participants, with 2 participants reporting more than 1 SIB. Median interruption of sports participation after a SIB was 11 (IQR 4—21) days.

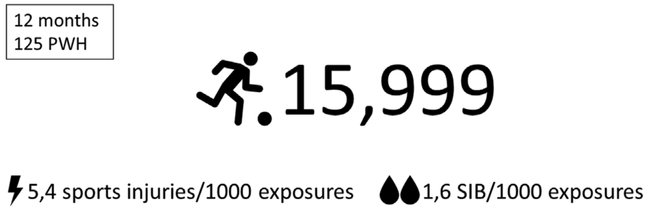

FIGURE 2 Sports injuries and SIBs were rare when the total sports exposure over the 12-month follow-up was considered. The vast majority of sports exposures did not cause an injury or SIB. On a total of 15,999 sports exposures, only 87 sports injuries were reported (0.5%), while only 26 SIBs were reported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

Most SIBs (14/26; 54%) were sustained during HR sports. As in sports injuries, SIBS were stable across seasons (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 73% of injuries and 100% of SIBs in soccer were sustained by participants with severe haemophilia.

Sports induced bleeds according to severity are shown in Figure 3 and occurred more frequently in participants with severe haemophilia (14/60 (23%) vs. 6/65 (9%) in non-severe haemophilia). Although the median number of SIBs/participant was 0 (0–0) for both severe and non-severe haemophilia, severe haemophilia showed more variation (range: 0–4 vs. 0–2; $p = .03$). This was also observed for the median SIBs/1000 h with a range of 0—71 for severe, and a range of 0—42 for non-severe participants ($p = .04$). Participants with severe haemophilia reported a trend towards shorter interruption from sports participation following an SIB (median 7 (IQR 4—19) vs. 19 (IQR 9—37) days; $p = .13$). While about half of the SIBs occurred during HR sports (59%), only one quarter (23%) occurred during HI sports. A sensitivity analysis showed similar proportions of SIBs due to HR sports before and after COVID restrictions (26% (CI: 14%—41%) vs. 31% (12%—58%); $p = .72$). An additional analysis showed that 20% of sports injuries and 15% of SIBs occurred in a combined HR/HI sports setting, which is much lower than HR and HI sports separately. This seems to indicate that a combination of HR and HI in sports did not increase the injury or bleeding risk.

3.3 | Sports induced bleeds according factor levels

Table 4 shows the characteristics of sports injuries who developed into an SIB and those who did not. Development of SIB was associated with 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; $p = .03$, Figure 4). Most participants on prophylaxis who developed an SIB (71%) had their last infusion more than 12 h before their sports activity and thus had not adhered to the recommendation to infuse prophylaxis shortly before sports participation.

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

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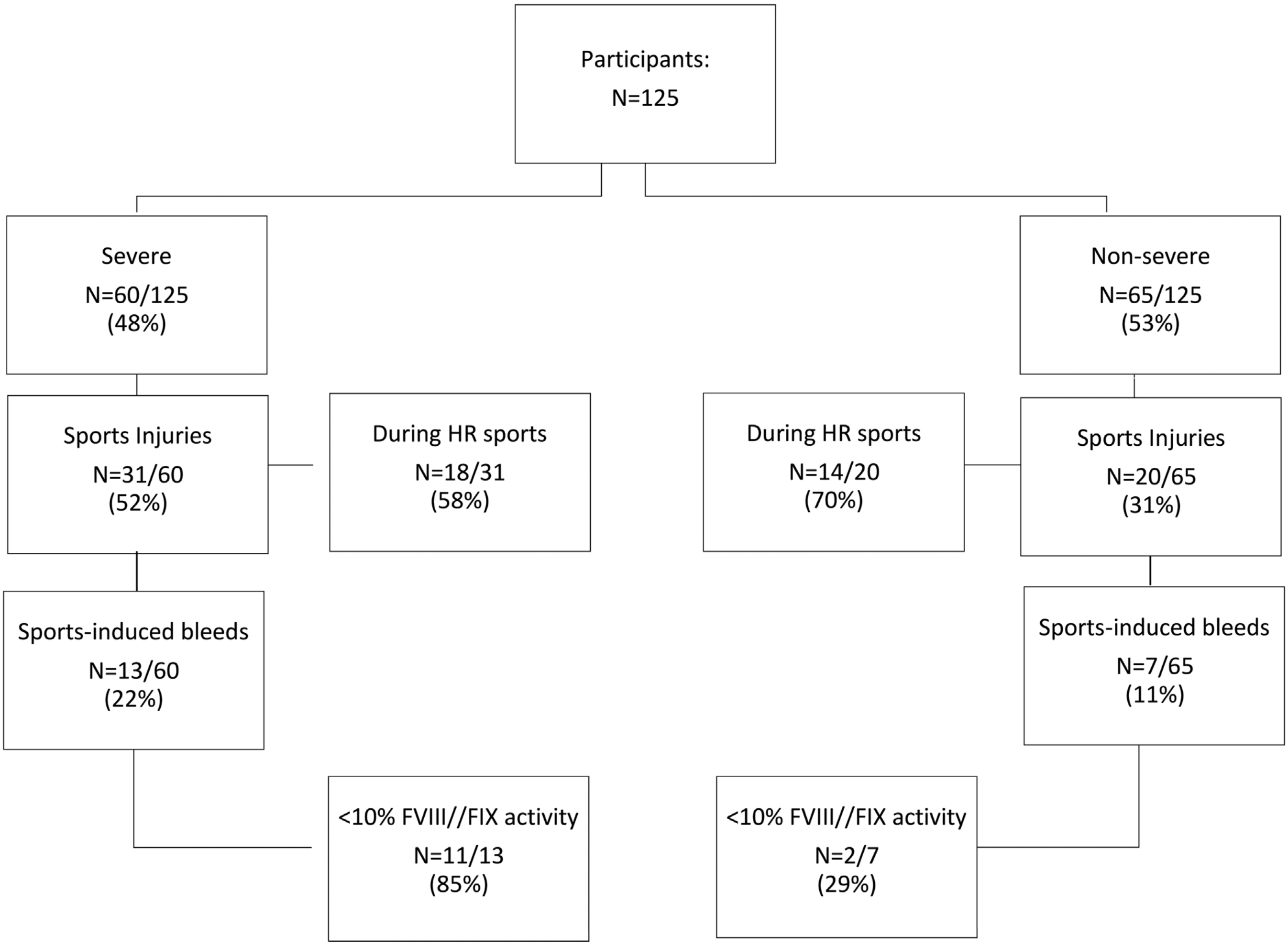

FIGURE 3 Number and proportion of participants sustaining an SIB following a sports injury according to severity during the 12 month' follow up. Participants with severe haemophilia and factor levels below 10% at the time of injury reported most SIBs.

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)	.52
Severe haemophilia	69%	69%	.97
Factor level @time of injury (IU/dL)	6.0 (2.8–14.0)	12.3 (5.4–22.3)	**.03**
ABR	1 (0–4)	0 (0–4)	.64
AJBR	0 (0–2)	0 (0–1)	.47
Last prophylactic infusion > 12 h[a]	72%	41%	**.02**
Last prophylactic infusion > 24 h[a]	54%	51%	.80
HJHS ≥4	31%	15%	.09
Total annual sports exposure (h/yr)	148 (68–241)	168 (81–271)	.62
Injury during HR sports[b]	54%	61%	.56
Injury during high-intensity sports	23%	33%	.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 h 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.[6]

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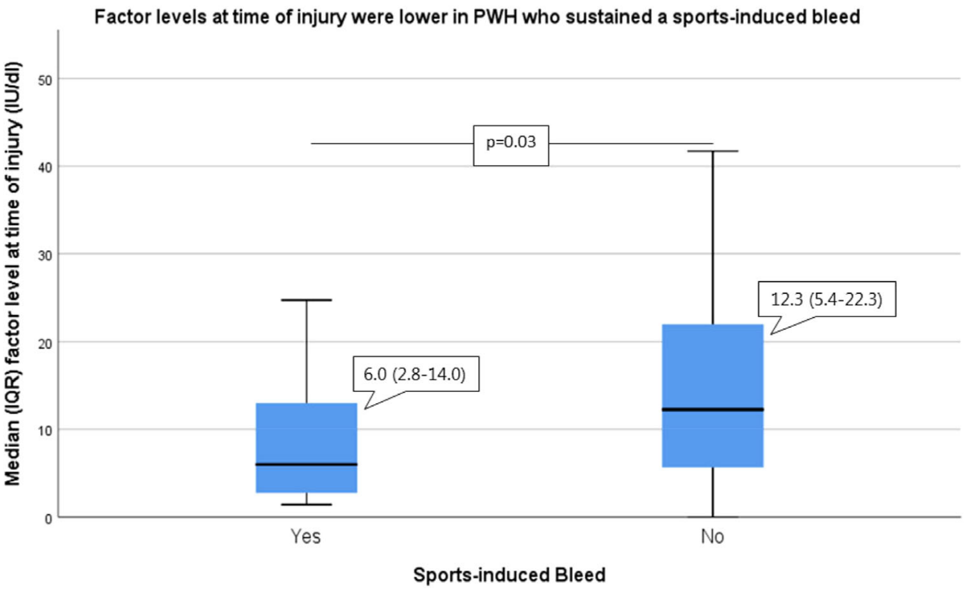

FIGURE 4 Factor levels at time of injury were lower in people with haemophilia who developed an SIB than those who did not develop an SIB.

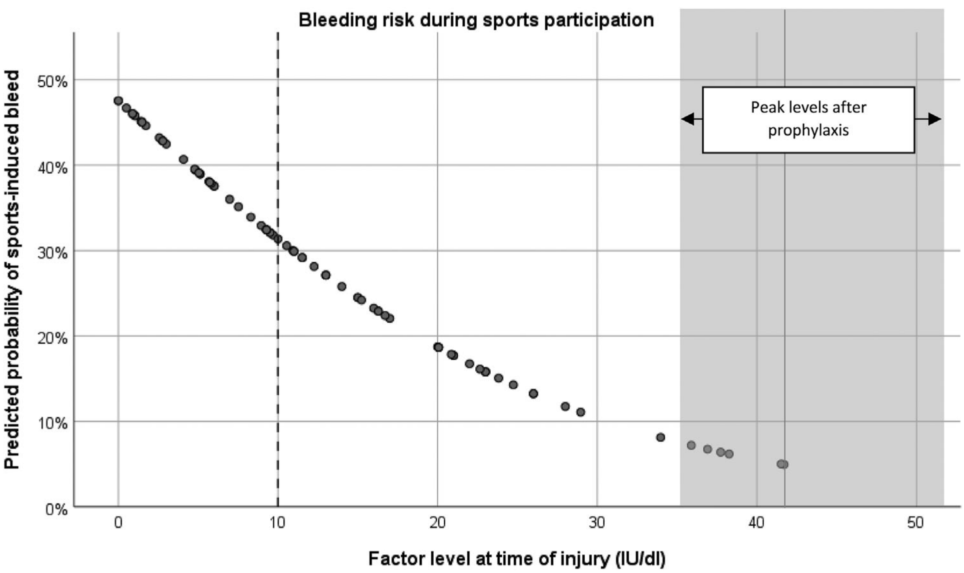

FIGURE 5 The predicted probability of SIBs after sustaining a sports injury was higher with lower factor levels at the time of injury. Multivariable regression analysis identified a factor level >10% factor level at the time of injury as the only independent predictor (OR: 0.93 (CI 0.88–0.98); $p = .02$). 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).

a sports injury. Logistic regression showed that SIBs were associated with factor levels at time of injury (OR: .93/ % increase in FVIII/FIX (CI 0.88–0.99); $p = .02$; independent of age, joint health, HR sports, HI sports, total annual exposure and haemophilia severity 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%. A sensitivity analysis including only those with recent data showed similar results, albeit with wider a confidence interval (OR: 0,93; CI: 0.87–1.01) due to lower patient numbers.

4 | DISCUSSION

In a large prospective study in children and adults with haemophilia, a total of 87 sports injuries and 26 SIBs were observed during 15,999 exposures. Only 25% of all injuries and 16% of all bleeds were sports related. Although participants with severe haemophilia sustained more sports injuries and SIBs, regression analysis showed that FVIII/IX levels at the time of sports injury were the most important independent determinant of bleeding risk, rather than haemophilia severity. Participants with factor levels ≤10 IU/dL at the time of injury had twice the

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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. These results suggest that sports participation for PWH is safe while at sufficient factor levels.

4.1 | Strengths and limitations

Internal validity was promoted by the prospective design with detailed follow-up. External validity was promoted by the inclusion of participants aged 6–49, which is the age group with the highest sports participation. The risk of selection bias is considered low as 68% of Dutch PWH play sports.[8] External validity was reinforced by the use of intermediate dose prophylaxis, which may be more globally applicable.

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 (team)sports as these were most restricted.[35] In theory, this could have led to an underestimation of the true number of sports injuries during the COVID-19 restrictions, but this was not supported by the sensitivity analysis.

In absence of a formal definition, an SIB was defined as a bleed occurring as a result of a sports injury. Participants were asked to interpret their complaints and assess whether this was an SIB or not, the haemophilia treatment centre was only consulted in a minority (31%) of sports injuries. PWH have shown to regularly misinterpret musculoskeletal complaints and bleeds,[37] Given the lack of direction in this misinterpretation, this could be either an over- or underestimation SIBs.

Ideally, recent factor levels of each participant would have been used to estimate FVIII/FIX activity at the time of injury. Recent factor levels were available for the majority of participants, while some were estimated by the WAPPS team. A sensitivity analysis showed similar results when only including those with recent factor levels.

4.2 | Comparison with other studies

Data on sports injuries in people with haemophilia are limited and have covered up to age 20 years.[9,12,13,38] The only prospective study to date reported a transient increased bleeding rate in the first 8 h after vigorous exercise in 104 Australian boys with moderate or severe haemophilia (aged 4–18; 86% on prophylaxis). As in the present study, most bleeds were not associated with physical activity, although without providing details.[38] In addition, two retrospective studies in American boys with haemophilia ($N = 48$ and $N = 37$) failed to identify an association between (high-intensity) sports participation and injury risk.[12,13] A retrospective Dutch study ($N = 102$,age 6–18; 55% on prophylaxis) reported similar injury rates similar to the GP and across haemophilia severity.[6,9]

Regarding optimum protective factor levels during sports, the present study corroborates the publication of den Uijl et al., which showed that bleeds were rare in PWH with factor levels of at least 10%–15%.[39]

4.3 | Clinical relevance and future directions

This study contributes to the debate of sports-associated bleeding risk 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 only determinant of developing a SIB/bleed, independent of haemophilia severity. This was confirmed by a repeated time to event analysis.[40] Therefore, the higher bleeding rates in severe patients could be attributed to lower factor levels at the time of sports injury. Although external factors contribute to bleeding risk, factor levels remain the primary candidate for intervention. The observation 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).[41]

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 sports-related bleeding in patients on non-replacement therapy. Given the significant protection reached at minimum FVIII activity levels of 10%, the present data do not support infusing FVIII before sports in patients using emicizumab. In addition, a repeated-time-to-event analysis including repeated assessment of each sports exposure and clotting factor level at the time of sports exposure may provide more information on the protective effect of factor levels.[42]

5 | CONCLUSIONS

This first-time study assessed sports injuries and SIBs in children and adults with haemophilia and compared this to sports injuries in the GP. Participants with haemophilia 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.

AUTHOR CONTRIBUTIONS

Olav Versloot, Kathelijn Fischer, Janjaap van der Net, and Casper F. van Koppenhagen were involved in the design of the study. Olav Versloot collected the data, Ellen Kemler provided additional data from the GP. Olav Versloot, Janjaap van der Net, and Kathelijn Fischer analysed the data and wrote the initial version of the report. All authors were involved in data interpretation and review of the paper. All authors approved the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

Olav Versloot has received speaker's fees from Novo Nordisk and received research support from Bayer. All fees were paid to the van Creveldkliniek. Merel Timmer received a research grant from SOBI, Novo Nordisk and Pfizer. All fees were paid to the institution. Karin P. M. van Galen received unrestricted research grants from CSL Behring and Bayer in the past and speakers fee from Takeda and Amgen. Paul R. van der Valk received a research grant from Shire . All fees were paid to the institution. Lize F. D. van Vulpen received a research grant from CSL Behring and Grifols, is consultant for CSL Behring, Sobi and Tremeau. All fees were paid to the institution. Roger E. G. Schutgens has received research support from CSL Behring and Sanquin. Kathelijn Fischer The Van Creveldkliniek has received speaker's fees from Bayer, Baxter/Shire, SOBI/Biogen, CSL Behring and NovoNordisk; consultancy fees from Bayer, Biogen, CSL-Behring, Freeline, NovoNordisk, Roche and SOBI; and research support from Bayer, Baxter/Shire, Novo Nordisk, Pfizer and Biogen for work done by KF. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the Ethical Review Board of the UMC Utrecht under IRB number 181-41, and registered under ID NTR6769 on www.clinicaltrialregister.nl. All data were collected in accordance with the declaration of Helsinki.

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