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Factors associated with physical activity in young people with haemophilia A on prophylaxis

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Abstract

Introduction: Physical activity (PA) is influenced by numerous factors, and the literature describing why people with haemophilia (PWH) are physically active or not is inconclusive.

Aims: To investigate factors associated with PA (mean min/day in light (LPA), moderate (MPA), vigorous (VPA) and total PA, and proportion meeting World Health Organization (WHO) weekly moderate-to-vigorous (MVPA) recommendations) among young PWH A.

Methods: Forty PWH A on prophylaxis from the HemFitbit study were included. PA was measured using Fitbit devices and participant characteristics were collected. Potential factors associated with PA were investigated by univariable linear regression models for continuous PA outcomes, and descriptively for teenagers meeting/not meeting WHO MVPA recommendations only, because all except one adult met PA recommendations.

Results: Mean age (n = 40) was 19.5 years (SD 5.7). Annual bleeding rate was nearly zero and joint scores were low. We found an increase of four min/day in LPA (95% confidence interval (CI) 1–7) per year increase in age. Participants with 'Haemophilia Early Arthropathy Detection with Ultrasound' (HEAD-US) score ≥1 engaged in mean 14 min/day less MPA (95% CI −23.2 to −3.8), and 8 min less VPA (95% CI −15.0 to −0.4) compared to participants with HEAD-US score 0. Teenagers who met PA recommendations had slightly better joint status compared to those who did not meet recommendations.

Conclusion: These findings indicate that presence of mild arthropathy does not affect LPA but may have a negative impact on PA of higher intensities. Early start of prophylaxis may be an important determinant of PA.

KEYWORDS

factors associated with physical activity, haemophilia, haemophilia A, physical activity, physical activity correlates

1 | INTRODUCTION

Haemophilia A is a bleeding disorder caused by a genetic deficiency in coagulation factor VIII, affecting (mainly) males.[1] Untreated, it is characterised by spontaneous or trauma induced recurrent bleeding, especially in joints and muscles, which can cause haemophilic arthropathy, impaired function, and in turn reduced participation in physical and social activities and reduced quality of life.[2] Due to increased risk of bleeding in relation to physical activity (PA), this was previously discouraged for people with haemophilia (PWH).[3] However, with modern medical treatment (primarily clotting factor substitution), the risk of bleeds and bleed related problems have decreased substantially, health-related quality of life has improved,[4,5] and PA is now recommended for this population.[2] Encouragingly, it appears that PA levels of younger PWH are higher than those of older patients, and similar to general population peers.[6]

Nowadays, most people are aware that regular PA is recommended and can provide numerous health benefits.[7,8] However, we know that PA behaviour is complex and influenced by several factors at the individual, social, environmental and policy levels.[9] It is thus challenging to determine why people are physically active or not. Research into factors associated with PA indicate that the barriers and facilitators to PA for PWH are mostly similar to that of the general population, but that this patient group may face some unique challenges related to disease severity, inhibitors, (lack of) treatment, (fear of) bleeds and/or existing arthropathy.[10] For instance, studies have shown less PA among adults who started prophylaxis >3 versus ≤3 years of age,[11] and a decrease in vigorous intensity PA and activity bouts,[12] as well as in number of sports activities undertaken per week with increasing arthropathy.[13] With recent improvements in treatment, joint status, and function, though, it might be that disease-specific factors are becoming less important for PWH's PA.

Historically, both in the general population and among PWH, self-report instruments such as questionnaires have been used to measure PA. However, objective methods such as activity trackers are recommended to reduce bias and obtain more accurate PA estimates.[14] In a previous paper from the 'HemFitbit study' (NCT04181697) we measured PA objectively and compared the habitual PA of young PWH with moderate to severe haemophilia A on continuous prophylaxis to general population peers. In summary, PA levels of PWH A were comparable to controls. However, a substantial percentage of teenaged PWH A did not reach PA recommendations, and we recommended a particular focus on PA promotion for this group.[17] A better understanding of factors associated with PA in patient subgroups is needed to tailor advice, care and develop successful interventions to improve PA in PWH.

Therefore, we aimed to investigate demographic and haemophilia-related factors associated with objectively measured PA outcomes (mean daily minutes in light, moderate, and vigorous intensity PA, total daily PA, and proportion meeting the World Health Organization (WHO) recommendations of moderate-to-vigorous PA per week) among PWH A within the HemFitbit study.

2 | METHODS

2.1 | Study design and participants

The HemFitbit study is an observational, cross-sectional, single-centre study including 40 Norwegian young males (aged 13–30 years) with moderate to severe haemophilia A on continuous prophylaxis (defined as the intent to treat for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration)[15] and without inhibitors. The lower age of 13 years was set due to this being the age limit for creating a Fitbit account, and the maximum age of 30 years was chosen because PWH born in the 1990s were the first to receive prophylaxis from their first years of life in Norway.[16] These inclusion criteria were chosen to obtain a patient cohort prone to bleeds and arthropathy on prophylaxis, to investigate whether/how joint status and other factors impact the PA of patients who have had access to current prophylactic treatment regimens throughout their lives. Study participants included in the current analysis are all the 40 PWH included in the HemFitbit study, which represent 73% (40/55) of identified potential eligible participants. Participant recruitment, data collection procedures and ethical considerations have been described elsewhere.[17] Briefly, participants were identified from Norway's national registry of people with bleeding disorders, and all of those identified were initially invited to participate. Only one study visit to Oslo University Hospital's Haemophilia Comprehensive Care Centre was required, where anthropometrics were measured, joint status evaluated, Fitbit devices for tracking of PA provided, and self-reported health-related quality of life (HRQoL) recorded. The study was granted ethical approval from the Regional Committee for Medical and Health Research Ethics South East (2019/549) and the Oslo University Hospital Data protection officer (19/14125), and signed informed consent was obtained from all participants. Data was collected between October 2019 and August 2020.

2.2 | Physical activity outcomes

The PA outcomes were minutes per day spent in light- (LPA), moderate- (MPA), and vigorous intensity (VPA) PA, total PA, and numbers of participants meeting weekly WHO MVPA recommendations. Minutes per day of LPA, MPA and VPA were collected using the activity tracker Fitbit Charge 3 over a 12-week measurement period for each participant. One overall daily average per PA parameter was computed per participant over all valid measurement days, defined as >1000 steps.[18] Average total PA (min/day) was calculated by summarising LPA+MPA+VPA. Additionally, a weekly average of minutes of moderate-to-vigorous PA (MVPA) was calculated for each participant by multiplying the respective daily averages of MPA+VPA by seven. Based on this, a binary variable was created classifying participants into meeting or not meeting weekly WHO MVPA recommendations; for teenagers this was defined as ≥420 min/week and for adults as ≥150 min/week, respectively.[7]

2.3 | Potential factors associated with physical activity

We considered age, height, weight, and BMI as demographic factors, and the remaining factors as haemophilia related.

Information on age, haemophilia severity, treatment intensity (factor VIII prophylactic dose), age at start of prophylaxis, age of first joint bleed, history of inhibitor and joint surgery, number of joint bleeds and other serious bleeds and number of days absent from school/work during the last 12 months were extracted from electronic patient records and/or participant logs.

At the study visit, information was collected on *presence of target joints* (defined as ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period[15]), *height* (in cm), *weight* (in kg) and *waist circumference* (in cm) were measured, and index *joint scores* (elbows, knees and ankles) were evaluated using 'Hemophilia Joint Health Score' (HJHS) version 2.1[19] and 'Hemophilia Early Arthropathy Detection with Ultrasound' (HEAD-US)[20] (both tests described previously).[17] HJHS was performed by physiotherapists, and HEAD-US by haematologists.

Body mass index (BMI) was calculated (kg/m^2) and classified into categories. For adults (ages 18–30 years), categories were; Underweight (<18.5), Normal weight, (18.5–24.9), Overweight (25.0–29.9) and Obese (≥30).[21] For teenagers, BMI categories are age- and sex-dependent (BMI-for-age), and categorisation is based on percentiles relative to population norms. We used 'The International Obesity Task Force' criteria to classify teenaged boys' BMI-for-age into Underweight (<5th percentile), Normal weight (5th to <85th percentile), Overweight (85th to <95th percentile) and Obese (≥95th percentile).[22]

HRQoL was self-reported using the Norwegian version of the EuroQol 5-dimension 3-level instrument (EQ-5D-3L), which is a standardised and generic descriptive system of HRQoL, consisting of two sections. The first section describes health states via the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[23] Each dimension is divided into three levels, indicating no problem (1), some or moderate problems (2) and extreme problems (3). Combinations of these levels define various health states described by a five-digit number, representing each of the five dimensions. Full health is indicated by 11111 (no problems with any dimensions), and the poorest health state by 33333 (extreme problems with all dimensions). After initial investigation of health state results, we found that most participants reported no problems, and none reported extreme problems for any domain. Based on this, our limited sample size, and a presentation option suggested in the EQ-5D-3L user guide,[24] we dichotomised *EQ-5D-3L* results into those reporting no problems (health state 11111) and those reporting any problem (any other health state than 11111). The second section of the EQ-5D is a visual analogue scale (*VAS*) including a vertical 20 cm line where individuals rate their HRQoL on the day they fill out the questionnaire. The VAS scale ranges from 0–100, representing worst to best imaginable health state.[23]

In addition to investigating the aforementioned variables in their continuous form, we dichotomised the following variables to increase clinical meaningfulness and comparability to previous research: HJHS joint score was dichotomised into scores of ≤3 or above (based on the findings that a total joint score of ≤3 is normal in healthy people[25] (gait score was excluded because no participants in the referenced study obtained scores for global gait)), age for starting prophylaxis into ≤3 years or above (based on a previous study finding differences in PA levels between groups of PWH with this cut-off[11]), and HEAD-US score into zero and above, considering a score of zero as a sign of pristine joints (based on indications of HEAD-US being more sensitive than HJHS in detecting early, subclinical joint changes[26]). In addition, because lower limb joint status (i.e., excluding upper limb joint status) may have a larger impact on PA than total HJHS and HEAD-US scores, we also calculated lower limb scores for the respective tests by summarising right knee + left knee + right ankle + left ankle scores.

2.4 | Statistical analysis

Analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, TX, USA). A two-sided *p*-value of <.05 was considered statistically significant. Most data were approximately normally distributed. Descriptive statistics are presented as means with standard deviations (SDs) for continuous data and numbers with percentages for categorical variables. To assess the association between potential factors associated with PA and PA, we performed univariable linear regression models for each of the continuous PA outcomes (mean min/day LPA, MPA, VPA, total PA) and aforementioned potential associated factors. Due to small numbers, we did not perform any multivariable models.

Among adult participants (n = 20), only one did not meet the PA recommendations. We therefore investigated potential correlates of meeting/not meeting WHO MVPA recommendations in teenagers only (n = 20). Due to several cells of zero and the small sample size, we did not perform any logistic regression but investigated factors associated with PA in descriptive tabulations.

For the variables 'age at first joint bleed', 'global gait' in HJHS and 'absence from work/school due to haemophilia A the last 12 months', we had missing information for 12, 2 and 1 participants, respectively. All analyses were performed on complete case data only.

3 | RESULTS

3.1 | Participant characteristics and physical activity outcomes

Fifteen (out of 55 identified) PWH were not enrolled in the study, and the reasons were: unable (n = 4, e.g., because they were not allowed to wear the Fitbit at work), not interested (n = 4), unable to contact (n = 1), turned 31 years before study visit (n = 1) and enrolment concluded because target number was reached (n = 5).[17]

Characteristics of the 40 study participants are presented in Table 1. There were no participants who withdrew or were lost to

TABLE 1 Participant characteristics ($n = 40$ males with haemophilia A).

	Mean (SD) or *n* (%)
Age at enrolment (years)	19.5 (5.7)
Body mass index (kg/m2)	23.5 (4.3)
Category	
Underweight	1 (2.5%)
Normal weight	28 (70.0%)
Overweight	4 (10.0%)
Obese	7 (17.5%)
Waist circumference (cm)	80.5 (11.6)
Haemophilia severity	
Moderate	3 (7.5%)
Severe	37 (92.5%)
Age at first joint bleed[a] (years)	1.8 (1.1)
Age at start of prophylaxis (years)	3.9 (3.8)
Started at age ≤3 years ($n = 27$)	1.9 (.8)
Started at age > 3 years ($n = 13$)	7.8 (4.5)
History of inhibitor	
Yes	3 (7.5%)
No	37 (92.5%)
Factor VIII prophylactic dose (IU/kg/week)	70.2 (26.8)
Joint bleeds last 12 months (AJBR) (*n*)	0.5 (0.8)
Other serious bleeds last 12 months (*n*)	0.0 (0.2)
Target joint	
Yes	1 (2.5%)
No	39 (97.5%)
History of joint surgery	
Yes[b]	2 (5.0%)
No	38 (95.0%)
HJHS 2.1	
Total score	6.3 (7.8)
Left ankle	1.5 (2.3)
Right ankle	2.0 (2.6)
Left knee	0.3 (0.9)
Right knee	0.5 (1.7)
Left elbow	0.4 (1.1)
Right elbow	0.8 (2.2)
Global gait[c]	0.9 (1.4)
Lower limb score	4.3 (5.1)
Joint score ≤3	25 (62.5%)
Joint score >3	15 (37.5%)
HEAD-US	
Total score	2.6 (5.4)
Left ankle	0.8 (1.7)
Right ankle	0.9 (1.7)
Left knee	0.1 (0.4)
Right knee	0.2 (0.9)
Left elbow	0.1 (0.5)
Right elbow	0.4 (1.2)
Lower limb score	2.0 (3.9)
Score 0	22 (55.0%)
Score ≥1	18 (45.0%)
Absence from work/school due to HA last 12 months[d]	
Yes	6 (15.0%)
No	33 (85.0%)
EQ-5D-3L health status	
No problems	24 (60.0%)
Any problems	16 (40.0%)
EQ VAS score	83.7 (16.7)

HJHS 2.1 contains scores of 0–20 per joint plus four for gait, with a maximum potential total score of 124. HEAD-US contains a score of 0–8 points for each joint, thus with a potential maximum total score of 48. Lower scores equal better joint status for both tests.

Abbreviations: AJBR, Annual Joint Bleeding rate; EQ VAS, EuroQol Visual Analogue Scale; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; HA, haemophilia A; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS, Hemophilia Joint Health Score; IU, International Units; SD, Standard Deviation.

The number of patients (*n*) is noted if deviating from the total number:

[a] $n = 28/40$, data missing for 12 participants.

[b] Both were ankle synovectomies.

[c] $n = 38/40$, global gait not evaluable for two participants.

[d] $n = 39/40$, data missing for one participant.

follow-up. Mean age was 19.5 years and most had a BMI classified as normal weight. All received continuous prophylaxis in the form of clotting factor concentrates (CFCs). The majority (28/40, 70%) used standard-half-life products and 12/40 (30%) used an extended-half-life product. Mean age when starting prophylactic treatment was 3.9 years. Three participants had a history of high-titre inhibitors (>5 Bethesda units/mL), that is, alloantibodies to factor VIII neutralising the function of infused CFCs,[15] and their inhibitors were eradicated through immune tolerance induction. Number of bleeds during the last 12 months was close to zero, only one participant had a target joint, and the two joint surgeries that had been performed were ankle synovectomies. HJHS and HEAD-US scores were low. The majority (22/40, 55%) had pristine joints, as defined by HEAD-US score of zero. Six persons (6/39, 15%) had been absent from school/work related to haemophilia during the previous 12 months, with a mean of 3.7 (SD 3.1) days of absence. Self-reported HRQoL using EQ-5D-3L and EQ VAS was good overall, and the majority (24/40, 60%) reported no problems.

PA was measured with the Fitbit device over 12 weeks (84 days) for each PWH. For unknown reasons, seven measurement days were not registered for three participants, and a total of 3353 measurement

TABLE 2 Physical activity outcomes in 40 males with haemophilia A.

	Mean	SD
LPA (min/day) all	227	100
Teenagers	212	93
Adults	241	105
MPA (min/day) all	31	34
Teenagers	33	36
Adults	29	33
VPA (min/day) all	26	31
Teenagers	27	31
Adults	26	31
MVPA (min/day) all	57	59
Teenagers	60	61
Adults	55	58
Total PA (min/day) all	284	130
Teenagers	272	129
Adults	295	129
Meet WHO weekly MVPA recommendations	**Number**	**%**
Total	27	68
Teenagers ($n = 20$)	8	40
Adults ($n = 20$)	19	95

Abbreviations: LPA, Light intensity Physical Activity; MPA, Moderate intensity Physical Activity; MVPA, Moderate to Vigorous intensity Physical Activity; PA, Physical Activity; SD, Standard Deviation; VPA, Vigorous intensity Physical Activity; WHO, World Health Organization.
MVPA = MPA + VPA. Total PA = LPA + MPA + VPA. Meeting WHO weekly MVPA recommendations is defined as yes if ≥ 150 min for adults, and ≥ 420 min for teenagers.

days were thus included in our dataset. Out of these, 3023 days (90.2%) were defined as valid and included in the analysis. Mean number of valid measurement days per PWH was 75.6 (SD 12.3, range 37–84).[17] We obtained data for all PA outcomes for all valid days.

Participants spent most time in LPA and achieved on average almost 60 min per day of MVPA. All except one adult (95%) met weekly MVPA recommendations, while the minority (40%) of teenagers did (Table 2).

3.2 | Factors associated with physical activity

Results from linear regression models are presented in Table 3. The only factor significantly associated with LPA was age, with a 4-min average increase in daily LPA (95% CI 1–7) per year increase in age. Pristine joints (defined as HEAD-US score of 0) was the only factor significantly associated with MPA and VPA. Participants without pristine joints ($n = 18$) (i.e., HEAD-US score of ≥1) engaged in on average 14 min less MPA (95% CI −23.2 to −3.8, $p = .008$), and 8 min less VPA (95% CI −15.0 to −0.4, $p = .034$) per day as compared to participants with pristine joints ($n = 22$) (Table 3 and Figure 1: Mean (and 95% CIs) daily minutes of moderate and vigorous PA for 40 PWH with HEAD-US scores of 0 ($n = 22$) vs. ≥1 ($n = 18$)).

Characteristics of teenagers meeting and not meeting PA recommendations were largely similar, except those who met recommendations had somewhat better joint status, represented by less joint bleeds, lower joint scores, and none of them having HJHS joint score >3 or HEAD-US score ≥1 (Table 4).

4 | DISCUSSION

The aim of this study was to identify factors associated with objectively measured PA in a group of young PWH A on prophylaxis. We found that LPA was on average 4 min higher per day per year increase in age, and that participants with pristine joints (HEAD-US score of zero) engaged in 14 and 8 min more MPA and VPA per day, respectively, compared to those with signs of arthropathy (HEAD-US score of ≥1). Based on inspection of descriptive results, teenagers who met PA recommendations appeared to have slightly better joint status compared to those who did not meet recommendations. All except one adult met PA recommendations and we could therefore not identify factors associated with meeting/not meeting recommendations in this age group.

We investigated several demographic and haemophilia related factors considered to be potential predictors of PA, but found significant association with PA outcomes for only a few of them. Similar to our results, Goto et al.[27] did not find any relationship between PA and BMI or annual joint bleeding rate. While Khawaji et al.[11] found a statistically significant difference in PA between those who commenced prophylaxis before or after the age of three years, we did not, although we did see a tendency of less MPA and VPA among those who started prophylaxis later. This discrepancy could be related to the small sample size in our study, and differences in age and arthropathy between cohorts (older age and higher HJHS scores in Khawaji-study), and that those who started prophylaxis "late" in our study, did so at a slightly younger age (mean 10.1 (range 3–22) vs. 7.8 (range 3–18) years).

Our findings show that LPA increased with mean 4 min/day (95% CI 1–7) per year increase in age. This is a small increase, and it is unclear whether it is of clinical importance. However, recent research indicates that PA of all intensities, including LPA, is important to health,[28] and the latest WHO guidelines emphasise the importance of limiting sedentary time and underscore that any increase in PA is positive.[29] The finding of increased LPA with increasing age despite accompanying higher joint scores (i.e., more arthropathy) may appear peculiar since it common to see lower levels of PA with increasing age, both in the general and the haemophilia population.[6,30] One explanation could be that limited arthropathy (we found overall low joint scores in our cohort) has little impact on the ability to perform PA of low intensity. On the other hand, it is also possible that PWH with increased age and more arthropathy move from higher to lower intensity PA. We do not see such a tendency in our data, but this could be due to the young cohort and limited sample size. In contrast to our finding, several other studies have demonstrated an inverse relationship between total PA and age (results not reported by intensities).[27,31,32] However, it is likely

TABLE 3 Correlates of PA outcomes from univariable regression models in 40 males with haemophilia A.

	Light PA (min/day)		Moderate PA (min/day)		Vigorous PA (min/day)		Total PA (min/day)	
	β-coefficient (95%CI)	*p*-value	*β*-coefficient (95%CI)	*p*-value	*β*-coefficient (95%CI)	*p*-value	*β*-coefficient (95%CI)	*p*-value
Continuous variables								
Age (years)	4.0 (0.9 to 7.1)	**.014**	−0.3 (−1.2 to 0.7)	.578	0.1 (−0.6 to 0.8)	.761	3.8 (−0.02 to 7.7)	.051
BMI (kg/m^2)	−0.6 (−5.1 to 3.9)	.781	0.4 (−0.8 to 1.7)	.504	0.5 (−0.4 to 1.3)	.313	0.2 (−5.1 to 5.6)	.927
Waist circumference (cm)	−0.8 (−1.7 to 1.5)	.920	0.2 (−0.2 to 0.7)	.338	0.2 (−0.2 to 0.5)	.353	0.3 (−1.6 to 2.2)	.759
FVIII consumption (IU/week)	−0.5 (−0.8 to 0.7)	.886	−0.1 (−0.3 to 0.1)	.283	−0.3 (−0.2 to 0.1)	.687	−0.2 (−1.0 to 0.7)	.662
Age at start of prophylaxis (years)	3.7 (−1.2 to 8.6)	.138	−0.6 (−2.0 to 0.8)	.390	−0.7 (−1.7 to 0.3)	.193	2.4 (−3.6 to 8.4)	.418
Age at first joint bleed (years)	−0.4 (−22.5 to 21.7)	.971	0.1 (−5.7 to 5.8)	.978	−1.1 (−5.3 to 3.1)	.599	−1.4 (−26.5 to 23.7)	.909
Joint bleeds last year (*n*)	−3.5 (−27.1 to 20.1)	.765	−4.2 (−10.6 to 2.2)	.193	−2.6 (−7.3 to 2.1)	.274	−10.3 (−38.3 to 17.7)	.461
Other serious bleeds last year (*n*)	−72.3 (−191.9 to 47.2)	.228	−11.3 (−45.0 to 22.3)	.500	−7.2 (−31.7 to 17.3)	.556	−90.9 (−233.3 to 51.5)	.204
HJHS score[a]	1.5 (−1.0 to 3.9)	.230	−0.4 (−1.1 to 0.3)	.230	−0.2 (−0.7 to 0.3)	.351	0.8 (−2.1 to 3.7)	.574
HJHS lower limb score[b]	3.1 (−0.6 to 6.7)	.099	−0.4 (−1.4 to 0.7)	.447	−0.2 (−1.0 to 0.5)	.547	2.4 (−2.0 to 6.9)	.277
HEAD-US score[c]	1.0 (−2.6 to 4.5)	.587	−0.9 (−1.8 to 0.0)	.061	−0.3 (−1.0 to 0.4)	.386	−0.2 (−4.5 to 4.0)	.907
HEAD-US lower limb score[d]	1.9 (−2.9 to 6.8)	.424	−1.1 (−2.4 to 0.2)	.083	−0.4 (−1.4 to 0.6)	.386	0.4 (−5.5 to 6.2)	.900
EQ VAS score[e]	0.3 (−0.8 to 1.5)	.555	−0.1 (−0.5 to 0.2)	.362	0.0 (−0.2 to 0.2)	.919	0.2 (−1.2 to 1.6)	.765
Categorical variables								
Age group		.077		.487		.935		.197
Teenagers (*n* = 20)	Ref		Ref		Ref		Ref	
Adults (*n* = 20)	32.8 (−3.7 to 69.3)		−3.6 (−14.2 to 6.9)		−0.3 (−8.0 to 7.4)		28.8 (−15.6 to 73.2)	
BMI categories		.101		.388		.712		.180
Normal weight (*n* = 29)	Ref		Ref		Ref		Ref	
Overweight (*n* = 4)	31.4 (−29.8 to 92.6)		10.3 (−7.4 to 27.9)		5.2 (−7.9 to 18.2)		46.9 (−27.3 to 121.1)	
Obese (*n* = 7)	−42.1 (−90.4 to 6.2)		6.3 (−7.6 to 20.2)		1.6 (−8.7 to 11.9)		−34.3 (−92.8 to 24.3)	
History of inhibitor		.434		.402		.340		.765
No (*n* = 37)	Ref		Ref		Ref		Ref	
Yes (*n* = 3)	28.0 (−43.7 to 100.0)		−8.3 (−28.2 to 11.6)		−6.9 (−21.3 to 7.5)		12.8 (−73.3 to 98.9)	

(Continues)

TABLE 3 (Continued)

	Light PA (min/day)		Moderate PA (min/day)		Vigorous PA (min/day)		Total PA (min/day)	
	β-coefficient (95%CI)	*p*-value	*β*-coefficient (95%CI)	*p*-value	*β*-coefficient (95%CI)	*p*-value	*β*-coefficient (95%CI)	*p*-value
Previous joint surgery		.755		.788		.132		.652
No ($n = 38$)	Ref		Ref		Ref		Ref	
Yes ($n = 2$)	13.5 (−73.6 to 100.7)		−3.2 (−27.5 to 21.0)		13.0 (−4.1 to 30.1)		23.3 (−80.6 to 127.3)	
Start prophylaxis		.363		.280		.195		.771
Age (y) ≤3 ($n = 27$)	Ref		Ref		Ref		Ref	
Age (y) > 3 ($n = 13$)	18.3 (−21.9 to 58.5)		−6.0 (−17.1 to 5.1)		−5.2 (−13.3 to 2.8)		7.0 (−41.4 to 55.5)	
HJHS joint score		.086		.926		.449		.202
Score ≤3 ($n = 25$)	Ref		Ref		Ref		Ref	
Score > 3 ($n = 15$)	33.0 (−4.8 to 70.7)		−0.5 (−11.4 to 10.4)		−3.0 (−10.9 to 4.9)		29.5 (−16.4 to 75.4)	
HEAD-US score		.900		**.008**		**.034**		.406
Score 0 ($n = 22$)	Ref		Ref		Ref		Ref	
Score ≥1 ($n = 18$)	2.4 (−35.8 to 40.6)		−13.5 (−23.2 to −3.8)		−7.7 (−15.0 to −0.4)		−18.8 (−64.0 to 26.4)	
Work/school absence		.647		.407		.552		.632
No ($n = 33$)	Ref		Ref		Ref		Ref	
Yes ($n = 6$)	11.8 (−40.2 to 63.9)		6.0 (−8.5 to 20.6)		−3.2 (−14.0 to 7.6)		14.7 (−47.0 to 76.3)	
EQ-5D-3L		.850		.407		.195		.802
No problems ($n = 24$)	Ref		Ref		Ref		Ref	
Any problems ($n = 16$)	3.7 (−35.2 to 42.5)		−4.4 (−15.1 to 6.3)		−5.0 (−12.7 to 2.7)		−5.8 (−52.1 to 40.6)	

Note: Reference categories for categorical covariates are underlined, and effect estimates are presented on the row corresponding to the other category/categories. The 'normal weight' category includes one person that was categorised as underweight.

Abbreviations: BMI, Body mass index; CI, Confidence interval; EQ VAS, EuroQol Visual Analogue Scale; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; FVIII, factor VIII (8); HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS, Hemophilia Joint Health Score; IU, International units; PA, physical activity; Ref, reference category.

[a]HJHS score range 0–124.

[b]HJHS lower limb score = sum right knee + left knee + right ankle + left ankle scores.

[c]HEAD-US score range 0–48.

[d]HEAD-US lower limb score = sum right knee + left knee + right ankle + left ankle scores.

[e]EQ VAS score range 0–100.

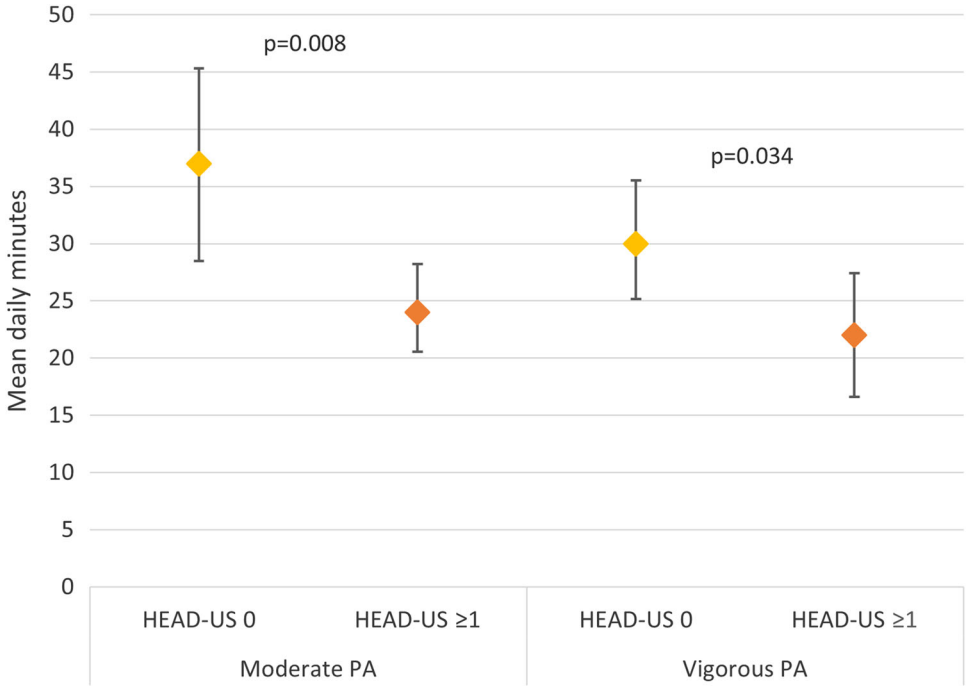

FIGURE 1 Mean (and 95% CIs) daily minutes of moderate and vigorous PA for 40 PWH with HEAD-US scores of 0 ($n = 22$) versus ≥1 ($n = 18$).
Note: Error bars represent 95% confidence intervals (CI). *p*-values from univariable regression models. HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; PA, physical activity.

that these discrepant findings are related to differences in participant characteristics, and perhaps especially to age. In the Tiktinsky et al. study[32] age was similar to our cohort (mean 18, range 12–25 years), but those patients were not on prophylaxis and mean number of bleeds was significantly higher (6.4 per month, vs. 0.5 per year in the current study). Compared to our cohort, the PWH in the Sherlock et al. study[31] were older (mean 38, range 16–63 years) and had functional limitations (reported via Haemophilia Activities List). In the Goto et al. cohort,[27] mean age was also higher (41, range 18–64 years), but the youngest participants, that is, those similar in age to the young adults of our study, were the most physically active. Furthermore, it is known from the general population that PA levels tend to decrease as children get older, and that a large proportion of adolescents fail to achieve the 60 min/day MVPA recommended by the age of 13–15 years.[33,34] The lower volume of LPA among the youngest individuals in our sample could thus be related to a typical decrease in PA during the teenage years. Another possibility is that physical literacy increases with age, meaning that those slightly older may have a higher motivation, confidence, physical competence, knowledge and understanding to value and take responsibility for engagement in PA.[35,36]

We found no clear impact of continuous HJHS and HEAD-US scores on PA outcomes, which may be due to overall low scores and most participants displaying normal joints. Interestingly though, when HEAD-US score was dichotomised, we found that those with pristine joints (HEAD-US score of zero) engaged in some more higher intensity PA (MPA and LPA) than those with HEAD-US scores ≥1. This could mean that the presence of even minimal arthropathy has some impact on the PA intensity undertaken by PWH. The contrasting lack of significant differences in PA between those with HJHS scores ≤3/>3 is noteworthy and may mean that HJHS is not sensitive enough to pick up on early signs of arthropathy of relevance to PA intensity. Further exploration of these findings in future studies would be interesting.

4.1 | Clinical implications

The current findings imply that it is essential to prevent even minimal arthropathy to facilitate moderate and vigorous intensity PA among young PWH. In order to achieve this, joint bleeds must be prevented, meaning that prophylaxis must be started early, be sufficiently intensive, tailored, and taken regularly, as recommended in global and Nordic treatment guidelines.[2,37] Furthermore, the limited haemophilia-related problems in our cohort suggest that with good treatment, it is mostly other factors than those related to diagnosis and treatment which affect the PA of young PWH A. This patient subgroup can thus likely profit from the same recommendations and targeted interventions for PA as the general population.

4.2 | Strengths and limitations

The main strength of this study is that PA was measured objectively over a considerable period of time, likely capturing a representative estimate of participants' total habitual PA. The study's main limitation is the small sample size, a common trait of studies including PWH since haemophilia is a rare disease. However, despite the small number, our

TABLE 4 Characteristics of teenagers with haemophilia ($n = 20$) meeting and not meeting PA recommendations.

	Meeting PA recommendations	
	No	Yes
	$n = 12$ (60%)	$n = 8$ (40%)
Continuous variables	**Mean (SD)**	**Mean (SD)**
Joint bleeds last 12 months (n)	0.8 (1.1)	0.1 (3.5)
FVIII prophylactic dose (IU/kg/week)	72.4 (25.9)	75.8 (37.0)
Age at start prophylaxis (y)	2.3 (1.4)	2.5 (2.7)
Age at first joint bleed (y)	1.8 (1.0)[a]	1.3 (0.5)[b]
HJHS score	2.7 (2.3)	0.8 (0.89)
HEAD-US score	0.4 (0.7)	0.0 (0.0)
EQ VAS	84.2 (16.5)	86.8 (18.3)
Categorical variables	***N* (%)**	***N* (%)**
HJHS		
Joint score ≤3	10 (83)	8 (100)
Joint score > 3	2 (17)	0 (0)
HEAD-US		
Score 0	8 (67)	8 (100)
Score ≥1	4 (33)	0 (0)
EQ-5D-3L health status		
No problems	10 (83)	6 (75)
Any problems	2 (17)	2 (25)

Abbreviations: BMI, Body mass index; EQ VAS, EuroQol Visual Analogue Scale; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels.
FVIII, factor VIII (8); HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS, Hemophilia Joint Health Score; IU, International units; PA, physical activity.
[a]$n = 9$.
[b]$n = 7$ (data on age at first joint bleed missing for four teenagers).

study includes 73% of all eligible participants from the national registry of people with bleeding disorders. Nonetheless, 15 participants out of the 55 identified potential participants were not included,[17] and we do not know whether our results would have been different if the entire eligible population had been included. We do, however, consider the chance of non-response bias as low because reasons for non-enrolment was out of individual's control and random (e.g., not being allowed to wear a watch at work, or that enrolment was concluded) for the majority (11/15) of those not included. Given the cross-sectional nature of this study, temporality or causality between variables cannot be established. Lastly, we investigated a homogenous cohort (young men with haemophilia A who had been on continuous prophylaxis from early in life, had relatively high PA levels, overall good joint- and general health status, with HRQoL (as measured by EQ VAS) similar to the Norwegian population norm[38]), and we would probably have identified more factors associated with PA if a larger group with higher and more heterogenous disease burden had been included. Larger, multi-centre studies investigating not only individual and disease- and treatment related factors, but also environmental and social aspects, could provide even better insight into the specific PA correlates of this population.

5 | CONCLUSION

Among young PWH A on prophylaxis, we found that light intensity PA increased with age and that those with pristine joints engaged in some more moderate and vigorous intensity PA as compared to those with signs of arthropathy. This indicates that presence of mild arthropathy does not affect light intensity PA but may have a negative impact on PA of higher intensities. Results should, however, be interpreted with caution due to the limited sample size and homogeneity of the cohort. Our results suggest that early start of prophylaxis and intensive prophylactic treatment is important to preserve optimal joint function and enable higher intensity PA, and that factors associates with PA among these young PWH A encouragingly are mostly related to factors other than those related to haemophilia.

AUTHOR CONTRIBUTIONS

REDM, PAH, HG, CSR and MG designed the study. REDM collected the clinical data. REDM and CSR analysed the data. REDM drafted the manuscript. All authors contributed to data interpretation and manuscript revision. All authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

PAH and REDM have received funding to institution from Bayer HealthCare for research carried out in this work. HG, CSR and MG stated that they had no interests which may be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

The data supporting the study findings are not publicly available due to privacy or ethical restrictions. Data may be made available upon reasonable request to the corresponding author.

ETHICS STATEMENT

This study is part of the 'HemFitbit study' which has been granted ethical approval from the Regional Committee for Medical and Health Research Ethics South East (2019/549) and the Oslo University Hospital Data protection officer (19/14125). All participants (and/or their guardians) provided written informed consent prior to participation in the study.

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