ORIGINAL ARTICLE

Physical activity and health outcomes in persons with haemophilia B

X. NIU,* J. L. POON,* B. RISKE,† Z. Y. ZHOU,‡ M. ULLMAN,§ M. LOU,* J. BAKER,¶ M. KOERPER,** R. CURTIS†† and M. B. NICHOL*

*University of Southern California, Los Angeles, CA; †University of Colorado, Denver, CO; ‡Analysis Group, Boston, MA; §Gulf States Hemophilia & Thrombophilia Center, University of Texas Health Science Center at Houston, TX; ¶University of California Los Angeles and The Center for Comprehensive Care & Diagnosis of Inherited Blood Disorders, Orange, CA; **University of California, San Francisco, CA; and ††Factor VIII Computing, Berkeley, CA, USA

Summary. Regular participation in physical activity helps to prevent damage and maintain joint health in persons with haemophilia. This study describes self-reported physical activity participation among a sample of people with haemophilia B in the US and measures its association with health-related quality of life (HRQoL). Data on 135 participants aged 5–64 years were abstracted from Hemophilia Utilization Group Study Part Vb. The International Physical Activity Questionnaire assessed physical activity among participants aged 15–64 years, and the Children's Physical Activity Questionnaire abstracted from the Canadian Community Health Survey was used for participants aged 5–14 years. SF-12 was used to measure HRQoL and the EuroQol (EQ-5D-3L) was used to measure health status for participants older than 18 years of age. PedsQL was used to measure HRQoL in children aged 5–18 years. Sixty-two percent of participants in the 15–64 year-old age cohort reported a high level of physical activity, 29% reported moderate activity and 9% reported low activity. For children aged 5–14 years, 79% reported participating in physical activity for at least 4 days over a typical week. Based on the 2008 Physical Activity Guidelines for Americans, 79% of adults achieved the recommended physical activity level. Multivariable regression models indicated that adults who engaged in a high level of physical activity reported EQ-5D Visual Analogue Scale (VAS) scores that were 11.7 (P = 0.0726) points greater than those who engaged in moderate/low activity, indicating better health outcomes. Among children, no statistically significant differences in health outcomes were found between high and moderate or low activity groups.

Keywords: haemophilia B, health outcome, HUGS, IPAQ, physical activity, quality of life

Introduction

Physical activity produces long-term health benefits for individuals of all ages [1]. Among children and adolescents, physical activity helps build healthy bones and muscles, control weight and may reduce anxiety and stress [1]. Among adults, physical activity helps prevent obesity and other conditions including heart disease, hypertension, diabetes, colon cancer and premature mortality [1].

The United States (U.S.) Department of Health and Human Services recommends that adults engage in at least 150 min of moderate-intensity, or 75 min of vigorous-intensity aerobic activity per week, or an equivalent combination of moderate- and vigorous-intensity aerobic activity [1]. Children and adolescents should participate in 60 min or more of activity daily [1]. The 2011 Behavioral Risk Factor Surveillance System (BRFSS), a cross-sectional nationwide telephone survey initiated by the Centers for Disease Control and Prevention (CDC), reported that a median of 51.6% of adults participated in 150 min or more of aerobic physical activity per week [2]. Another study reported that among a sample of U.S. students aged 11-16 years, the average number of days per week in which they participated in at least 60 mins of physical activity was 4.53. [3].
Haemophilia is a rare inherited bleeding disorder characterized by recurrent bleeding into muscles and joints, leading to painful haemarthroses and disabling haemophilic arthropathy \cite{4,5}. Individuals with haemophilia are at risk of physical functioning impairment \cite{6}. Participation in physical activity is essential for individuals with haemophilia to maintain their health and to obtain additional benefits \cite{6–8}, including improved muscular strength \cite{9}, increased joint stability \cite{10}, increased bone density \cite{11} and improved emotional and social well-being \cite{12}. In this context, it is recommended that physical activity be incorporated into the daily routine of people with haemophilia to successfully prevent joint damage and maintain joint health \cite{10}.

Several international surveys of haemophilia patients have reported on levels of physical activity. Studies conducted in The Netherlands and Ireland concluded that persons with severe haemophilia were as active as the general population \cite{13,14}. In contrast, Broderick \textit{et al.} \cite{15} reported that less than half of Australian children with moderate or severe haemophilia met the government’s physical activity guidelines. Another study conducted in Germany indicated that adults with haemophilia had higher activity levels and a healthier body mass index (BMI) but poorer physical performance compared with healthy controls \cite{16}.

Research on daily physical activity achieved by adolescents with haemophilia in the U.S. demonstrated that physical activity levels in persons with haemophilia were slightly higher than those in healthy controls \cite{17}. However, the actual time spent in physical activity among the U.S. haemophilia population has not been well studied. This study describes self-reported physical activity participation among a sample of people with haemophilia B [factor IX (FIX) deficiency] in the U.S. and relates activity level to health-related quality of life (HRQoL).

**Materials and methods**

**Study design and participation**

The Hemophilia Utilization Group Study Part Vb (HUGS Vb) is a prospective, longitudinal, multicentre cohort study. Data were collected from 148 persons with haemophilia B who obtained comprehensive haemophilia care from 10 federally supported speciality haemophilia treatment centres (HTCs), serving 11 geographically diverse states of the U.S. Patient information was obtained at initial interview based on patient self-report for adult patients or parent-proxy report for children less than 18 years. This included socio-demographics, health insurance status, co-morbidities, physical activity and HRQoL. Clinical information, such as body weight, height and FIX severity level, was abstracted through clinical chart review.

Participants were enrolled in the HUGS Vb study between June 2009 and April 2013. The collection and research use of the HUGS data were approved by human subjects review boards at each participating HTC and at the University of Southern California.

**Eligibility criteria**

The inclusion criteria for participation in the current study were: (i) age 5–64 years; (ii) FIX level \(\leq 30\%\), with or without history of inhibitor; (iii) received at least 90\% of haemophilia care at a participating HTC; (iv) obtained care at the HTC within 2 years prior to the initiation of data collection; and (v) English or Spanish speaking. Individuals were excluded if they were cognitively impaired or had an additional bleeding disorder.

**Physical activity measurements**

Participants aged 15–64 years reported their physical activity using the short version of the International Physical Activity Questionnaire (IPAQ). Parents of participants aged 5–14 years completed the Children’s Physical Activity Questionnaire (CPAQ) adapted from the Canadian Community Health Survey on their child’s behalf.

**IPAQ.** The short version of the IPAQ is a self-reported 7-day recall questionnaire designed to measure current level of physical activity \cite{18}. It was designed primarily for population surveillance of physical activity with young and middle-aged adults and was validated for use across 12 countries \cite{19}. The IPAQ asks about the duration (minutes) and frequency (days) of three types of activity in four domains including (i) leisure time physical activity, (ii) domestic and gardening activities, (iii) work-related physical activity and (iv) transport-related physical activity. The three types of activity assessed are vigorous-intensity activities, moderate-intensity activities and walking. The energy expenditure of activity can be computed by weighting each type of activity by its energy requirements to yield a score in metabolic equivalents of task (MET)-minutes. Participants are categorized as having high, moderate or low level of physical activity, based on the total MET-minutes or duration and frequency of each type of physical activity \cite{20}.

**CPAQ.** The measure of physical activity among children aged 5–14 years was obtained from the Canadian Community Health Survey cycle 2.2 Nutrition Children’s Physical Activity \cite{21}. The questionnaire comprised eight multiple-choice questions that assess the frequency (days) and duration (hours) of physical activity in a specific period, including the
past 7 days, a typical week, free time at school, class time at school and outside school. Time spent in watching television or on the computer is also captured. Participants are categorized as having high, moderate or low level of physical activity if they are physically active for at least 60 min daily for at least 4 days, 2–3 days, or 0–1 day over a typical week respectively.

Adult participants achieve the recommended physical activity level if they are engaged in at least 150 min of moderate-intensity, or 75 min of vigorous-intensity activity per week, or an equivalent combination of moderate- and vigorous-intensity activity, according to the 2008 Physical Activity Guideline for Americans. As HUGS Vb data were not designed to assess the percentage of children who meet the recommendation, we were not able to conduct such analysis among the paediatric subset.

Clinical measurements

**BMI.** Body mass index was calculated as weight in kilograms divided by height in metres squared [22]. For adults aged ≥20 years, BMI was categorized into underweight, normal, overweight or obese according to the recommendations of the CDC [22]. For children under 20 years of age, BMI was plotted on sex-specific BMI-for-age growth charts developed by the CDC to obtain a percentile ranking [23]. This percentile ranking was used to categorize weight status.

**Joint pain and motion limitation.** Joint pain was self-reported using a 5-point scale, ranging from ‘1: No pain’ to ‘5: Severe pain all the time’. Similarly, joint motion limitation was self-reported using a 4-point scale, ranging from ‘1: no limitation’ to ‘4: severe limitations’. The questions were developed by the HUGS team based on clinicians’ expert opinion and were used in several previous studies in haemophilia patients [24].

Health outcomes measurements

Health outcomes were measured by self-reported HRQoL and health status at the initial patient interview. The general health of adults (≥18 years of age) was assessed using the 12 items Short Form Health Survey Version 1 (SF-12) and EQ-5D-3L. The SF-12 assesses eight dimensions of HRQoL and provides two summary scores: physical component summary and mental component summary [25]. The scores are norm based and standardized to the general U.S. population with a mean score of 50 and a standard deviation of 10 [25]. A higher score represents better health.

The first part of the EQ-5D-3L is the descriptive system including five dimensions assessing the domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression [26]. The U.S. population-based preference weights were used to calculate the index score. It ranges from −0.11 (worst health scenario) to 1.0 (best health scenario) where 0.0 = death and 1.0 = perfect health [27]. The second part is a 20-cm visual analogue scale (EQ-VAS) that yields a score in which 100 indicates the best imaginable health state and 0 indicates the worst imaginable health state [26].

The PedsQL 4.0 generic core scale was used for participants younger than 18 years of age and was reported by either parents or themselves [28]. The questionnaire consists of 23 items and each item has a 5-point response scale. Items are reverse scored and linearly transformed to a scale measuring 0–100 with higher scores indicating better HRQoL [28].

Statistical analysis

Descriptive statistics were used to characterize the study population. Chi-square or Fisher’s Exact test for categorical variables and Wilcoxon–Mann–Whitney or Kruskal–Wallis statistics for continuous variables tested differences between subgroups due to a small sample size. A two-sided P value of 0.05 or less was considered to indicate statistically significant differences between groups. Multivariate imputation was used to impute the missing values in IPAQ [29]. Multivariate regression models were used to detect the independent association between HRQoL scores and physical activity levels controlling for age, disease severity and BMI. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Results

A total of 135 HUGS Vb participants aged 5–64 years were included in this analysis. The mean age in the 15–64 year-old sample was 35.2 ± 15.5 years and was 9.6 ± 2.6 years in the sample aged 5–14 years. Ninety-nine percent of the participants were male. Fifty-six (41%) participants had severe haemophilia B. The IPAQ was administered to 82 participants in the 15–64 age sample and 53 parent proxies in the 5–14 age cohort reported on the CPAQ.

Physical activity among participants aged 15–64 years

Sixty-nine (84%) of 82 participants completed the IPAQ. Multivariate imputation was applied to maximize the statistical power of the analyses. The number of participants with high, moderate or low levels of physical activity was 51 (62%), 24 (29%) and 7 (9%) respectively (Table 1). The patients with high-level physical activity (mean age = 29.6 years) were signifi-
Severe disease

Age (years) 0.93 0.89 0.97 0.0001

Joint pain (vs. no pain) 1.24 0.41 3.80 0.7062

BMI (body mass index) 0.98 0.89 1.08 0.6573

BMI*, Race: white, n

Age, mean (SD) 29.6 (13.1) 41.9 (15.2) 52.7 (11.7)

Number of participants 51 (62) 24 (29) 7 (9) 42 (79) 11 (21)

Disease severity, n

Self-reported joint pain, n

Self-reported motion limitation, n

Pain at least some of the time 20 (39) 10 (42) 7 (100) 2 (5) 2 (18)

Affect activities 17 (33) 8 (33) 7 (100) 2 (5) 2 (18)

Self-reported motion limitation only when bleed 34 (67) 19 (79) 5 (71) 0.0404 28 (67) 4 (36)

P value

High Moderate Low

Physical activity level, 5–14 years (n = 53)  

Percentage does not sum up to 100% due to missing value.

BMI, body mass index. BMI (kilograms) (height (metres)2; (a) age ≥ 20 years: BMI < 18.5, underweight; 18.5 ≤ BMI < 25.0, normal; 25.0 ≤ BMI < 30.0, overweight; BMI ≥ 30.0, obese; (b) age < 20 years: BMI percentile < 5th, underweight; 5th ≤ BMI percentile < 85th, normal; 85th ≤ BMI percentile < 95th, overweight; BMI percentile ≥ 95th, obese.

Wilcoxon–Mann-Whitney (or Kruskal-Wallis) test for continuous variables and Fisher’s Exact test for categorical variables.

cantly younger than those with moderate (mean age = 41.9 years) and low-level (mean age = 52.7 years) physical activity (P < 0.0001). Similarly, participants with mild/moderate haemophilia engaged in more physical activity than participants with severe haemophilia (P = 0.0413), as did participants categorized as underweight or normal compared to those who were overweight or obese (P = 0.0051). More than half of the sample (52%) was overweight or obese. Among participants reporting low physical activity (n = 7), all of them indicated that they experienced joint pain at least some of the time and joint motion limitation that affected physical activities. However, multivariate analysis indicated that joint pain was not independently associated with engaging in high level of physical activity, after controlling for age, disease severity and BMI (Table 2). Mean (median) time spent in walking, moderate-intensity or vigorous-intensity physical activity per week was 512 ± 541 (210) min, 370 ± 401 (217) min and 251 ± 357 (82) min respectively. Among 73 adults (age ≥18 years, 58 (79%) achieved the recommended physical activity level by engaging in at least 75 min of vigorous-intensity or 150 min of moderate-intensity activity a week, or an equivalent combination of moderate- and vigorous-intensity activity. Mean (median) age was 34.9 ± 13.9 (29.4) years among participants who achieved the recommended physical activity level, compared to that of 47.3 ± 14.6 (48.3) years among those who did not achieve the recommended physical activity level (P = 0.0005). No significant differences were observed in disease severity (P = 0.095) and weight status category (P = 0.7882) between participants who achieved the recommended level of physical activity and those who did not.

Physical activity among participants aged 5–14 years

Among 53 parents completing the physical activity questionnaire for their children, only two reported that their child did not engage in any physical activity on a regular basis. More than three quarters (79%) of parents reported that their child participated in physical activity on at least 4 days over a typical week. Nineteen (36%) participating children were overweight or obese. However, there were no statistically significant differences in physical activity levels by either disease severity or weight status category (Table 1). The majority of parents reported that their child had no joint pain/pain only when bleeding (87%) and no joint motion limitation/limitation only when bleeding (92%).

The majority of parents (68%) reported that their child obtained most of his or her physical activity (at least 4 h a week) during free time at school and through participating in unorganized activities outside school. Among all children, 35% reported that they

Table 2. Multivariate logistic regression showing independent association of joint pain with engaging in high physical activity level among participants aged 15–64 years.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Point estimate</th>
<th>95% Wald confidence limits</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.93</td>
<td>0.89</td>
<td>0.97</td>
</tr>
<tr>
<td>Severe disease (vs. mild/moderate)</td>
<td>0.46</td>
<td>0.16</td>
<td>1.37</td>
</tr>
<tr>
<td>BMI (body mass index)</td>
<td>0.98</td>
<td>0.89</td>
<td>1.08</td>
</tr>
<tr>
<td>Joint pain (vs. no pain)</td>
<td>1.24</td>
<td>0.41</td>
<td>3.80</td>
</tr>
</tbody>
</table>

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did not participate in organized activities after school. In addition, more than half of all parents (55%) reported that their child watched television or played video games for 2 or 3 h a day.

**Association between physical activity and health outcomes in adults**

Due to the small sample size in moderate and low physical activity level groups, data were combined for two groups. Mean SF-12 physical component scores were 48.8 ± 9.6 and 41.0 ± 12.2 among individuals with high and moderate/low levels of physical activity \((P = 0.0069)\) respectively (Table 3). Both EQ-5D index scores \((P = 0.0178)\) and VAS scores \((P = 0.0014)\) were significantly different between high and moderate/low physical activity levels (Table 3).

After controlling for age, disease severity and BMI, adult participants who engaged in high level of physical activity reported EQ-5D VAS scores that were 11.7 \((P = 0.0726)\) points greater than those who engaged in moderate/low activity (Table 4). Participants engaging in high level of physical activity reported better physical component scores and EQ-5D index scores, though this was not statistically significant. Furthermore, adult mental health was not affected by physical activity level.

Among adults with haemophilia B, both physical component scores and time spent on physical activity decreased with age, with a significant drop in physical activity participation among subjects aged between 25 and 34 years (Fig. 1). However, mental component scores increased with age for participants older than 35 years of age.

**Discussion**

Physical activity is encouraged by the World Federation of Haemophilia to promote physical fitness and normal neuromuscular development among the haemophilia population [30]. In our sample, 58 out of 73 adults (79%) achieved the recommended physical activity level according to the guidelines from the U.S. Department of Health and Human Services. This is consistent with the study from Ireland measuring physical activity level by IPAQ, in which 74% of adults with haemophilia demonstrated physical activity levels in line with current recommendations [14].

When comparing results with the BRFSS survey which measures physical activity participation among healthy adults in the U.S. [2], we found that a higher proportion of individuals with haemophilia achieved the recommended physical activity level. Although both the BRFSS survey on physical activity and the IPAQ use a 1-week recall of frequency and duration of vigorous and moderate physical activity, evidence

### Table 3. Univariate association of physical activity level and health outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physical activity level</th>
<th>Adults, 18–64 years</th>
<th>Children, 5–17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High ( (n = 43) )</td>
<td>Moderate/low ( (n = 30) )</td>
<td>High ( (n = 30) )</td>
</tr>
<tr>
<td>SF-12 Physical component score</td>
<td>48.8 (9.6)</td>
<td>41.0 (12.2)</td>
<td>84.2 (12.6)</td>
</tr>
<tr>
<td>EQ-SD index</td>
<td>0.85 (0.18)</td>
<td>0.76 (0.22)</td>
<td>72.4 (20.5)</td>
</tr>
<tr>
<td>EQ-SD VAS</td>
<td>77.8 (24.0)</td>
<td>60.6 (27.2)</td>
<td>79.2 (15.6)</td>
</tr>
</tbody>
</table>

Data were represented as mean (standard deviation). Due to the small sample size, moderate and low physical activity levels were combined. VAS, visual analogue scale.

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from the previous literature showed that the estimated proportion of adults in general population who meet recommendations were higher on IPAQ than BRFSS by 0.2–9.7% [31].

While the benefits of physical activity are widely known for haemophilia patients, this study did not measure patient knowledge. However, a study conducted in Germany indicated that 79% of adolescents and 81.5% of adults with haemophilia considered exercise as part of their daily routine to be important [32]. Among children, a high proportion (79%) of participants engaged in physical activity for at least 4 days per week. This is comparable to the mean number of days adolescents in the general U.S. population spend participating in more than 60 min of physical activity per week of 4.53 days [3]. Children with haemophilia should participate in physical activity under the care of a health care provider as opposed to unstructured activities, where protective equipment and supervision may be lacking [30]. However, the majority of parents (68%) in our sample reported that their child obtained most of their physical activity during free time at school and through participating in unorganized activities outside school. HTC may play a role in providing extensive training and developing individualized exercise programmes for haemophilia patients and their families.

Obesity has become a major health concern in the haemophilia population [33]. It has been found that obesity in this population is associated with significant impairment of daily activities, compared to normal weight haemophilia patients [34]. This study showed that overweight subjects had lower levels of physical activity and poorer HRQoL. Healthy life habits, including both healthy eating and physical activity, should be encouraged among persons with haemophilia.

There are several limitations in this study. First, although HUGS Vb is one of the largest prospective studies among the U.S. haemophilia B population, the sample size, particularly among children (n = 53), may result in biased statistical inferences. Second, the IPAQ combines four domains (occupational, leisure/exercise, transportation and walking) of physical activity in the questions, which may lead to over-reporting of vigorous- and moderate-intensity activity [35]. Accordingly, the percentage of haemophilia patients who achieved the recommended level of physical activity may be overestimated in this study. Third, these cross-sectional analyses do not allow for derivation of causal inferences about the relationship between physical activity and health outcomes. Finally, the joint pain instrument was developed by the authors and has not been validated through comparisons with other instruments such as the WOMAC (Western Ontario and McMaster Universities Arthritis Index). Future studies should validate haemophilia-related pain instruments.

**Conclusion**

This study provides an initial indication of the physical activity patterns in individuals with haemophilia B who obtained care at HTC in the HUGS Vb study sample. A large proportion of adult haemophilic patients achieved the U.S. Department of Health and Human Services recommended physical activity level by engaging in at least 150 min of moderate-intensity, or 75 min of vigorous-intensity aerobic activity per week, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Higher levels of physical activity are independently associated with better health.
status as measured by EQ-VAS among adult hemophilia B patients. Among children, no statistically significant differences in health outcomes were found between high and moderate or low activity groups.

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References


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