Quality of life in haemophilia A: Hemophilia Utilization Group Study Va (HUGS-Va)

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Summary. This study describes health-related quality of life (HRQoL) of persons with haemophilia A in the United States (US) and determines associations between self-reported joint pain, motion limitation and clinically evaluated joint range of motion (ROM), and between HRQoL and ROM. As part of a 2-year cohort study, we collected baseline HRQoL using the SF-12 (adults) and PedsQL (children), along with self-ratings of joint pain and motion limitation, in persons with factor VIII deficiency recruited from six Haemophilia Treatment Centres (HTCs) in geographically diverse regions of the US. Clinically measured joint ROM measurements were collected from medical charts of a subset of participants. Adults (N = 156, mean age: 33.5 ± 12.6 years) had mean physical and mental component scores of 43.4 ± 10.7 and 50.9 ± 10.1, respectively. Children (N = 164, mean age: 9.7 ± 4.5 years) had mean total PedsQL, physical functioning, and psychosocial health scores of 85.9 ± 13.8, 89.5 ± 15.2, and 84.1 ± 15.3, respectively. Persons with more severe haemophilia and higher self-reported joint pain and motion limitation had poorer scores, particularly in the physical aspects of HRQoL. In adults, significant correlations (P < 0.01) were found between ROM measures and both self-reported measures. Except among those with severe disease, children and adults with haemophilia have HRQoL scores comparable with those of the healthy US population. The physical aspects of HRQoL in both adults and children with haemophilia A in the US decrease with increasing severity of illness. However, scores for mental aspects of HRQoL do not differ between severity groups. These findings are comparable with those from studies in European and Canadian haemophilia populations.

Keywords: factor VIII, haemophilia A, joint range of motion, PedsQL, quality of life, SF-12

Introduction

Haemophilia is a rare, chronic, inherited disease primarily affecting males, characterized by a deficiency in a specific clotting factor, resulting in the inability of the blood to clot normally [1]. Haemophilia A is characterized by a deficiency of factor VIII, with an incidence in the United States (US) of one in every 5000 male births [1]. Major clinical manifestations of haemophilia are bleeding episodes, most frequently into knee, ankle and elbow joints. Repeated bleeding may eventually lead to chronic haemophilic arthropathy, resulting in both acute and chronic joint pain and a reduction in joint range of motion [2]. Bleeding-related arthropathy is a major cause of haemophilic morbidity, affecting everyday function and contributing to disability. These clinical manifestations negatively impact not only the physical functioning of persons with haemophilia, but may also affect their mental and social health and functioning, leading to an impaired health-related quality of life (HRQoL).

Most studies of the relationship between haemophilia and HRQoL have used generic HRQoL measures. These include the Medical Outcomes Study Short Form-36 (SF-36) [3–9] and Short Form-12 Health Survey (SF-12) [10,11] for adults, PedsQL for children [9,12], and the Health Utilities Index (HUI) [13] for both adults and children. More recently, several
Haemophilia-specific HRQoL instruments have been developed and validated. These include Hemofilia-QoL [14] and Hemolin-QoL [15] for adults and Haemophil-QoL [16] and the Canadian Hemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT) for children [12]. Generic HRQoL instruments are used to assess general health across different health problems and summarize a spectrum of domains of health or quality of life applicable to different impairments, illnesses, patients and populations [9], providing a common metric with which to compare HRQoL between diseases. Disease-specific instruments are designed to identify constructs that are unique and important in the disease state or patient population for which they were intended, such as changes due to therapy, side effects and other disease-specific complications.

Previous studies examining the impact of haemophilia on patients’ HRQoL and its relationship with clinically evaluated disease manifestations were conducted mostly in Europe and Canada. Most of these studies had small sample sizes and generally focused on specific subpopulations such as adults only [3,8], adults with specific haemophilia severity [4,6,7], haemophilia patients who required a total knee arthroplasty [10], haemophilia patients with inhibitors [11], or patients who were part of validation studies for haemophilia-specific instruments [9]. In these studies, individuals with haemophilia in the various subpopulations studied reported poorer HRQoL than the general population in their respective study countries, particularly in the physical aspects, although they were comparable in the mental aspects [3–6,8,10,11]. However, because these studies examined specific haemophilia subpopulations, it is difficult to fully characterize the HRQoL of the haemophilia A population. In addition, differences in treatment practices, payment patterns and individual demographic characteristics among geographic regions may all result in variation in HRQoL between patients, making results from Europe or Canada less generalisable to a US population.

Previously published US studies have compared the HRQoL of individuals in association with haemophilia treatment adherence [17] or evaluated the HRQoL of children with haemophilia as part of the development and validation of a haemophilia-specific HRQoL instrument for children [18]. Like the European and Canadian studies, these studies had small sample sizes, pooled haemophilia A and B participants, or were conducted in specific subpopulations, posing a challenge for those wishing to understand how having haemophilia A affects HRQoL in general.

To fully characterize the HRQoL of US individuals with haemophilia A, this study included both adults and children with all haemophilic disease severities. It aims to understand how the US adult and paediatric haemophilia A populations compare to the general healthy US population or to other chronic disease populations and to learn whether there are similarities to the results of the European and Canadian studies previously reported in the literature.

The objectives of this study are to describe the health status of individuals with factor VIII deficiency in the US and to describe its association with physical manifestations of the condition such as joint pain and motion limitation.

Materials and methods

Study design and data collection

The Hemophilia Utilization Group Study Part-Va (HUGS-Va), was a 2-year, multicenter observational cohort study conducted among six Haemophilia Treatment Centres (HTCs) located in geographically diverse regions of the US. The study methods and baseline characteristics of the study population have been previously reported [19]. Data were collected at initial interview from participant self-report, health care providers, and patient chart reviews. Information regarding clinical aspects of the disease, such as treatment regimen, arthropathy and comorbidities were collected, as well as information regarding HRQoL and the economic consequences of having haemophilia.

Study participants were enrolled at each HTC in accordance with study enrollment criteria following informed consent from adult patients and from parents of minor children. A total of 329 participants (164 adults and 165 children) with factor VIII deficiency were recruited into the HUGS-Va study between July 2005 and July 2007.

The University of Southern California (USC) served as the data and coordinating center, and the study protocol was approved by the Institutional Review Board of USC (IRB number: HS-046012) and that of each participating HTC.

Eligibility criteria

The inclusion criteria for participation in HUGS-Va included: (i) ages 2–64 years; (ii) factor VIII level ≤30% with or without a history of inhibitor; (iii) received at least 90% of haemophilia care at the participating HTC; (iv) obtained care at the HTC within 2-years prior to study enrollment and (v) English speaking. Individuals determined to be cognitively impaired or having an additional bleeding disorder were excluded from participation.

HRQoL instruments

Adult general health was assessed using the SF-12 Health Survey Version 1, which has been used in previous haemophilia studies [10,11]. HRQoL of participants younger than 18 years was assessed using the
PedsQL™ 4.0 generic core scales. The PedsQL has previously been used in a haemophilia population in Canada to validate the haemophilia-specific CHO-KLAT [9,12]. Generic HRQoL instruments were used instead of a haemophilia-specific tool in order to provide a basis for comparison with other disease populations. As validated haemophilia-specific HRQoL instruments were not available at the time of data collection, we were unable to administer both generic and disease-specific instruments in tandem. Differences in HRQoL may not always be statistically significant but may nevertheless be clinically meaningful [20]. Therefore, we refer to the Minimally Clinically Important Difference (MCID), which is defined as: ‘the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management’ [20]. In the absence of a measured MCID, clinical significance can be considered to be half the standard deviation of the mean normalized scores [21].

**SF-12 health survey version 1.** The SF-12 is an abbreviated, 12-item version of the widely-used SF-36 generic questionnaire derived from the Medical Outcomes Study and is designed to reduce respondent burden while accurately reproducing the scores of the SF-36 [22]. The instrument assesses eight specific dimensions of HRQoL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, to yield two summary scores, physical component score (PCS-12) and mental component score (MCS-12). Both summary scores were calculated using the 1998 US scoring algorithm, which is norm-based and standardized to the 1998 US general population to have a mean score of 50 and standard deviation of 10. Scores above or below 50 can be interpreted as being better than or worse than the general US population norm, respectively. The SF-12 has been shown to be able to discriminate well between groups of patients who differ in severity of physical and mental health [22], making it appropriate for use in identifying discrete impairments in HRQoL within our study population. In this context, MCID is considered to be a difference in score of 5.0 points.

**PedsQL 4.0 generic core scales.** The PedsQL is a generic, non-disease specific HRQoL instrument developed in the US for children and adolescents [23]. It has been shown to be valid and reliable for both self and parent-proxy administration [24] and has also been found to be sensitive to differences between disease types and between severity groups within the same disease [25]. Parents of participants aged 2–7 years and participants aged 8–17 years (or their parents) self-administered the questionnaire in our study. The PedsQL consists of 23 items that assess four subscales of functioning: physical, emotional, social and school-related. These contribute to a total score as well as to two summary scores: physical health and psychosocial health. The physical health summary score is comprised of the physical functioning subscale, while the psychosocial summary scale is comprised of the emotional, social, and school functioning subscales. Scores are reported on a scale of 0–100, with a higher score indicating better HRQoL. The total, physical health and psychosocial health scores for a healthy pediatric population have been determined to be 83.8 ± 12.7, 87.5 ± 13.5 and 81.9 ± 14.1, respectively [25]. The assessment of HRQoL in children should ideally be through self-report. However, in situations where this is not possible due to the child being too young or ill, parent-proxy reports are generally used. Across the PedsQL scales, moderate to good inter-rater agreement has been shown between patients and proxies [24], allowing for parent-proxy scores to be used. The MCID of the PedsQL has been determined to be 4.4 for child self-report and 4.5 for parent-proxy-report [26]. In this study, because the majority of pediatric responses were obtained by parent-proxy report (95.7%), an MCID of 4.5 is used.

**Joint pain and motion limitation.** Joint pain was determined by self-report using a 5-point scale, ranging from ‘1: No pain’ to ‘5: Severe pain all the time’. Similarly, motion limitation was self-reported using a 4-point scale, ranging from ‘1: No limitation’ to ‘4: Severe limitations’.

**Range of motion.** Joint range of motion (ROM) measurements were abstracted from participants’ clinical chart. Measurements based on methods developed by the American Academy of Orthopaedic Surgeons were made on 10 joints (bilateral hips, knees, shoulders, elbows and ankles) by a physical therapist or trained healthcare provider. For each participant, an overall joint index was calculated by taking the sum of all flexion and extension measurements on the 10 joints. The total joint ROM limitation was calculated as the difference between the normal overall joint index value (1690 degrees) and the participant’s overall joint index. From this, the percent overall joint limitation was determined by taking the participant’s total joint ROM limitation and dividing it by the overall normal joint index (1690 degrees), then multiplying the fraction by 100 [27]. Negative values of percent overall joint limitation indicate that the participant has excessive joint mobility relative to normal.

**Statistical analysis**

Descriptive statistics were computed to characterize the study population. One-way analysis of variance
(ANOVA) between subjects with post hoc testing using Scheffe’s multiple comparison procedure for unbalanced sample sizes was used to identify differences in SF-12 or PedsQL scores across subgroups of interest. The subgroups were self-reported joint pain levels, self-reported motion limitation levels, haemophilic severity, and prophylaxis status for participants with severe haemophilia. Analyses were conducted separately for adults and children. Spearman correlation coefficients were computed to examine the correlation between clinically measured percent ROM limitation and self-reported pain or motion limitation, as well as between clinically measured percent ROM limitation and HRQoL scores. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Of the 329 participants (164 adults and 165 children), 156 adults completed the SF-12 and the self-reported pain and motion limitation evaluations. Among children, 164 (157 parent-proxies, 7 self-completed) complete records were available for both the PedsQL and self-reported pain evaluation, while 163 (156 parent-proxies, 7 self-completed) complete self-reported motion limitation evaluations were available. Clinical ROM measurements were obtained from the medical charts of 146 participants (91 adults, 55 children) for whom measurements had been recorded within 6 months of their initial HUGS-Va interview.

Baseline characteristics of the study population are summarized in Table 1. Characteristics of interest include mean ages, haemophilic severity, treatment type, mean HRQoL scores, and mean clinical ROM measurements for both adults and children.

Adult participants had lower physical component scores (PCS-12) (mean: 43.4 ± 10.7) than the general US population, with PCS-12 scores decreasing with increasing haemophilic severity (Table 1). The mean mental component score (MCS-12) of 50.9 ± 10.1 was comparable to the general US population. No significant differences in HRQoL were found between individuals with severe haemophilia on prophylaxis (mean PCS-12: 43.1 ± 9.9; mean MCS-12: 52.0 ± 9.9) and on-demand treatment (mean PCS-12: 40.4 ± 10.5; mean MCS-12: 50.2 ± 10.9).

Among pediatric participants, the mean total PedsQL score was 85.9 ± 13.8; the physical functioning subscale score was 89.5 ± 15.2 and the psychosocial health subscale score was 84.1 ± 15.3. As observed among the adults, PedsQL scores among the children generally decreased with increasing haemophilic severity, and no significant differences were found between severe haemophilia patients on prophylaxis (mean total PedsQL: 84.1 ± 14.2) and on-demand treatment (mean total PedsQL: 86.5 ± 12.4).

Using the self-reported joint pain and motion limitation measures, one-third of adults (30.1%) reported some pain in at least one joint some of the time even when not bleeding, while many children (43.6%) reported no pain in any joints. Similarly, half (49.7%) of the adults reported motion limitation affecting their daily activities while many children (43.6%) reported no such limitation.

The mean HRQoL scores at baseline, categorized by self-reported joint pain and motion limitation, are presented in Tables 2 and 3, respectively. Due to the

Table 1. Baseline characteristics of study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total mean (SD)</th>
<th>Mild (N = 42)</th>
<th>Moderate (N = 16)</th>
<th>Severe (N = 99)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>N = 157</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>33.5 (12.6)</td>
<td>38.4 (14.2)</td>
<td>34.2 (12.9)</td>
<td>31.3 (11.4)</td>
<td>0.0087</td>
</tr>
<tr>
<td>On prophylaxis (%)</td>
<td>40 (25.5)</td>
<td>1 (3.4)</td>
<td>1 (6.3)</td>
<td>38 (38.4)</td>
<td>-</td>
</tr>
<tr>
<td>Range of motion limitation #1*</td>
<td>10.2 (9.1)</td>
<td>5.4 (4.5)</td>
<td>12.3 (14.7)</td>
<td>12.2 (12.0)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Adult SF-12 measures</td>
<td>N = 165</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS-12</td>
<td>43.4 (10.7)</td>
<td>46.7 (10.8)</td>
<td>46.5 (11.5)</td>
<td>41.5 (10.2)</td>
<td>0.0140</td>
</tr>
<tr>
<td>MCS-12</td>
<td>50.9 (10.1)</td>
<td>53.1 (9.0)</td>
<td>50.0 (11.4)</td>
<td>50.9 (10.4)</td>
<td>0.9275</td>
</tr>
<tr>
<td>Children</td>
<td>N = 165</td>
<td>N = 36</td>
<td>N = 20</td>
<td>N = 109</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>9.7 (4.5)</td>
<td>9.7 (4.7)</td>
<td>8.7 (3.7)</td>
<td>9.9 (4.6)</td>
<td>0.5630</td>
</tr>
<tr>
<td>On prophylaxis (%)</td>
<td>91 (55.2)</td>
<td>2 (5.6)</td>
<td>1 (5)</td>
<td>88 (80.7)</td>
<td>-</td>
</tr>
<tr>
<td>Range of motion limitation #1*</td>
<td>-2.8 (4.5)</td>
<td>-3.6 (4.1)</td>
<td>-3.3 (2.3)</td>
<td>-2.5 (4.7)</td>
<td>0.7592</td>
</tr>
<tr>
<td>Children PedsQL measures</td>
<td>N = 165</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>85.9 (13.8)</td>
<td>90.8 (12.2)</td>
<td>85.6 (13.4)</td>
<td>84.3 (14.1)</td>
<td>0.0473</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>89.5 (15.2)</td>
<td>95.2 (7.3)</td>
<td>90.5 (13.0)</td>
<td>87.3 (17.0)</td>
<td>0.0238</td>
</tr>
<tr>
<td>Psychosocial health</td>
<td>84.1 (15.3)</td>
<td>88.4 (16.0)</td>
<td>82.9 (15.1)</td>
<td>82.8 (15.0)</td>
<td>0.1541</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>82.2 (19.1)</td>
<td>86.3 (21.9)</td>
<td>80.8 (18.9)</td>
<td>81.1 (18.1)</td>
<td>0.3548</td>
</tr>
<tr>
<td>Social functioning</td>
<td>87.7 (16.9)</td>
<td>92.1 (15.6)</td>
<td>84.8 (17.3)</td>
<td>86.8 (17.1)</td>
<td>0.1886</td>
</tr>
<tr>
<td>School functioning</td>
<td>81.6 (17.3)</td>
<td>85.9 (17.1)</td>
<td>82.9 (18.0)</td>
<td>79.9 (17.1)</td>
<td>0.2145</td>
</tr>
</tbody>
</table>

1Clinically evaluated joint range of motion using methods developed by American Academy of Orthopaedic Surgeons; Negative scores indicate excess joint mobility relative to normal.

2Adults, N = 91; Mild, N = 27; Moderate, N = 5; Severe, N = 59.

3Children, N = 55; Mild, N = 12; Moderate, N = 2; Severe, N = 41.

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small sample size of children who indicated joint pain as '4: Pain most of the time' (N = 9) and '5: Severe pain all the time' (N = 1), these two groups were combined for analysis. Similarly, due to the small sample of children indicating motion limitation as '3: Limitation affects activities' (N = 14) and '4: Severe limitations' (N = 2), these two groups were also combined for analysis.

In adults, PCS-12 decreased as the severity of joint pain increased (Table 2). There were also statistically significant (P < 0.05) and minimally clinically important differences in mean PCS-12 score between groups with little or no joint pain and those with more severe joint pain. Similarly, there was a downward trend in mean PCS-12 scores with increasing motion limitation (Table 3), as well as statistically significant (P < 0.05) and minimally clinically important differences between motion limitation severity groups. Such findings were not observed with MCS-12 scores.

In children, mean total PedsQL scores as well as mean scores across all PedsQL subscales decreased as the severity of joint pain increased (Table 2), with statistically significant (P < 0.05) and minimally clinically important differences between groups with no or little joint pain and those with more severe joint pain. With increasing motion limitation, mean total PedsQL as well as all PedsQL subscale scores also decreased (Table 3). Statistically significant (P < 0.05) and clinically important differences were also observed in the total PedsQL, physical functioning, psychosocial health, and social functioning scores.

The mean percent of ROM limitation, grouped by severity of self-reported joint pain and motion limitation, are shown in Figs 1 and 2, respectively, for both adults and children. In general, clinically measured ROM limitation increased as pain or motion limitation increased; adults are generally more severely affected than children. A significant and positive correlation was observed between clinically evaluated joint ROM limitation and self-reported joint pain in the combined subsample, with correlation coefficient $\rho = 0.50$ (P < 0.0001). While a significant, positive correlation remained within the adult subsample, coefficient $\rho = 0.28$ (P = 0.0081), it was not observed in the subsample of children. The same positive correlation was observed in the relationship between joint ROM limitation and self-reported motion limitation in

Table 2. Mean scores for quality of life and self-reported joint pain.

<table>
<thead>
<tr>
<th></th>
<th>1. No pain</th>
<th>2. Pain with joint bleed</th>
<th>3. Some pain sometimes</th>
<th>4. Pain most of the time</th>
<th>5. Severe pain all the time</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>N = 15</td>
<td>N = 36</td>
<td>N = 49</td>
<td>N = 42</td>
<td>N = 21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCS-12</td>
<td>53.9 (6.2)</td>
<td>48.1 (9.7)</td>
<td>44.8 (8.7)</td>
<td>38.8 (9.4)</td>
<td>32.1 (8.8)</td>
<td>0.0682</td>
</tr>
<tr>
<td>MCS-12</td>
<td>53.4 (7.7)</td>
<td>54.7 (8.6)</td>
<td>49.1 (10.5)</td>
<td>49.4 (10.0)</td>
<td>49.0 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>N = 72</td>
<td>N = 59</td>
<td>N = 24</td>
<td>N = 9</td>
<td>N = 1</td>
<td></td>
</tr>
<tr>
<td>Total PedsQL</td>
<td>90.8 (10.6)</td>
<td>87.0 (11.1)</td>
<td>77.0 (12.1)</td>
<td>65.6 (23.2)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical functioning summary</td>
<td>95.7 (7.3)</td>
<td>90.6 (11.8)</td>
<td>80.2 (16.0)</td>
<td>56.9 (25.8)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Psychosocial health summary</td>
<td>88.0 (13.7)</td>
<td>85.2 (13.4)</td>
<td>75.4 (13.6)</td>
<td>70.3 (24.9)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>86.4 (17.9)</td>
<td>83.3 (18.3)</td>
<td>71.7 (15.9)</td>
<td>70.5 (26.7)</td>
<td></td>
<td>0.0017</td>
</tr>
<tr>
<td>Social functioning</td>
<td>91.3 (14.1)</td>
<td>88.4 (13.7)</td>
<td>83.3 (18.6)</td>
<td>68.8 (30.6)</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>School functioning</td>
<td>86.1 (14.5)</td>
<td>83.0 (15.3)</td>
<td>71.0 (19.8)</td>
<td>66.9 (23.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Levels 4 and 5 are combined for children due to small sample sizes.

Table 3. Mean scores for quality of life and self-reported motion limitation.

<table>
<thead>
<tr>
<th></th>
<th>1. No limitation</th>
<th>2. Limitation with joint bleed</th>
<th>3. Limitation affects activities</th>
<th>4. Severe limitations</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>N = 156</td>
<td>N = 26</td>
<td>N = 41</td>
<td>N = 76</td>
<td>N = 13</td>
</tr>
<tr>
<td>PCS-12</td>
<td>53.8 (5.3)</td>
<td>47.5 (8.7)</td>
<td>40.2 (8.8)</td>
<td>30.3 (9.4)</td>
<td></td>
</tr>
<tr>
<td>MCS-12</td>
<td>53.0 (8.4)</td>
<td>52.7 (9.6)</td>
<td>49.5 (10.0)</td>
<td>48.6 (14.3)</td>
<td>0.2076</td>
</tr>
<tr>
<td>Children</td>
<td>N = 163</td>
<td>N = 88</td>
<td>N = 59</td>
<td>N = 14*</td>
<td>N = 2*</td>
</tr>
<tr>
<td>Total PedsQL</td>
<td>89.2 (11.4)</td>
<td>84.6 (12.2)</td>
<td>71.7 (21.8)</td>
<td>66.1 (28.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical functioning summary</td>
<td>94.0 (9.0)</td>
<td>87.9 (13.1)</td>
<td>74.9 (20.6)</td>
<td>76.6 (22.0)</td>
<td>0.1462</td>
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<tr>
<td>Psychosocial health summary</td>
<td>86.5 (14.2)</td>
<td>82.9 (14.5)</td>
<td>79.8 (19.1)</td>
<td>73.0 (26.4)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>84.8 (18.4)</td>
<td>87.8 (15.8)</td>
<td>80.3 (16.0)</td>
<td>73.7 (22.0)</td>
<td>0.0780</td>
</tr>
</tbody>
</table>

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social functioning, correlation was noted between joint ROM limitation and other HRQoL scores were not found to be significant. Correlations between joint ROM limitation and all PCS-12 was lower in study participants with severe haemophilia compared with the US general norm (mean: 50 ± 10). Similarly, the PCS-12 scores of the study population declined as expected with increasing pain or motion limitation. In order to place HRQoL in haemophilia in the context of other chronic diseases, US studies were identified that also used the SF-12. With the exception of the group experiencing the most severe joint pain or motion limitation, the haemophilic population had better MCS-12 and PCS-12 than obese subjects with two or more of the following: diabetes, hypertension and hyperlipidemia [28], and individuals with type 2 diabetes [29]. When compared with a group of male asthmatics between the ages of 18 and 64, the adult haemophilic population also reported better MCS-12, but poorer PCS-12, except for the group reporting no pain or motion limitation [30].

When comparing the paediatric study sample to published reports of a sample of California children defined as healthy, children with haemophilia had a HRQoL better than or comparable to the healthy sample (mean: 83.8 ± 12.7), as measured by the PedsQL subscales across all haemophilic severity levels. Among children with mild or no joint pain or motion limitation, HRQoL scores in the haemophilic sample were higher than those found in the healthy, non-haemophilic population [25]. With the exception of those who reported severe joint pain or motion limitation, children with haemophilia also reported higher PedsQL scores than published reports of children with diabetes, end-stage renal disease, gastrointestinal conditions, cardiac diseases, asthma, cancer, psychiatric disorders or rheumatoid conditions [25].

The haemophilia A population in this study, both adults and children, displayed mental functioning scores (MCS-12 or psychosocial functioning) comparable to or better than the individuals who were healthy (mean: 50 ± 10 and 81.9 ± 14.1, respectively) or had other chronic diseases [25,28–30]. Due to the physical manifestations of haemophilia, however, poorer physical

Discussion

This study used generic instruments to measure HRQoL, allowing comparison of the scores of participants with haemophilia A to those of the general healthy US population as well as to other disease populations reported in the literature. For a rare disease like haemophilia, which generally results in studies with small sample sizes, this study captures the HRQoL of a larger population than those of previous published reports. Studies on HRQoL in haemophilia using generic measures would help providers, decision- and policy-makers understand how the needs of individuals with haemophilia differ from those individuals with other chronic disease conditions, allowing stakeholders to identify and address the specific needs of people with haemophilia.

In adults, considering the minimally clinically important difference (MCID) on the SF-12 to be half the standard deviation of the mean normalized scores [21], the study population had MCS-12 similar to the US general norm (mean: 50 ± 10), but poorer physical functioning (PCS-12). Stratified by disease severity, PCS-12 was lower in study participants with severe haemophilia compared with the US general norm (mean: 50 ± 10). Similarly, the PCS-12 scores of the study population declined as expected with increasing pain or motion limitation. In order to place HRQoL in haemophilia in the context of other chronic diseases, US studies were identified that also used the SF-12. With the exception of the group experiencing the most severe joint pain or motion limitation, the haemophilic population had better MCS-12 and PCS-12 than obese subjects with two or more of the following: diabetes, hypertension and hyperlipidemia [28], and individuals with type 2 diabetes [29]. When compared with a group of male asthmatics between the ages of 18 and 64, the adult haemophilic population also reported better MCS-12, but poorer PCS-12, except for the group reporting no pain or motion limitation [30].

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functioning among those with greater morbidity was observed as compared with the healthy population. Despite this, the study population generally reported better physical functioning than either the general population or most other chronic disease populations reported in the literature [25,28–30]. In participants with greater morbidity, these findings are similar to those of the European, Canadian and US studies mentioned previously, which found haemophilia patients to have similar mental, but poorer physical functioning compared with healthy populations [3–6,8,10,11]. One possible explanation for these findings could be that persons with haemophilia may have adapted to their life-long condition and are able to lead lifestyles that are minimally disruptive to their quality of life. Since this study population is drawn from those receiving care from HTCs, it could also be attributed to the comprehensive care that they receive, thereby helping manage their disease in a more predictable way compared to patients with other conditions, like asthma. Further studies of the non-HTC population and populations across several countries could help researchers identify factors that influence the HRQoL of persons with haemophilia A. Such studies would help determine whether the similar patterns in mental and physical scores among haemophilia patients and the general population that has been observed in Europe, Canada and the US are driven by the same sociodemographic, health care delivery and clinical characteristics.

Prophylactic factor replacement therapy is commonly practiced by patients with severe haemophilia in order to prevent bleeding episodes and has been shown to achieve better joint health maintenance outcomes compared with on-demand therapy [31,32]. One study has shown that initiating prophylaxis before the age of 3 years has also been shown to result in better HRQoL, especially in the physical domains, than if prophylaxis is initiated after age three [7]. The same study showed both mental and physical HRQoL of early prophylaxis patients to be comparable to that of the general population [7]. In the current study, the lack of significant or clinically important differences in HRQoL between the prophylactic and on-demand treatment groups may be due to the inability of a cross-sectional study to identify differences between groups or may be a result of the large variation in the overall length of time participants received prophylactic treatment (mean years on prophylaxis for adults: 6.8 ± 6.8 years). In addition, due to the length of time required to develop severe joint disability, differences between children using prophylaxis (mean years on prophylaxis: 5.9 ± 4.1 years) compared with those using on-demand treatment may not yet be quantifiable. A longitudinal comparison of the two groups may enhance understanding of the differences in HRQoL experienced by those using prophylaxis or on-demand regimens and should be a subject of future analysis.

In this study, the SF-12 and PedsQL were used to measure HRQoL. In the physical aspects of health, the SF-12 was able to discriminate between adult participants with differing levels of self-reported morbidity (joint pain and motion limitation). Similarly, the PedsQL was able to discriminate between participants with differing levels of self-reported morbidity, both in the physical and psychosocial aspects of health. In addition to the SF-12, other generic HRQoL measurement alternatives in the adult population have also demonstrated good discrimination between various subpopulations of persons with haemophilia. The SF-36 discriminates well between severe haemophilia patients of different age groups and between those who required orthopaedic treatment or treatment for joint pain and those who did not [4], as well as between haemophilic severities and between patients and the healthy population [3]. The Health Utilities Index, a generic instrument that measures utilities, has also demonstrated validity in haemophilia patients with hepatitis and/or HIV [13]. In children, the PedsQL previously exhibited high correlations with disease-specific instruments like the CHO-KLAT and HaemoQoL [9,12], although all three measures were unable to distinguish between patients with moderate and severe disease, which the authors attributed to the small study sample and the hypothesis [12].

The strong correlations found between self-reported joint pain, self-reported motion limitation, and clinically measured ROM limitation suggest a potential clinical role for the use of self-reported joint pain and motion limitation scales. In the absence of a physical therapist or a health professional trained in ROM measurement, these scales may be of value in assessing clinical trends over time or between clinical evaluations.

Limitations

The results of this study indicate that many persons with haemophilia treated in HTCs, with a few exceptions, are able to maintain a HRQoL comparable to that of healthy individuals in the US. This result is encouraging, but because the study sample did not include individuals treated outside of the HTC setting, the findings may not be representative of all persons with haemophilia in the US. Additional studies that include both HTC and non-HTC treated populations may help us discern whether the high HRQoL scores reported in our study may be attributed in part to differences in delivery system of quality of care provided in HTCs and non-HTCs. Despite this limitation, the study sample is representative of the regional populations served by these study sites.

A second limitation is the use of the SF-12, which yields aggregate scores that provide some insight but are unable to generate reliable domain scores that can be compared with other HRQoL instruments such as the
eight SF-36 domains [22]. However, the SF-12 is a shorter questionnaire than the SF-36, which shortens the time needed to administer the questionnaire and also reduces respondents’ burden.

Lastly, clinical ROM measurements were available for only half the sample population, as this data was collected through chart reviews and these specialized measurements were not available for all study subjects during the data collection period.

Conclusions

The HUGS-Va study provides one of the largest and most representative studies of HRQoL among both children and adults with Factor VIII deficiency treated in HTCs in the US. The findings indicate that children and adults with haemophilia have HRQoL scores comparable to those of the healthy US population, except among those individuals with manifestations of severe haemophilic disease. Future studies are necessary to elicit the factors that influence HRQoL in persons with factor VIII deficiency in the US. Future studies should also examine how HRQoL in this population changes over time and is influenced by the model of care, especially by treatment regimen and by the onset of acute medical events.

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