RESEARCH ARTICLE

Young adults with hemophilia in the U.S.: demographics, comorbidities, and health status

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Improvements in hemophilia care over the last several decades might lead to expectations of a near-normal quality of life for young adults with hemophilia. However, few published reports specifically examine health status indicators in this population. To remedy this knowledge gap, we examined the impact of hemophilia on physical and social functioning and quality of life among a national US cohort of 141 young men with hemophilia aged 18–34 years of age who received care at 10 geographically diverse, federally funded hemophilia treatment centers in 11 states between 2005 and 2013 and enrolled in the Hemophilia Utilization Group Studies. Indicators studied included educational achievement, employment status, insurance, health-related quality of life, and prevalence of the following comorbidities: pain, range of motion limitation, overweight/obesity, and viral status. The cohort was analyzed to compare those aged 18–24 to those aged 25–34 years. When compared to the general US adult population, this nationally representative cohort of young US adults with hemophilia experienced significant health and social burdens: more liver disease, joint damage, joint pain, and unemployment as well as lower high-school graduation rates. Nearly half were overweight or obese. Conversely, this cohort had higher levels of health insurance and equivalent mental health scores. While attention has typically focused on newborns, children, adolescents, and increasingly, on older persons with hemophilia, our findings suggest that a specific focus on young adults is warranted to determine the most effective interventions to improve health and functioning for this apparently vulnerable age group.

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Introduction

Historically, bleeding due to hemophilia is characterized primarily by joint bleeding leading to joint arthritis and pain. Infectious diseases also have posed significant morbidity and mortality, namely, human immunodeficiency virus (HIV) and hepatitis B and C infections associated with virally contaminated blood products until the late 1980s and early 1990s in the United States (US) [1,2]. Improvements in care were disseminated through implementation of a nationwide regional network of hemophilia treatment centers (HTCs) [3]. Through this specialty care network, therapeutic advancements during the last several decades—including home infusion, prophylaxis, and blood safety developments—gave rise to the first cohort of young adults free from blood product-related comorbidities. These collective advancements, balanced by the outcomes from viral contamination, should be reflected in enhanced health and quality of life for young adults with hemophilia. Despite emerging concerns about health problems in older persons with hemophilia [4–6], scant information exists about the impact of hemophilia on young adults in the US, specifically pain [7] and other comorbidities. The purpose of this article is to examine the impact of pain and other comorbidities on social functioning and quality of life in a national cohort of 18–34-year-old (born 1971–1992) US residents with hemophilia.

Hemophilia-related chronic pain is well studied in adulthood. Increased pain is associated with disease severity, episodic treatment, and reduced joint range of motion [8,9]. Surprisingly, little attention focuses on the specific experience of pain in younger vs older adults, however. Because hemophilia is rare, and mortality was high during the HIV epidemic, obtaining access to a sufficient number of young adults for study poses logistical challenges [10]. Hence, most pain studies were country- [11] or HTC-specific [12]. Most studies use age 18 as the lower age range, while upper age ranges reach the 60s and even the 80s, and mean ages the 30s–40s [13,14]. By not stratifying adults into discrete age groups, potentially informative results were lost. Thus far, only one large recent study has compared associations between age, target joint development, and health-related quality of life (HRQoL) across groups of adults aged 18–24, 25–34, and 35–44 [14]. Unfortunately, the inclusion in this study of European subjects, who have a different healthcare system than the US, introduced biases, nor was pain explicitly studied. The international Hemophilia Experiences, Results and Opportunities (HERO) study provides new evidence [15], but the composition of that international cohort from

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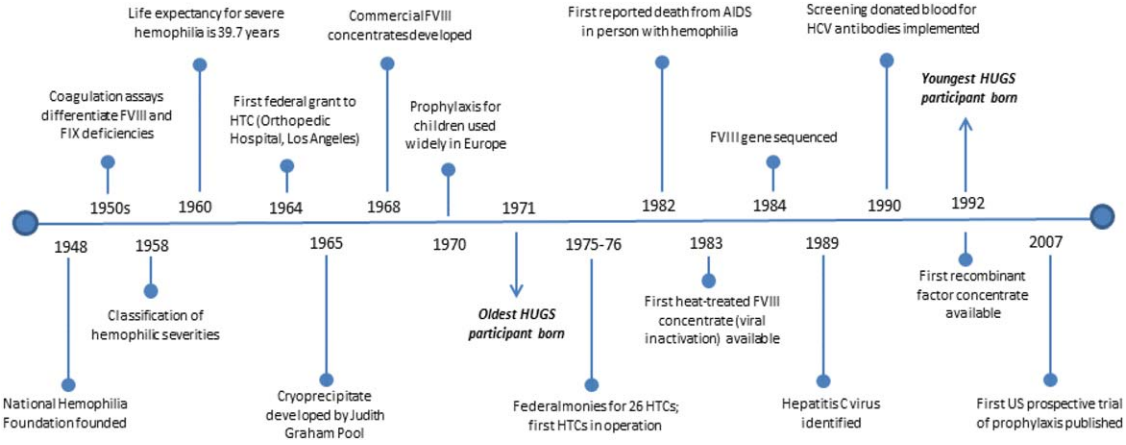

Figure 1. US hemophilia milestones and HUGS cohort.

TABLE I. Characteristics Among Young Adults with Hemophilia

Variables, *N* (%)	Age 18–24 years (*N* = 75)	Age 25–34 years (*N* = 66)
Age in years, median (range)	21.2 (18.7–24.9)	29.0 (25.4–34.8)
Hemophilia type		
Hemophilia A	52 (69%)	51 (77%)
Hemophilia B	23 (31%)	15 (23%)
Married/with a partner	8 (11%)	31 (48%)
Employment status		
Full-time	25 (33%)	38 (58%)
Part-time	21 (28%)	12 (18%)
Unemployed[a]	12 (16%)	15 (23%)
Student	17 (23%)	1 (2%)
Race		
White/non-Hispanic	53 (71%)	40 (61%)
Black/non-Hispanic	2 (3%)	2 (3%)
Hispanic	13 (17%)	18 (27%)
Other[b]	7 (9%)	6 (9%)
Insurance type[c]		
Private	45 (62%)	38 (58%)
Any public	24 (33%)	18 (27%)
No insurance	4 (5%)	10 (15%)
Education >12 years	44 (59%)	43 (65%)
Income >$20,000/year	58 (77%)	48 (73%)
Disease severity		
Mild/moderate	28 (37%)	24 (36%)
Severe	47 (63%)	42 (64%)

[a] Participants who were students were excluded from the unemployment status.
[b] Other races include American Indian, Alaskan Native, Asian/Pacific Islander, and other.
[c] *N* = 73 for age 18–24 years due to missing values.

10 countries is dominated by subjects from three developing nations whose healthcare systems and access to care differ from the US experience, decreasing generalizability about pain.

Educational levels achieved by both the US and European hemophilia populations have been examined beginning in the 1960s [16] and continuing into subsequent decades [17–19], including a recent international systematic review [20] and large US cohort [21]. All demonstrate that the educational attainment of persons with hemophilia is equal to or greater than national standards for the general US population.

Employment rates in Europe among persons with hemophilia [22–24] appear to be lower than the general European populace. There is a dearth of US hemophilia employment literature regarding young adults. Because of hemophilia's inordinate expense in the US, and because healthcare insurance is critical to US health services access, it is important to examine rates of health insurance among young adults with hemophilia, [25,26] which we demonstrate in this article.

Materials and Methods

Study design and data collection. The Hemophilia Utilization Group Studies Part V (HUGS V) consists of two prospective, longitudinal, and multicenter cohort studies. From 2005 to 2007, persons with factor VIII deficiency and from 2009 to 2013, persons with factor IX deficiency were enrolled in HUGS Va (hemophilia A) and HUGS Vb (hemophilia B) from 6 and 10 federally supported HTCs, respectively. These HTCs provide hemophilia specialty care to patients in 11 states: California, Colorado, Indiana, Massachusetts, Michigan, Mississippi, Montana, Ohio, Texas, Washington, and Wyoming (Fig. 1).

In total, 141 participants (103 with hemophilia A and 38 with hemophilia B) aged 18–34 years were included in this analysis. Data were collected through patient initial interview and 2-year follow-up surveys, and included sociodemographic characteristics (age, race, marital status, education, household income, employment status, etc.), insurance type, comorbidities, joint health, and HRQoL. Self-reported comorbid conditions included liver disease/hepatitis, arthritis, and human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS). Clinical chart review recorded data on hemophilia type, severity, treatment strategy, inhibitor status, history of immune tolerance, hepatitis A, B and C antibody status, and height and weight characteristics (used to calculate BMI) (Table I).

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

Eligibility criteria. The inclusion criteria for participation in this analysis were (i) age 18–34 years; (ii) factor VIII or factor IX level $\leq$30%, with or without a history of inhibitor; (iii) received at least 90% of hemophilia care at the participating HTC; (iv) received care at the HTC within 2 years prior to study enrollment; and (v) English or Spanish speaking. Individuals determined to be cognitively impaired or having an additional bleeding disorder were excluded.

Self-reported joint pain and motion limitation. Joint pain was determined by self-report using a five-point scale, ranging from "1: no pain" to "5: severe pain all the time." Similarly, motion limitation was self-reported using a four-point scale, ranging from "1: no limitation" to "4: severe limitations."

HRQoL instruments Short Form-12 (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. The SF-12 has been used in previous hemophilia studies [27,28] to allow for comparison with other disease populations. The SF-12 was used in this study and assessed eight specific dimensions of HRQoL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The instrument yields two summary scores: physical component score (PCS-12) and mental component score (MCS-12). Scores were calculated using the 1998 US validated scoring algorithm, which is norm-based and standardized to the 1998 US general population (mean score = 50, standard deviation = 10) [29].

Statistical analysis. The study population was stratified in the analyses by hemophilic type and severity, and age group (18–24 vs 25–34 years) was determined by the date of initial interview. Descriptive statistics were performed between groups on sociodemographic clinical characteristics. Analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, NC).

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TABLE II. Comorbidities Among Young Adults with Hemophilia by Age Group

	Total sample (N = 141)	Age 18–24 years (N = 75)	Age 25–34 years (N = 66)
Have 1 or more comorbidities	89 (63%)	39 (52%)	50 (76%)
Arthritis	47 (33%)	18 (24%)	29 (44%)
Liver disease/hepatitis	67 (48%)	22 (29%)	45 (68%)
HCV	70 (50%)	25 (33%)	45 (68%)
HIV/AIDS	20 (14%)	2 (3%)	18 (27%)
Overweight[a]	33 (23%)	14 (19%)	19 (29%)
Obese[b]	34 (24%)	16 (21%)	18 (27%)

[a] Overweight
[b] Obese were calculated based on initial clinician form of height and weight; overweight is defined as BMI (=weight (kg)/height^2 (m)) ≥25 and <30; obese is defined as BMI ≥30.
Note: all other comorbidities were generated from patient self-report. HCV was generated from clinical chart review.

TABLE III. Pain Interference Among Young Adults with Hemophilia During the Past 4 Weeks

Variables, N (%)	Total sample (N = 140)	Age 18–24 years (N = 74[a])	Age 25–34 years (N = 66)
Not at all	49 (35%)	28 (38%)	21 (32%)
A little bit	44 (31%)	23 (31%)	21 (32%)
Moderate	23 (16%)	11 (15%)	12 (18%)
Quite a lot	20 (14%)	11 (15%)	9 (14%)
Extreme	4 (3%)	1 (1%)	3 (5%)

[a] Data do not sum up to N = 75 due to missing value.

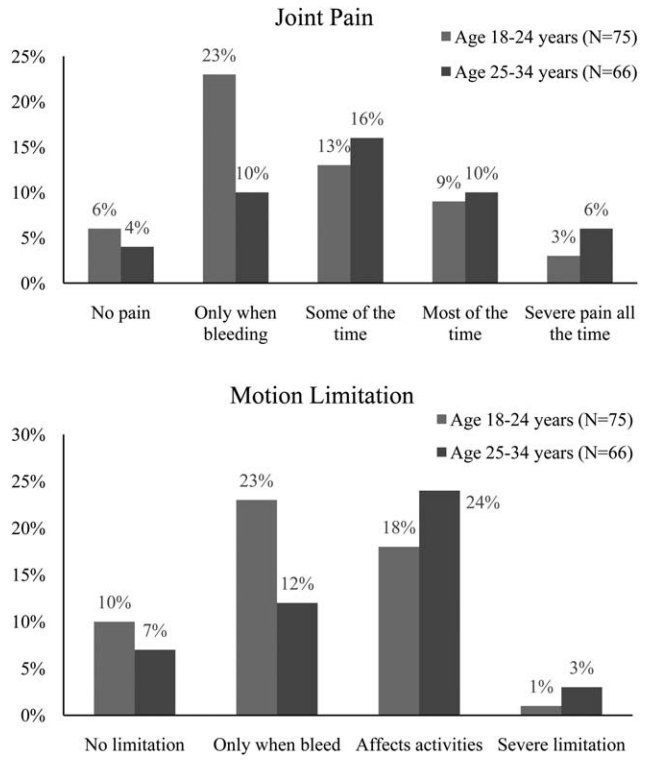

Figure 2. Self-reported joint pain and joint motion limitation among young adults with hemophilia by age group.

Results

Education, employment, and insurance in young adults with hemophilia

Among study participants aged 18–24 and 25–34 years, 59% and 65%, respectively, completed at least high school, compared to 78% and 86%, respectively, of age-matched cohorts in the general US population [30]. In the 18–34-year-old study cohort, the unemployment rate among nonstudents was 19%. No comparable US population cohort data are available due to the difference in definitions of employment status in the US population compared to the method of data collection used in this study. The uninsured rate in the study cohort aged 18–35 years was 9.9% compared to 18.4% for the general US adult population.

Comorbidities

Comparisons of comorbidities in the hemophilia study population with the general US population demonstrated significant differences. Liver disease affected 47.5% of the study population aged 18–34 years compared with 1.1% in the general US population. The study population's HIV infection rate among individuals aged 18–34 years was 14.2%; among the same age cohort in the US population, the rate was 0.25% [31] (Table II).

Overweight/obesity: Nearly one-half (48%) of our entire cohort was either overweight or obese; rates increased as the young adult cohort aged from 18–24 to 25–34 years. We found that among younger participants, a larger proportion were obese (21%) than were overweight (19%). Among the older group, 27% were obese and 29% were overweight.

Joint pain

The overall rate of hemophilic joint arthritis in the study population was 33.3%; for ages 18–24, the rate was 24% and for ages 25–34, the rate was 44%. In the US population, the arthritis rate among males aged 18–44 years was 6.8%. Hemophilia joint arthritis has an inflammatory component, whereas the general US population's arthritis is typically degenerative. Joint pain affected 90% of our cohort aged 18–34. However, pain's scope varied in breadth and depth (Table III). As shown in Fig. 2, joint pain ranged from 33% who experienced pain only with a joint hemorrhage to 29% who reported pain in at least one joint some vs 19% most of the time, to 9% who reported severe pain in at least one joint all the time. Despite pain's constancy, its interference with daily activities was varied (Table III). One-third (35%) reported pain interfered, "not at all," 48% described pain's inference with daily activities as "a little bit" and "moderate," and 17% indicated pain interfered "quite a lot" or "extreme."

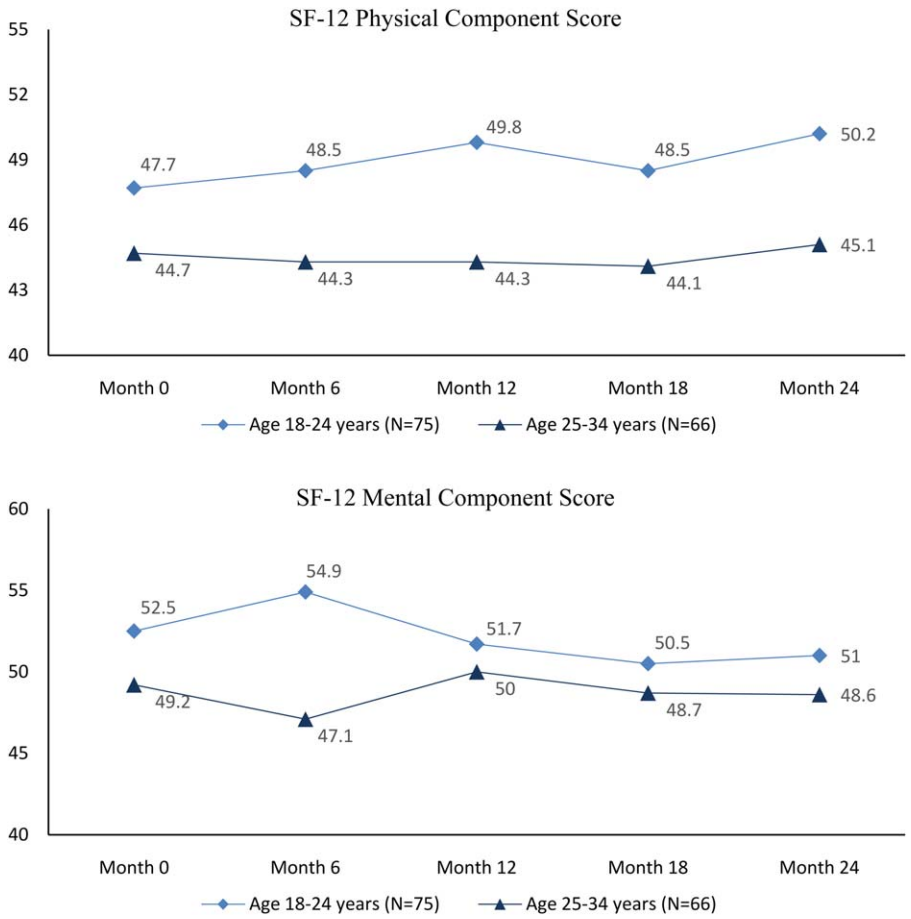

Figure 3. Mean SF-12 scores in young adults with hemophilia. Note: Mean PCS scores in US norms were 54.0 ± 7.0 among 18–24 years cohort and 54.1 ± 6.6 among 25–34 years cohort. Mean MCS scores in US norms were 49.5 ± 7.1 among 18–24 years cohort and 51.0 ± 7.6 among 25–34 years cohort.

Health-related quality of life

Physical component scores (PCS-12) and mental component scores (MCS-12) of the SF-12 were examined at baseline and 6-month intervals across 2 years. Figure 3 indicates that the scores remained fairly consistent across 2 years, demonstrating no significant longitudinal effects. However, scores were significantly different across age groups. The mean PCS were age 18–24 years: 47.7 ± 9.2, age 25–34 years: 44.7 ± 9.7 and MCS were age 18–24 years: 52.4 ± 10.1, age 25–34 years: 49.2 ± 10.6 at baseline. Comparison of mean MCS to the US general population demonstrated no significant differences. However, mean PCS of each age group in our study cohort were lower than national norms. Mean PCS also demonstrated a trend of degradation with age that was greater than that of the normative group.

Discussion

This nationally representative cohort of young US adults with hemophilia experienced significant health and social burdens: more liver disease, joint damage, joint pain, and unemployment as well as lower high-school graduation rates compared to age-matched counterparts in the general US population. Conversely, this hemophilic cohort had higher levels of health insurance and higher mental health scores.

This young adult hemophilia cohort, who were aged 18–34 at study enrollment (born 1971–1992), grew up during a period of therapeutic and health care delivery advances in US hemophilia care [32]. These "comprehensive care" advances included widespread adoption of medically supervised home infusion of clotting factor concentrates [33], initiation of prophylaxis regimens [34,35] that fostered early treatment of bleeds and thus minimized disruption to family and personal life, and access to the regionally organized US HTC network, which uses multidisciplinary specialty teams to provide expert diagnosis, clinical care, prevention education, outreach, surveillance, and research [36,37].

However, the first randomized clinical trial of prophylaxis benefits in the world was not published until 2007 [38]. Moreover, the vast majority of this cohort were children during the years when HIV and hepatitis B/C contaminated the blood supply, and there were concerns about the potential presence of other pathogens in plasma-derived and recombinant factor concentrates using human albumin. These infectious disease threats aborted the widespread adoption of prophylaxis and immune tolerance induction [39,40]. Hence, our findings of hepatitis C and HIV infection rates were not unexpected. Moreover, over one-third of our cohort was either a racial or an ethnic minority, groups that experience disparities in care access and quality [41]. Our cohort reflected the growing US racial and ethnic diversity [42].

Education

Our cohort's high-school graduation rate was relatively low compared to the age-matched cohort in the US population. In Drake et al. [21], among a cohort of 7,842 males with hemophilia enrolled in Centers for Disease Control and Prevention (CDC) surveillance through the HTC network, high-school graduation rates were comparable with the US age-matched males. Therefore, we assume that the relatively smaller size of our cohort, and its higher proportion of

African Americans and Hispanics, who historically have lower educational attainment than their Caucasian counterparts [43], was not as representative as Drake's larger national hemophilia cohort.

Employment

Nearly one quarter of 25–34-year-olds in our sample were unemployed, compared to 6% in the general US population of males aged 20 or older. High rates of unemployment among these young men due to hemophilia-related disability may be a result of decades of lost productivity prior to modern, effective hemophilia treatments. The unemployment rate in the hemophilia population, as documented in the literature, has historically been and continues to be higher than in the general population, comparing age and gender. Unemployment among young adults with hemophilia continues to be an issue of concern from a societal perspective.

Insurance: Persons with hemophilia are faced with the burden of obtaining insurance for treatment of their hemophilia, a costly disorder. Moreover, for people who are underemployed or unemployed, insurance coverage may be relegated to state or federal insurance programs or to uninsured status, adding societal burden. However, the uninsured rate in our study cohort was considerably lower than found in the general US population. This may be due to the HTC's multidisciplinary approach, which features prevention education and includes social workers as core HTC members to help navigate the insurance marketplace. Furthermore, in some of the states participating in this study, specific public insurance plans provide coverage for adults with hemophilia.

Comorbidities

Overweight/obesity: Overweight/obesity in hemophilia currently is receiving increased attention [44], given the negative impact of weight on joint health, joint range of motion, and cost of care. To our knowledge, this was the first study to specifically characterize overweight and obesity prevalence in a young adult cohort. Nearly one half of our young adult cohort (47.5%) was either overweight or obese. Previous research indicates that the prevalence of combined overweight and obesity in the overall adult (age 20 and older) hemophilia population (63%) was lower than that of the general adult (age 20 and older) US population (71%) [45,46].

Overweight and obesity present unique health implications for persons with hemophilia beyond the risks generally associated with above-normal weight, such as heart disease, hypertension, Type 2 diabetes, stroke, and sleep apnea [47]. The rate of loss in joint range of motion has been shown to be greater among overweight or obese men than among those of normal weight [48]. Above-normal BMI has also been associated with decreased use of two beneficial treatment options that are at the heart of modern hemophilia treatment: home infusion and self-infusion [45]. The inability to use these treatment options may lead to delayed treatment of bleeds, reduce the effectiveness of treatment, and place those with elevated BMI at increased risk of hemophilic complications. Factor concentrates, used to treat hemophilia, are dosed based on weight and persons who are overweight or obese use higher relative doses compared to their normal weight counterparts, costing more health care dollars.

Liver disease: Because hemophilia treatment requires the replacement of missing blood coagulation components, liver disease is common due to exposure to human viruses in blood products. Prior to 1990, both HIV and hepatitis C were transmitted in blood replacement products, causing a relatively higher prevalence of liver disease and HIV in this population [1]. It is concerning that despite the virally attenuated products available following 1990, 29% of the youngest individuals in our cohort (ages 18–24) had liver disease.

Arthritis: Arthritis is an expected outcome of hemophilia-related bleeding. While the prevalence of 33.3% in the study cohort was considerably higher than the age-matched US population, the finding in the study population was not unexpected.

Pain

Our finding that 90% of the young adult hemophilia cohort experienced at least some pain, some of the time was unexpected, given the improvements in therapies and care developed during their youth. However, this finding mirrors results detailed in the US HERO cohort described in this article [49]. Despite the prevalence of pain, more than one-third of study participants reported that their pain does not interfere with daily activities, suggesting resiliency and adaptation. To our knowledge, this was the first multicenter US study to examine pain experienced by young adults with hemophilia.

HRQoL

Although hemophilia care has improved, our analyses indicated that affected individuals continue to demonstrate lower physical functioning (PCS-12) than the general US population, consistent with the greater prevalence of comorbidities also reported. This study population displayed mental functioning scores (MCS-12) comparable to the general US population. While this result may suggest that mental health concerns do not differ significantly from the normative sample, other research indicates that depression may be more common in persons with hemophilia (37%) [50], with prevalence rates more similar to other individuals with chronic illness than the general population. This study did not look at depression rates in our cohort.

Limitations

Several limitations should be considered when interpreting the results of this study. First, our sample included only patients who received care through the network of US HTCs, and therefore cannot be generalized to individuals who receive hemophilia care through non-HTC providers. Additionally, our sample included a higher proportion of individuals with severe hemophilia A than reported by the CDC's Universal Data Collection (UDC) Project (65% vs 53%) [51]. The joint pain and joint motion limitation instrument was developed by the authors and has not been validated through comparisons with other instruments [52]. Employment status was collected only during participants' initial interview, so changes in status that may have occurred during the study period were not captured. Finally, our ability to accurately compare our study sample with the general US population was in some cases limited by a lack of published data regarding adult men in a comparable age range (18–34 years).

Conclusion

Improvements in hemophilia care over the last several decades might understandably lead policy makers to expect a near-normal quality of life for young persons with hemophilia. However, our cohort of young adults with hemophilia, aged 18–34 years, ranked worse on levels of educational achievement, employment, liver disease, joint damage, joint pain, and physical health, compared to the general US population. Our cohort ranked equivalent to the US general population in mental health scores, and had better levels of health insurance. While attention has typically focused on newborns, children, adolescents, and increasingly, on older persons with hemophilia [53–55], our findings suggest that a specific focus on young adults is warranted to determine the most effective interventions to improve health and functioning for this apparently vulnerable age group.

Disclosures

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