Title
Physical Functioning in Boys with Hemophilia in the U.S.

Journal
American Journal of Preventive Medicine, 41(6)

ISSN
07493797

Authors
Monahan, Paul E
Baker, Judith R
Riske, Brenda
et al.

Publication Date
2011-12-01

DOI
10.1016/j.amepre.2011.09.017

Peer reviewed

Physical Functioning in Boys with Hemophilia in the U.S.

Paul E. Monahan, MD, Judith R. Baker, MHSA,
Brenda Riske, MS, MBA, MPA, J. Michael Soucie, PhD

Background: Hemophilia is the most common inherited severe bleeding disorder. Although the most frequent complication of repeated hemorrhages is a crippling joint disease that begins in childhood, the extent of resultant joint functional impairment varies widely within the hemophilia population.

Purpose: The goal of this exploratory analysis was to examine a national database that collects information on boys with hemophilia, an X-linked severe congenital bleeding disorder, to determine characteristics associated with increased risk of developing limitations in physical functioning as an outcome of recurrent hemorrhages.

Methods: A standard set of data is collected annually at ~130 U.S. comprehensive hemophilia treatment centers (HTCs) in a voluntary surveillance program called the Universal Data Collection (UDC) program. Fifteen potential predictors for poor outcomes of physical functioning related to bleeding were examined for boys (aged ≤18 years) from 1998 to 2008. Bivariate and multivariate analyses of these predictors performed in 2009 examined associations with self-reported limitation of activities, absenteeism from work or school, and reliance on assistive devices for ambulation and mobility.

Results: Multiple characteristics of underlying hemophilia severity and disease chronicity (in particular, increasing age, presence of joint bleeding, and inhibitor antibodies) were independently associated with increased risk of limitations of physical function. Nonwhite race/ethnicity was associated with each of the poorer functional outcomes in bivariate analyses. After controlling for the potential confounding effects of the multiple population characteristics on race, only African-American race was independently associated with activity restrictions, and African-American and Asian/Pacific Island ethnicity with absenteeism. With the exception of indicators of underlying disease severity, only obesity and medical insurance coverage with Medicaid rather than commercial insurance were independently associated with multiple poor outcomes.

Conclusions: Interventions focused on eliminating inhibitors, improving outcomes for African-American children with hemophilia, and maintaining healthy body weight are warranted. In addition, strategies are needed to assure adequate insurance coverage for all people with hemophilia to eliminate economic barriers to optimal functional outcomes.
(Am J Prev Med 2011;41(6S4):S360–S368)

Introduction

Hemophilia results from the X-linked congenital deficiency of blood clotting factor VIII (hemophilia A) or factor IX (hemophilia B). Individuals with hemophilia are at risk for frequent recurrent musculoskeletal bleeding and more infrequent life-threatening hemorrhage. Hemophilic arthropathy resulting from recurrent bleeding into joints is the most common morbidity.[1] It is caused by blood and the inflammatory response to blood within joints and, in the most severe form, leads to gradual painful and deforming joint degeneration. Regular infusions of treatment product preventing bleeding (prophylaxis) started in early childhood have

From the Department of Pediatrics, Hematology/Oncology (Monahan), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; the Department of Pediatrics, Hematology/Oncology (Baker), University of California Los Angeles, Los Angeles, California; Mountain States Regional Hemophilia Center (Riske), University of Colorado Health Sciences Center, Denver, Colorado; and the Division of Blood Disorders (Soucie), National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

Address correspondence to: Paul E. Monahan, MD, Department of Pediatrics, Hematology, Harold R. Roberts Comprehensive Hemophilia Diagnostic and Treatment Center, University of North Carolina at Chapel Hill, CB# 7016, 3rd Floor Physicians Office Building, 170 Manning Drive, Chapel Hill NC 27599-7016. E-mail: Paul_Monahan@med.unc.edu.

0749-3797/$36.00
doi: 10.1016/j.amepre.2011.09.017

been shown to decrease hemophilic arthropathy considerably.[2] Care for individuals with hemophilia in the U.S. is delivered principally via a network of comprehensive hemophilia treatment centers (HTCs). More than 130 HTCs receive federal support to establish and maintain multidisciplinary teams to provide prospective, preventive, and family-centered surveillance and management of this rare chronic genetic blood coagulation disorder,[3] including data collection on outcomes related to hemophilia.

A system of standardized clinical data collection and routine viral testing known at the Universal Data Collection (UDC) was implemented nationwide in 1998 in partnership with the U.S. CDC. In the ensuing decade, HTCs have collected data on more than 25,000 people with bleeding disorders during 80,000+ comprehensive care visits.[4] The availability of data collected on restrictions of activity, days missed from school due to joint problems, and the use of assistive devices for mobility in a large cohort of boys with hemophilia provided the opportunity to conduct an exploratory analysis to identify independent predictors of poor outcomes of physical function. Such information may inform interventions designed to maintain physical function of patients with hemophilia.

Methods

Data are collected annually by HTC teams using instruments designed by a multidisciplinary team of clinical and epidemiologic experts. All participants or parents of minor children give informed consent, and the study is monitored by the IRBs of all participating institutions. Data collected at the most recent UDC visit for boys (aged ≤18 years) with physician-diagnosed hemophilia A or B were used for the study, with the analysis performed in 2009. Hemophilia severity was based on the percent plasma level of factor activity compared to normal (normal levels are 50%–150% in most clinical laboratories) and categorized as mild (>5% to 50%), moderate (≥1% to 5%), or severe (<1%). Age at diagnosis, categorized as at birth versus after birth, and age at first visit to an HTC, designated as ≤2 years versus >2 years, were both based on either medical records or patient self-report. On the basis of previous visit history, HTC staff categorized utilization of the HTC as frequent if once per year or more, infrequent if less than once per year, or first HTC visit.

Self-reported race and ethnicity was recorded as white, African American, Hispanic, Native American, Asian or Pacific Islander, and other. Data collected on place of birth was used to categorize participants as born inside or outside of the U.S. Clinic records were used to determine whether the participant had health insurance and to identify the type of primary insurance used if more than one was indicated, categorized as follows: commercial, Medicaid, Medicare, state program, TRICARE (government healthcare coverage for military personnel and their families), other, and uninsured. Participants were designated as a student or employed if they reported current attendance at school and/or either part-time or full-time employment at the time of the visit.

Prescribed treatment regimen was categorized as episodic if anti-hemophilic factor was used only in response to a bleed, prophylaxis if used on a regular basis (e.g., every other day) to prevent bleeding, and immune tolerance if infusions were given to treat an inhibitor. Inhibitors (antibodies to treatment product) were categorized as either present, if the subject had a reported inhibitor titer of ≥0.5 Bethesda units at any visit or if the subject was receiving immune tolerance therapy for an inhibitor, or absent, if otherwise. The number of bleeding episodes in the joints experienced by the subject during the previous 6 months was based on either infusion logs or subject self-report and was categorized for analytic purposes as 0, 1–4, or ≥5 episodes. BMI was calculated from height and weight measurements. On the basis of this measure, each subject was categorized according to Year 2000 CDC Growth Charts for the U.S.[5] as either obese, overweight, or normal, defined as having a BMI above the 95th, between the 85th and 95th, and below the 85th percentile for gender and age, respectively.

Four measures of physical functioning outcome were used for the study. During the clinic visit, participants were asked to evaluate their current overall activity level as follows: (1) unrestricted school/work and recreation activities; (2) full school/work but limited recreation activities; (3) limited school/work and recreation activities; (4) limited school/work, recreational, and self-care activities; or (5) requires assistance for school/work/self-care and unable to participate in recreational activities. Limitations could be the result of either pain, loss of motion, or weakness. Participants were also asked about the number of days during the last year they had missed work or school because of either upper or lower extremity joint problems. Days missed were designated as ≤11 days versus >11 days, corresponding to categories used by the National Survey of Children with Special Healthcare Needs.[6] Finally, participants were asked to categorize as "never," "intermittently," or "always" their use in the preceding year of a cane, crutches, or walker and separately their use of a wheelchair for mobility.

Differences in the distribution of demographic and clinical characteristics across levels of each of the four physical functioning outcomes were assessed for statistical significance in separate analyses using chi-square tests. In preliminary analyses, relatively small numbers of these young individuals had any activity limitations, so this outcome was collapsed into two levels: no activity restriction (overall activity level 1, as defined in the previous paragraph) versus any restriction in school/work, recreation, or self-care (overall activity levels 2 through 5). Similarly, due to small numbers of children reporting the use of a cane, crutches, or walker or a wheelchair "always" for mobility, these outcomes were both categorized as no use versus ever use.

Separate logistic regression analyses were used to identify risk factors significantly associated with the four musculoskeletal outcomes. All studied risk factors were entered into the regression model so that the potential confounding effects of multiple factors could be accounted for by the procedure. All analyses were performed using SAS Version 9 statistical software.

Results

Between May 1998 and December 2008, some 6419 boys with hemophilia aged ≤18 years were enrolled in the UDC. The most recent UDC data were collected at an HTC visit after 2001 for 90% of the participants (with 75% of visits after 2004). The distribution of participant

Table 1. Characteristics of boys with hemophilia and bivariate relationships with decreased activity, absenteeism, and use of assistive devices

Characteristic	Patients, *n* (%)[b]	Decreased activity	>11 days lost from work or school[a]	Use of cane/ crutches/walker	Use of wheelchair
Age group, years					
<6	983 (15.3)	5.6 (<0.001)	1.1 (<0.001)	2.0 (<0.001)	2.0 (<0.001)
6–12	2808 (43.7)	10.6	4.6	14.2	5.4
13–18	2629 (41.0)	18.4	7.0	20.0	5.1
Race/ethnicity					
White	3989 (62.1)	10.7 (<0.001)	4.2 (<0.001)	14.2 (<0.001)	4.0 (<0.01)
Black	836 (13.0)	20.9	10.0	19.9	6.8
Hispanic	1094 (17.0)	12.3	5.8	14.0	5.7
Asian/Pacific Islander	178 (2.8)	12.9	10.0	14.6	7.3
Native American	51 (0.8)	19.6	5.3	13.7	5.9
Other	272 (4.2)	23.5	5.2	10.3	4.0
Birthplace					
U.S.	6122 (95.4)	12.8 (<0.05)	5.4 (NS)	14.7 (NS)	4.7 (NS)
Outside U.S.	275 (4.3)	17.1	6.7	15.3	5.8
Disease type					
Hemophilia A	5069 (79.0)	14.0 (<0.001)	5.7 (NS)	15.5 (<0.001)	5.2 (<0.001)
Hemophilia B	1351 (21.0)	9.1	4.9	11.8	3.0
Disease severity					
Mild	1630 (25.4)	5.5 (<0.001)	2.2 (<0.001)	8.6 (<0.001)	1.7 (<0.001)
Moderate	1559 (24.3)	12.1	4.2	13.7	3.7
Severe	3225 (50.2)	17.2	7.7	18.3	6.8
Diagnosed at birth					
Yes	168 (2.6)	13.8 (NS)	2.2 (NS)	17.4 (NS)	7.2 (NS)
No	6252 (97.4)	13.0	5.6	14.6	4.7
Age in years at first HTC visit					
>2	1526 (23.8)	12.6 (NS)	5.1 (NS)	13.0 (<0.05)	3.7 (<0.05)
≤2	4588 (71.5)	13.2	5.6	15.2	5.0
HTC utilization					
Frequent	5520 (86.0)	13.3 (NS)	5.5 (NS)	15.2 (<0.05)	4.8 (<0.05)
Infrequent	624 (9.7)	10.6	4.8	11.2	3.4
1st visit	276 (4.3)	12.0	6.6	14.1	7.2
Treatment					
Prophylaxis	2334 (36.4)	13.2 (<0.01)	5.6 (NS)	16.6 (<0.001)	5.2 (<0.001)
Episodic	3987 (62.1)	12.6	5.4	13.4	4.2
Immune tolerance	92 (1.4)	23.9	7.7	25.0	18.5

(continued on next page)

Table 1. *(continued)*

Characteristic	Patients, *n* (%)[b]	Decreased activity	>11 days lost from work or school[a]	Use of cane/ crutches/walker	Use of wheelchair
Home infusion and age at initiation					
No home infusion	1964 (30.6)	10.4 (<0.001)	4.0 (<0.001)	10.7 (<0.001)	3.6 (<0.001)
<30 months	1522 (23.7)	13.7	5.9	15.8	6.6
<6 years	940 (14.6)	18.0	6.7	21.8	6.1
≥6 years	655 (10.2)	22.8	9.8	22.8	4.9
Insurance					
Commercial	3480 (54.2)	9.6 (<0.001)	3.5 (<0.001)	13.4 (<0.001)	3.7 (<0.001)
Medicaid	2212 (34.4)	17.3	9.0	17.0	6.5
Medicare	87 (1.4)	18.4	6.0	19.5	2.3
Other	96 (1.5)	36.5	4.4	3.1	2.1
State program	215 (3.4)	12.1	5.2	14.4	8.4
TRICARE	81 (1.2)	4.9	3.4	17.3	2.5
Uninsured	172 (2.7)	14.0	5.5	12.8	4.1
BMI					
Normal	4055 (63.2)	12.9 (<0.05)	5.2 (<0.05)	14.0 (<0.001)	4.4 (<0.001)
Overweight	1035 (16.1)	11.1	4.3	12.1	3.3
Obese	1330 (20.7)	14.8	7.1	19.1	7.1
Joint bleeds					
None	3702 (57.7)	6.3 (<0.001)	1.4 (<0.001)	5.5 (<0.001)	1.6 (<0.001)
1–4	1909 (29.7)	15.6	6.1	23.8	6.7
≥5	809 (12.6)	37.6	21.1	35.6	14.6
Student or employed					
No	1059 (16.5)	7.9 (<0.001)	6.4 (NS)	6.1 (<0.001)	2.4 (<0.001)
Yes	5361 (83.5)	14.0	5.5	16.4	5.2
Inhibitor					
No	5519 (86.0)	11.0 (<0.001)	4.4 (<0.001)	13.4 (<0.001)	3.4 (<0.001)
Yes	901 (14.0)	25.4	12.3	23.1	12.9

Note: Values are %, with significant *p*-value in parentheses when appropriate, unless otherwise indicated.
[a]Limited to 5204 subjects of school or work age
[b]Not all categories sum to 100% due to missing data.
HTC, hemophilia treatment center; NS, not significant; TRICARE, civilian health care program of the U.S. Department of Defense

characteristics is shown in Table 1. As expected from existing prevalence studies in hemophilia populations, 80% of this cohort had hemophilia A, and about one half had severe factor deficiency.

The racial/ethnic composition of this pediatric population roughly reflected the general demographic trends in the U.S. Of the total study population, 4.3% were born outside of the U.S. More than half of this U.S. pediatric hemophilia population is covered by commercial insurance (54.2%), and 34.4% are covered by Medicaid; only 2.7% of study children were uninsured. Most patients infused clotting factor at home as needed for bleeding; regular prophylactic infusion of clotting factor to prevent bleeding was practiced by 36.4%. Among all participants, 14% had evidence of an inhibitory antibody to factor concentrates. At the most recent UDC visit, 16.1% of boys were overweight, and an additional 20.7% were obese. Slightly more than 40% of the boys had reported one or more joint bleeds during the previous 6 months (Table 1).

Table 2. Characteristics of boys with hemophilia and multivariate relationships with decreased activity, absenteeism, and use of assistive devices

Characteristic	Decreased activity	>11 days lost work/school	Use of cane/ crutches/walker	Use of wheelchair
Age group, years, vs <6 years				
6–12	1.8 (1.2–2.7)*	3.4 (1.1–10.5)*	7.2 (3.9–13.2)*	2.3 (1.2–4.3)*
13–18	3.3 (2.2–5.0)*	4.7 (1.5–14.5)*	9.2 (4.9–17.0)*	1.8 (0.9–3.6)
Race/ethnicity vs white				
Black	1.6 (1.3–2.1)*	1.7 (1.2–2.5)*	1.2 (0.9–1.6)	1.1 (0.8–1.7)
Hispanic	0.8 (0.6–1.1)	0.9 (0.6–1.4)	0.9 (0.7–1.2)	1.2 (0.8–1.7)
Asian/Pacific Islander	1.0 (0.6–1.7)	2.6 (1.2–5.5)*	1.3 (0.8–2.1)	1.7 (0.9–3.4)
Native American	2.0 (0.9–4.7)	1.2 (0.2–5.6)	1.3 (0.5–3.2)	1.4 (0.4–4.9)
Other	1.3 (0.8–2.1)	0.7 (0.3–1.5)	0.7 (0.4–1.2)	0.7 (0.3–1.8)
Disease type vs hemophilia A				
Hemophilia B	0.7 (0.6–0.9)*	1.2 (0.8–1.8)	1.0 (0.8–1.3)	0.8 (0.5–1.2)
Disease severity vs mild				
Moderate	1.5 (1.1–2.1)*	0.8 (0.4–1.3)	0.8 (0.6–1.1)	1.4 (0.8–2.5)
Severe	1.6 (1.2–2.3)*	0.8 (0.5–1.4)	0.7 (0.6–1.0)	1.6 (0.9–2.8)
HTC utilization vs frequent				
Infrequent	1.1 (0.8–1.5)	1.4 (0.8–2.3)	0.8 (0.6–1.1)	1.0 (0.6–1.8)
1st visit	1.1 (0.7–1.9)	2.5 (1.2–5.2)*	1.2 (0.7–1.9)	2.9 (1.5–5.3)*
Treatment vs prophylaxis				
Episodic	1.3 (1.0–1.5)*	1.0 (0.8–1.5)	1.0 (0.8–1.3)	1.2 (0.8–1.6)
Immune tolerance	1.2 (0.7–2.3)	0.5 (0.2–1.6)	1.5 (0.8–2.7)	2.1 (1.0–4.2)*
Home infusion and age at first infusion vs none				
<30 months	1.0 (0.8–1.3)	1.0 (0.7–1.6)	1.2 (0.94–1.6)**	1.1 (0.8–1.7)
<6 years	0.9 (0.7–1.2)	1.0 (0.6–1.5)	1.3 (1.0–1.7)*	1.0 (0.6–1.5)
≥6 years	1.2 (0.9–1.6)	1.3 (0.8–2.0)	1.4 (1.0–1.8)*	0.9 (0.6–1.5)
Insurance vs commercial				
Medicaid	1.6 (1.3–2.0)*	2.1 (1.5–2.9)*	1.2 (1.0–1.5)*	1.4 (1.0–1.9)*
Medicare	1.3 (0.6–2.5)	1.2 (0.4–3.8)	1.4 (0.7–2.6)	0.5 (0.1–2.0)
Other	6.0 (3.0–11.7)*	1.5 (0.4–5.7)	0.2 (0.1–1.8)	0.3 (0.1–2.6)
State program	1.1 (0.7–1.9)	1.4 (0.6–3.1)	1.1 (0.7–1.8)	2.3 (1.2–4.2)*
TRICARE	0.6 (0.2–1.7)	0.5 (0.1–4.1)	1.8 (0.9–3.7)	0.8 (0.2–3.6)
Uninsured	1.2 (0.7–2.2)	1.0 (0.4–3.0)	1.1 (0.6–1.9)	0.5 (0.1–1.7)
BMI vs normal				
Overweight	0.8 (0.7–1.1)	0.8 (0.5–1.2)	0.7 (0.6–0.9)*	0.7 (0.4–1.0)
Obese	1.2 (0.9–1.5)	1.5 (1.0–2.0)*	1.3 (1.1–1.6)*	1.5 (1.1–2.1)*

(continued on next page)

Table 2. *(continued)*

Characteristic	Decreased activity	>11 days lost work/school	Use of cane/ crutches/walker	Use of wheelchair
Joint bleeds vs none				
1–4	2.2 (1.8–2.7)*	3.6 (2.3–5.6)*	4.4 (3.6–5.4)*	3.2 (2.2–4.7)*
≥5	6.5 (5.1–8.3)*	18.6 (12.0–29.0)*	7.6 (6.0–9.7)*	8.1 (5.5–12.1)*
Student or employed	1.1 (0.8–1.5)	0.5 (0.2–1.4)	1.6 (1.1–2.2)*	1.7 (0.96–2.9)**
Inhibitor	2.2 (1.7–2.7)*	2.4 (1.7–3.5)*	1.4 (1.1–1.8)*	2.7 (2.0–3.7)*

Note: Values are OR (95% CI).
*$p<0.05$
**Borderline significance ($p\simeq0.05$)
HTC, hemophilia treatment center; TRICARE, civilian health care program of the U.S. Department of Defense

In analyzing the outcome measures of this study, 13% of boys reported any activity limitation, 5.5% reported more than 11 days of missed school or work, 14.7% reported any use of a cane, crutches, or walker, and 4.8% reported any use of a wheelchair for ambulation (Table 1).

Associations between patient characteristics and each of the four physical functioning outcome limitations were examined in four separate bivariate analyses (Table 1). The following demographic characteristics were significantly associated with all four outcomes: age, race/ethnicity, and primary health insurance category. The following clinical and treatment characteristics were also significantly associated with all four outcomes: disease severity, BMI category, joint bleeding frequency, presence of an inhibitor, and age at initiation of home factor infusion. Most of the remaining patient characteristics were associated with at least one of the outcomes. Only neonatal diagnosis was not associated with any of the outcomes.

Multivariate Analysis

The patient characteristics that were independently associated with the outcomes in separate multivariate analyses varied depending on the physical outcome under analysis. Therefore, the results (Table 2) are presented in the following text, separately for each outcome.

Activity level. Subjects with the following characteristics were more likely to report decreased activity level: increased age, African-American race, moderate or severe disease, episodic treatment, Medicaid or "other" insurance, any joint bleeding, and presence of an inhibitor (Table 2). Subjects with hemophilia B were less likely to report decreased activity than those with hemophilia A.

Days missed from school or work. Subjects with the following characteristics were more likely to report >11 days missed from school or work due to a joint problem: increased age, African American and Asian/ Pacific Islanders, first time HTC attendees, Medicaid insurance, obesity, any joint bleeding, and presence of an inhibitor.

Use of a cane, crutches, or walker. Subjects with the following characteristics were more likely to report any use of a cane, crutches, or walker for ambulation: increased age, older age at the start of home infusion, Medicaid insurance, overweight or obesity, any joint bleeding, students or employed subjects, and the presence of an inhibitor.

Use of a wheelchair. Subjects with the following characteristics were more likely to report any use of a wheelchair for ambulation: increased age, attendance at the HTC for the first time, Medicaid or State Program insurance coverage, obesity, any joint bleeding, and presence of an inhibitor.

Discussion

The objective of the exploratory study was to analyze UDC data to identify variables associated with outcomes of limited physical functioning in the U.S. population of boys with hemophilia. The observed independent associations of increasing age, frequent joint bleeding episodes, inhibitor antibody with increased risk of physical limitation are consistent with the underlying pathophysiology of hemophilia. Additionally, obese hemophilic children were significantly more likely to have absenteeism and to have required assistive devices for ambulation, and these limitations in functioning are consistent with previous observations from the UDC that documented, using objective measurements of joint range of motion (ROM), that obesity was associated with greater loss of ROM in the weight-bearing joints.[7]

Historically, the disease phenotype of hemophilia A and B has been thought to be similar at a given level of factor deficiency. Very recently, it has been suggested that severe hemophilia A may be associated with a more severe phenotype than severe hemophilia B.[8–10] Interestingly, in the current study, the outcome of self-reported limitations of activity, although not the other outcomes, was independently more strongly associated with hemophilia A than with hemophilia B, adjusting for hemophilia severity. Although the issue remains controversial, if true phenotypic differences exist in terms of speed of progression to poor outcomes, the differences may be more clearly appreciated by analyzing hemophilia A and B populations that have progressed into adulthood.

The impact of race and ethnicity on the health of the American population is widely documented. Hispanics, African Americans, and Native Americans are particularly disadvantaged in several areas, including poorer health status outcomes, access to insurance and care, and mortality.[11–13] Disparities are reported among adolescents[14] and among children with special healthcare needs (CSHCN).[15–18] Reports on the impact of race and ethnicity in hemophilia have been limited to the higher prevalence of African Americans who develop inhibitors,[19,20] septic arthritis,[21] and joint ROM limitations.[7] There are no comprehensive reports on the impact of race and ethnicity on the pediatric U.S. hemophilia population.

In this study, race was significantly associated with each of the poor functional outcomes in the bivariate analysis. In considering the causes of this association, the evaluation of intrinsic (e.g., genetic) association of race/ethnicity with disparate health outcomes can be confounded by multiple comorbid and socioeconomic conditions.[22,23] As an example, increased BMI is associated with greater degrees of loss of joint ROM in boys with hemophilia, as noted in the previous text.[7] In the general population (aged 2–19 years), Mexican-American boys and non-Hispanic African-American boys are each more likely than non-Hispanic white boys to have a BMI above the 97th percentile.[24] Obesity in African-American and Hispanic boys was significantly more prevalent than in non-Hispanic white and Asian preschoolers.[25] In the UDC, male white non-Hispanics have the lowest frequency of obesity (17.7%), and Hispanic patients have the highest (28.3%) frequency.

Inhibitors, the main complication of coagulation factor therapy, have been previously reported to be more prevalent in African-American and Mexican-Hispanic boys with hemophilia and are strongly associated with the poorer outcomes examined in the current study.[26,27] White non-Hispanic boys in this pediatric cohort had an inhibitor prevalence of 11.4%, whereas the prevalence was 16.1% among Hispanic and 22.9% among African-American boys.

After controlling for other potential predictor variables, a significant association with African-American race was independently associated with increased self-reported limitations of activity and absenteeism. No other independent associations of race/ethnicity with outcome were observed with the exception of increased absenteeism in the small cohort of Asian/Pacific Islanders, and no group had increased use of assistive devices compared to non-Hispanic whites. A forward stepwise model was examined to determine which factors were the most significant confounders for the apparent race effects observed in the bivariate analysis. As expected, frequent joint bleeds, inhibitors, insurance source (the only surrogate variable for socioeconomic status in this analysis), and BMI most significantly contributed to the apparent race effects (data not shown).

With the exception of age, severity of factor deficiency, number of joint bleeds and inhibitors, the most consistent predictor variable associated with the outcome limitations was Medicaid rather than private/commercial source of insurance. Medicare is the principal source of insurance for only 1.4% of the boys in this cohort. Medicaid, in contrast, is the primary insurance for nearly a third of boys with hemophilia in this analysis. Each state sets its own guidelines regarding Medicaid eligibility and services, and large differences exist between states across the nation.

Numerous studies examine the impact of insurance on children's health, with the uninsured having the poorest access to needed services. Health insurance can improve the quality of life for children who have special healthcare needs.[28] Among CSHCN, minorities are more likely than white children to be uninsured, and access barriers are particularly disparate for Hispanic children.[12] In 2007, 8.9% of U.S. children under age 18 years were uninsured.[13] Only 2.6% of the boys in the UDC are uninsured. Nevertheless, an examination of the primary insurance source for boys in the UDC reveals that 66.6% of white (non-Hispanic) boys are covered by commercial private insurance, and 25.3% rely primarily on Medicaid. The situation is reversed for African-American and Hispanic boys; 60.2% of African Americans and 52.2% of Hispanics have Medicaid insurance, with commercial insurance in 31.8% and 33.6%, respectively. Children with public coverage have better access to specialty care than those who are uninsured, but poorer access compared to those who are privately insured.[29–31] Given the extraordinary cost of medication alone for hemophilia care (prophylactic therapy for an adolescent with uncomplicated severe hemophilia typically costs $200,000–$300,000

annually),[32] developing comprehensive HTC care approaches with uniform, adequate insurance coverage may be one policy priority suggested by the findings of this outcome study.

There are several limitations that should be considered when evaluating the results of this study. Because the study used cross-sectional data, the associations that were observed do not necessarily imply causality. Some of the risk factors may have changed as a result of a poor outcome (e.g., home infusion or prophylaxis initiation in response to deterioration of function). The current analysis relies on the information collected at the most recent UDC clinic visit, e.g., the number and type of bleeding episodes experienced in the prior 6 months. It is not possible to assess the cumulative lifetime bleeding event rate, and using the 6-month bleeding history as a surrogate marker for lifetime bleeding events might introduce bias. One also could argue that frequent bleeding episodes in some patients (especially older boys) are themselves a poor outcome.

Outcomes were based on self-report without means of objective confirmation. It is possible that participants may have either over-reported or under-reported their activity levels or the number of days that they missed school or work due to joint problems. However, the activity level choices were well defined and unlikely to be confused. We have no reason to believe that these measures would be reported differently depending on race or other demographic characteristics that would have led to a bias in our results. Another limitation concerns the multiple interpretations that can be attributed to the use of assistive devices. Use implies a physical disability although use of assistive devices can also associated with effective rehabilitation, access to rehabilitative resources including physical therapy, and efforts to perform activities that would otherwise be impossible. In our analyses, participants who were students or employed were more likely to use assistive devices. Clearly, this association results from the rehabilitative function of these devices rather than any deleterious effect of school or work on joint outcomes.

In conclusion, these analyses of the national UDC population suggest a number of areas for targeted intervention to improve physical outcomes that result from hemophilic bleeding. Although an association between nonwhite race/ethnicity and poor outcomes of physical function is documented, the fact that no independent association exists after adjusting for factors such as joint bleeding frequency and inhibitor antibodies suggests that these populations would benefit from early and aggressive therapies to prevent and eliminate these hemophilic complications. The data especially support vigilance and interventions to optimize outcomes for African-American boys. Consistent with previous reports on the health of weight-bearing joints in hemophilic boys, preventing obesity is an especially important public health goal for this population. Ultimately, given the tremendous costs of medication and care for this condition, interventions designed to maximize the health impact of these therapies and strategies to assure adequate insurance coverage for all boys with hemophilia are needed.

The authors acknowledge all of the dedicated caregivers at the network of >130 HTCs who collect the data for the UDC program surveillance project. The authors also acknowledge Rodney Presley for data analysis and acknowledge the additional effort of the Regional Coordinators from the 12 regions of the U.S. HTC network (USHTCN) who validated specific data elements and categories to verify the precision of this study: Ann D. Forsberg, Mariam Voutsis, Amanda Wade, Steven Humes, Karen Droze, Tami Wood-Lively, Mary Anne Schall, John H. Drake, Becky Dudley, and Robi Ingram-Rich (with JRB and BR).

Publication of this article was supported by the Centers for Disease Control and Prevention through a Cooperative Agreement with the Association for Prevention Teaching and Research award # 09-NCBDDD-01.

No financial disclosures were reported by the authors of this paper.

References

1. Hoots WK, Rodriguez N, Boggio L, Valentino LA. Pathogenesis of haemophilic synovitis: clinical aspects. Haemophilia 2007;13(S3):4–9.
2. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007;357(6):535–44.
3. Baker JR, Crudder SO, Riske B, Bias V, Forsberg A. A model for a regional system of care to promote the health and well-being of people with rare chronic genetic disorders. Am J Public Health 2005; 95(11):1910–6.
4. Soucie JM, McAlister S, McClellan A, Oakley M, Su Y. The universal data collection surveillance system for rare bleeding disorders. Am J Prev Med 2010;38(4S):S475–S481.
5. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. Vital Health Stat 2002;11(246):1–190.
6. National Survey of Children with Special Health Care Needs 2005–2006. http://mchb.hrsa.gov/cshcn05/NF/2healthfs/missed.htm.
7. Soucie JM, Wang C, Siddiqi A, Kulkarni R, Recht M, Konkle BA, and the Hemophilia Treatment Center Network. The longitudinal effect of body adiposity on joint mobility in young males with haemophilia A. Haemophilia 2011;17:196–203.
8. Makris M. Is VIII worse than IX? Blood 2009;114:750–1.
9. Tagariello G, Iorio A, Santagostino E, et al. Comparison of the rates of joint arthroplasty in patients with severe factor VIII and IX deficiency: an index of different clinical severity of the 2 coagulation disorders. Blood 2009;114:779–84.
10. Biss T, Chan AK, Blanchette VS, et al. The use of prophylaxis in 2663 children and adults with haemophilia: results of the 2006 Canadian national haemophilia prophylaxis survey. Haemophilia 2008;14:923–30.

11. Agency for Healthcare Research and Quality. National healthcare disparities report 2008. Rockville MD: Agency for Health Care Policy and Research. March 2009. www.ahrq.gov/qual/qrdr08.htm.
12. Kilbourne AM, Switzer G, Hyman K, Crowley-Matoka M, Fine MJ. Advancing health disparities research within the health care system: a conceptual framework. Am J Public Health 2006;96(12):2113–21.
13. Cohen RA Martinez ME, Free HL. Health insurance coverage: early release of estimates from the National Health Interview Survey, 2007. Atlanta GA: CDC, 2007. www.cdc.gov/nchs/data/nhis/earlyrelease/insur200806.htm.
14. Fox HB, McManus MA, Zarit M, et al. Racial and ethnic disparities in adolescent health and access to care. Washington DC: National Alliance to Advance Adolescent Health, 2007.
15. Newacheck PW, Hung YY, Wright KK. Racial and ethnic disparities in access to care for children with special health care needs. Ambul Pediatr 2002;2(4):247–54.
16. Newacheck PW, Strickland B, Shonkoff JP, et al. An epidemiologic profile of children with special health care needs. Pediatrics 1998;102(1 Pt 1): 117–23.
17. van Dyck PC, Kogan MD, McPherson MG, Weissman GR, Newacheck PW. Prevalence and characteristics of children with special health care needs. Arch Pediatr Adolesc Med 2004;158(9):884–90.
18. Chevarley FM. Utilization and expenditures for children with special health care needs. Research Findings 2006; No. 24. Rockville MD: Agency for Healthcare Research and Quality. http://www.meps.ahrq.gov/mepsweb/data_files/publications/rf24.pdf.
19. Ragni MV, Ojeifo O, Feng J, et al. Risk factors for inhibitor formation in haemophilia: a prevalent case–control study. Haemophilia 2009;15(5): 1074–82.
20. Viel KR, Ameri A, Abshire TC, et al. Inhibitors of factor VIII in black patients with hemophilia. N Engl J Med 2009;360(16):1618–27.
21. Ashrani AA, Key NS, Soucie JM, Duffy N, Forsyth A, Geraghty S. Septic arthritis in males with haemophilia. Haemophilia 2008;14(3):494–503.
22. Kaufman JS, Cooper RS, McGee DL. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. Epidemiology 1997;8(6):621–8.
23. Duncan G, Magnuson K. Off with Hollingshead: socioeconomic resources, parenting and child development. In: Bornstein MH, Bradley RH, eds. Socioeconomic status, parenting, and child development. London, UK: Lawrence Erlbaum Associates, 2003.
24. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among U.S. children and adolescents, 2003–2006. JAMA 2008;299(20):2401–5.
25. Anderson SE, Whitaker RC. Prevalence of obesity among U.S. preschool children in different racial and ethnic groups. Arch Pediatr Adolesc Med 2009;163(4):344–8.
26. Aledort LM, Dimichele DM. Inhibitors occur more frequently in African-American and Latino haemophiliacs. Haemophilia 1998;4(1):68.
27. Carpenter S, Soucie JM, Sterner S, Presley RJ. Increased prevalence of inhibitors in Mexican-Hispanic patients with severe hemophilia A enrolled in the Universal Data Collection Project. ASH Annual Meeting Abstracts. Blood 2009;114(22):3488.
28. Jeffrey AE, Newacheck PW. Role of insurance for children with special health care needs: a synthesis of the evidence. Pediatrics 2006;118(4): e1027–38.
29. Skinner AC, Mayer ML. Effects of insurance status on children's access to specialty care: a systematic review of the literature. BMC Health Serv Res 2007;7:194.
30. Kogan MD, Newacheck PW, Blumberg SJ, et al. Underinsurance among children in the United States. N Engl J Med 2010;363:841–51.
31. Bisgaier J, Rodes KV. Auditing access to specialty care for children with public insurance. N Engl J Med 2011;364:2324–33.
32. Roosendaal G, Lafeber F. Prophylactic treatment for prevention of joint disease in hemophilia—cost versus benefit. N Engl J Med 2007; 357(6):603–5.