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The Role of Disease Severity in Influencing
Body Mass Index in People with Hemophilia

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M.D., Emory University, 2013

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An Abstract of
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James T. Laney School of Graduate Studies of Emory University
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ABSTRACT

Background: Hemophilia is a heredity bleeding disorder characterized by deficiency of clotting factor VIII or IX. Severity of hemophilia is determined by the blood levels of the deficient factor. The life expectancy for those affected now approaches that of the general population. Paralleling this trend, rates of chronic diseases including obesity are increasing among patients with hemophilia (PWH). It is not known how the severity of disease influences weight gain in PWH. HIV, chronic liver disease and decreased physical activity are more common in severe cases and may also cause weight gain. The central hypothesis of this study is that PWH with severe disease have higher body mass index (BMI) than those with mild and moderate disease.

Methods: To investigate the relationship between disease severity and BMI, a cross-sectional study was performed. Eighty-eight adult males with hemophilia were enrolled. Intermediary variables such as infectious complications of factor replacement (HIV and chronic liver disease from hepatitis C) and physical activity were also studied.

Results: Patients with mild disease had 13.81% higher BMI (95% CI 2.92-25.85, $p = 0.012$) than those with severe disease and patients with moderate disease had 9.36% higher BMI (95% CI -1.03-18.91, $p = 0.079$) than those with severe disease, after controlling for age. Among HIV negative subjects, patients with mild disease had 17.39% higher BMI (95% CI, $p = 0.016$) than those with severe disease and patients with moderate disease had 18.08% higher BMI (95% CI, $p = 0.018$) than those with severe disease. There were no patients with mild disease and HIV in this cohort.

Conclusions: This study suggests that mild and moderate hemophilia are associated with higher BMI than severe hemophilia, which is the opposite of the original hypothesis. The analysis also suggested that physical activity mediates the relationship. Effect modification by HIV status was detected. Further study into the cause of differences in BMI associated with disease severity is warranted and should evaluate family history, diet and socioeconomic status.

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INTRODUCTION

Hemophilia is a hereditary bleeding disorder caused by a deficiency of clotting factor VIII or IX. With appropriate replacement of the deficient factor, the use of safer blood products and effective treatment for human immunodeficiency virus (HIV) and hepatitis C, people with hemophilia (PWH) now enjoy a life expectancy that approaches that of the general population. [1-3] With this improving longevity, the rate of obesity in PWH parallels the rate for those without hemophilia. [4-7] Joint disease, a particularly burdensome consequence of obesity, is also a severe complication of hemophilia because of damage caused by repeated bleeding into joint spaces. [8-10] The increasing prevalence of obesity in the aging population of PWH may have an additive effect on joint disease, both as a risk factor for decreased physical activity and as a result of increased weight bearing. Furthermore, the relationship between hemophilia and body mass index can be conceptualized within the framework of disease severity. PWH who have severe disease, as measured by blood levels of the deficient factor, may be especially susceptible to obesity because of decreased physical activity and higher risk of blood-borne diseases such as HIV and hepatitis C.

There is currently little understanding of the association between body mass index (BMI) and disease severity. This study is a secondary analysis of cross-sectional data originally designed to examine a connection between hemophilia variables and bone density. In this current study, we present the results of an investigation into the association between body mass index and disease severity in a cohort of adults with

hemophilia. An understanding of how the sequelae of obesity are manifested in PWH is critical for adapting care to meet the needs of this aging population.

BACKGROUND

Hemophilia is an inherited X-linked recessive disorder caused by the deficiency of a single clotting factor in the coagulation cascade. Hemophilia A is characterized by a deficiency of clotting factor VIII affecting 1/5000 live male births and hemophilia B is characterized by a deficiency of clotting factor IX affecting 1/35000 live male births. The classification system for severity of disease is based on serum levels of the deficient factor. Those with less than 1% of normal factor (<0.01 IU/mL) have severe disease typically becoming clinically apparent within the first year of life. Those with 1-5% of normal factor (< 0.010-0.05 IU/mL) are considered to have moderate disease. Those with ≥ 5% and < 40% of normal factor (≥ 0.05 and < 0.40 IU/mL) are considered to have mild disease. (Table 1a) Clinical manifestations of hemophilia include spontaneous bleeding or excessive bleeding in response to trauma. Hemorrhage can occur anywhere in the body, with common sites including the central nervous, gastrointestinal, genitourinary, and musculoskeletal systems.

The mainstay of therapy for hemophilia is replacement of the deficient clotting factor. Prior to the advent of recombinant technology, factor concentrates were derived from the pooled, whole blood of donors. Since the early 1990s recombinant factor products have been available. Factor replacement therapy can occur either as a scheduled prophylaxis or on an intermittent, on-demand basis for treatment of bleeding events. Those with severe disease and who receive higher quantities of factor are at risk for developing an inhibitor, which is immunologic response to the factor replacement

product that blocks the replacement factor from facilitating clotting. This is a serious complication that prevents the standard therapy from adequately preventing bleeding episodes. Furthermore, prior to the advent of viral testing to screen blood products, factor replacement also introduced the possibility of acquiring viral illnesses hepatitis C or HIV. [1-3]

One of the most devastating and debilitating complications of hemophilia is chronic arthropathy from bleeding into the joint space. This bleeding causes pain and progressive deterioration of the joint, as intra-articular blood causes a destructive immune response. This resultant inflammation predisposes to future bleeding. The most frequently affected joints are those that bear weight including hips, knees and ankles. Several different types of joint replacements are performed in PWH as patients approach end-stage arthropathy and unremitting debilitation. Those patients with severe disease, meaning lower baseline factor levels, are known to have more frequent joint bleeding and disability. [11]

Despite these complications, adequate clotting factor replacement and prophylaxis have allowed PWH to enjoy a lifespan that approaches that of the general population. Current estimates project that PWH have a lifespan that ranges between 65 and 75 years, depending on disease severity whereas those without hemophilia live on average 76 years in the US. [1, 2] As PWH live longer, their risk for common public health issues such as overweight and obesity increases. Current estimates project that 18-33% of PWH are obese. [4, 6] Obesity is a devastating public health issue with a high cost-burden and wide-reaching complications, including diabetes, osteoarthritis and cardiovascular

disease. Prevalence of obesity and overweight in PWH is now estimated between 18 and 33% depending on geographic location. [6, 12] This trend parallels that which is occurring in the general population, where current estimates project that 25-33% of non-hemophiliac patients are obese. [5]

Obesity is measured by body mass index (BMI). A BMI > 30 kg/m^2 defines obesity, whereas a BMI of ≥ 25 kg/m^2 and < 30 kg/m^2 is considered overweight. A measurement of 18.5 kg/m^2 > and < 25 kg/m^2 is considered a normal BMI. (Table 1b)

The sequelae of obesity in both the general population and in PWH are wide-ranging and devastating. In the general population, patient-specific complications of obesity include joint disease from increased weight bearing, diabetes, hypertension and cardiovascular disease that may require surgical intervention and malignancy. The public health burden of obesity in the general population includes higher costs of care and disability frequently leading to unemployment. [5] In PWH, patient-specific complications include all of those present in the general population in addition those that are hemophilia-specific. Increased weight bearing likely causes increased stress on joints and induces further bleeding. [8-10] Furthermore, from a cost-based and public health standpoint, factor replacement becomes much more expensive as it is dosed by weight and obese patients are likely to require more factor to treat more frequent bleeding. [13] There are several known risk factors for obesity in the general population, including non-white race, lower socioeconomic status, comorbid illness, alcohol consumption, smoking, decreased physical activity, and increased caloric intake. [5] While these risk factors theoretically exist in equal prevalence in PWH, it is unknown how the severity of one's

hemophilia impacts BMI and weight gain. Prevalence studies have discrepant findings. Some studies have demonstrated that severe patients are heavier than those with mild or moderate disease, while another demonstrated no significant difference in BMI. [12, 14] To date, no study conducted analyses with adjustment of potential confounders and intermediaries to investigate a potential mechanism. There are several plausible risk factors for obesity that are associated with severe hemophilia that this study seeks to investigate. Those risk factors with disease severity associations include (1) decreased physical activity because joint disease and fear of traumatic bleeding, and (2) infectious complications of factor replacement including HIV and liver disease secondary to hepatitis C infection.

It is well known that decreased physical activity is associated with weight gain in any population, but PWH have disease-specific, severity-associated reasons to be more sedentary. Those with severe disease are more prone to spontaneous bleeding and have a higher incidence of traumatic bleeding. Thus, their risk for chronic arthropathy is much higher which severely limits physical activity as it becomes debilitating over time. Furthermore, avoidance of activity is a likely result of fearing traumatic bleeding in persons with severe disease. [15, 16] Up to 60% of PWH believe that activity limitation is a form of disease management. [17] Thus, PWH with severe disease are at risk for decreased physical activity and subsequent weight gain.

Infectious complications due to factor replacement, namely HIV and chronic liver disease due to hepatitis C infection, may be linked to weight gain. HIV is known to be associated with weight gain, primarily because of the adverse effects of antiretroviral

medication. [18, 19] It has also been suggested that HIV introduces pro-inflammatory, potentially metabolic derangements that predispose to weight gain. [18] While there is no direct evidence in the literature linking chronic liver disease due to hepatitis C infection to weight gain, it is a highly prevalent disease among PWH and was studied for its potential intermediary effect on the relationship between disease severity and BMI. Thus, the central hypothesis of this study is that severe hemophilia is associated with higher body mass index. This study will investigate two primary areas of inquiry: (1) whether or not the severity of one's disease influences BMI and (2) to what extent this association is mediated by physical activity and infectious complications such as HIV and chronic liver disease.

MATERIALS AND METHODS

Hypothesis

More severe disease is associated with higher body mass index in people with hemophilia.

Study Design

This is a cross-sectional observational study of a cohort of 88 male patients with hemophilia.

Study Population

All subjects being treated at the Emory Comprehensive Hemophilia Treatment Center who are males with hemophilia A or B (factor VIII or IX activity ≤ 40%) and age 25 years or older were eligible for inclusion. After Institutional Review Board approval, patients were sent information about the study and invited to participate. Subjects who had not responded to the mailed invitation were approached during their regularly scheduled visit.

Data Collection

Historical information was obtained from review of the medical record and from the patient with self-reported questionnaires, administered by between 4/22/2010 and 9/1/2011. Information obtained from review of the medical record included: type of

hemophilia, baseline level of factor VIII or IX, HCV antibody status, presence of HCV in serum and liver biopsy results. Information obtained from patient self-report included age (calculated by the difference between date of birth and calendar date of study visit), race, alcohol and tobacco use, past medical history, past medication history, HIV status, physical activity, current or past use of prophylaxis, and inhibitor status. A patient was deemed to have chronic liver disease if they had (1) positive hepatitis C antibody status and a positive viral load, (2) was receiving hepatitis C treatment and had any abnormal finding on liver biopsy (grade I fibrosis or more). Physical examination included measurement of height and weight to calculate BMI using World Health Organization standards. The patient's weight in kilograms was divided by the patient's height in meters squared.

Disease severity was classified into severe, moderate and mild categories, based on the percentage of a patient's clotting ability compared to a normal referent or baseline blood levels of the patient's deficient clotting factor. Those with less than 1% of normal factor (<0.01 IU/mL) were assigned the category of severe hemophilia. Those with greater than 1% of normal factor (< 0.010-0.05 IU/mL) were assigned the category of moderate hemophilia. Those with greater than to 5% and less than 40% of normal factor ($\geq$ 0.05 and < 0.40 IU/mL) were assigned the category of mild disease. Disease severity was modeled as a class variable with severe hemophilia as the referent.

The Framingham Physical Activity Index was used to quantify physical activity with a single score per participant. [20] The information on activity habits was obtained from patient interview at the baseline examination. This included average number of

hours spent per day in various levels of activity intensity, including no activity such as sleeping or lying down, sedentary activity such as sitting or standing, slight activity such as walking on level ground, moderate activity such as gardening or light carpentry, and heavy activity such as shoveling or digging. Each participant received a composite score that was derived from summing the products of number of hours spent in each category of activity intensity and a weighting factor that was derived from oxygen consumption of that particular activity. A score of less than or equal to 27 is considered sedentary. [20] The score was divided into quartiles and modeled as a class variable, with the least active quartile acting as the referent.

Data Analysis

A pre-analysis power calculation was conducted. For BMI as the outcome of interest and using the mean (IQR) BMI of 27.0 (6.2), 88 subjects gave 90% power to detect an R-squared of 0.05 with one independent variable and an R-squared of 0.54 with five independent variables. Power analysis was conducted using PASS v 11 (Kaysville, UT).

Cohort characteristics were summarized by means and standard deviations in the case of normally distributed data and by medians and the interquartile range (25th – 75th percentiles) in the case of skewed data. Differences in baseline characteristics between categories of disease severity was determined with chi-square tests for discrete variables, one way analysis of variance for continuous, normally distributed variables and non-parametric testing (Wilcoxon-rank sum test) for skewed, continuous variables. The

hypothesis was tested using linear regression, with BMI as the outcome of interest and comparisons of disease severity as the main exposure. Mild versus severe disease and moderate versus severe disease served as the two indicator variables representing disease severity in the analyses.

The required assumptions of linear regression were verified before proceeding with modeling stages. In order to satisfy normality, BMI was logarithmically transformed when studied as the outcome of interest in testing the first hypothesis. An examination of residual plots between the outcomes of BMI and tested covariates demonstrated random scattering. Collinearity was assessed with variance inflation factors and conditional indices. Correlation matrices were examined for homoscedasticity.

The association between disease severity and BMI tested with linear regression in a multiplicative model. Percent change in BMI for different levels of all covariates were obtained by reversing the logarithmic transformation with the following equation:

$$\% \text{ change in BMI} = [1 - e^{(\text{Parameter estimate} * \text{level of covariate})}] * 100.$$

A preliminary series of bivariate analyses were first conducted to assess crude relationships between BMI and disease severity, hemophilia and demographic covariates.

Bivariate associations between BMI and potential covariates and confounders were first assessed to determine those variables appropriate for model inclusion. A variable was a candidate for model inclusion if it demonstrated a p-value of less than 0.20 on bivariate analysis or was known to be associated with the outcome of interest. Variables were serially inputted into the model one at a time in several different orders to

evaluate confounding with the main exposure and the outcome of interest. Confounding was detected where parameter estimates changed by 10% or more.

Interaction was investigated with a two-step method. First, a stratified analysis was performed to examine the mean BMI for the three levels of disease severity both for the entire cohort and among the strata of a particular variable that was a suspected source of interaction. If this suggested that the effect of disease severity on BMI depended on the level of that particular variable, the percent change in BMI was then modeled among different strata of that variable and an interaction term was modeled. The p-value for the interaction term was used to confirm the presence of statistical interaction.

RESULTS

The characteristics of this population were first studied. (Table 3) The median age (IQR) of 42.5 (13.5), indicating an adult population, the vast majority of whom received potentially contaminated blood products before appropriate screening. A statistically significant difference with age was observed, where persons with severe disease were younger. All participants were male, in keeping with the hereditary pattern of hemophilia. This was a racially diverse population with 61.4% reporting white race and the remainder reporting African American, Hispanic or Asian race. The median BMI (IQR) was 27.0 kg/m^2 (6.2), indicating an overweight population. With regards to the distribution of BMI categories, 29 (33.0%) had normal BMI, 43 (48.9%) were overweight and 16 (18.1%) were obese. This population was evenly distributed with regards to disease severity, with 38 (43.7%) with severe, 24 (25.3%) with moderate, and 26 (31%) patients with mild hemophilia. With regards to the type of hemophilia, 71 (80.7%) had hemophilia A. The mean physical activity index was 32.5 ± 7, indicating an inactive population where the threshold for sedentary status is a score of less than or equal to 27. With regards to HIV, 26 participants were HIV positive (30%), 11 of whom were on anti-retroviral medication at the time of study. Lastly, 47 (53%) of the cohort had HCV chronic liver disease. Those with severe disease had a statistically significantly higher proportion of infectious complications.

The crude relationship between disease severity and BMI was first examined. (Table 4) Those with mild disease had a BMI 12.31% more than patients with severe

disease (95% CI 1.84-20.78, p=0.022). Those with moderate disease were found to have a BMI 9.41% greater than those with severe disease (-1.04-19.02, p = 0.084). The least active quartile of the physical activity score weighed 11.60% less than the most active quartile (95% CI -91.00- -0.006, p = 0.040). No other comparison of quartiles of physical activity was statistically significant. (Table 4)

The remaining tested covariates were not significantly associated with BMI, nor did they suggest a relationship with BMI, including HIV, chronic liver disease, current or past use of prophylaxis, age in 10-year increments and white versus any other race. (Table 4) A diagnosis of HIV was associated with a 5.94% decrease in BMI compared to those who are HIV negative (-14.31-3.25, p =0.198). A diagnosis of chronic liver disease was associated with a 5.14% decrease in BMI (-12.98-3.35, p = 0.228). Current prophylaxis use is associated with a 6.90% decrease in BMI (-15.87-3.03, p= 0.167). A 10-year increase in age was associated with 0.008% decrease in BMI (-0.34-0.33, p = 0.643). White race, as compared to any other self-reported race, was associated with a 0.88% increase in BMI (-7.63-10.18, p = 0.845). See Table 3 for the full results of all tested bivariate relationships with BMI.

The parameter estimate for the percent change in BMI for mild versus severe disease changed from 12.31% (95% CI 1.84-20.78) in the crude association to 13.81% (95% CI 2.92-25.85) in the age-adjusted model. (Table 4, Table 5a) The R-squared for the crude model was 0.064 and for the age-adjusted model was 0.077. Neither white versus any other race nor current use of prophylaxis demonstrated a significant effect on the parameter estimate for the percent change in BMI associated with mild versus severe

disease or moderate versus severe disease that required inclusion in the final model. See Table 5a for the race and prophylaxis-adjusted models.

In the age adjusted model, those with mild disease were estimated to have a BMI that is 13.81% greater than those with severe disease (95% CI 2.92-25.85, p = 0.012) and those with moderate disease were estimated to have a BMI that is 9.36% greater than those with severe disease (95% CI -1.03-18.91, p=0.079). (Table 5b)

The effect of each intermediary variable was then tested in an individual model with disease severity as the main exposure of interest, controlling for age (Table 6). The parameter estimates for percent change in BMI for mild versus severe disease and moderate versus severe disease were compared in the models only adjusted for age and in the models adjusted for age and the potential intermediary variable of interest (HIV positive status, presence of HCV liver disease and physical activity).

HIV positive status was modeled with disease severity. Those with mild disease had 13.25% higher BMI (95% CI -0.01-0-27.43, p = 0.039) than those with severe disease and those with moderate disease had 9.22% higher BMI (95% CI -1.54-21.15, p = 0.096) than those with severe disease. The R-squared = 0.077, the p-value for overall F-test = 0.149 and the p-value for HIV positive status = 0.865.

Liver disease was also modeled with disease severity, controlling for age. Those with mild disease had 13.66% higher BMI (95% CI 1.06-27.83, p = 0.033) than those with severe disease and those with moderate disease had 9.32% higher BMI (95% CI -1.45-21.26, p = 0.092) than those with severe disease. The p-value for liver disease was 0.963. The R-squared = 0.077 and the p-value for overall F-test = 0.150.

Physical activity, divided into quartiles, was also modeled with disease severity, controlling for age. Those with mild disease had 11.82% higher BMI (95% CI 0.06 - 24.32, p = 0.039) than those with severe disease and those with moderate disease had 9.31% higher BMI (95% CI -2.54-21.36, p = 0.095) than those with severe disease. The R-squared = 0.100 and the p-value for overall F-test = 0.065. (Table 6)

All potential intermediaries were modeled with disease severity, controlling for age. Those with mild disease had 12.44% higher BMI (95% CI -1.11-27.84, p = 0.074) than those with severe disease and those with moderate disease had 9.49% higher BMI (95% CI -1.70-21.96, p = 0.099) than those with severe disease. The R-squared = 0.100 and the p-value for overall F-test = 0.187. (Table 6)

Interaction was suggested when the data was stratified by HIV status. Among HIV negative patients, the median BMI (IQR) was 25.6 kg/m2 (8.0) for those with severe disease, 27.2 kg/m2 (6.2) for patients with moderate disease, and 27.3 kg/m2 (4.7) for patients with mild disease. (Table 7a) Among HIV positive patients, the median BMI (IQR) was 25.8 kg/m2 (3.1) for patients with severe disease and 23.5 kg/m2 (5.6) for patients with moderate disease. There were no patients with mild disease and comorbid HIV in this cohort. The stratified analysis demonstrates that, among patients with moderate disease, HIV negative patients have a median BMI that is 3.7 kg/m2 greater than those with HIV. (Table 7a)

In addition to a stratified analysis, interaction between HIV status and disease severity was investigated with a multivariate linear regression. Among HIV negative patients, those with mild disease had 17.39% (95% CI 3.00-33.78, p = 0.016) higher BMI

than those with severe disease. And those with moderate disease had 18.08% (95% CI 2.87-35.55, p = 0.018) higher BMI than those with severe disease. (Table 7b) On the other hand, among HIV positive patients, those with moderate disease had a BMI that was 4.22% (95% CI -16.98-10.73, p = 0.567) less than those with severe disease. (Table 7c) We were unable to determine the percent change in BMI comparing mild to severe patients among HIV positive patients due to unpopulated strata. The p-value for an interaction term between moderate versus severe hemophilia and HIV status was used to further assess interaction. The p-value was 0.057. These models control for age only. Age demonstrated a parameter change of greater than 10% for disease severity, though age, race and current prophylaxis use were investigated for potential confounding properties.

DISCUSSION

The primary aim of this study was to evaluate the influence of hemophilia disease severity on BMI. There are several determinants of higher body mass index that are caused by low baseline factor levels. The central hypothesis of this study was that more severe hemophilia is associated with higher body mass index. We also sought to study the role of HIV, chronic liver disease caused by HCV and decreased physical activity in mediating the relationship between disease severity and BMI. The prevalence of obesity is increasing in PWH, which highlights the importance of understanding the disease-specific risk factors for increasing BMI in an especially vulnerable population.

This study demonstrates that mild and moderate hemophilia are associated with a higher BMI than severe disease. Confounding was detected when age was modeled with disease severity and it was controlled for in all subsequent analyses. After adjustment for age, it was found that those with mild disease had a BMI of 13.81% higher (95% CI 2.92-25.85, $p = 0.012$) and those with moderate disease had a BMI of 9.36% higher (95% CI -1.03-18.91, $p = 0.079$) than those with severe disease. Physical activity, HIV and chronic liver disease caused by HCV did not account for a significant amount of the weight gain associated with comparison of disease severity levels. This was evidenced by comparing the parameter estimates in the crude and adjusted models.

To date, three prevalence studies reported discrepant findings on the relationship between disease severity and BMI. This is the first study to investigate a causal mechanism between increasing BMI and disease severity among adults and quantify a

change in BMI in comparing different levels of hemophilia severity. This study was performed on a uniformly adult, racially diverse patient population with a larger cohort than prior studies, which may have accounted for different results. Revel-Vilk et al found that younger boys with severe disease were more likely to be obese in a larger cohort, but did not perform adjustment for age as a potential confounder. [14] It may be that younger patients have yet to receive sufficient lifestyle counseling to affect health behaviors that lead to a lower BMI. Majumdar et al found that, in a cohort of children and adults PWH from Mississippi, no significant difference in obesity trends according to disease severity. [12] However, potential confounders that are geographically specific to a region with extreme obesity trends may have masked an association between disease severity and BMI. Hofstede et al performed a prevalence analysis of a cohort of adults and found that overweight was more prevalent in PWH with non-severe disease compared those with severe disease while obesity was equally prevalent. [6] It possible that severe hemophilia is a risk factor for weight gain in childhood and adolescence but that over time either more healthy diets are adopted by adults with severe hemophilia or other factors into play.

Differing degrees of health consciousness correlating with disease severity one potential explanation as to why patients with milder disease have higher BMI, particularly among those without HIV. Those with severe disease practice more hemophilia-related health maintenance, such as prophylaxis and frequent factor dosing. This effect is magnified among those with HIV as they adhere to complicated antiretroviral regimens. While this study was underpowered to address this possibility

among HIV positive patients, we did observe the opposite effect with statistical significance in HIV negative patients. It is possible that the discipline learned from disease management is applied to other aspects of self-management that affect weight gain, including diet and aspects of physical activity unmeasured by the Framingham index that influence weight management. Also, with more frequent exposure to physicians and hemophilia treatment centers, those with severe disease have the opportunity receive more lifestyle counseling than their counterparts with milder hemophilia. Perhaps these patients extend those behaviors to overall lifestyle management.

There are several limitations to this study. The main limitation of this study is a lack of statistical power. This is a rare disease, so power is a challenge. There were no patients with mild disease and HIV in this cohort. Some cross sectional data was used, including BMI, HIV status, HCV chronic liver disease, prophylaxis use and age. It is important to note, however, that disease severity is a longitudinal variable and may be causally linked to BMI. Though our population is racially diverse, it is important to note that all subjects were recruited from a single center. Unmeasured factors in this study include socioeconomic status, diet and family history, among others.

This study is strengthened by adjustment for intermediary and demographic covariates. Age, race and prophylaxis use were tested for confounding. HIV status, presence of HCV chronic liver disease and physical activity were examined for their role in mediating the relationship between BMI and disease severity. Age was identified as a confounder and activity was found to account for some of the weight gain caused by

milder forms of hemophilia. Also, HIV and HCV liver disease were examined for interaction, which lends itself to the thoroughness of this analysis.

As PWH enjoy longer lives, they have more opportunity to acquire chronic diseases that afflict the general population. Obesity is of particular concern, with the patient complications among PWH, involving worsening hemophilic arthropathy, secondary to increased weight bearing. It is of particular interest, in managing this aging population, to inform guidelines of care and tailor preventive measures. Severe hemophilia, with its sequelae of activity limitations partially due to joint disease and higher rates of infectious complications linked to metabolic syndrome, was hypothesized to be a risk factor for weight gain. Regardless as to the underlying mechanism, care of patients with moderate and mild disease must include regular lifestyle coaching to address risk factors for weight gain.

The intermediaries considered in this analysis account for only a small portion of the relationship between disease severity and body mass index. This is evidenced by the small change in percent increase in BMI that was observed in comparing mild to severe disease and moderate to severe disease when HIV, chronic liver disease and physical activity. Furthermore, the R2 increased from 0.072 to 0.081 in moving from the crude to full model, which demonstrates only a ten percent gain in understanding the variability. With only 8.1% of the variation in BMI explained by the full model, we must consider other unmeasured factors that influence BMI in this study population. It is likely that the same factors at work in the general population that cause overweight and obesity,

including diet, family history, and endocrinopathies, are also causing weight gain in PWH. Further directions of study include measures of these factors.

The detection of interaction between HIV and disease severity suggests that HIV negative patients with mild and moderate hemophilia have an even greater percent increase in BMI. No difference was observed between different strata of HIV for persons with severe disease. While the interaction term was not statistically significant, the differences observed in median BMI suggest effect modification that this study is underpowered to detect. Persons with moderate disease have an even higher percent increase in BMI than the aggregated, non-stratified analyses. Among HIV negative PWH, we detected a statistically significant change in BMI in comparing moderate to severe disease. This analysis indicates that counseling PWH on health habits and lifestyle management should take HIV status into account, with a higher degree of suspicion for weight gain among those with moderate disease without HIV.

Overall, this study suggests that, in this cohort of adult males with hemophilia, those with severe disease have a lower BMI than those with mild or moderate disease. Further direction for study would include measuring other actors known to cause obesity that were unmeasured here, including family history, diet, socioeconomic status and comorbidities.

As PWH enjoy longer lives, they have more opportunity to acquire chronic diseases that afflict the general population. Obesity is of particular concern as an added burden of mortality and morbidity among PWH, particularly with regards to hemophilic arthropathy. An understanding of how severity of hemophilia affects weight gain will

inform guidelines of care in an aging population, the characteristics of which are shifting. This study highlights the importance of regular lifestyle coaching disease to address risk factors for weight gain, especially among HIV negative patients and those with moderate and mild disease. Further study to understand the influence of other measures of health consciousness, including a more thorough assessment of physical activity and diet, may reveal more about the relationship between disease severity and body mass index.

Table 1a: Severity classifications of hemophilia in general clinical use

Disease severity	% Factor Level	Age at Diagnosis
Severe	<1%	<1 year of age
Moderate	1-5%	1-2 years of age
Mild	>5% and <40%	> 2 years of age

Table 1b: Classification of body mass index (BMI) in general clinical use

Category	Corresponding BMI
Normal	18.5 $kg/m^2 \geq$ and < 25 kg/m^2
Overweight	25 $kg/m^2 \geq$ and < 30 kg/m^2
Obese	30 $kg/m^2 \geq$ a

Table 2: Factors that may be associated with increasing body mass index

Hemophilia Specific	**General Population**
Disease severity	Age
Hemophilic joint disease	Non-white race
HIV	Physical activity
Chronic liver disease	Alcohol use
Prophylaxis use	Tobacco use
Presence of an inhibitor	
Hemophilia A	

Table 3: Cohort characteristics of study population

Characteristic	Overall	Mild (n=26)	Moderate (n=24)	Severe (n=38)	P-value
Age, years (IQR)	42.5 (13.5)	48.5 (31)	37.5 (13.5)	40.3 (18.0)	0.086*
Caucasian race (%)	54 (61.4)	19 (73.1)	12 (50)	23 (60.5)	0.120
Median BMI (IQR)	27.0 (6.2)	27.3 (4.7)	26.2 (6.9)	25.4 (6.4)	0.259*
Haemophilia A (%)	71 (80.7)	19 (73.1)	19 (79.2)	33 (86.8)	0.192
Prophylaxis use (%)	20 (22.7)	2 (7.7)	4 (16.7)	14 (36.8)	0.017
Physical activity ± SD	32.5 ± 7	34.5 ± 7.4	31.7 ± 5.7	31.5 ± 7.5	0.216
HIV positive (%)	26 (30)	0 (0)	8 (33.3)	18 (47.4)	<0.001
HCV chronic liver disease (%)	47 (53)	7 (26.9)	13 (54.6)	28 (73.7)	<0.001
Alcohol use (%)	45 (51)	16 (57.7)	13 (54.2)	19 (50)	0.633
Tobacco (%)	18 (20)	6 (23.2)	3 (12.5)	9 (23.7)	0.723
Chronic pain medication (%)	9 (10.2)	2 (7.7)	3 (12.5)	4 (10.5)	0.852

SD, standard deviation; IQR, interquartile range; BMI, body mass index; HIV, human immunodeficiency virus; ARV, anti-retroviral; WFH, World Federation of Haemophilia; HCV, hepatitis C virus

*Wilcoxon-rank sum test used

Table 4: Bivariate associations with BMI*

Variable	% change in BMI (95% CI)	P-value
Mild vs severe hemophilia	12.31 (1.84-20.78)	0.022
Moderate vs severe hemophilia	9.41 (-1.04-19.02)	0.084
Physical activity (quartiles)		
Least active (Q1) vs most active (Q4)	-11.60 (-91.00- -0.01)	0.041
More active (Q2) vs least active (Q4)	-4.58 (-14.52-6.45)	0.399
Less active (Q3) vs least active (Q4)	-6.45 (-18.37-7.25)	0.339
HCV chronic liver disease	-5.14 (-12.98-3.35)	0.228
HIV positive	-5.94 (-14.31-3.25)	0.198
Current use of prophylaxis	-6.90 (-15.87-3.03)	0.167
Age (10 year increase)	-0.008 (-0.34-0.33)	0.643
Caucasian race vs other	0.88 (-7.63-10.18)	0.845

BMI, body mass index; CI, confidence interval; Q, quartile; HIV, human immunodeficiency virus

* Indicates logarithmic transformation

Table 5a: Investigating potential confounders

Model	% Change in BMI Mild vs Severe (95% CI)	% Change in BMI Moderate vs Severe (95% CI)	R^2
Crude	12.31 (1.84-20.78)	9.41 (-1.04-19.02)	0.064
Crude + A	13.81 (2.92-25.85)	9.36 (-1.03-18.91)	0.077
Crude + R	12.52 (1.73-24.44)	9.24 (-1.45-21.10)	0.067
Crude + P	11.11 (0.01-20.98)	8.60 (-2.18-20.56)	0.072
Crude + ARP	12.72 (1.11-25.65)	8.35 (-2.48-20.38)	0.084

BMI, body mass index; CI, confidence interval
1 – First adjusted model = Crude + age, race, prophylaxis
A = age, R = race, P = prophylaxis

Table 5b: Age adjusted model

Variable	% Change in BMI	95% Confidence Limits	
Mild vs severe	13.81	2.92	25.85
Moderate vs severe	9.36	-1.03	18.91

BMI, body mass index

Table 6: Effects of intermediaries on the relationship between disease severity and percent change in BMI[§]

Model	% Change in BMI Mild v Severe (95% CI)	% Change in BMI Moderate v Severe (95% CI)	R^2
First adjusted	13.81 (2.92-25.85)	9.36 (-1.03-18.91)	0.077
+ HIV	13.25 (0.66-27.43)	9.22 (-1.54-21.15)	0.077
+ liver disease	13.66 (1.06-27.83)	9.32 (-1.45-21.26)	0.077
+ activity	11.82 (0.58-24.32)	9.31 (-2.54-21.36)	0.100

BMI, body mass index; HIV, human immunodeficiency virus; SD, standard deviation
§ - controlling for age

Table 7a: Mean BMI according to disease severity and HIV status

Category of Disease Severity	HIV Negative Median BMI (IQR)	HIV Positive Median BMI (IQR)
Severe	25.6 (8.0)	25.8 (3.1)
Moderate	27.2 (6.2)	23.5 (5.6)
Mild*	27.3 (4.7)	x

HIV, human immunodeficiency virus; BMI, body mass index; SD, standard deviation
*No patients with mild disease and HIV

Table 7b: Relationship between disease severity and BMI among HIV negative patients

Category of Disease Severity	% Change BMI (95% CI)	P-value
Mild vs severe	17.39 (3.00-33.78)	0.016
Moderate vs severe	18.08 (2.87-35.55)	0.018

HIV, human immunodeficiency virus; BMI, body mass index; SD, standard deviation

Table 7c: Relationship between disease severity and BMI among HIV positive patients

Category of Disease Severity	% Change BMI (95% CI)	P-value
Mild vs severe*	x	x
Moderate vs severe	-4.22 (-16.98-10.73)	0.567

HIV, human immunodeficiency virus; BMI, body mass index; SD, standard deviation
*No patients with mild disease and HIV in this cohort

APPENDIX

The Framingham Physical Activity Index

The Framingham Physical Activity Index is a method for quantifying physical activity based on the metabolic requirements of various levels of intensity of activity. It is calculated by multiplying the average hours of sedentary, slight, moderate and heavy activity by a weighting factor that represents relative amounts of oxygen consumption of each physical state. The patient is interviewed about sleep habits, physical activity related to work and extracurricular activities.

Level of activity, examples and the associated weighting factor [20]

Level of Activity	Examples	Weighting Factor
No activity	Sleeping, lying down	1.0
Sedentary	Sitting, standing	1.1
Slight	Walking on level ground	1.5
Moderate	Gardening, light carpentry	2.4
Heavy	Shoveling, digging	5.0

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