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High prevalence of overweight/obesity in adult persons with hemophilia in Utah and a review of the literature

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Abstract

Objectives: 1) To determine the prevalence of overweight/obesity in adult persons with hemophilia (PwH) in Utah, and to explore the association between age, disease severity and race with BMI. 2) To provide recent data on the prevalence of overweight/obesity in the hemophilia population via a review of the literature.

Methods: We conducted a retrospective cross section study of adult PwH who were seen at a Utah hemophilia treatment center from January 1, 2017 to December 31, 2019. The electronic database PubMed was searched for studies with observation periods from 01 January 2012 to 31 December 2019.

Results: The age-adjusted prevalence for overweight/obesity in the adult Utah hemophilia population was higher than the overall Utah population and the general US population. After adjusting for race and age, mild hemophilia was associated with a 7.7% higher BMI (95% CI, 0.023 – 15.98%, P<0.05). Review of the literature demonstrated high levels of overweight/obesity in hemophilia communities globally with considerable heterogeneity between studies.

Conclusions: Despite increasing awareness, prevalence of overweight/obesity in the hemophilia population remains high in comparison to the general population. There is a critical need to address this issue acutely at hemophilia treatment centers due to the considerable burden of obesity.

Keywords

Hemophilia; obesity; overweight; prevalence

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Authorship

Contributions: M.Y.L. designed the study, analyzed the data and wrote the manuscript. G.W. and A.P.P. analyzed the data and reviewed the manuscript. P.B. and G.M.R. reviewed and edited the manuscript; all authors approved the final version of the manuscript.

Conflict-of-interest disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

Introduction

Hemophilia A and B are rare X-linked congenital bleeding disorder caused by a deficiency in coagulation factor VIII (FVIII) or factor IX (FIX), respectively. It is characterized by bleeding manifestations, including spontaneous bleeding episodes into muscles and joints, especially in persons with severe hemophilia (FVIII or FIX activity levels <1 international units per deciliter [IU/dl]) [1, 2]. Joint bleeding, which commonly affects weight-bearing joints, such as knees or ankles, can lead to the development of painful, disabling hemophilic arthropathy [3]. As a result, persons with hemophilia (PwH) often have limited exercise potential resulting in a sedentary lifestyle and difficulties in maintaining a healthy weight. Once overweight, the excess adiposity further accelerates loss-of-mobility in weight bearing joints, leading to further functional impairment [4]. This then becomes a vicious cycle that is difficult to overcome.

The use of prophylaxis clotting factor concentrates, regardless of age of initiation, is effective in reducing joint bleeding rates, total bleeding rates, and target joint bleeding [5]. More importantly, the early initiation of prophylaxis prior to age 4 years has been shown to result in preservation of overall joint motion [5]. However, this benefit was offset by having a higher than normal weight (overweight or obese) [5].

Obesity is a major public health problem in the US, especially in the adult population. From 1999 – 2000 through 2017 – 2018, the age-adjusted prevalence of obesity among US adults increased from 30.5% to 42.4% [6]. In addition, the prevalence of obesity varies by race and age groups. Among adults, the prevalence of obesity was highest in non-Hispanic black adults (49.6%) and among middle-aged adults aged 40 – 59 years (44.8%) [6].

To date, there have been several papers reviewing the epidemiological data on the prevalence of overweight and obesity in the US hemophilia population, as well as globally, with a call for increased awareness, diagnosis and recommended strategies for prevention and management [7–9]. However, these epidemiological studies occurred predominantly in the 1990s to late 2000s [10–15].

The aims of this study are 2-fold. Firstly, we set out to determine the prevalence of overweight and obesity in adult PwH in Utah and to explore the association between age, disease severity and race with BMI. Second, we sought to provide recent data on the prevalence of overweight and obesity in the hemophilia population via a systematic review of the literature.

Materials and Methods

Study population

The Utah Center for Bleeding & Clotting Disorders at the University of Utah Health is the only adult hemophilia treatment center (HTC) in the state of Utah. Adult persons with hemophilia (> 18 years of age) who have been seen at least once from January 1, 2017 to December 31, 2019 were included in this study. The following information were collected from the last clinic visit in the electronic medical record: age on the date of the last clinic

visit, self-reported race and ethnicity, hemophilia severity, height, and weight. Race and ethnicity were reported as White, Asian, Hispanic (corresponding to White or Black race), American Indian/Alaskan Native and other.

Definitions

Hemophilia severity was classified as either severe (FVIII or FIX activity level <1 IU/dL), moderate (FVIII or FIX activity level 1 – 5 IU/dL) or mild (FVIII or FIX activity level >5 IU/dL and <40 IU/dL) [16]. PwH were divided into age categories that covered young adults (18 to 35 years), middle age (36 to 55 years), and older adults (56 years and older). Body mass index (BMI) was calculated based on the following equation, $BMI = \text{weight(kilograms)}/[\text{height (meters)}]^2$. As per definitions by the Centers for Disease Control and Prevention (CDC), a normal BMI was defined as a BMI in the range 18.5 kg/m² to <25 kg/m². Underweight was defined as a BMI <18.5 kg/m², overweight was defined as a BMI 25 to 29.9 kg/m² and obesity was defined as a BMI ≥ 30 kg/m². For the obesity category, this was further subclassified as class 1 (BMI 30 to <35 kg/m², class 2 (BMI 35 to <40 kg/m²) and class 3 (BMI ≥ 40 kg/m²). Our focus was on the prevalence of overweight or obesity “overweight/obesity”. As this was a retrospective study, the study protocol was deemed exempt and approved by the University of Utah Institutional Review Board.

Statistical analysis for Utah study population

Descriptive statistics were used for the study population. Continuous variables were reported as medians and inter-quartile ranges (IQR). The crude prevalence of overweight/obesity was determined for the overall study population. The age-adjusted prevalence of overweight/obesity was calculated based on direct standardization to the 2000 U.S. Standard Population [17]. The prevalence of overweight and obese was also calculated for the different patient groups: age category, disease severity and race. Due to limited numbers, race and ethnicity were analyzed as non-Hispanic whites vs. all others. The chi-squared or Fisher’s exact test (when expected cell counts were less than 5) was used to compare the differences in prevalence of overweight/obesity with age, disease severity and race.

Linear regression was used to compare BMI with age, disease severity and race, where BMI was logarithmically transformed to achieve approximate normality. Hemophilia disease severity was categorized into mild or non-mild (moderate and severe) severity. We determined the percent difference in BMI corresponding to white vs non-white and mild vs non-mild disease by exponentiating the regression model coefficients, subtracting one and multiplying by 100%. Age was divided by 10 to enable interpretation of results as a 10-year increase in age. All three variables were included in the multivariable model as they were found to be associated with BMI or previously known to be associated with BMI. Ninety-five percent confidence intervals (CIs) and p-values were also reported. Statistical significance was assessed at the 0.05 level and all tests were two-tailed.

Studies selected for literature review

To determine the prevalence of overweight/obesity in the adult (≥ 18 years of age) hemophilia population, we searched the electronic database PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) for published studies where the observation period was

within the last 8 years (01 January 2012 – 31 December 2019). The search strategies used are available in Supplemental Material 1. If a study encompassed at least 2 years of the specified observation period, the study was included. If the observation period was not stated, then the year of publication was used instead. References cited within these studies were also manually reviewed for additional studies of interest. Abstracts from the American Society of Hematology annual meetings (2012 – 2019), the International Society on Thrombosis and Hemostasis meetings (2012 – 2019) and the World Federation of Hemophilia biannual meetings (2012 – 2020) were also comprehensively searched. Studies specifically looking at the pediatric hemophilia population were excluded. If a study included hemophilia patients between the ages of 18 and 21, but was part of a pediatric study, the study was excluded if the adult data was not extractable. Studies specifically looking at a cohort of PwH with hepatitis B, hepatitis C, cardiovascular disease and/or HIV were excluded to avoid confounding the association between hemophilia and obesity. Articles were also excluded if they were non-English language and non-human articles, contained no original data, no relevant data, or were duplicate studies. For each study included, data regarding the number of hemophilia patients, age of the study population, country of enrolled patients and prevalence of overweight/obesity were extracted.

Statistical analysis for literature review

Studies were grouped by region (North America, Europe and global). Pooled estimates were calculated using a random-effects model. The pooled prevalence of overweight/obesity overall and by region were each expressed as weighted mean prevalence with 95% CIs. Heterogeneity among studies was quantified using between-study variance τ^2 , the percentage of variation due to heterogeneity rather than chance I^2 , and H^2 statistics [18]. Cochran's Q test assessed statistically significant differences in heterogeneity across studies. All statistical analyses were performed using the meta commands in Stata v16.1 (College Station, TX, USA) [19].

Results

Study population characteristics

A total of 149 adult PwH were seen at the Utah Center for Bleeding & Clotting Disorders at the University of Utah Health within the study period. Five PwH had no height documented and were excluded from the study. The baseline demographics of the 144 adult PwH are presented in Table 1. Over two-thirds of the study population have hemophilia A, and over half have severe hemophilia. The study population largely self-identified as White ($n=124$, 86.1%).

The median age was 33 years (IQR, 25 – 45). Over half of the cohort ($n=84$, 58.3%) were in the young adults category, whereas only 9.7% ($n=14$) were in the older adults category. The oldest patient was 79 years and the youngest was 18 years. The median BMI was 27.5 kg/m² (IQR, 23.6 – 31.0), falling within the overweight range. A normal BMI was found in 31.3% ($n=45$), whereas 38.2% ($n=55$) were overweight and 28.5% ($n=41$) were obese. Three adult PwH were in the underweight category. The highest BMI was 45.8 kg/m² and the lowest BMI was 17.3 kg/m².

Prevalence of overweight/obesity

Two-thirds of the study population were either overweight (38.2%, $n=55$) or obese (28.5%, $n=41$). The age-adjusted prevalence of overweight/obesity in adult PwH and comparisons with the Utah population and general US population are shown in Table 2 [20, 21]. The age-adjusted prevalence of overweight/obesity adult PwH was 73.2% (95% CI, 58.5 – 87.7), whereas for an obese adult PwH, the age-adjusted prevalence was 31.4% (95% CI, 21.8 – 41.0). The prevalence of overweight/obesity in adult PwH in Utah based on age category, disease severity and race are shown in Figure 1.

Prevalence by age category, disease severity and race

Across all age categories, the majority of PwH were overweight/obese. With increasing age, the prevalence of overweight adult PwH increased from 36% ($n=30$) in young adults to 57% ($n=8$) in older adults. Similarly, the prevalence of adult PwH with obesity increased from 21% ($n=18$) in young adults to 36% ($n=5$) in older adults. The prevalence of overweight/obesity was significantly lower for PwH in young adults than for those in middle age ($P < 0.05$) and older adults ($P < 0.05$) (Figure 1). There was no significant difference in this prevalence between middle age PwH and those in older adults ($P > 0.05$).

The prevalence of overweight/obesity was significantly higher for PwH with mild disease, as compared to moderate disease ($P < 0.05$) or severe disease ($P < 0.05$). The difference in this prevalence was not statistically significant between those with moderate and severe disease ($P > 0.05$). There were no differences in overweight/obesity by race.

Bivariate and multivariable analysis

On bivariate analysis, persons with mild hemophilia were found to have a 10.6% higher BMI than persons with moderate or severe hemophilia (95% CI, 3.24 – 18.6%, $P < 0.05$). For each 10-year increase with age, BMI increased by 3.16% (95% CI, 0.76 – 5.61%, $P < 0.05$). After adjusting for race and age category, only mild hemophilia was associated with a 7.7% higher BMI (95% CI, 0.023 – 15.98%, $P < 0.05$) (Table 3).

Pooled prevalence for overweight/obesity

A total of 162 records were identified and assessed for inclusion by a single reviewer (M.Y.L). Of these, 150 were excluded and 12 studies remained in the final analysis (Figure 2 and Table 4) [22–33].

Using epidemiological observation data from the last 8 years (2012 – 2019), the prevalence of being overweight/obese in adult PwH varied widely from 12% to 74.6%. In North America, this prevalence ranged from 59.3% to 74.6% ($I^2=36.98\%$ of variability due to heterogeneity). A similar prevalence but with wider variability was seen in Europe, ranging from 46.6% in Germany to as high as 73.6% in Czech Republic ($I^2=92.55\%$). Globally, there were only 3 epidemiological studies reporting the prevalence of overweight/obese in PwH: 12% in Ivory Coast, 15.3% in Brazil and 54% in Taiwan ($I^2=95.40\%$).

The overall pooled prevalence of overweight/obesity in the global adult hemophilia population was 50.7% (95% CI, 36.9 – 64.6%) (Supplemental Figure 3A). When assessing

the North American and European population alone, this estimation rose to 66.1% (95% CI, 59.6 – 72.6%) and 56.5% (95% CI, 40.4 – 72.7%), respectively.

Focusing on the prevalence of obesity only, this ranged from 7.7% in Germany to 40.7% in Kentucky, USA. The overall pooled prevalence of obesity in the global adult hemophilia population was 22.5% (95% CI, 16.3 – 28.7, $I^2 = 88.94\%$) (Supplemental Figure 3B). This estimation was higher in the North American population (28.7%, 95% CI, 22.9 – 34.5, $I^2 = 64.05\%$) but lower in the European population (14.4%, 95% CI, 8.2 – 20.6, $I^2 = 72.73\%$).

Discussion

This cross-sectional retrospective study indicates that 2 out of 3 adult PwH in the state of Utah have higher than normal weight, of which adult PwH with obesity make up 28.5%. However, given that Utah is known to be the youngest state population in the US with a median age of 31 years vs 38.2 years nationally, we calculated the age-adjusted prevalence for comparison purposes [34]. After adjusting for age, the prevalence for overweight and obese in the adult Utah hemophilia population was higher than the overall Utah population and the general US population. As for obesity, the prevalence in the adult Utah hemophilia population was higher than the Utah population but similar to the general US population. This is particularly concerning since Utah is a relatively healthy state, consistently ranking fifth from the bottom (46 out of 51) for obesity for the past 5 years (2013 – 2017) [35]. These findings are alarming and highlight a critical need to address the issue acutely at our HTC. Despite the increased awareness, we do not routinely address the impact of weight and lack a protocol to do so, similar to what has been reported by the majority of US HTCs [36, 37]. We plan to address this deficiency by formally incorporating guidelines and lifestyle interventions as described in the review by Wilding *et al* as part of our hemophilia comprehensive visit [8].

It has been suggested that the higher prevalence of overweight/obesity may be due to chronic hemophilic arthropathy in the severe hemophilia population, which make up half of the overall hemophilia population. However, the association between overweight/obesity with hemophilia severity has been conflicting, either showing no association or a negative association with severe hemophilia [12, 38, 39]. In our study, we found that PwH with mild severity had higher BMI, which persisted after adjusting for age and race. To some extent, this corroborates the findings of McNamara *et al* who reported that severe hemophilia was associated with 15.1% lower BMI as compared to non-severe hemophilia [38]. A key difference in our study is that we looked at the association of BMI among mild hemophilia vs non-mild (moderate and severe) hemophilia. This categorization was made a priori due to the fact that more than half of the moderate severity cohort in our study were on prophylaxis factor concentrate regimen, suggesting that they had a more severe phenotype, similar to those with severe hemophilia.

Results from the literature review demonstrate high levels of overweight/obesity in hemophilia communities globally. However, the majority of epidemiological data are from North American and Europe, and there is considerable heterogeneity between studies which should lead to caution in the interpretation of the results. More data outside developed

countries are needed to further clarify the prevalence of overweight/obesity in the global hemophilia population, particularly in developing countries. This need could feasibly be addressed by incorporating overweight/obesity data elements as part of the questionnaire in the World Federation of Hemophilia (WFH) Annual Global Survey that is completed nationally by WFH members. Emerging data can be used to increase awareness, and advocate for better care with targeted strategies for the hemophilia population.

Our study had several strengths. For the variables age and BMI, we determined associations using BMI classifications (normal, overweight and obese) and age categories, as well as age and BMI as continuous variables. The former method is helpful for visualization and is easier to conceptualize, but the cutoff used, especially in the age categories, can over- or under-estimate the effect seen. The use of continuous variables in a multivariable analysis removes this limitation. As for the pooled prevalence of overweight and/or obesity, we only used epidemiological studies from the past 8 years to determine a current estimate as the prevalence of obesity in the US, and globally continues to increase on an annual basis.

The main limitation of this study is that besides age, race and hemophilia severity, we did not explore other possible associations such as human immunodeficiency virus (HIV) status, hepatitis C status, chronic liver disease, or physical activity – all of which could have confounded the results. A second limitation is that there are a small number of adult PwH whose care is being actively managed by community oncology practices due to insurance restrictions. Thus, our findings may not be representative of the Utah haemophilia population. However, in the last 2 years, due to efforts from the Payer Relations and Contracting Department at our institution, the Utah Center for Bleeding & Clotting Disorders is now an in-network facility for a majority of payers, resulting in a transfer of care of adult PwH to our HTC for ongoing management. Third, our hemophilia cohort was predominantly White, which is representative of the state of Utah, but may not be generalizable to the general US population.

In conclusion, we demonstrated that the prevalence of overweight/obesity in the Utah hemophilia population is alarmingly high, especially after adjusting for age, with mild hemophilia disproportionately affected as compared to non-mild hemophilia. The obesity burden on the hemophilia population cannot be overstated given that obesity worsens hemophilic arthropathy, influences pharmacokinetics of weight-based clotting factor dosing, and is a risk factor for cardiovascular diseases, among others. If we hope to make an impact, weight management should be formally incorporated into the hemophilia care pathway, and considered equally as important as managing breakthrough bleeds during the comprehensive care visit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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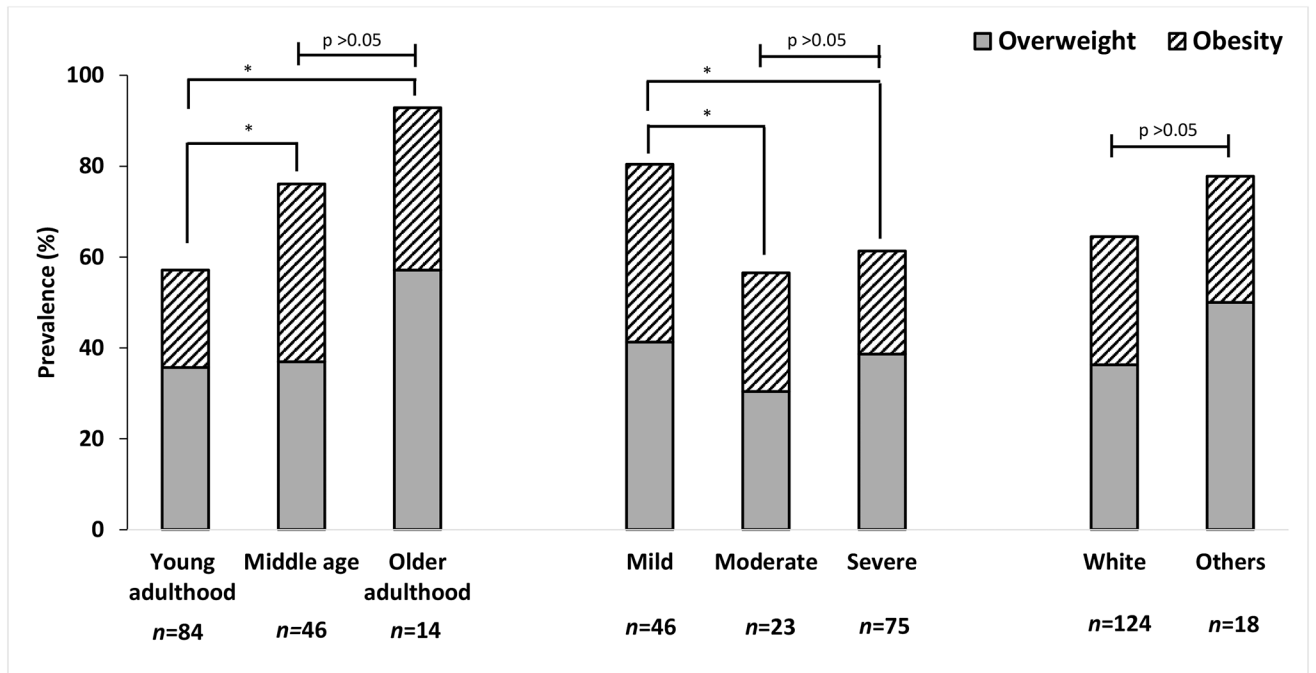


Figure 1. Prevalence of being overweight and obese among adult PwH in Utah based on age category, severity of disease and self-reported race
 * P < 0.05

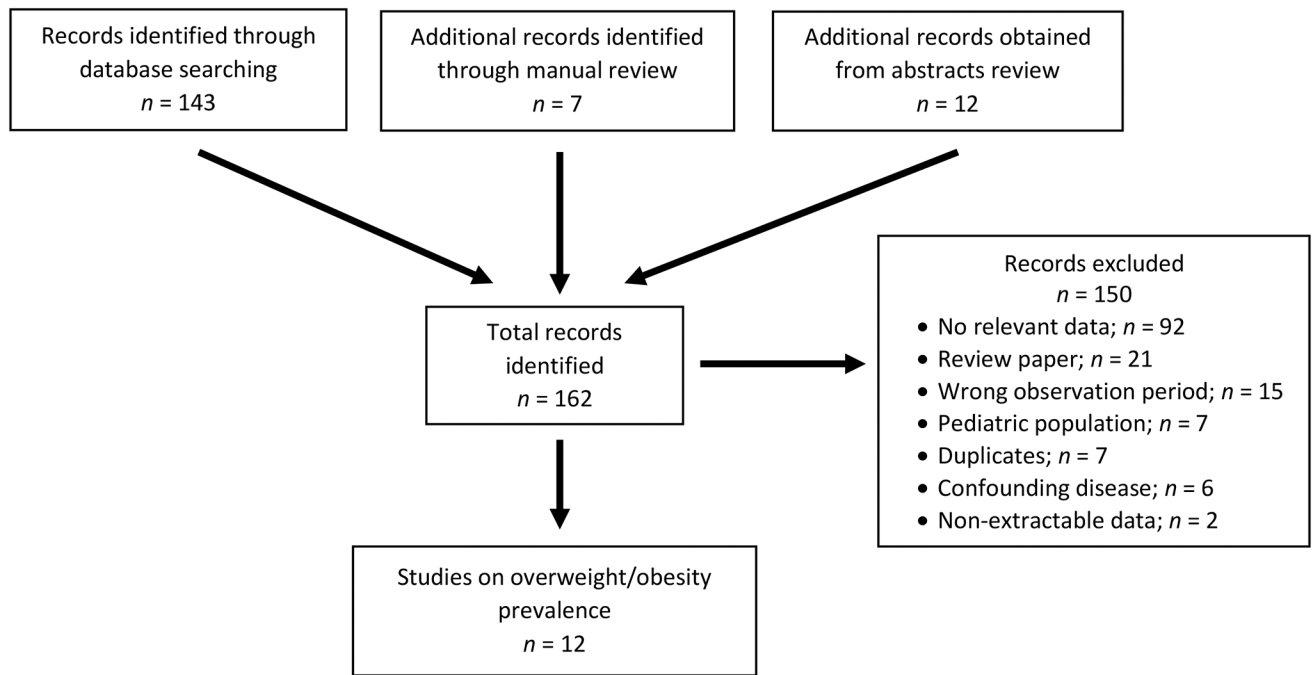


Figure 2.
Study selection

Table 1.

Baseline demographics of the 144 adult Utah PwH included in the study

Characteristics	<i>n</i>	%
Type and severity		
Hemophilia A	98	68.1
Mild	29 (20.1)	
Moderate	5 (3.5)	
Severe	64 (44.4)	
Hemophilia B	46	31.9
Mild	17 (11.8)	
Moderate	18 (12.5)	
Severe	11 (7.6)	
Self-reported race		
White or Caucasian	124	86.1
Asian	4	2.8
Hispanic	8	5.6
American Indian and Alaska Native	1	0.7
Other	5	3.5
Decline to disclose	2	1.4
Age category		
Young adult	84	58.3
Middle age	46	32.0
Older adult	14	9.7
BMI category		
Underweight	3	2.1
Normal	45	31.3
Overweight	55	38.2
Obese	41	28.5
Class I	24 (16.7)	
Class II	12 (8.3)	
Class III	5 (3.5)	

The subcategories for disease severity and BMI are presented as *n* (percentages). The percentage is based on the overall study population, *n*=144.

Table 2.

Age-adjusted prevalence of overweight and/or obese in adult PwH in Utah, the general Utah population and the general US population

Age-adjusted prevalence	Adult PwH in Utah (% , 95% CI)	Utah population (% , 95% CI) *	US population (% , 95% CI) **
Overweight or obese	73.2 (58.5, 87.7)	63.4 (62.2, 64.6)	65.9 (65.5, 66.2)
Obese	31.4 (21.8, 41.0)	28.4 (27.3, 29.5)	31.1 (30.8, 31.4)

* Based on 2018 Utah Data: Behavioral Risk Factor Surveillance System, Office of Public Health Assessment, Utah Department of Health [18, 19]

** Based on 2018 U.S. Data: Behavioral Risk Factor Surveillance System (BRFSS), Division of Behavioral Surveillance, CDC Office of Surveillance, Epidemiology, and Laboratory Services [18, 19]

Table 3.

Bivariate and multivariable associations with percent change in body mass index (BMI) using data from the Utah adult hemophilia population

Variable	Bivariate analysis			Multivariable analysis		
	% Change in BMI per unit	95% CI	p-value	% Change in BMI per unit	95% CI	p-value
White vs non-White	1.53	-8.1, 12.2	0.7663	0.46	-8.97, 10.86	0.927
Age (per 10-year increase)	3.16	0.76, 5.61	0.0099	2.3	-0.22, 4.88	0.074
Mild vs non-mild severity	10.6	3.24, 18.6	0.0045	7.7	0.023, 15.98	0.049

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Table 4. Epidemiology studies for prevalence of overweight and obesity in adult PwH, 2012 – 2019

Study	Location	Type of Study	Observation Period	Study Population	Age (yrs)	No. of PwH	Prevalence (%)		
							Overweight	Obese	At least overweight
North America									
Cisak [22]	Kentucky	Single-center	2005–2014	All severity HA and HB	30	59	33.9% (n=20)	40.7% (n=24)	74.6% (n=44)
Ullman [23]	US	Multiple centers	2009–2013	All severity HB	18–64	54	NR	NR	59.3% (n=32)
Sun [24]	US & Canada	Two centers	US (2011–2014); Canada (2010–2014)	All severity HA and HB	18	135	NR	21% (n=29)	NR
Sood [25]	US	Multiple centers	2012–2015	Moderate/severe HA and HB	54–73	200	NR	29.5% (n=59)	NR
Witkop [26]	US	Multiple centers	2013–2014	All severity HA and HB; History of joint bleeding or joint pain	18	381	36.2% (n=138)	28.6% (n=109)	64.8% (n=247)
Europe									
Holme [27]	Europe	16 centers	2011–2013	All severity HA and HB	40	532	41.4% (n=220)	13% (n=69)	54.4% (n=289)
Olivieri [28]	Germany	Seven centers	2015	Severe HA with negative inhibitor history	18	78	26.9% (n=21)	7.7% (n=6)	46.6% (n=27)
Hrdlickova [29]	Czech Republic	Single-center	2016*	All severity HA and HB	18	76	56.6% (n=43)	17% (n=13)	73.6% (n=56)
Von Mackensen [30]	United Kingdom	4 centers	2016*	All severity HA and HB	17–66	50	38% (n=19)	26% (n=13)	64% (n=32)
Global									
Chang [31]	Taiwan	Two centers	2006–2014	Moderate/severe HA and HB	18	137	29.2% (n=40)	24.8% (n=34)	54% (n=74)
					18–29	45	35.6% (n=16)	11.1% (n=5)	46.7% (n=21)
					30–39	34	23.5% (n=8)	38.2% (n=13)	61.8% (n=21)
					40–49	33	24.2% (n=8)	36.4% (n=12)	60.6% (n=20)
Lambert [32]	Ivory Coast	Single-center	2017	All severity HA and HB	50	25	32% (n=8)	16% (n=4)	48% (n=12)
					>18	25	NR	NR	12% (n=3)
Duarte [33]	Brazil	Single-center	2019*	All severity HA and HB	30	59	NR	NR	15.3% (n=9)

* Year of publication used

US, United States; yrs, years; PwH, persons with hemophilia; NR, not reported