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Obesity Prevalence

Obesity in the global haemophilia population: prevalence, implications and expert opinions for weight management

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Summary

Overweight and obesity may carry a significant disease burden for patients with haemophilia (PWH), who experience reduced mobility due to joint inflammation, muscle dysfunction and haemophilic arthropathy. This review aimed to define the prevalence and clinical impact of overweight/obesity in the global population of PWH. A detailed literature search pertaining to overweight/obesity in haemophilia in the last 15 years (2003–2018) was conducted, followed by a meta-analysis of epidemiological data. The estimated pooled prevalence of overweight/obesity in European and North American PWH was 31%. Excess weight in PWH is associated with a decreased range in motion of joints, accelerated loss of joint mobility and increase in chronic pain. Additionally, the cumulative disease burden of obesity and haemophilia may impact the requirement for joint surgery, occurrence of perioperative complications and the prevalence of anxiety and depression that associates with chronic illness. Best practice guidelines for obesity prevention and weight management, based on multidisciplinary expert perspectives, are considered for adult and paediatric PWH. Recommendations in the haemophilia context emphasize the importance of patient education and tailoring engagement in physical activity to avoid the risk of traumatic bleeding.

Keywords: Haemophilia, obesity, prevalence, weight management.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CVD, cardiovascular disease; FIX, factor IX; FVIII, factor VIII; HIV, human immunodeficiency virus; MSK, musculoskeletal; PK, pharmacokinetics; PWH, patients with haemophilia; US, United States; WHO, World Health Organization.

Introduction

Haemophilia is an X-linked, hereditary disorder of haemostasis caused by the deficiency or complete absence of clotting factor VIII (FVIII, haemophilia A) or factor IX (FIX, haemophilia B) (1). The condition is estimated to affect 400,000 people globally and is characterized by easy bruising, excessive bleeding and haemorrhage into the joints (2). Spontaneous joint bleeds comprise up to 80% of all bleeding episodes in patients with haemophilia (PWH), with recurrent bleeding into 'target joints' progressively leading to pain, restriction of movement and potentially irreversible structural damage that form the hallmark of haemophilic arthropathy (2,3).

Patients are treated with intravenous replacement of coagulation FVIII and FIX as standard of care. Replacement factor is dosed according to body weight and aims to arrest or prevent excessive bleeding when administered on-demand or as prophylaxis (2). Historically, patients were not treated routinely with replacement factor amid fear of viral contamination or due to lack of access to treatment in developing nations, leading to an older haemophilia population with damaged joints, decreased mobility and chronic synovitis (4,5). As access to virus-free coagulation factor has increased, younger PWH in developed countries are often treated with routine intensive prophylaxis regimens and benefit from a reduced physical impact of haemophilia and preservation of musculoskeletal function (2,5). However, the availability of replacement factor for prophylactic treatment still varies between regions, with continued restricted access in developing nations and poor long-term outcomes observed with episodic treatment (2,5). Emerging therapies, such as non-factor replacement therapy and gene therapy, have the potential to correct haemostasis and improve treatment outcomes for PWH (6). Advances in treatment may allow greater scope to address comorbidities that impact haemophilia management, including overweight and obesity. Despite any prospective improvements in treatment, the risk of excessive bleeding is likely to remain a serious problem for the foreseeable future.

'Overweight' and 'obesity' are often classified according to the following body mass index (BMI) categories in adults: healthy weight (BMI 18.5–24.9 kg m^{-2}), overweight (BMI 25–29.9 kg m^{-2}), obese (BMI $\geq$30 kg m^{-2}) or severely obese (BMI $\geq$40 kg m^{-2}) (7,8). The World Health Organization estimates that obesity prevalence in the general population has tripled since 1975 and now affects approximately 13% of adults globally; a further 39% of adults are classified as overweight (7). The obesity epidemic carries significant health implications for the general population, including increased risk of high blood pressure, type 2 diabetes, stroke, coronary heart disease, osteoathritis, sleep apnea, kidney disease, liver disease, clinical depression and certain types of cancer (7–12).

In the context of haemophilia, overweight and obesity are expected to further add to the burden of disease; however, their prevalence in the global haemophilia population is currently unclear. This review was carried out with three main objectives: (i) to review available data on the global prevalence of overweight/obesity in haemophilia, and whether this differs to the general population; (ii) to define the impact of overweight/obesity, as the disease may carry worse implications for the haemophilia population; and (iii) to outline weight management guidelines that are relevant for promoting safe and effective weight loss, suggesting best practice for weight management in PWH, based on multidisciplinary expert perspectives.

Methodology

Literature search

To identify all relevant studies for potential inclusion in this review, a detailed search pertaining to overweight/obesity and haemophilia was conducted. A systematic search of manuscripts published within the last 15 years (01 January 2003–18 January 2018) was performed in the electronic database PubMed (https://www.ncbi.nlm.nih.gov/pubmed), using the following search terms in all possible combinations: *obese, obesity, overweight, weight, weight management, body weight, adiposity, haemophilia, hemophilia*. Non-English language and non-human articles were excluded from the results.

The literature search identified 476 articles, of which 90 were deemed potentially relevant for inclusion following manual review. Results have been reported as a flow diagram (Fig. 1).

Meta-analysis

To investigate the prevalence of overweight and/or obesity in the global population of PWH, a meta-analytical evaluation of prevalence data in epidemiological studies was performed. Studies included in the analysis were selected from the 90 records identified in the original literature search. Of these 90 records, the 28 studies that reported the number of enrolled PWH with overweight and/or obesity, or the percentage prevalence, were included in the meta-analysis (Table 1).

For each study included, data regarding sample size, age of the study population and country of origin of enrolled patients were extracted. The primary analysis was the assessment of the pooled prevalence of overweight and/or obesity in the global population of PWH. Due to a lack of world data, an additional analysis was performed for pooled prevalence in European and North American PWH. For the sensitivity analyses, results were stratified according to age group (adult versus paediatric PWH) and

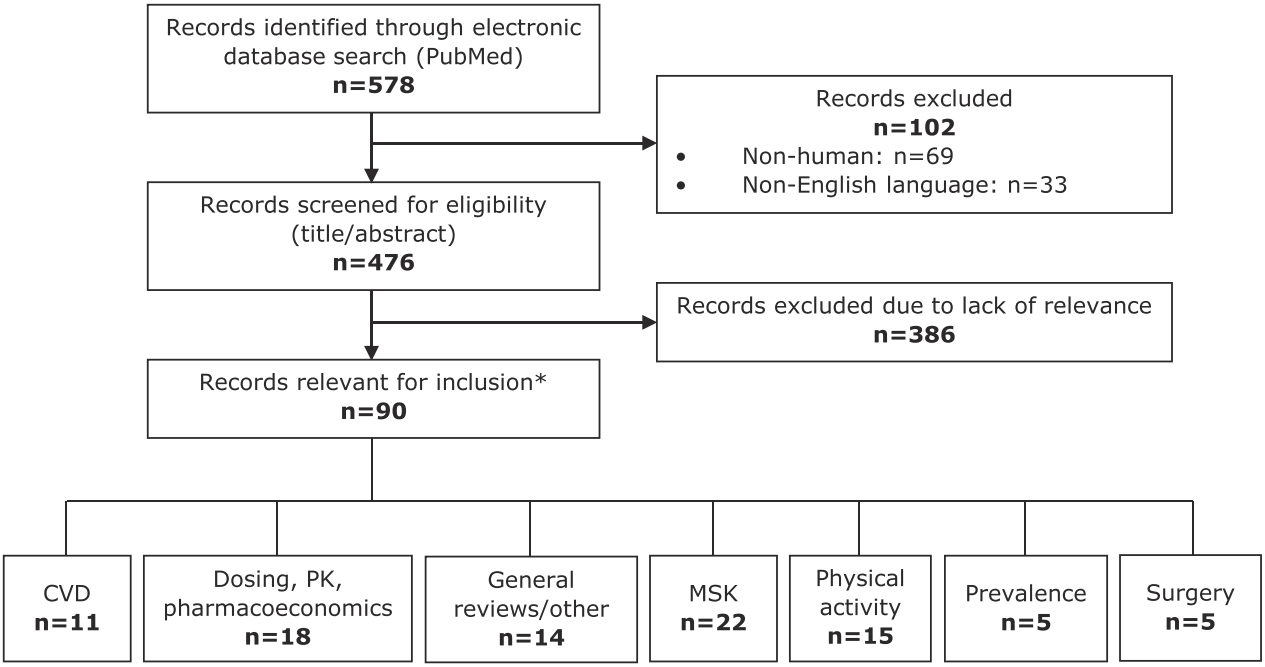

Figure 1 Study selection flow diagram. *Several of the records identified are relevant for multiple subcategories. CVD, cardiovascular disease; MSK, musculoskeletal; PK, pharmacokinetics.

region (North American versus European PWH). Statistical analysis was carried out using Comprehensive Meta-analysis Software (Version 2, Biostat, Englewood NJ, 2005). The prevalence of overweight and/or obesity was expressed as weighted mean prevalence with pertinent 95% confidence intervals (CI). The overall effect was tested using *z*-scores, with significance set at $p < 0.05$.

How prevalent is obesity in patients with haemophilia?

There is a growing population of PWH surviving to advanced ages due to improved management of haemophilia from routine access to replacement coagulation factors (4). Consequently, the ageing population of PWH are at risk of age-related diseases, including obesity and associated conditions, such as type 2 diabetes (4,41). Epidemiological studies were assessed to determine the prevalence of PWH across different age groups and regions.

The majority of available epidemiological data for PWH and non-haemophilic controls suggest that the prevalence of overweight/obesity in haemophilia is comparable with that observed in the general population. In the USA, in a 2011 study, 34.6% of 185 PWH had obesity compared with 36.2% in a national survey of the general population (23). Similarly, 58.0% of adult PWH in the 2005 US Universal Data Collection Program had overweight/obesity versus 54.9% in the general population (42). In Europe, a cross-sectional assessment of 709 PWH from the Netherlands and UK identified total rates of overweight/obesity as 58% in the haemophilia context versus 61% in the general age-matched population (31). The overall rates of overweight/obesity reported in a 2001 paediatric Dutch population of PWH and a non-haemophilia control group were 15% and 17%, respectively (33). More recently in 2011, a separate Dutch population of adult PWH recorded higher rates of obesity in 100 PWH (19%) versus 200 non-haemophilic, age-matched controls (13%) (28).

However, some studies of global populations of PWH report a reduced prevalence of overweight/obesity when compared with the general population. An obesity prevalence rate of 19.6% was observed in a US population of 56 adult PWH (2006–2009), which was lower than the 31.9% observed in the comparison population of non-haemophilic individuals (15). In Germany, 10% of 29 elderly (≥60 years) PWH were affected by obesity versus 21% in an age-matched control population (2006–2008) (36). In Taiwan, obesity was observed in 9% of PWH in a population-based analysis of 1,054 PWH versus 30% in 10,540 members of the general, age-matched population (1997–2010) (40). Additionally, a lower mean BMI (19.1 kg m^{-2}) was reported in 50 Indian PWH compared with age-matched, non-haemophilic controls (23.6 kg m^{-2}) (43). In Mexico, the cumulative rate of overweight/obesity was lower in 62 paediatric PWH (34%) versus the same number of age-matched controls (42%) (39).

To provide a more definitive estimate of global overweight/obesity prevalence in PWH, a meta-analytical

Table 1 Epidemiology data included in the meta-analysis for overweight/obesity in adult and paediatric populations of PWH from different regions

Authors	Year	Region	Age group	Year of analysis	*N*, PWH and [non-haemophilic controls]*	Prevalence in PWH and [non-haemophilic controls]* (%)		
						Overweight (BMI 25–29.9 kg m^{-2})	Obesity (BMI ≥30 kg m^{-2})	Overweight and obesity (BMI ≥25 kg m^{-2})
North America								
CDC (13)	2011	US	Adult	2011	10,094	33.1	–	–
		US	Paediatric	2011	8,164	20.8	–	–
Curtis R et al. (14)	2015	US	Adult	2005–2013	141	23	24	47
Lim MY et al. (15)	2011	US	Adult	2006–2009	56	–	19.6 [31.9]	–
Majumdar S et al. (16)	2010	US	Adult	2008–2010	59	36	32	68
		US	Paediatric	2008–2010	73	21	16	37
McNamara M et al. (17)	2014	US	Adult	2010–2011	88	48.9	18.2	67.0
Minuk L et al. (18)	2015	Canada	Adult	2000–2011	294	–	23.5	–
Monahan PE et al. (19)	2011	US	Paediatric	1998–2008	6,420	16.1	20.7	36.8
Revel-Wilk S et al. (20)	2011	Canada	Paediatric	1999–2005	170	14.1	14.7	28.8
Ross C et al. (21)	2009	US	Paediatric	2005–2007	37	16	3	19
Seaman CD et al. (22)	2016	US	Adult	2009–2011	3,607 [8,025,025]	–	5.2 [9.0]	–
Sharathkumar AA et al. (23)	2011	US	Adult	2004–2008	185	–	34.6 [36.2]	–
Sood SL et al. (24)	2015	US	Adult	2010–2012	165	–	30.3	–
Soucie JM et al. (25)	2011	US	Paediatric	1998–2008	6,347	15.1	17.4	32.5
Ullman M et al. (26)	2014	US	Adult	1998–2008	10,814*	35	28	63
		US	Adolescent	1998–2008		16	22	38
		US	Paediatric	1998–2008		16	20	36
Wiktop M et al. (27)	2017	US	Adult	2013–2014	381	36.2	28.6	64.8
Europe								
Biere-Rafi S et al. (28)	2011	The Netherlands	Adult	–	100 [200]	–	19 [13]	–
Douma-van Riet DC et al. (29)	2009	The Netherlands	Paediatric	2007	158	11.4	4.4	15.8
Fransen van de Putte DE et al. (30)	2012	The Netherlands	Adult	1985–2010	408	–	8.5 [11.2]	49 [52]
Fransen van de Putte DE et al. (31)	2013	The Netherlands	Adult	2009–2011	388	44 [37]	9 [12]	53 [49]
		UK	Adult	2009–2011	321	42 [41]	22 [20]	64 [61]
Henrard S et al. (32)	2011	Belgium	Adult	2003–2010	46	30.4	13.0	43.5
Hofstede FG et al. (33)	2008	The Netherlands	Adult	2001	734	35 [50]	8 [8]	42 [58]
		The Netherlands	Paediatric	2001	332	10 [14]	6 [3]	15 [17]

(*Continues*)

Table 1 (Continued)

Authors	Year	Region	Age group	Year of analysis	*N*, PWH and [non-haemophilic controls]*	Prevalence in PWH and [non-haemophilic controls]* (%)		
						Overweight (BMI 25–29.9 kg m^{-2})	Obesity (BMI ≥30 kg m^{-2})	Overweight and obesity (BMI ≥25 kg m^{-2})
Holme PA et al. (34)	2016	Europe (cross-sectional)	Adult	2011–2013	531	41.4	13.0	54.4
Khair K et al. (35)	2012	UK	Paediatric	2012	84	15	13.8	28.8
Miesbach W et al. (36)	2009	Germany	Adult	2006–2008	29	52 [53]	10 [21]	62 [74]
Sartori MT et al. (37)	2008	Italy	Adult	2008	40 [40]	–	–	42.5 [50]
von Mackensen S et al. (38)	2016	UK	Adult	2016	50	38	26	64
Global Tlacuilo-Parra A et al. (39)	2007	Mexico	Paediatric	–	62 [62]	17 [16]	17 [26]	34 [42]
Wang JD et al. (40)	2015	Taiwan	Adult/Paediatric	1997–2010	1,054 [10,540]	–	9 [30]	–

*Additional data included for non-haemophilic control populations were available. BMI, body mass index; CDC, Centers for Disease Control and Prevention; N, number of patients assessed for overweight/obesity; PWH, patients with haemophilia.

evaluation of epidemiological data was performed across studies from different regions (Table 1). The overall pooled prevalence of overweight/obesity from available data in the global haemophilia population was 17% (95% CI: 15.0–19.3); this estimation rose to 31% (95% CI: 26.8–36.2%) when assessing European and North American populations alone. Stratification by patient age showed an increased prevalence in adult (43.3%) versus paediatric (26.9%) patients (Fig. 2). The overall pooled prevalence of overweight/obesity by region was higher in European adults (49.1%) versus North American adults (38.5%), but lower in European paediatric patients (18.8%) when compared with their North American counterparts (30.6%). A progressive increase in obesity prevalence over time was seen both in adult and paediatric populations (Fig. 3), reflecting trends observed in the global obesity population (7). However, an ~20% increase in overweight/obesity was reported in adults during a 10-year period, whereas an ~40% increase was observed in children (Fig. 3).

Results from the meta-analysis demonstrate significant levels of overweight/obesity in haemophilia communities from Europe and North America, especially with regard to adult patients, which may in part be influenced by an ageing

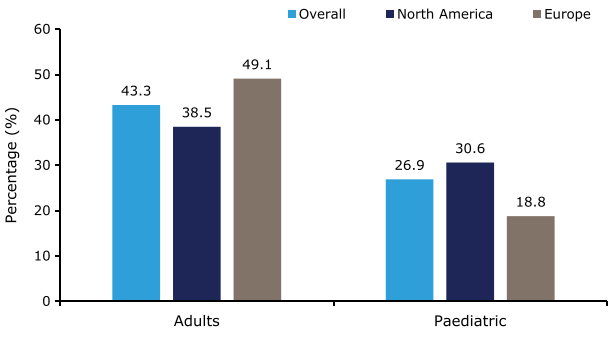

Figure 2 Pooled prevalence of overweight/obesity in adult and paediatric populations of North American and European PWH. PWH, patients with haemophilia.

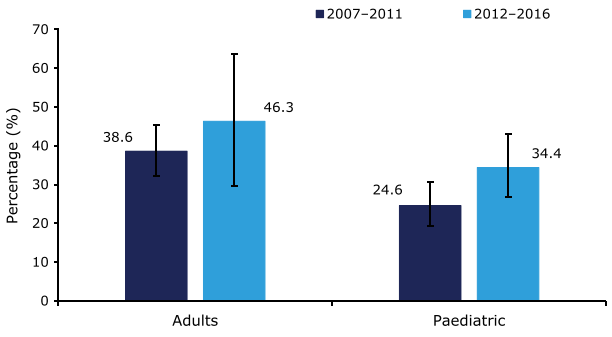

Figure 3 Changes in prevalence of overweight/obesity in global adult and paediatric populations of PWH over time. PWH, patients with haemophilia.

population of PWH. The estimated rate of 31% overweight/obesity in European and US PWH, as well as the rapid increase in overweight/obesity prevalence in paediatric PWH over a relatively short period is cause for significant concern (16,17,26,27,31,36,38). Overweight/obesity data for PWH are available from a limited number of countries; more epidemiological data from outside Europe and North America are needed to further elucidate the prevalence of overweight/obesity in the global haemophilia population. Additionally, as the majority of epidemiological studies in PWH fail to account for percentage body mass or lean body mass, the occurrence of clinically significant excess weight in PWH may be underestimated (44). Further studies that directly compare overweight/obesity between PWH and age-matched, non-haemophilic controls will help to define the prevalence of obesity in haemophilia.

What is the clinical impact of obesity in patients with haemophilia?

Dosing and administration of factor replacement

Intravenous replacement coagulation factor products are the standard of care for the management of haemophilia and are dosed according to body weight (2). Pharmacokinetic outcomes of factor dosing are influenced by overweight/obesity due to reduced plasma volume in adipose tissue (45). Investigation into the pharmacokinetic implications of overweight/obesity in PWH suggests that increased body weight has no significant impact on FVIII activity, half-life, mean residence time and endogenous thrombin potential of coagulation products (46,47). However, *in vivo* recovery of FVIII is significantly dependent on BMI in PWH (48); infusing a similar amount of clotting FVIII would result in a higher circulating FVIII level in plasma of a person with obesity versus without, suggesting that this cohort is likely being 'over'-treated (47–50). Conversely, PWH who have a reduced BMI (<20 kg m^{-2}) may experience lower FVIII recovery; if underdosed, these patients would be at greater risk of spontaneous bleeds and subsequent joint damage (49).

For PWH B, FIX has a higher clearance, longer half-life and a larger volume of distribution compared with FVIII (51). Consumption of FIX will increase in people with overweight/obesity due to dosing by body weight (51); however, further investigation is needed to explore the impact of excess adiposity on *in vivo* recovery and FIX pharmacokinetics.

Individual variations in response to treatment mean that standard weight-based prophylaxis regimens may fail to adequately prevent bleeding in some patients or be overused/excessively administered in others. Personalized prophylaxis, with flexibility in dose and frequency of administration, may therefore offer the opportunity to dose PWH who are affected by underweight, overweight and obesity with greater efficiency (41). Additionally, some evidence suggest that dosing according to 'ideal body weight' for height may allow for a significant reduction in factor consumption in people with overweight/obesity, which can reduce the healthcare cost of prophylaxis while maintaining patient safety (52,53).

Overweight/obesity also has implications on the administration of coagulation factor. PWH who have overweight/obesity were less likely to use home-infusion or self-infusion of factor concentrate prophylactically in a population of 10,814 male PWH A and B versus normal-weight individuals, possibly due to increased difficulty with venous access (26). Therefore, this cohort may be unable to take full advantage of benefits associated with home treatment, including an improvement in quality of life and a reduction in pain, disability and time spent in hospital (26).

Musculoskeletal health

Spontaneous joint bleeds comprise up to 80% of bleeding phenotype in PWH (2). For patients with severe disease, intra-articular changes resulting from recurrent bleeding into the joints lead to restricted movement, structural damage and the development of haemophilic arthropathy (3). Muscle haematomas can further contribute towards long-term damage, causing inflammation, infections, muscle dysfunction or a decreased range of motion (54,55). For the population of PWH in the USA who are affected by overweight/obesity, excess adiposity has been associated with a decreased range in motion in weight-bearing joints and accelerated loss of joint mobility (25,56,57). In Europe, this reduction was reflected in paediatric PWH with overweight/obesity, who experienced a significant decrease in active range in flexion of the knees and elbows (29). Furthermore, it has been reported that overweight/obesity increased the number of joint bleeds and reduced function of the lower limbs in a Dutch haemophilia cohort, while others have identified an association between obesity and the occurrence of chronic pain (27,58).

Evidence suggests that severe haemophilia may potentially induce sarcopenia and decrease maximal muscle strength, possibly due to reduced engagement in physical activity to prevent bleeds and preserve joint health (59–62). Furthermore, the reduced mobility and loss of muscle function observed with severe haemophilic arthropathy leads to inactivity and subsequent muscle atrophy, which may in turn increase the risk of weight gain (2). In the general population, overweight/obesity is significantly associated with reductions in whole muscle and fascicle strength (63), with a negative impact on skeletal muscle maintenance and regeneration, and reduction in muscle functionality and deterioration in muscle mass (64–67). Although there is currently no evidence in the context of PWH affected by

overweight/obesity, it can be postulated that comorbidity with excess weight and haemophilia may place patients at a greater risk of reduced muscle strength and function.

In addition to joint health and muscle strength, several European, US and global studies have identified osteopenia and osteoporosis as severe comorbidities of haemophilia (59,68–70). In the general population, high BMI is reported to have a positive correlation with bone mineral density (BMD), suggesting a protective effect of overweight/obesity against the occurrence of osteoporosis; however, discrepancy in the literature regarding the impact of excess adiposity on fracture risk means that the relationship between obesity and bone health remains unclear (71,72). Similarly, for PWH, the true impact of BMI on BMD has not been established. One study reported a 58% prevalence of osteoporosis/osteopenia in an Iranian population of PWH and noted that patients with osteoporosis had a significantly higher mean BMI than patients with osteopenia or a normal BMD (73). By contrast, assessment of 30 US PWH found a significant association with osteoporosis and lower BMI (74). Furthermore, a meta-analysis including European, Asian, South American, North African and Australian PWH assessing the lumbar spine found no evidence that BMI could be used to predict BMD (75). Despite this inconsistency within the literature, the association of low BMD with increased haemophilic arthropathy, reduced mobility and muscle atrophy (2) stresses the importance of addressing bone health and identifying the impact that overweight/obesity has on BMD in the context of haemophilia.

Invasive procedures

The availability of replacement factor concentrates has allowed major surgical procedures to be performed safely in PWH, who often require joint replacement surgery following recurrent bleeding into target joints and subsequent chronic arthropathy (76). In the general population, obesity can accelerate the development of osteoarthritis due to increased mechanical load or metabolic disruption, placing patients at greater relative risk for total knee or hip arthroplasty (77). Additionally, it has been reported in the USA that people with obesity undergoing total joint arthroplasty are subject to greater risk of perioperative complications (78).

In the context of haemophilia, total knee replacement carries an increased reported infection prevalence (0–17%) versus the non-haemophilic population (1–2%) (76). Furthermore, obesity is associated with a more rapid impairment of joint function in PWH versus patients without obesity, implying a greater requirement for surgery (25,57). Although further evidence in the context of haemophilia is needed, these findings suggest that the risk for joint surgery and perioperative complications may be further increased in PWH who are affected by overweight/obesity, highlighting the importance of effective weight management to reduce the requirement for surgical intervention.

Cardiovascular impact

Overweight and obesity are well-established risk factors for cardiovascular disease (CVD), diabetes risk, hypertension, type 2 diabetes and metabolic syndrome (79–82). For haemophilia, there is discrepancy in the literature regarding its impact on CVD. A recent 2017 review noted a lack of consensus for haemophilia's effect on CVD risk factors, including diabetes and atherosclerosis (83). Despite those authors determining an increased prevalence of hypertension in PWH (83), more recent literature has demonstrated conflicting results. A cross-sectional study of European PWH reported a 45% prevalence of hypertension, which was comparable with the non-severe haemophilia and non-haemophilic population (34). Meanwhile, a 2017 study found a significantly decreased prevalence of hypertension in a cross-sectional analysis of US haemophilic (39.5%) versus non-haemophilic (56.3%) individuals (22).

There are also contradictory reports over the impact of haemophilia on the occurrence of CVD events. One review identified studies reporting reduced risk, comparable risk or elevated risk of CVD events, such as ischaemic stroke and peripheral arterial disease, in PWH compared with the general population (84). In the context of overweight/obesity, excess adiposity was not a risk factor for CVD events in a population of US PWH (23). Similarly, another report found no association between obesity and the incidence of atherothrombotic events in Taiwanese patients (40). However, BMI was significantly associated with increased risk for hypertension in European PWH (34). This continued discrepancy in the literature highlights the need for investigational studies to determine the impact of haemophilia on CVD prevalence and risk factors, explore the effect of other predictors of CVD incidence, and investigate the implications of increased BMI in PWH. However, the large epidemiological studies required to identify BMI as an independent risk factor for CVD in the general population (85,86) may pose a considerable challenge to reproduce in the comparatively limited global population of PWH.

Psychological impact

Chronic illnesses carry a significantly increased risk of clinical depression compared with the general population, which may be caused by anxiety about health outcomes and disease management, or by the biological impact of the disease (87,88). Despite a lack of clinical data on excess weight in the context of haemophilia, the psychological impact of overweight/obesity in PWH is likely to be

significant. In the general population, overweight/obesity is associated with stigmatization and discrimination that can lead to the development of low self-esteem, depression, dysfunctional eating behaviours, mood disorders, compromised perceived quality of life, anxiety and impaired body image (10,89).

Within the haemophilia community, the prevalence of depression and psychological implications of the condition are also significant. The prevalence of depression was 32% in a cohort of 307 PWH A in the UK, who were experiencing anxiety over managing stigma associated with having a bleeding disorder or contracting human immunodeficiency virus or hepatitis C through contaminated blood products (90). Similarly, 37% of patients suffered from depression in an analysis of 41 US PWH, with over two-thirds reporting that symptoms relating to their depression caused functional impairment of daily activities (91). The incidence of depression in this population was consistent with adults suffering from other chronic illnesses, and significantly higher than rates of depression observed in the general population of US males (4%) (91). High prevalence was also observed in Iranian PWH, where anxiety, depression and psychiatric features were present in >60% of patients and were associated with chronic stress caused by fear of bleeding (92). Additionally, almost half (43%) of young adult PWH participating in the global Haemophilia Experiences, Results and Opportunities initiative reported the occurrence of stress, depression, insomnia and anxiety; 26% of patients attributed this directly to having haemophilia (93). Despite recommendations for psychological support in haemophilia guidelines, these patients indicated a lack of involvement from counsellors and social workers as part of their haemophilia treatment (93). Along with the significant incidence of depression in patients with chronic illnesses, including both overweight/obesity and haemophilia, these outcomes highlight the need for psychological support as an important aspect of disease management in PWH affected by overweight/obesity.

How can prevention and treatment of overweight/obesity be addressed in patients with haemophilia? Expert opinion on weight management strategies

Although haemophilia itself is unlikely to be a causal factor for obesity, the disease may indirectly lead to weight gain or difficulty in weight loss if patients reduce levels of exercise due to muscle/joint pain, restricted range of movement or fear of bleeding. According to a 2006 US survey, as many as 60% of paediatric and adolescent PWH avoid physical activity to help manage their haemophilia (62). The risk of weight gain may be especially relevant for the older population of PWH who were not treated routinely with prophylaxis during their childhood and suffer from advanced arthropathy, muscular atrophy and impaired mobility, which are in turn risk factors for obesity (4).

The management of haemophilia is a major burden for patients, especially with regard to frequent injections for prophylaxis and the resolution of bleeding events (94). Treatment of overweight/obesity in PWH should be highly integrated into the haemophilia treatment pathway to reduce the psychological impact of disease burden. Additionally, dosing of replacement coagulation factor according to body weight highlights the importance of monitoring and managing weight in all PWH, regardless of BMI. Specific guidelines for weight management in the context of haemophilia do not currently exist; however, established guidelines for identifying, preventing and treating overweight/obesity can be adapted to the haemophilia population.

Screening tools for the identification of overweight/obesity in haemophilia

Measurement of BMI is one of the most commonly used and widely recommended methods for diagnosing the incidence of overweight/obesity (95,96). In an evaluation of 90 US haemophilia treatment centres, 67% of centres reported measuring BMI at clinic visits (97). However, BMI does not accurately predict body fat, as it does not discriminate between body fat percentage and lean mass (95,96). For example, patients with a high muscle mass may classify as having 'overweight' or 'obesity' according to their BMI, even in the absence of excess fat. Therefore, alternative screening tools may be required to provide a definitive diagnosis of overweight/obesity (8). The measurement of waist circumference has been identified as a strong predictor of visceral obesity and a more accurate measure than BMI for determining obesity health risks (95). Alternatively, waist-to-height ratio has been reported as the most accurate predictor of whole body fat percentage and visceral adipose tissue when compared with BMI, waist circumference and waist-to-hip ratio (98). These alternative screening tools should be considered as an additional assessment in conjunction with BMI in order to more accurately record body weight composition. Additionally, plotting BMI and height–weight percentile charts may help to assess the development of overweight/obesity over time and subsequent need for weight management intervention in PWH (95,99).

Prevention of overweight/obesity

Patients with haemophilia of a healthy weight (BMI 18.5–24.9 kg m^{-2}) should be encouraged to maintain healthy lifestyle habits that prevent the occurrence of overweight/obesity (100,101); however, 89% of 90 haemophilia treatment centres assessed in the USA had no protocol in place to address healthy weight in PWH (97). Early intervention is especially important in the paediatric

Table 2 Lifestyle interventions for preventing overweight and obesity in PWH

Intervention	Recommendations for the general population (100,101,103)	Considerations in haemophilia
Energy intake	• Estimated average requirements for energy per day: ○ Adult men: 10.9 MJ per day (2,605 kcals per day) ○ Adult women: 8.7 MJ per day (2,079 kcals per day)	• Energy intake guidelines for preventing obesity should be similar between the general population and PWH • For PWH affected by overweight/obesity who are less able to engage in sport/exercise due to physical limitations or disability, energy intake may need to be reduced accordingly
Physical activity	• Engage in at least 150 min of moderate-intensity activity ○ i.e. 30 min exercise on at least 5 days a week • **OR** 75 min of vigorous-intensity aerobic activity • Avoid extreme physical activity (e.g. obsessive exercising, high-intensity exercise that is difficult to sustain) that may not provide wider health improvements	• Recommendations for the intensity, type and duration of physical activity will differ between the general population and PWH, as physical activity is accompanied by a risk of traumatic bleeding in PWH (104) • Please see '*Additional considerations for physical activity in patients with haemophilia*'
Dietary habits	• Reduce the overall energy density of the diet • Increase consumption of fruits, beans, pulses and wholegrains • Limit consumption of energy dense food and drinks, particularly 'fast' or 'takeaway' foods • Avoid food and drink with high sugar content • Reduce total fat intake • Decrease size of food portions • Include breakfast without increasing daily calorie intake • Avoid snacking between meals	• Dietary guidelines for preventing obesity should not differ between the general population and PWH • When limiting consumption of certain foods, PWH should ensure that adequate consumption of iron is maintained due to risk of iron deficiency with frequent bleeding (105) • PWH should limit consumption of food/nutrients that may reduce clotting ability (e.g. vitamin E and fish oil) (106,107) • Additional considerations may be relevant for PWH who are infected with hepatitis C or HIV

HIV, human immunodeficiency virus; PWH, patients with haemophilia.

population to embed healthy lifestyle behaviours and monitor weight status (102). Addressing weight management may be easier in both adult and paediatric populations of PWH owing to frequent contact with the haematologist (97). Recommendations for preventing excess weight gain and the occurrence of overweight/obesity in PWH are summarized in Table 2 alongside established guidelines for the general population.

Management of overweight and obesity

Recommendations for management of overweight/obesity in adult and paediatric patients in PWH are summarized in Tables 3 and 4, respectively, alongside established guidelines for the general population.

Additional considerations for weight management

Goal setting

The management of overweight/obesity requires setting appropriate goals for weight loss and emphasizing realistic targets (108). Several European and US guidelines advise that a sustained weight loss of 5–10% body weight can lead to clinically meaningful benefits in the general population, such as reducing CVD risk factors and diabetes risk (103,108,114,115). However, despite 5–10% loss in body weight often being stated as a realistic weight management target, the National Institute for Health and Care Excellence in the UK notes that average weight loss following participation in a weight loss programme is ~3% (116).

Regional considerations

It is important to acknowledge that the global management of overweight/obesity varies between different regions. The World Health Organization definition for excess adiposity for Caucasian populations uses a BMI cut-off point of $\geq$25 kg m^{-2}, which is supported by several European-specific and US-specific guidelines (7,103,108,117). However, at a given BMI, South Asian, Southeast Asian and East Asian communities have a higher percentage body fat than their Caucasian counterparts and are at greater risk of developing obesity-related comorbidities. Therefore, it is recommended that a lower BMI cut-off point of $\geq$23 kg m^{-2} be used to identify excess adiposity in these populations (117,118).

Additionally, perceptions of body weight may influence motivation for people with overweight/obesity to participate in weight loss programmes. For example, in some African communities, excess weight is traditionally associated with wealth, good health and higher socioeconomic status, while being thin associates with incidence of chronic illness (119,120). An assessment of 78 focus group participants in South Africa found a low perception of threat to health from excess weight, and the belief that overweight is normal, rather than a disease (121). This poses a considerable challenge for healthcare providers to control excess weight in these populations (121).

Management in children

Children are often screened for excess adiposity using age-specific and sex-specific 'BMI-for-age' growth charts, which

Table 3 Guidelines for weight loss in adult PWH with overweight/obesity

Intervention	General recommendations for adults (103,108)	Considerations in haemophilia
Energy intake	• Energy (calorie) intake should be reduced by 500–1,000 kcal per day or 15–30% ○ Restriction should be individualized and acknowledge nutritional habits, physical activity, comorbidities and previous dieting attempts	• Energy intake guidelines for weight loss should not differ between the general population and adult PWH
Physical activity	• Engage in at least 150 min of moderate-intensity aerobic exercise, combined with 1–3 training sessions per week of resistance exercise to increase muscle strength • Increase non-exercise and active leisure activities (biking, walking, gardening, golf) to reduce sedentary behaviour	• *As in Table 2*
Dietary habits	• *As above (prevention of overweight/obesity)* • Providing an energy-restricted diet may require support from a nutritionist or dietitian • Food selection should be guided by available foods, which vary from country to country	• *As in Table 2*
Behavioural therapy	• Includes interventions that enhance patient prescriptions to reduce calorie intake and increase physical exercise • Interventions include self-monitoring of weight/food intake and physical activity, reasonable goal-setting, stimulus control, controlling the process of eating and patient education	• Patient education is especially important in PWH. PWH affected by overweight/obesity should be made more aware that ○ Haemophilia cannot be properly controlled without addressing BMI ○ The time and energy invested in haemophilia treatment, and the benefits from treatment, are at risk if patients do not maintain a healthy weight
Pharmacotherapy	• Can be considered for people with obesity (BMI ≥30 kg m^{-2}) or overweight with a BMI ≥27 kg m^{-2} with an obesity-related disease (e.g. hypertension and type 2 diabetes) • Pharmacotherapy should be used only as an adjunct to lifestyle therapy and not as stand-alone treatment • Clinicians should consider differences in efficacy, adverse side effects, cautions and warnings that characterize approved medications, and consider the presence of weight-related complications and medical history • Some interventions may reduce absorption of fat soluble vitamins (A, D, E and K) and may require supplementation	• Pharmacotherapy guidelines for weight loss should not differ between the general population and adult PWH
Bariatric surgery	• Should be considered for patients with a BMI ≥40 kg m^{-2} (or 35.9–39.9 kg m^{-2} with comorbidities) in the general population of people affected by obesity • Requires lifelong medical monitoring and should only be considered if other weight loss attempts fail	• Haemophilia may not be a contraindication to bariatric surgery (109) • However, the procedure requires careful consultation for PWH due to increased bleeding risk. As with the general population, bariatric surgery may only be appropriate for a select group of patients • Some procedures (e.g. Roux-en-Y gastric bypass surgery) are associated with malabsorption of iron and B12, folate deficiency, and reduced absorption of fat soluble vitamins (including vitamin K needed for synthesis of clotting factors) can occur (110,111) ○ Hence, monitoring and replacement of micronutrients are a particular concern for PWH due to bleeding risk
Psychological support	• Psychological support and/or treatment is an integral part of obesity management and may require referral to a specialist where there is evidence of eating disorders, anxiety, depression or stress	• Psychological support provided for obesity management should also address psychological implications regarding the burden of haemophilia

BMI, body mass index; PWH, patients with haemophilia.

have defined overweight (85–<95th percentile) and obesity (≥95th percentiles) categories (99). For patients with overweight/obesity, the US Centers for Disease Control and Prevention recommends that consultation from a healthcare professional should be provided before placing paediatric patients on a weight loss programme; as children are still growing, they may only need to maintain body weight or slow their rate of weight gain (122).

Weight management in children is influenced by the weight, eating habits and lifestyle behaviours of family members. Children living with overweight parents/grandparents were found to be at greater risk of childhood

Table 4 Guidelines for weight loss in paediatric PWH with overweight/obesity

Intervention	General recommendations for children/adolescents (112,113)	Considerations in haemophilia
Energy intake	• Reduce energy intake so that it falls below energy expenditure	• Energy intake guidelines for weight loss should not differ between the general population and paediatric/adolescent PWH
Physical activity	• Engage in 60 min of moderate or greater intensity physical activity each day • Encourage increase in physical activity, even in the absence of weight loss • Encourage a reduction in sedentary behaviour, such as playing video games and watching television	• As in Table 2
Dietary habits	• Minimize or eliminate sugar-sweetened drinks • Tailor dietary changes to food preferences and allow for a flexible and individual approach to reducing calorie intake • Dietary recommendations must be part of a multicomponent intervention	• As in Table 2
Behavioural therapy	• Includes stimulus control, self-monitoring, goal-setting, rewards for reaching goals, problem-solving • Encouragement and reinforcement from parents/caregivers	• As in Table 3
Pharmacotherapy	• Generally not recommended for children <12 years, except in exceptional circumstances (e.g. extreme comorbidity) • Weight loss medication is approved for some adolescent patients and may be appropriate in select cases as an adjunctive therapy when lifestyle intervention alone has been ineffective	• Pharmacotherapy considerations should not differ between the general population and paediatric/adolescent PWH
Bariatric surgery	• Generally not recommended in children or young people ○ There are exceptional circumstances for consideration for surgery, where the patient must be physically mature, have a BMI of ≥50 kg m^{-2} (or ≥40 kg m^{-2} with significant comorbidities) and have failed other formal weight loss programmes	• Surgical considerations should not differ between the general population and paediatric/adolescent PWH

BMI, body mass index; PWH, patients with haemophilia.

overweight and obesity (123). To address excess weight in children, National Institute for Health and Care Excellence recommends active involvement of the patient's family members/carers, who can provide positive reinforcement of weight management prescriptions and help improve weight loss outcomes (124). Additionally, they report evidence that targeting both parents and children, or whole families, is effective in reducing BMI scores by the end of a weight management programme, emphasizing the importance of family involvement (124,125).

Genetic effect

Genetic variation is an additional consideration with regard to individualized weight management programmes. Heterogeneous variations between patients may influence their susceptibility to different weight loss interventions. However, the use of genomic data to individualize weight management programmes is currently speculative and requires further research (126).

Sugar consumption

Some evidence suggest that the excess consumption of fructose or monosaccharides in high-sugar diets is associated with lipid accumulation in the liver and skeletal muscle, inducing insulin resistance and greater risk of type 2 diabetes (127). Additionally, diets rich in free sugar may increase the chance of excess energy intake and indirectly promote the development of type 2 diabetes and CVD through weight gain (128). Although further evidence is required to verify the impact of high-sugar diets on body weight, the potential metabolic effects of excess sugar consumption highlight the importance of restricting sugar intake as part of weight loss programmes.

Additional considerations for physical activity in patients with haemophilia

Engagement in physical activity is an important component of weight management and in PWH can lower the risk of overweight/obesity (38,129). However, increased risk of bleeding in PWH means that advice about physical exercise should be individualized to the physical capabilities and preferences of the patient. Two reviews of physical activity in haemophilia recommend that the development of an exercise regimen involves active input from the patient, haemophilia treatment team, and a physiotherapist who is knowledgeable on the pathophysiology of bleeding disorders (130,131). Additionally, the exercise prescription

should include patient education around physical activity and regular assessment of musculoskeletal health (131). Prophylactic administration of replacement coagulation factors can help to reduce bleeding risk during exercise, and should be tailored to the individual needs of the patient (130).

A number of guidelines exist to assess the risk for trauma and bleeding prior to PWH participating in physical activity. The World Federation of Hemophilia encourages participation in noncontact sports (e.g. badminton, cycling, golf and swimming) and suggests avoiding high contact and collision sports (e.g. soccer and hockey) (2). However, for some PWH, racquet sports may be associated with microbleeding, chronic synovitis and early haemophilic arthropathy of the joints, which may not become apparent until more permanent damage has been caused (N Zourikian, personal communication) (132). Similarly, the National Hemophilia Foundation 'Playing it Safe' recommends regular engagement in noncontact sport and cites aquatics, hiking and Frisbee® as examples of low-risk activities (133). One study reported that activities least associated with risk of injury include water polo, walking, cross-country skiing and swimming (134); however, water polo may still carry a high risk of injury due to body contact that occurs underwater (135). Despite recommendations for low-impact sports, a lack of difference in rates of injury and frequency of bleeds has been observed when comparing low-impact versus high-impact sports, suggesting that with proper supervision, PWH should be able to engage in a wide range of activities (21,136).

Benefits of physical activity

Physical activity offers PWH significant health benefits with regard to joint, muscle and psychological health. Regular physical activity has been seen to strengthen joint-supporting muscles and help slow or prevent haemophilic arthropathy by reducing the risk of damage, improving joint flexibility and allowing better recovery from bleeds (104,130). In 50 adult PWH from the UK, there was a significant improvement in overall health-related quality of life and physical performance in patients participating in higher levels of sport (38). An assessment of exercise in a population of 30 Egyptian paediatric PWH demonstrated that aerobic and resistance training increased BMD, muscle strength and functional ability (137). The benefits of physical activity are further supported by evidence in the general population. Even in the absence of weight loss, physical activity can increase lean body mass by initiating skeletal muscle growth and have a positive effect on mental well-being, reducing levels of clinical depression (138). In addition, resistance training can promote lean mass and improve overall muscle strength/endurance in patients with limited mobility (139).

Table 5 Research questions for overweight/obesity in PWH

	Research questions/topics in haemophilia
1	What impact does overweight/obesity have on the implementation and efficacy of new treatment options in haemophilia, such as gene therapy?
2	What impact does haemophilia have on body composition and how does it relate to future risk of diabetes and cardiovascular disease?
3	How efficacious and safe are pharmacotherapy interventions and bariatric surgery in PWH affected by overweight/obesity?
4	How successful are lifestyle interventions in the context of PWH?
5	What impact does overweight/obesity have on bone mineral density in PWH?
6	What is the psychological impact of overweight/obesity in the context of PWH?
7	Does overweight/obesity increase the risk for joint surgery in PWH?
8	What is the effect of overweight/obesity on the pharmacokinetics of FIX?

FIX, factor IX; PWH, patients with haemophilia.

Conclusion

The global trend of increasing rates of overweight/obesity in the general population is a cause for significant concern. Epidemiological data suggest that the prevalence of overweight/obesity in European and US PWH generally reflects that observed in the non-haemophilic population; however, further assessment of PWH in developing nations is needed to identify prevalence globally. The burden of overweight/obesity may be particularly extensive in the haemophilia community, which is already at risk of blood-induced joint inflammation, muscle dysfunction and reduced range of motion due to spontaneous bleeding and haemophilic arthropathy. Overweight/obesity has implications for pharmacokinetics, musculoskeletal health, CVD and psychological health, although further research is required to fully elucidate the impact of excess adiposity in the context of haemophilia. Key research questions requiring further investigation by the community of clinicians treating haemophilia and obesity have been outlined in Table 5. The prevention and management of overweight/obesity in the context of PWH has additional considerations with regard to patient education, psychological support and, perhaps most importantly, engagement in physical exercise. Weight management considerations need to be strongly integrated into the haemophilia treatment pathway.

Conflict of interest statement

John Wilding has served as a consultant for Astellas, AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceutica, Lilly, Napp Pharmaceuticals, Novo Nordisk and Sanofi. Nichan Zourikian has no competing interests. Matteo Di Minno has served as a board member for Bayer, Novo Nordisk and Pfizer; a consultant for Bayer and Novo

Nordisk; a member of a speaker's bureau for Pfizer; and has received grants from Novo Nordisk and Pfizer; and funding for educational presentations for Novo Nordisk. Kate Khair has received travel funding and served as a consultant for Novo Nordisk. Natascha Marquardt has received travel funding from Novo Nordisk; has served as a consultant for Bayer, CSL Behring, Novo Nordisk, Pfizer and Sobi; a member of a speaker's bureau for Baxalta/Shire, Bayer, Octapharma, Pfizer, Roche/Chugai and Sobi; has received an institutional research grant from Pfizer; received funding for educational presentations for Novo Nordisk; and funding for additional activities from Baxalta/Shire, Novo Nordisk and Octapharma. Gary Benson has received travel funding from Novo Nordisk and served as a consultant and a member of a speaker's bureau for Novo Nordisk. Margareth Ozelo has received an institutional research grant from Bioverativ, Novo Nordisk, Pfizer and Shire; received travel support from Novo Nordisk; has served as a consultant for Novo Nordisk; has served as a board member for BioMarin, CSL Behring, Pfizer, Roche and Shire; and has served as a member of a speaker's bureau for Pfizer, Roche and Shire. Cedric Hermans has received travel funding and served as a consultant for Novo Nordisk.

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Data accessibility

This study included an analysis of existing data published in the MEDLINE database of references, which are available through PubMed (https://www.ncbi.nlm.nih.gov/pubmed). Data included in the meta-analysis can be obtained from the corresponding author.

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