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Distribution and predictors of haemophilia-related costs in the United Kingdom: analysis of the CHESS I and CHESS II burden of illness studies

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Abstract

Background Few studies have evaluated direct medical or societal costs of haemophilia in the United Kingdom (UK), and how patient characteristics impact future costs is uncertain. Cost predictors were identified and examined using cross-sectional data from the CHESS I and II studies.

Methods Patient- and physician-reported outcomes were analysed for UK adult males aged ≤ 65, with haemophilia A or B and no recent clinical trial participation. Demographics, haemophilia type and severity, inhibitors, annual bleed rate (ABR), problem joints (PJs), treatment type, and comorbidities, were utilised in regression analyses. Health-related quality of life was assessed using EQ-5D. Generalised linear models estimated expected non-drug haemophilia-related direct medical costs (DMC) and societal costs (non-drug DMC, direct non-medical and indirect costs). Average marginal effects (AMEs) determined predictors of cost.

Results Costs for 378 patients were analysed. Mean age was 33 years and 79% (299) had haemophilia A. Mean annual per-patient DMC were £165,001 (including factor treatment costs) and £4,091 when excluding factor replacement treatment costs (non-drug DMC). Mean annual per-patient non-treatment societal costs were £11,550 (standard deviation £20,171) among those with data available ($n = 51$). Number of PJs, ABR, and treatment regimen were significant determinants of haemophilia-related non-drug DMC (all $P < 0.001$). Non-drug DMC increased as ABR increased (AMEs were £2,018 for ABR 1–5, £3,101 for ABR 6–10 and £5,785 for ABR ≥ 11, vs. ABR 0) and by £1,869 per additional PJ. No significant predictors of non-drug haemophilia-related societal costs were identified. Mean EQ-5D score was 0.66, with lower scores observed for people with haemophilia B (0.48) compared with haemophilia A (0.71) and with increasing haemophilia severity.

Conclusions UK direct medical and societal costs of haemophilia are substantial. Non-drug DMC were particularly associated with ABR and number of PJs. These findings may be useful for real-world evaluations of the economic burden of haemophilia in the UK.

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Keywords Haemophilia, Burden, Cost, Annual bleed rate, Problem joint, Quality of life

Background

Congenital haemophilia is a rare genetic bleeding disorder caused by deficiency or absence of clotting factor VIII (haemophilia A) or IX (haemophilia B), and characterised by spontaneous bleeding episodes and delayed haemostasis [1]. Levels of endogenous clotting factor determine disease severity. Patients with <1 IU/dL (or <1%) of expected clotting factor have severe disease. Those with ≥1–5% have moderate disease and those with >5% to <40% have mild disease [2, 3]. Modern research designs also account for a 'moderately severe' category, where patients have levels between ≥1 to ≤2% and experience frequent bleeding episodes [4, 5]. Both subtypes of haemophilia are far more common in men, and in general, haemophilia A is approximately four times more prevalent than haemophilia B [6, 7]. In the United Kingdom (UK), from April 2022 to March 2023 inclusive, there were 6,662 males with haemophilia A (5,032 aged≥18 years, of whom 2,421 were treated with factor replacement or emicizumab) and 1,342 males with haemophilia B (1,022 aged≥18 years, of whom 479 were treated with factor replacement) [7].

In people with haemophilia, repeated bleeding episodes into muscles and joints, along with other organs or tissues, lead to musculoskeletal damage and acute and chronic pain. Bleeding negatively effects daily functioning substantially [8–11]. Persistent joint damage also leads to functional impairments and reduces health-related quality of life (HRQoL), for both people with haemophilia and their caregivers [10, 12]. More generally, daily life and HRQoL of people with haemophilia have been demonstrated to be significantly impacted by the condition [8, 10, 13–15]. The "problem joint" definition was developed to account for the holistic, patient-centric impact of joint morbidity, identifying any joint that has been permanently damaged as a result of a bleeding disorder, with or without persistent bleeding, as a joint of clinical interest [16, 17].

For people with moderate or severe haemophilia, prophylactic replacement of clotting factor has been the established standard of care for decades, to prevent or reduce bleeding episodes and associated morbidity [18–20]. More recently, a number of other therapies have emerged. Emicizumab, licensed in the UK for individuals with severe haemophilia A with or without inhibitors, is currently the only bispecific monoclonal antibody that mimics the function of missing activated factor VIII available in the market [21]. In addition, several investigational gene therapies for haemophilia A and haemophilia B are in development, and several gene therapy products are now licensed for the treatment of haemophilia A or B, in various countries.

Haemophilia-related socio-economic cost is substantial and it imposes a significant burden on patients, caregivers, the healthcare system, and society as a whole. Direct medical costs (DMC) of haemophilia are driven primarily by haemophilia drug costs (i.e., costs of factor replacement and other treatments), which are influenced by clinical factors such as disease severity and joint morbidity [22, 23]. Total societal costs (the total costs borne by society as a whole) of haemophilia are larger still, and are inclusive of DMC, direct non-medical costs and indirect costs. Direct non-medical costs are comprised of costs associated with a professional caregiver, travel, self-medication, walking aids and home adjustments, for which a direct cost is present, not born by the healthcare system, and is related to haemophilia. Indirect costs relate to work productivity outcomes (such as patient/caregiver absenteeism or early retirement) as well as caregiver burden (hours of care per week) of haemophilia [24–26].

A large body of literature examines the burden of haemophilia drug costs on healthcare systems [8, 26–28], but most of the available research is focused on very specific sub-populations, on examining costs of specific treatment regimens in different clinical scenarios, or on healthcare systems different from the UK [13, 22, 29–33]. To the authors' knowledge, there is no recent literature assessing UK-specific non-drug direct medical costs (non-drug DMC) and their drivers. Analysing non-drug DMC (i.e., once costs of factor replacement treatments and other drug treatments for haemophilia [if applicable] are excluded), combined with analysis of broader societal costs of haemophilia and their drivers, provides a useful insight into the healthcare system burden of haemophilia management aside from drug costs, which is frequently overlooked, and often substantial. Since the haemophilia treatment landscape is rapidly changing, these elements require more attention to allow emerging therapies to be evaluated from a holistic perspective. Also, as chronic joint damage is inherently interlinked with bleeding and is already present in many people with haemophilia, deeper understanding is needed of the impact of both chronic and acute outcomes related to joint bleeds and other bleeds, upon non-drug haemophilia costs.

The Cost of Haemophilia in Europe: A Socioeconomic Survey ('CHESS I' and 'CHESS II') studies were comprehensive 'bottom up' cost / burden of illness studies, designed to obtain and analyse the real-world economics and humanistic burden of haemophilia, including their relationship to various demographic and clinical variables and health outcomes. Conducted in several European countries, the CHESS studies illustrate that there are significant direct and indirect costs associated with haemophilia [26, 28]. While the CHESS I and CHESS II studies included approximately 300 and 255 patients with haemophilia from the UK, respectively, previous analyses of direct and indirect costs associated with haemophilia care using data from these studies also included data collected from patients in other European countries in their analyses [26, 28].

There is, therefore, limited published evidence assessing non-drug DMC of haemophilia and their drivers, as well as the broader societal costs of haemophilia, specifically in the UK. There also exists a paucity of information on how haemophilia-related costs may differ by demographic or clinical considerations, and on how to anticipate future costs. Therefore, UK-specific data from both CHESS I and II studies were merged and analysed to better understand direct medical and societal costs of haemophilia in the UK. Regression analyses were also conducted to identify predictors of haemophilia-related non-drug DMC (excluding factor replacement treatment costs), and predictors of societal costs (encompassing non-drug DMC, direct non-medical and indirect costs).

Table 1 Cost components included in cost calculations

Cost type	Category	Element
Direct medical	Hospitalisations	Day case Outpatient (e.g. for planned treatments) Inpatient – and lengths of stay
	Surgical procedures	Number, location and type of surgeries Length of stay Time spent in intensive care
	Acute events	Actions taken and management
	Consultant visits	Haematologist Other specialties
	Tests and examinations	Blood tests (factor-assay, haemoglobin, etc.) Other tests and examinations (diagnostic imaging, coagulation tests, etc.)
	Coagulation factor	Brand Dosage Frequency
Direct non-medical	Professional caregiver	Hourly wage Hours per week
	Travel costs	Car Public transport
	Requirement for aids/equipment	Walking aids Home adjustments
	Self-medication and alternative therapies	Over the counter (OTC) medications Holistic therapies Exercise and physiotherapy
Indirect	Work productivity impact	Absenteeism / presenteeism Early retirement
	Caregiver burden	Hours per week Work productivity impact for caregiver

Methods

CHESS I and CHESS II are cross-sectional studies of European male adults (≥18 years old) with haemophilia A or B. Both studies, while capturing many clinical and humanistic outcomes, focused on direct and indirect costs, recruiting patients through care providers based in hospitals and clinics [26, 28]. CHESS I included patients with severe haemophilia from the UK, France, Germany, Italy, and Spain. CHESS II included patients with haemophilia and any level of severity from Denmark, France, Germany, Italy, the Netherlands, Romania, Spain and the UK. This analysis only included patients from the UK who were ≤65 years of age on enrolment and were not currently participating in a clinical trial (and had not participated in a clinical trial in the previous 12 months), to optimise analysis of real-world evidence from patients in the UK on currently available treatments for haemophilia. Physicians had recruited consecutive eligible patients regardless of the reason for consultation visit, completing a web-based form with information derived from their medical history and previous consultations. Some patients also completed a paper-based questionnaire on self-reported health status, non-medical costs, and work impairment. Data were collected between 2014 and 2015 for CHESS I and 2018–2020 for CHESS II. All data were anonymised and encrypted to protect patients' personal data.

Outcomes

Primary objectives were to characterise DMC of haemophilia and identify predictors of non-drug DMC in the UK, as this could be useful to inform future haemophilia economic evaluations focused on the UK healthcare system perspective. DMC components were reported from physician review of patient medical charts, covering encounters occurring 12 months prior to enrolment. Haemophilia-related DMC included costs of physician consultation visits, hospitalisations, surgical procedures, tests and examinations, and factor replacement treatment costs (more details provided in Table 1). Factor replacement treatment costs were calculated based on drug costs sourced via the British National Formulary (BNF) and other publicly available sources.

Publicly available UK unit costs were applied to individual DMC components. These were obtained from the National Schedule of Reference Costs, the Electronic Medicines Compendium (EMC), the National Institute for Health and Care Excellence (NICE) and the British National Formulary (BNF). All direct medical costs are reported in 2020 GBP values.

Secondary objectives were to characterise haemophilia-related societal costs and identify predictors of these costs, and also to characterise patient-reported health-related quality of life (HRQoL) of adult males with haemophilia in the UK, which may be helpful for implementation of the societal perspective in future haemophilia economic evaluations. Societal costs were defined as the sum of all direct medical, direct non-medical and indirect costs (see Table 1 for components). Direct non-medical costs were estimated based on patient reports of their expenses and were collected within the patient survey. Societal costs were also captured at the patient level and covered the preceding 12 months.

Data on patient-reported HRQoL were captured using the 3-level EQ-5D in CHESS I and 5-level EQ-5D in CHESS II (www.euroqol.org). The EQ-5D includes five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-3 L offers 3 levels of severity for each domain ("none", "some", and "extreme/unable") and the EQ-5D-5 L offers 5 levels ("no problems", "slight problems", "moderate problems", "severe problems", or "extreme problems").

As the two CHESS studies used different scales, the EQ-5D-5 L domain observations from CHESS II were mapped onto the EQ-5D-3 L value set using the cross-walk mapping function developed by van Hout and colleagues [34], yielding similar results to method function developed by Hernandez Alava and colleagues [35]. A health state utility index was calculated for each patient's EQ-5D responses, ranging from 0 (equivalent to "dead") to 1 ("perfect health"). Health state utility values from published UK population norms were used to compare results with the general population [36].

Statistical analysis

Patient demographic and clinical characteristics, as well as DMC (both including and excluding factor replacement treatment costs), societal costs and patient-reported HRQoL scores, were summarised using descriptive statistics. Regression models were developed to identify predictors of non-drug DMC (primary objective) and societal costs (secondary objective). These models excluded factor replacement treatment costs, which are known to account for the vast majority of costs for treated patients [22], as this analysis sought to understand other drivers of medical and societal costs of haemophilia in the UK.

Model covariates included: age, body mass index (BMI), employment status, type of haemophilia (A or B), haemophilia severity, presence of inhibitors, annual bleed rate (ABR), problem joint (PJ) number, chronic pain severity, treatment regimen, annualised factor treatment consumption (in international units [IU]), physician-reported treatment adherence, and presence of various comorbidities (Appendix Table A1).

ABR was calculated as the sum of major and minor bleeds over the previous 12 months.

Minor bleeds were defined as mild pain, minimal swelling, and minimal restrictions of motion resolving within 24 h of treatment. Major bleeds were defined as involving pain, effusion, limitation of motion and failing to respond to treatment within 24 h. Problem joints (PJs) were defined as "chronic joint pain and/or limited range of movement due to compromised joint integrity, such as chronic synovitis and/or haemophilic arthropathy". This covariate was based on the presence or absence of problem joint(s) [16, 17]. Chronic pain severity was defined as "none" (no functional deficit; no analgesic use except with acute haemarthrosis), "mild" (does not interfere with occupation nor with activities of daily living, may require occasional non-narcotic analgesic), "moderate" (partial or occasional interference with occupation or activities of daily living; use of non-narcotic medications), or "severe" (interferes with occupation or activities of daily living; requires frequent use of non-narcotic and narcotic medications). Treatment regimen was defined as "No treatment", "On-demand" and "Prophylaxis" (with "Prophylaxis" also encompassing on-demand use of additional factor treatment due to bleeding events, surgical procedures or during hospitalisation) and was based on data abstracted by the physicians from the patients' medical charts.

Treatment adherence was based on physician perception of a patient's adherence to their current treatment regimen, indicated as "low", "moderate", or "high". Comorbidities were based on current record of diagnoses in medical charts at time of data extraction.

Target joints are defined as a joint where three or more spontaneous bleeds into a single joint occur within a consecutive 6-month period. Where there have been ≤2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint [2]. Though available in the dataset, this variable was not included in analyses due to overlap with the problem joint (PJ) metric and potential for collinearity with ABR. Additionally, as adherence is contingent on treatment type, and both on-demand and prophylaxis regimens were considered in this analysis, adherence was excluded from the list of covariates to avoid overlap with treatment strategy.

In exploration of the direct cost dependent variable in the primary model, costs tended to be heavily right skewed, so a generalised linear model with Gamma distribution and log-link function was applied to estimate expected haemophilia-related costs. Average marginal effects (AME) were computed to determine the effect of each covariate (predictor) on the dependent variable (non-drug DMC). Statistical significance was determined at the 5% alpha level ($P<0.05$) with corresponding 95% confidence intervals (CI).

Sensitivity analyses for the non-drug DMC model were conducted to examine results by haemophilia type (A or B) and severity (mild, moderate, moderately severe, or severe). Since societal costs were not available for the entire sample population, DMC and non-drug DMC were also explored among those with information on societal costs to explore consistency with the primary analysis population. No imputation of missing values was performed; patients with missing responses were excluded from the analysis. All analyses were performed using STATA® 16 (StataCorp LLC, College Station, Texas; www.stata.com).

Results

Patient characteristics

378 patients met the eligibility criteria and were included in the primary analysis of haemophilia-related DMC in the UK (300 from CHESS I, 78 from CHESS II). 51 patients (13.5%) also provided data for analysis of societal costs and HRQoL. Mean age for the overall cohort was 33 years, and most patients had haemophilia A ($n=299$; 79%; Table 2).

93% of patients had severe haemophilia of either type. At the time of data capture, 12 patients (3%) were diagnosed with an inhibitor to factor replacement therapy (haemophilia A: 10; haemophilia B: 2). 50% of patients were receiving a prophylaxis treatment regimen, 45% were receiving on-demand treatment (any treatment regimen that does not encompass continuous ongoing prophylaxis, also encompassing intermittent/situational prophylaxis) and 5% had no treatment recorded in patient charts in the preceding 12 months. All patients who received prophylaxis or on-demand treatment regimens were on standard half-life (SHL) factor replacement treatments. No patients in the study cohort received extended half-life (EHL) therapy, bispecific antibodies, re-balancing agents or gene therapy. In this working age cohort, aged ≥ 18 to ≤65 years, most patients reported full-time employment (68%), with 9% unemployed and 4% retired or physically unable to work.

Overall mean ABR was 3.8 (standard deviation [SD], 4.84). This differed numerically between haemophilia A and haemophilia B patients (3.4 and 5.1, respectively). ABR was also numerically different between patients receiving no treatment, on-demand, or prophylaxis (Table 2). Approximately half of the patients had at least one PJ and 60% reported to suffer from some level of chronic pain. The cohort of patients with evaluable information on societal costs and HRQoL ($n=51$) was slightly older (mean age of 38 years), with higher mean ABR (4.6). This sub-group included a higher proportion of patients with ≥1 PJ (63%) and with at least some level of chronic pain (73%) compared with the overall analysis cohort (Appendix Table A2).

Descriptive analysis

Cost outcomes

In the combined analysis of patients with haemophilia A or B, and considering all reported treatment regimens, mean annual haemophilia-related DMC were £165,001 per patient (SD, £192,398; $n=378$). More details and DMC associated with different treatment regimens are available in Table 3. Factor replacement (drug) costs constituted 98% (£160,910 [SD, £191,226]) of the total DMC.

Mean annual non-drug DMC was £4,091 per patient (SD, £6,939). Mean non-drug DMC varied by haemophilia type and severity (Table 3): mean (SD) non-drug DMC were £3,995 (£7,199.97) and £4,453 (£5,876.45) for patients with haemophilia A and B, respectively.

Mean non-drug DMC were highest in individuals receiving factor replacement on a prophylactic treatment regimen (£4,991 [£8,829]; $n=190$) and lowest in those receiving no treatment (£951 [£606]; $n=17$). This cost was found to increase with an increasing number of physician-reported ABR, with £1,761 (£3,363, $n=47$) for "0" ABR vs. £4,422 (£7,249, $n=331$) for ">0" ABR. Among those experiencing ">0" ABR, non-drug DMC were found to increase along with the number of reported bleeding events, ranging from £3,473 (£4,742) for "1–5" ABR, to £13,742 (£13,087) for "11–15" ABR. A similar pattern was observed for PJs (£1,939 [£2,372], $n=198$ for 0 PJ; £4,501 [£4,781], $n=98$ for 1 PJ; £8,795 [£12,213], $n=82$ for ≥2 PJs). Non-drug DMC were higher among patients with blood-borne viruses compared with those without (Table 3), and in those with inhibitors (£16,451 [£24,148], $n=12$ for inhibitors present vs. £3,686 [£5,194], $n=366$ for inhibitors absent) (Table 3).

Mean annual non-drug societal costs (sum of all non-drug direct medical, direct non-medical and indirect costs) were £11,550 per patient (SD £20,171; $n=51$). Societal costs appeared higher with worsening disease, such as among patients with at least 1 annual bleeding event compared with those with none (£11,768 for ABR>0 vs. £626 for ABR=0, respectively), and with an increasing number of PJs (£19,737 with ≥2 PJs; £4,048 with none) (Table A3).

The mean indirect cost was £9,140 per patient (SD £18,493; $n=51$) and represented, on average, 79% of the overall non-drug societal costs. Due to the negligible nature of direct non-medical costs (0.005% of total costs), these were aggregated into indirect costs in this analysis. Indirect costs were numerically higher in older patients, with a mean of £26,341 for patients aged over 55 years, compared with £6,071 for patients aged 18–25 years. Indirect costs also appeared numerically higher with

Table 2 Patient characteristics

Characteristic	Haemophilia A	Haemophilia B	Total
	(*n* = 299)	**(*n* = 79)**	**(*n* = 378)**
Age, mean (SD), in years	32.4 (12.54)	35.4 (14.11)	33.0 (12.93)
Age group (years), n (%)			
18–25	119 (40)	27 (34)	146 (39)
26–35	80 (27)	19 (24)	99 (26)
36–45	49 (16)	12 (15)	61 (16)
46–55	31 (10)	12 (15)	43 (11)
> 55-≤65	20 (7)	9 (11)	29 (8)
Body mass index category, n (%)			
Normal (18.5–24.9)	145 (49)	38 (48)	183 (48)
Underweight (Below 18.5)	14 (5)	2 (3)	16 (4)
Overweight (25.0–29.9)	115 (39)	25 (32)	140 (37)
Obese (30.0 and Above)	25 (8)	14 (18)	39 (10)
Employment status, n (%)			
Employed	204 (68)	51 (65)	255 (68)
Student	52 (17)	12 (15)	64 (17)
Unemployed	21 (7)	13 (17)	34 (9)
Retired or physically unable to work	12 (4)	3 (4)	15 (4)
Other	10 (3)	0	10 (3)
Haemophilia severity, n (%)*¥			
Mild	8 (3)	1 (1)	9 (3)
Moderate	12 (4)	3 (4)	15 (4)
Moderately severe	2 (1)	0	2 (1)
Severe	254 (92)	71 (95)	325 (93)
Missing severity on record	*n* = 23	*n* = 4	*n* = 27
Presence of inhibitors, n (%)	10 (3)	2 (3)	12 (3)
ABR, mean (SD)			
Major and minor bleeds	3.4 (4.18)	5.1 (6.63)	3.8 (4.84)
No treatment	2.1 (1.14), *n* = 14	4.0 (1.00), *n* = 3	2.4 (1.33), *n* = 17
Mild	1.3 (0.96), *n* = 4	3.0 (-), *n* = 1	1.6 (1.14), *n* = 5
Moderate	1.0 (-), *n* = 1	4.0 (-), *n* = 1	2.5 (2.12), *n* = 2
Moderately severe	0	0	0
Severe	0	0	0
On-demand treatment	3.1 (3.93), *n* = 135	4.6 (3.53), *n* = 36	3.4 (3.88), *n* = 171
Mild	1.3 (0.96), *n* = 4	0	1.3 (0.96), *n* = 4
Moderate	2.9 (1.51), *n* = 11	6.0 (4.24), *n* = 2	3.4 (2.18), *n* = 13
Moderately severe	2 (0), *n* = 2	0	2 (0), *n* = 2
Severe	3.2 (4.30), *n* = 109	4.6 (3.57), *n* = 33	3.5 (4.17), *n* = 142
Prophylaxis treatment	3.8 (4.54), *n* = 150	5.7 (8.71), *n* = 40	4.2 (5.70), *n* = 190
Mild	0	0	0
Moderate	0	0	0
Moderately severe	0	0	0
Severe	3.8 (4.61), *n* = 145	5.8 (8.92), *n* = 38	4.2 (5.81), *n* = 183
ABR category 1, n (%)			
0	35 (12)	12 (15)	47 (12)
> 0	264 (88)	67 (85)	331 (88)
ABR category 2, n (%)			
0	35 (12)	12 (15)	47 (12)
1–5	213 (71)	42 (53)	255 (68)
6–10	36 (12)	17 (22)	53 (14)
11–15	10 (3)	4 (5)	14 (4)
>15	5 (2)	4 (5)	9 (2)
Problem joints			

Table 2 (continued)

Characteristic	Haemophilia A (*n* = 299)	Haemophilia B (*n* = 79)	Total (*n* = 378)
Mean (SD)	0.8 (1.07)	0.87 (1.27)	0.82 (1.12)
0	158 (53)	40 (51)	198 (52)
1	75 (25)	23 (29)	98 (26)
≥ 2	66 (22)	16 (20)	82 (22)
Chronic pain, n (%)			
No pain	118 (40)	34 (43)	152 (40)
Mild	104 (35)	31 (39)	135 (36)
Moderate	64 (21)	11 (14)	75 (20)
Severe	13 (4)	3 (4)	16 (4)
Treatment regimen, n (%)			
Prophylaxis	150 (50)	40 (51)	190 (50)
Mild	0	0	0
Moderate	0	0	0
Moderately severe	0	0	0
Severe	145 (97)	38 (95)	183 (96)
Missing severity on record	5 (3)	2 (5)	7 (4)
On demand	135 (45)	36 (46)	171 (45)
Mild	4 (3)	0	4 (2)
Moderate	11 (8)	2 (6)	13 (8)
Moderately severe	2 (1)	0	2 (1)
Severe	109 (81)	33 (92)	142 (83)
Missing severity on record	9 (7)	1 (3)	10 (6)
No treatment	14 (5)	3 (4)	17 (5)
Mild	4 (29)	1 (33)	5 (29)
Moderate	1 (7)	1 (33)	2 (12)
Moderately severe	0	0	0
Severe	0	0	0
Missing severity on record	9 (64)	1 (33)	10 (59)
Treatment adherence, n (%)			
Low	101 (34)	34 (43)	135 (36)
Moderate	83 (28)	25 (32)	108 (29)
High	93 (31)	15 (19)	108 (29)
Not applicable	22 (7)	5 (6)	27 (7)
Presence of comorbid condition, n (%)			
Anaemia	27 (9)	3 (4)	30 (8)
Anxiety	36 (12)	8 (10)	44 (12)
Blood-borne viruses	26 (9)	7 (9)	33 (9)
Hepatitis B virus	4 (1)	2 (3)	6 (2)
Hepatitis C virus	13 (4)	5 (6)	18 (5)
Human immunodeficiency virus	15 (5)	2 (3)	17 (5)
Depression	21 (7)	15 (19)	36 (10)
Diabetes	14 (5)	0	14 (4)
Other	99 (33)	30 (38)	129 (34)

*Excludes patients with missing values (haemophilia A, 23; haemophilia B, 4; total, 27)

¥Haemophilia severity is defined as follows: Mild (factor level > 5 to < 40 IU/dl); Moderate (≥ 1 to 5 IU/dl); Moderately severe (≥ 1 to ≤ 2 IU/dl and experience frequent bleeding events); Severe (≤ 1 IU/dl)

ABR annual bleed rate, *SD* standard deviation

increasing condition severity, with notable differences between the mild and severe haemophilia groups (£85 vs. £10,441, respectively).

Increasing indirect costs were also observed between patients with at least 1 annual bleeding event compared with those with none (£9,322 vs. £32, respectively) and also in patients with an increasing number of PJs (£14,944 with ≥2 PJs; £3,199 with none) (Table A4). Patients with haemophilia A and ≥2 PJs had higher average non-drug societal costs than those with no PJs (£12,515 [£16,653],

Table 3 Annual per-patient haemophilia-related direct medical costs by key clinical characteristics

Subgroup, mean (SD) unless noted	Haemophilia A (*n* = 299); costs in £	Haemophilia B (*n* = 79); costs in £	Overall (*n* = 378); costs in £
Overall			
Excluding factor costs	3995.17 (7199.97)	4452.57 (5876.45)	4090.76 (6939.46)
Including factor costs[a]	148990.90 (161388.60)	225597.00 (273320.20)	165001.20 (192398.10)
Age group (years)			
18–25	4311.60 (8471.39)	2712.73 (3824.79)	4015.92 (7836.61)
26–35	3011.58 (3776.09)	4181.38 (5755.28)	3236.09 (4218.13)
36–45	5495.80 (10078.41)	6672.85 (7355.40)	5727.35 (9560.38)
46–55	3224.14 (3889.92)	4727.30 (6430.67)	3643.63 (4701.52)
> 55	3565.26 (3988.61)	6917.93 (7657.29)	4605.75 (5480.85)
Employment status			
Employed	3620.36 (5311.46)	4168.24 (6117.14)	3729.93 (5473.70)
Student	5070.40 (11654.48)	3589.44 (5372.16)	4792.72 (10739.35)
Unemployed	3845.09 (5167.50)	5164.18 (5763.82)	4349.45 (5356.08)
Retired or physically unable to work	8346.26 (12976.79)	9655.04 (1675.48)	8608.01 (11532.85)
Other	1143.96 (1049.58)	NE	1143.96 (1049.58)
Haemophilia severity			
Mild			
Excluding factor costs	1039.44 (472.64)	2176.35 (-)	1165.76 (582.31)
Including factor costs[a]	2899.44 (5403.88)	2176.35 (-)	2819.10 (5060.61)
Moderate			
Excluding factor costs	2513.20 (2329.76)	2050.87 (680.16)	2420.73 (2089.83)
Including factor costs[a]	32978.20 (34204.49)	34850.87 (45601.01)	33352.73 (34884.24)
Moderately severe			
Excluding factor costs	2592.42 (393.50)	NE	2592.42 (393.50)
Including factor costs[a]	55152.42 (2661.21)	NE	55152.42 (2661.21)
Severe			
Excluding factor costs	4290.20 (7726.63)	4704.45 (6143.12)	4380.70 (7402.76)
Including factor costs[a]	169845.10 (164889.50)	248839.80 (278832.50)	187102.40 (197728.60)
Treatment regimen			
Prophylaxis			
Excluding factor costs	4700.85 (9231.26)	6080.63 (7117.28)	4991.33 (8829.03)
Including factor costs[a]	255155.10 (159338.60)	411137.40 (273620.90)	287993.50 (198821.00)
On demand			
Excluding factor costs	3543.30 (4320.70)	2873.62 (3775.73)	3402.31 (4210.13)
Including factor costs[a]	46399.58 (64639.07)	38099.71 (57082.13)	44652.23 (63053.70)
No treatment			
Excluding factor costs	791.55 (517.67)	1692.54 (437.33)	950.55 (605.79)
Including factor costs[a]	791.55 (517.67)	1692.54 (437.33)	950.55 (605.79)
ABR category 1			
0	2219.67 (3799.49)	423.37 (256.00)	1761.04 (3363.43)
>0	4230.55 (7509.80)	5174.22 (6109.01)	4421.57 (7249.48)
ABR category 1, median (IQR)			
0	1219.04 (1178.77)	451.37 (357.55)	791.23 (921.13)
>0	1948.65 (3248.11)	1949.68 (7019.76)	1949.68 (3729.15)
ABR category 2			
0	2219.67 (3799.49)	423.37 (256.00)	1761.04 (3363.43)
1–5	3279.39 (4647.87)	4454.57 (5142.73)	3472.95 (4742.41)
6–10	6576.02 (13631.82)	3083.76 (4611.29)	5455.86 (11589.93)
11–15	13653.64 (15103.25)	13963.85 (7597.92)	13742.27 (13086.79)
>15	9016.47 (8696.68)	12825.33 (8681.90)	10709.30 (8373.28)
ABR category 2, median (IQR)			
0	1219.04 (1178.77)	451.37 (357.55)	791.23 (921.13)

Table 3 (continued)

Subgroup, mean (SD) unless noted	Haemophilia A ($n=299$); costs in £	Haemophilia B ($n=79$); costs in £	Overall ($n=378$); costs in £
1–5	1632.38 (2058.14)	1848.15 (6191.65)	1632.38 (2601.76)
6–10	2960.89 (4651.52)	1302.12 (1163.16)	2348.13 (4162.64)
11–15	8213.85 (3493.33)	14191.55 (12319.83)	8659.62 (12422.98)
>15	4214.36 (5140.21)	12515.32 (11947.75)	9033.33 (10041.06)
Number of problem joints			
0	1926.37 (2273.01)	1991.18 (2760.56)	1939.46 (2372.10)
1	4498.61 (4544.63)	4509.89 (5597.41)	4501.26 (4781.46)
≥ 2	8375.64 (13095.51)	10523.66 (7637.25)	8794.77 (12212.80)
Comorbidities[b]			
HBV			
No	3978.64 (7239.29)	4508.72 (5941.18)	4088.36 (6986.23)
Yes	5214.19 (3387.20)	2291.02 (1156.74)	4239.80 (3070.85)
HCV			
No	4024.10 (7321.17)	4157.36 (5533.40)	4051.49 (6984.28)
Yes	3358.57 (3728.70)	8821.73 (9440.56)	4876.12 (6092.97)
HIV			
No	3848.34 (7214.70)	4116.79 (5467.17)	3905.60 (6873.19)
Yes	6775.01 (6521.96)	17380.36 (8886.76)	8022.70 (7386.48)
Presence of inhibitors			
No	3518.77 (4993.73)	4311.36 (5879.02)	3685.52 (5194.02)
Yes	17762.93 (26468.33)	9889.31 (2473.19)	16450.66 (24148.39)

ABR annual bleed rate, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IQR* interquartile range, *NE* not evaluable, *SD* standard deviation

Direct medical costs exclude factor replacement treatment costs unless noted

[a]Drug costs sourced via the British National Formulary (BNF)

[b]Comorbidities reflect current diagnoses recorded in the medical chart at the time of data extraction

$n=10$ vs. £2,521 [£6,663], $n=18$; Table A3) and lower patient-reported HRQoL scores (0.69 [0.27] vs., 0.80 [0.17]; Table A5).

Health related quality of life

The mean HRQoL (EQ-5D) score in the whole haemophilia group was 0.66 (SD, 0.32; $n=51$). This appeared to decrease with worsening clinical status (severe haemophilia: 0.61; mild haemophilia: 0.92) (Appendix Table A5). Descriptive evaluation of HRQoL showed numerically worse scores among patients with haemophilia B (0.48 [0.47]; $n=10$) compared with those with haemophilia A (0.71 [0.26]; $n=41$) (Table A5). HRQoL scores also decreased as haemophilia A severity increased (EQ-5D: 0.66 [0.28], $n=30$ for severe haemophilia A vs. 0.74 [0.15], $n=3$ for moderate haemophilia A and 0.92 [0.12], $n=2$ for mild haemophilia A). The sample of patients with haemophilia B and HRQoL scores was too small for descriptive comparison by severity. EQ-5D scores progressively worsened with increasing number of bleeding episodes (range: -0.31 to 1.00). Moreover, those with either a hepatitis C virus (HCV) or human immunodeficiency virus (HIV) diagnosis had lower mean EQ-5D scores than those without such a diagnosis. These trends were also observed when broken down by haemophilia subtype.

Regression analysis of haemophilia-related costs

The regression model identified that number of PJs, ABR, and treatment regimen (prophylaxis or on-demand vs. none) were significant determinants of haemophilia-related non-drug DMC (Table 4). For all patients, holding all other variables constant including haemophilia subtype, non-drug DMC increased by £1,869 (per PJ) as the number of PJs increased ($P<0.001$).

Compared with patients with an ABR of 0, non-drug DMC increased by £2,018 for those with ABR 1–5, by £3,101 for those with ABR 6–10, and by £5,785 for those with ≥11 ABR (all $P<0.001$) (Table 4). Compared with patients not receiving any haemophilia treatment, non-drug DMC were £2,097 greater for those receiving on-demand treatment and £2,662 greater for those receiving prophylaxis (both $P<0.001$). Age, haemophilia type and presence of inhibitors were not significant predictors of non-drug DMC (Table 4).

Subgroup analyses by haemophilia type and severity yielded similar findings to those arising from the primary direct cost models, with some exceptions (Appendix Table A6). PJs, ABR, treatment regimen (prophylaxis or on-demand vs. none), and presence of inhibitors were significant predictors of non-drug DMC in the model exclusive to patients with haemophilia A ($n=299$),

Table 4 Predictors of haemophilia-related non-drug direct medical costs

Predictor	Incremental Cost vs. Reference Value	95% CI	*P* Value
Age (years)	£6	(–33, 45)	*P* = 0.755
Haemophilia type, B vs. A	£–209	(–1364, 945)	*P* = 0.722
Inhibitors, Yes vs. No	£4920	(–592, 10432)	*P* = 0.080
ABR, vs. 0			
1–5	£2018	(1197, 2839)	*P* < 0.001
6–10	£3101	(1446, 4757)	*P* < 0.001
≥ 11	£5785	(2282, 9287)	*P* < 0.001
Problem joints[a]	£1869	(1149, 2589)	*P* < 0.001
Treatment regimen, vs. none			
On demand	£2097	(892, 3303)	*P* < 0.001
Prophylaxis	£2662	(1427, 3898)	*P* < 0.001
Comorbidities, Yes vs. No			
Blood-borne virus[b]	£–427	(–2124, 127)	*P* = 0.622
Other	£701	(–337, 1738)	*P* = 0.186

ABR, annual bleed rate; CI, confidence interval

[a] Effect on haemophilia-related direct medical cost per problem joint

[b] Presence of a comorbid blood-borne virus (*n* = 33) vs. no recorded blood-borne virus (*n* = 345) was associated with numerically but not statistically significantly lower direct medical costs

whereas only ABR and prophylaxis were significant among those with haemophilia B (*n* = 79).

Only 9 patients were included in the model of patients with mild haemophilia, where PJs, ABR (1–5 vs. 0), and on-demand treatment were significant predictors of non-drug DMC. Among patients with moderate haemophilia (*n* = 15), age, ABR (6–10 vs. 0), having haemophilia B (vs. A), presence of inhibitors, and having 'other' comorbidities, were significant determinants of non-drug DMC. A moderately severe haemophilia model was not feasible as only 2 patients were in this sub-group. Among patients with severe haemophilia (*n* = 325), number of PJs and all ABR categories (above 0) were significant predictors of non-drug DMC (Table A6).

The regression model for societal costs identified no significant predictors of haemophilia-related non-drug societal costs (sum of all non-drug direct medical, direct non-medical and indirect costs) among the demographic and clinical parameters available for analysis (*n* = 51; Appendix Table A7).

Discussion

This study examined haemophilia-related direct medical and societal costs and their predictors, and HRQoL scores, in UK adult males with haemophilia A or B, based on CHESS I and II data. Prominent indicators of clinical status (ABR and number of PJs), and haemophilia treatment regimen (prophylaxis, on-demand or no current treatment) were predictive of haemophilia-related non-drug DMC. Increasing ABR and number of PJs predicted increasing non-drug DMC, suggesting that non-negligible healthcare resource use is required to manage clinical outcomes such as repeated bleeding and subsequent joint damage sequelae, and these have a meaningful influence on the DMC of haemophilia after excluding the costs of factor replacement treatment. These increased costs are likely due to increased emergency room and hospital visits, more frequent haematologist consultations, tests and diagnostic procedures, increased need for joint procedures and increased use of analgesics, and other OTC medications. While the descriptive assessment of societal costs showed large discrepancies based on clinical status, including greater costs in those with a higher ABR and a higher number of PJs, the regression model did not identify any significant predictors of non-drug societal costs among the covariates available for analysis.

Indirect costs showed wide discrepancies dependent on clinical status, with the largest differences identified in relation to ABR, number of PJs and severity of haemophilia, and also relation to demographic characteristics, including age. Additionally, indirect costs were identified as a major societal cost component, representing almost 80% of overall non-drug societal costs. The descriptive assessment of patient-reported HRQoL scores suggested worse health state evaluations with worsening condition severity, increased frequency of bleeding outcomes, and increased treatment frequency (continuous prophylaxis versus on-demand).

Investigation of subgroups suggested that fundamental indicators of clinical status tended to predict non-drug DMC. Increased ABR was predictive of non-drug DMC in patients with haemophilia A or B, at any level of haemophilia severity. Having more PJs was also a significant predictor of non-drug DMC for those with haemophilia A and for those with mild or severe disease. Treatment regimen was also observed to be a significant predictor of non-drug DMC in both haemophilia A and B (only prophylaxis was significant for haemophilia B) and for mild haemophilia. Presence of inhibitors was an influential variable among those with moderate disease or with haemophilia A, commensurate with a greater observed prevalence of inhibitors within patients with haemophilia A versus haemophilia B in this cohort.

HRQoL scores were lower for patients with haemophilia B versus A, and in fact HRQoL scores for haemophilia A patients in this UK cohort appeared comparable with those in the larger European CHESS studies (mean EQ-5D scores, 0.71 and 0.73 from 41 to 514 patients, respectively) [37]. The HRQoL scores in the haemophilia B cohort illustrate the impact of the presence of comorbidities, high bleeding rates and disability.

To the authors' knowledge there are no other studies which currently provide context to these findings. Analyses of haemophilia-related costs in other countries, typically the United States, generally tend to focus on costs of factor replacement therapy and/or include populations too fundamentally different from this UK analysis to lend contextual merit (such as US Medicare beneficiaries aged ≥ 65 years) [22, 31–33].

Our findings showed that approximately half of the sample were receiving a prophylaxis treatment regimen, 45% were receiving on-demand treatment and 5% had no record of recent treatment in the past 12 months, in line with results from a 2017 report by Berntorp and colleagues [38], based on 2012–2014 data from 7 European countries, including the UK. However, our analysis benefitted from the use of real-world data from medical chart extractions and physician- and patient-reported outcomes. The procurement of data regarding key clinical outcomes such as ABR and PJs from the medical chart may be more relevant to policy and population health evaluations than stringent clinical definitions. As such, the applicability of our findings should be useful to those examining the burden of haemophilia within and across the UK. However, these results should be interpreted with care owing to the limited sample size in our study, therefore future research with larger sample sizes and longitudinal data collection is warranted.

We also provided descriptive assessments of the outcomes of interest based on merged data from CHESS I and CHESS II and conducted rigorous regression analyses to identify influential variables for the dependent outcomes (direct medical and societal costs after excluding the costs of factor replacement treatment). However, clinical guidance regarding prophylaxis treatment for patients with moderate or severe haemophilia has been updated since these data were collected [3, 39], therefore patients included in this study may have received different treatment regimens, using different products, compared with current UK standard of care.

Additionally, results may have been influenced by the larger proportion of patients with severe haemophilia present in the sample, compared with the number with mild and moderate haemophilia. The limited sample size, as well as the potential for selection and reporting biases inherent to observational data sources and self-reported outcomes, the time period of data collection (2015 for CHESS I and 2018–2020 for CHESS II) and the potential differences between publicly available list prices and costs of factor replacement treatments actually incurred by the NHS, should also be considered when interpreting results, including the potential for these to affect generalisability to the total UK population with haemophilia. Additionally, despite screening of data by the research team based on general clinical and demographic characteristics (i.e., date of birth, date of diagnosis, type and severity of haemophilia) to prevent duplication, due to the de-identified nature of the data analysed in the context of CHESS I and CHESS II, some of the participants may have been part of both studies at different points in time, potentially leading to some level of confounding.

Unmeasured variables, such as perceived severity of condition-related outcomes, patient condition knowledge, or household income, may have also influenced results. The lack of significant predictors of non-drug societal costs in our model may, in part, be attributable to such factors.

Conclusions

This study has shown that DMC of haemophilia in the UK, beyond the costs of factor replacement therapy, are significantly associated with key determinants of clinical status, particularly frequency of bleeding events (ABR) and chronic joint damage (presence of PJs). Indicators of greater disease burden, such as greater haemophilia severity and a higher number of PJs, tended to predict increased direct medical and societal costs, as well as worse patient-reported HRQoL.

These findings highlight the economic and societal importance of optimising joint health and minimising bleeding events in haemophilia management. By demonstrating the significant economic, clinical and humanistic burden of haemophilia in the UK, this study may also be useful in informing valuations of the real-world burden of haemophilia in the UK. This may inform policy and health technology assessments of emerging treatments for haemophilia that aim to further reduce ABR and improve overall clinical outcomes.

Abbreviations

ABR	Annual bleed rate
AME	Average marginal effects
BMI	Body mass index
BNF	British National Formulary
CHESS	Cost of Haemophilia in Europe: A Socioeconomic Survey
CI	Confidence interval
DMC	Direct medical costs
EHL	Extended half-life therapy
EMC	Electronic Medicines Compendium, a National Schedule of Reference Costs
EQ-5D	Standardised measure of health-related quality of life developed by the EuroQol Group
HBC	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IQR	Interquartile range
IU	International units
NICE	National Institute for Health and Care Excellence
OTC	Over-the-counter
PJ	Problem joint
SD	Standard deviation
SHL	Standard half-life therapy
UK	United Kingdom

Supplementary Information

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Supplementary Material 1

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Authors' contributions

TB, EFG and JOH designed the study, and analysed and interpreted the data. IW, JB, JG and ML contributed to the study design and interpretation of the data. LR and AC also contributed to interpretation of the data. All authors participated in the manuscript development and final approval for submission.

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Data availability

The dataset supporting the conclusions of this article may be available from HCD Economics Ltd., but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may be available from the authors upon reasonable request and with permission of HCD Economics Ltd.

Declarations

Ethics approval and consent to participate

The CHESS I and CHESS II studies were approved by the Research Ethics Sub Committee of the Faculty of Health and Social care within the University of Chester and conducted in correspondence with regional and relevant guidelines. Patient consent for use of clinical data was not required (as per European Pharmaceutical Market Research Association [EPhMRA] guidelines). Patient consent was obtained via tick box selection for the patient-reported element of the studies.

Consent for publication

Not applicable.

Competing interests

This study was sponsored by Pfizer Ltd. TB and EFG are employees of HCD Economics Ltd., which was a paid consultant to Pfizer Ltd. in connection with the development of this manuscript and for study design, data analysis and interpretation. EFG: Speakers' bureau: Sobi, Roche, Novo Nordisk, BioMarin, CSL Behring; Advisory boards: Sobi, Roche, BioMarin, Pfizer. IW and LR are employees of Pfizer Ltd., the study sponsor. JOH was an employee of HCD Economics Ltd. during the conduct of the study. IW, AC, JB and LR were employees of Pfizer Ltd. during the conduct of this study. JB is currently employed by BioMarin Pharmaceutical Inc. ML was a paid consultant to Pfizer Ltd. in relation to study design and data interpretation for this study and also declares the following: Consultant to AstraZeneca, Silence, Hemab; Research grant support from BioMarin; Speaker fees from Pfizer, Bayer, Takeda, Leo Pharma, Sobi, AstraZeneca, Chugai/Roche; Advisory boards: Takeda, LFB, Roche/Chugai, Sobi, Bayer, Pfizer, CSL Behring, BioMarin. JG was a paid consultant to Pfizer Ltd. in relation to study design and data interpretation for this study and has been a paid consultant to HCD Economics Ltd. in relation to a separate haemophilia study.

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