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CLINICAL RESEARCH

Real-world clinical and psychosocial outcomes among people with mild or moderate haemophilia A treated on-demand in the Italian CHESS II cohort: a real-world data analysis

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Analysis of the Italian cohort of adults with mild or moderate haemophilia A in the CHESS II dataset shows a meaningful clinical and psychosocial burden of disease, impacted by bleeding events, chronic pain, anxiety, depression, and limitations on activities of daily life

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Background: The burden of severe haemophilia A (HA) has been studied extensively owing to the higher bleeding frequency and associated treatment requirements, leaving a clear unmet need for research focused on the burden of mild and moderate HA. **Aims:** This study sought to characterise the clinical and psychosocial burden of mild and moderate HA in the Italian cohort of the CHESS II study. **Methods:** This was a retrospective analysis of clinical and psychosocial outcomes in a cohort of male adults (≥18 years old) with mild or moderate HA who participated in the cross-sectional CHESS II study (October 2019-November 2020). Treatment patterns, acute and chronic clinical outcomes and mental health indicators were collected via physician-completed forms. Psychosocial outcomes related to impact of HA on social activities, exercise, opportunities, and lifestyle were collected via a participant self-complete questionnaire. All results were reported descriptively. **Results:** A total of 113 people with haemophilia A (PwHA) were included, 79 (70%) with moderate HA and 34 (30%) with mild HA, with mean age of 41.4 and 36.6 years, respectively. No one in the sample was receiving a prophylaxis at the time of data capture, with factor VIII use in the 12 months prior reported in 30% and 29% of moderate and mild PwHA, respectively. Ninety-one PwHA (81%) experienced ≥1 bleeding event in the preceding 12 months. People with moderate HA had higher mean annual bleed rate (2.9 vs. 1.1, respectively) and higher prevalence of chronic pain (74% vs. 35%), anxiety (20% vs. 12%), and/or depression (15% vs. 3%). Target joints were reported in 22% and 12% of moderate and mild PwHA, and problem joints in 51% and 12%, respectively. Of 113 participants, 44 (39%) completed the self-complete form (moderate HA, 57%; mild HA, 43%). Overall, 40% vs. 10% of those with moderate vs mild HA reported reducing or giving up social activities, 44% vs. 21% reducing or giving up exercise, 36% vs. 26% missing out on opportunities, and 48% vs. 26% reported HA impacted their lifestyle. **Conclusion:** Moderate PwHA from the Italian CHESS II cohort appeared to have greater clinical morbidity and lifestyle impact than mild PwHA. Psychosocial outcomes were also worse among moderate PwHA, but significant burden was also observed among mild PwHA. These findings, and the absence of prophylactic treatment in the sample examined, highlight that improving management for potentially undertreated mild/moderate PwHA may aid the avoidance long-term clinical morbidity and negative psychosocial impact.

Keywords: *Haemophilia A, Annual bleeding rate, Joint arthropathy, Pain, Patient-reported outcomes, Health-related quality of life, Psychosocial burden*

Haemophilia A (HA) is a congenital X-linked bleeding disorder characterised by periodic bleeding events caused by an absence or deficiency of clotting Factor VIII (FVIII) [1,2]. The severity of HA is determined by endogenous FVIII activity levels, classified as mild (>5% to <40% of normal FVIII levels), moderate (1% to 5%), or severe (<1%) [2,3]. Across severity levels, the prevalence of HA is estimated to be approximately 24.6 cases per 100,000 male births [4]. Spontaneous or traumatic intra-articular or intra-muscular bleeding events are associated with substantial clinical sequelae and an ongoing burden on work productivity and health-related quality of life (HRQoL) [5-8].

The burden of severe HA has been studied more extensively than that of mild or moderate HA owing to the greater frequency of bleeding events and associated treatment requirements with mild or moderate HA generally being regarded as less severe, with long-term effects of cumulative bleeding events and impact on quality of life of people with haemophilia (PwH) with mild or moderate condition given less consideration [6,9-14]. Additionally, due to the lack of focus on this population, the burden of mild and moderate haemophilia has not been well characterised, with the need for more research on the impact of mild and moderate HA has emphasiSed in recent publications [15,16]. The scarce available literature highlights potential challenges in seeking or obtaining care, prevalence of chronic and acute pain and joint health issues and potential for substantial physical and psychosocial impact [17]. However, European data remains sparse and heterogeneous, making the characterisation of burden difficult [15].

In recent years, the Cost of Haemophilia in Europe: A Socioeconomic Survey II (CHESS II) population study has provided insight into the real-world burden of HA in Europe, with some analyses seeking to quantify the differential impact of severe vs mild or moderate HA on health-related quality of life (HRQoL) and costs [18,19]. However, the need for European and country-specific research focused on the burden of mild and moderate HA remains.

Haemophilia care in Italy has been historically heterogeneous due to the country's peculiar regional health organisation model, where each of the 20 regions holds financial and administrative responsibility

on the provision of healthcare [20]. In larger regions, haemophilia care is often organised with the 'hub and spoke' model [20,21], with a national network of 54 accredited centres between comprehensive care centres (CCCs) and haemophilia treatment centres (HTCs) [22,23]. Recent efforts have been put in place by the Association of Italian Haemophilia Centres (AICE) to improve access to care and standardise the organisation and professional accreditation of haemophilia centres in Italy. This aims to address differences in availability and access to care across the country, in the context of previous reports of considerable proportions of PwH having to travel long distances and/or relocate to access care, or reporting difficulties/delays in treatment dispensation or in accessing their centre [20,24,25].

Mild and moderate HA represent approximately 56% of the Italian HA population monitored via the National Registry of Congenital Coagulopathies; however, this figure may be under-representing reality due to the potential under-diagnosis of milder bleeding disorders [16,22,26]. While a substantial proportion of participants in the CHESS II study have been from Italy [19,27,28], no analyses have been performed at the national level specifically focusing on mild/moderate HA. To this end, this analysis sought to characterise the clinical and psychosocial burden of mild and moderate HA in the Italian cohort of the CHESS II study.

METHODS

Data source and study population

We conducted a retrospective analysis of clinical and psychosocial outcomes among adults with mild or moderate HA living in Italy who participated in the CHESS II study. The design, methods and primary findings from the broader CHESS II study cohort have been reported previously [29]. The CHESS II study is a panel-based cross-sectional burden of illness study of male adults (≥18 years old) with congenital haemophilia A or B of any severity, with or without inhibitors, conducted between October 2018 and November 2020 in eight European countries (France, Germany, Italy, Spain, the United Kingdom, Romania, Denmark, and the Netherlands). The panel was composed by 173 haematologists (or haemophilia care providers, in France) treating at least eight PwH and practicing in one of the countries of interest. All demographic and clinical characteristics, as well as treatment patterns and health resource utilisation information, were reported by the treating physicians via a web-based form and abstracted from medical notes. Upon consenting to participate in the study, PwH were invited by their physician to complete a patient questionnaire with information relating to their health status (via the EQ-5D-5L) [30], work productivity and activity impairment (via the WPAI instrument) [31], and non-medical haemophilia-related costs, as well as information on the overall humanistic impact of haemophilia. People with severe HA or with haemophilia B and who were not living in Italy at the time of data collection were excluded from this analysis.

All participants who completed the patient questionnaire in the CHESS II study provided informed consent. The CHESS II study was approved by the Research Ethics Sub-Committee of the Faculty of Health and Social Care within the University of Chester, conducted in correspondence with regional and relevant guidelines and governed by an expert reference group. Participant consent for use of physician-reported clinical data was not required as per European Pharmaceutical Market Research Association (EPhMRA) guidelines. Participant consent was obtained via tick box selection from PwH wishing to also complete the patient questionnaire prior to the collection of any patient-reported data.

Variables and outcomes

This study evaluated treatment patterns and corresponding clinical and psychosocial outcomes among a sample of people with mild or moderate HA in Italy stratified by HA severity. Data were collected from a physician-completed, web-based clinical record form (CRF) and a corresponding linked patient self-complete (PSC) questionnaire completed by the participating person with HA. The CRF contained information about the person's medical history and consultations, and the PSC covered non-medical costs, psychosocial outcomes, HRQoL, and work impairment. This analysis focused on physician-reported clinical outcomes and on self-reported psychosocial outcomes from the PSC questionnaire.

Treatment patterns included the physician-reported treatment strategy for each person with HA including the number of on-demand FVIII infusions in the 12 months immediately prior to data collection. The number of on-demand FVIII infusions was estimated via the physician reported total 12-month yearly IU consumption and the reported IU/kg dosage.

Clinical endpoints of interest were reported by physicians and included annual bleeding rate

(ABR) in the 12 months immediately preceding data capture, target joints, problem joints, chronic pain, and prevalence of anxiety and/or depression. A target joint was defined according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) as "three or more spontaneous bleeds into a single joint 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" [3]. A problem joint was defined as "any joint that has been permanently damaged as a result of a bleeding disorder, with or without persistent bleeding, and may involve chronic pain and/or limited range of movement due to compromised joint integrity such as chronic synovitis and/or hemophilic arthropathy" [32]. The patient-centric 'problem joint' definition aims to characterise joint damage associated with chronic joint pain and/or limited range of motion due to compromised joint integrity, as distinguished from the historical target joint definition of the ISTH [32]. Chronic pain was reported by the physician as part of the CRF, taken from clinical consultations including patient-reported pain, functional limitations due to pain and use of analgesics. The proportion of people with HA who experienced anxiety and/or depression was captured within the comorbidity section of the CRF from the physician-extracted medical records.

Psychosocial outcomes were captured in the PSC using a 5-point Likert scale. Participants reported having to 'reduce or give up' social activities or exercise, missing out on opportunities, and having feelings of frustration with the impact of HA on their lifestyle ranging from 'strongly agree' to 'strongly disagree'.

Statistical analysis

Descriptive statistics were used to summarise participant characteristics, treatment patterns, and clinical and psychosocial outcomes. Means and standard deviations (SD) were used to describe continuous variables and frequency and proportions to describe categorical variables. All characteristics were reported by HA severity (mild or moderate). By assuming a 40 IU/kg dose (agreed as a relevant median dosage by the haemophilia clinical experts) and based on the physician-reported 12-month FVIII IU consumption, the number of on-demand infusions was estimated as (Total yearly IU consumption)/(weight ×40) . All analyses were conducted using STATA version 17.0 (StataCorp LLC, College Station, TX, SUA; www.stata.com).

RESULTS

Study population

Of the 1337 participants in the CHESS II study, 406 (30%) were residents of Italy at the time of data collection, of whom 278 (69%) had HA of any severity. The final study cohort comprised 113 people, of whom 34 (30%) had mild HA and 79 (70%) had moderate HA. People with moderate HA were slightly older than those with mild HA (mean age, 41.4 and 36.6 years, respectively), and a greater proportion were categorised as having a normal body mass index (61% and 53%, respectively) (Table 1).

Treatment patterns and clinical characteristics

No participants in this mild/moderate HA subsample of the Italian CHESS II cohort was receiving a prophylaxis treatment regimen at the time of data collection, with 29% and 30%, respectively, reporting any FVIII use (on-demand) in the 12 months preceding data collection (Table 1). Based on total physician-reported IU consumption in the 12 months prior to data collection, it was estimated that the mean (SD; median) number of on-demand FVIII infusions were 9.6 (8.1; 6.5) and 13.0 (13.0; 9) for those with mild or moderate HA, respectively.

Overall, the majority of those within the sample had ≥1 bleeding event in the 12 months preceding data collection (n=91/113, 81%). Compared with mild HA, people with moderate HA had a higher mean ABR (2.9 vs. 1.1, respectively), and a greater proportion of those with moderate vs. mild HA were reported to suffer from chronic pain (74% vs 35%), anxiety (20% vs 12%), and/or depression (15% vs 3%) (Table 1). The majority of people with mild (74%) or moderate (85%) HA had ≥1 bleeding event in the year immediately preceding data collection. While in the mild HA cohort all bleeding events were reported as post-traumatic, mean (SD) spontaneous ABR was 0.88 (0.93) in the moderate cohort, with 72% reported to have experienced spontaneous bleeding. Reported mean baseline FVIII levels were 21.0 (10.3) and 3.5 (1.2) for mild and moderate cohort, respectively. No relevant differences were found in baseline FVIII level between the cohort with ≥1 bleeding event and those with no bleeding, regardless of severity (Table 1). Approximately one-fifth (19%, n=21) of all people with mild or moderate HA in the cohort had ≥1 target joint, and more than one-third (39%, n=44) had ≥1 problem joint. Target joints were prevalent in 12% and 22% of those with mild or moderate HA, and problem joints in 12% and 51%, respectively.

Table 1. Demographic characteristics and clinical outcomes of people with mild or moderate haemophilia A

	MILD HA (N=34)	MODERATE HA (N=79)
Age		
Mean (SD)	36.6 (12.0)	41.4 (14.1)
Median (IQR)	37.0 (27.0, 42.0)	41.0 (29.0, 54.0)
Age, n (%)		
18-35	15 (44)	31 (39)
36-59	16 (47)	39 (49)
≥60	3 (9)	9 (11)
Body mass index, n (%)		
Underweight	0 (0)	1 (1)
Normal weight	18 (53)	48 (61)
Overweight	16 (47)	28 (35)
Obese	0	2 (3)
Current treatment regimen, n (%)		
On-demand	10 (29)	24 (30)
No recent FVIII treatment[a]	24 (71)	55 (70)
Prophylaxis	0	0
ABR (all cause)		
Bleeding reported, n (%)	24 (71)	67 (85)
Mean (SD)	1.1 (0.9)	2.9 (2.7)
Median (Q1, Q3)	1.0 (0.0, 2.0)	2.0 (1.0, 4.0)
ABR (spontaneous)[b]		
Spontaneous bleeding reported, n (%)	-	57 (72)
Mean (SD)	-	0.88 (0.93)
Median (Q1, Q3)	-	0.6 (0, 1.2)
ABR, n (%)		
0	10 (29)	12 (15)
1	14 (41)	14 (18)
≥2	10 (29)	53 (67)
Baseline factor level (overall)		
Mean (SD)	21.0 (10.3)	3.5 (1.2)
Median (Q1, Q3, range)	20 (11, 30, 5.01-40)	4 (3, 5, 1-5)
Baseline factor level in those reporting a bleeding event		
Mean (SD)	21.3 (9.8)	3.4 (1.3)
Median (Q1, Q3, range)	20 (15, 27, 5.1-37)	3.3 (2.3, 5, 1-5)
Target joints		
Mean (SD)	0.1 (0.3)	0.3 (0.7)
Median (Q1, Q3)	0	0
Target joints, n (%)		
0	30 (88)	62 (79)
1	4 (12)	11 (14)
≥2	0	6 (8)
Problem joints		
Mean (SD)	0.1 (0.4)	0.7 (0.8)
Median (Q1, Q3)	0	1.0 (0.0, 1.0)
Problem joints, n (%)		
0	30 (88)	39 (49)
1	3 (9)	26 (33)
≥2	1 (3)	14 (18)
Chronic pain level, n (%)		
None	22 (65)	21 (27)
Mild pain	11 (32)	41 (52)
Moderate pain	1 (3)	17 (22)
Severe pain	0	0
Anxiety, n (%)	4 (12)	16 (20)
Depression, n (%)	1 (3)	12 (15)

Note: Proportions may not sum to 100% due to rounding
[a] "No recent FVIII treatment" was indicated if no FVIII therapy had been used in the preceding 12 months
[b] The spontaneous ABR was extrapolated using the physician-reported proportion of spontaneous bleeding events and the all cause ABR
ABR: annual bleeding rate
HA, haemophilia A
Q1, Q3: Quartile 1, Quartile 3
SD, standard deviation

Psychosocial outcomes

Of the 113 CHESS II participants with mild or moderate HA living in Italy at the time of data collection, 44 (39%) completed the PSC (mild HA, n=19, 43%; moderate HA, n=25, 57%). A greater proportion of those with mild HA (n=19/34, 56%) completed the PSC than those with moderate HA (n=25/79, 32%). Similar to the overall cohort, people with moderate vs. mild HA had more annual bleeding events, greater joint morbidity and chronic pain (Supplementary Table S1).

Consistent with the clinical outcomes among the cohort completing the patient questionnaire, a greater proportion of people with moderate HA than mild HA reported having to compromise psychosocial aspects of life, including social activities, exercise, and opportunities, due to their HA (Figure 1). Overall, 40% vs. 10% of those with moderate vs mild HA, respectively, had to reduce or give up on social activities ('Agree' or 'Strongly agree'), 44% vs. 21% had to reduce or give up exercise, 36% vs. 26% reported missing out on opportunities, and 48% vs. 26% felt frustrated by the influence of HA on their lifestyle.

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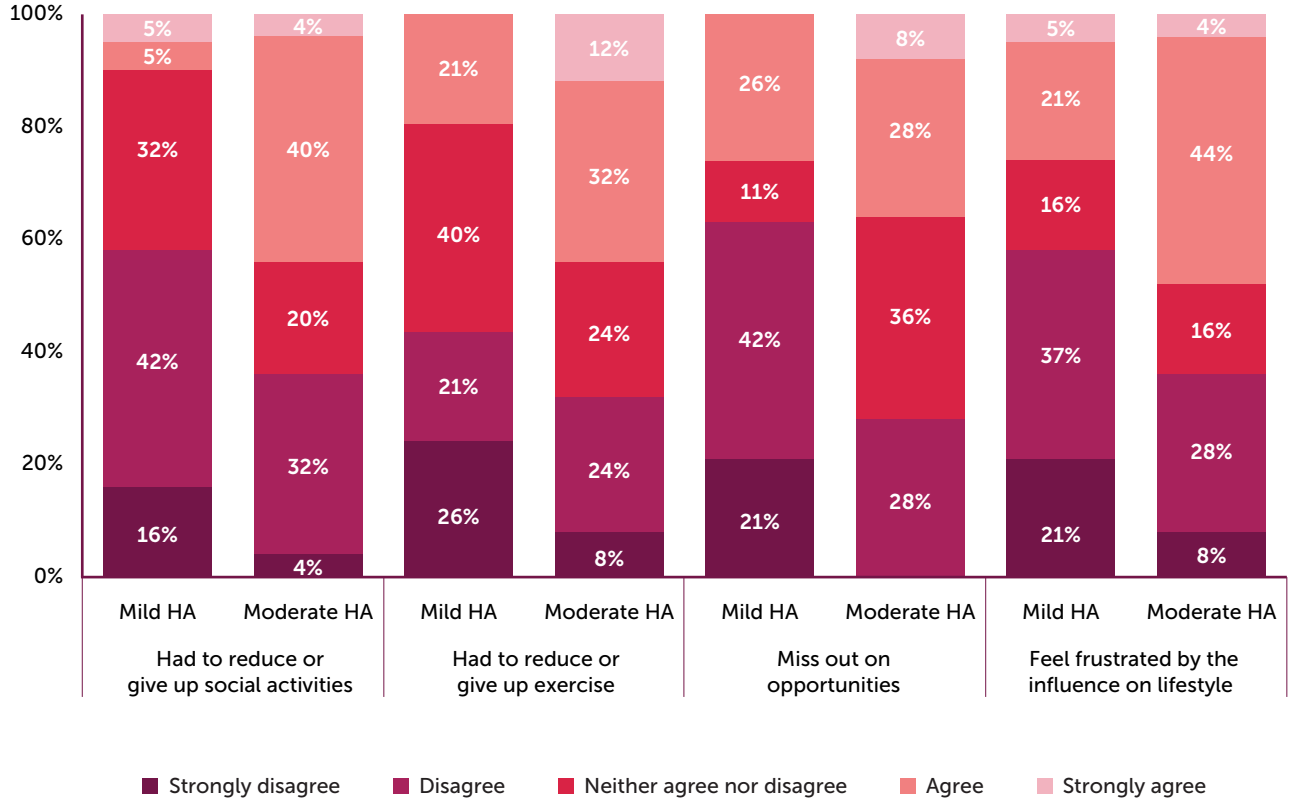
Figure 1. Psychosocial impact of haemophilia A among participants completing the patient self-complete questionnaire



Note: the figure above is relative to the subsample who also provided a patient-questionnaire composed by n=19 with mild HA and n=25 with moderate HA
HA: haemophilia A

DISCUSSION

This study analysed the clinical and psychosocial burden of mild or moderate HA in the Italian cohort of CHESS II participants. Overall, bleeding events were common among people with mild and moderate HA, as was joint-associated morbidity as indicated by target joint and problem joint frequency. People with moderate HA appeared to have greater clinical morbidity and a greater negative impact of HA on their lifestyle than those with mild HA. People with moderate HA had more overall bleeding events per year and worse joint morbidity, chronic pain, and anxiety and/or depression compared with those with mild HA. In turn, among those providing a PSC, more people with moderate HA reported reducing or giving up essential activities of living, missing out on opportunities in life, and feeling frustrated by the limitations of HA on their lifestyle.

Recent findings highlight self-reported moderate-to-severe anxious and depressive symptoms in as many as 51% of adult people with moderate haemophilia [17]. Our findings from physician-reported data confirmed a substantial presence of anxiety or depression with 35% of the moderate cohort affected. Albeit generally less so than for those with moderate HA, those with mild condition also reported a meaningful clinical and psychosocial burden of HA. Consistent with our findings of 26% of people with mild HA reporting having missed out on opportunities or feeling frustrated by the effect of haemophilia on their lifestyle and 21% reporting having to give up exercise, 38% of a mild cohort examined as part of the multi-national PROBE (Patient Reported Outcomes, Burdens and Experiences) study reported an effect on the activities of daily living [13].

These findings emphasise the importance of clinical and mental health management for people with mild or moderate HA. This may often be overlooked in comparison to severe HA, and may therefore be undertreated, however paucity of evidence around treatment and bleeding patterns renders assessment difficult [13,16,33,34]. The potential under-management of mild or moderate HA is likely to contribute to long-term joint damage and downstream psychosocial outcomes. Accordingly, a systematic literature review by Di Minno et al. (2013) reported findings of similar bleeding event occurrence rates between PwH with severe and moderate disease

(6.4% and 7.7%) [35]. When examining a non-severe haemophilia cohort within the PROBE study, however, Chai-Adisaksopha and colleagues found that 83% of males with moderate haemophilia had experienced ≥2-3 bleeding events in the preceding 12 months [13], in line with our findings, which revealed that 85% of the moderate cohort in this analysis experienced at least one bleeding event of some kind within the same timeframe, as well as a substantial proportion experiencing spontaneous bleeding. This potentially signals an underestimation of bleeding events or of the burden imposed by moderate haemophilia within the available literature [13,16]. A similar finding was also described by den Ujil et al., who, when comparing the outcomes of moderate haemophilia to those of mild or severe condition, reported that 73% of moderate PwH in the cohort assessed reported at least one bleeding event in the preceding 12 months [34]. In the same systematic literature review, signs of arthropathy in moderate haemophilia were reported as anywhere between 15% and 70%, while our findings place the Italian CHESS II moderate HA cohort towards the upper end of this range, with 51% reported to have at least one problem joint [35].

While published evidence is limited, it is clear that moderate HA poses a substantial burden on affected individuals. Based on the very limited evidence of a standard approach to an effective preventative treatment for this patient category, as well as the clinical and psychosocial burden highlighted by the literature and our analysis, a real need for appropriate and standardised clinical management of moderate HA is evident.

When considering mild haemophilia, in a Spanish single-centre cohort described by De la Corte-Rodriguez et al. (2022), presence of arthropathy was reported as 36.5% [36]. While not as prevalent, our findings confirm the presence of joint health burden among people with mild HA, with 12% of our cohort reporting at least one problem joint. In another single-centre experience describing a longitudinal cohort with mild haemophilia, Tagliaferri and colleagues (2012) report that 91% of the cohort experienced some type of bleeding event during the follow-up period, with mean bleed/year/patient reported as 0.56 [37]. Joint health was also explored, and signs of joint damage were detected in 33% of people with mild haemophilia [37]. These findings are consistent with our analysis, where mean ABR for mild PwH was 1.1.

Our results and the available literature confirm a remaining burden of mild and moderate haemophilia. Despite recent efforts to better understand its natural history, moderate and mild HA remain understudied. Management and diagnosis issues, as well as patient-physician disconnect (due to difficulties both in communication and shared decision-making) and difficulties in recognising and identifying symptoms by PwH with mild or moderate HA still linger, potentially affecting short- and long-term clinical and psychosocial outcomes of people with mild or moderate haemophilia, as well as their quality of life [13,15,16,37,38].

Recently, the inherent value of FVIII levels as a predictor of severity of haemophilia and its outcomes has been questioned in a consensus piece from an ISTH working group, with the classical severity definition theorised as being oftentimes inadequate in the management of PwH [16,39]. Anecdotal evidence indicates that in as many as 30% of PwH bleeding phenotype is more correlated to idiopathic variables specific to the PwH rather than residual FVIII presence [16]. Clinicians should be vigilant in encouraging people with mild or moderate HA to learn about their condition and to seek appropriate care in order to minimise long-term joint damage, pain and impediments to daily life. Where conditions make it relevant and necessary, clinicians should suggest and implement early prophylaxis initiation, particularly when managing severe bleeding phenotypes in people with moderate condition [16]. This is particularly important in the context of the analysis of this cohort, where people with mild or moderate HA not receiving prophylaxis at the time of data collection exhibited relevant clinical and psychosocial burden, while being estimated to have needed a non-negligeable number of infusions (9.6 and 13, in mild and moderate HA respectively) in the 12 months preceding data collection.

A recent systematic literature review by Peyvandi et al. (2019) explored evidence on the burden of mild HA, with findings revealing substantial prevalence of joint pain (~20%) and non-negligeable bleeding rates (between 0.44-4.5 bleeding episodes a year) [15]. However, the authors also reported chronic paucity of available evidence specifically assessing mild haemophilia populations.

In a retrospective multi-centre study, Lindvall et al. (2010), with data collected via a self-administered questionnaire, highlighted a relative lack of condition knowledge on the part of people with mild haemophilia, as well some difficulties in recognising and treating bleeding events timely, which may lead to additional, and potentially undetected, bleeding events as well as the progression of chronic joint damage [40]. This finding was confirmed in a qualitative

study conducted by Nilson and colleagues (2012), who attempted to identify knowledge and behaviours in people with mild haemophilia in Canada, finding that communication between PwH and the healthcare team was oftentimes less than optimal, and identifying gaps in condition knowledge as well as bleeding event recognition and management [41]. A recent report also highlighted some difficulties from PwH with mild or moderate condition in accessing factor treatment or finding an appropriate treatment centre, further exacerbating potential communication issues [17].

These studies, coupled with the findings of existing clinical and psychosocial burden within our analysis, highlight the importance of appropriate, standardised and timely ongoing clinical management for people with mild or moderate haemophilia, which can approximate the burden of severe haemophilia [1]. The potential undertreatment of mild and moderate haemophilia has been identified and a number of initiatives have been implemented to ensure effective clinical management, however consensus on definitions and precise recommendations is still lacking [14-16]. To achieve it, a holistic approach to patient assessment and management is essential, and where an individual falls outside the ranges of factor expression levels denoting severe haemophilia, effective and appropriate management must also be considered.

Strengths and limitations

Results from this study should be considered in the context of certain strengths and limitations. To our knowledge, this is the first non-single-centre analysis of the clinical and psychosocial burden of HA specifically focused on Italian adults with mild or moderate condition. CHESS II is a cross-sectional population study using real-world data abstracted from medical charts and patient-reported outcomes, and as such is subject to the inherent limitations that characterise observational research and secondary data analysis. Therefore, despite efforts to minimise it, a degree of information and/or recall bias cannot be excluded which may have caused an underestimation of the clinical burden of people with mild haemophilia due to the potential lack of condition knowledge. Additionally, due to the observational nature of the CHESS II study, the use of convenience sampling, the characteristics of the population, and the rarity of the condition, a degree of selection bias cannot be excluded. Efforts to minimise this were, however, put in place by encouraging physicians to recruit the next eight PwH they consulted with, regardless of the reason for the consultation. While patient-reported information is essential to informed decision-making, it should be noted that only a subset of the cohort completed the PSC questionnaires. It is possible that unmeasured variables could have had an impact on these results, which is a known limitation of observational research. Efforts to minimise bias were put in place; however, the findings of this analysis should be interpreted with care, owing to the specificity of the subgroup and the small sample size, which may limit generalisability of results to the Italian mild/moderate HA population. Finally, as inclusion of clinical data in the study was contingent on having at least one consultation, there remains a lack of information on the people with mild or moderate HA who struggle to access care or have minimal contact with their treatment centres. Therefore, further research with more representative sample sizes is warranted to capture and fully evaluate condition burden of mild and moderate HA in the context of evolving treatment practices in Italy.

CONCLUSION

This analysis showed a meaningful clinical and psychosocial burden of both mild and moderate HA in an Italian cohort of adults from the CHESS II dataset who did not receive prophylaxis at the time of data collection, with an incrementally greater burden apparent among those with moderate HA. The observed frequency of bleeding events, including joint bleeds, chronic pain, anxiety, depression, and limitations to activities of daily life, highlight a remaining unmet clinical and psychosocial need for people with mild or moderate HA within the sample examined. Clinicians would be well advised to closely support and encourage people with mild and moderate HA to seek appropriate treatment, in addition to those with severe HA, to support an appropriate long-term management regime that might reduce long-term arthropathy, pain, and humanistic burden. Further research investigating the limited use of prophylaxis in this population, particularly among the moderate cohort, would be valuable to inform both clinical and health policy decisions. This potential undertreatment of people with mild or moderate HA may contribute to the clinical and psychosocial burden observed in this study, and to downstream societal costs in addition to the burden on people with HA and their families.

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EFG, TB1, and TB2 are employees of HCD Economics. LS, RT and SB are employees of Roche SpA.

Ethics approval and consent to participate

The CHESS II study was 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, and was conducted in collaboration with the UK Haemophilia Society and governed by a steering committees chaired by Mr. Brian O'Mahony. Patient consent was obtained via tick box selection for the patient-reported element of the study.

Data availability statement

The datasets generated and/or analysed during the current study are held under license by the University of Chester and are not publicly available. Upon reasonable request, and subject to review, the corresponding author will provide the analyses that support the findings of this research. Subject to certain criteria, conditions, and exceptions, access to the related data for researchers who provide a methodologically sound proposal may be considered by data owners HCD Economics and the University of Chester. The data will be provided in compliance with applicable privacy laws, data protection, and requirements for consent and anonymisation.

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REFERENCES

1. Berntorp E, Dolan G, Hay C, et al. European retrospective study of real-life haemophilia treatment. *Haemophilia* 2017; 23(1): 105-14. doi: 10.1111/hae.13111.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020; 26(Suppl 6): 1-158. doi: 10.1111/hae.14046.
3. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: Communication from the SSC of the ISTH. *J Thromb Haemost* 2014; 12(11): 1935-9. doi: 10.1111/jth.12672.
4. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries. *Ann Intern Med* 2019; 171(8): 540-6. doi: 10.7326/M19-1208.
5. Mingot-Castellano ME, Parra R, Núñez R, Martorell M. Improvement in clinical outcomes and replacement factor VIII use in patients with haemophilia A after factor VIII pharmacokinetic-guided prophylaxis based on Bayesian models with myPKFiT®. *Haemophilia* 2018; 24(5): e338-43. doi: 10.1111/hae.13540.
6. O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health Qual Life Outcomes* 2018; 16(1): 84. doi: 10.1186/s12955-018-0908-9.
7. O'Hara J, Walsh S, Camp C, et al. The relationship between target joints and direct resource use in severe haemophilia. *Health Econ Rev* 2018; 8(1): 1-7. doi: 10.1186/s13561-018-0185-7
8. Witkop M, Neff A, Buckner TW, et al. Self-reported prevalence, description and management of pain in adults with haemophilia: methods, demographics and results from the Pain, Functional Impairment, and Quality of life (P-FiQ) study. *Haemophilia* 2017; 23(4): 556-65. doi: 10.1111/hae.13214.
9. Ay C, Perschy L, Rejtö J, Kaider A, Pabinger I. Treatment patterns and bleeding outcomes in persons with severe hemophilia A and B in a real-world setting. *Ann Hematol* 2020; 99(12): 2763-2771. doi: 10.1007/s00277-020-04250-9.
10. Khair K, Nissen F, Silkey M, et al. Effect of moderate and severe hemophilia a on daily life in children and their caregivers: A CHESS paediatrics study analysis. *Blood* 2020; 136: 43-5. doi: 10.1182/blood-2020-134658.
11. O'Hara J, Hughes D, Camp C, Burke T, Carroll L, Diego DAG. The cost of severe haemophilia in Europe: the CHESS study. *Orphanet J Rare Dis* 2017; 12(1): 106. doi: 10.1186/s13023-017-0660-y.
12. Warren BB, Thornhill D, Stein J, et al. Young adult outcomes of childhood prophylaxis for severe hemophilia A: Results of the joint outcome continuation study. *Blood Adv* 2020; 4(11): 2451-9. doi: 10.1182/bloodadvances.2019001311.
13. Chai-Adisaksopha C, Noone D, Curtis R, et al. Non-severe haemophilia: Is it benign? – Insights from the PROBE study. *Haemophilia* 2021; 27 Suppl 1: 17-24. doi: 10.1111/hae.14105.
14. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. *Blood Transfus* 2018; 16(6): 535-44. doi: 10.2450/2017.0150-17.
15. Peyvandi F, Tavakkoli F, Frame D, et al. Burden of mild haemophilia A: Systematic literature review. *Haemophilia* 2019; 25(5): 755-63. doi: 10.1111/hae.13777.
16. Castaman G, Peyvandi F, De Cristofaro R, Pollio B, Di Minno DMN. Mild and moderate hemophilia A: neglected conditions, still with unmet needs. *J Clin Med* 2023; 12(4): 1368. doi: 10.3390/jcm12041368.
17. Witkop M, Wang M, Hernandez G, Recht M, Baumann K, Cooper DL. Impact of haemophilia on patients with mild-to-moderate disease: Results from the P-FiQ and B-HERO-S studies. *Haemophilia* 2021; 27(S1): 8-16. doi: 10.1111/hae.14251.

18. Burke T, Ferri Grazzi E, Shaikh A, Hawes C, Camp C, O'Hara J. Exploring the relationship between condition severity and health-related quality of life in haemophilia A. Abstract PB0804. ISTH 2020 Congress. Available from *https://abstracts.isth.org/abstract/exploring-the-relationship-between-condition-severity-and-health-related-quality-of-life-in-haemophilia-a/*.
19. Rodriguez-Santana I, DasMahapatra P, Burke T, et al. Differential humanistic and economic burden of mild, moderate and severe haemophilia in european adults: a regression analysis of the CHESS II study. *Orphanet J Rare Dis* 2022; 17: 148. doi: 10.1186/s13023-022-02300-1.
20. Arcieri R, Molinari AC, Farace S, et al. Uncovered needs in the management of inherited bleeding disorders in Italy. *Blood Transfus* 2014; 12 (Suppl 3): s563-566. doi: 10.2450/2014.0036-14s.
21. Calizzani G, Candura F, Menichini I, et al. The Italian institutional accreditation model for Haemophilia Centres. *Blood Transfus* 2014; 12 (Suppl 3): s510-4. doi: 10.2450/2014.0058-14s.
22. Abbonizio F, Biffoni M, Arcieri R, Associazione Italiana Centri Emofilia, Giampaolo A. Rapporto ISTISAN 22/38 – Registro Nazionale Coagulopatie Congenite. Rapporto 2020. Francesca Abbonizio, Mauro Biffoni, Romano, Associazione Italiana Centri Emofilia (AICE), Adele Giampaolo [Internet]. Rome: Istituto Superiore di Sanità; 2022. (ISTISAN). Report No.: 22/38. Available from *https://www.iss.it/-/rappporto-istisan-22/38-registro-nazionale-coagulopatie-congenite.-rapporto-2020.-francesca-abbonizio-mauro-biffoni-romano-arcieri-associazione-italiana-centri-emofilia-aice-adele-giampaolo* (accessed February 2024).
23. Centri affiliati | AICE online [Internet]. Available from: *https://aiceonline.org/?page_id=758* (accessed February 2024).
24. Cortesi PA, Rocino A, Preti D, et al. Haemophilia management and treatment: An Italian survey on patients', caregivers' and clinicians' point of view. *Haemophilia* 2022; 28(2): 254-63. doi: 10.1111/hae.14504.
25. Calizzani G, Vaglio S, Arcieri R, et al. Models for institutional and professional accreditation of haemophilia centres in Italy. *Haemophilia* 2013; 19(4): e248-255. doi: 10.1111/hae.12141.
26. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. *Blood Transfus* 2018; 16(6): 535-44. doi: 10.2450/2017.0150-17.
27. McLaughlin P, Hermans C, Asghar S, et al. Problem joints and their clinical and humanistic burden in children and adults with moderate and severe hemophilia A: CHESS Paediatrics and CHESS II. *Blood* 2020; 136(Supplement 1): 33-4. doi: 10.1182/blood-2020-140306.
28. Nissen F, Burke T, Asghar S, et al. An insight into clinical outcomes in mild, moderate, and severe hemophilia A (HA): A preliminary analysis of the CHESS II study. Abstract OC 09.3. ISTH 2020 Congress. Available from *https://abstracts.isth.org/abstract/an-insight-into-clinical-outcomes-in-mild-moderate-and-severe-hemophilia-a-ha-a-preliminary-analysis-of-the-chess-ii-study/*.
29. Ferri Grazzi E, Sun SX, Burke T, O'Hara J. The impact of pharmacokinetic-guided prophylaxis on clinical outcomes and healthcare resource utilization in hemophilia a patients: real-world evidence from the CHESS II Study. *J Blood Med* 2022; 505-16. doi: 10.2147/JBM.S363028.
30. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. applied health economics and health policy. *Appl Health Econ Health Policy* 2017; 15(2): 127-137. doi: 10.1007/s40258-017-0310-5.
31. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993; 4(5): 353-65. doi: 10.2165/00019053-199304050-00006.
32. Burke T, Rodriguez-Santana I, Chowdary P, et al. Humanistic burden of problem joints for children and adults with haemophilia. *Haemophilia* 2023; 29(2): 608-18. doi: 10.1111/hae.14731.
33. den Uijl I, Biesma D, Grobbee D, Fischer K. Outcome in moderate haemophilia. *Blood Transfus* 2014; 12(Suppl 1): s330-6. doi: 10.2450/2012.0091-12.
34. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Clinical outcome of moderate haemophilia compared with severe and mild haemophilia. *Haemophilia* 2009; 15(1): 83-90. doi: 10.1111/j.1365-2516.2008.01837.x.
35. Di Minno MND, Ambrosino P, Franchini M, Coppola A, Di Minno G. Arthropathy in patients with moderate hemophilia A: A systematic review of the literature. *Semin Thromb Hemost* 2013; 39(7): 723-31. doi: 10.1055/s-0033-1354422.
36. De la Corte-Rodriguez H, Rodriguez-Merchan EC, Alvarez-Roman MT, Martin-Salces M, Rivas-Pollmar I, Jimenez-Yuste V. Arthropathy in people with mild haemophilia: Exploring risk factors. *Thromb Res* 2022; 211: 19-26. doi: 10.1016/j.thromres.2022.01.010.
37. Tagliaferri A, Di Perna C, Riccardi F, Pattacini C, Rivolta GF, Franchini M. The natural history of mild haemophilia: a 30-year single centre experience. *Haemophilia* 2012; 18(2): 166-74. doi: 10.1111/j.1365-2516.2011.02617.x.
38. Nossair F, Thornburg CD. The role of patient and healthcare professionals in the era of new hemophilia treatments in developed and developing countries. *Ther Adv Hematol* 2018; 9(8): 239-49. doi: 10.1177/2040620718784830.
39. Makris M, Oldenburg J, Mauser-Bunschoten EP, Peerlinck K, Castaman G, Fijnvandraat K. The definition, diagnosis and management of mild hemophilia A: communication from the SSC of the ISTH. *J Thromb Haemost* 2018; 16(12): 2530-3. doi: 10.1111/jth.14315.
40. Lindvall K, Colstrup L, Loogna K, Wollter IM, Grönhaug S. Knowledge of disease and adherence in adult patients with haemophilia. *Haemophilia* 2010; 16(4): 592-6. doi: 10.1111/j.1365-2516.2009.02189.x.
41. Nilson J, Schachter C, Mulder K, et al. A qualitative study identifying the knowledge, attitudes and behaviours of young men with mild haemophilia. *Haemophilia* 2012; 18(3): e120-5. doi: 10.1111/j.1365-2516.2011.02714.x.

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SUPPLEMENTARY DATA

Table S1. Clinical outcomes of participants who completed the patient self-complete questionnaire, by haemophilia A severity

	MILD HA (N=19)	MODERATE HA (N=25)
Age		
Mean (SD)	37.7 (13.1)	39.6 (14.6)
Median (Q1, Q3)	37.0 (27.0, 46.0)	31.0 (28.0, 47.0)
Age, n (%)		
18-35	8 (42)	14 (56)
36-59	9 (47)	7 (28)
≥60	2 (11)	4 (16)
Body mass index, n (%)		
Underweight	0 (0)	0 (0)
Normal weight	11 (58)	13 (52)
Overweight	8 (42)	11 (44)
Obese	0	1 (4)
Current treatment regimen, n (%)		
On-demand	8 (42)	9 (36)
No recent FVIII treatmenta	11 (58)	16 (64)
Prophylaxis	0	0
ABR (all cause)		
Mean (SD)	1.3 (0.9)	3.0 (2.7)
Median (IQR)	1.0 (1.0, 2.0)	2.0 (1.0, 4.0)
Target joints		
Mean (SD)	0.1 (0.3)	0.3 (0.6)
Median (IQR)	0	0
Target joints, n (%)		
0	17 (90)	20 (80)
1	2 (11)	3 (12)
≥2	0	2 (8)
Problem joints		
Mean (SD)	0.1 (0.5)	0.6 (0.7)
Median (IQR)	0	0
Problem joints, n (%)		
0	18 (95)	13 (52)
1	0	9 (36)
≥2	1 (5)	3 (12)
Chronic pain level, n (%)		
None	11 (58)	5 (20)
Mild pain	8 (42)	14 (56)
Moderate pain	0	6 (24)
Severe pain	0	0
Anxiety, n (%)	2 (11)	3 (12)
Depression, n (%)	0	2 (8)

Note: Proportions may not sum to 100% due to rounding
a "No recent FVIII treatment" was indicated if no FVIII therapy had been used in the preceding 12 months
ABR: annual bleeding rate HA: haemophilia A
Q1, Q3: Quartile 1, Quartile 3 SD: standard deviation