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New challenges for an expanding generation of older persons with haemophilia

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Background: Increasing survival among people with haemophilia means that more individuals are at risk of developing age-related morbidity. Little is known about morbidity and health-related quality of life (HRQoL) in different age groups within a single large population of people with haemophilia. **Aim:** This study aimed to explore the association between increasing age and comorbidity among people with haemophilia and to compare their HRQoL with that of a sample of the general population in England. **Methods:** The prevalence of comorbidity recorded in medical records and HRQoL assessed by EQ-5D were compared by age group in participants in the Cost of Haemophilia in Europe: A Socioeconomic Survey study (CHESS) in Europe. HRQoL was compared with that of a sample of the general population taken from the 2012 Health Survey for England (HSE). **Results:** Younger adults in CHESS were more likely to have received prophylaxis from an early age. The mean number of affected joints in younger adults was 1.0; participants aged 41-50 (1.25) and 51-60 years (1.41) had the highest mean number of affected joints. The prevalence of comorbidity was 36% in patients aged 18–30, 61% in 31–60-year-olds and 68% in those aged 61+. HRQoL impairment in young adults with haemophilia was comparable with that in the HSE population aged over 60. **Conclusions:** Older people with haemophilia have impaired quality of life compared with younger adults and an increasing prevalence of several age-related disorders affecting mental health and cardiovascular and bone health.

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The advent of prophylaxis has raised expectations that people with haemophilia will develop less joint damage and experience a normal life expectancy compared with earlier generations – but considerations around quality of life and age-related disorders must also be taken into account

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Young adults with haemophilia report impaired HRQoL comparable with that in a general population aged 61+.

Keywords: *haemophilia, ageing, comorbidity, quality of life, observational study*

About 30% of people with haemophilia A or B in Europe have severe haemophilia, defined as factor VIII or factor IX activity ('level') of <1 IU/dl (1%) (normal range 50–150 IU/dl) [1,2,3]. If untreated, it is associated with frequent recurrent and spontaneous bleeds, often involving the musculoskeletal system and in particular bleeding into joints [3,4]. Repeated joint bleeds cause joint stiffness, diminished range of movement, acute pain, chronic pain from arthropathy and disability.

The health burden carried by the current generation of adults with haemophilia is due both to the complications of haemophilia and the increasing risk of age-related long-term conditions such as diabetes and heart disease [5]. People with haemophilia share common cardiovascular risk factors and comorbidities with the general population but appear to develop them earlier in life [6,7], though a potential protective effect of lower factor levels against cardiovascular events cannot be excluded. Little is known about morbidity and health-related quality of life in different age groups within a single large population of people with haemophilia.

AIM

This study describes the association between increasing age and prevalence of comorbidities in 1,227 participants of the CHESS survey (Cost of Haemophilia in Europe: A Socioeconomic Survey) [8], and the impact of ageing on health-related quality of life (HRQoL) in that population and in a sample of the general population taken from the 2012 Health Survey for England [9].

METHODS

Source of data

Data for this study were sourced from CHESS, a cross-sectional retrospective study of patients with severe haemophilia A or B in France, Germany, Italy, Spain and the United Kingdom. Data were collected through two questionnaires. The first was administered to physicians, who were asked to provide information on direct medical resource utilisation and clinical data for their haemophilia patients via a web-based case record form (CRF). The physicians asked the same patients to complete corresponding patient self-completion (PSC) questionnaires covering information on patient reported outcomes that determine HRQoL. Data were collected between December 2014 and April 2015.

Patients with a current inhibitor diagnosis were excluded (n=58) but those with a previous diagnosis were included and followed up as per the rest of the study population. The study sample included CRF data for 1,227 patients, of whom 523 (43%) completed the corresponding PSC. In CHESS, factor consumption was documented by the physician in the CRF. The treatment strategies were categorised as: prophylaxis from diagnosis (PX), on prophylaxis, previously on-demand (PXOD), always been on-demand (AOD) and previously on prophylaxis and moved to on-demand regimen (PPOD). For on-demand regimens, factor consumption for the most recent three-month period was annualised; for prophylaxis regimens, mean IU per infusion was multiplied by the weekly infusion rate, and annualised.

Bleeding frequency reported in this study was a combination of minor and major bleeding events occurring in the preceding 12-month period prior to enrolment in the study and recorded in the CRF (annual bleeding rate, ABR). A minor bleed was defined as: mild pain, minimal swelling, minimal restrictions of motion and resolution within 24 hours of treatment. A major bleed was defined as pain, effusion, limitation of motion and failure to respond within 24 hours.

The International Society on Thrombosis and Haemostasis defines a target joint as three or more spontaneous bleeds into a single joint within six consecutive months; joints meeting that definition which subsequently have two or fewer bleeds in 12 consecutive months are no longer considered target joints [1]. In CHESS, a target joint was defined by the clinicians, taking into account bleeding frequency and period of observation; this approach means that joints affected by bleeding are included when they no longer meeting the criteria for a target joint but have been affected by chronic synovitis secondary to prior joint bleeding. For clarity, joints identified in this way will be described as 'affected joints'. The number of affected joints for each patient was recorded in the CRF.

Data analysis and statistics

We recorded the presence of comorbidities listed in the medical records of each patient, using categories defined in the CRF. HRQoL was measured using the EQ-5D, a self-administered, generic, preference-based instrument designed to measure the impact of

disease on an individual's health state. The instrument comprises the EQ-5D health state descriptive; and the EQ Visual Analogue Scale (EQ-VAS) [10]. The EQ-5D instrument consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. The responses across these five dimensions provide a description of the patient's current health state. As is standard practice, we compared EQ-5D values for the multinational CHESS population with those of a single state, in this case the UK, which had the biggest cohort in the CHESS population. Preference-based values for the EQ-5D health states were obtained using values associated with the health states derived in a UK population (tariff values) [11]. These UK-specific tariff values were applied to all patients in our sample, regardless of their country of origin. This approach ensures that additional variation due to differences in tariff values between countries was not introduced into the analysis. This allows us to compare each patient using the same tariff value, so that changes in EQ-5D are determined only by changes in domain scores. The EQ-VAS (visual analogue scale) is measured on a vertical visual analogue scale where the endpoints are described as 'best imaginable health state' and 'worst imaginable health state'.

We used a comparative general population sample from the 2012 Health Survey for England (HSE) [9]. This is an annual survey examining changes in the health and lifestyles of the population that includes EQ-5D domain scores and EQ-VAS scores. From this survey population, we selected a sub-sample mirroring CHESS of males aged over 18 years old. The UK population tariff values that were applied to the CHESS data were also applied to the HSE domain scores.

The unit of analysis was patient-level. Demographic and clinical data are presented by age groups (18–30, 31–40, 41–50, 51–60 and 61+). Means, medians and standard deviations or standard errors, where appropriate, were used to describe continuous variables; categorical variables are described as frequencies and proportions. Kruskal-Wallis and Chi-squared statistical tests were conducted in order to test for between-age-group differences based on the type of variable included. All analysis was performed in R version 3.3.3 [12].

All patients provided informed consent. The study protocol was approved by the Research Ethics Sub Committee of the Faculty of Health and Social Care within the University of Chester, UK.

RESULTS

The sample demographics are presented in Table 1. The response rate for the PSC component of the CHESS study was significantly higher among older individuals. The proportions of people with haemophilia A or B in the CHESS population were similar to those reported in the literature [13,14]. As expected, we observed a change in employment status across the age cohorts, with increasing retirement rates for older patients.

Treatment strategy and bleeds

Key differences between age groups were observed in the reported current treatment strategy in our study, where only patients in the 18–30 age group were categorised as having prophylaxis from diagnosis (PX) at the study recruitment date (n=217). This is reflective of what was reported by participating physicians; however, given the relatively novel nature of primary prophylaxis at the time, it is likely this is made up of patients who initiated prophylaxis at an early age (a mix of primary and other prophylaxis).

The mean ABR associated with each treatment type was significantly different only in the age groups 18–30 and 61+ (Kruskal-Wallis test, p-value <0.000 and 0.023 respectively). Table 2 presents the mean and median number of minor and major bleeds and ABR reported in the previous 12 months according to treatment strategy by age category. Overall, patients currently receiving on demand therapy (AOD, PPOD) had higher ABR than those receiving any prophylaxis therapy (PX, PXOD). Median ABR associated with PXOD and PPOD for the age groups of 18–30 years and 61+ years were the same. Median ABR associated with PXOD was higher than with PPOD for the age group 41–50 and 51–60 years. PXOD was consistently associated with higher ABR than PX, with rates similar to those associated with current on-demand treatment.

Affected joints

Figure 1 represents a box plot of the medians and ranges of the number of affected joints by age group. This shows that the medians were the same for each age group (1 affected joint) with the exception of age group 61+ (median 0). The range of number of affected joints increases with age. Younger age groups (18–30 and 31–40) had on average 1.00 $\pm$ 0.056 and 1.17 $\pm$ 0.079 affected joints. By contrast, patients aged 41–50 and 51–60 years had the highest mean number of affected joints at 1.25 $\pm$ 0.105 and 1.41 $\pm$ 0.174, respectively. As occurred with number of total bleeds,

Figure 1: Median number of affected joints by age category in the CHESS population

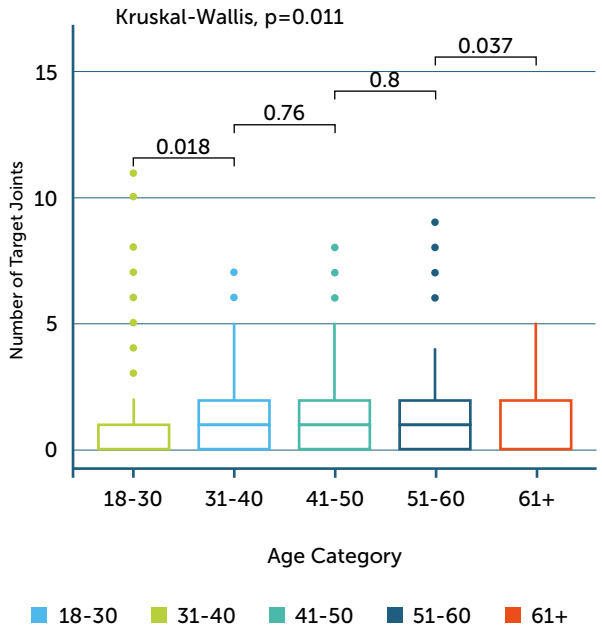
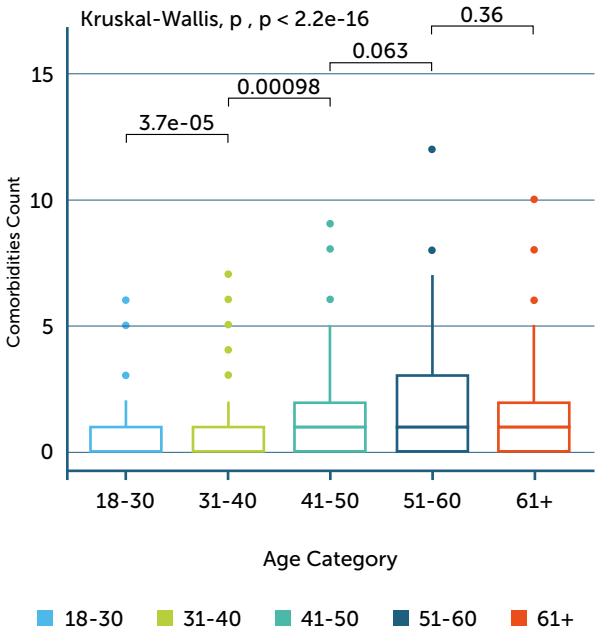


Figure 2: Median number of comorbidities by age group in the CHESS population



Note: Figures presents the median and inter-quartile range (IQR) of the number of affected joints for each age category. The Kruskal-Wallis test compares difference between the overall groups (global p-value). Individual, sequential pairwise comparison are made between each age category pairs based on Wilcoxon test. All variables presented are from the CRF.

the mean number of affected joints was lower in the 61+ age group (0.9 ± 0.116) and was significantly lower than in the 51–60 age group (p=0.037).

Comorbidity

Table 3 lists the prevalence of each of the comorbid conditions. The prevalence of comorbidity increased with age. While a significant proportion of our sample recorded no comorbidities (n=624), the prevalence of comorbidity increased from 36% in the 18–30 age group to 68% in the 61+ age group. The mean number of comorbidities for each age group ranged from 0.55 ± 0.037 for the 18–30 age group to 1.50 ± 0.176 in the over-40 group. Figure 2 shows that the median number of comorbidities increases significantly with age group up to age 60.

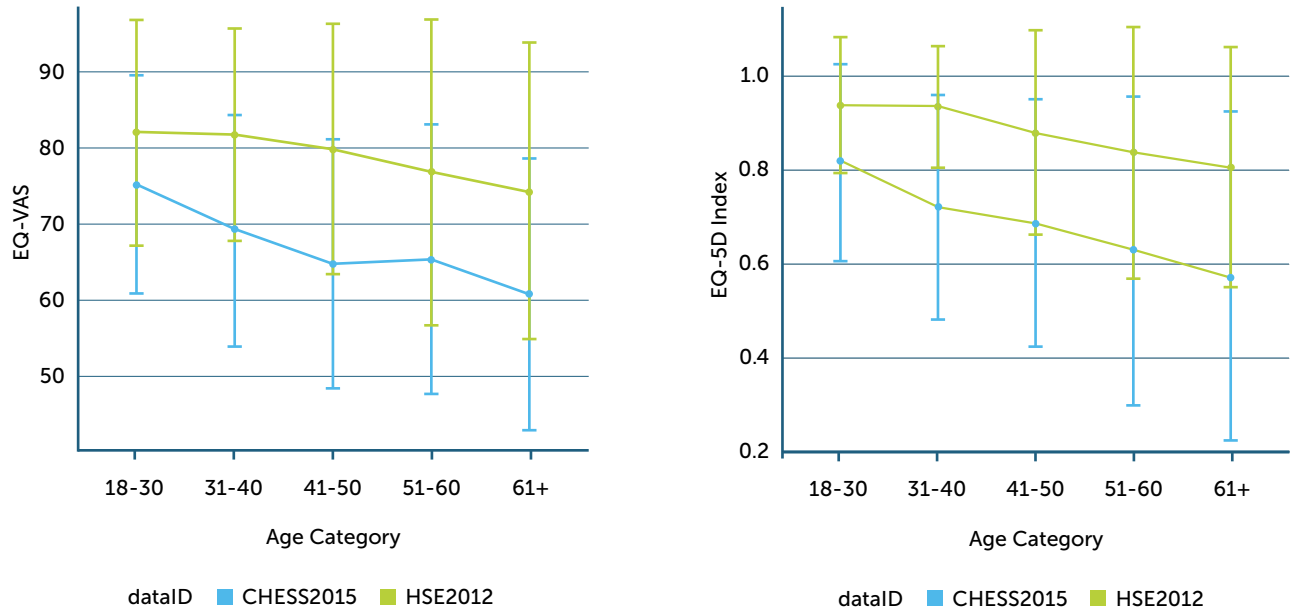
The three most frequently reported conditions were anxiety, depression and hypertension. The prevalence of multimorbidity, defined as the presence of two or more chronic medical conditions in addition to haemophilia, was most frequent in patients with osteoporosis (n=16) and rheumatoid arthritis (n=12), in whom the mean number of additional conditions was three or more. Anxiety and depression were the most prevalent morbidities occurring together (n=36) followed by hypertension and hypercholesterolaemia (n=10).

Health-related quality of life

Table 4 presents the proportion of both the CHESS and HSE sample within each of the levels (no problems, some problems, unable/extreme problems) for the EQ-5D domains (mobility, self-care, unusual activities, pain and anxiety/depression). Overall, a pattern of increasing impact on quality of life is noted in line with age for both the CHESS and HSE samples.

The proportion of patients in the CHESS population who reported some problems in the mobility domain increased with age; a similar trend was evident with extreme problems but comparatively few people were affected. For example, 63.5% of individuals in the 61+ age group reported some problems but 21.9% of those in the 18–30 age group did so. A similar pattern is apparent in the self-care domain: the proportion reporting extreme problems was consistently low across age-groups but the proportion of CHESS patients reporting some problems increased at 30–39 years (20.8%) and more than doubled among those aged 61+ (44.2%). Anxiety or depression affected 30% of 18–30-year-olds and over 60% of the 61+ group, with extreme problems reported by one in six of the older age group who were affected. The proportion reporting some or extreme problems in the pain domain was greater than for any other domain and high across all

Figure 3: EQ-Visual analogue scale (EQ-VAS) and EQ-5D index score by age category (standard errors)



Note: All variables presented in Figure 3 are from the PSC
Abbreviations: CHESS: The Cost of Haemophilia across Europe: a Socioeconomic Survey; HSE: Health Survey for England

age groups. Some problems were reported by 45.7% in the 18–30 age group (vs. 7.3% for self-care and 28.1% for anxiety/depression in the same age group). Almost 50% of people in the age group 18–30 reported some or extreme problems in the pain domain.

In the HSE population, 31.3% of patients in the 61+ age group reported some mobility problems whereas only 4.3% of the 18–30 age group did so. A small proportion of people in the HSE population reported problems with self-care and this increased only slightly with age. Problems with anxiety or depression were reported by 13.9% of the 18–30 age group and peaked at 20.7% among 51–60-year-olds. Pain was again the most frequently reported issue and prevalence increased with age, reaching 41.3% with some problems and 5.5% with extreme problems in the 61+ age group.

Both the EQ-5D index score and the EQ-VAS are illustrated in Figure 3 for both the CHESS and HSE sample populations. A consistent downward trend is noted for the EQ-5D index across age groups in both populations, with marked inter-individual variation. In CHESS, the mean index ranged from 0.82 in the 18–30 age group to 0.57 in the 61+ group (Table 4). The EQ-VAS, which is a self-reported measure, largely followed the same patterns. In the CHESS population, mean EQ-VAS score was 75.21 in the 18–30 age group and 60.92 in the 61+ group. In the HSE population, the mean EQ-5D index ranged from 0.94 among 18–30-year-olds and 0.81 in the 61+ group; the mean EQ-VAS among 18–30-year-olds was 81.98 and in the 61+ group it was 74.30.

DISCUSSION

The advent of prophylaxis has raised expectations that people with haemophilia will develop less joint damage and experience a normal life expectancy compared with earlier generations who used on-demand treatment. This study has shown that, compared with young adults, older people with haemophilia have impaired quality of life and increasing prevalence of several age-related disorders. We have shown that, even in the era of prophylaxis, 18–30-year-olds with haemophilia are still presenting with chronic joint damage and with some or extreme problems in all domains of quality of life. Our data provide no explanation for this observation but it is possible that the younger generation is more physically active and may therefore incur injuries more frequently. As a result, their quality of life is impaired to the extent reported in a general population aged over 60.

Data for this study were collected between December 2014 and April 2015, a period that predated the introduction of extended half-life clotting factors in Europe. The generation of young adults in the CHESS population was perhaps the first to begin using prophylaxis with traditional replacement clotting

factors at a young age. We cannot say from our data what proportion received only primary prophylaxis (i.e. no on-demand treatment) and how many initially received on-demand treatment that may have been associated with early joint damage. It is clear, however, that treatment aims were not fully met in this age group and it is hoped that outcomes would be improved in younger people exposed only to primary prophylaxis.

The median ABRs associated with current on-demand treatment (AOD and PPOD, Table 2) in the CHESS population were in the range 2–4. This is relatively low compared with published figures. For example, one review of European centres (Belgium, France, Germany, Italy, Spain, Sweden, UK) carried out between 2012 and 2013 reported median ABRs (in all locations) with on-demand treatment of 4.5–18.0 in children and adults with severe haemophilia A and 1.5–14 for severe haemophilia B [15]. In CHESS, ABRs were estimated solely from patients' records, an approach that probably underestimates the total number of bleeds because the majority of treatment is carried out at home and some bleeds may go unrecorded. However, the 2012/13 study obtained data from patient records for about 80% of patients who reported bleeding. Bleeds were reported in similar proportions of patients using on-demand treatment in CHESS (17.2%) and the 2012/13 study (17.8%). These differences therefore require further investigation.

The mean number of affected joints tended to increase with age in CHESS but was lower in the 61+ age group than in the 51–60 age group. Our data do not explain why this is so but it may be due to a milder phenotype among individuals who have survived into older age or by self-imposed limits on activity due to the nature of the condition. Younger cohorts of patients would be expected to develop less joint damage than older patients because they began prophylaxis earlier.

The emergence of cardiovascular and bone health comorbidities typically associated with ageing populations are evident in the CHESS population [16,17], highlighting the need for a multidisciplinary approach to treatment. This should include measures to address poor mental health, as indicated by a high self-reported frequency of problems with anxiety or depression.

The limitations of this study include its retrospective nature and a reliance on accurate recording by physicians. The quality of the data extracted in the CRF was assessed to ensure it accurately reflected the patients' records. Our analysis was based on complete cases, where appropriate; no adjustment for missing data was conducted. All the factor replacement therapy used by patients in CHESS was standard half-life products; future research is warranted to investigate the impact of the improved protection provided by extended half-life products. The categories of factor replacement therapy do not correspond exactly with the definitions of primary and secondary prophylaxis published by the International Society on Thrombosis and Haemostasis [1]. In CHESS, physicians were not required to determine bleeding history before the beginning of prophylaxis.

EQ-5D measured quality of life in the CHESS population and in that of a general population cohort from the UK. No multinational general population sample was available for comparison in this study. CHESS reflects the HRQoL across five European countries; differences between national approaches to haemophilia care might influence the domain scores at a country level. However, the proportions of patients receiving prophylaxis were similar (50–60%) in the participating countries.[8] Further, the EQ-5D utility values for the CHESS and HSE samples were generated using the same algorithm, avoiding further variation.

CONCLUSION

Older people with haemophilia have impaired quality of life compared with younger adults and an increasing prevalence of several age-related disorders affecting mental health and cardiovascular and bone health. Despite the advent of early prophylaxis (though probably not primary prophylaxis), younger adults (age 18–30 years) in this population using standard half-life factor products had developed chronic joint damage. They described problems in all domains of quality of life, with impairment comparable with that reported by a general population aged over 60. These findings emphasise the need for a multidisciplinary approach to management throughout life for people with haemophilia.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analysed during the current study are held under license by the University of Chester. They are not publicly available but are available from the corresponding author on reasonable request.

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shares. DH and/or his institution received research, service development, speaker and/or consultancy income from Bayer, Biomarin, Biotest, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark and Takeda. DN and SC declare they have no conflicts of interest.

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This article reports a retrospective study in which no human participants or animals are directly involved.

AUTHOR CONTRIBUTIONS

The analysis was designed and conducted by JO'H and DN. The manuscript was initially drafted by JO'H, DN, PK, K-JM and DH. It was reviewed and amended by all authors.

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Table 1: CHESS sample demographics

	18–29	30–39	40–49	50–59	60+	P-VALUE
CRF Complete (n)	569	261	186	110	101	
Age (mean (SD))	23.4 (3.77)	35.3 (2.85)	44.9 (2.87)	55.2 (2.76)	67.7 (5.30)	
PSC Complete	37% (n=211)	46% (n=120)	48% (n=89)	46% (n=51)	51% (n=52)	0.0064*
Haemophilia subtype						
A	77% (n=436)	79% (n=207)	82% (n=153)	71% (n=78)	74% (n=75)	0.1676†
B	23% (n=133)	21% (n=54)	18% (n=33)	29% (n=32)	26% (n=26)	
Education Level						
None	2% (n=4)	1% (n=1)	3% (n=3)	2% (n=1)	6% (n=3)	0.1493†
Primary	17% (n=35)	17% (n=20)	17% (n=15)	20% (n=10)	19% (n=10)	
Secondary	40% (n=85)	37% (n=44)	48% (n=43)	41% (n=21)	42% (n=22)	
Undergraduate	25% (n=53)	32% (n=38)	24% (n=21)	24% (n=12)	17% (n=9)	
Postgraduate	14% (n=30)	11% (n=13)	6% (n=5)	14% (n=7)	6% (n=3)	
Other	2% (n=4)	3% (n=4)	2% (n=2)	–	10% (n=5)	
Employment						
Full-time employed	26% (n=147)	46% (n=121)	44% (n=82)	31% (n=34)	8% (n=8)	<0.000†
Part-time employed	13% (n=75)	23% (n=61)	23% (n=43)	16% (n=18)	8% (n=8)	
Self-employed	6% (n=32)	12% (n=31)	11% (n=21)	14% (n=15)	12% (n=12)	
Student	45% (n=254)	2% (n=5)	1% (n=1)	–	–	
Retired	–	0% (n=1)	1% (n=1)	14% (n=15)	63% (n=64)	
Unemployed	9% (n=53)	10% (n=25)	10% (n=18)	14% (n=15)	4% (n=4)	
Homemaker	–	1% (n=2)	2% (n=3)	4% (n=4)	2% (n=2)	
Physically Unable Haem Related	1% (n=4)	5% (n=13)	9% (n=16)	6% (n=7)	3% (n=3)	
Physically Unable Other Reason	0% (n=2)	–	1% (n=1)	2% (n=2)	–	
Other	0% (n=2)	1% (n=2)	–	–	–	

All variables listed are from the CRF, with the exception of 'PSC Complete'
*Chi-square test, † Kruskal-Wallis test, $P < 0.05$ as significant
CRF: case record form; PSC: patient self-completion questionnaire; Haem: Haemophilia

Table 2: Mean (standard deviation) and median of minor, major and total bleeds in the previous 12 months by treatment strategy

	18–30				31–40				41–50				51–60				61+			
	N	MEDIAN	MEAN	SD	N	MEDIAN	MEAN	SD	N	MEDIAN	MEAN	SD	N	MEDIAN	MEAN	SD	N	MEDIAN	MEAN	SD
Minor Bleeds																				
PX	217	1	2.37	7.02	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PXOD	131	2	3.33	3.60	164	2	2.89	3.75	102	3	4.07	4.77	62	3	3.19	3.05	32	2	3.38	4.14
AOD	149	3	4.74	4.88	59	1	2.64	4.00	50	1	3.04	4.59	32	2	3.34	4.88	47	1	1.91	3.02
PPOD	72	2	3.94	4.20	38	2	2.97	3.04	34	2	4.91	10.33	16	2	3.69	4.25	22	2	3.41	2.61
Major Bleeds																				
PX	217	0	0.24	0.58	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PXOD	131	0	0.72	1.17	164	0	0.83	1.69	102	0	1.14	2.13	62	1	1.55	2.01	32	0.5	1.22	1.70
AOD	149	0	0.88	1.40	59	0	0.63	1.08	50	0	0.92	1.38	32	1	0.72	0.77	47	1	0.94	1.19
PPOD	72	0	0.83	1.45	38	0	0.82	1.64	34	0	2.00	6.83	16	0.5	0.69	0.79	22	1	1.41	1.87
ABR																				
PX	217	1	2.61	7.10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PXOD	131	3	4.05	4.12	164	2	3.72	5.10	102	3.5	5.21	6.12	62	4	4.74	4.62	32	3	4.59	5.41
AOD	149	4	5.62	5.51	59	2	3.27	4.66	50	2	3.96	5.64	32	2	4.06	5.11	47	2	2.85	4.02
PPOD	72	3	4.78	5.02	38	3	3.79	3.88	34	3	6.91	16.96	16	2	4.38	4.81	22	3	4.82	3.71

All variables listed are from the case record form (CRF)
ABR: Annnual bleed rate – a combination of minor and major bleeding events occurring in the 12-month period prior to enrolment in the study and recorded in the CRF
Minor bleed: mild pain, minimal swelling, minimal restrictions of motion and resolution within 24 hours of treatment
Major bleed: pain, effusion, limitation of motion and failure to respond within 24 hours
PX: prophylaxis from diagnosis
PXOD: on prophylaxis, previously treated on-demand
AOD: always been treated on-demaned
PPOD: previously on prophylaxis and moved to on-demand regimen

Table 2 (cont): Mean (standard deviation) and median of minor, major and total bleeds in the previous 12 months by treatment strategy

	MINOR BLEEDS				MAJOR BLEEDS				ABR			
AGE GROUP	PX	PXOD	AOD	PPOD	PX	PXOD	AOD	PPOD	PX	PXOD	AOD	PPOD
18–30												
n	217	131	149	72	217	131	149	72	217	131	149	72
Median	1	2	3	2	0	0	0	0	1	3	4	3
Mean	2.37	3.33	4.74	3.94	0.24	0.72	0.88	0.83	2.61	4.05	5.62	4.78
SD	7.02	3.60	4.88	4.20	0.58	1.17	1.40	1.45	7.10	4.12	5.51	5.02
Min	0	0	0	0	0	0	0	0	0	0	0	0
Max	100	30	30	18	4	8	8	8	100	30	38	22
31–40												
n	-	164	59	38	-	164	59	38	-	164	59	38
Median	-	2	1	2	-	0	0	0	-	2	2	3
Mean	-	2.89	2.64	2.97	-	0.83	0.63	0.82	-	3.72	3.27	3.79
SD	-	3.75	4.00	3.04	-	1.69	1.08	1.64	-	5.10	4.66	3.88
Min	-	0	0	0	-	0	0	0	-	0	0	0
Max	-	35	20	12	-	12	6	6	-	47	26	15
41–50												
n	-	102	50	34	-	102	50	34	-	102	50	34
Median	-	3	1	2	-	0	0	0	-	3.5	2	3
Mean	-	4.07	3.04	4.91	-	1.14	0.92	2.00	-	5.21	3.96	6.91
SD	-	4.77	4.59	10.33	-	2.13	1.38	6.83	-	6.12	5.64	16.96
Min	-	0	0	0	-	0	0	0	-	0	0	0
Max	-	30	20	60	-	15	6	40	-	33	26	100

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Table 2 (cont): Mean (standard deviation) and median of minor, major and total bleeds in the previous 12 months by treatment strategy

	MINOR BLEEDS				MAJOR BLEEDS				ABR			
AGE GROUP	PX	PXOD	AOD	PPOD	PX	PXOD	AOD	PPOD	PX	PXOD	AOD	PPOD
51–60												
n	-	62	32	16	-	62	32	16	-	62	32	16
Median	-	3	2	2	-	1	1	0.5	-	4	2	2
Mean	-	3.19	3.34	3.69	-	1.55	0.72	0.69	-	4.74	4.06	4.38
SD	-	3.05	4.88	4.25	-	2.01	0.77	0.79	-	4.62	5.11	4.81
Min	-	0	0	0	-	0	0	0	-	0	0	0
Max	-	16	24	15	-	10	3	2	-	26	26	16
61+												
n	-	32	47	22	-	32	47	22	-	32	47	22
Median	-	2	1	2	-	0.5	1	1	-	3	2	3
Mean	-	3.38	1.91	3.41	-	1.22	0.94	1.41	-	4.59	2.85	4.82
SD	-	4.14	3.02	2.61	-	1.70	1.19	1.87	-	5.41	4.02	3.71
Min	-	0	0	1	-	0	0	0	-	0	0	1
Max	-	16	20	12	-	6	7	8	-	22	27	14

ABR: Annnual bleed rate – a combination of minor and major bleeding events occurring in the 12-month period prior to enrolment in the study and recorded in the CRF
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Table 3: Prevalence of each comorbid disease and mean number of reported comorbidities

COMORBIDITIES	N	% WITH COMORBIDITY	MEAN COMORBIDITY ± SE	MEAN COMORBIDITY ± SD
None	624	-	-	-
Alcohol dependency	41	3%	1.93 ± 0.36	1.93 ± 2.33
Anaemia	73	6%	2.03 ± 0.24	2.03 ± 2.05
Anxiety	177	14%	1.29 ± 0.12	1.29 ± 1.53
Depression	167	14%	1.5 ± 0.13	1.5 ± 1.71
Diabetes mellitus	64	5%	1.84 ± 0.29	1.84 ± 2.33
Fibromyalgia	41	3%	1.85 ± 0.34	1.85 ± 2.19
Hepatitis B Virus	22	2%	2.55 ± 0.61	2.55 ± 2.84
Hepatitis C Virus	65	5%	1.92 ± 0.26	1.92 ± 2.11
HIV	35	3%	2.06 ± 0.38	2.06 ± 2.24
Hypertension	150	12%	1.61 ± 0.15	1.61 ± 1.89
Hypercholesterolemia	86	7%	2.48 ± 0.23	2.48 ± 2.13
Ischaemic heart disease	20	2%	3.8 ± 0.57	3.8 ± 2.57
Obesity	69	6%	2.09 ± 0.27	2.09 ± 2.24
Osteoarthritis	78	6%	2.35 ± 0.25	2.35 ± 2.25
Osteoporosis	16	1%	3.63 ± 0.82	3.63 ± 3.28
Rheumatoid arthritis	12	1%	3.67 ± 1.05	3.67 ± 3.65
Other	19	2%	2.11 ± 0.49	2.11 ± 2.13

Note: Mean comorbidity refers to the number of additional comorbidities excluding the stated index comorbidity
All variables listed in Table 3 are from the clinician report form

Table 4: Percentage of populations reporting problems for each EQ-5D domain and mean (standard error) of EQ-5D index and EQ-VAS for both the CHESS and HSE sample populations

AGE GROUP	18–30		31–40		41–50		51–60		61+	
POPULATION	CHESS	HSE	CHESS	HSE	CHESS	HSE	CHESS	HSE	CHESS	HSE
Mobility (n)	210	488	120	477	89	568	51	571	52	1090
No Problems	78.1%	95.5%	60.8%	94.1%	48.3%	90.0%	41.2%	80.9%	32.7%	68.6%
Some Problems	21.9%	4.3%	39.2%	5.9%	50.6%	10.0%	54.9%	18.2%	63.5%	31.3%
Unable/Extreme Problems	-	0.2%	-	-	1.1%	-	3.9%	0.9%	3.8%	0.1%
Self-care (n)	206	488	120	477	89	569	50	570	52	1076
No Problems	92.7%	99.4%	77.5%	98.7%	75.3%	96.1%	56.0%	93.5%	48.1%	89.9%
Some Problems	7.3%	0.6%	20.8%	1.3%	24.7%	3.5%	40.0%	6.1%	44.2%	9.8%
Unable/Extreme Problems	-	-	1.7%	-	-	0.4%	4.0%	0.4%	7.7%	0.4%
Usual Activities (n)	209	487	120	476	89	569	51	570	52	1085
No Problems	80.4%	93.6%	68.3%	94.7%	52.8%	88.6%	52.9%	84.7%	48.1%	76.6%
Some Problems	19.1%	6.2%	30.8%	5.0%	46.1%	10.7%	39.2%	13.5%	44.2%	20.9%
Unable/Extreme Problems	0.5%	0.2%	0.8%	0.2%	1.1%	0.7%	7.8%	1.8%	7.7%	2.5%
Pain (n)	210	488	120	477	89	569	51	571	52	1090
No Problems	51.9%	87.3%	31.7%	83.6%	31.5%	71.9%	33.3%	65.5%	34.6%	53.2%
Some Problems	45.7%	12.1%	65.8%	15.9%	65.2%	25.1%	58.8%	29.2%	57.7%	41.3%
Unable/Extreme Problems	2.4%	0.6%	2.5%	0.4%	3.4%	3.0%	7.8%	5.3%	7.7%	5.5%
Anxiety/depression (n)	210	487	119	477	89	565	51	570	52	1084
No Problems	70.0%	86.0%	59.7%	86.8%	55.1%	82.3%	51.0%	79.3%	38.5%	83.0%
Some Problems	28.1%	12.3%	34.5%	12.6%	37.1%	14.3%	47.1%	17.4%	50.0%	15.1%
Unable/Extreme Problems	1.9%	1.6%	5.9%	0.6%	7.9%	3.4%	2.0%	3.3%	11.5%	1.8%
EQ-5D Index Score (n)	205	483	119	476	89	564	50	565	52	1065
Mean (se)	0.82 (0.01)	0.94 (0.01)	0.72 (0.02)	0.94 (0.01)	0.69 (0.03)	0.88 (0.01)	0.63 (0.05)	0.84 (0.01)	0.57 (0.05)	0.81 (0.01)
EQ-VAS (n)	209	427	119	428	89	505	50	510	51	965
Mean (se)	75.21 (0.99)	81.98 (0.71)	69.29 (1.37)	81.76 (0.67)	64.96 (1.72)	79.84 (0.73)	65.50 (2.49)	76.73 (1.73)	60.92 (2.49)	74.30 (0.62)