

Real-world utilities and health-related quality-of-life data in hemophilia patients in France and the United Kingdom

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Purpose: Congenital hemophilia A and B are bleeding disorders characterized by deficiency of factors VIII and IX, respectively. This study aimed to collect health-related quality-of-life (HRQoL) and health-utility data from hemophilia patients with differing disease severity.

Methods: Individuals with hemophilia aged ≥ 12 years living in France or the UK completed a series of questionnaires, including the EQ-5D-3L and -5L and SF-36 version 2. Association with demographic and clinical variables was explored using linear regression, and health-utility comparison was completed using Pearson and intraclass correlation coefficients.

Results: A total of 122 patients in France and 62 in the UK completed the survey. The combined sample primarily consisted of hemophilia A patients, mean age of 41 years, 70% had severe hemophilia, and 56% were on long-term prophylaxis. Similar HRQoL and utility scores were observed across the French and UK samples. The presence of more than two target joints, occurrence of joint surgery, and increased joint-pain frequency were independent predictors of lower SF-36 — physical health summary scores and lower health-utility scores. No statistically significant reductions in SF-36 — mental health summary scores were observed, except for participants with target joints. Strong correlations were observed between health-utility values derived from the three instruments ($r=0.69-0.79$).

Conclusion: Results of this study reinforce the importance of appropriate treatment to limit the physical burden and long-term joint damage associated with hemophilia. Further, utility values collected here reflect real-world data, and can serve as health-state weights in future cost-utility analyses.

Keywords: quality-of-life, health utility, hemophilia A, hemophilia B, survey

Introduction

Hemophilia A and B are X-linked recessive hereditary bleeding disorders resulting from a deficiency in coagulation factor VIII (FVIII) and factor IX (FIX), respectively. Annual incidence is estimated at one in 5,000 to one in 10,000 male births in the US and in Europe.^{1,2} Severity of hemophilia is categorized as mild, moderate, or severe by the percentage of coagulation FVIII (type A) or FIX (type B) individuals have in their blood.

Symptoms are primarily bleeding episodes that occur spontaneously or following an injury, trauma, or surgical procedure. Repeated bleeding episodes can lead to long-term musculoskeletal complications, including synovitis, degenerative arthropathy, and articular deformities.³

Individuals living with hemophilia tend to have quality-of-life (QoL) issues that affect their physical, psychological, social, and economic well-being. Some individuals

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limit activities due to the potential risk of a bleeding incident, whereas others are limited in terms of mobility and functional status due to permanent and painful joint damage.^{4,5} Disease severity has also been shown to impact QoL among individuals with hemophilia A and B, where individuals with severe hemophilia report poorer QoL than those with mild–moderate based on the scores from the Short-Form Health Survey (SF)-36 and the EuroQol (EQ)-5D.⁶ Since the introduction of factor-replacement therapy, life expectancy and health-related QoL (HRQoL) in hemophilia patients have greatly improved.⁷ Using the standard gamble method, Naraine et al showed that scenarios with prophylaxis were preferred to scenarios with “on-demand treatment of bleeds” by both hemophilia patients and their parents, as well as the general public in the state of Ontario in Canada.⁸ However, treatment of hemophilia is perceived as very costly, with an estimated annual per-patient cost of €129,365 in the UK, and €196,117 in France.⁹

Assessment of patient benefit from interventions is the key concern for the economic evaluation process conducted by health technology–assessment bodies. One commonly employed approach is the use of quality-adjusted life-years, which requires changes in HRQoL to be expressed as health utilities. Ideally, changes in HRQoL should be reported directly by patients. A number of different methods can be used to measure HRQoL and subsequently produce utility values. However, results from different methods or instruments are difficult to compare. Given the need for consistency across assessments, some health technology–assessment agencies have stated a preference for the use of specific utility-elicitation approaches, such as the use of the EQ-5D-3L by the National Institute for Health and Care Excellence in the UK.¹⁰

This study aimed to elicit health utilities directly from individuals with hemophilia using the EQ-5D and collect additional QoL data using the generic QoL questionnaire SF-36. The overall objectives of the study included informing decision-making around potential product benefit, providing utility values to support economic modeling efforts, and improved dissemination efforts designed to convey the burden of hemophilia and its treatment to the scientific community using real-life data.

Methods

Study design and patients

This was a cross-sectional online survey conducted in hemophilia patients living in the UK and France. Eligible

participants were recruited through an advocacy group within each country. Prospective participants were invited via email in their native language to participate in the online survey. To be included in the study, participants had to read an information screen, provide their consent electronically, and complete a screening form prior to the survey. Participants had to meet inclusion criteria of male aged 13–17 years or adult aged 18 years or above, current resident in the targeted country (UK or France), diagnosed with hemophilia A or B, voluntarily agreeing to participate, electronically giving informed consent for adult participants, or parents of participants giving informed consent for participants, and not having already participated in this study. Eligible participants were asked to complete a sociodemographic and clinical form, the EQ-5D-3L, including the VAS, SF-36 version 2, and EQ-5D-5L without the VAS (as it is similar to the one from the EQ-5D-3L).

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. This study fell outside the scope of studies requiring mandatory ethical approval in the UK and France; therefore it was reviewed and approved by the US Quorum Review institutional review board, as well as reviewed by a French ethics committee (Comité de Protection des Personnes — Ile de France 8).

Outcome measures

Sociodemographic and clinical form

Basic sociodemographic data on participants (age, sex, marital status, employment status) and clinical information (eg, hemophilia type, severity, current treatment regimen) were collected through self-report. Forms were adapted according to the participant’s age (adolescent or adult), as described in the inclusion criteria, and only adults were asked about their marital and employment status.

In this form, “target joint” was defined as one that had bled three or more times in six months.¹¹ “On-demand regimen” was defined as episodic treatment as a bleed occurs, while long-term prophylaxis was defined as preventive regular injections and short-term prophylaxis as prolonged treatment following a bleed until full recovery and prophylaxis prior to physical activity.

EuroQol — five dimensions

The EQ-5D is a standardized instrument for measuring health outcomes in adolescents and adults.^{12,13} It exists as a three-

level (EQ-5D-3L) and five-level (EQ-5D-5L), five-dimensional questionnaire with the domains mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Participants are asked to indicate their current level of health by checking one of the three (EQ-5D-3L) or five (EQ-5D-5L) boxes indicating the level of problems or disability for each domain, ranging from no problems to complete inability to function with regard to that domain. Participants also indicated their current health on a 0–100 VAS. Health utilities were derived using a mapping algorithm, which used validated scoring methods and general-population weights,¹⁴ where a score of 1 represents full health, 0 a state equivalent to dead, and a negative score represents a state worse than being dead.

Short-Form Health Survey

The Medical Outcomes Study SF-36 version 2 is a generic questionnaire that measures generic health concepts relevant across different ages, diseases, and treatment groups in adults.^{15,16} It consists of 36 items comprising eight scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Two component-summary measures can be derived based on the eight health domain-scales score: physical component summary (PCS) and mental component summary (MCS). Normalized scores are approximately 20–60, with higher scores indicating better health and 50 corresponding to the mean in the US general population.¹⁵ A health-utility index (SF-6D) can also be calculated from eleven items of the SF-36 covering seven domains: physical functioning, role participation (combined role-physical and role-emotional), social functioning, bodily pain, mental health, and vitality. The resulting index is scored from 0 (worst health state) to 1 (best health state).^{17,18}

Statistical analysis

Missing scores due to missing items or questionnaires were not included. All data processing and analyses were performed with SAS for Windows version 9.2 or later (SAS Institute, Cary, NC, USA). The significance level was set at 5%.

Sociodemographic data are summarized in the form of frequencies and means (SDs). Mean, SD, median, and IQRs are presented for each patient-reported outcome (PRO) measure for the overall population, but also per subgroup based on severity of hemophilia (mild, moderate, severe) and type of treatment received by the participants (on-demand, prophylaxis). PRO scores were calculated according to

instrument guidelines. EQ-5D-3L and -5L single utility-index scores were generated by applying the UK weights specific for each of the EQ-5D instruments. US norm-based scoring was used for the SF-36, centering the US general population mean to 50 and the SD to 10 for all scales. This was based on the findings of Ware et al in the IQOLA project, where they found minimal differences in US norms and country-specific norms for nine European countries, which included France and the UK, and subsequently recommended standard scoring using US-derived scoring algorithms for purposes of multinational studies involving these ten countries.¹⁹ For all scales and summary measures, group mean scores <47 can be interpreted as being below the average range for the general population.¹⁵

Pearson correlation coefficients and intraclass correlation were calculated to assess the agreement among EQ-5D-3L index scores, EQ-5D-5L index scores, and SF-6D utility index scores.

To identify possible determinants of HRQoL and functional capacity in individuals living with hemophilia, bivariate analyses were performed for each PRO score, with characteristics collected in the demographic and clinical form. Multiple linear regression models were further conducted for each PRO score as a response variable, and predictor variables included any characteristics examined with $P < 0.10$ in the respective bivariate analysis.

Results

Population description

A total of 184 participants (122 in France and 62 in the UK) completed the entire survey (Table 1).

Overall, French and UK samples were comparable (Table 1). Most participants were adults (87% in the French sample with a mean age of 45 years and 85% in the UK sample with a mean age of 44 years) and had been diagnosed with hemophilia A (80% in the French sample and 86% in the UK sample). The majority of patients reported that their disease was severe (71% in the French sample and 69% in the UK sample). The overall distribution in terms of number of target joints (none, one to two, more than two), joint pain frequency (from every day to never), and history of joint surgery was balanced.

All except one participant with a mild condition reported receiving an on-demand regimen. The majority of participants (71%) with a moderate condition were also receiving an on-demand regimen. In contrast, the majority

Table 1 Population characteristics by country, treatment regimen, and hemophilia severity

	Country		Treatment regimen				Hemophilia severity			
	France (n=122)	UK (n=62)	On demand (n=73)	Long-term prophy- laxis (n=103)	Short-term prophy- laxis (n=8)	Mild (n=20)	Moderate (n=34)	Severe (n=130)		
Age (years), mean (SD)	41.3 (18.1)	39.8 (17.8)	46.9 (17.0)	36.8 (17.7)	35.9 (15.3)	41.6 (22.6)	42.2 (16.8)	40.3 (17.6)		
Type										
A	98 (80.3%)	53 (85.5%)	59 (80.8%)	85 (82.5%)	7 (87.5%)	18 (90.0%)	29 (85.3%)	104 (80.0%)		
B	24 (19.7%)	9 (14.5%)	14 (19.2%)	18 (17.5%)	1 (12.5%)	2 (10.0%)	5 (14.7%)	26 (20.0%)		
Age at diagnosis (years), mean (SD)	2.4 (4.5)	2.9 (7.0)	4.6 (8.1)	1.2 (1.4)	1.5 (1.5)	9.8 (13.0)	3.3 (4.8)	1.3 (1.3)		
Target joints										
None	47 (38.5%)	17 (27.4%)	36 (49.3%)	26 (25.2%)	2 (25.0%)	16 (80.0%)	19 (55.9%)	29 (22.3%)		
1–2	42 (34.4%)	29 (46.8%)	18 (24.7%)	49 (47.6%)	4 (50.0%)	4 (20.0%)	11 (32.4%)	56 (43.1%)		
>2	33 (27.0%)	16 (25.8%)	19 (26.0%)	28 (27.2%)	2 (25.0%)	0	4 (11.8%)	45 (34.6%)		
Joint pain										
Every day	51 (41.8%)	29 (46.8%)	26 (35.6%)	51 (49.5%)	3 (37.5%)	2 (10.0%)	10 (29.4%)	68 (52.3%)		
Few times a week	12 (9.8%)	7 (11.3%)	11 (15.1%)	7 (6.8%)	1 (12.5%)	1 (5.0%)	5 (14.7%)	13 (10.0%)		
Few times a month	22 (18.0%)	12 (19.4%)	14 (19.2%)	18 (17.5%)	2 (25.0%)	7 (35.0%)	5 (14.7%)	22 (16.9%)		
Never	37 (30.3%)	14 (22.6%)	22 (30.1%)	27 (26.2%)	2 (25.0%)	10 (50.0%)	14 (41.2%)	27 (20.8%)		
Joint surgery	55 (45.1%)	27 (43.5%)	27 (37.0%)	53 (51.5%)	2 (25%)	2 (10.0%)	10 (29.4%)	70 (53.8%)		
Experience of injury leading to long-term hospitalization	59 (48.4%)	49 (79.0%)	43 (58.9%)	57 (55.3%)	8 (100%)	13 (65.0%)	22 (64.7%)	73 (56.2%)		
Time on regimen (years), mean (SD)	19.7 (16.7)	17.8 (13.0)	31.3 (18.0)	12.8 (9.0)	11.5 (10.4)	18.6 (15.7)	22.8 (17.3)	18.2 (15.0)		
Medical visits										
>Once a month	3 (2.5%)	0	1 (1.4%)	2 (1.9%)	0	0	1 (2.9%)	2 (1.5%)		
Every 1–3 months	11 (9.0%)	16 (25.8%)	5 (6.8%)	21 (20.4%)	1 (12.5%)	2 (10.0%)	1 (2.9%)	24 (18.5%)		
Every 4–6 months	19 (15.6%)	23 (37.1%)	11 (15.1%)	30 (29.1%)	1 (12.5%)	3 (15.0%)	7 (20.6%)	32 (24.6%)		
Every 6–12 months	55 (45.1%)	21 (33.9%)	30 (41.1%)	40 (38.8%)	6 (75.0%)	7 (35.0%)	13 (38.2%)	56 (43.1%)		
<Every 12 months	34 (27.9%)	2 (3.2%)	26 (35.6%)	10 (9.7%)	0	8 (40.0%)	12 (35.3%)	16 (12.3%)		

of participants with a severe condition (77%) were on prophylaxis.

Patients with a severe condition were diagnosed at an earlier age, reported more target joints, more frequent experiences of joint pain, and a higher incidence of previous joint surgery than patients with moderate or mild hemophilia.

EQ-5D-3L, EQ-5D-5L, and SF-6D health utilities

Description of health-utility scores

Similar EQ-5D-3L values were observed across the French (0.69) and UK (0.66) samples ($P=0.507$). Similarly, SF-6D values observed across the French (0.70) and UK (0.69) samples ($P=0.433$) were similar (Table 2).

Comparison of EQ-5D-3L utility values in the pooled sample (French and UK samples combined) showed that adolescents ($n=25$) reported a statistically significant higher mean utility value (0.84 ± 0.24) than adults ($n=159$, 0.65 ± 0.30 ; $P=0.0039$). Similarly, the difference in SF-6D utility values in the pooled sample between adults and adolescents was statistically significant ($P=0.001$), with adolescents (0.78 ± 0.11) also reporting higher values than adults (0.69 ± 0.13).

Statistically significant differences were observed when comparing EQ-5D-3L utility values for participants based on severity of their hemophilia ($P=0.017$, Table 2): the more severe the disease, the lower the utility. In contrast, subgroups of participants according to hemophilia type did not report statistically significant differences in utility values ($P=0.831$, Table 2). Similarly, participants with differing treatment regimens did not report statistically significant differences in utility values ($P=0.738$, Table 2).

Participants who reported having more than two target joints had significantly lower EQ-5D-3L utility values (0.43 ± 0.35) than participants reporting no target joints (0.85 ; $P<0.001$, Table 3). Similarly, participants reporting a higher frequency of joint pain and history of joint surgery had statistically significantly lower EQ-5D-3L utility values than participants who did not experience joint pain or who had not had joint surgery previously ($P<0.001$, Table 3).

Participants with a history of long hospital stays due to hemophilia reported significantly lower EQ-5D-3L utility values ($P=0.002$, Table 4) than participants without such a history. Also, participants with more frequent visits to medical professionals due to their hemophilia reported

significantly lower EQ-5D-3L utility values ($P=0.002$, Table 4) than participants with less frequent visits.

Overall, similar findings were observed for the EQ-5D-5L and SF-6D.

The analysis was repeated with a focus on subjects with severe hemophilia only. Similar findings were found, with the exception that subjects with severe disease and receiving on-demand treatment had significantly lower EQ-5D-3L scores than those receiving prophylaxis ($P=0.048$, Supplementary material Tables S1 to S3).

Predictors of health utilities

In the multiple linear regression model (data not shown), the presence of more than two target joints and increased joint-pain frequency were independent predictors of lower EQ-5D-3L-derived utility values. In addition to those two factors, the occurrence of joint surgery was a third factor explaining the bulk of variability in the EQ-5D-5L-derived utility values. The presence of more than two target joints and increased joint-pain frequency were independent predictors of lower SF-6D-derived utility values. A statistically significant difference ($P<0.05$) in the EQ-5D-3L was observed only for patients who had more than two target joints (-0.18) compared to none and those who had joint pain (-0.33 , -0.15 , and -0.15 for every day, a few times a week, and a few times a month, respectively) compared to never. For the EQ-5D-5L, a statistically significant difference was observed only for those who had more than two target joints (-0.18) compared to none, those who had joint pain every day (-0.26) compared to never, and those without a history of joint surgery (0.10) compared to no history. For the SF-6D, a statistically significant difference was observed only for those who had more than two target joints (0.10) compared to none and those who had joint pain every day (-0.12) compared to never.

Comparison of EQ-5D- and SF-6D-derived health utilities

The correlation between the EQ-5D-3L and EQ-5D-5L was highest (Pearson correlation coefficient 0.79). Other correlations were slightly lower between the EQ-5D-5L and SF-6D (0.72) and between the EQ-5D-3L and SF-6D (0.69).

Although the instruments were well correlated, utility values obtained from each were not exactly the same, as indicated by an intraclass correlation of 0.50 (95% CI

Table 2 Health-utility values and health-related quality-of-life scores by country, hemophilia type, severity, and treatment regimen in the pooled sample (n=184)

	Country		Hemophilia type		Hemophilia severity			Treatment regimen			
	France (n=122)	UK (n=62)	Type A (n=151)	Type B (n=33)	Mild (n=20)	Moderate (n=34)	Severe (n=130)	On demand (n=73)	Long-term Ppx (n=103)	Short-term Ppx (n=8)	
EQ-5D-3L index score	Mean (SD)	0.69 (0.28)	0.66 (0.34)	0.68 (0.32)	0.67 (0.22)	0.85 (0.15)	0.69 (0.34)	0.65 (0.30)	0.70 (0.29)	0.67 (0.31)	0.67 (0.34)
	Median	0.71	0.71	0.73	0.69	0.82	0.78	0.69	0.73	0.69	0.69
	Range	-0.08-1	-0.48-1	-0.48-1	0.09-1	0.52-1	-0.24-1	-0.48-1	-0.48-1	-0.24-1	0.09-1
	P-value	0.507		0.831		0.017			0.738		
EQ-5D-5L index score	Mean (SD)	0.74 (0.23)	0.74 (0.30)	0.75 (0.26)	0.70 (0.24)	0.87 (0.15)	0.75 (0.30)	0.72 (0.25)	0.76 (0.26)	0.73 (0.26)	0.73 (0.26)
	Median	0.80	0.84	0.82	0.80	0.88	0.84	0.77	0.84	0.80	0.76
	Range	0.07-1	-0.10-1	-0.10-1	0.07-1	0.54-1	-0.10-1	0.04-1	-0.10-1	0-1	0.31-1
	P-value	0.837		0.252		0.051			0.834		
SF-6D score	Mean (SD)	0.70 (0.13)	0.69 (0.14)	0.70 (0.14)	0.68 (0.10)	0.75 (0.11)	0.73 (0.16)	0.68 (0.12)	0.71 (0.13)	0.69 (0.13)	0.71 (0.19)
	Median	0.69	0.68	0.69	0.67	0.74	0.74	0.67	0.71	0.67	0.62
	Range	0.43-1	0.39-1	0.39-1	0.47-0.87	0.54-0.91	0.39-1	0.39-1	0.39-1	0.39-1	0.47-0.95
	P-value	0.433		0.329		0.035			0.515		
SF-36 PCS	Mean (SD)	42.0 (12.3)	39.6 (14.1)	41.4 (13.0)	40.4 (12.8)	49.5 (10.7)	44.1 (13.0)	39.2 (12.6)	42.6 (12.7)	40.3 (13.0)	40.4 (14.6)
	Median	41.2	39.7	41.5	40.2	51.9	48.5	38.1	43.4	38.8	43.9
	Range	16.3-66.6	16.4-63.8	16.3-63.8	20.9-66.6	16.4-62.0	19.6-66.6	16.3-63.8	16.4-66.6	16.3-63.8	21.4-55.4
	P-value	0.238		0.701		0.001			0.493		
SF-36 MCS	Mean (SD)	48.0 (11.6)	47.4 (11.2)	48.4 (11.2)	44.9 (12.5)	49.1 (9.3)	48.0 (13.7)	47.5 (11.2)	48.8 (11.1)	46.9 (11.9)	50.5 (8.6)
	Median	50.3	48.8	50.1	45.3	51.6	54.5	49.3	51.2	49.0	49.1
	Range	18.3-70.1	19.8-66.9	19.8-68.7	18.3-70.1	26.2-61.7	18.3-66.9	22.6-70.1	18.3-65.4	19.8-70.1	37.7-60.2
	P-value	0.757		0.115		0.849			0.431		

Abbreviations: EQ-5D-3L, EuroQol — five dimensions, three levels; SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS; Ppx, prophylaxis.

Table 3 Health utility values and health-related quality-of-life scores by number of target joints, joint pain, and joint surgery occurrence in the pooled sample (n=184)

Variable	Target joints			Joint pain			Joint surgery		
	None (n=64)	1 to 2 (n=71)	>2 (n=49)	Every day (n=80)	Few times a week (n=19)	Few times a month (n=34)	Never (n=51)	Yes (n=82)	No (n=102)
EQ-5D-3L index score									
Mean (SD)	0.85 (0.17)	0.70 (0.24)	0.43 (0.35)	0.49 (0.30)	0.70 (0.17)	0.75 (0.23)	0.93 (0.15)	0.54 (0.31)	0.79 (0.24)
Median	0.85	0.69	0.62	0.62	0.73	0.80	1	0.62	0.80
Range	0.29–1	–0.08–1	–0.48–0.85	–0.48–0.85	0.19–1	–0.02–1	0.29–1	–0.48–1	–0.02–1
P-value	<0.001			<0.001			<0.001		
EQ-5D-5L index score									
Mean (SD)	0.88 (0.13)	0.75 (0.24)	0.55 (0.27)	0.57 (0.25)	0.79 (0.18)	0.81 (0.21)	0.95 (0.10)	0.62 (0.27)	0.84 (0.20)
Median	0.93	0.81	0.62	0.64	0.84	0.85	1	0.69	0.92
Range	0.55–1	–0.10–1	0–1	–0.10–1	0.38–1	0.26–1	0.57–1	–0.10 to 1	0.26–1
P-value	<0.001			<0.001			<0.001		
SF-6D score									
Mean (SD)	0.78 (0.11)	0.69 (0.12)	0.61 (0.11)	0.63 (0.11)	0.69 (0.10)	0.72 (0.13)	0.80 (0.09)	0.65 (0.12)	0.74 (0.13)
Median	0.77	0.67	0.61	0.61	0.68	0.71	0.82	0.64	0.76
Range	0.54–1	0.47–0.95	0.39–0.85	0.39–0.90	0.54–0.95	0.43–1	0.60–1	0.39–0.95	0.43–1
P-value	<0.001			<0.001			<0.001		
SF-36 PCS									
Mean (SD)	49.7 (10.6)	40.3 (12.0)	31.4 (9.1)	30.7 (8.4)	41.7 (8.5)	45.9 (10.1)	54.3 (6.2)	33.7 (10.8)	47.2 (11.3)
Median	52.1	39.6	29.9	29.9	41.2	47.6	54.5	31.1	50.6
Range	16.4–66.6	16.3–61.6	18.9–54.1	16.3–57.1	21.4–54.3	27.2–60.1	36.6–66.6	16.3–61.1	19.8–66.6
P-value	<0.001			<0.001			<0.001		
SF-36 MCS									
Mean (SD)	49.7 (10.6)	48.3 (10.3)	44.4 (13.4)	45.7 (13.0)	49.6 (8.9)	47.3 (10.5)	50.7 (9.8)	46.3 (13.0)	49.0 (9.9)
Median	53.7	49.3	45.1	45.2	50.6	48.6	53.9	48.4	51.4
Range	18.3–65.0	22.6–66.9	19.8–70.1	19.8–70.1	34.6–64.8	26.2–60.3	18.3–61.7	19.8–70.1	18.3–65.4
P-value	0.042			0.085			0.121		

Abbreviations: EQ-5D-3L, EuroQol — five dimensions, three levels; SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS.

Table 4 Health-utility values and health-related quality-of-life scores by history of long hospital stays and frequency of visits to medical professionals due to hemophilia in the pooled sample (n=184)

Variable	History of long hospital stays		Frequency of visits to a medical professional due to hemophilia				
	Yes (n=108)	No (n=76)	>Once a month (n=3)	Every 1–3 months (n=27)	Every 4–6 months (n=42)	Every 6–12 months (n=76)	<Once every 12 months (n=36)
EQ-5D-3L index score							
Mean (SD)	0.62 (0.33)	0.76 (0.22)	0.32 (0.41)	0.57 (0.30)	0.60 (0.37)	0.74 (0.24)	0.76 (0.27)
Median	0.69	0.80	0.09	0.59	0.69	0.75	0.80
Range	–0.48–1	–0.02–1	0.08–0.80	–0.02–1	–0.48–1	–0.02–1	–0.02–1
P-value	0.002		0.002				
EQ-5D-5L index score							
Mean (SD)	0.70 (0.27)	0.81 (0.22)	0.51 (0.33)	0.69 (0.24)	0.66 (0.33)	0.78 (0.22)	0.81 (0.20)
Median	0.75	0.84	0.33	0.76	0.77	0.82	0.84
Range	–0.10–1	0.07–1	0.31–0.88	0.08–1	–0.10–1	0.07–1	0.19–1
P-value	0.004		0.013				
SF-6D score							
Mean (SD)	0.68 (0.14)	0.72 (0.12)	0.59 (0.18)	0.63 (0.09)	0.67 (0.14)	0.72 (0.12)	0.75 (0.13)
Median	0.67	0.73	0.55	0.61	0.71	0.71	0.77
Range	0.39–1	0.52–1	0.43–0.79	0.52–0.85	0.39–0.89	0.49–1	0.50–1
P-value	0.024		<0.001				
SF-36 PCS							
Mean (SD)	38.8 (13.3)	44.7 (11.6)	33.5 (7.3)	36.6 (10.0)	37.6 (15.2)	42.6 (11.5)	46.5 (13.0)
Median	37.0	43.8	33.0	33.5	35.6	42.9	49.6
Range	16.3–63.8	19.8–66.6	26.4–41.0	24.3–56.7	16.3–63.8	19.8–59.8	21.2–66.6
P-value	0.002		0.004				
SF-36 MCS							
Mean (SD)	47.1 (12.0)	48.8 (10.6)	39.2 (22.2)	44.0 (8.7)	46.6 (12.4)	49.6 (10.8)	48.9 (11.9)
Median	49.3	50.7	26.6	45.3	49.1	52.3	52.5
Range	19.8–70.1	18.3–65.4	26.2–64.7	24.9–56.6	19.8–70.1	22.6–66.9	18.3–68.7
P-value	0.313		0.113				

Abbreviations: EQ-3D-3L, EuroQol — five dimensions, three levels; SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS.

0.13–0.75) between the EQ-5D-3L and SF-6D, 0.78 (95% CI 0.56–0.90) between the EQ-5D-3L and EQ-5D-5L, and 0.58 (95% CI 0.24–0.79) between the EQ-5D-5L and SF-6D. As shown in Tables 2–4, the EQ-5D-3L tended to give lower utility values than the EQ-5D-5L and tended to be distributed over a broader range. SF-6D-utility values were distributed over a smaller range than EQ-5D-3L values. For example, EQ-5D-3L mean utility values related to the various level of joint-pain severity ranged from 0.49 for participants experiencing joint pain every day to 0.93 for participants not experiencing any joint pain. For the same characteristic, SF-6D mean utility values were 0.63–0.80.

SF-36 quality-of-life

Description of SF-36 scores

Similar PCS and MCS scores were observed across the French (PCS 42.0±12.3, MCS 48.0±11.6) and UK (PCS 39.6±14.1, MCS 47.4±11.2) samples ($P=0.238$, $P=0.757$; Table 5). These norm-based scores show that while there was impairment on patient physical function, their MCS scores within range of the average in the general US population.

Statistically significant differences were observed when comparing SF-36 PCS scores for participants based on severity of their hemophilia ($P=0.001$, Table 2): the more severe the disease, the lower the score. In contrast, subgroups of participants based on hemophilia type or treatment regimen did not reveal differences in SF-36 PCS scores.

Participants who had more than two target joints had significantly lower SF-36 PCS and MCS scores than participants with no target joints. Participants reporting a higher frequency of joint pain and previous joint surgery had statistically significantly lower SF-36 PCS scores than participants who did not experience joint pain or who had not had joint surgery ($P<0.001$, Table 3). In contrast, no significant differences were found for SF-36 MCS scores.

Participants with a history of long hospital stays due to hemophilia reported significantly lower SF-36 PCS scores ($P=0.002$, Table 4) than those without such a history. Also, patients with more frequent visits to medical professionals regarding hemophilia reported significantly lower SF-36 PCS scores ($P=0.004$, Table 4) than those with less frequent visits. In contrast, no significant differences were found for SF-36 MCS scores.

Table 5 US-norm-based SF-36-dimension and -component summary scores by country

	France (n=122)	UK (n=62)
Physical functioning		
Mean (SD)	43.2 (12.6)	39.4 (15.6)
Median	46.5	41.3
Range	17.1–57.0	14.9–57.0
Role — physical		
Mean (SD)	41.2 (11.4)	41.4 (13.0)
Median	40.9	44.6
Range	20.1–56.9	17.7–56.9
Bodily pain		
Mean (SD)	45.2 (11.5)	43.6 (10.9)
Median	46.1	41.6
Range	24.1–62.1	19.9–62.1
General health		
Mean (SD)	42.0 (10.6)	39.9 (13.7)
Median	41.0	39.8
Range	21.0–63.9	16.2–63.9
Vitality		
Mean (SD)	48.2 (9.9)	44.5 (12.6)
Median	49.0	42.7
Range	20.9–67.7	20.9–70.8
Social functioning		
Mean (SD)	44.5 (11.3)	44.4 (10.8)
Median	45.9	45.9
Range	13.2–56.9	18.7–56.9
Role — emotional		
Mean (SD)	46.1 (11.0)	44.7 (12.8)
Median	48.1	48.1
Range	17.0–55.9	13.1–55.9
Mental health		
Mean (SD)	46.6 (11.7)	46.3 (11.3)
Median	50.0	47.2
Range	10.6–64.1	19.0–64.1
PCS		
Mean (SD)	42.0 (12.3)	39.6 (14.1)
Median	41.2	39.7
Range	16.3–66.6	16.4–63.8
MCS		
Mean (SD)	48.0 (11.6)	47.4 (11.2)
Median	50.3	48.8
Range	18.3–70.1	19.8–66.9

Abbreviations: SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS.

The analysis was repeated with a focus on subjects with severe hemophilia only. Similar findings were

found, with the exception that subjects with severe disease and receiving on-demand treatment had significantly lower SF-36 PCS scores than those receiving prophylaxis ($P=0.048$, Supplementary material Tables S1 to S3).

Predictors of SF-36 physical and mental component scores

Based on the bivariate analyses (data not shown), the PCS score varied per group based on age, severity of emophilia, number of target joints, frequency of joint pain, previous joint surgery, and long-term hospitalizations, as well as frequency of visits to medical professionals due to hemophilia. Hemophilia type and treatment regimen did not result in significant differences across the compared groups. Furthermore, a statistically significant difference ($P<0.05$) in SF-36 PCS scores was observed only for those who had more than two target joints (-5.7) compared to those who had none, had joint pain every day (-19.3) or every week (-6.7) compared to never, and those with a history of joint surgery (4.7) compared to those without. In contrast, MCS scores were significantly different in bivariate analysis only when comparing by group based on the number of target joints ($P=0.042$). However, no statistically significant differences were observed in the multiple-regression model.

Discussion

The objectives of this study were to collect real world HRQoL and health-utility data from hemophilia patients of varying severity. The results of this study could be used to convey the burden of hemophilia and its management and inform decision-making around potential treatment benefit by providing evidence to support economic modeling efforts.

Similar EQ-5D-3L-index scores were observed across the French (0.69) and UK (0.66) samples. These health-utility values were below mean scores for the general population: 0.90 for France²⁰ and 0.86 for the UK.²¹ Noone et al reported mean EQ-5D-3L-derived health-utility values for men aged 18–35 years with severe hemophilia in France ($n=14$) as 0.687 and in the UK ($n=13$) as 0.768.²² SF6D values observed across the UK (0.69) and French (0.70) samples ($P=0.433$) were lower than the 0.81 value published for males in the general population from the UK.²³ Independently of the instrument used, the values in our sample highlight the burden of the disease.

With regard to HRQoL, similar PCS and MCS scores were observed across the French (PCS 42.0, MCS 48.0) and UK (PCS 39.6, MCS 47.4) samples ($P=0.757$, $P=0.238$). These norm-based scores showed that while there was impairment in patient physical function, their MCS was within range of the average in the general US population. Our findings were consistent with what has been reported in the literature on German and Austrian hemophilia patients: the domains that contribute most to the MCS score (vitality, social functioning, role-emotional, mental health) were comparable between German and Austrian hemophilia patients and general populations.^{24,25} These results showed that individuals with hemophilia have a good level of mental health, which could be linked to continuous support, education, and efforts made by health-care professionals and patient-advocacy groups to help individuals with hemophilia.

The presence of more than two target joints and increased joint-pain frequency were independent predictors of lower health-utility scores across all three utility measures, as well as predictors of lower SF-36 PCS scores. Interestingly, when examining subgroup PCS scores and the health-utility values by presence of target joint, participants who reported no target joint had mean PCS (49.7) and EQ5D3L scores (0.85) similar to values reported in the general population. However, patients with one to two or more than two target joints, had a substantial drop in score, reinforcing the fact that chronic joint inflammation is a key burden of hemophilia affecting HRQoL.

Adolescents ($n=25$) reported statistically significantly higher mean values and scores than adults ($n=159$) for both health-utility values and PCS scores. While it has been shown that younger respondents tend to report higher utility scores,²¹ this could also be due to younger hemophilia patients not having yet developed complications and having different treatment history.²⁶

A larger decrease was observed between mild and moderate patients compared to the decrease between moderate and severe patients with mean EQ-5D-3L utility values of 0.85 for mild hemophilia (0.87 for the French sample and 0.82 for the UK sample), 0.69 for moderate hemophilia (0.72 for the French sample and 0.63 for the UK sample), and 0.65 for severe hemophilia (0.66 for the French sample and 0.64 for the UK sample). These values were very close to the values we obtained in our previous study, where we used the VAS and time trade-off valuation exercises with members of the general

public in France, Germany, Italy, Sweden, the UK, and US. Utility values for the mild health state were 0.79 for France and 0.82 for the UK, with a mean value across all six countries of 0.80. Values for the moderate health state were 0.74 for France and 0.79 for the UK, with a mean value across all countries of 0.73. Finally, values for the severe health state were 0.68 for France and 0.64 for the UK, with a mean value across all countries of 0.67.²⁷ The smaller decrease in utility values between moderate and mild disease in that study compared to ours could be linked to the fact that patients may interpret the progression differently in severity than members of the general public. The decrease between mild and moderate has also been observed by others. A Belgian single-center study that administered the SF36 to 71 adult males (59 with hemophilia A and 12 with hemophilia B) found a mean SF-6D utility score of 0.66, with differences in scores by hemophilia severity: 0.63 for severe (n=44), 0.66 for moderate (n=15) and 0.74 for mild (n=12).²⁸ This could be explained by the fact that patients with moderate hemophilia may receive prophylaxis treatment at a later point in life compared to the severe population.

While it has been theorized in the literature that hemophilia B could be associated with a milder-bleeding phenotype and less need for hemophilia-related surgery,^{29,30} our study did not detect any differences in health utilities or QOL between patients with hemophilia A and hemophilia B. In our study, we did not detect any significant difference in EQ-5D or SF-36 scores between patients on prophylaxis and patients on on-demand treatment either. This could be explained by variation in patient clinical profiles and individual management. Older patients, those with mild hemophilia, and those without target joints were more likely to receive on-demand treatment.

Comparison with another joint disease, rheumatoid arthritis, in a meta-analysis showed that patients with rheumatoid arthritis had a mean SF-36 PCS score of 34.1 and MCS score of 45.6.³¹ These values are very close to those observed for patients with severe hemophilia or those with experience of more than two target joints. While similar findings have been observed for patients with psoriatic arthritis (PCS around 33 and MCS around 50), PCS scores were close to the normative value of 50 for patients with psoriasis and no psoriatic arthritis, and MCS scores of these patients was slightly lower.³² This further highlights the physical burden of joint disease on patients' lives.

Our study is the first to assess utilities in hemophilia using three distinct tools. There are major differences in the number of items, response options, domains covered, and recall period between the HRQoL questionnaires (today for the EQ-5D versus the last 4 weeks for the SF-6D). Despite the high correlations indicating similar trends, each instrument led to unique utility values. In general, the EQ-5D-5L gave higher values than the EQ-5D-3L, while the SF-6D was localized within a small range compared to the EQ-5D-3L and -5L. This finding supports the EQ-5D-3L, -5L, and SF-6D not being used interchangeably in assessments of hemophilia patients. This finding is comparable to that reported in the literature for other conditions, such as coronary heart disease or chronic obstructive pulmonary disease,^{33,34} and in line with the National Institute for Health and Care Excellence, which does not recommend concurrent use of the EQ-5D-3L and -5L.³⁵

While the survey was comprehensive and lasted approximately 20–30 minutes, some key disease characteristics, such as history and presence of inhibitors, history of musculoskeletal complications, and history of traumatic bleeds versus spontaneous bleeds were not collected, limiting interpretability of the reported findings. Another limitation of this study was regarding the potential selection bias of our population, in particular when concluding on whether advocacy-group support could be a reason for good mental health. Finally, despite the participation of adolescents, our data should be read keeping in mind the fact that the sample had a relatively high mean age with probably stable and established joint disease, and may have thus learned to cope with the disease and its complications.

Conclusion

This study quantified the impact of hemophilia and its complications on patients' lives. The collected utility values reflected real-world data and can potentially serve as health-state weights in future cost–utility analyses, although it is important not to use EQ-5D-3L-, EQ-5D-5L-, and SF-6D-derived utility values interchangeably. The HRQoL data further documented the physical burden linked to hemophilia and its complications. These results were consistent overall with the literature, and reinforce the importance of appropriate treatment to limit the physical burden and long-term joint damage associated with hemophilia.

Abbreviation list

HRQoL, health-related quality-of-life; PRO, patient-reported outcome; EQ-5D, EuroQol — 5 dimensions; SF-36, 36-item Short-Form Health Survey; PCS, physical component summary; MCS, mental component summary.

Data-sharing statement

Data sets generated during and/or analyzed during the current study are available from the corresponding author (XYL) on reasonable request.

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Author contributions

XYL, MZ, JL, and KB contributed to concept and design, analysis and interpretation of data; LC contributed to the data collection and the interpretation of data. GB contributed to the interpretation of the data. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

JL is an employee of Mapi, an ICON plc company, was also a paid consultant to Novo Nordisk and Roche. KB is an employee of Mapi, an ICON plc company, was also a paid consultant to Novo Nordisk. LC is an employee of the Haemophilia Society, which has received financial compensation from Novo Nordisk. XYL and MZ are employees of Novo Nordisk. GB was part of the advisory board for Novo Nordisk and received speaker fees from Novo Nordisk, Bristol Myers Squibb, Shire and Bayer. LC reports financial compensation from Novo Nordisk, outside the submitted work. GB reports personal fees from Bristol Myers Squibb Bayer, Baxalta, Pfizer, personal fees and non-financial support from Sobi and Novo Nordisk,

outside the submitted work. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Health-utility values and health-related quality-of life-scores by country, hemophilia type, and treatment regimen in the subsample of subjects with severe hemophilia (n=130)

	Country		Hemophilia type		Treatment regimen		
	France (n=87)	UK (n=43)	Type A (n=104)	Type B (n=26)	On demand (n=30)	Long-term Px (n=95)	Short-term Px (n=5)
EQ-5D-3L index score							
	Mean (SD)	0.66 (0.28)	0.64 (0.33)	0.64 (0.32)	0.67 (0.20)	0.53 (0.33)	0.65 (0.25)
	Median	0.69	0.69	0.69	0.67	0.62	0.66
	Range	-0.08-1	-0.48-1	-0.48-1.0	0.09-1	-0.48-1	0.29-1
P-value	0.715		0.647		0.048		
EQ-5D-5L index score							
	Mean (SD)	0.71 (0.24)	0.74 (0.28)	0.73 (0.25)	0.68 (0.25)	0.63 (0.27)	0.71 (0.21)
	Median	0.74	0.83	0.78	0.74	0.70	0.65
	Range	0.07-1	0.04-1	0.04-1	0.07-1	0.04-1	0.46-1
P-value	0.624		0.327		0.092		
SF-6D score							
	Mean (SD)	0.69 (0.12)	0.67 (0.13)	0.69 (0.13)	0.67 (0.10)	0.65 (0.11)	0.67 (0.15)
	Median	0.67	0.64	0.67	0.65	0.62	0.61
	Range	0.43-1	0.39-0.89	0.39-1	0.52-0.85	0.39-0.86	0.57-0.95
P-value	0.315		0.643		0.286		
SF-36 PCS							
	Mean (SD)	39.7 (12.0)	38.0 (14.0)	39.3 (12.8)	38.6 (12.3)	34.3 (10.4)	38.1 (14.6)
	Median	38.4	37.9	38.5	35.7	30.7	38.5
	Range	16.3-61.6	18.9-63.8	16.3-63.8	20.9-61.6	18.9-59.8	21.35-55.38
P-value	0.773		0.806		0.048		
SF-36 MCS							
	Mean (SD)	47.9 (11.7)	46.8 (10.1)	48.3 (10.8)	44.3 (12.2)	47.7 (11.6)	48.0 (8.7)
	Median	49.8	48.7	49.8	40.5	49.5	45.6
	Range	22.6-70.1	24.9-62.7	22.6-68.7	27.4-70.1	27.4-65.4	37.7-60.2
P-value	0.591		0.101		0.993		

Abbreviations: EQ-5D-3L, EuroQol — five dimensions, three levels; SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS; Px, prescription.

Table S2 Health-utility values and health-related quality-of-life scores by number of target joints, joint pain, and joint surgery occurrence in the subsample of subjects with severe hemophilia (n=130)

	Target joints			Joint pain			Joint surgery		
	None (n=29)	1 to 2 (n=56)	>2 (n=45)	Every day (n=68)	Few times a week (n=13)	Few times a month (n=22)	Never (n=27)	Yes (n=70)	No (n=60)
EQ-5D-3L index score									
Mean (SD)	0.86 (0.16)	0.69 (0.23)	0.46 (0.33)	0.50 (0.28)	0.69 (0.20)	0.70 (0.25)	0.96 (0.08)	0.55 (0.30)	0.76 (0.26)
Median	I	0.69	0.62	0.62	0.73	0.77	I	0.64	0.80
Range	0.59–I	–0.08–I	–0.48–0.85	–0.48–0.85	0.19–I	–0.02–I	0.73–I	–0.48–I	–0.02–I
P-value	<0.001			<0.001			<0.001		
EQ-5D-5L index score									
Mean (SD)	0.89 (0.14)	0.75 (0.23)	0.57 (0.26)	0.59 (0.23)	0.78 (0.21)	0.79 (0.24)	0.96 (0.07)	0.64 (0.25)	0.82 (0.22)
Median	0.94	0.81	0.65	0.65	0.85	0.85	I	0.70	0.92
Range	0.55–I	0.12–I	0.04–I	0.04–I	0.38–I	0.26–I	0.67–I	0.04–I	0.26–I
P-value	<0.001			<0.001			<0.001		
SF-6D score									
Mean (SD)	0.78 (0.09)	0.69 (0.12)	0.62 (0.11)	0.63 (0.11)	0.68 (0.08)	0.70 (0.13)	0.80 (0.09)	0.65 (0.12)	0.72 (0.12)
Median	0.77	0.67	0.61	0.61	0.67	0.67	0.81	0.65	0.73
Range	0.61–I	0.47–0.95	0.39–0.85	0.39–0.90	0.57–0.81	0.43–0.95	0.60–I	0.39–0.95	0.43–I
P-value	<0.001			<0.001			0.003		
SF-36 PCS									
Mean (SD)	49.4 (10.9)	39.8 (12.1)	31.9 (9.3)	31.3 (8.6)	41.2 (9.2)	43.5 (11.3)	54.5 (5.9)	34.5 (11.2)	44.6 (12.1)
Median	53.9	38.7	29.9	30.3	41.2	42.5	54.8	31.8	47.3
Range	27.2–63.8	16.3–61.6	18.9–54.1	16.3–57.1	21.4–54.3	27.2–60.1	38.6–63.8	16.3–61.1	19.8–63.8
P-value	<0.001			<0.001			<0.001		
SF-36 MCS									
Mean (SD)	49.6 (10.4)	48.1 (10.2)	45.5 (12.7)	46.6 (12.3)	48.7 (8.5)	46.5 (10.8)	50.1 (9.4)	47.3 (12.3)	47.8 (9.7)
Median	53.2	49.3	45.3	48.5	48.8	46.8	53.2	49.0	49.8
Range	27.4–65.0	22.6–64.3	24.9–70.1	22.6–70.1	34.6–64.7	26.6–60.2	29.3–60.7	22.6–70.1	26.6–65.4
P-value	0.282			0.527			0.816		

Abbreviations: EQ-5D-3L, EuroQol — five dimensions, three levels; SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS.

Table S3 Health-utility values and health-related quality-of-life scores by history of long hospital stays and frequency of visits to medical professionals due to hemophilia in subsample of subjects with severe hemophilia (n=130)

	History of long hospital stays		Frequency of visits to medical professionals due to hemophilia				
	Yes (n=73)	No (n=57)	>Once a month (n=2)	Every 1–3 months (n=24)	Every 4–6 months (n=32)	Every 6–12 months (n=56)	<Once every 12 months (n=16)
EQ-5D-3L index score							
Mean (SD)	0.57 (0.32)	0.75 (0.23)	0.44 (0.50)	0.55 (0.31)	0.64 (0.34)	0.71 (0.26)	0.66 (0.30)
Median	0.66	0.74	0.44	0.59	0.69	0.71	0.67
Range	–0.48–1	–0.02–1	0.08–0.80	–0.02–1	–0.48–1	–0.02–1	–0.02–1
P-value	<0.001		0.248				
EQ-5D-5L index score							
Mean (SD)	0.66 (0.26)	0.79 (0.23)	0.60 (0.39)	0.68 (0.25)	0.71 (0.30)	0.75 (0.23)	0.71 (0.22)
Median	0.73	0.88	0.60	0.77	0.83	0.79	0.73
Range	0.04–1	0.07–1	0.33–0.88	0.08–1	0.04–1	0.07–1	0.19–1
P-value	0.005		0.750				
SF-6D score							
Mean (SD)	0.66 (0.12)	0.72 (0.12)	0.61 (0.25)	0.63 (0.09)	0.69 (0.14)	0.71 (0.12)	0.70 (0.13)
Median	0.64	0.72	0.61	0.61	0.72	0.68	0.66
Range	0.39–0.95	0.52–1	0.43–0.79	0.52–0.85	0.39–0.89	0.49–1	0.50–0.94
P-value	0.006		0.105				
SF-36 PCS							
Mean (SD)	36.3 (12.7)	42.9 (11.6)	37.0 (5.7)	36.5 (10.1)	38.3 (15.3)	41.1 (12.2)	38.5 (12.4)
Median	32.8	41.0	37.0	34.1	37.6	40.5	37.6
Range	16.3–63.8	19.8–61.6	33.0–41.0	24.3–56.7	16.3–63.8	19.8–59.8	21.2–61.1
P-value	0.003		0.627				
SF-36 MCS							
Mean (SD)	46.3 (11.6)	49.1 (10.5)	45.7 (27.0)	44.3 (9.0)	47.6 (11.8)	48.7 (11.0)	48.6 (12.0)
Median	48.0	50.9	45.7	45.4	49.6	50.2	49.9
Range	24.9–70.1	22.6–65.4	26.6–64.7	24.9–56.6	26.4–70.1	22.6–65.4	28.3–68.7
P-value	0.147		0.593				

Abbreviations: EQ-5D-3L, EuroQol — five dimensions, three levels; SF, Short-Form Health Survey; PCS, physical component summary; MCS, mental CS.

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