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Quality of life in a large multinational haemophilia B cohort (The B-Natural study) – Unmet needs remain

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Abstract

Introduction: The B-Natural study is a multicentre, multinational, observational study of haemophilia B (HB) designed to increase understanding of clinical manifestations, treatment and quality of life (QoL).

Aim: To characterise and compare QoL in HB across disease severity groups and individuals with inhibitors to identify gaps in treatment.

Methods: A total of 224 individuals from 107 families were enrolled from a total of 24 centres in North America ($n = 16$), Europe ($n = 7$) and Asia ($n = 1$). Of these, 68 (30.4%) subjects had severe (<1 IU/dL), median age 15.6 years, 114 (50.9%) moderate (1–5 IU/dL), age 13.3 years, and 42 (18.8%) mild (>5–< 40 IU/dL), age 12.1 years, disease. Twenty-nine participants had inhibitors or a history of inhibitors. Three versions of the EQ-5D instrument were used as a measure of QoL: proxy (ages 4–7), youth (ages 8–15) and self (age 16+). Each instrument included a visual analogue scale ranging from 100 (best health) to 0 (worst health) to assess current day's health (EQ VAS). Range-of-motion (ROM) for elbows, knees and ankles was assessed using a four-point scale, from which a composite score was calculated.

Results: In all severity groups, a proportion of subjects showed less than optimal QoL. The majority of the mild and moderate severe participants reported a normal EQ-5D health profile (79% and 72%, respectively), whereas about half (47%) of the severe participants and only 13% of the inhibitor participants reported this profile.

Conclusion: The B-Natural study reveals impacted QoL in all disease severities of HB including those with inhibitors. Unmet needs remain and include nonsevere HB.

KEYWORDS
EQ-5D, FIX, haemophilia B, inhibitor, prophylaxis, QoL

1 | INTRODUCTION

Haemophilia B (HB) is caused by a deficiency or lack of clotting factor (F) IX.[1] In contrast to HB, individuals with FVIII deficiency (haemophilia A [HA]) are better studied mainly due to the fact that HA is approximately five times more common than HB (about one in 30,000 male births).[2] Measures of disease control and outcomes of therapy include an annualised bleed rate (ABR) and development of joint disease, usually assessed via physical scoring systems. More recently, patient related outcomes (PRO) measures such as quality of life (QoL) have become incorporated in medical parameters. Interestingly, QoL has been reported to be reduced not only in severe disease but also in moderate and mild haemophilia.[3–5] In fact, there are indications that individuals with severe haemophilia on prophylaxis may do better than moderate haemophilia patients who are not treated with prophylactic regimens to the same extent.[3] Due to the rarity of HB, most outcome reports focus solely on HA with the occasional inclusion of a small number of HB subjects. Recently, the B-HERO-S study investigating a US cohort of 299 adult subjects with HB reported a high degree of unmet needs in HB with poorer health status in moderate haemophilia compared to those with mild and severe cases. Anxiety/depression was observed in >50% of adult respondents.[4]

The B-Natural study is a multicentre, multinational, observational study of HB including both retro- and prospectively collected data, designed to increase understanding of clinical manifestations, treatment, QoL, inhibitor development, immune tolerance induction (ITI) outcome, renal function, and create a biorepository for future investigations.[6] The objective of the current paper is to characterise and compare QoL across disease severity groups and individuals with inhibitors in this large, international HB cohort to gain a deeper understanding of the patients' health problems and to identify gaps in treatment.

2 | MATERIAL AND METHODS

Demographics of the B-Natural cohort were recently described.[6] Subjects were eligible to participate if they had FIX deficiency and were part of an affected sibling pair/group; and/or had a current or history of inhibitor, defined as >.6 Bethesda units (BU). A total of 224 individuals from 107 families were enrolled from a total of 24 centres in North America ($n = 16$), Europe ($n = 7$) and Asia ($n = 1$). The recruitment rate per centre ranged from 17% to 100% with a median of 50%. Of these, 68 (30.4%) subjects had severe (<1 IU/dL), 114 (50.9%) moderate (1–5 IU/dL)) and 42 (18.8%) mild (>5–< 40 IU/dL) disease. Twenty-nine participants had inhibitors or a history of inhibitors, all of whom had severe disease. The study included four female subjects, all with mild disease. Age distributions as measured by the median [25th; 75th percentile] for the severe, moderate and mild disease severity groups were 15.4 [11.0; 32.3], 13.3 [8.58; 20.3] and 12.1 [7.65; 20.8] years, respectively, and 16.5 [8.08; 31.9] years for the group with inhibitors. Few individuals above 50-years-old were enrolled whereas the age distribution below 50 was rather even across the groups.

2.1 | Health-related quality of life

The EQ-5D instruments[7] were used to measure patient reported health in a broad, 'generic' manner as this instrument is applicable to a wide range of health conditions and treatments. The five-dimension EQ-5D-5L self-administered health questionnaire was used for participants 16+ years of age, the EQ-5D-5L proxy version was completed by a caregiver for participants aged 4–7 years, and the EQ-5D-Y youth version for those 8–15 years of age. Using a set of levels ranging from 1 to 5, with 1 being the best and 5 the worst, the EQ-5D-5L self-administered and proxy versions assess the dimensions of mobility, self-care, usual activity, pain/discomfort and anxiety/depression (given in this order as EQ-5D profiles in Section 3). The EQ-5D-Y youth version uses three levels for each dimension.

The EQ-5D questionnaire consists of two parts. The first is the EQ-5D descriptive system. Participants are asked to check boxes to indicate the level of problem they experience on each of the five dimensions. The combination of these checked boxes under each dimension describes that participant's EQ-5D self-reported health state, often called an 'EQ-5D profile'.

The EQ-5D profile data can be supplemented by using a 'scoring' or 'weighting' system to convert profile data to a single number: EQ-5D values also sometimes referred to as the EQ-5D index. The index value reflects how good or bad a health state is according to the preferences of the general population of a country/region and facilitate the calculation of quality-adjusted life years (QALYs). The preferences of the general population of a country/region for different health states represent the societal perspective. We were unable to create EQ-5D indices in this study because (1) value sets were unavailable for three of the seven countries/regions, (2) even for countries with available value sets, our patient population is not representative of the general population (e.g., large Amish study population at several sites in the US) and (3) the low number of participants in some of the sampled regions/countries. As our focus is to provide descriptive information, we focus on the analysis of the profile data themselves.

We summarised the severity of the EQ-5D profiles with the level sum score (LSS) which treats each dimension's level as a number rather than a category.[8] To produce the LSS each dimension's level is added up to produce a score between 5 (best possible score) and 15 or 25 (worst health state), for the three-level youth and five-level self and proxy versions, respectively. Devlin et al. 2018[9] have shown the relationship of the LSS with the English value set and demonstrated that as the LSS increases (states worsen), the values decline; hence, the LSS is a valid, albeit crude, measure of severity.

The second part of the questionnaire is the EQ VAS. Each instrument includes a visual analogue scale (VAS) to assess the participant's or proxy's overall assessment of health ('Health Today') on a scale from 100 (best health imaginable) to 0 (worst health imaginable). The EQ VAS is complementary to the EQ-5D profile as the overall score reflects both the relative importance the participant/proxy places on the different aspects of their health that are included in the EQ-5D descriptive system and other dimensions of health that are not.

2.2 | Joint assessment

Range-of-motion (ROM) for elbows, knees and ankles was assessed by qualified treatment centre staff trained in joint measurements. A four-point scale was used: 0 = No loss of total full range of motion (FROM); 1 = Loss of < 10% of total FROM; 2 = Loss of 10–33⅓% of total FROM; 3 = Loss of >33⅓% of total FROM. This method was chosen primarily for feasibility and the expectation that each centre would be able to reliably provide these measurements. A composite score was calculated for participants without any missing FROM scores by summing the FROM scores for each joint according to the following formula:

$$\begin{aligned} Composite\ Score\ &= Ankle_{left} + Ankle_{right} + Knee_{left} + Knee_{right} \\ &+ Elbow_{left} + Elbow_{right} \end{aligned}$$

The composite score ranges from 0 (no loss of FROM in any joint evaluated) to 18 (loss of >33⅓ in all joints).

2.3 | Statistical analyses

All statistical analyses were performed in the R language.[10] Descriptive statistics including means (standard deviations) and medians [25th percentile; 75th percentile] were used. Relationships between continuous variables were examined by means of exploratory univariate linear regression and Pearson correlation coefficients. Interpretation of the correlation coefficients' strengths followed the naming conventions of Chan.[11] To test whether the number of subjects reporting a problem differed by severity group, Fisher's exact tests were used. Differences in QoL scores between severity and/or treatment groups were assessed using Wilcoxon tests. Intrasibling correlations were not taken

into account in the statistical analyses and will be explored in a separate paper.

2.4 | Ethical approval

The procedures followed were approved by the ethical committees in each participating centre. B-Natural is registered at ClinicalTrials.gov (NCT02502409).

3 | RESULTS

3.1 | QoL questionnaires

Table 1 provides a summary of completion for the age-specific EQ-5D QoL instruments by disease severity group. Fifteen participants were too young, <4 years of age, to complete the instrument, two participants had a missing EQ-5D questionnaire for unknown reasons and one inhibitor participant had incomplete data (not shown in table); these participants were excluded from the analyses. Participants with inhibitors were slightly older than those in the noninhibitor group, thus were more likely to complete the self-administered EQ-5D than the proxy or youth versions. Moderate HB represented the largest group (n = 114), whereas severe and mild participants were fewer (39 and 42, respectively). The smallest group (n = 29) comprised those with inhibitors, all of whom had severe disease. Complete cohort demographics and clinical characteristics can be found in our recent study publication.[6]

3.2 | EQ-5D profiles

Supplemental Tables S1a and S1b list the frequencies of the observed health profiles by severity group for subjects that filled out the 5-level EQ-5D self or proxy version and the 3-level EQ-5D youth, respectively. Of the many possible health profiles, a total of only 39 unique health profiles were reported across all subjects (30 unique profiles in the self/proxy version respondents, and 16 in the youth respondents). The top three most frequently reported profiles represented 75% of all respondents (profiles 11111, 11112, 11121). A large proportion of observations were accounted for by profile 11111 (no problems in any dimension). The majority of the mild and moderate severe participants reported this 11111 profile (79% and 72%, respectively), whereas about half (47%) of the severe participants and only 13% of the inhibitor participants reported this profile.

Dichotomised (problems/no problems), pooled self, proxy and youth EQ-5D responses are shown in Figure 1. All severity groups, including those with an inhibitor, included subjects reporting problems in most every dimension of the EQ-5D (Figure 1A). Inhibitor participants reported lower QoL in all domains compared to the groups without an inhibitor, and severe subjects without inhibitor had consistently worse QoL than moderate or mild HB (Figure 1B). At least 50% of inhibitor participants reported problems in the mobility (54%), pain/discomfort (58%) and anxiety/ depression (50%) domains. A rather high proportion of these inhibitor participants reported problems with self-care (29%) and usual activities (46%). As illustrated in Figure 1B, the severe HB group followed a similar pattern as those with inhibitors but with a slightly lower proportion reporting problems in each domain and with relatively lower proportions of reported problems in the anxiety/depression and mobility domains. The moderate and mild severity HB participants appeared very similar in pattern although the moderate participants seemed to report relatively more problems in the pain/discomfort domain.

The mild and moderate HB participants have similar LSS distributions with a median and interquartile range (IQR) of 5.0 or 5.5.0–6.0 for the moderate group in the self/proxy respondents, reflecting that the nonsevere participants mainly reported no problems in any of the dimensions (in line with the majority reporting the 11111 health profile noted above). The severe HB participants had a higher median and more variation (median = 6, IQR = [5,8] in both the self/proxy and youth respondents) whereas the inhibitor participants had the highest median (self/proxy: median = 8.0, IQR = [6,11]; youth: median = 7, IQR = [6,10]).

TABLE 1 Summary of completion for versions of the EQ-5D and EQ VAS QoL instruments by HB severity group

			No inhibitor		
Characteristic	***N***	**Inhibitor** ***n*** **= 29**[a]	**Severe (<1%)** ***n*** **= 39**[a]	**Moderate (1%–5%)** ***n*** **= 114**[a]	**Mild (>5%)** ***n*** **= 42**[a]
EQ-5D version	224				
Self		14 (48%)	12 (31%)	44 (39%)	18 (43%)
Proxy		3 (10%)	7 (18%)	20 (18%)	8 (19%)
Youth		7 (24%)	17 (44%)	42 (37%)	15 (36%)
Missing[b]		5 (17%)	3 (8%)	8 (7%)	1 (2%)
EQ VAS	224	24 (83%)	36 (92%)	104 (91%)	38 (90%)

HB, haemophilia B; QoL, quality of life; VAS, visual analogue scale.

[a]Statistics presented: *n* (%).

[b]Includes 15 subjects who did not meet minimum age requirement of 4 years old.

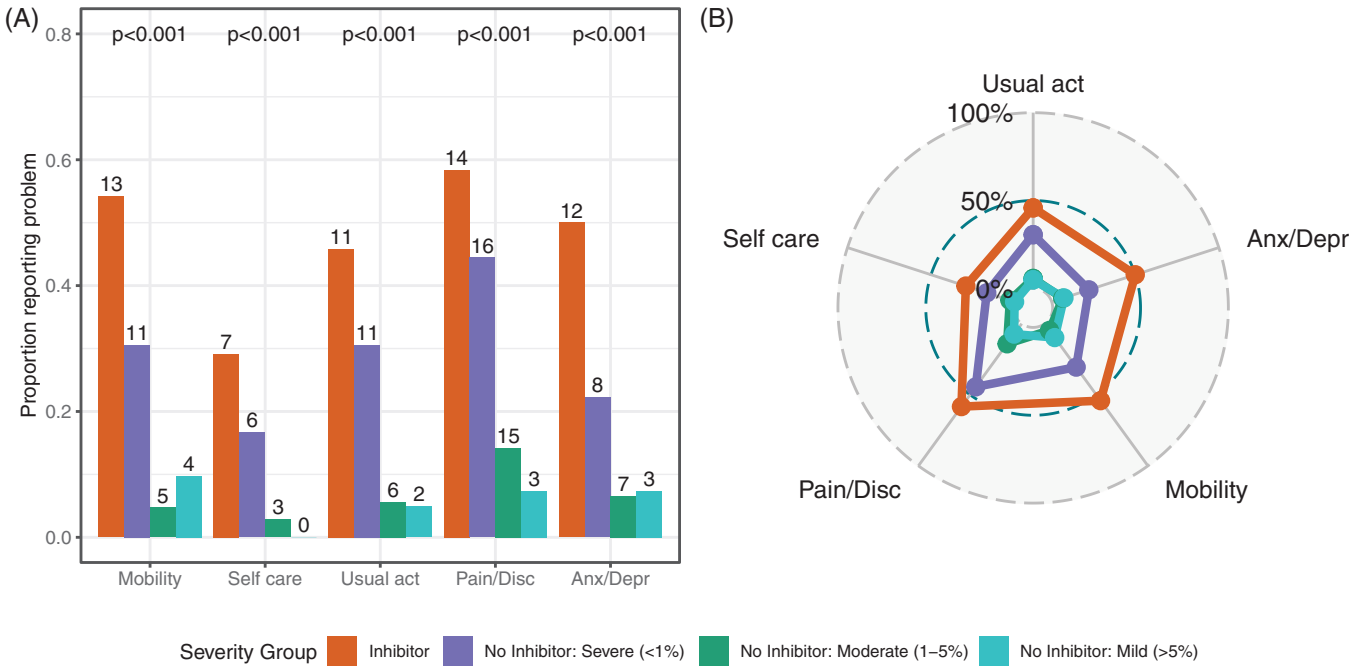

FIGURE 1 Proportion of subjects reporting impaired QoL by HB severity group and QoL score dimension. (A) Bar chart showing the proportion of participants reporting a problem within severity group based on dichotomised, combined EQ-5D-5L response. Bars are displayed for all five response dimensions. Number of subjects is denoted above each bar, as well as significance levels from Fisher exact tests comparing between severity groups within each dimension. (B) Radar plot showing percentages of participants with impaired health-related QoL by severity group. Similar to (A), QoL scores are based on dichotomised, combined EQ-5D-5L responses within response dimension. HB, haemophilia B; QoL, quality of life

3.3 | EQ VAS

Inhibitor participants tended to report lower EQ VAS scores ($M = 76.4$, SD = 20.2) than the other groups followed by the severe HB participants ($M = 85.9$, SD = 14.4). In turn, the moderate and mild HB cases had higher scores than the severe cases ($M = 94.9$, SD = 8.06 and $M = 95.3$, SD = 7.89, respectively). Additionally, and as expected (since the EQ-5D is complementary to the EQ-5D health profile), we observed significant negative correlations within each severity group between the EQ VAS and the LSS summary scores.

Participants reporting no problems on any of the EQ-5D dimensions have higher EQ VAS scores across all ages than those reporting problems. However, the EQ VAS declines with age in a similar fashion in those reporting problems and those that do not. No significant differences were observed when comparing EQ VAS scores by treatment received (continuous replacement therapy/prophylaxis versus on-demand treatment) within severity groups (Figure 2). When comparing between severity groups (pooled prophylaxis and on-demand treatments), significantly lower scores were observed in the severe HB group when compared to moderate and mild HB ($p < .001$). Scores were not significantly different between the moderate and mild groups. It should be noted that the sample sizes of several of the groups were small and firm conclusions cannot be drawn.

The EQ VAS score was negatively correlated with the composite joint score (only including individuals without missing data, $n = 202$) with a fair Pearson correlation coefficient of −.49 (95% confidence interval [CI]: [−.59, −.37]; $p < .001$). Significant poor and fair negative correlations were observed between EQ VAS and both BMI (−.19, 95% CI [−.32, −.06]; $p = .006$) and age (−.38, 95% CI [−.49, −.26]; $p < .001$). Additionally, age and composite joint score were positively correlated (.54, 95% CI [.44–.63]; $p < .001$). Although correlations were statistically significant, their clinical value for a single subject is uncertain.

4 | DISCUSSION

The B-Natural study represents a large, international cohort of FIX deficient participant spanning all severities including inhibitor participants, with a broad age range spanning 1–50 years with a few individuals >50. This diverse study population provides an opportunity to compare QoL in a broad spectrum of different clinical entities of HB reflecting real-world experience. Using EQ-5D health profiles and EQ VAS, we found that participants with inhibitors reported lower QoL compared to the those without inhibitors. Participants with severe disease without inhibitors had worse QoL scores than those with moderate and mild HB. Severe participants on prophylaxis tended to have higher reported QoL compared to those treated on-demand and had scores similar to those with moderate and mild disease of whom the majority were treated on-demand. We also observed that increased joint score (i.e. presence of joint disease), high BMI and older age has a significant, negative correlation with QoL by EQ VAS. These findings are close to what has been reported for HA[12] and again underscores

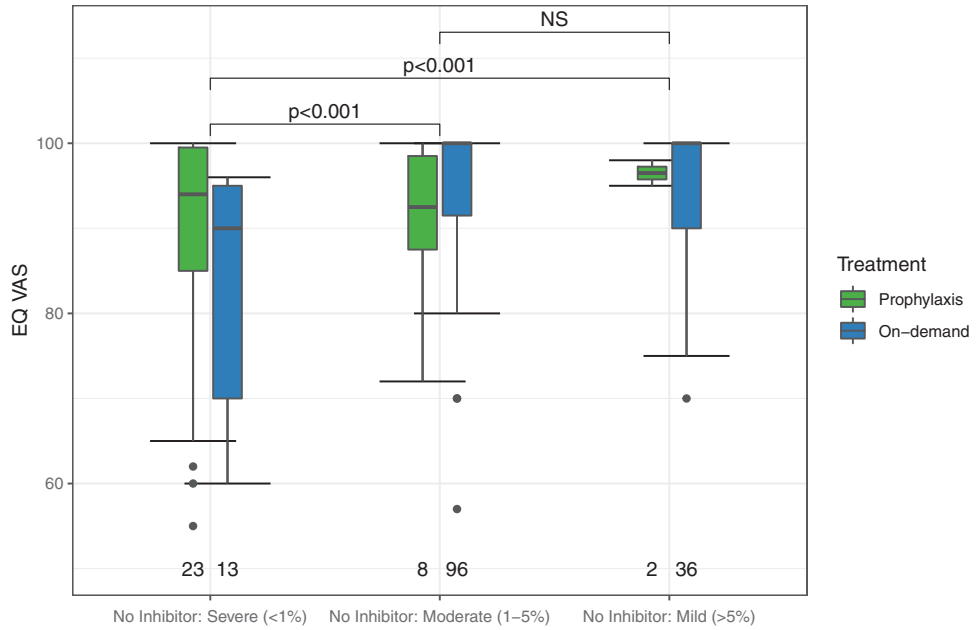

FIGURE 2 Distribution of EQ VAS scores by HB severity group and treatment received. Boxes represent the interquartile range, with a line for the median. Whiskers extend to 1.5 times the IQR. Significance levels from Wilcoxon tests comparing between severity groups are annotated. All comparisons between treatments within severity groups were not significant and are not displayed in the figure. HB, haemophilia B; IQR, interquartile range; NS, not significant; VAS, visual analogue scale

the importance of long-term surveillance and individualised treatment of haemophilia including both HA and, as shown here, HB. Importantly, some participants with moderate and mild HB had lower than optimal QoL and presence of joint disease, and those with severe HB on prophylaxis did not differ from nonsevere HB. These findings indicate that in the B-Natural cohort (1) prophylaxis alone is not sufficient for normalising QoL and (2) individuals with nonsevere HB may require additional treatment, that is more intense/earlier start of prophylaxis and psycho-social support to normalise their QoL relative to an age-matched, nondiseased population. This is strengthened by the previously reported pattern of joint disease in B-Natural[6] and significant correlation between joint disease and QoL in the present study. In a recent report by Jiang et al,[13] US population norms for the EQ-5D-5L were reported. Their respondents were representative of the general US adult population with a mean age of 46.9 years in the face-to-face acquired sample (similar results were obtained in the online sample); these subjects are considerably older than the ones in our cohort. They did not find any gender difference but an age dependent decline in utility and VAS was observed up till the 45–54 year old cohort when norms levelled out. The VAS score was 84.9 in their youngest cohort (<25 years) whereas we found scores ≥90 in our nonsevere subjects. In the Jiang paper, the prevalence of any problems in each dimension increased with advancing age except for anxiety/depression. In our cohort pain/discomfort stands out in moderate haemophilia and is twice as common (14% vs. 6.6%) as anxiety/depression compared to rather similar results between these dimensions in the study by Jiang et al. Considering the caveat that our study is different from theirs in several respects and results are presented differently, it seems as if pain/discomfort is dominating in moderate haemophilia compared to population norms. The low number of subjects in our study prevents firm conclusions. Our findings in moderate HB support prior reports from studies in both HA and HB that show that moderate haemophilia may have decreased QoL compared to severe haemophilia where treatment with prophylaxis is more commonly used. In the B-Hero study, 299 subjects with HB were evaluated using several questionnaires including EQ-5D-5L with VAS.[4] Pain, functional impairment and anxiety/depression were present in higher than expected levels in HB and a large proportion of individuals with nonsevere HB with reduced health status suggested significant unmet needs in this population. In the study by Lindvall et al.,[3] 144 adult participants with HA or HB (22.9% of total population had HB) were evaluated for QoL using the SF-36 questionnaire. In the 35–64 years age group QoL was significantly reduced in a few of the domains (general health, mental health). Participants with moderate disease reported more impairment in general health and mental health compared to those with severe or mild haemophilia. The notion that individuals with moderate haemophilia may benefit from prophylactic therapy has been raised by several studies.,[14–16] The PROBE study[12] also showed a significantly impaired QoL in participants with nonsevere haemophilia. The PROBE questionnaire includes three domains: general health, specific haemophilia A or B related questions and the third domain includes the EQ-5D-5L as well as EQ VAS. Of the 236 respondents with haemophilia, 102 had mild and 134 moderate disease of whom the vast majority had HA. The PROBE study results corroborate other studies in that nonsevere haemophilia is not optimally treated in terms of joint disease outcome and support the finding in our study that QoL is impaired in this group of participants we can state that prophylaxis affects joint health, that is the physical domain in EQ-5D, and is still important for the well-being of the patient.

Nonsevere haemophilia is often a 'forgotten' disorder.[5] The prevalence of HB is low and participants having baseline factor levels above 3–5 IU/dL rarely experience spontaneous hemarthroses that result in severe arthropathy, and their expected survival is higher than in participants with severe haemophilia.[17,18] It has been shown for HA participants, although data are still not conclusive, that to achieve zero spontaneous joint bleeds throughout all ages, levels of 15 IU/dL or higher need to be maintained.[16] Consequently, a large proportion of nonsevere haemophilia patients remain at risk for developing long-term sequelae if they are not treated more intensively as demonstrated in the present cohort. Nonsevere HB constitutes a larger proportion of subjects with HB as compared to HA[2] and thus may represent a greater fraction of individuals who experience clinical problems, an issue that has not consistently been considered. There is an ongoing discussion as to whether HB expresses a milder phenotype as compared to HA given the same level of residual clotting factor. The observation remains controversial,[19,20] and could hypothetically be explained by the different mutation pattern with less null mutations in severe HB. We recommend that a high clinical alertness is introduced in the surveillance of nonsevere haemophilia and hence initiation of prophylaxis, especially in subjects with factor levels below 3%–5% or having signs of a serious bleeding phenotype, in line with what has been recommended by other authors[15,21,22]

The strengths of our study include its size, diversity of participant age and geographical area. Our data depict the treatment results of HB that have occurred over many years in wealthy countries. The study also provides important insight into the QoL in different disease severities, and in participants with inhibitors.

There are limitations to the B-Natural study. Although the number of subjects is high, especially for such a rare disorder, when divided by age and disease severity groups the numbers are diminished. Enrollment from areas of the world with a variety of standards of care for HB adds to the diversity of the cohort yet makes generalisation of the results to specific countries or centres not feasible. The quality of the reported data in a multicentre, multinational study is likely less well controlled as compared to single country or centre studies. The study included many siblings and as the focus of this paper was descriptive in nature, we did not take the intrasibling correlation into account in any of the statistical analyses; however, we will explore this in an upcoming paper.

5 | CONCLUSIONS

The B-Natural study reveals a lower than optimal QoL in all disease severities of HB especially in those with inhibitors. Unmet needs remain as joint disease is present in a proportion of patients and include improved treatment algorithms to prevent adverse outcomes also in nonsevere HB; our findings are congruent with other studies in HA and in HB. B-Natural is designed to describe outcomes in a nonselected population over a large geographical area and hence adds further knowledge to the unmet needs in the contemporary treatment of HB.

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AUTHOR CONTRIBUTIONS

Jan Astermark, Erik Berntorp and Amy D. Shapiro conceptualised and designed the study, acquired, analysed and interpreted the data, drafted and finalised the manuscript. Margaret V. Ragni, Munira Borhany, Yasmina L. Abajas, Michael D. Tarantino, Katharina Holstein, Stacy E. Croteau, Raina Liesner, Cristina Tarango, Manuela Carvalho, Catherine McGuinn, Eva Funding, Christine L. Kempton, Christoph Bidlingmaier, Alice Cohen, Johannes Oldenburg, Susan Kearney, Christine Knoll, Philip Kuriakose, Suchitra Acharya, Ulrike M. Reiss, Roshni Kulkarni and Michelle Witkop acquired the data, reviewed and participated in the critical review and final approval of the version to be submitted. Stefan Lethagen designed the study and participated in critical review and final approval. Petra LeBeau and Rebecca Krouse analyzed and interpreted the data, drafted and finalised the manuscript.

CONFLICT OF INTERESTS

EB: has acted as paid consultant to Bayer, CSL Behring, Octapharma, Sobi, Takeda, and has received funding for research carried out in this work from Sobi and Bioverativ. PL: has received research funding from Takeda, Biogen/Bioverativ and Sobi. MVR: has been a consultant to Alnylam, BioMarin, Bioverativ MOGAM and Spark Therapeutics, and has research funding from Alnylam, Bayer, BioMarin, Bioverativ, Sangamo and Spark Therapeutics. MB: has no competing interests to declare. YLA: has no competing interests to declare. MDT: is a past advisor for Grifols, Novo Nordisk, speaker for Biomarin, Grifols, Pfizer, Takeda, clinical investigator for Spark, Takeda and a grant reviewer for Pfizer. KH: received honoraria for Advisory Boards and/or speaker fees from Biotest, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda, Sobi and unrestricted grants from CSL Behring and Pfizer. SEC: has received honoraria or consulting fees from Bayer, CSL-Behring, Genentech and Pfizer and has received institutional research support from Novo Nordisk and Spark Therapeutics. RL: has no competing interests to declare. CT: has received honoraria for Advisory Boards for Takeda/Shire and Sanofi, and sits on a study Steering Committee for Bayer. MC: has received support for attending scientific meetings and honoraria (speaker fees/consultant for Advisory Boards) from Bayer, Baxalta (Shire), CSL Behring, Novo Nordisk, Octapharma, Pfizer, Sobi, Siemens and Stago. CM: has acted as a paid consultant for BioMarin, Bayer, Octapharma and Genentech/Roche. She is a site PI study investigator for Pfizer, Spark Therapeutics, Sanofi and Genentech/Roche. EF: has received honoraria from Roche and Shire, and chaired a symposium for Roche. EF was invited to ISTH 2015 by Novo Nordisk, EAHAD 2016 by Octapharma, ASH 2016 by Shire, EAHAD 2017 by Pfizer and to an AOP orphan pharmaceuticals meeting in 2019. CLK: has received honoraria for participation on Advisory Boards for Spark Therapeutics, Pfizer and Genentech and has received research funding from Novo Nordisk. CB: has acted as a paid speaker and consultant and has received funding for research from Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Shire/Takeda and Sobi. AC: has no competing interests to declare. JO: reports grants and personal fees from Bayer, personal fees from Biogen, grants and personal fees from Biotest, personal fees from Chugai, grants and personal fees from CSL Behring, personal fees from Grifols, grants and personal fees from Novo Nordisk, grants and personal fees from Octapharma, personal fees from Pfizer, personal fees from Roche, personal fees from Sobi, grants and personal fees from Takeda, outside the submitted work. Personal fees were received for travel support, participation in Advisory Boards and participation in symposia as Chair or Speaker. SK: has no competing interests to declare. CK: is a paid member of the Novo Nordisk Advisory Board. PK: has no competing interests to declare. SA: received research funding for investigator-initiated study from Bayer. UMR: has no competing interests to declare. RK: has served on Advisory Boards for Sanofi/Bioverativ, BPL, Genentech, Bayer, Pfizer, Takeda, Catalyst Bioscience, Novo Nordisk; has received clinical trials support from Sanofi/Bioverativ, Bayer, BioMarin, Takeda, Novo Nordisk, Freeline. Speakers Bureau, stocks, shares: none. MW: has no competing interests to declare. SL: a full-time employee of Sobi. RK: has received research funding from Takeda, Biogen/Bioverativ and Sobi. ADS: Dr. Shapiro reports the following; however, she does not retain any personal honoraria. All is paid to the Indiana Hemophilia and Thrombosis Center, Inc. Dr. Shapiro does not have personal financial interest in any healthcare related companies. Clinical research support: Agios, BioMarin, Bioverativ, Daiichi Sankyo, Genentech (Roche), Glover Blood Therapeutics, Kedrion Biopharma, Novartis, Novo Nordisk, OPKO, Octapharma, Pfizer, ProMetic Bio Therapeutics, Sangamo, Takeda. Speaker's Bureau: Genentech (Roche), Novo Nordisk. Advisory Board: Bioverativ, Genentech, Novo Nordisk, Sangamo, Sigilon Therapeutics. JA: has received research grants from Sobi, CSL Behring, Takeda/Shire and Bayer. Speaker's fee and consultant for Octapharma, Novo Nordisk, Pfizer, Bayer, Sobi, CSL Behring, Takeda/Shire, BioMarin, Uniqure and Spark Therapeutics.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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