INTRODUCTION

Prophylaxis with clotting factor replacement therapy has been the gold standard of care for the treatment in haemophilia A since the 1990s. It prevents bleeding events and reduces short- and long-term complications. One of the stated goals of therapy is to preserve musculoskeletal function; prophylactic treatment slows the progression of joint disease and improves the quality of life, but it does...
not reverse established joint damage.\textsuperscript{4,5} Ideally, prophylaxis should be initiated before the onset of clinically evident joint disease, in which case it is defined as primary (started before the second clinically evident large joint bleed and age 3 years) or secondary (started after 2 or more bleeds into large joints); prophylaxis may also be initiated after the onset of joint disease (tertiary) or used intermittently (to treat bleeding episodes for up to 45 weeks per year).\textsuperscript{6}

Though prophylaxis is superior to on-demand treatment of bleeding episodes in people with moderate-to-severe haemophilia,\textsuperscript{7} people who use prophylaxis nonetheless experience significant morbidity. One international cross-sectional study in 90 people with severe haemophilia, who began prophylaxis at a median age of 3.4 years, reported a median of 7 joint bleeds over a 5-year period despite high quality-of-life scores.\textsuperscript{8} In young adults who received primary or secondary prophylaxis, the prevalence of at least occasional pain or pain/discomfort exceeded 80%, a figure that was comparable with the prevalence reported among people using on-demand treatment.\textsuperscript{9,10}

Prophylaxis improves quality-of-life measures compared with on-demand treatment.\textsuperscript{7,11} However, the Hemophilia Experiences, Results and Opportunities (HERO) study reported similar prevalence for the EQ-5D measure anxiety or depression for different treatment strategies (43% of participants receiving prophylaxis, 49% of those using on-demand treatment and 47% among those treated with on-demand and intermittent prophylaxis).\textsuperscript{9}

It is therefore unsurprising that people with haemophilia using prophylaxis report limitations on daily activity and mobility. In HERO, 64% of the total population currently using prophylaxis (n = 207) reported limitation (‘some’ or ‘severe’ impact) on mobility and 43% reported limitation of daily activity.\textsuperscript{9} These figures included countries with relatively high rates of bleeding but the result was similar when the analysis was restricted to the United States, with 51% and 45% of the patients treated with prophylaxis reporting limitations on mobility and daily activities, respectively.

These data show that people with haemophilia continue to experience pain and impaired quality of life despite receiving the gold standard of care. However, much of this information is drawn from studies involving patients who may have started prophylaxis after the onset of joint disease and prior management with on-demand treatment and little has been published about the outcomes associated with primary prophylaxis. Longer duration of prophylaxis offers superior outcomes, and primary prophylaxis is associated with the lowest prevalence of pain.\textsuperscript{11} In the Pain, Functional Impairment and Quality-of-life (P-FiQ) study, about half of participating patients reported joint problems and three-quarters reported a joint procedure or surgery.\textsuperscript{12} The prevalence of acute, chronic, and acute and chronic pain was 11%, 8% and 6%, respectively, among 37 participants with a history of joint bleeding who had ‘always been on prophylaxis’ and 16%, 29% and 47%, respectively, among the 109 participants who received prophylaxis for 25%-49% of their lifetime.

We sought to evaluate morbidity among people with severe haemophilia managed with primary prophylaxis using the Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS) database.\textsuperscript{13}

\section*{2 \ Methods}

Data on patients with haemophilia were obtained from the 2014/15 Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS), a database of patients with haemophilia A (n = 996) or B (n = 289) that captured the economic and psychosocial burden of severe haemophilia in the five largest European countries (EUS: France, Germany, Italy, Spain and the United Kingdom).\textsuperscript{13} In summary, CHESS collected clinical, economic and demographic information from clinicians and, from patients, information about direct non-medical resource use, health-related quality of life (using the self-administered EuroQol EQ-5D-3L), work productivity impact (Work Productivity and Activity Impairment Questionnaire, WPAI) and therapy adherence.\textsuperscript{14,15} All measures were applied prospectively and utilized at a single time point. Analysis was conducted on the subgroup of patients with haemophilia A who were aged 18-35 years at the time of enrolment in the study, who had been treated with prophylaxis with standard half-life (SHL) clotting factors since diagnosis (primary prophylaxis), as reported by physicians, and who did not have a history of inhibitors or inhibitor therapy (PPX group, n = 166). Compliance to PPX was physician reported as 70% high/full and only 5% reporting low levels.

EQ-5D-3L measures health-related quality of life across five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression and uses three levels of severity (no problems, some problems and extreme problems).\textsuperscript{14} It has been validated in many countries in Europe and is widely used.\textsuperscript{16} The participant rates utilities on a scale in which death has a value of 0 and perfect health a value of 1, with negative values (ie a state worse than death) being possible. Validated country-specific adult value sets obtained via the EuroQol website were used, with the exception of Italy, for which values were taken from published literature.\textsuperscript{17} EQ-5D index score and visual analogue scale score (VAS) for the EU5 countries were captured the economic and psychosocial burden of severe haemophilia.\textsuperscript{13}

WPAI is a validated self-reported quantitative assessment of work-related absenteeism (absence from work due to health impairment), presenteeism (attending work with impairment) and daily general activity impairment (impairment in the total population, not employment-specific) attributable to general health or a specific health problem.\textsuperscript{15,18} The participant answers five questions about the effect of their health on work attendance and performance in the preceding week.

Several comparator groups were used to place in context the outcomes of the PPX group, as summarized in Table 1.
## TABLE 1 Comparator groups

| Source population | Population | Endpoints assessed |
|-------------------|------------|--------------------|
| CHESS non-PPX or treated on-demand (non-PPX group)<sup>12</sup> | CHESS population subgroup, age range 18-35 No history of inhibitors Prior therapy before starting prophylaxis or always treated OD | Comorbidities, clinical outcomes |
| EQ-5D database<sup>19</sup> | General EU5 population Age range 18-35 | EQ-5D: index utility score, components |
| 2012 US NHWS survey<sup>20</sup> | General US population Age 35+ | WPAI |
| 2011 EU5 NHWS survey<sup>21</sup> | EU5 population with osteoarthritis Age 55-75 | WPAI |

## TABLE 2 Demographic and health characteristics of the study population

| Demographics | Patients on primary prophylaxis (PPX group) N = 166 | Patients on secondary prophylaxis or on-demand (non-PPX group) N = 349 |
|--------------|-----------------------------------------------------|--------------------------------------------------------|
| Age (median, IQR) | 24 (21, 26) | 26 (21, 32) |
| Country (N) | | |
| UK | 51 | 85 |
| Spain | 43 | 45 |
| Italy | 14 | 83 |
| Germany | 26 | 68 |
| France | 31 | 67 |
| Median (range) number of bleed events in the last 12 mo | 1 (0, 3) | 2 (1, 5) |
| % of patients with at least 1 bleed | 122 (73%) | 298 (85%) |
| Target joint<sup>a</sup> | | |
| Any target joint | 65 (39%) | 216 (62%) |
| Upper target joint | 24/65 (37%) | 91/216 (42%) |
| Lower target joint | 50/65 (77%) | 173/216 (80%) |
| Joint intervention<sup>b</sup> | 2/65 (3%) | 8/216 (4%) |
| Prevalence of chronic pain<sup>a</sup> | | |
| No pain | 89 (54%) | 141 (40%) |
| Mild pain | 63 (38%) | 140 (40%) |
| Moderate pain | 14 (8%) | 61 (17%) |
| Severe pain | 0 | 7 (2%) |
| Other chronic conditions<sup>a</sup> | | |
| Anxiety | 27 (16%) | 45 (13%) |
| Depression | 3 (2%) | 11 (3%) |
| Comorbidities<sup>a</sup> | | |
| Hepatitis B | 2 (1%) | 3 (1%) |
| Hepatitis C | 1 (1%) | 8 (2%) |
| HIV | 0 | 3 (1%) |

<sup>a</sup>Reported by clinicians

<sup>b</sup>Includes arthroplasty, arthrodesis, arthrocentesis, arthroscopy and synovectomy
Comorbidities (including viral infection (hepatitis B or C, HIV), chronic pain, other chronic conditions (anxiety, depression) and physician-reported outcomes (recurrent bleeding into a joint (‘target joint’) in the PPX group) were compared with those in other CHESS participants with haemophilia A aged 18-35, who had begun prophylaxis after first receiving other treatment strategies (secondary prophylaxis) or who were using on-demand factor replacement, but had no inhibitors (non-PPX group; n = 349).

We compared the impact of haemophilia and its treatment on quality of life (using EuroQol EQ-5D-3L) and work impairment (using WPAI) in the PPX group with normative data obtained from the general population and, for WPAI only, from people with osteoarthritis.

Data sources for comparison were identified using PubMed, CINAHL and general search databases in order to identify comparative data amongst the general populations. Raw national demographic data were extracted from country databases. Normative aggregate data for health-related quality of life for the EU5 (United Kingdom, Germany, France, Spain, Italy) were obtained from the international EQ-5D database, which comprises data drawn from uniform survey methodology carried out largely after 2000, with some UK data obtained in 1993. The proportion of patients reporting each outcome was reported for each country and summarized as median and range.

Normative data for WPAI outcomes were obtained from analyses of the 2012 US National Health and Wellness Survey (n = 71,141). The comparator osteoarthritis population with WPAI outcomes was obtained from an analysis of the 2011 National Health and Wellness Survey in the 5 EU countries (n = 57,512), which included 3,750 people with self-reported peripheral joint osteoarthritis. Of these, 1,263 (34%) were in full or part-time employment and therefore able to complete the WPAI assessment.

The primary analyses were quality of life in people with haemophilia A managed by primary prophylaxis comparing the general population and work impairment, compared with the 2012 US National Health and Wellness Survey population and people with OA reporting chronic pain.

### RESULTS

#### 3.1 Comorbidities and outcomes

The PPX group comprised a young adult population with a median age of 24 years, similar to that of the non-PPX/on-demand comparator group (Table 2). Most patients in the PPX group came from the UK (31%), Spain (26%) and France (19%), whereas a higher proportion of non-PPX/on-demand patients came from Germany and Italy.

Seventy-three per cent of the patients in the CHESS PPX group experienced at least one bleed in the 12 months prior to survey. Thirty-nine per cent of them presented target joints, mostly located in the upper joints; neck, shoulder, elbow, wrist or spine (37%) or lower joints; and hip, knee or ankle (30%). Two patients needed a surgical intervention on the joint.

Almost half of the patients in the PPX group reported some level of chronic pain, with 8% experiencing moderate pain. In comparison, 60% of the patients in the non-PPX group had chronic pain, with 19% having moderate or severe pain.

Anxiety or depression had similar prevalence in the PPX and non-PPX groups (17%-18% and 2%-3%, respectively). The prevalence of chronic viral infection (hepatitis B, hepatitis C and HIV) was low (<2%) and comparable between the two groups.

#### 3.2 Psychosocial burden

EQ-5D-3L data were available for 55 patients in the PPX group (33%) and 2,576 people from the normative EU5 general population (Table 3). A numerically higher proportion of PPX patients reported moderate or extreme problems across all domains compared with...
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EU5 norms, the differences being greatest for anxiety/depression (31% in the PPX group compared with 3%-12% in the 5EU countries), pain and discomfort (38% vs 10%-21% in the 5EU countries) and mobility (20% vs 2%-6% in the 5EU countries), but also substantial for activity impairment (9% vs 2%-8% in the 5EU countries) and self-care (5% vs 0.3%-1% in the 5EU countries). Meaningful statistical analysis was not possible due to limitations of aggregate data used amongst general population.

3.3 | Work impairment

Table 4 presents the WPAI analyses for the patients in the PPX group who completed the WPAI assessment (n = 55), the sample population of people with osteoarthritis in the 5EU states and the population of 2012 US National Health and Wellness Survey. Median age in the PPX group was 23.4 years, considerably lower than the two comparator groups (58.9 years and 44.2 years, respectively).

Patients in the PPX group reported no lost work time; people with osteoarthritis reported losing about twice as much work time as the general population. However, the level of presenteeism in the PPX group was similar to that reported by people with osteoarthritis and numerically double compared with that in the general population (25.6% vs 12.9%). Work impairment and activity impairment were comparable in the PPX group to the levels in the general population, and less than reported in the older osteoarthritis population.

4 | DISCUSSION

This study highlights important unmet needs in patients with severe haemophilia managed with PPX, currently the best standard of care. Observations provide indications that PPX patients experience joint health impairment, impaired health status and quality of life, and they have lower employment and higher presenteeism, compared with the general population.

Consistent with published studies, joint damage and chronic pain were less prevalent in patients treated with primary prophylaxis compared to those treated with secondary/intermittent prophylaxis or using on-demand treatment.11,12,24,25 Nevertheless, almost 40% of patients in the PPX group presented with joints affected by recurrent bleeding, suggesting that control of bleeding is suboptimal and raising the possibility that chronic joint disease may develop in later life.11,24,25 Pain in the CHESS population was reported by clinicians from medical records, whereas other large studies9,12 have relied on patient self-reporting within a larger questionnaire (eg on quality of life). Medical records provide evidence of a confirmed diagnosis; this approach may underestimate pain prevalence by missing unreported pain, but it provides robust data on a problem that has reached clinical attention.

The frequency of clinical anxiety/depression reported by the physician was similar in the two treatment groups, suggesting that superior bleed control provided by primary prophylaxis treatment does not fully translate into full improvements in quality-of-life measures. This is consistent with the observation that more patients treated with PPX report problems affecting all quality-of-life domains compared with a general population, with the differences greatest for pain, mobility and anxiety/depression.

Compared with other treatments, longer duration of prophylaxis offers superior outcomes and primary prophylaxis is associated with the lowest prevalence of pain.11 In the CHESS population, fewer PPX patients reported pain of any severity compared with those using on-demand treatment. The Pain, Functional Impairment and Quality-of-life (P-FiQ) study reported the prevalence of acute, chronic and

| Table 4 | Psychosocial burden: WPAI outcomes in the PPX group, people with osteoarthritis and in the general populations |
|---------|---------------------------------------------------------------------|
| Outcome | CHESS Primary prophylaxis (PPX) N = 55 | Osteoarthritis (5EU)a N = 1263 | General population (US)b N = 71 141 |
| Mean age (SD) | 23.5 (3.5) | 58.9 | 44.2 (13.5) |
| Age range | 18-35 | <55->75 | >18 |
| Employed | 24 (44%) | 1263 (34%) | 51% |
| WPAI score (% impairment from 0 to 100) | | | |
| Mean proportion reporting work time missed | 0 | 7.4% | 3.5% |
| Mean presenteeism | 25.6% | 24.7% | 12.9% |
| Mean overall work impairment | 16.2% | 28.8% | 15.0% |
| Mean activity impairmentc | 23.1% | 38.3% | 22.1% |

Numbers of patients are totals across France, Germany, Italy, Spain and the United Kingdom (EU5).a Health data from National Health and Wellness Survey (NHWS) of the US populations in 2012.20b Percentages included total population (employed and not employed).c
both acute and chronic pain was 11%, 8% and 6%, respectively, among 37 participants with a history of joint bleeding who had ‘always been on prophylaxis’. By contrast, patient-reported pain prevalence among 109 participants who received prophylaxis for 25%-49% of their lifetime was 16%, 29% and 47%, respectively. Joint problems were less common in the larger CHESS population than in P-FIQ overall (figures were not separately reported for those using primary prophylaxis), but pain prevalence in PPX patients was higher in CHESS (38% reporting pain/discomfort vs 25% reporting pain in P-FIQ).

These young adults, though less physically impaired than the group with osteoarthritis, have a level of impaired work performance that is similar to this much older age group (68% of whom were aged ≥55) which reported more extensive joint damage (median 2 affected joints) and greater prevalence of pain (41% reported mild pain, 48% moderate pain and 12% severe pain). Quality of life in this population with osteoarthritis was assessed using the 12-item Short Form and is not directly comparable with measures used in the CHESS study.

The HERO study showed that limitation due to anxiety/depression among people with haemophilia, as measured by EQ-5D, is almost as common with primary prophylaxis (43%) as with on-demand treatment (49%). This was also true in the CHESS population, where anxiety was reported in one in every 7-8 people by their clinician. The prevalence of people reporting some or extreme problems in the anxiety/depression domain was at least twofold greater than in the general population. This suggests that the burden of care associated with PPX may not be balanced by a substantial improvement in mental health.

The 44% employment rate reported by the CHESS PPX population appears to be lower than that reported in the general populations. Population-wide employment rates are not reported for the age range of CHESS PPX participants (18-35), but within the Organisation for Economic Co-operation and Development, the rates for the UK, Italy, Germany and France (none are available for Spain) range from 17% to 51% among 15- to 24-year-olds and 69% to 84% among 25- to 54-year-olds (OECD, 2018). In the US population, employment rates are 66% for 20- to 24-year-olds and 79% for 25- to 54-year-olds. This finding suggests that people with severe haemophilia may be disadvantaged in the jobs market despite receiving what is regarded as optimal management.

Even for those in employment, severe haemophilia appears to impose an additional burden. The proportion of employed people reporting presenteeism is considerably higher among PPX patients compared with the general population, and similar to that in a much older population with osteoarthritis.

To our knowledge, this is the first study to show that presenteeism is as common among young adult PPX patients as it is among people with osteoarthritis. This has profound implications for people with haemophilia. Young adults are in the early phases of their careers, a time when performance is likely to influence future success. The prevalence of suboptimal work productivity we found among PPX patients is similar to that reported among older people with more extensive joint disease and chronic pain. This population of people with osteoarthritis was far from healthy in other respects: most comorbidities were not reported, though 40% were overweight, 30% were obese and 54% exercised less than once per month. These differences help to explain the lower prevalence of work and activity impairment reported by PPX patients, but not why presenteeism affects so many PPX patients. Presenteeism is associated with increased risks of suboptimal self-rated health and future sickness absence, but its long-term implications for individual well-being are presently unclear. Further studies to explore the implications of this finding are needed.

5 | STRENGTHS AND LIMITATIONS OF THIS STUDY

This study describes the experiences of 166 patients, one of the largest groups of patients with severe haemophilia managed with primary prophylaxis reported to date. They were selected from the CHESS population, drawn from patients actively receiving care in five major European countries and using data obtained as recently as 2014/15. Clinical data in CHESS were obtained directly from clinicians, strengthening confidence in diagnostic information and medical outcomes. We have also been able to use common instruments to compare work impairment and quality of life in disparate populations to more accurately gauge well-being among people with haemophilia relative to population norms.

The strength of the findings was limited by the study’s cross-sectional design and the reliance on previously published aggregate data for comparisons. A larger sample size and more detailed population data would enable more meaningful associations yielded by a formal hypothesis. Ideally, outcomes would be determined prospectively, though this would be both time-consuming and relatively costly. Our choice of osteoarthritis as a comparator model of chronic pain among people living in the community provides a robust standard against which to assess the impact of haemophilia, but the comparison is limited by the different medical and treatment histories of the people affected and their risk factors. The number of PPX patients, though large relative to other published studies, meant that the number of some events recorded during the 12 months of data capture in CHESS was low—for example, there were cases of depression and few bleeding events—and quality-of-life assessments would have been more representative if obtained from a larger population.

6 | CONCLUSION

Primary prophylaxis represents the best available care for young adults with severe haemophilia, but for many, analysis presented could indicate that clinical outcomes and quality of life remain impaired compared with the general population. Primary prophylaxis is associated with the levels of anxiety and depression that are similar
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