Burden of mild haemophilia A: Systematic literature review

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Abstract

Introduction: Although the clinical manifestations of severe haemophilia A (HA) are well studied, the challenges, if any, of living with mild HA are not clearly delineated to date.

Aim: To assess available evidence of clinical risks and societal/economic impacts of disease in adult patients with mild HA using a systematic literature review.

Methods: Prespecified study selection criteria were applied in a comprehensive literature search. Included studies varied in design and reported outcomes of interest for adults (≥13 years of age) with mild HA.

Results: Seventeen studies with a total of 3213 patients met eligibility criteria (published or presented in English, 1966–2017). Most studies were observational, and the outcomes reported were too sparse and dissimilar to support a formal meta-analysis. Mean annual bleeding rates ranged from 0.44 to 4.5 episodes per patient per year. Quality of life (QoL; SF-36 General Health) was impacted compared to healthy controls. Health care costs and productivity were seldom assessed and no robust comparisons to healthy controls were available.

Conclusion: Quantifying outcomes for adult patients with mild HA remains challenging, with estimates of key QoL and cost data often based on small data sets and without comparison to population norms. Therefore, the clinical impact of mild haemophilia may be under-represented and unmet needs may remain unaddressed. As paradigm-changing therapies for HA emerge, stronger knowledge of mild HA can guide the development of care options that minimize burden and enhance the QoL for this segment of the haemophilia community, and for the haemophilia community in totality.

KEYWORDS
acute bleeding, disease burden, haemophilia, quality of life
1 INTRODUCTION

Haemophilia A (HA) is an X-linked bleeding disorder caused by a deficiency of blood coagulation factor VIII (FVIII), occurring in approximately 1 out of every 5000 male live births.\(^1\) HA can be a life-threatening condition that requires lifelong monitoring and/or treatment. Management strategies include the use of plasma-derived or recombinant factor concentrates and can vary between treatment centres and disease severity.\(^2\)

Factor VIII replacement therapy, however, is not without risk (eg the development of inhibitors) and is expensive, ranging from US$50 000 to nearly US$300 000 annually in a recent US study, depending on disease severity and treatment approach.\(^3\) Severity levels for HA have generally been defined by baseline FVIII activity: severe <1% of normal or <1 IU/dL, moderate 1% to <5% and mild 5%-40%.\(^4\) The clinical manifestations and cost impacts of severe HA are well studied, particularly with regard to the clinical benefit, but high cost, of ongoing FVIII prophylaxis.\(^2,5,6\)

In contrast, the clinical burden, societal impact and economic impact of mild HA are not as clearly understood. Patients with mild HA often require and receive less intense therapy and medical attention, but may still experience limitations in daily activities and impacts of the disease on their morbidity, quality of life (QoL) and health care utilization.\(^7,8\) It is also unclear to what extent variations in treatment strategies, patient characteristics and geographic location are associated with clinical outcomes and potential delay in diagnosis and treatment. In this study, we sought out published estimates of the burden of mild HA from clinical, patient, payer and/or societal perspectives.

2 MATERIALS AND METHODS

This systematic literature review was performed using recommended best practices, including a prespecified protocol defining the search strategy, inclusion criteria and statistical analysis plan addressing the burden of disease and clinical risks associated with mild HA in adults. This review was conducted and reported according to PRISMA guidelines.\(^7\) The protocol for the review was agreed to in advance by all authors but was not submitted to an external registry.

The population of interest was adults (defined as being 13 years of age or older) with mild HA. We were unable to find any recent summary of the literature in this population, and the clinical picture may be distinct from both moderate/severe HA and mild haemophilia B. Because we anticipated small numbers of studies focused exclusively on mild HA adults over 18 years of age, we included studies of mild HA individuals 13 years of age and older. Studies of any design (interventional or observational, controlled or uncontrolled) were eligible so long as they reported data for at least 10 patients in the population of interest. This lower limit of 10 patients was prospectively defined in order to exclude studies of insufficient sample size, for which outcomes may not be generalizable as they may focus on reports of unusual cases. Outcomes of interest included bleeding events (any event as defined or described by authors), QoL, joint pain, function/disability, health care utilization and cost (direct health care cost and/or indirect societal cost). As our goal was to assess the burden of disease, no specific intervention or comparison was required in the included studies.

2.1 Data sources and search strategies

A comprehensive search of English-language biomedical literature was conducted. We searched electronic repositories including PubMed/MEDLINE, the Cochrane Library and EMBASE for all available dates up to the search cut-off date of 31 December 2017. The search terms used for each database are detailed in Appendix S1. In addition to published journal articles, recent haematology meetings (2016-2017) were searched for abstract presentations of eligible studies which may not yet have been published in full. Finally, we hand-searched the reference lists of eligible articles and recent reviews.

2.2 Study selection

Two levels of screening were performed on all non-duplicate citations downloaded from the search and each level of screening involved up to two reviewers. Level I screening was conducted on the title and abstract of each citation to identify potentially eligible studies, including haemophilia populations with mixed severity. Level I screening was performed by a single reviewer, with any questions resolved by consultation with a second reviewer. Level II screening was conducted as defined in the protocol, by reviewing the full text of each article to identify eligible studies that fit with study selection criteria. Level II screening was conducted by one reviewer and verified by a second reviewer. A published study would be included in our analysis and moved forward for data extraction only if both reviewers in the Level II screening agreed that study selection criteria were met.

Per predefined exclusion criteria, meeting abstracts or presentations prior to 2016, white papers, publications with no primary data, animal or in vitro studies, studies exclusively in FVIII inhibitor patients or paediatric patients (age <13 years), and studies of mixed/unspecified haemophilia populations, with data not separable by disease severity, were excluded.

2.3 Data collection and outcomes

For the purposes of this assessment, mild HA is defined by FVIII levels of 5%-40% and adults are defined as being 13 years of age and older. Where data were available for a subset of patients meeting this definition, we included the article and extracted data only for the subset of interest. Studies without at least one outcome separately reported for at least 10 patients of interest were excluded. The primary endpoint was the rate of bleeding events, on a mean episodes per year basis or any other units reported by authors. We summarized all events reported by authors, regardless of whether bleeds required treatment, and captured the definition of bleeding events if reported. As mild HA patients tend to bleed less frequently and typically only after trauma,
to fully characterize the clinical, patient-reported and societal burden of mild HA, additional outcomes were captured. Secondary outcomes included QoL; joint pain; function/disability, including productivity and employment; other morbidity or mortality attributed to HA; and health care utilization and cost.

Dual review was used to collect data from each eligible study using a standardized template. Any discrepancies in interpretation between the two reviewers were resolved through a discussion of the text of the original articles. Each included study was appraised for quality and risk of bias using the Oxford Center for Evidence-Based Medicine (Oxford CEBM) Levels of Evidence.10 Industry sponsorship was captured for each included study, based on author disclosures or affiliations.

2.4 | Synthesis of results

We planned to conduct a meta-analysis if sufficient comparable data were found for a primary or secondary outcome. Differences in author definitions of the primary endpoint, the rate of bleeding events, were available. These were captured and reviewed for comparability (eg only bleeds requiring treatment, only spontaneous bleeds unrelated to surgical or dental procedures, any bleeding event). Where data were too sparse or too heterogeneous to be combined across studies, descriptive statistics were performed in order to qualitatively summarize available evidence. The risk of bias across studies was assessed informally based on study design, level of evidence, size, and representativeness of the population of interest, and comparability of estimates from different studies.

3 | RESULTS

3.1 | Study selection

The search identified 1845 unique citations across all sources. After screening of the titles and abstracts, 139 potentially eligible studies were obtained in full text for review (Figure 1). Application of eligibility criteria resulted in 17 included studies, comprising 20 publications due to separate reports on the same or overlapping study populations.3,8,11-28 The primary reasons for study exclusion were that patients with haemophilia were not separated by severity (or only moderate/severe HA patients were included), or study populations were mixed with regard to type of haemophilia (A/B/other coagulopathies) and/or age (adults and children). In addition, 14 studies did not report an outcome of interest and 20 studies were reviews, case reports or studies not containing at least 10 mild HA patients.

3.2 | Study characteristics

The 17 studies included data for 3213 mild HA patients aged 13 years and older. These patients were a subset of the overall study population in all cases. The total number of haemophilia patients (all ages, severities and types) in the 17 studies was 20,587. Eligible studies were conducted in Europe (59%), North America (35%) and Japan (6%) (Table 1). Most studies were observational in nature, and few details on typical treatment protocols were available. A variety of treatments were described by authors, including FVIII concentrates, recombinant FVIII and DDAVP. Fewer than 1% of patients had prophylactic use of FVIII,11,13,27 except in one study reported as a meeting abstract, for which long-term use of FVIII concentrate was required.18

3.3 | Risk of bias

Most evidence was Oxford Level of Evidence IB or IIIB, consisting of prospective or retrospective cohort studies, in many cases from a single centre (Table 1). No randomized controlled trials meeting inclusion criteria were identified. The risk of selective reporting/outcome availability bias was high, as mild HA adults were typically a subset of the entire study population, and not all outcomes were

**FIGURE 1** Study attrition
TABLE 1 Characteristics of included studies

| Number of | Number of mild HA adults |
|-----------|--------------------------|
| Total     | 17                       | 3213                      |
| Country/sites |                      |                           |
| Europe    | 10                       | 1045                      |
| North America |                    | 6                         | 2049                      |
| Japan     | 1                        | 119                       |
| Patient population of entire studya | | |
| Mild HA adults and age-matched healthy controls | 1           | 47                        |
| Mild/moderate HA, mild HA/ HB | 3          | 217                       |
| HA, any severity | 5              | 122                       |
| HA or HB | 5                        | 2044                      |
| Various coagulopathies | 3            | 783                       |
| Year of publication | | |
| 1996-2007b | 2                        | 56                        |
| 2008-2017 | 15                       | 3157                      |
| Level of evidence/study design | | |
| IB (Prospective cohort or registry) | 6          | 1517                      |
| IIB (Retrospective cohort) | 6          | 316                       |
| IIC (Outcomes research, survey data) | 5           | 1380                      |

aData were extracted for the subset of patients of interest (mild HA adults) in this review.

bSearch dates extended back to 1966 (the initiation of MEDLINE database), but the earliest study meeting eligibility criteria was published in 1996.

3.4  Clinical burden: bleeding events

Clinical burden of mild HA was reported in a variety of formats in the included studies. We sought data on annual bleeding rates (ABR) or other characterizations of bleeding risk. Most often, bleeding events were reported as a percentage of patients with any bleeding episode over a period of time (cumulative incidence), with both follow-up duration and the definition of events varying between studies (Table 2). One multicentre, prospective study from the US reported a mean ABR of 4.5 ± 10.0 episodes/year in 23 mild HA adult patients; however, other estimates were lower by an order of magnitude. Most studies meeting inclusion criteria did not report mean ABR.

Bleeding events in mild HA, such as joint bleeds or cerebral bleeds, may not be readily apparent. One study used cerebral MRI to assess mild HA adults with no prior symptomatic cerebral bleeding: 5.5% (1/18) of patients had evidence of a previous cerebral microbleed.

3.5  Other morbidity

Joint pain and damage resulting from subclinical joint bleeds may also be problematic in mild HA. Joint score data, like data for bleeding events, were not reported in a standard way across studies (Table 3). In a small cross-sectional survey study from 1996, 20% of mild HA patients age 16 or older experienced moderate or severe pain in the previous year, with pain and disability increasing with age. Another study comparing mild HA adults with age-matched controls found the maximum joint score to be significantly higher (worse) in mild HA. Development of inhibitors to FVIII in mild HA reached a cumulative incidence of 4.0%-7.8% over 10 years in two retrospective cohort studies with long-term follow-up.

3.6  Quality of life

Patient-reported outcomes were available in three studies, all of which were published in the past 10 years (Figure 2). Each study used a different QoL instrument: the SF-36, SF-12 and HAEMO-QoL-A. SF-36 general health was lower for mild HA vs age-matched healthy controls in a Canadian cohort (58.1 vs 70.8, P < 0.05, n = 47). No other studies reported QoL in mild HA adults compared to healthy controls or population norms.

In a prospective US study, SF-12 physical component summary was higher (better QoL) for mild HA compared to severe HA (P = 0.014, n = 42), while mental component summary was not significantly different between mild and severe HA. No differences between severe and mild HA were found using the Haemo-QoL-A, in a small UK survey study reported to date only as a meeting abstract. It is notable that this study required long-term use of FVIII concentrate, meaning that mild HA patients in this study were probably not representative of the overall mild HA population.

3.7  Societal impacts

Societal impacts, which should include productivity loss, disability and time lost from work/school, were mentioned in five studies, but were not often quantified in ways that would allow comparison to populations without HA. One study estimated 5 disability-adjusted life years (DALYs) lost per case of mild HA, using a modelling approach to assess lifetime burden of disease. Employment of mild HA patients was 60% (27/45) compared to 68% (21/31) for healthy controls in a Canadian cohort; the difference did not reach statistical significance. In a multicentre US study, mild HA patients missed an average of 6.2 work days per year, of which 4.7 days (76%) were due to HA. Finally, a retrospective study in Italy noted 3.4 missed days of work per year, with no benchmark provided for patients without HA. Table 4 summarizes the data available for health care cost and utilization and societal impacts (direct and indirect costs of mild HA).
3.8 | Health care cost and utilization

We sought details on health care utilization (clinic visits, hospitalization days, etc) and health care costs (direct costs) in adults with mild HA; while such costs are a topic of discussion in recent literature, we found they were generally reported for HA overall. Mild HA health care costs were reported in 2 studies, with rather different health care settings: a 2015 study from Portugal reported mean costs of 793€/year, 36% of which was the cost of clotting factor. In contrast, a US-based study conducted in 1995 estimated annual costs of $22,182 for mild HA, 81% of which was clotting factor. Health care utilization was not reported for adults with mild HA in any of the studies in our review.

4 | DISCUSSION

Limited data were available on ABR in mild HA adults (three studies meeting our eligibility criteria, reporting between 0.44 and 4.5 mean bleeding episodes/year). Because data were scarce and estimates varied, we consulted studies not meeting inclusion criteria to provide context for ABR. Two studies were found with an ABR estimate for mild HA patients of all ages (including children); mean ABR centred on 0.5-0.6 episodes per year. Mild HA patients in our review also experienced other morbidity, QoL impacts and economic impacts.

Quantifying outcomes for adult patients with mild HA remain challenging, with estimates of key QoL and cost data often based on small subsets of a single study. One complicating factor is the definition of mild HA based on FVIII levels, which can fluctuate. In general, the mild HA population is defined as patients with FVIII levels >5% (or 5 IU/dL) and up to 40% (or 40 IU/dL). However, there has been occasional variation in this range, as shown in Table 2, as well as in a recent communication from the Scientific Subcommittee (SSC) of the International Society of Thrombosis and Haemostasis. Few studies put mild HA outcomes in the context of population norms; therefore, the clinical impact of mild HA may be under-represented.

### TABLE 2  Bleeding episodes reported in mild HA patients

| Study                          | Population (FVIII level/ age) | Follow-up period | % (n/N) of patients with bleeding | episodes/pt year (SD) |
|-------------------------------|-------------------------------|------------------|----------------------------------|----------------------|
| Prospective cohort (US, Canada) | 6%-40% (median NR) <br> Age NR | 5 y (2002-2006) | 36% (4/11) had bleeding score >0; indicating at least one bleeding episode other than surgery, dental procedures and major accidents | NR |
| Cross-sectional survey (Finland) | 5%-40% (median NR) <br> Age ≥16 | 1 y (years NR; publication 1996) | 40% (8/20) had at least one episode of moderate bleeding; none had severe bleeding | NR |
| Retrospective cohort (Italy) | 0.6-0.33 IU/mL <br> Median age 35 (range 3-88) | 10 y (range 1-39; 1985-2010) | 91% (68/75) had at least one bleed during follow-up: 27% joint, 35% muscle, 73% mucocutaneous, 13% postoperative, 21% after dental work | 0.56 (0.67) includes all bleeds regardless of treatment |
| Retrospective cohort (Slovenia) | 5%-40% (mean 8.5%) <br> Age 13-54 | 6 y (2007-2014) | 57% (8/14) includes surgery, trauma, dental procedures | 0.44 includes all bleeds regardless of treatment |
| Retrospective cohort (Canada) | 5%-40% (median age 18) <br> Adults ≥18 (mean age 46) | 5 y (year NR; publication 2008) | 17% (8/46) with 2 or more bleeds requiring medical assessment or therapy in past 5 y | NR |
| Prospective cohort (Italy) | NR (median NR) <br> Adults ≤18 | Duration NR (2011-2013) | 5.5% (1/18) had evidence of cerebral microbleed | NR |
| Prospective cohort (US) | 6%-30% (median NR) <br> Adults ≤18 | 2 y (2005-2007) | NR (23 patients with data) | 4.5 (10.0) definition of bleeding episodes not available |

Abbreviation: NR, not reported.

aBleeding score calculated from 5 y mean scores of haemarthrosis and soft tissue haematoma.
bBleeding histories were divided into severity based on symptom clustering across the whole cohort of coagulation disorders (n = 224); most episodes were joint and soft tissue bleeds.
cOutcomes may include some patients under 13 y; study was retained due to long follow-up duration and detailed reporting. Three patients had FVIII inhibitors.
dEleven soft tissue bleeds occurred in one patient who developed FVIII inhibitors.
eSubjects are from large kindred with specific mutation (VAL2016ala).
fPatients without prior symptomatic brain bleeding were assessed for evidence of asymptomatic bleeding using cerebral MRI.
gThis analysis of HUGS-Va included only participants with complete follow-up data.
and unmet needs remain unaddressed. While mean ABRs were relatively low, mild HA had measurable impact on QoL and represents an area of therapeutic concern requiring further study. Until recently, treatment goals in haemophilia were FVIII trough levels of >1%, to prevent major bleeding. With the advent of extended half-life FVIII concentrates and novel non-replacement therapies, and the

| Study                      | Population (FVIII level/age) | Follow-up period | Number of mild HA patients | Study score (name of scale) | Pain or overall severity score (name of scale) |
|----------------------------|------------------------------|------------------|----------------------------|-----------------------------|-----------------------------------------------|
| Prospective cohort (US)    | 6%-30% (median NR) Age ≥18   | 2 y (2005-2007)  | 23                         | Joint range of motion limitation (AAOS): 5.4 ± 4.5 | NR                             |
| Cross-sectional survey     | 5%-40% (median NR) Age ≥16   | 1 y (years NR, publication 1996) | 20                         | NR                          | Pain in previous year: 5% (1/20) severe, 15% (3/20) moderate |
| Retrospective cohort       | 0.06-0.33 IU/mL (median 0.15 IU/mL) Median age 35 (range 3-88) | 10 y (range 1-39) (1985-2010) | 75                         | Mean physical joint score 0.88 ± 1.78 (scale NR) | NR                             |
| Retrospective cohort       | 5%-40% (mean 0.15 IU/mL Age ≥18 (mean age 46) | 5 y (year NR, publication 2008) | 47                         | Max joint score by Colorado PE0.5: 5.3 mild haemophilia vs 2.8 control (P < 0.05) | HAQ pain score: 0.51 haemophilia vs 0.61 controls (no significant difference) |

Abbreviations: AAOS, American Academy of Orthopaedic Surgeons; Colorado PE0.5: Scale based on modified World Federation of Haemophilia (WFH) Physical Joint Examination instrument. NR, not reported.

ªThis analysis of HUGS-Va included only participants with complete follow-up data.

ªPain and disability increased with age.

Outcomes may include some patients under 13 y; study was retained due to long follow-up duration and detailed outcome reporting.

Subjects are from large kindred with specific mutation (VAL2016ala). Normative data are from age-matched healthy controls (n = 32).

![Figure 2](image-url) Quality of life scores in mild HA (as % of maximum score). Physical component summary (PCS) and mental component summary (MCS) for SF-36 and SF-12 use norm-referenced scoring (not available as transformed/scaled scores) and are shown as % of the closest available age and country norms. For HUGS-Va, normative data were not reported within the study, so SF-12 norms for Utah, age >18 were used. * P < 0.05 vs comparison.
| Study                                      | Population (FVIII level/age) | Follow-up period | Number of mild HA patients | Annual direct cost (mean or median, with currency and year) | Indirect cost/productivity |
|-------------------------------------------|------------------------------|------------------|----------------------------|------------------------------------------------------------|---------------------------|
| Retrospective cohort (US)\(^{14}\)        | 6%-50% (median NR) Adults   | 12 mo            | 36                         | 22 182 USD (1995; mean) total cost 18 017 USD factor cost\(^a\) | NR                        |
| Retrospective cohort (Portugal)\(^{21b}\)  | 5%-40% (median NR) Age ≥18\(^c\) | 12 mo            | 16                         | €793 (year of currency NR; mean or median not specified) €506 hospital costs + €287 clotting factor | NR                        |
| Cost model (Belgium)\(^{16}\)             | 6%-40% Adults                | Lifetime (simulated 2011 birth cohort, projected to future) | N/A (simulated cohort) | NR                                                        | Disability weight vs norms: 0.054 Lifetime DALYs per mild haemophilia case: 5 (95% CrI 2.10)\(^d\) SF-36D data used for disability weights |
| Prospective cohort (US)\(^{3,20,28e}\)     | 6%-30% (median NR) Age ≥18   | 2 y (2005-2007)  | 23                         | NR                                                        | 6.2 d lost from work per year (total) 4.7 per year due to HA |
| Retrospective cohort (Italy)\(^{8e}\)     | 0.06-0.33 IU/mL (median 0.15 IU/mL) Median age 35 (range 3-88) | 10 y (range 1-39) (1985-2010) | 75                         | NR                                                        | 64% employed/in training (mild HA adults) |
| Prospective cohort (Italy)\(^{23e}\)      | >5% (median NR) Age NR (assumed 17-65, based on reporting of employment status) | 12 mo (2005)    | 109                        | NR                                                        | 3.4 d lost from work per year |
| Retrospective cohort (Canada)\(^{26}\)    | 5%-40% (mean 0.15 IU/mL) Age ≥18 (mean age 46) | 5 y (years NR, publication 2008) | 47                         | NR                                                        | 60% (27/45) employed mild HA vs 68% (21/31) controls. HAQ standard disability score: 0.24 vs 0.12 controls |

Abbreviations: 95% CrI, 95% credible interval; DALY, disability-adjusted life year; NR, not reported; SD, standard deviation.

\(^a\)Costing by CPT code using Medicare fee schedule. A substantial portion of the study population was HIV+.

\(^b\)Data on outpatient visits, hospital admissions and surgeries are not available by severity.

\(^c\)Costs are not reported separately for adults and children; authors stated no statistical difference.

\(^d\)Sensitivity analyses under different discounting assumptions: 1-2 lifetime DALYs after discounting. No excess mortality was assumed for mild or moderate haemophilia patients.

\(^e\)No normative/healthy control data available.

\(^f\)Subjects are from large kindred with specific mutation (VAL2016ala). No significant difference between mild HA and age-matched healthy controls.
potential for gene therapies, understanding around target trough levels is evolving to suggest there may be additional benefit in targeting non-haemophilia levels (ie >40%), as opposed to levels within the mild HA range. Such targets may be achievable through recent therapeutic advances such as those in adeno-associated viral vector-mediated gene therapy, which may enable sustained expression of FVIII activity following a one-time infusion.\textsuperscript{32} We would need to consider currently unmeasured, cumulative benefits to those living with mild HA. This review should be followed by further prospective studies to understand the need of all patients with mild haemophilia.

Strengths of this systematic review include the comprehensive search and rigorous methodology including a prospective plan, using current best practices for systematic literature review. Limitations relate primarily to the availability and comparability of published evidence. Data on mild HA adults are frequently aggregated with moderate HA, mild haemophilia B and/or mild HA paediatric patients in the published literature. Despite our efforts to extract clinical and humanistic outcomes data for comparable populations (mild HA adults), meta-analysis was ultimately not feasible due to variability in reporting. Studies used different measures, scales and time points, with too few studies using consistent formats. The body of evidence in mild HA is also limited by missing data and selective availability of outcomes, making it difficult to gain a comprehensive picture of disease burden across all outcomes of interest.

This review has revealed a lack of evidence in the specific population of mild HA adults; evidence is low quality in part because data had to be separated out for the population of interest. Considering the limitations of the current body of evidence, higher quality studies in this area are needed. Such studies would report both bleeding and other clinical outcomes based on common definitions and for a representative population of mild HA adults. Areas for further research include more robust comparison to healthy controls or population norms, especially for QoL and other patient-reported outcomes. A recent multi-stakeholder effort to define core outcomes for trials in haemophilia highlighted the importance of mental health outcomes; this is an area where existing published evidence for mild HA adults is lacking.\textsuperscript{33}

5 | CONCLUSION

To the best of our knowledge, this is the first systematic review to assess available evidence of clinical risks and societal/economic impacts of disease in adult patients with mild HA. Based on our review, data from adult patients with mild HA are frequently aggregated with other types of haemophilia in the published literature. Few studies to date have focused on this population alone, nor have many authors described mild HA outcomes in the context of population norms. While mean ABRs were relatively low, mild HA had measurable impact on QoL and productivity and represents an area of therapeutic need requiring further study.

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DISCLOSURES

FP has received honoraria for participating as a speaker at satellite symposia and educational meetings organized by Sanofi, Grifols, Novo Nordisk, Roche, Takeda, Sobi, Bioverativ, Spark Therapeutics, Symex and CSL Behring; moreover, she is a member of the scientific advisory board of Sanofi. QJ, BK, AL, MCL, and WYW are employees and stockholders of BioMarin. FT was an employee of BioMarin at the time of the study. DF has received consulting fees from BioMarin. FP defined the publication need and scope. DF and ER managed data collection and curation. DF drove manuscript drafting and revisions. All authors made intellectual contributions to protocol content and study inception; aided in the interpretation of results; and reviewed and approved the final manuscript.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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