**Systematic Review**

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# Prevalence of pain in adult patients with moderate to severe haemophilia: a systematic review

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**Abstract**

**Objectives:** Patients with haemophilia (PwH) often suffer from joint pain due to repetitive haemarthroses and resulting arthropathy. Literature focuses so far on pain causes, diagnosis or treatment. A summary of prevalence rates, providing facts on the absolute occurrence of pain, is not sufficiently described so far. This review aimed to explore and systematically review different pain conditions, focussing on prevalence rates of pain in adult PwH.
**Methods:** A review of English articles using PubMed and Web of Science was conducted in February 2020. The search strategy included patients with haemophilia A or B suffering from pain. The articles were selected based on defined PICOS-selection criteria.
**Results:** Out of 606 identified articles, 13 studies matched the given eligibility criteria and indicated pain prevalence rates. The weighted mean (WM) for the prevalence rate (varying timeframes) for chronic pain was 40% whereas for point prevalence the rate was WM=75%. Regarding pain intensity, findings of the EQ-5D-3L revealed moderate pain to be more present (61.0%) compared to extreme (11.6%). The main problem was the inconsistency of the definition of both acute and chronic pain as well as for prevalence types.
**Conclusions:** Pain is a major problem in patients with haemophilia. Pain therapy should be carried out taking into account the difference between bleeding-related or arthropathy-related causes of pain. In addition, the intensity and duration of pain should be recorded consistently to better monitor therapy and allow comparison with existing data.

**Keywords:** haemophilic arthropathy; pain; prevalence.

## Introduction

**Rationale:** Haemophilia is an x-linked recessive coagulation disorder due to deficiency of factor VIII (haemophilia A) or IX (haemophilia B) [1]. This congenital disease is classified as a rare disease [2, 3]. According to Srivasta et al. [2] the severities can be distinguished based on factor level: mild haemophilia is categorized as five to <40% of standard factor level, where severe bleedings occur with trauma or surgery. Moderate haemophilia prevails a clotting factor level of one to five percent, going along with occasional spontaneous bleedings and with minor trauma or surgery. In patients with severe haemophilia, with a clotting factor level of less than one percent, spontaneous bleeding frequently occurs mostly into joints or muscles. However, through replacement therapy, patients inject missing coagulation factors (factor XIII or IX) either on-demand or prophylactic [4]. Especially in severe haemophilia, prophylactic therapy is effective to prevent haemophilic arthropathy as it reduces the number of (spontaneous) bleeds [5].

Patients with haemophilia (PwH) often suffer from pain typically affecting joints, which is due to bleeding episodes (i.e., hemarthrosis) and can lead to musculoskeletal changes [3, 6]. Repetitive hemarthroses induce synovitis, cartilage damage as well as bone destruction. This process results in haemophilic arthropathy [7]. Knees, ankles, and elbows are the joints most often affected by changes in the structure of articulation [8, 9]. Hence, joint pain is present in many individuals with haemophilia and is considered a burden especially in patients with moderate-severe haemophilia [10, 11].

Both acute (in most studies linked to bleeding) and chronic (in most studies associated with joint degeneration) pain play a central role in the daily life in PwH, though literature in the field of haemophilia does not provide

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conclusive definitions in their distinction [8, 12]. Pain is a complex experience and the contributing mechanisms are not yet fully understood [12]. High intensities of joint pain can be a result of both arthropathies as well as bleeding. Besides, sudden flare ups (sudden increases of pain intensity) might lead to pain experiences [12]. Additionally, it is known that PwH may suffer from hyperalgesia [12, 13], which is an increased sensitivity towards noxious stimuli as a result of tissue damage. However, research is in a preliminary phase, as the aetiology and pathogenesis of pain in PwH remains fairly unclear.

Moreover, pain assessment implies a difficulty, as there is a lack of standardized measurements of pain in haemophilia research. Pain is a subjective perception, which is commonly diagnosed via questionnaires, adjusted with clinical assessment [7]. However, the subjectivity of pain causes limitations when comparing different pain assessments.

**Objectives:** This paper will systematically review the literature exploring prevalence and incidence of pain in patients with moderate to severe haemophilia A or B. We will focus on pain prevalence, which is defined by the actual existing occurrence of pain either at a particular point of time (point prevalence), or during a period (period prevalence), or within a total lifetime (lifetime prevalence) [14]. Point prevalence examines the pain perception at one specific time point, which can imply both acute and chronic pain. Incidence is defined as the rate of new occurrence of pain [14]. Both are decisive criteria to improve pain management [15]. Evidence on prevalence rates allows an estimation of the degree to which the problem is relevant [16].

## Materials and methods

**Protocol:** This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [17]. A study selection process, methodological quality assessment and data analysis was performed by two independent investigators (PR, SK).

**Eligibility criteria:** Studies were defined as eligible for inclusion if they discussed an adult population (≥18 years) suffering from moderate to severe haemophilia A or B with or without inhibitors. Furthermore, studies analysing prevalence and/or incidence and/or epidemiology of pain were eligible outcome parameters. Studies discussing other types of haemophilia, mild haemophilia, other bleeding disorders or children were excluded. Only original reports written in English and published after 2000 were considered eligible.

**Information sources**: Online databases PUBMED (Medline) as well as Web of Science were used for search in February 2020.

**Search:** The final key words used for the search were ((a, haemophilia) OR (b, haemophilia) AND pain). The search strategy was developed based on the following PICOS selection criteria [18]. Population (P): Adults with moderate to severe haemophilia type A or B, with or without inhibitors; Intervention (I): assessment tool; Control (C): was not defined; Outcome (O): Acute and/or chronic (joint) pain, incidence, prevalence, epidemiology; Study design (S): Original reports (randomized control trials, cohort studies, case-control studies). In order not to miss relevant studies, a wide search was performed.

**Study selection:** A first screening of the results on PUBMED and Web of Science was conducted, and eligibility was checked based on title and abstract. The remaining articles were extracted based on full-text screenings in a second step.

**Data collection process:** Two independent researchers (PR, SK) derived and discussed all relevant data. In case of disagreement, the consensus was found via discussion.

**Data items:** Variables, such as author, year of publication, study design, demographic details of the participants (age, number, type and severity of haemophilia, treatment), assessment tool (name of questionnaire and highest possible scores), methodological screening scores and results were listed and structured in a Microsoft Excel (2013) sheet.

**Risk of bias in individual studies:** Methodological quality was assessed via the "notes for methodology checklist 3: cohort studies" by the Scottish Intercollegiate Guidelines Network (SIGN) [19]. This validated tool evaluates articles based on 14 questions, which need to be answered either "yes", "no", "can`t say" or in some cases "not applicable" (item 1.2, 1.3, 1.4, 1.6, 1.8, 1.11, 1.12). Among others, the items address the research question (1.1), selection bias (1.3) as well as level of evidence (1.13). The methodological screening as well as the scoring of the articles were conducted by two independent researchers (PR, SK).

**Summary measures:** This paper discusses the prevalence of pain in PwH. With this intent, an individual descriptive analysis of the results on prevalence as well as a comparison between the results was performed. Expressive data are presented in form of weighted means (WM). Here we multiplied the prevalence rate of each study with the corresponding number of subjects participating. The sum of patients with pain in each subcategory is then divided by the number of subjects in the subcategory respectively (e.g., for point prevalence rates):

$$wM_{\text{point}} = \frac{\text{Sum}\left(\text{Prev Rate}_{\text{point}} * \text{Subjects}_{\text{point}}\right)}{\text{Sum}\left(\text{Subjects}_{\text{point}}\right)}$$

**Planned methods of analysis:** This item is not applicable to this paper as no statistical analyses were performed.

**Risk of bias across studies:** Prevalence rates postulated by the studies are compared to each other, though a selective reporting bias across studies might be present due to inconsistent provision of information.

**Additional analysis:** This item is not applicable to this paper as no additional analyses were performed.

## Results

**Study selection:** In total, 606 articles were considered to be relevant and hence screened based on title and abstract. Afterwards 126 studies were included for full-text evaluation. Main reasons for exclusion were population (i.e., children, von-Willebrand-disease, mild haemophilia) and study design (i.e., review, case reports, meta-analyses). A total of 13 full text studies were included in the analysis for this review (Figure 1).

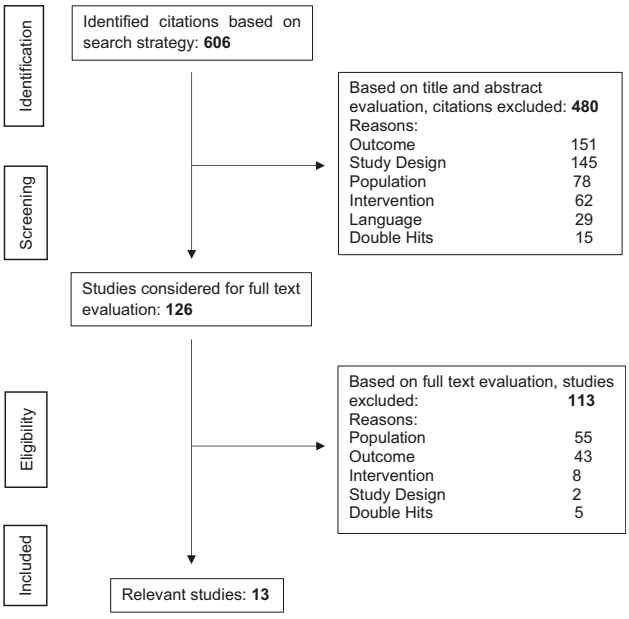


**Figure 1:** Flow chart of study selection.

**Study Characteristics:** The 13 included studies were categorized as cross-sectional studies. Table 1 demonstrates the study characteristics as well as the used assessment tools. All studies used self-reported questionnaires for assessing pain level. The Visual Analogue Scale (VAS) [20] as well as the European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) [21] represent the questionnaires most often used to gain information on pain intensity.

Authors of six different studies developed a new questionnaire for the respective study, emphasizing lack of validity [15, 22–26]. Furthermore, the study by Molho et al. [27] and Windyga et al. [28] used the WFH Physical Examination Score, which assesses pain associated with interference with activities of daily living [29]. The analysed studies investigated male patients suffering from moderate-severe or only severe patients with haemophilia A or B, regardless any development of inhibitors. Though, the study by Davari, Gharibnaseri, Ravanbod, & Sadeghi [30], Molho et al. [27] as well as van Genderen et al. [26] excluded patients with inhibitors. Five of the studies described the replacement therapy used by

**Table 1:** Overview of included studies, patients' characteristics and risk of bias.

| No. | Author, year | Country | Patient characteristics | | | | | Sign ranking** | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Participants, n | Age in years (mean ± SD or median (range)) | Type of haemophilia | Severity of haemophilia | Treatment strategy | | |
| 1 | Davari et al. [30] | Iran | 38 | n/a | A without inhibitors | Severe | n/a | 2+ | C |
| 2 | Elander and Barry [33] | UK | 68 | 41 ± 14 | n/a | Severe | n/a | 2++ | B |
| 3 | Holstein et al. [22] | European countries* | 2,224 | >18 | n/a | Severe | On-demand (n=1303) Prophylactic (n=921) | 2++ | B |
| 4 | Kim et al. [34] | Korea | 46 | 31.4 ± 14.3 | A (n=36) B (n=10) | Severe | n/a | 2++ | B |
| 5 | Lechner et al. [25] | Germany | 22 | n/a | n/a | Severe | On-demand (n=13) Prophylactic (n=10) | 2++ | B |
| 6 | Lorenzato et al. [23] | Brazil | 100 | 30.5 (18–61) | A and B with or without inhibitors | Moderate-severe | n/a | 2++ | B |
| 7 | Molho et al. [27] | France | 116 | 23 ± 3.3 | A (n=96) B (n=20) | Severe | n/a | 2++ | B |
| 8 | van Genderen et al. [26] | Netherlands | 78 | 40.5 (32.0–52.0) | A (n=65) B (n=13) | Severe | n/a | 2++ | B |
| 9 | von Mackensen et al. [32] | Germany | 28 | n/a | A (n=21) B (n=7) | Severe | On-demand (n=6) Prophylactic (n=22) | 2++ | B |
| 10 | Wallny et al. [24] | Germany | 71 | 43.2 (21–63) | A (n=71) | Severe | On-demand (n=9) | 2++ | B |

**Table 1:** (continued)

| No. | Author, year | Country | Patient characteristics | | | | | Sign ranking** | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Participants, n | Age in years (mean ± SD or median (range)) | Type of haemophilia | Severity of haemophilia | Treatment strategy | | |
| | | | | | | | Prophylactic (n=62) | | |
| 11 | Windyga et al. [28] | Poland | 92 | 26.6 ± 4.3 | A and B with or without inhibitors | Severe | On-demand (n=92) | 2++ | B |
| 12 | Witkop et al. [31] | USA | 66 | 26 (18–30) | A and B with or without inhibitors | Moderate-severe | On-demand (n=33) Prophylactic (n=33) | 2++ | B |
| 13 | Witkop et al. [15] | USA | 312 | 34 (26–47) | A and B with or without inhibitors | Moderate-severe | On-demand (n=143) Prophylactic (n=164) | 2++ | B |

*European countries: Spain, Italy, Germany, UK, Netherlands, France, Belgium, Switzerland, Portugal, Sweden, Poland, Slovakia, Norway, Greece. *Abbreviations:* M, mean; SD, standard deviation; m, median; VAS, visual analogue scale. EQ-5D-3L, European quality of life questionnaire 5 dimensions 3 level. **SIGN, Scottish intercollegiate guidelines network [19]; interpretation of the grading: B: A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.

their patients (i.e., either on demand or prophylactic) [15, 25, 28, 31, 32]. The other studies did not discuss the therapy strategy, neither replacement therapy, nor pain medication. Data was gathered in different countries (Table 1).

**Risk of bias within studies:** Methodological quality of the included articles has been assessed using SIGN for cohort studies [19]. Out of 13 studies, 12 were rated as "2++", categorized as B (low risk of bias), whereas one

**Table 2:** Pain prevalence rates.

| No. | Author, year | n | Pain assessment tool | Joint pain prevalence type* | Pain prevalence rate (in %) |
|---|---|---|---|---|---|
| 1 | Davari et al. [30] | 38 | EQ-5D-3L | Point prevalence (today) | 94.6 |
| 2 | Elander and Barry [33] | 68 | Haemophilia adapted CSQ | Acute (defined as bleeding related) | 88 |
| | | | | Chronic | 30 |
| 3 | Holstein et al. [22] | 2.224 | Self-made survey | Chronic | 38 |
| 4 | Kim et al. [34] | 46 | WHO-quality of life-abbreviated version | Chronic | 47.8 |
| 5 | Lechner et al. [25] | 22 | Self-made survey | Chronic | 91.3 |
| 6 | Lorenzato et al. [23] | 100 | EQ-5D-3L | Point prevalence (today) | 64 |
| 7 | Molho et al. [27] | 116 | WFH-score (pain scale 0–18) | Associated with interference with activities of daily living | 66 |
| 8 | van Genderen et al. [26] | 78 | Self-made survey VAS (0–10) | Point prevalence | 81 |
| 9 | von Mackensen et al. [32] | 28 | VAS (0–10) | Chronic | 67.9 |
| 10 | Wallny et al. [24] | 71 | Self-made survey VAS (0–10) | Chronic** | 100 |
| 11 | Windyga et al. [28] | 92 | WFH-score (pain scale 0–18) | Associated with interference with activities of daily living | 91.3 |
| 12 | Witkop et al. [31] | 66 | EQ-5D-3L VAS 0-100 | Point prevalence (today) | 73 |
| 13 | Witkop et al. [15] | 312 | Self-made survey VAS (0–100) | Acute (defined as bleeding related) | 18.9 |
| | | | | Chronic | 34.2 |
| | | | | Acute & chronic | 34.2 |

CSQ, a brief haemophilia coping questionnaire. Note: *Chronic pain is assessed for undefined pain types. **49.3% of PwH reported continuous haemarthropathic pain, whereas 50.7% reported daily intermitted pain. Though all patients suffer from chronic pain.

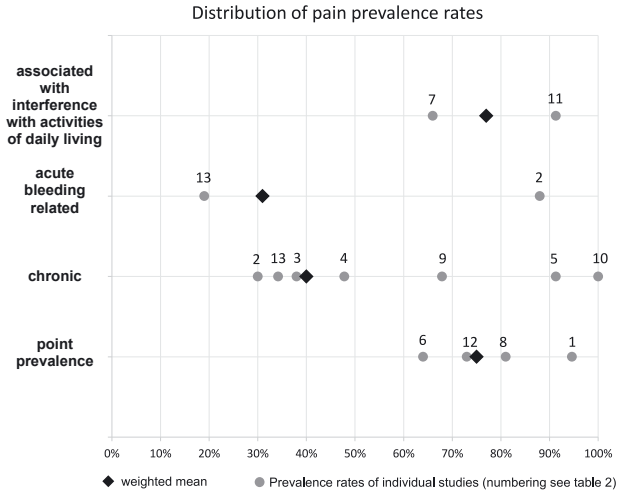


**Figure 2:** Distribution of pain prevalence rates.

study was rated as "2+", which displays grade C (medium risk of bias; Table 1).

**Results of individual studies:** Individual studies were analysed regarding prevalence of pain (Table 2). Data on pain intensities as well as the location of pain and results on pain types were considered and structured in the illustrations below (Figures 3 and 4).

Prevalence: Prevalence of pain in PwH was not explicitly assessed in the studies. Though, based on the provided information on the number or percentage of moderate to severe PwH, who did or respectively did not experience pain in a given period, rates were calculated and means were weighted according to the different subcategories (Table 2, Figure 2).

Prevalence rate for today is emphasized as the EQ-5D-3L questionnaire asks for "suffering pain today", which does not differentiate between acute and chronic pain nor between possible different causes of pain. The rates ranged from 64 to 94.6%. Overall, WM=75% PwH suffer from pain today.

Two studies [15, 33] equate acute pain with bleeding related pain, indicating that 88% suffer acute pain which was linked to bleeding [33], while Witkop et al. [15] indicated that 18.9% PwH suffer from pain only when bleeding occurs.

The prevalence rate for chronic pain is WM=39% (30–100%). Witkop et al. [31] further highlighted that out of the patients suffering from pain, 43% experienced pain only when presumed bleedings occur, 14% all the time and 39% reported pain all the time and pain getting worse with bleeds. Noticeably, chronic pain is defined differently regarding the time component, though considered as haemarthropathic joint pain [15, 22, 24, 25, 32–34].

Two studies assessed pain based on the WFH score showing that 66% [27] and 91.3% [28] of patients experience pain associated with interference with activities of daily living [35].

The distribution of the pain prevalence rates including the corresponding WM is further visualized in Figure 2.

Pain Intensity: In total, five out of 13 studies revealed varying mean pain intensities for patients with moderate/severe haemophilia using different assessment tools. Four studies did not mention pain intensities [22, 25, 33, 34].

Two studies explicitly used VAS scores, revealing a score of 2.3/10 [26] and 4.8/10 [24].

Three studies examined pain severity via the EQ-5D-3L, which differentiates between moderate and extreme pain/discomfort [23, 30, 31]. All studies demonstrate higher values of EQ-5D-3L in patients suffering from moderate pain compared to patients suffering from extreme pain (Figure 3).

Further, two studies with low risk of bias assessed the mean pain level using the WFH score and showed a mean result of 2.5/18 and 3.5/18 for all ankle, knee, and elbow joints [27, 28]. No differentiation for a single joint was made.

Moreover, Witkop et al. [15] divided the sample size into groups based on pain (acute, chronic pain, or both) revealing patients with severe haemophilia to be more frequently present in each group (acute, chronic or both)

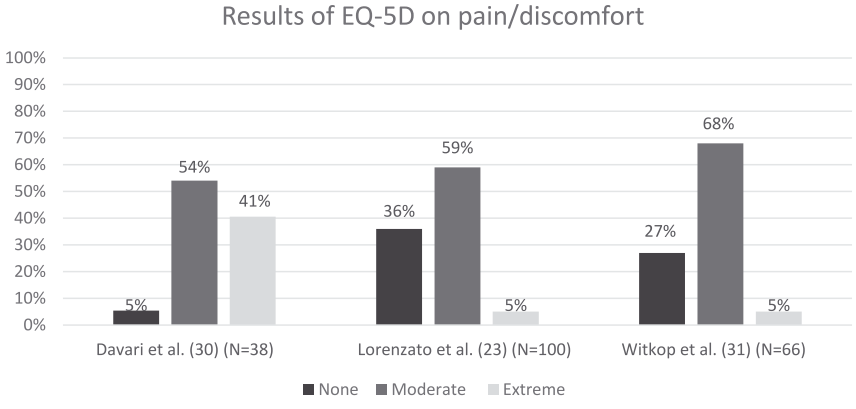


**Figure 3:** Distribution of moderate and extreme pain based on EQ-5D-3L results. *Explanation: Data from Davari et al. [30] (N=38), Lorenzato et al. [23] (100) and Witkop et al. [31] (N=66) was included and assembled (N=204).* No differentiation between chronic, acute or both was made.

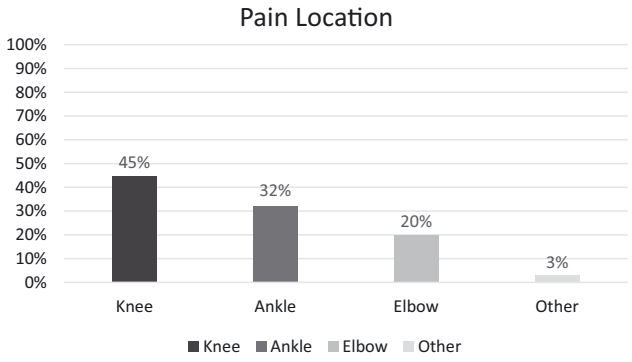


**Figure 4:** Major pain locations in PwH.

compared to moderate or mild haemophilia. Lechner et al. [25] support these findings.

Pain location: Location of pain is discussed in four studies with low risk of bias [15, 24, 26, 27]. Three studies [15, 24, 27] asked for the one joint most often affected, whereas the study by van Genderen et al. [26] displayed general distribution of pain regions. Witkop et al. [15] did not differentiate between mild and moderate/severe haemophilia and is therefore excluded in Figure 4. However, all studies agree that knees, ankles and elbows are the joints most often affected. Additionally, the spine represents an additional painful region in PwH [24, 33]. Three out of four studies show the same ranking, stating the ankle to be most often affected, followed by knee and elbow [15, 24, 26]. Only the study by Molho et al. [27] indicates the knee joint to be more often affected by joint pain followed by ankle and elbow.

**Syntheses of results:** This item is not applicable to this paper, as no statistical analyses were performed.

**Risk of bias across studies:** Comparison of prevalence rates is limited given a selective reporting bias across studies. Two studies declared chronic pain as a comorbidity [23, 31]. Hereby types of chronic pain are not further differentiated. This might imply that not only arthropathic joint pain but also other body areas affected by chronic pain are included in the presented studies.

**Additional analyses:** This item is not applicable to this paper, as no additional analyses were performed.

# Discussion

**Summary of evidence:** The purpose of this systematic review was to evaluate the current research status of prevalence of pain in PwH. Thirteen studies were included in this analysis, discussing different aspects of pain. Main findings indicate high point prevalence pain rates, (WM=75%) as well as high prevalence rates for pain associated with interference with activities of daily living (66–91.3%) expressively demonstrating that pain is of major implication and present in most of the patients. Self-reported chronic pain was present in WM=40% of PwH. Overall, the analysis revealed that pain is rated as mild-moderate [36], whereas the prevalence of pain is high in PwH.

Five studies utilized self-made surveys, which are not validated and therefore enforcing the already limited degree of comparison. Moreover, it is a major problem for comparability that studies use different definitions of both acute and chronic pain. Elander & Barry [33], Lechner et al. [25] as well as Witkop et al. [31] define acute pain as bleeding related pain. Hence, the genesis of pain is the defining mechanism, though flare-ups as well as exacerbation of pain are not considered. Holstein et al. [22] highlight the different haemophilia care centres using a variety of definitions on chronic pain following time periods (e.g., one month, six weeks, more than 3–6 months), pointing that the European Haemophilia Therapy Strategy Board agreed on a definition:

Continuous and/or intermittent pain, related to the pathophysiology of haemophilia, requiring intervention (pharmacological or non-pharmacological pain treatment), in which the cause of pain cannot be readily removed, occurring more than once a week and lasting three months or more.

The International Association for the Study of Pain defines pain to be chronic when it lasts longer than three months, emphasizing that using subcategories in the individual disease is recommended [37]. However, it is suggested to stick to one definition by specialized pain researchers, when investigating pain prevalence.

Another aspect that needs to be highlighted is the EQ-5D-3L, which asks for pain today and does not differentiate between acute, chronic or an exacerbation of persistent pain. Further, this can also imply flare ups. It needs to be emphasized that flare ups are not discussed in any of the included articles. Additionally, time plays a major role in joint pain as in e.g., start-up or stress-induced pain. Finally, the included studies fail to report if the patient took pain medication that day.

There are further confounding factors in research with PwH. The age of PwH plays a major role in the severity of joint degeneration as there was a change of treatment strategy (prophylactic vs. on-demand) and better medication [5]. The joint status is therefore assumed to be better in young patients resulting in less pain [11, 38]. Ten included studies of this review investigated “relatively” young patients as the mean age is below 45 years. Especially Witkop

et al. [31] observed young adults (18–30 years) only, but they still show a high prevalence rate of 73% for pain today. Hereby it can be highlighted that 33/66 participants are treated on-demand, as treatment regime represents another confounding factor. It is assumed that prophylaxis therapy leads to a lower annual bleeding rate compared to on-demand therapy, especially in severe haemophilia [39, 40]. However, only seven of 13 studies provided information on the treatment strategy, with an equal distribution between prophylactic and on-demand therapy. Bearing in mind that data was gathered in several countries, the diverging medical supply needs to be considered. For instance, the study by Windyga et al. [28] points towards a problematic medication availability within different areas of Poland.

Incidence of pain was not examined in any of the articles, whereas the prevalence rates could be estimated in each study, taking into account the fact that these studies did not directly study the prevalence of pain in PwH. It would be of major interest to examine incidence in order to draw conclusions on primary prevention. However, these findings point to the problematics of haemophilia research, as the current studies provide insufficient details.

Even though the prevalence rates were notably high, the actual intensities of pain in different measurement tools were rather moderate. The VAS scale indicated pain intensities of 3.7 (±1.2). Overall, severe pain was indicated by 11.6% of PwH only. In contrast, 61% of patients reported moderate pain. These findings are supported by prior literature [39]. The results of the WFH score also suggest low pain awareness (M=2.5/18; M=3.5/18) [27, 28], bearing in mind that the WFH score investigates pain associated with interference with activities of daily living. These findings might also be explained by different pain medications or the way PwH react to pain (i.e., sparing themselves since no stress for the joints leads to less pain) [6]. Moreover, pain experience does also dependent on structural joint damage, which is likely to go along with severity [10]. Some studies did not differentiate sufficiently between the three severities, when demonstrating results of the joint status [15, 32]. In addition, it is hard to draw conclusions from the pain scores, if the medication is not described sufficiently. The study by Windyga et al. [28] does consider characteristics such as start of replacement therapy and shift from different products but does not indicate any relationship with pain.

The review`s findings for pain location go along with previous literature. It remains evident that knees, ankles and elbows are the joints most affected by haemophilic arthropathy, and are hence often associated with pain [3, 9, 38]. Four of the included studies discussed pain location by agreeing on the three main joints (knees, ankles and elbows). Slight disagreement was found on the ranking of the joint that is most often affected. Degenerative joint changes and pain lead to compensation mechanisms, which can also cause other musculoskeletal complaints in further localisations, such as the spine. Thus, it is suggested to investigate pain in non-haemophilia-specific joints but also in other body parts.

**Limitations:** Given the fact that the amount of relevant literature after screening with the PICOS is relatively small, studies using non-validated questionnaires were included. Moreover, quality of the studies was assessed via "SIGN" adapted for cohort-studies (see Table 2). SIGN is a validated measurement tool to assess methodological quality. In this case, it was not always suitable as it inspects several aspects, which were not given in the present studies, such as comparison groups. Thus, it was not possible to score higher than grade B.

## Conclusions

This systematic review evaluates the current research status of the prevalence of pain in PwH. The results indicate that the pain prevalence in PwH is high, whereas the pain intensity is rated as rather moderate. Incidence was not considered in any of the assessed studies to analyse the number of new pain occurrences. It is assumed that better treatment strategies (e.g., extended half-life factor concentrates) might enable fewer annual bleeds, which in turn might facilitate a pain free childhood for boys. However, haemophilic arthropathy and associated joint pain occur later and should be focussed, emphasizing new research options. Still, a remaining problem represents the correlation between joint status and pain. Future research is needed to unravel the different types of pain, thereby emphasizing which type is most relevant in PwH. Hereby pain medication as well as the therapy strategy should also be focussed on to further develop tailored pain killer treatment regimes. Since the definition of pain as well as for prevalence is unclear and research is lacking, use of validated questionnaires and sensibilisation on pain data is strongly recommended for researchers and clinicians.

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**Author contributions:** Pia Ransmann and Steffen Krüger and Nathalie Roussel performed the research and analysed

the data. Pia Ransmann wrote the paper with support of Steffen Krüger, Thorsten Hagedorn, Thomas Hilberg and Nathalie Roussel.

**Competing interest:** S. Krüger has received honoraria and travel support from Shire/Takeda and Swedish Orphan Biovitrum. S. Krüger was an employee at the Department of Sports Medicine during his work on the review and when the manuscript was written but is now employed by Takeda.

**Informed consent:** This is not applicable as this article reviews prior literature.

**Ethical approval:** This is not applicable as this article reviews prior literature.

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