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REVIEW ARTICLE

Screening for subclinical synovial proliferation in haemophilia: A systematic review and meta-analysis comparing physical examination and ultrasound

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Abstract

Introduction: Ultrasound is increasingly used as addition to physical examination for detection of subclinical joint changes in haemophilia. However, the added value of ultrasound to physical examination for detecting synovial proliferation is not fully established.

Aim: To determine the diagnostic accuracy of swelling at physical examination for ultrasound-detected synovial proliferation in haemophilia.

Methods: PubMed and EMBASE were searched up to 2 August 2022. Studies reporting original data on occurrence of swelling at physical examination and synovial proliferation on ultrasound of index joints in persons with haemophilia were included. Risk of bias and applicability were assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. Diagnostic accuracy parameters of swelling at physical examination for ultrasound-detected synovial proliferation were determined. Summary sensitivity and specificity were calculated using a bivariate random-effects model.

Results: Fifteen studies reporting on swelling at physical examination and synovial proliferation on ultrasound in 2890 joints of 627 patients were included. Prevalence of subclinical synovial proliferation ranged between 0% and 55%. Sensitivity of swelling was low [summary estimate .34; 95% confidence interval (CI) .24-.46], while specificity was high (summary estimate .97; CI .92-.99). Predictive values varied widely due to inter-study differences in prevalence of synovial proliferation.

Conclusion: Joint swelling has low sensitivity for presence of ultrasound-detected synovial proliferation in haemophilia, suggesting underestimation of synovial proliferation by physical examination alone. Consequently, ultrasound screening may generate important information on synovial changes which would otherwise remain undetected.

KEYWORDS
haemophilia, physical examination, synovitis, systematic review [Publication Type], ultrasonography

1 | INTRODUCTION

Haemophilic arthropathy, caused by recurrent intra-articular bleeds in the ankles, knees and elbows (index joints), still causes major disease burden in persons with haemophilia.[1–4] Haemophilic arthropathy results from a multifactorial process in which synovial inflammation plays an important role. Several studies have reported that synovial proliferation is associated with increased bleeding and progression of arthropathy.[4–8] Through termination of the vicious circle of joint bleeding and inflammation, early detection and treatment of synovial proliferation might enable adaptation of treatment and improve outcome.

Traditionally, physical examination, according to, for example the Haemophilia Joint Health Score (HJHS),[9] is used to monitor joint health.[10] During physical examination, synovial proliferation may be characterized by painless swelling and subtle range of motion limitations. Yet, physical examination is thought to be relatively insensitive for detection of early joint changes such as synovial proliferation.[10–12] More sensitive methods for monitoring joint health are needed since progression of arthropathy is observed despite low joint bleeding rates.[13] These findings suggest that subclinical bleeding and inflammation may contribute to joint deterioration. With the expected reduction in joint bleed rates following intensive haemophilia treatment, the detection of early, subclinical cases of synovial proliferation[14] becomes even more relevant for clinical management.

Imaging techniques such as magnetic resonance imaging (MRI) and ultrasound may offer this increase in diagnostic accuracy. Although MRI is the current gold standard for detection of joint changes in haemophilia, routine MRI assessments of multiple joints is challenging due to duration, high costs and limited availability.[10] Ultrasound is a low-cost, widely available modality that provides real time information, which makes it easy to implement in clinical practice. Moreover, high to excellent agreement between ultrasound and MRI has been reported for detecting soft tissue abnormalities in joints of people with haemophilia.[15–21] The high accuracy makes ultrasound a good screening tool for presence of abnormal soft tissue. If clinically relevant, MRI can be used subsequently to differentiate the nature of the tissue. Over the past years, ultrasound is increasingly used as point-of-care addition to the existing check-up routine.[22,23]

Several studies have compared the accuracy of ultrasound and physical examination for detecting (early) joint abnormalities in people with haemophilia during routine assessment. Most literature on this topic has focused on detecting haemophilia arthropathy as a whole and less on detecting specific parameters such as synovial proliferation.[11,12,15,24–28] Only one study specifically compared physical examination and ultrasound for detection of synovial proliferation.[29] However, the ability of physical examination compared to ultrasound to detect synovial proliferation is of particular interest, as synovial proliferation is potentially reversible and timely treatment may prevent further damage.

Our hypothesis is that swelling at physical examination is not highly sensitive for synovial proliferation and therefore ultrasound may have added value in screening for subclinical synovial proliferation. The aim of this study was to systematically review and meta-analyse the existing literature on swelling at physical examination and synovial proliferation on ultrasound in joints of people with haemophilia. We determined the diagnostic accuracy of swelling at physical examination for ultrasound-detected synovial proliferation. The diagnostic accuracy of swelling for ultrasound-detected synovial proliferation quantifies the underestimation of synovial proliferation based on swelling alone, providing an estimate of the added value of ultrasound for screening for subclinical synovial proliferation.

2 | MATERIALS AND METHODS

The conduct of this systematic review was guided by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[30] and was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Diagnostic Test Accuracy (PRISMA-DTA) guideline.[31]

2.1 | Literature search

PubMed and EMBASE were searched up to 2 August 2022 for relevant publications. Search queries were built with the help of an experienced librarian (mentioned in acknowledgements) and included synonyms, MeSH and Emtree terms for 'haemophilia', 'physical examination' and 'ultrasound'. The complete search strategy is provided in Supplement S1. Additionally, reference lists of included studies were checked for relevant publications.

2.2 | Eligibility criteria and study selection

Observational studies reporting original data from routine physical examinations and ultrasound of index joints in children and/or adults with haemophilia A or B and related diseases, regardless of disease severity, were included. Data on presence of swelling at physical examination and synovial proliferation on ultrasound for individual joints had to be available from the publications or had to be provided by the authors upon request. Only publications written in English or Dutch and published in peer-reviewed journals were considered. To avoid overlap in study populations, publications reporting on the same cohort were identified and only the study providing the most complete description of the cohort was included. Studies on acute painful (bleeding) episodes or intra-articular interventions were excluded, since these studies were not considered to represent routine joint assessment and were therefore beyond the scope of this review. All publications were screened for eligibility based on title and abstract and subsequently relevant publications' full text were independently assessed by two reviewers (FL and MT). Discrepancies of evaluations were discussed upon consensus between the two reviewers or resolved by a third reviewer (WF).

2.3 | Quality assessment

Assessment of the risk of bias and applicability of the studies to our research question was performed according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.[32] The tool was tailored as described in the QUADAS-2 background document to specifically fit the current review question. The main refinement was no downgrading for unblinded ultrasound examinations as blinding for joint swelling seemed unfeasible and not in-line with clinical practice. The risk of bias assessment was categorized into four key domains: 'patient selection', 'index test', 'reference standard' and 'flow and timing'. Concerns about applicability were assessed for the first three domains. Per domain risk of bias and applicability concerns were scored as 'low', 'high' or 'unclear'. The tailored QUADAS-2 tool is available in Supplement S4. Two reviewers (FL and MT) independently assessed all studies, and discrepancies in the judgements were discussed upon consensus or resolved by the third reviewer (WF).

2.4 | Data extraction and data analysis

Data on study design, patient characteristics, conduct of physical and ultrasound examinations and occurrence of swelling and synovial proliferation at joint level were extracted from the publications or requested from the authors by one reviewer (FL) using the data extraction form in Supplement S3. Authors were given a 2-month response period for providing additional data with a reminder sent after 2–4 weeks. Swelling was defined as 'absent' (HJHS/Gilbert score swelling = 0) or 'present' (HJHS/Gilbert score swelling > 0) and definitions used for synovial proliferation were 'absent' (ultrasound synovial proliferation score = 0, according to the HEAD-US score, Doria et al. or Klukowska et al.) or 'present' (ultrasound synovial proliferation score > 0).[9,18,33–35] Diagnostic accuracy parameters (sensitivity, specificity, positive and negative predictive values) on joint level were calculated for each individual study using the original study data. The parameters' 95% confidence intervals (CI) were calculated according to the Clopper-Pearson 'exact' method. Heterogeneity between studies' sensitivities and specificities was assessed visually in forest plots and by Higgin's I^2 statistics. Based on the judgement for the 'patient selection' domain of the of QUADAS-2, the included studies were divided into two groups: 'screening of index joints' where the evaluated joints were not preselected based on joint status and were therefore considered to represent a routine screening setting (e.g. assessment of all six index joints or a random selection of a subset of index joints) or 'preselected joints' where evaluated joints were selected based on joint status (e.g. preselection based on available HJHS/radiological Pettersson scores[36] or assessment of the most/least affected joint only). To estimate the diagnostic accuracy of swelling for ultrasound-detected synovial proliferation in routine screening, summary estimates for sensitivity and specificity with their CI were calculated using a bivariate random-effects model adjusting for between-study heterogeneity.[37] In addition, subgroup analyses for treatment modality, disease severity, age and risk of bias were performed, and forest plots of the diagnostic accuracy parameters of the studies sorted by prevalence of synovial proliferation and joint status were visually inspected for trends in the parameters based on these study characteristics. Analyses were performed in RStudio (version 1.3.1093), using the GenBinomApps (version 1.2), meta (version 6.0-0) and mada (version .5.11) packages.

3 | RESULTS

The process of literature search is shown in Figure 1 and yielded a total of 1814 individual publications. Cross-reference searching did not identify additional publications. After title and abstract screening, full text publications of 188 studies were assessed for eligibility. The reasons for excluding studies based on full text are summarized in Supplement S2. Eventually, 15 studies[11,12,15,24,29,38–47] were included in the systematic review. The 15 included studies reported on occurrence of swelling and synovial proliferation in 2890 joints of 627 patients. The study populations varied between children (n = 7), adults (n = 4) and mixed populations (n = 4) and patients investigated mostly had severe haemophilia A. Physical examination was performed according to the HJHS in 14/15 studies and the Gilbert score[33] in the remaining study. Ultrasound examinations were mainly performed according to the HEAD-US protocol (12/15 studies). In two studies an ultrasound protocol described by Zukotynski et al.[48] was used. Prevalence of synovial proliferation ranged between 4.8% and 95%. A detailed summary of the included studies is presented in Table 1.

3.1 | Quality assessment

A summary of the risk of bias assessment and the applicability concerns is presented in Table 2, additional details are available in Supplement S5. In 4 out of 15 studies,[11,12,15,42] preselected joints were included resulting in a high risk of selection bias with corresponding applicability concerns in the patient selection domain. Results of these studies were not generalizable to a routine screening setting and were not included in the meta-analysis. The conduct of the physical examination was assessed with 'high risk of bias' in 3 of 15 studies because of non-blinded operators (n = 2)[12,47] and operators who were not experienced/trained in the use of the HJHS (n = 1).[38] For Di Minno et al.,[15] the applicability concerns of the physical examination performance were 'high' due to the use of the Gilbert score instead of the HJHS. Although use of the Gilbert score by Di Minno et al. was scored as a concern regarding the applicability in the quality assessment, its impact on the generalisability of the results to a setting in which the HJHS will be used is considered minimal. The performance of ultrasound examinations did not raise high risk of bias nor applicability concerns. A time window > 24 h between physical examination and ultrasound assessment introduced a high risk of bias in the 'flow and timing' domain in three studies.[11,40,47] Three studies scored 'high risk of bias' in the

TABLE 1 Summary of studies included in the analysis

	Study	Population								Examinations		
		N (joints)	Age (years)		Haemophilia A	Severe	Prophylaxis	Joint status (HJHS)	Physical examination		Ultrasound		Time window
				Median/mean				Median	Operator(s)	Score	Operator(s)	Protocol	PE-US
Screening of index joints	Adramerina (2022)	120	Children	11.5	90%	80%	100%	0	1 PT	HJHS	1 Physician	HEAD-US	<24h
	De la Corte-Rodriguez (2022)	361	Mixed	34	85%	80%	92%	na	1 RP	HJHS	1 RP	HEAD-US	<24h
	Roussel (2022)	59[†]	Adults	39.4	87%	80%	83%	21[†]	1 PT	HJHS	1 PT	HEAD-US	<24h
	Daffunchio (2021)	480[†]	Children	10.8	89%	100%	42.5%	0	1 PT	HJHS	1 PT & 1 Orthopaedist	HEAD-US	<24h
	Kavakli (2021)	438[†]	Mixed	18	85%	93%	100%	3	PTs & Haematologists[†]	HJHS	2 Radiologists[†]	HEAD-US	<24h
	Måseide (2021)	693	Mixed	28	61%	0%	38%	4	PTs	HJHS	PTs & Physicians	HEAD-US	<24 h/ <1year[§]
	Plut (2021)	168	Mixed	33	100%[†]	100%	100%	1	2 Haematologists[†]	HJHS	1 Radiologist	HEAD-US	<24h
	Prasetyo (2021)	120	Children	9.35	100%	100%	0%	3	1 PT & 1 RP	HJHS	1 Radiologist	HEAD-US	<24h
	Stephensen (2018)	63	Adults	29.14	100%[†]	100%	100%[†]	na	3 PTs[†]	HJHS	6 PTs	HEAD-US	<3months
	Timmer (2017)	76	Adults	53	80%	53%	33%	0	1 PT	HJHS	1 Physician	HEAD-US	<24h
	Altisent (2016)	124	Children	8.3	100%	100%	100%	0	1 RP	HJHS	2 Radiologists	HEAD-US	<24h
Preselected joints	Guha (2020)	30	Children	7.4	70%	na	10%	na	1 Physician[†]	HJHS	1 Radiologist[†]	HEAD-US	<24h
	Foppen (2016)	63	Children	11.5	88%	94%	100%	0	2 PTs[†]	HJHS	1 Physician	HEAD-US	<24h
	Poonnoose (2016)	55	Children	15	88%	100%	na	na	Experienced investigators	HJHS	Radiologists	Zukotynski	<36h
	Di Minno (2013)	40	Adults	22.45	100%	100%	70%	0	1 Orthopaedic surgeon	Gilbert	1 Haemophilia physician[†]	Zukotynski	<24h

[†]Details provided by the author upon request, na: not available, Gilbert: Gilbert score[29], HJHS: Haemophilia Joint Health Score[9], PT: physiotherapist, RP: Rehabilitation Physician, HEAD-US: Haemophilia Early Arthropathy Detection with UltraSound protocol[30], Zukotynski: ultrasound protocol as described by Zukotynski et al.[46], PE: Physical examination, US: Ultrasound, [§]In 8/118 examined patients time window > 24 h.

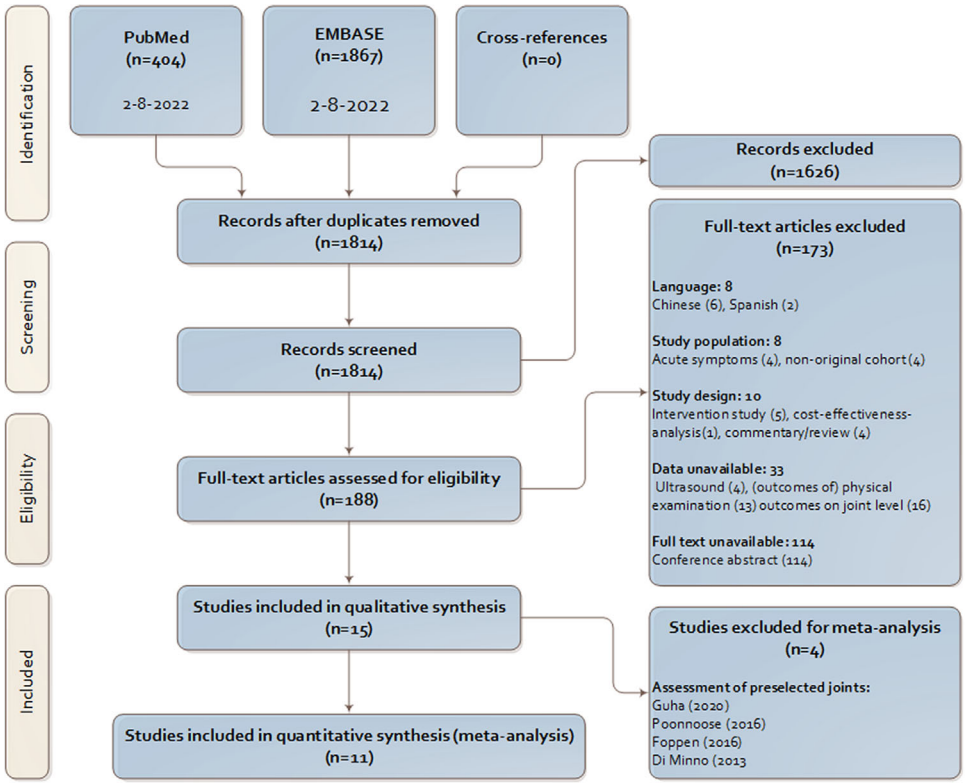


FIGURE 1 Flow chart of literature screening and study selection

latter domain because examinations were not performed in all eligible joints[41,44] or not all data from the examined joints was available for analysis.[12]

3.2 | Diagnostic accuracy of swelling for detection of synovial proliferation

The prevalence of subclinical synovial proliferation ranged from 0% to 55%. Calculated sensitivity, specificity, positive and negative predictive values (PPV, NPV) of swelling for detection of synovial proliferation from the individual studies are available in Figure 2 and Tables 3 and 4. Sensitivity was mostly low to moderate, with a few outliers ranging from .00 to 1.00. The overall low sensitivity indicates that only a small proportion of the joints with synovial proliferation on ultrasound showed swelling at physical examination. Specificity was mainly high, yet outliers were observed as well (range .14-1.00). The mostly high specificity of swelling indicates that absence of synovial proliferation on ultrasound was likely to correspond to absence of swelling in the included studies. Heterogeneity of included studies was considerable for sensitivity (Higgins' I^2 79.7%, CI 67.3-87.4) and specificity (Higgins' I^2 85.9%, CI 78.3-90.8). For positive predictive values, large variation was observed (range .48-1.00), where studies with a high prevalence of synovial proliferation showed higher PPVs. Negative predictive values varied widely as well (range .13-1.00) with increasing NPVs with decease of the synovial proliferation prevalence in the study population. The wide ranges in predictive values indicate that the probability that presence or absence of swelling truly corresponds with presence or absence of synovial proliferation on ultrasound respectively varied widely between studies, depending on the prevalence. Subgroup analyses for treatment, disease severity, age and risk of bias showed no significant differences between sensitivity and specificity in the subgroups. Visually, sensitivity and specificity of swelling appeared not to be associated with joint status, nor with prevalence of synovial proliferation. Results of subgroup analyses are available in Supplement S6.

3.3 | Meta-analysis of screening studies

Eleven out of 15 included studies were considered 'screening of index joints' studies[24,29,38–41,43–47] and were thus included in a bivariate random-effects model to determine summary estimates for sensitivity and specificity. Subclinical synovial proliferation was found in 4.6-41.7% of the joints in these studies. The diagnostic accuracy parameters of the 11 individual studies are available from Table 3. The summary estimates obtained in the meta-analysis were .34 for sensitivity (CI .24-.46) and .97 (CI .92-.99) for specificity, indicating that in routine assessment no synovial proliferation on ultrasound corresponded to no swelling in most cases, yet only a part of the ultrasound-detected synovial proliferation cases showed swelling at physical examination.

TABLE 2 Tabular presentation of the results of the QUADAS-2 assessment

Study Author (year)	Risk of Bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow & Timing	Patient selection	Index test	Reference standard
Adramerina (2022)	L	L	L	L	L	L	L
De La Corte-Rodriguez (2022)	L	L	L	L	L	L	L
Roussel (2022)	L	L	L	H	L	L	L
Daffunchio (2021)	L	L	L	L	L	L	L
Kavakli (2021)*	L	L	L	L	L	L	L
Måseide (2021)*	L	H	L	H	L	L	L
Plut (2021)*	L	H	L	L	L	L	L
Prasetyo (2021)	?	L	L	L	L	L	L
Stephensen (2018)*	L	L	L	H	L	L	L
Timmer (2017)	L	L	L	L	L	L	L
Altisent (2016)	L	L	L	H	L	L	L
Guha (2020)*	H	?	L	L	H	?	L
Foppen (2016)*	H	H	L	H	H	L	L
Poonnoose (2016)	H	L	L	H	H	L	L
Di Minno (2013)*	H	L	L	L	H	H	L

L Low Risk. H High Risk. ? Unclear Risk.
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2 .
*Judgement based on additional data provided by the authors.

3.4 | Diagnostic accuracy in selected joints

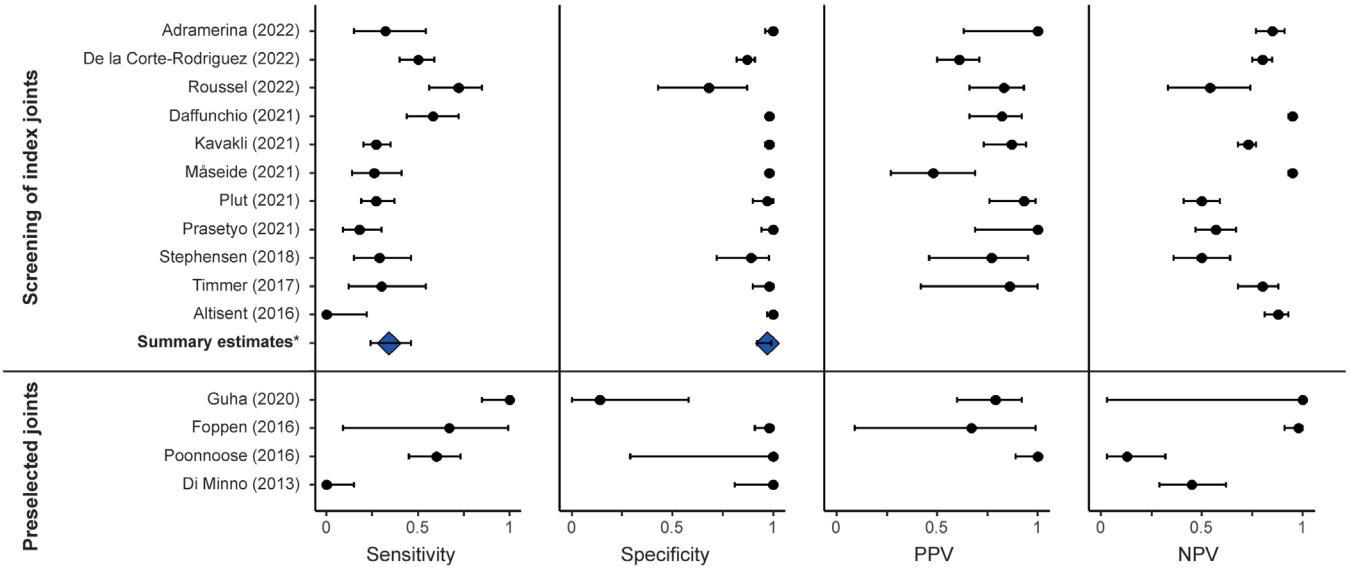
Four out of 15 studies investigated preselected joints. The diagnostic accuracy parameters of these studies are summarized in Table 4. Di Minno et al.[15] investigated subclinical arthropathy in 40 'healthy joints' of Italian adults with severe haemophilia A and found subclinical synovial proliferation on ultrasound in 55% of joints. The diagnostic accuracy parameters based on this study were similar to the estimates found in the screening studies. PPV could not be determined due to the absence of swelling in this study. Guha et al.[42] conducted a study including the most affected joints, according to HJHS, of 30 Indian children and did not observe any subclinical synovial proliferation (0%). In contrast to the other studies, this study showed high sensitivity (1.00, CI .85-1.00) and low specificity (.14, CI .00-.58) of swelling for ultrasound-detected synovial proliferation. Lastly, two studies investigated heterogeneous groups of joints in which the prevalence of haemophilic arthropathy was dependent on joint selection. Foppen et al.[12] performed a side-to-side comparison of the joint with the highest risk of arthropathy with its contralateral joint in 32 Dutch children. Poonnoose et al.[11] preselected joints based on their x-ray Pettersson scores to establish the full spectrum of arthropathy severity including 50% of joints with negligible to mild haemophilic arthropathy. The

TABLE 3 Diagnostic accuracy parameters of swelling at physical examination compared to ultrasound for detection of synovial proliferation in screening of index joints

Study	Population										Diagnostic accuracy parameters			
	Age	Severe	Prophylaxis	Joint status (HJHS)	Synovial proliferation Prevalence Median	N (joints)	TP	FP	FN	TN	Sensitivity [CI]	Specificity [CI]	PPV [CI]	NPV [CI]
Adramerina (2022)	Children	80%	100%	0	20.8%†	120†	8†	0†	17†	95†	.32 [.15-.54]	1.00 [.96-1.00]	1.00 [.63-1.00]	.85 [.77-.91]
De la Corte-Rodriguez (2022)	Mixed	80%	92%	na	29.6%†	361	53†	34†	54†	220†	.50 [.40-.59]	.87 [.82-.91]	.61 [.50-.71]	.80 [.75-.85]
Roussel (2022)	Adults	80%	83%	21†	67.8%†	59†	29†	6†	11†	13†	.72 [.56-.85]	.68 [.43-.87]	.83 [.66-.93]	.54 [.33-.74]
Daffunchio (2021)	Children	100%	42.5%	0	11.0%	480	31†	7†	22†	420†	.58 [.44-.72]	.98 [.97-.99]	.82 [.66-.92]	.95 [.93-.97]
Kavakli (2021)	Mixed	93%	100%	3	33.3%†	438†	39†	6†	107†	286†	.27 [.20-.35]	.98 [.96-.99]	.87 [.73-.94]	.73 [.68-.77]
Måseide (2021)	Mixed	0%	38%	4	6.2%	693	11	12	32	638	.26 [.14-.41]	.98 [.97-.99]	.48 [.27-.69]	.95 [.93-.97]
Plut (2021)	Mixed	100%	100%	1	57.1%†	168	26†	2†	70†	70†	.27 [.19-.37]	.97 [.90-1.00]	.93 [.76-.99]	.50 [.41-.59]
Prasetyo (2021)	Children	100%	0%	3	47.5%†	120	10†	0†	47†	63†	.18 [.09-.30]	1.00 [.94-1.00]	1.00 [.69-1.00]	.57 [.47-.67]
Stephensen (2018)	Adults	100%	100%†	na	55.6%†	63	10†	3†	25†	25†	.29 [.15-.46]	.89 [.72-.98]	.77 [.46-.95]	.50 [.36-.64]
Timmer (2017)	Adults	53%	33%	0	26.9%†	76	6†	1†	14	55†	.30 [.12-.54]	.98 [.90-1.00]	.86 [.42-1.00]	.80 [.68-.88]
Altisent (2016)	Children	100%	100%	0	12.1%	124	0†	0†	15†	109†	.00 [.00-.22]	1.00 [.97-1.00]	na	.88 [.81-.93]
Summary estimates from meta-analysis*											.34 [.24-.46]	.97 [.92-.99]	-	-

†Details provided by the author upon request, HJHS: Haemophilia Joint Health Score, na: not available, TP: true positive, FP: false positive, FN: false negative, TN: true negative, CI: 95% confidence interval, PPV: positive predictive value, NPV: negative predictive value. *Summary estimates were calculated using a bivariate random-effects model by Reitsma et al[37].

Interpretation: *Reported diagnostic accuracy parameters reflect the performance of swelling at physical examination compared to ultrasound for detection of synovial proliferation. Swelling at physical examination was the test under investigation, with ultrasound serving as reference standard.*



*Summary estimates from meta-analysis. The summary estimastes for sensitivity and specificity were calculated using a bivariate radom-effects model by Reitsma et al.[37]
PPV: positive predictive value, NPV: negative predictive value

FIGURE 2 Diagnostic accuracy parameters of swelling at physical examination compared to ultrasound for detection of synovial proliferation

difference in synovial proliferation prevalence of 4.8% in the study by Foppen and 94.5% in the study by Poonnoose was reflected in the obtained predictive values, with a high NPV (.98, CI .91-1.00) and moderate PPV (.67, CI .09-.99) based on Foppen et al. as opposed by low NPV (.13, CI .03-.32) and high PPV (1.00, CI .89-1.00) based on Poonnoose et al.

4 | DISCUSSION

This systematic review and meta-analysis estimated the diagnostic accuracy of swelling for ultrasound-detected synovial proliferation based on 15 studies reporting on 2890 joints of 627 patients. Prevalence of subclinical synovial proliferation in the studies ranged between 0% and 55%. Overall, sensitivity of swelling was low indicating an underestimation of ultrasound-detected synovial proliferation based on swelling alone. Specificity of swelling was high, indicating that joints without ultrasound-detected synovial proliferation usually show no swelling. NPV and PPV varied widely corresponding to the variation in prevalence of synovial proliferation in the various studies. Summary estimates of sensitivity and specificity for studies performed in a routine screening setting showed low sensitivity (.34; CI .24-.46) and high specificity (.97; CI .92-.99) of swelling for ultrasound-detected synovial proliferation. These summary estimates indicate fair evidence for the added value of ultrasound in screening for subclinical synovial proliferation.

4.1 | Strengths and limitations

A strength of this review is the systematic literature search with the retrieval of additional data from authors, combined with evaluation according to the Cochrane guidelines. As a result, this review provides the most complete overview possible of currently existing published and unpublished data on the occurrence of swelling at physical examination and synovial proliferation on ultrasound during routine joint assessment in study populations varying in age, disease severity, treatment, and/or joint status. However, using unpublished data also introduces a risk of information bias since the data provided by authors cannot be fully checked for accuracy. A possible limitation of this review is the focus on swelling as only clinical indicator for synovial proliferation, while disregarding minimal pain and slight loss of range of motion as potential signs of synovial proliferation.[10] However, synovial proliferation on ultrasound only shows weak correlation with pain ($r < .3$), and no significant correlation with range of motion.[26] A focus on assessment of swelling alone is therefore expected to be of minimal influence on the results of the current study. Lastly, we compared swelling on physical examination with ultrasound for detecting synovial proliferation. The ultrasound was serving as the reference standard in this regard. However, ultrasound is an imperfect reference standard, since the established gold standard for diagnosing synovial proliferation is MRI.[49] As a result, the diagnostic accuracy parameters presented only reflect performance of swelling relative to ultrasound. Due to the possible misclassification of outcome by ultrasound, the diagnostic accuracy parameters cannot be viewed as the performance of swelling for detecting the true disease status as determined by MRI.

4.2 | Quality of evidence

Limitations for drawing high-quality evidence conclusions from this review are the risk of selection and information bias, the considerable between-study heterogeneity of the included studies, and their limited sample sizes. For 12 of 15 included studies, additional data on the

TABLE 4 Diagnostic accuracy parameters of swelling at physical examination compared to ultrasound for detection of synovial proliferation in preselected joints

Study	Population						Diagnostic accuracy parameters							
	Joint selection	Age	Severe	Prophylaxis	Joint status (HJHS) Median	Synovial proliferation Prevalence	N (joints)	TP	FP	FN	TN	Sensitivity [CI]	Specificity [CI]	PPV [CI]	NPV [CI]
Guha (2020)	Most affected joint	Children	na	10%	na	76.7%[†]	30	23[†]	6[†]	0[†]	1[†]	1.00 [.85-1.00]	.14 [.00-.58]	.79 [.60-.92]	1.00 [.03-1.00]
Foppen (2016)	High risk & contralateral joint	Children	94%	100%	0	4.8%	63	2	1	1	59	.67 [.09-.99]	.98 [.91-1.00]	.67 [.09-.99]	.98 [.91-1.00]
Poonnoose (2016)	Negligible - severe HA	Children	100%	na	na	94.5%[†]	55	31[†]	0[†]	21	3	.60 [.45-.73]	1.00 [.29-1.00]	1.00 [.89-1.00]	.13 [.03-.32]
Di Minno (2013)	Healthy joints	Adults	100%	70%	0	55.0%	40	0	0	22	18	.00 [.00-.15]	1.00 [.81-1.00]	na	.45 [.29-.62]

Healthy joints: clinically asymptomatic joints never involved by overt bleeding events with Gilbert score = 0, Most affected joint: most affected joint based on HJHS v2.1 assessment, Negligible – severe HA: preselected joints based on Pettersson score, representing a spectrum ranging from negligible to severe haemophilic arthropathy, High risk & contralateral joint: Joint with the highest risk of arthropathy based on life-time bleed reports and the contralateral joint for side-to-side comparison, [†]Details provided by the author upon request, na: not available, HJHS: Haemophilia Joint Health Score, TP: true positive, FP: false positive, FN: false negative, TN: true negative, CI: 95% confidence interval, PPV: positive predictive value, NPV: negative predictive value.

presence of swelling and synovial proliferation for individual joints were provided by the authors upon request. In addition, the majority of studies were not specifically designed to compare physical examination and ultrasound for detection of synovial proliferation specifically, resulting in potential selection and/or information bias in 9 of 15 studies. While 12 of 15 included studies reported on the correlation between HJHS and ultrasound[11,12,46,47,24,29,39–42,44,45] and 7 of 10 aimed at investigating the correlation between HJHS and ultrasound,[11,29,39,40,44,45,47] only De la Corte-Rodriguez et al.[29] aimed at comparing the separate items of the HEAD-US and HJHS. The large between-study heterogeneity made pooling of all studies to obtain summary estimates of diagnostic accuracy inappropriate. However, with use of bivariate random-effects modelling, heterogeneity-corrected summary estimates were generated for studies performed in a routine screening setting, thus providing evidence for the added value of ultrasound for screening of subclinical synovial proliferation.

4.3 | Clinical implications and future research

This review provides fair evidence that there is added value of ultrasound to routine physical examination for screening of subclinical synovial proliferation: absence of swelling does not represent absence of synovial proliferation on ultrasound. The clinical relevance of ultrasound screening may be highest in (relatively) healthy joints, since detection of subclinical synovial proliferation in these joints may have the largest impact. Early treatment of synovitis may limit bleeding and joint deterioration, and thereby prevent progression to haemophilic arthropathy in these relatively healthy joints. From a treatment perspective, it is important to distinguish between reversible synovial inflammation and irreversible fibrotic synovial changes. As fibrotic synovial changes may occur in joints following recurrent joint bleeding,[50] ultrasound-detected synovial proliferation may not reflect active synovial inflammation in all joints affected by previous bleeding or haemophilic arthropathy. MRI might be used to differentiate between active synovitis and fibrotic synovial changes.[21] Increased synovial vascularisation detected by Power/Colour Doppler imaging on ultrasound might help in distinguishing between active inflammation and fibrotic synovium, yet its diagnostic accuracy in haemophilic joints is a topic of debate and has not been established.[51] Longitudinal ultrasound studies are needed to establish the clinical relevance of ultrasound-detected synovial proliferation with or without increased vascularisation by monitoring the effect of treatment alterations after diagnosis of synovitis.

5 | CONCLUSION

Studies evaluating swelling at physical examination and synovial proliferation on ultrasound show large heterogeneity, causing variability in the observed diagnostic accuracy parameters. Overall low sensitivity of swelling for ultrasound-detected synovial proliferation suggests underestimation of synovial proliferation by physical examination

alone. This review provides fair evidence that ultrasound has added value in a routine setting for detecting subclinical synovial proliferation. Future studies may identify patient subgroups in which ultrasound examination is most clinically relevant. Additionally, the clinical consequences of detection of synovial proliferation by ultrasound need to be established.

AUTHOR CONTRIBUTIONS

FL, MT, WF and KF contributed to the conception and design of the study. FL and MT acquired and analysed the data. All authors contributed to the interpretation of data for the work. FL drafted the manuscript. MT, PJ, KF and WF revised the manuscript critically for important intellectual content. All authors approve the final version of the manuscript to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article and from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was performed in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

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

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