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REVIEW ARTICLE

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The effect of resistance exercise on strength and safety outcome for people with haemophilia: A systematic review

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Abstract

Introduction: Haemophilia is a congenital bleeding disorder with severe musculoskeletal complications. Resistance exercise is important to increase joint stability and to improve physical performance.

Aim: This review aimed to investigate the safety and efficacy of resistance exercise interventions on people with haemophilia (PwH) and evaluate whether the American College of Sports Medicine resistance exercise criteria for healthy adults are valid for this population.

Methods: A systematic search in literature was conducted, using the databases PubMed, MEDLiNE, CINAHL, SCOPUS, PEDro and Cochrane Library. Out of 2.440 studies published between 1960 and November 2019, 14 studies (9 randomized controlled trials, 1 controlled trial, 4 single-group prospective studies) applying resistance exercise in juvenile and adult PwH corresponded to the inclusion criteria.

Results: Studies performed dynamic, isokinetic or a combination of isometric and dynamic resistance training. Most interventions were carried out in the context of a multimodal training. Resistance was provided using fixed and free weights, body weight, resistance bands and water resistance. Study protocols included clinical and home-based settings. Several studies suggest that training intensities lower than those known to increase the strength of healthy people are effective in increasing the strength of PwH. Resistance exercise seems to be a safe intervention if it is adequately monitored, individually adapted and applied with sufficient factor therapy. Due to the heterogeneity of study designs, training interventions and outcome measures a meta-analysis could not be performed.

Conclusions: Further studies of higher methodological quality are needed to determine the optimal types of exercise, optimal dosage and timing.

KEYWORDS

exercise, haemophilia, haemophilia, resistance, safety, strength, training

1 | INTRODUCTION

Haemophilia is an X-chromosome linked rare congenital bleeding disorder caused by a deficiency of coagulation factor VIII (in haemophilia A) or factor IX (in haemophilia B).[1,2] Haemorrhages mainly affect large joints and muscles.[1,2] Recurrent haemarthroses lead to chronic haemophilic arthropathy associated with strength deficits, muscle atrophy, contractures and angular deformities and may finally lead to joint ankylosis and disability.[1,2]

Several studies verified a deficit in the basic motor functions in people with haemophilia (PwH),[3-8] this is why a multimodal training is necessary. Regarding strength performance, studies have shown reduced strength in certain muscle groups and patient groups: adults with haemophilia seem to have strength deficits in the upper and lower extremities as well as in the back muscles. This affects especially elderly adults, moderately to severely affected patients and those with a worse joint status.[3,9-12] Studies on children and adolescents showed contradictory results which might be connected to the severity of the disease, the factor therapy, the joint affection and the method of examination. In younger PwH, the muscles surrounding the elbow and knee joints appear to be a major problem, depending on the joint condition.[7,10,13-17]

In healthy subjects, improved muscular strength is associated with significantly better cardiometabolic risk factor profiles, reduced general mortality and a lower risk of developing functional limitations.[18] In addition, resistance exercise (RE) improves bone mass and can reduce pain and disability, for example, in persons with osteoarthritis.[18] In haemophilic arthropathy, RE combined with coordination and endurance training is important to improve joint stability and to control exaggerated end-range of motion joint movements, thereby reducing the risk of injuries, falls and haemarthroses.[1,19-21] Therefore, adapted physical activity, including muscle strengthening and weight-bearing activities to promote bone density, is recommended by the World Federation of Haemophilia.[1]

According to the American College of Sports Medicine (ACSM) guidelines for healthy adults, RE can increase power, muscular endurance and muscle strength, depending on the training intensity and the number of sets and repetitions.[18] According to these guidelines, dynamic training with intensities of at least 40%-50% of the one-repetition maximum or the appropriate correlate in maximum isometric force with ≤15 repetitions is required to improve muscular strength.[18] Training is recommended two to three times weekly.[18]

To our knowledge, no systematic literature review has so far focused solely on RE for PwH. RE is an important part of the multimodal training concept to stabilize the joints and to improve physical performance but may carry the risk of bleeding and overloading if the training is not applied appropriately. There are no recommendations regarding training intensities that are needed to improve muscular strength for PwH yet. Primary aim of our review was to evaluate the efficacy of RE interventions and clarify whether the ACSM RE criteria for healthy people[18] might also be valid for PwH. Secondary aim was to evaluate whether the RE interventions used so far caused training-induced adverse effects in terms of bleeding, pain or worsened symptoms.

2 | METHODS

2.1 | Identification and selection of studies

A systematic review of the existing scientific literature was conducted based on the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[22] The review protocol was not registered. Search included the electronic databases PubMed, Scopus, Medline, Cinahl, Cochrane Library and PEDro. Trials with the keywords 'haemophilia and exercise', 'haemophilia and resistance exercise', 'haemophilia and strength exercise', 'haemophilia and training', 'haemophilia and resistance training' and 'haemophilia and strength training' were extracted and considered for inclusion. No restrictions were placed on the year of publication. A total of 2.440 studies published between 1960 and November 11th, 2019 was found and screened for eligibility by title and abstract. A total of 2.334 studies were rejected as non-includable, and 106 studies were selected for full-text analysis. Fourteen articles corresponded to the inclusion criteria. Systematic literature search was independently performed by two researchers (BW, TiHa), disagreements in selection were resolved through discussion.

2.1.1 | Inclusion and exclusion criteria

Table 1 presents the inclusion and exclusion criteria regarding study design, participants, interventions and outcome evaluation. To find which intensities are needed to increase strength in PwH, any actively performed RE intervention with a sufficient training protocol was included into this literature review. Studies were included if training protocols followed FITT (frequency, intensity, time, type) criteria. If the intensity of RE was not reported (mostly in cases were body weight or resistance bands were used to provide resistance), a training protocol was judged as being sufficiently documented if sufficient documentation of the training extent (number of repetitions or duration of contraction) or a detailed description of the performed exercises (which allowed the estimation if a sufficient training stimulus was applied) was provided. Studies were excluded if none of those criteria were fulfilled, and therefore, an estimation of the individual load was not possible.

2.2 | Data collection and analysis

For eligible papers, full texts were screened independently by two researchers (BW, DH) who extracted the following data: study characteristics (author and year of publication, study design, sample sizes, comparison characteristics), patient characteristics (type of haemophilia, severity, mean age), intervention characteristics (training modalities performed, type of RE provided, muscle groups exercised, exercise setting, training frequency/duration/intensity, strength outcome measure) and outcome data. When information regarding study

TABLE 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Study design, comparison	RCT, comparative controlled trial or single-group prospective study	Case studies, pilot studies, retrospective studies, cross-sectional studies, reviews, conference papers and abstracts, book chapters
	Training intervention vs either no intervention or a different training intervention (with/without passive additional therapy)	Studies that were published in languages other than English and German
		Unconcluded studies
Participants	People with haemophilia A, B	Animal trials
	Children, adults	
	Any level of severity	
	All kinds of joint affection, comorbidities	
Interventions	Any RE intervention with a training protocol that was judged as being sufficiently documented (details given under 'methods–inclusion and exclusion criteria')	RE intervention without a training protocol judged as being sufficiently documented (details given under 'methods–inclusion and exclusion criteria')
	RE solely or in combination with any other exercise modality	Studies that performed neuromuscular electrical stimulation (NMES)
	Clinical setting or home-based training	
Outcome measures	Efficacy: containing outcome measure muscular strength	
	Safety: reporting on	
	• Bleeding frequency (number of bleeds per year, month or week), bleeding incidents detected during training period	
	• Worsening of symptoms during or after the training	
	• Pain intensity (measured through relevant pain scales)	

characteristics, patient characteristics or intervention characteristics was not given in the respective studies the information was stated as 'not available'. In one case, intensity measure was not indicated in the respective study and authors were contacted for further details.[8]

Primary outcome parameter was muscular strength. Secondarily, safety was assessed by evaluating bleeding frequency, bleeding incidents detected during the training period, pain intensity and training-induced adverse effects (Table 1). Data were presented by means of the mean difference between groups or within a study group and their statistical significance (Table 2). Few studies provided effect sizes, none of the included studies reported the corresponding interval estimates (eg the confidence intervals) for the mean differences. Effect sizes were calculated by the authors if the studies provided the relevant data to do so. The criteria for determining these effect sizes according to[23,24] are listed in the legend of Table 2.

A meta-analysis could not be performed due to the substantial heterogeneity on study designs, interventions and assessment methods of outcome measures. There were no outcome variables available that were measured with the same assessment method in five or more of the included studies. A serious meta-analysis, therefore, was not possible as results are considered unreliable when a small number of heterogeneous studies is assessed.[25]

As trials differed in their study design, two tools were used to assess the methodological quality of the included studies. Studies with a randomized controlled trial (RCT) design were assessed by implementing the Cochrane Collaboration's tool for assessing risk of bias.[26] The Methodological Index for Non-Randomized Studies (MINORS) was chosen for assessing non-randomized interventional studies.[27,28] This index contains 12 items, the first eight being specifically for non-comparative studies. Items were scored 0-2 according to whether they were reported and reported adequately. The global ideal score was 16 for non-comparative and 24 for comparative studies. The risk of bias assessment was independently performed by two researchers (BW, DH), differences were resolved through discussion.

3 | RESULTS

3.1 | Flow of studies

After the described selection process, 14 articles were considered eligible for investigating the effects of RE on PwH. Details on the systematic literature search and the selection process are presented in Figure 1.

3.2 | Characteristics of studies

3.2.1 | Quality

Table 3 shows the quality assessment using the Cochrane Collaboration's tool for assessing the risk of bias of the nine included RCT's.[8,29-36] The majority of the studies was judged to have a low risk of selection bias regarding random sequence generation (6/9) and allocation concealment (5/9). Eight/9 studies were assessed to have an unclear risk, one to have a high risk of performance bias.

TABLE 2 Effect of resistance exercise on outcome parameters strength, bleeding frequency, pain

Study	Primarily evaluated outcome	Domain, subgroup	Comparison		MD[n]	*P*-value (as stated in respective paper)	Effect size
			IG-IG[k]	IG pre-post[l]			
Training of higher intensity (ACSM criteria for healthy adults[18] met): outcome strength							
Runkel et al 2016[8]	Relative max. complex isometric strength (N/kg)	M. biceps brachii		x	NA	**≤.000**[i]	η^2 = 0.373 [L]
		M. triceps brachii		x	NA	**≤.000**[i]	η^2 = 0.356 [L]
		M. latissimus dorsi		x	NA	**≤.000**[i]	η^2 = 0.266 [L]
		M. rectus abdominis		x	NA	**≤.000**[i]	η^2 = 0.324 [L]
		M. biceps femoris [right, left]		x	NA	**.001**[i]	η^2 = 0.217 [right], 0.197 [left] [L]
		M. quadriceps femoris [right, left]		x	NA	**.003** [right], **.001** [left][i]	η^2 = 0.164 [right], 0.209 [left] [L]
Mulvany et al 2010[37]	Maximal isometric strength (N)	Hip extension		x	7.3	**≤.01**[f]	*dz* = 1.66 [L]
		Hip flexion		x	4.3	**≤.01**[f]	*dz* = 0.68 [M]
		Hip abduction		x	4.7	**≤.01**[f]	*dz* = 0.59 [M]
		Knee flexion		x	3.5	**≤.01**[f]	*dz* = 0.73 [M]
		Knee extension		x	5.5	**≤.01**[f]	*dz* = 0.71 [M]
		Elbow flexion		x	0.6	**≤.01**[f]	*dz* = 0.08 [S]
		Elbow extension		x	2.5	**≤.01**[f]	*dz* = 0.3 [M]
Eid et al 2014[29a]	Knee flexors isokinetic peak torque strength (N/m)	Group (2)[a]: group (1) + RE, AE		x	10.99	**.0001**[f]	*dz* = 1.25[e] [VL]
		Group (2) vs group (1)	x		9.3	**.02**[f]	*dz* = 0.88[e] [L]
	Knee extensors isokinetic peak torque strength (N/m)	Group (2)[a]: group (1) + RE, AE		x	19.02	**.0001**[f]	*dz* = 1.33[e] [VL]
		Group (2) vs group (1)	x		14.42	**.01**[f]	*dz* = 1.01[e] [L]
Parhampour et al 2014[30c]	One-repetition maximum (kg)	Chest press		x	0.82	**≤.05**[f]	*dz* = 0.92[e] [L]
		Shoulder press		x	1.0	**≤.05**[f]	*dz* = 1.27[e] [VL]
		Scapular retraction		x	0.86	**≤.05**[f]	*dz* = 1.05[e] [L]
		Hip flexion		x	1.03	**≤.05**[f]	*dz* = 1.62[e] [VL]
		Hip extension		x	1.0	**≤.05**[f]	*dz* = 1.72[e] [VL]
		Hip abduction		x	1.04	**≤.05**[f]	*dz* = 1.68[e] [VL]
		Knee extension		x	0.92	**≤.05**[f]	*dz* = 1.59[e] [VL]

(Continues)

TABLE 2 (Continued)

Study	Primarily evaluated outcome	Domain, subgroup	Comparison		IG pre-post[l]	MD[n]	*P*-value (as stated in respect. paper)	Effect size
			IG-CG[m]	IG-IG[k]				
Training of lower intensity (ACSM RE criteria for healthy adults[18] not met): outcome strength								
Hilberg et al 2003[6]	Maximal isometric strength (Nm)	Knee extensor both legs			x	84	NA	*dz* = 0.62[e] [M]
		Knee extensor right leg			x	33	NA	*dz* = 0.40[e] [S]
		Knee extensor left leg			x	33	NA	*dz* = 0.49[e] [S]
		Knee extensor both legs	x[d]			NA	**<.05**[e,h]	NA
	Maximal isometric strength (N)	Leg press both legs			x	500	NA	*dz* = 0.92[e] [L]
		Leg press right leg			x	208	NA	*dz* = 0.60[e] [M]
		Leg press left leg			x	283	NA	*dz* = 0.83[e] [L]
		Knee extensor both legs	x[d]			NA	**<.05**[e,h]	NA
Cuesta-Barriuso et al 2014[31a]	Isometric gastrocnemius strength (rupture test, 0-5 points)[†]	MT group[a]: RE + manual therapy			x	−0.075	.08[f]	*dz* = −0.33 [S]
		E group[a]: RE + multimodal			x	−0.105	.10[f]	*dz* = −0.28 [S]
Cuesta-Barriuso et al 2018[33a]	Biceps brachii strength (rupture test, 0-5 points)[†]	E group[a]: RE + multimodal			x	0.0	.333[f]	*dz* = −0.00
Greene et al 1983[39]	Isokinetic peak torque strength (ft. lbs.)	Knee extensors (all ages)			x	7.8	**<.001**[f]	NA
		Knee extensors (7-12 y)			X	−1.8	>.05[e,f]	NA
		Knee extensors (13-18 y)			x	7.3	**<.05**[e,f]	NA
		Knee extensors (>18 y)			x	10.6	**<.01**[e,f]	NA
		Knee flexors (all ages)			x	8.6	**<.001**[f]	NA
		Knee flexors (7-12 y)			x	2.9	>.05[e,f]	NA
		Knee flexors (13-18 y)			x	9.0	**<.01**[e,f]	NA
		Knee flexors (>8 y)			x	9.6	**<.001**[f]	NA
Goto et al 2014[34b]	Max. isometric quadriceps strength (Nm/kg)	Knee extensors			x	0.41	**.000**[i]	*dz* = 0.72[e] [M]
Zaky et al 2013[35a]	Maximum isometric quadriceps strength (kg)	Group A[a]: RE			x	11.23	**<.001**[f]	*dz* = 2.27[e] [H]
		Group B[a]: A + partial weight bearing			x	17.60	**<.001**[f]	*dz* = 2.49[e] [H]
		Group A vs. group B		x		6.37	**<.001**[f]	*dz* = 0.87[e] [L]

(Continues)

TABLE 2 (Continued)

Study	Primarily evaluated outcome	Domain, subgroup	Comparison			MD[n]	*P*-value (as stated in respect. paper)	Effect size
			IG-CG[m]	IG-IG[k]	IG pre-post[l]			
Kargarfard et al 2013[36]	Isokinetic peak torque strength (Nm)	Knee flexors right			x	17.21	**.001**[f]	*dz* = 0.87[e] [L]
		Knee flexors left			x	15.2	**.001**[f]	*dz* = 0.68[e] [M]
		Knee extensors right			x	17.93	**.001**[f]	*dz* = 0.41[e] [S]
		Knee extensors left			x	16.56	**.001**[f]	*dz* = 0.36[e] [S]
		Knee flexors right		x		19.89	**<.001**[j]	*dz* = 1.08[e] [L]
		Knee flexors left		x		18.55	**<.001**[j]	*dz* = 0.92[e] [L]
		Knee extensors right		x		23.59	**.003**[j]	*dz* = 0.62[e] [M]
		Knee extensors left		x		22.71	**<.001**[j]	*dz* = 0.61[e] [M]
Eid et al 2014[29a]	Knee flexors isokin. peak torque strength (Nm)	Group (1)[a]: multimodal incl. RE			x	0.28	.55[f]	*dz* = 0.02[e] [VS]
	Knee extensors isokin. peak torque strength (Nm)	Group (1)[a]: multimodal incl. RE			x	0.38	.14[f]	*dz* = 0.03[e] [VS]

Study	Primarily evaluated outcome	Domain, subgroup	Comparison		MD[n]	*P*-value (as stated in respect. paper)	Effect size
			IG-CG[m]	IG pre-post[l]			
Training of lower intensity (ACSM RE criteria for healthy adults[18] not met): outcome bleeding frequency							
Czepa et al 2008[38]	Number of bleedings/y	1st year of training		x	−2.2	>.05[g]	*dz* = −0.09[e] [VS]
		2nd year of training		x	−3.4	>.05[g]	*dz* = −0.14[e] [VS]
Greene et al 1983[39]	Number of bleedings/6 mo			x	−1.3	NA	NA
Goto et al 2014[34b]	Number of bleedings/month			x	−1.0	.091[i]	*dz* = −0.41[e] [S]
Khriesat et al 2000[40]	Number of bleedings/month			x	NA	**.04**[f]	*r* = −0.55 [M]
Training of lower intensity (ACSM RE criteria for healthy adults[18] not met: outcome pain							
Cuesta-Barriuso et al 2014[31a]	VAS score (0-10 points) for ankle [65]	MT group[a]: RE + manual therapy		x	−1.85	**.00**[f]	*dz* = −0.77 [M]
		E group[a]: RE + multimodal		x	−0.395	.10[f]	*dz* = −0.27 [S]

(Continues)

TABLE 2 (Continued)

Study	Primarily evaluated outcome	Domain, subgroup	Comparison		MD[n]	*P*-value (as stated in respect. paper)	Effect size
			IG-CG[m]	IG pre-post[l]			
Cuesta-Barriuso et al 2017[32]	VAS score (0-10 points) [65]	Ankle		x	−1.15	**.007**[i]	*dz* = −0.73[e] [M]
		Knee		x	−0.25	.510[i]	*dz* = −0.16[e] [VS]
		Elbow		x	−0.07	.148[i]	*dz* = −0.43[e] [S]
		Ankle	x		−0.02	.338[f]	*dz* = −0.03[e] [VS]
		Knee	x		0.40	.511[f]	*dz* = 0.51[e] [M]
		Elbow	x		0.75	.241[f]	*dz* = 5.89[e] [H]
Cuesta-Barriuso et al 2018[33a]	VAS score (0-10 points) for elbow [65]	E group[a]: RE + multimodal		x	0.0	.164[f]	*dz* = −0.20 [S]
Goto et al 2014[34b]	VAS (mm) [65]			x	2.5	.493[i]	0.18[e] [VS]

Abbreviations: %, per cent; 95% CI UB, 95% confidence interval upper bound; 95%CI LB, 95% confidence interval lower bound; ACSM, American College of Sports Medicine[18]; AE, aerobic exercise; CG, control group (no intervention); *dz*, Cohen's *d*[23]; E group, exercise group; ft. lbs., foot pound; gr, group; gr (1), group 1; gr (2), group 2; IG, intervention group; incl, including; kg, kilogram; m, metre; MD, mean difference; mm, millimetre; MT group, manual therapy group; N, Newton; NA, not available; *r*, the Pearson product – moment correlation coefficient; RE, resistance exercise; VAS, Visual Analog Scale; vs, versus; y, year; η^2, eta-square (effect size measurement for the analysis of variance).

[VS]: very small effect size, [S]: small effect size, [M]: medium effect size, [L]: large effect size, [VL] very large effect size, [H] huge effect size; criteria for determining effect sizes for Cohen's *d* calculated by the authors: [VS]: *dz* 0.01-<0.20, [S]: *dz* < 0.5, [M]: *dz* < 0.8, [L]: *dz* < 1.2, [VL]: *dz* < 2.0, [H]: *dz* ≥ 2.0 according to[23,24]; criteria for determining effect sizes not calculated by the authors are stated in the respective studies.

[a]Study with different training intervention groups, intervention groups that performed RE are listed.

[b]Study with 2 training intervention groups (training ± self-monitoring), only the intervention group with self-monitoring is listed.

[c]Study with different intervention groups (RE ± passive modality, passive modality solely), intervention group that performed solely RE is listed.

[d]IG of haemophilic patients is compared to passive healthy controls.

[e]Values calculated by authors.

[f]*t* test.

[g]Wilcoxon.

[h]Mann-Whitney-*U*.

[i]ANOVA.

[j]ANCOVA.

[k]IG-IG: comparison of 2 different training interventions postintervention.

[l]IG pre-post: comparison of the values pre and postintervention within the IG.

[m]IG-CG: comparison IG vs passive CG postintervention.

[n]MD: mean difference.

[†]Manual muscle strength test according to Daniels et al[51] scale 0-5 (0 = normal force, 5 = no muscle contraction).

One study stated that no blinding was performed.[34] The majority of the studies (6/9) was judged to have unclear risk, three studies to have low risk of detection bias. Three studies reported that blinding of outcome assessment was carried out.[32,33] The majority of the studies was judged to have low risk of attrition bias (6/9), low risk of other bias (9/9) and unclear risk of reporting bias (8/9). One study was assessed to have a high risk of reporting bias, as it informed that participants had received a questionnaire after the training, but the results of the questionnaire had not been reported.[36]

Table 4 shows the quality assessment of the five non-randomized studies according to the MINORS tool. The mean MINORS score was 16/24 for the comparative controlled trial[6] and 10/16 (range 7-12/16) for the four single-group prospective studies.[37-40] The majority of the studies reported adequately on a clearly stated aim (5/5), on the inclusion of consecutive patients (3/5), on a prospective collection of data (5/5), on endpoints (4/5) and on a follow-up period (5/5) appropriate to the aim of the study. The majority of the studies (4/5) did not report on an unbiased assessment of the study endpoint, in one study it was reported but inadequate. The majority of the studies (4/5) did not have a loss to follow-up of less than 5% (in one case loss to follow-up was not reported) and did not report on a prospective calculation of the study size (5/5). The comparative trial reported on an adequate control group, on contemporary groups and on an adequate baseline equivalence of the groups. The same study reported on statistical analyses without calculating confidence intervals or relative risk.

Table 5 gives an overview of the characteristics of the included studies, additionally outlining study design, comparison characteristics and sample sizes.

3.2.2 | Participants

A total of 461 PwH or other bleeding disorders (three female persons with von Willebrand disease in[37]) were included in the exercise intervention studies, out of whom 94 were assigned to passive control groups. The other PwH were assigned to either a training intervention group or a control group that also received (less intense) exercise. Nineteen healthy persons were assigned to control groups in a study of Hilberg et al.[6]

Table 6 presents an overview of the patient characteristics. The majority of the included patients had severe haemophilia A. Two studies reported that they included inhibitor patients in their active groups.[8,38] Age ranged between seven[39,40] and 66[8] years. Patients received factor replacement therapy either prophylactic or on demand, three studies did not report on the factor therapy.[35,36,39] The joint condition was only heterogeneously outlined in seven studies.[6,8,31-33,37,40] Four studies reported on sport activity prior to the programme.[6,8,30,37]

3.2.3 | Intervention

Table 7 presents an overview of the training intervention characteristics. Training characteristics revealed a large heterogeneity regarding training intensity and duration, training modalities and the RE type applied, muscle groups exercised as well as the way RE was targeted and measured. Four studies conducted dynamic RE interventions using training intensities that suggest increasing muscular strength according to the ACSM RE criteria.[8,29,30,37] The other studies carried out training with lower intensity, using isometric,[32] dynamic[6,36,38] and isokinetic[39] training or a combination of all. Three studies focused on RE only[30,35,39] while the other training interventions performed multiple exercise modalities including proprioception/coordination, endurance, flexibility and relaxation techniques. One study performed aqua training.[36] Training focused mainly on the knee joint[34,35,39,40] or trained upper and lower limbs and the trunk.[6,8,29,30,32,36-38] Seven studies performed home-based training.[8,31-34,38,39]

Most studies compared exercise to no intervention (Table 5). Two studies compared an intervention to another with an expanded training protocol.[29,35] Three studies compared different interventions (including passive modalities) to no intervention.[30,31,33] One study compared the same intervention with and without feedback monitoring.[34] Tables 2 and 7 present the outcomes regarding the relevant RE intervention groups of the respective studies and state whether comparison was made within an intervention group or compared to another intervention or a passive control group.

Study durations lasted from 6 weeks[30,35,37] to 2 years[38] and were applied twice a week[6,8,31,37] to daily.[31,33,34,39]

3.2.4 | Outcome

Primarily evaluated outcome: strength (efficacy)

Different assessment methods were used to evaluate strength performance (Table 2). The majority of the studies measured maximal isometric strength,[6,8,31,33-35,37] others isokinetic peak torque strength.[29,36,39] Only one study assessed the one-repetition maximum.[30]

Secondarily evaluated outcomes: bleeding frequency, pain, adverse events (safety)

Ten studies evaluated whether a bleeding episode was detected during the training period,[6,8,30,31,33,34,37-40] four studies reported on the bleeding frequency.[34,38-40] Pain was assessed in four studies[31-34] using Visual Analog Scales.[41] Only Mulvany et al[37] evaluated other adverse effects.

3.3 | Effect of resistance exercise interventions on muscular strength (efficacy)

RE interventions applying intensities according to the ACSM RE criteria[8,29,30,37] could significantly increase isometric,[8,37] dynamic[30] and isokinetic[29] strength performance in the intervention group after training. These findings came along with small to large[37] and large to very large[8,29,30] effect sizes (Table 2).

Regarding those studies applying training with lower intensities, five[6,34-36,39] out of eight studies could likewise demonstrate

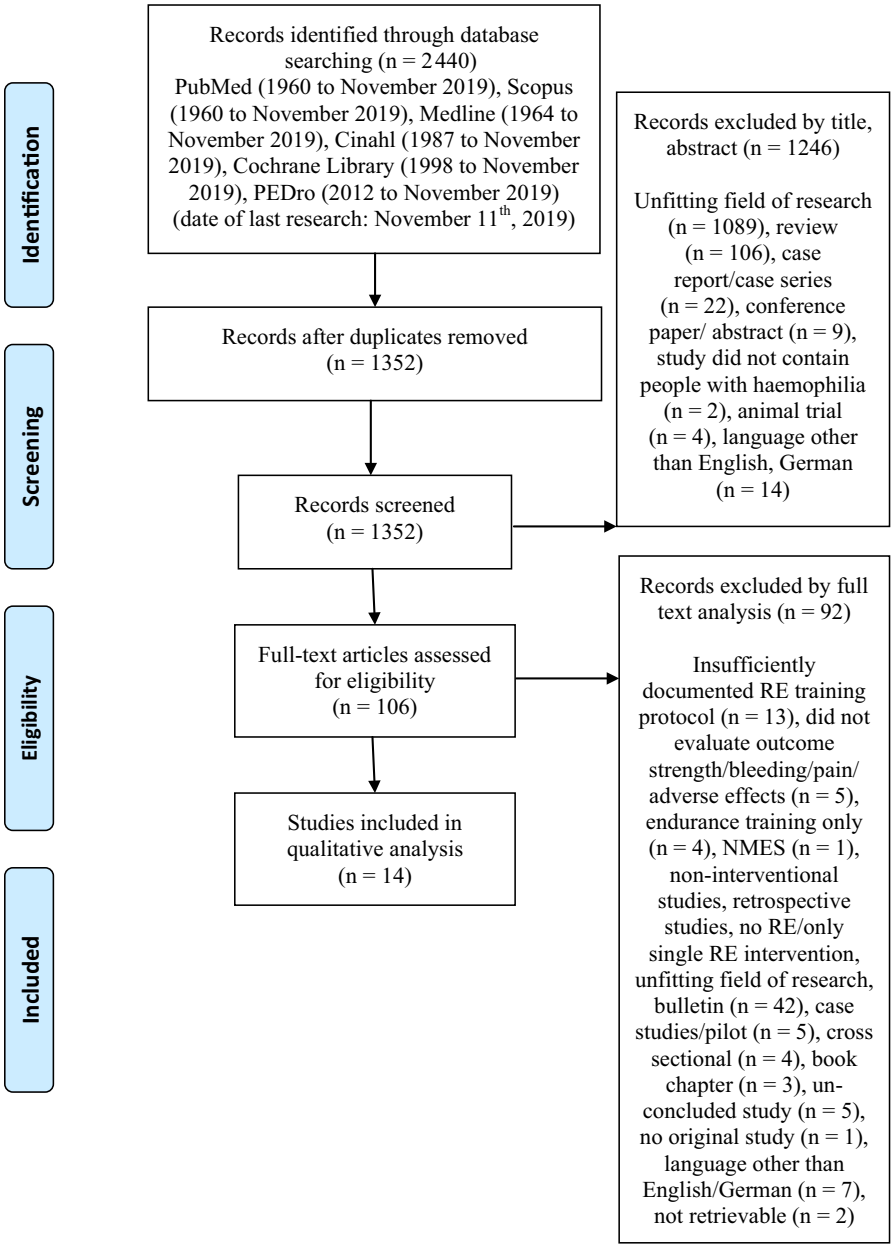

FIGURE 1 Flowchart of the systematic literature research and the selection process [Colour figure can be viewed at wileyonlinelibrary.com]

significant strength increase in the intervention group after training (the low intense control group of Eid et al[29] was counted as a separate intervention). Out of these, effect sizes could be provided for four studies which showed a small to large,[6,36] medium[34] and huge[35] effect. The outcome was improved when weight was added to static and short arc training.[35] Three studies showed no significant strength increase with no to small change regarding the effect size, whereby two studies performed RE for only 2 weeks (the whole multimodal training intervention lasting 12 weeks).[31,33]

3.4 | Effect of resistance exercise interventions on bleeding frequency, pain, adverse events (safety)

No increased bleeding episodes were detected during the training period,[6,8,30,31,33,34,37-40] although in Runkel et al[8] it is mentioned that in one case a bleeding incident could have possibly been due to the training, without giving further details. One study reported a significant decrease in bleeding frequency with a medium effect size[40] (Table 2).

After the intervention, pain either showed no statistically significant improvement[33,34] or revealed a short-term pain reduction with a medium effect for a certain joint/treatment modality in the intervention group after training[31,32] (Table 2). No other adverse events in training were mentioned by Mulvany et al.[37]

4 | DISCUSSION

4.1 | Efficacy and safety of RE interventions

Primary aim of this review was to evaluate the efficacy of RE interventions. So far, only four studies[8,29,30,37] have applied RE with

TABLE 3 Risk of bias assessment according to the Cochrane Collaboration's tool[26] for assessing risk of bias for RCT's (n = 9)

Criteria	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Runkel et al 2016[8]	+	+	?	?	+	?	+
Eid et al 2014[29]	?	?	?	?	?	?	+
Parhampour et al 2014[30]	+	+	?	?	+	?	+
Cuesta-Barriuso et al 2014[31]	+	+	?	+	+	?	+
Cuesta-Barriuso et al 2017[32]	+	+	?	+	+	?	+
Cuesta-Barriuso et al 2018[33]	+	+	?	+	+	?	+
Goto et al 2014[34]	+	?	–	?	+	?	+
Zaky et al 2013[35]	?	?	?	?	?	?	+
Kargarfard et al 2013[36]	?	?	?	?	?	–	+

Note: +: low risk, –: high risk, ?: risk unclear.

TABLE 4 Quality assessment according to the MINORS tool[27,28] for assessing non-randomized interventional studies (n = 5)

Criteria	Mulvany et al 2010[37]	Czepa et al 2008[38]	Greene et al 1983[39]	Khriesat et al 2000[40]	Hilberg et al 2003[6]
1. A clearly stated aim	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	0	0
3. Prospective collection of data	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	0	2
5. Unbiased assessment of the study endpoint	1	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2
7. Loss to follow-up < 5%	1	1	0	1	1
8. Prospective calculation of the study size	0	0	0	0	0
Additional criteria (comparative study)					
9. An adequate control group					2
10. Contemporary groups					2
11. Baseline equivalence of groups					2
12. Adequate statistical analyses					1
Total score	12/16	11/16	10/16	7/16	16/24

Note: 0 = not reported, 1 = reported but inadequate, 2 = reported and adequate; highest archievable score: 16 (non-comparative studies), 24 (comparative studies).

intensities that suggest increasing muscular strength according to the ACSM RE criteria and could demonstrate strength increase. The existing literature suggests that low-intensity dynamic, isokinetic or isometric-dynamic RE of sufficient frequency and duration seems to be able to likewise increase muscular strength in PwH.[6,34-36,39] Therefore, the ACSM RE criteria for healthy persons may not be valid in this population. Due to the low baseline fitness levels of PwH,[3,4,6-8,42] lower exercise intensity might provide a sufficient stimulus of muscular adaptions. A meta-analysis on elderly (non-haemophilic) cohorts concluded that RE at lower intensities of load than traditionally recommended may suffice to induce substantial gains in muscle strength if a sufficient number of repetitions is performed.[43] This might also be true for younger, previously untrained PwH.

Secondary aim was to evaluate the safety of RE interventions. The included studies did not report on training-induced bleedings or on an increase of pain. One low-intensity study of low quality even found weak evidence for a decrease in bleeding frequency with a medium effect size.[40] This correlates with a pilot study that suggests that RE might be able to reduce bleeding frequency.[19] Only one study[37] commented on other training-induced adverse events and negated adverse reactions. RE seems to be a safe intervention for children and adults with haemophilia if it is adequately monitored, adapted and applied with sufficient factor therapy. It is important to be cautious when applying intervention protocols on patients with severe haemophilia, insufficient factor therapy, on patients with an inhibitor or with certain comorbidities.[2] Adequate

TABLE 5 Characteristics of the included studies (n = 14)

Characteristics of included studies			
Study	**Design**	**Comparison**	**n**
Runkel et al 2016[8]	RCT	Training vs no intervention	64
Mulvany et al 2010[37]	Single-group prospective study	Single-group design	33
Eid et al 2014[29]	RCT	Training + additional training vs training	30
Parhampour et al 2014[30]	RCT	Training vs training + passive modality vs passive modality only vs no intervention	48
Hilberg et al 2003[6]	Comparative controlled trial	Training (patients) vs training (healthy persons) vs no intervention (healthy controls)	28
Czepa et al 2008[38]	Single-group prospective study	Single-group design	14
Cuesta-Barriuso et al 2014[31]	RCT	Training + manual therapy vs different training vs no intervention	31
Cuesta-Barriuso et al 2017[32]	RCT	Training vs no intervention	20
Cuesta-Barriuso et al 2018[33]	RCT	Training vs manual therapy vs no intervention	27
Greene et al 1983[39]	Single-group prospective study	Single-group design	32
Goto et al 2014[34]	RCT	Training + self-monitoring vs training	37
Zaky et al 2013[35]	RCT	Training + additional training vs training	30
Khriesat et al 2000[40]	Single-group prospective study	Single-group design	17
Kargarfard et al 2013[36]	RCT	Training vs no intervention	20

Abbreviations: n: total number of patients included into the trial; RCT: randomized controlled trial.

factor therapy can be a limiting factor for exercise in several countries.

There are certain safety aspects to consider in training PwH. Due to the underlying bleeding disorder, RE training protocols applied in the literature differ from those that are common in a healthy population. Training with relatively maximum resistance loads and roughly six to 10 repetitions in order to increase muscle mass and peak strength in healthy adults would cause a substantially higher risk of injury for PwH.[20] To strike a balance between strength improvement and low risk of joint injury, several authors suggest decreasing the risk in PwH by initially learning to use the proper technique, training with submaximal loads, at a lower velocity, in limited joint ranges or even isometrically at various joint angles.[20] As demonstrated in the included studies, exercise should always be adapted to the individual's needs. It should be prescribed by health care professionals trained in haemophilia care who ensure adequacy and sufficient factor treatment.[1,42] The selection of the proper training intervention should depend on the patient's joint status, range of motion and pain as well as the individual's fitness level and basal muscle strength.[18,21,44,45] Therefore, it is important to report on these parameters when presenting data of RE training interventions. The protocol used by Mulvany et al[37] might be especially applicable.[21] This study group made the attempt to adapt the training load to the different levels of joint affection.

4.2 | Quality

Nine out of the 14 studies included were designed as RCT's,[8,29-36] with five studies[8,30-33] being of higher methodological quality (≥4 low risk of bias out of 7 criteria). The general risk of bias of most of the other included RCT's was assessed as unclear. As common in this population, sample sizes were small with a maximum sample size of 64 people.[8] Due to the heterogeneity of study designs, training interventions, patient characteristics and outcome measures a direct comparison between studies and a meta-analysis of the results was not possible. Findings were therefore juxtaposed in the respective tables to give a comprehensive overview of the current literature. Most results compare improvements within an intervention group which reduces the strength of evidence. Most studies drew their conclusions based on the statistical significance of the *P*-value. Only five[8,31,33,37,40] out of 14 papers reported on effect sizes. Certainly, no study reported confidence intervals for the mean differences between pre and postintervention or between the intervention and control group, respectively. Ten studies provided data to calculate effect sizes[6,29-32,34-38] in order to evaluate the clinical relevance of the results.[46] The majority of the studies did not perform a post hoc analysis or a correction for multiple testing. Given these limitations, the statements that were drawn conducting this review should be understood as tentative evidence and should be considered with caution.

4.3 | Training prescription, progression, strength measurement

A constitutive review by Winters-Stone et al[47] emphasized the principles of training (specificity, progression, overload, initial values), exercise prescription details regarding frequency, intensity, time, type (FITT formula) and adherence to the training protocol for cancer patients. This should also be applied to interventions performed with

TABLE 6 Patient characteristics of the included studies (n = 14)

Patient characteristics of the included studies						
Study	**n**	**Disease severity**	**Haemophilia**	**Age**	**Mean age IG year [range]**	**Factor therapy**
Runkel et al 2016[8]	64	Severe (92%), moderate	A, B	Adults	41.9 (IG), 40.3 (CG), [19-66]	P (92% in IG, 86% in CG), OD (0% in IG, 7% in CG), no specification - self-assessment (8% in IG, 7% in CG) (substitution according to haemophilic centre)
Mulvany et al 2010[37]	33	Severe (78.8%), moderate, mild	NA	Children, adults	Adults: 20 [19-57], Children: 14 [7-18]	Severe: P (factor infusion ≤2 h prior to exercise), others: had appropriate coagulation therapy available
Eid et al 2014[29]	30	Moderate	A	Children	12.0 (group 2), 12.13 (group 1), [10-14]	All had recombinant factor VIII replacement
Parhampour et al 2014[30]	48	Severe (100%)	A	Adults	NA [20-35]	P (100%)
Hilberg et al 2003[6]	28	Severe (100%)	A	Adults	Patients: 32.4 [17-44]	Prophylactic replacement therapy was individually possible, but not generally recommended
Czepa et al 2008[38]	14	Severe (92.9%), moderate	A, B	Adults	46 [35-62]	P (% NA) or OD
Cuesta-Barriuso et al 2014[31]	31	Severe (61.3%), moderate	A, B	Adults	35.29 [NA]	P (54.8%) or OD (continued regimen as prescribed by haematologist)
Cuesta-Barriuso et al 2017[32]	20	Severe (50%), moderate, mild	A, B	Adults	30.95 [NA]	P (35.0%), OD
Cuesta-Barriuso et al 2018[33]	27	Severe (63.0%), mild	A, B	Adults	34.48 [NA]	P (55.6%) or OD (continued regimen as prescribed by haematologist)
Greene et al 1983[39]	32	Severe (87.5%), moderate	A, B	Children, adults	20.8 [7-51]	NA
Goto et al 2014[34]	37	Severe (84.3%), moderate, mild	A, B	Adults	NA [26-64]	P (78.1%) or OD
Zaky et al 2013[35]	30	Moderate	NA	Children	9.93 [8-12]	NA (all had haematologist approval)
Khriesat et al 2000[40]	17	Severe (NA%), moderate	A	Children	10 [7-13]	All had factor VIII (dosage of 30-40 IU/kg iv daily for 5 d followed by the PT programme)
Kargarfard et al 2013[36]	20	Moderate	NA	Adolescents, adults	22.9 [NA] (IG), 18.1 [NA] (CG)	NA

Abbreviations: CG, control group; h, hours; iv, intravenously; IG, intervention group; kg, kilogram; moderate haemophilia, factor levels < 5%; N, total number of patients included into the trial; NA, not available; OD, on demand factor therapy; P, prophylaxis; PT, physiotherapy; severe haemophilia, factor levels < 1%; SG, study group.

PwH.[47] It is especially important to report on the training progression to document sufficient supercompensation. Progression was documented in the studies applying training of higher intensity with little to no information available in the studies applying lower intensity. Regarding training frequency, the ACSM guidelines for healthy adults recommend training two to three times weekly with a period of rest in order to promote cellular adaptions.[18] Therefore, training only once a week might not sufficiently improve an outcome, but daily training might not be appropriate either—at least if higher intensities are applied. Several studies suggest that training intensities lower than those known to increase the strength of healthy people seem to be able to increase the strength of PwH. A training duration of 6 weeks did already show a significant strength increase,[30,35,37] 2 weeks of training did not significantly improve strength.[31,33] Regarding the type of RE training, static, dynamic and isokinetic exercise can be part of a rehabilitation programme for PwH, as also recommended by Pietri et al.[17] Souza et al[21] suggest providing resistance using water resistance, elastic resistance bands or free weights, which was frequently used in the literature. Two recent cross-sectional studies on people with severe haemophilia undergoing prophylactic treatment showed that externally resisted exercises (using elastic resistance bands, machine resistance and free weights) at moderate intensities for the upper and lower extremities mostly provided greater muscle activity than conventional non-resisted exercises, were safe and well tolerated.[48,49] Elastic resistance bands are portable, inexpensive and avoid possible impacts. Therefore, they are a promising alternative for supervised rehabilitation programmes and the first choice for home-based training.[48,49]

Measuring maximum isometric strength has shown a high reliability in PwH[12,50] and might be a good option to determine strength outcome in this population.

TABLE 7 Training characteristics of the included studies

Training characteristics of the included studies (A)				
Study	**Modality**	**Setting**	**Muscle groups exercised**	**RE training type (resistance provided)**
Training of higher intensity (ACSM RE criteria[18] met)				
Runkel et al 2016[8]	RE, coordination, mobility, AE	Home-based	Upper/lower limbs, trunk	Dynamic (strength training devices in fitness studios)
Mulvany et al 2010[37]	RE, flexibility, AE	Clinical	Upper/lower limbs, trunk	Dynamic (fixed and free weights, elastic resistance bands)
Eid et al 2014[29a] group (2)	RE, flexibility, AE	Clinical	Upper/lower limbs	Isometric, dynamic (free weights)
Parhampour et al 2014[30c]	RE	Clinical	Upper/lower limbs, trunk	Dynamic (fixed and free weights, body weight)
Training of lower intensity (ACSM criteria[18] not met)				
Hilberg et al 2003[6]	RE, flexibility, proprioception	Clinical	Upper/lower limbs, trunk	Dynamic (elastic resistance bands)
Czepa et al 2008[38]	RE, coordination, mobility, awareness	Home-based	Upper/lower limbs, trunk	Dynamic (elastic resistance bands, body weight)
Cuesta-Barriuso et al 2014[31a] manual therapy group	RE, proprioception + manual/passive therapy	Clinical	Ankle	Isometric, dynamic (NA)
Cuesta-Barriuso et al 2014[31a] home-training group	RE, flexibility, proprioception, AE	Home-based	Ankle	Isometric, dynamic (NA)
Cuesta-Barriuso et al 2017[32]	RE, flexibility, proprioception, AE	Home-based	Upper/lower limbs	Isometric (NA)
Cuesta-Barriuso et al 2018[33a] gr E (home training)	RE, flexibility, proprioception, AE	Home-based	Elbow	Isometric, dynamic (NA)
Greene et al 1983[39]	RE	Home-based	Knee flexors/extensors	Isokinetic (simultaneous contraction knee flexors/extensors)
Goto et al 2014[34b]	RE, flexibility, balance, (AE)	Home-based	Knee extensors	Isometric, dynamic (body weight, resistive training)
Zaky et al 2013[35a] group B	RE	Clinical	Knee extensors	Isometric, dynamic (body weight)
Zaky et al 2013[35a] group A	RE	Clinical	Knee extensors	Isometric, dynamic (body weight, + partial weight bearing)
Khriesat et al 2000[40]	RE, AE	Clinical	Knee extensors	Isometric, dynamic, isokinetic (resistive weight bearing, isokinetic exercise machines)
Kargarfard et al 2013[36]	RE, AE	Clinical	Upper/lower limbs	Dynamic (water resistance)
Eid et al 2014[29a] group (1)	RE, flexibility, AE	Clinical	Upper/lower limbs	Isometric (NA)

Training characteristics of the included studies (B)			
Study	**Time, frequency, duration (h) [#multimodal, ##RE only]**	**Intensity measure**	**Strength outcome measure**
Training of higher intensity (ACSM RE criteria[18] met)			
Runkel et al 2016[8]	1.5 h/d × 2/wk × 24 wk [72 h#]	BORG scale [52]	Rel. max. isometric strength of multiple muscle groups (N/kg)
Mulvany et al 2010[37]	time: NA, 2/wk × 6 wk	% MIF, elastic resistance band	Maximal isometric strength of multiple muscle groups (N)
Eid et al 2014[29a] – group (2)	1.66 h/d# (0.59 h/d##) × 3/wk × 12 wk [60 h#, 21 h##]	Equivalent RM	Isokinetic peak torque strength knee extensors/flexors (Nm)
Parhampour et al 2014[30c]	0.5-0.66 h/d × 3/wk × 6 wk [9-12 h##]	% 1RM	1RM of multiple muscle groups (kg)
Training of lower intensity (ACSM criteria[18] not met)			
Hilberg et al 2003[6]	2 h/d × 2/wk × 24 wk [96 h#]	Not measured	Max. isometric strength of knee extensor (Nm), leg press (N)

(Continues)

TABLE 7 (Continued)

Training characteristics of the included studies (B)			
Study	**Time, frequency, duration (h) [#multimodal, ##RE only]**	**Intensity measure**	**Strength outcome measure**
Czepa et al 2008[38]	Time: NA, recommended: 2-3/wk × 96 wk (2 y)	Not measured	not evaluated
Cuesta-Barriuso et al 2014[31a] manual therapy group	1 h/d# (0.17 h/d##) × 2/wk × 12 wk [24 h#, 4 h##]	Not measured	Maximal isometric strength of gastrocnemius (rupture test†)
Cuesta-Barriuso et al 2014[31a] home-training group	0.33-0.5 h/d × 2-7/wk × 12 wk [~27 h#], 0.33 h/d × 7/wk × 2 wk [4.7 h##]	Not measured	Maximal isometric strength of gastrocnemius (rupture test†)
Cuesta-Barriuso et al 2017[32]	0.33-0.44 h/d × 6/wk × 15 wk [~31 h#], 0.33 h/d × 6/wk × 2 wk [4 h##]	Not measured	Not evaluated
Cuesta-Barriuso et al 2018[33a] E (home training) group	0.33-0.5 h/d × 7/wk × 12 wk [28-42 h#], 0.33 h/d × 7/wk × 2 wk [4.7 h##]	Not measured	Maximal isometric strength of biceps brachii (rupture test†)
Greene et al 1983[39]	0.25 h/d × 7/wk × 24 wk [42 h##]	Max. force tolerated	Isokinetic peak torque strength knee extensors/flexors (ft. lbs.)
Goto et al 2014[34 b]	time: NA, 7/wk × 8 wk	Not measured	Maximal isometric strength of quadriceps (Nm/kg)
Zaky et al 2013[35]: group B[a]	time: NA, 2-3/wk × 6 wk	Not measured	Maximal isometric strength of quadriceps (kg)
Zaky et al 2013[35] group A[a]	time: NA, 3/wk × 6 wk	Not measured	Maximal isometric strength of quadriceps (kg)
Khriesat et al 2000[40]	time: NA, 2/d × 24 wk	Not measured	Not evaluated
Kargarfard et al 2013[36]	0.66-1 h/d# (0.17 h/d##) × 3/wk × 8 wk [16-24 h#, 4 h##]	Max. force tolerated	Isokinetic peak torque strength knee extensors/flexors (Nm)
Eid et al 2014[29a]: group (1)	1 h/d# (0.25 h/d##) × 3/wk × 12 wk [36 h#, 9 h##]	Not measured	Isokinetic peak torque strength knee extensors/flexors (Nm)

Abbreviations: %, per cent; ACSM, American College of Sports Medicine[18]; AE, aerobic exercise; d, day; ft. lbs., foot pound; gr: group; h, hour; kg, kilogram; m, metre; MIF, maximal isometric force; N, Newton; NA, not available; RE, resistance exercise; rel, relative; RM, repetition maximum; wk, week; y, year.

[a]Study with different training intervention groups, intervention groups that performed RE are listed.

[b]Study with 2 training intervention groups (training ± self-monitoring), only the intervention group with self-monitoring is listed.

[c]Study with different intervention groups (RE ± passive modality, passive modality solely), intervention group that performed solely RE is listed.

†The manual muscle strength test according to Daniels et al[51,53]: scale 0-5 (0 = normal force, 5 = no muscle contraction).

4.4 | Limitations of the present review

The authors decided to include comparative controlled and single-group prospective studies in order to present a comprehensive overview of the current literature. This reduces the methodological quality of the trials and thereby the significance of the results. The lack of descriptions of side effects and the incomplete reporting on the coagulation therapy regimen in the included studies compromise the safety of the reported interventions.

5 | CONCLUSION

Several studies suggest that the ACSM criteria for healthy persons regarding RE may not be valid, as even low-intensity interventions appear to increase the strength of PwH, if the training is applied with sufficient frequency and duration. None of the studies reported bleeding caused by training. To ensure safety, training should be prescribed and supervised through a multidisciplinary team. The team should include haematologists/paediatricians who are responsible for factor replacement therapy and musculoskeletal specialists with experience in the field of haemophilia who should adapt the training individually according to how severely the joints are affected. Static, dynamic and isokinetic exercise can be part of a rehabilitation programme. Optimal types of exercise and optimal dosage (frequency, intensity and time) have yet to be determined. The results must be considered with caution due to quality issues of the included studies and the inability to pool the results because of heterogeneous study designs and outcome measures.

5.1 | Implications for future research

Future studies should aim to:

- improve the quality of future studies, for example by choosing an RCT study design that is based on a sample size calculation, performing a post hoc analysis or a correction for multiple testing.
- report on the effect size and an estimate of their precision such as the confidence interval to describe the clinical relevance of results rather than drawing conclusions based only on the statistical significance of the *P*-value.
- consistently report patient characteristics such as age, severity, presence of an inhibitor, joint status and factor therapy as these parameters affect the choice of training.
- continue to evaluate the safety of RE interventions (especially when training is applied to inhibitor patients, patients with severe haemophilia/joint affection, patients with limited factor supply and when training of higher intensity is performed).
- conduct future trials with homogenous outcome assessment (in order to allow future meta-analysis). For this purpose, it would be important to achieve an international consensus about the best way to measure strength performance on PwH.[2]
- provide sufficient details regarding the RE FITT criteria, as well as training progression and exercise adherence.
- evaluate the optimum type, frequency, intensity and duration of RE interventions for PwH. Thereby it is advisable to homogenize participants by age, disease severity and joint status.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias. The authors have no competing interests.

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