Exercise variables and pain threshold reporting for strength training protocols in people with haemophilia: A systematic review of clinical trials

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Abstract

Introduction: Although strength exercise is often prescribed for people with haemophilia (PWH), it remains unknown how exercise variables and pain thresholds are used to prescribe strength training in PWH.

Aim: To analyse how strength exercise variables and pain thresholds have been used to prescribe strength training in PWH.

Methods: A systematic search was conducted in PubMed, Embase, Web of Science, CENTRAL and CINAHL databases from inception to September 7, 2022. Studies whose intervention included strengthening training in adults with haemophilia were included. Two independent reviewers were involved in study selection, data extraction and risk of bias assessment.

Results: Eighteen studies were included. The least reported variables among the studies were: prophylactic factor coverage (11.1%), pain threshold/tolerability (5.6%), intensity (50%), total or partial range of motion (27.8%), time under tension (27.8%), attentional focus modality (0%), therapist experience in PWH (33.3%) and adherence assessment (50%). In contrast, weekly frequency (94.4%), duration (weeks) (100%), number of sets/repetitions (88.9%), repetitions to failure/not to failure (77.8%), types of contraction (77.8%), rest duration (55.6%), progression (55.6%), supervision (77.8%), exercise equipment (72.2%) and adverse event record (77.8%) had a higher percentage of reported (>50% of studies).

Conclusion: Future research on strength training for PWH should improve information on pain threshold and other important variables such as prophylactic factor coverage, intensity, range of motion, time under tension, attentional focus modality, therapist experience in PWH and adherence assessment. This could improve clinical practice and comparison of different protocols.

Keywords: Hemophilia, therapeutic exercises, pain, resistance, training

Introduction

In people with haemophilia (PWH) the musculoskeletal system is frequently affected due to repeated joint bleeds. Repeated intra-articular haemorrhages lead to irreversible change in the cartilage and bone tissue,[1] resulting in motor impairment (i.e., reduced muscle strength and exercise capacity) and pain.[2–4] A recent systematic review has reported that the prevalence the chronic pain in PWH is 46%,[5] which can interfere with daily activities and affect the quality of life.[6]

Although strength exercise is often prescribed for PWH, it remains unknown how individual pain thresholds and exercise variables are used to prescribe strength training in PWH. Strength training is usually prescribed for PWH to prevent joint disease, increase motor function and relieve pain.[7,8] With adequate prophylaxis of clotting factor concentrate, this type of exercise seems safe and effective for PWH.[8,9] Pain is a central issue in the lives of PWH, posing a significant challenge for clinicians and researchers.[5] In people with chronic pain (e.g., fibromyalgia), the perception of pain may interfere with exercise adherence and progression.[10] In addition, the perception of pain during exercise may limit the ability to apply maximal voluntary contraction torque and thus the underestimation of strength capacity by clinicians and patients.[11] Although strength training is known to be safe and beneficial for people with chronic pain.[7,8] The effect of strength exercises in which pain is allowed (e.g., using a threshold) compared with non-painful exercises on clinical outcomes in PWH is unknown. A systematic review in chronic musculoskeletal pain (e.g., low back pain, shoulder pain) reported that painful exercises offer a small but significant benefit compared with pain-free exercises in the short-term.[11] However, it is unknown whether

clinicians and researchers indicate painful exercise (threshold or tolerability), or pain-free exercises in PWH. Likewise, other exercise variables for strength training prescription are critical to increase adherence, induce neural and structural adaptations, and progress towards a more functional state.[12–14] However, variables for prescribing strength training are rarely described in full, making protocol comparison difficult[15] and, more importantly, hampering clinical practice. For instance, traditional reports of strength training protocols often describe intensity and number of repetitions or sets, but lack information on many others aspects, such as range of movement (ROM), time under tension, performing concentric- or eccentric-only or concentric–eccentric phase, rest between sets, and cognitive modality such as attentional focus, and whether the exercise is performed to failure.[15] Other variables such as exercise equipment, supervision during protocols and therapist experience in PWH are also important for adherence of exercise programs.[16]

The aim of this systematic review was to analyse how strength exercise variables and pain thresholds have been used to prescribe strength training in PWH. Knowledge of how research prescribes strength training may help clinicians and researchers for improving the quality of future research and clinical practice in PWH.

Methods

This systematic review was performed following the recommendations of the PRISMA 2020.[17] The protocol was previously registered in the PROSPERO (CRD42022304487) on February 18, 2022.

Inclusion and exclusion criteria

This review includes studies in English applying the PIOs (participants/population; intervention; outcome; study design) approach. Studies were included according to the following inclusion criteria; i) participants/population: studies with adults (+18 years) with a clinical diagnosis of haemophilia according to international guidelines (mild, moderate or severe haemophilia A or B); ii) intervention: studies including muscle strengthening exercises as part of a stand-alone intervention or as part of a combined programme with other exercise or rehabilitation modalities; iii) outcome: pain threshold and exercise variables used to prescribe strength training; iv) study design: randomised controlled trials (RCTs), controlled intervention studies and before and after (pre-post) studies. All editorials, letters, review articles, systematic reviews and meta-analyses, as well as in vivo and in vitro studies were excluded.

Information sources and search strategy

PubMed/MEDLINE, Embase, Web of Science, Cochrane Library and CINAHL databases were searched from inception to 7 September 2022 using the following terms: I) For the condition: hemophilia OR haemophilia OR haemophilic arthropathy; II) For the main intervention: resistance exercise OR strength exercise OR strength training OR resistance OR endurance exercise OR endurance training; III) For participants/population: adults OR elderly. The selected terms were combined using Boolean logical operators (OR, AND, NOT). In addition, a manual search of references included in previous systematic reviews was performed.[8,18] All references were analysed in Rayyan software (http://rayyan.qcri.org). Duplicate records were eliminated.

Selection process

First, the titles and abstracts of all articles were independently reviewed by two researchers (C.C-M and A.C-H) according to predefined eligibility criteria. Irrelevant references were removed and discrepancies were resolved by a third reviewer (R.N-C). The full-text articles were then independently reviewed for eligibility by two reviewers (R.N-C and A.C-H). Any discrepancies were resolved by consensus with a third reviewer (C.C-M).

Data collection process and data items

Data extraction was performed independently by two authors (R.NC., B.CA.) using a standardised extraction table. The following variables were collected for each study: author, year of publication, country, study design, number of participants, mean age, type of haemophilia, severity, hemostatic treatment regimen (prophylaxis/ on-demand), type of exercise, and the following eighteen exercise prescription variables according to international guidelines for the management of haemophilia,[9] the Consensus on Exercise Reporting Template (CERT),[16] and recommendations from previous studies[15]: i) prophylactic factor coverage, ii) pain threshold/tolerability; iii) frequency; iv) duration; v) intensity; vi) number of sets and repetitions; vii) repetitions to failure/not to failure; viii) full or partial ROM; ix) type of muscle contraction; x) time time under tension; xi) internal or external focus; xii) time of rest between sets; xiii) exercise progression; xiv) supervised or unsupervised; xv) exercise equipment; xvi) therapist experience in PWH; xvii) measurement of exercise adherence; xviii) assessment of adverse events. We established that adequate reporting of the variable was when it was reported in the majority of studies (i.e., >50%).

Study Risk of Bias Assessment

The risk of bias of the included studies was assessed with the Cochrane Risk of Bias (RoB) tool for RCTs and ROBINS-I for non-randomized clinical trials.[19] Studies were scored independently by two reviewers (R.N-C and A.C-H). Then, the score was compared and discrepancies were classified by a third reviewer (C.C-M).

Results

Study selection

A total of 478 potentially eligible records were identified through initial database searches. A total of 111 duplicate studies were then eliminated. After screening articles by title and abstract, 30 studies were potentially eligible for inclusion. Finally, full-text articles were retrieved and, after applying the eligibility criteria, 18 studies remained to be included in this systematic review (Figure 1).[20–37]

Study characteristics

The included articles were published between 2003 and 2022, of which 11 were RCTs, five Before-After studies and two non-randomized clinical trials. Of the total number of articles selected, 12 were from Europe, five from Asia and one from Oceania (Table 1). Only four studies evaluated the effect of isolated strength training,[27,33,34,37] while the rest of the interventions combined muscle strengthening with other modalities such as manual therapy,[24,26,31,32,35] balance training,[20,21,25] coordination and mobility,[23,28–30] flexibility,[25,26,31,32] psychological intervention[36] and aerobic exercise.[22]

Participants

In total, 561 PWH were enrolled in the included studies. In terms of severity, 68.5% had severe haemophilia, 28.1% had moderate haemophilia and 3.4% had mild haemophilia. Three studies did not report the level of severity. Sample size ranged from 9 to 64 participants, and mean age ranged from 24 ± 9 to 46.8 ± 4.4 years.

Hemostatic treatment

Most studies (15/18, 77.8%) reported the treatment regimen (prophylaxis or on-demand) of the enrolled patients. However, only 2/18 studies (11.1%)[34,35] reported information regarding whether exercise coincided with the day they received factor treatment (e.g., within 24 hours of prophylaxis administration).

Pain threshold or tolerability

None of the included studies reported the use of a specific pain threshold for the prescription of strength training. One study 1/18 (5.6 %) specified that exercise was performed within the limits of tolerated mobility and pain (Table 2).[35]

Other exercise variables

The exercise variables in the strength training protocols are presented in table 2. Weekly exercise frequency was reported by 17/18 (94.4%), which varied within protocols from once a week to 7 days a week. The duration of strength training was reported by 18/18 (100%), which ranged from 5 weeks to 12 months. Exercise intensity was reported in 9/18 (50%) of the studies. Four studies used repetition maximum (RM) to prescribe intensity and five used perceived exertion. The number of repetitions and sets per muscle was reported by 16/18 (88.9%) of the studies. A total of 14/18 (77.8%)

studies reported repetitions to failure/not to failure or this was deductible according to intensity. None of the studies prescribed exercise to failure. Five studies (27.8%) reported whether the strength training was performed with full or partial ROM (full ROM: three studies; partial ROM: two studies). The type of muscle contraction was reported or inferred in 14/18 (77.8%) studies. Most studies prescribed dynamic exercises (13/18), while five studies prescribed isometric exercises. Time under tension was reported in 5/18 (27.8%) of the studies, ranging from 1 to 20 seconds. None of the studies (0/18) detail the cognitive modality used to prescribe exercise, such as attentional focus (internal or external). Rest duration between sets was reported in 10/18 (55.6%) studies, which was generally 5-10 seconds between repetitions and 1 minute between each exercise. Regarding exercise progression, 10/18 (55.6%) studies performed progressive strength training, while the rest did not provide details. The supervision modality was reported in 14/18 (77.8%) studies. Ten studies performed supervised exercise, one unsupervised and three hybrids. Exercise equipment was reported in 13/18 (72.2%) studies. Five studies used elastic resistance bands, three studies used exercise machines and six studies used dumbbells, barbells, hydrobells or similar. Therapist experience in PWH was reported in 6 studies (33.3%). On the other hand, 50% of the studies reported the adherence assessments used (e.g., exercise diary, percentage of attendance, other), while the other half did not provide any information. Finally, regarding adverse events, 14/18 (77.8%) studies evaluated the frequency of bleeding during strength training. The rest of the studies did not report information.

Overall, these results indicate that 10/18 (56%) of the variables studied for strength exercise prescription in PWH are correctly described in the studies (i.e. >50% of studies report this) (Figure 2).

Study Risk of Bias Assessment

Eleven RCTs were assessed with the RoB tool. In the domain of random sequence generation, 7/11 (63.6%) studies had a low risk of bias and 4/11 (36.4%) had an uncertain risk of bias. In the domain of allocation concealment, 4/11(36.4%) studies had a low risk of bias and 7/11 (63.6%) had an unclear risk of bias. Five studies (45.5%) scored high risk in the domain of blinding of participants and personnel, while 1/11 (9.1%) studies had a low risk of bias and 5/11(45.5%) had an unclear risk of bias. Two studies (18.2%) had a high risk of bias in the outcome assessment domain, while 5/11(45.5%) studies had a low risk of bias and 4/11(36.4%) had an unclear risk of bias. Two studies (18.2%) had a high risk of bias due to incomplete outcome data, the remaining studies (9/11, 81.8%) had a low risk of bias. In the domain of selective reporting, 6/11 (54.5%) studies had a low risk of bias and 5/11 (45.5%) had an unclear risk of bias. Finally, none of the studies had a high risk of bias due to other sources of bias. Details of the risk of bias for each study are presented in Figure 3. Six studies were evaluated using the ROBINS-I tool. The results are presented in Table S1 (Supplementary Material).

Discussion

The present systematic review clearly shows that prophylactic factor coverage and the pain threshold is under-reported in the prescription of strength training in PWH, along with intensity, full or partial ROM, time under tension, attentional focus modality, therapist experience in PWH and adherence assessment. While the strength training

prescription variables such as weekly frequency, duration (weeks), number of repetitions, repetitions to failure/not to failure, types of contraction, rest duration between series, progression, supervision, exercise equipment and recording of adverse events were well reported across studies (i.e., >50 %).

Pain intensity during strength training

Only one study specified that exercise was performed within the limits of tolerability. In chronic musculoskeletal pain, painful exercises have been reported to offer a small but significant benefit over pain-free exercises in the short term.[11] Chronic musculoskeletal pain may does not correlate with the level of tissue damage, including in PWH.[38,39] Catastrophizing and fear avoidance behaviours may play an important role in pain responses and exercise tolerability.[40] However, literature on behavioural pain coping strategies and associated factors in PWH are still scarce and poorly understood.[41] Considering that the prevalence of the chronic pain in PWH is 46%,[5] future studies should consider reporting whether prescription is based on painful exercise (threshold or tolerability), or pain-free exercises in PWH, and the association of behavioural coping strategies with tolerability response to exercises modalities.

Others strength training prescription variables

Exercise intensity, full or partial ROM, time under tension, modalities of attentional focus, therapist experience in PWH and adherence assessment lacked information across studies in PWH. In a systematic review in healthy individuals, gains in 1RM (repetition maximum) strength were significantly greater with of high (>60% 1RM) - vs. low-intensity (≤60% 1RM) training, while no significant differences were found for isometric strength between conditions, and muscle hypertrophy.[42] However, in people

with arthropathy, such as knee osteoarthritis, there is insufficient evidence to determine the efficacy of high-intensity strength exercise over low-intensity strength exercise.[43] The ROM during strength exercise and time under tension may also play an important role in maximising muscle strength. Since ROM may be restricted in PWH, especially at the elbows, knees and ankles, studies should better report ROM during strength exercise (i.e., full or partial ROM). In this review, only five of the included studies that reported on this variable were identified. A systematic review in healthy individuals informed that full ROM is more effective than partial ROM in maximising muscle strength, muscle hypertrophy, and functional performance.[44] Time under tension may also be a relevant variable when clinicians prescribe strength exercises in PWH. This review identified that time under tension was reported in less than one-third of the included studies. Time under tension plays an important role in improving strength and muscle morphology in healthy individuals, where 6 s per repetition has been shown to produce the largest effect size among older adults.[45] However, it is unknown the efficacy of different strength training modalities in PWH. All of the above variables (exercise intensity, total or partial ROM, duration under stress) should be better described in future studies, as well as compared in strength programs to better understand the physiological and clinical effects of strength exercise on PWH.

Other variables, such cognitive attentional focus, were not reported in PWH. In healthy individual, the internal focus (also called mind-muscle connection) may increase muscle activity, especially at low-moderate intensities.[46] In addition, focusing on maximal contraction of a muscle group (e.g., internal focus) during strength exercise has been reported to be superior to increase muscle thickness than external focus (or simply moving the load during strength exercise).[47] In contrast, external focus or

297 distraction manoeuvres using dual tasks have been reported to improve muscular
298 endurance.[48–50] Future studies are needed to investigate the effects of these cognitive
299 variables on muscle strength and PWH functionality.
300 Weekly frequency, duration (weeks), number of repetitions and sets, repetitions to
301 failure/not to failure, contraction types and rest duration between sets were well
302 reported in all studies. In PWH the weekly frequency varied within protocols from once
303 a week to seven days a week and the duration of strength training was reported by
304 18/18 (100%), which ranged from 5 weeks to 12 months. In healthy adults, the weekly
305 frequency of resistance training has been reported to have no significant impact on
306 muscle hypertrophy when volume is matched.[51] In adults over 55 years of age, longer
307 duration training (>8 weeks) had a greater effect on strength gains compared to shorter
308 duration protocols.[52] Regarding the sets per muscles in PWH, sets per exercise group
309 vary between 1 and 3. Sets per exercise have also been shown to be relevant for
310 muscle hypertrophy, where 3-4 sets per exercise have been shown to be greater than
311 single-set training.[53] In PWH almost all studies do not reach task failure. In healthy
312 adults, it has been shown that repetitions to failure are not superior to repetitions below
313 not failure in muscle hypertrophy and muscle strength using equal exercise volume.[54]
314 The type of contraction and rest time between sets may also be relevant for clinical
315 outcomes. In our systematic review, the most frequently prescribed type of
316 strengthening exercise in PWH was dynamic exercise, while isometrics were
317 prescribed by a few studies. Isometric exercise may help in the early phases of
318 recovery from acute events in PWH. However, the main limitation of isometric exercise
319 is the intensity dosing. To control the intensity the, which is usually controlled by
320 subjective scales can be use (e.g. Borg).[55] The force and electromyography
321 biofeedback system are other ways for an effective pain control and for improving

quadriceps strength and function with isometrics after orthopaedic knee surgeries.[56] In PWH, electromyography biofeedback may be an alternative to prescribe and control the progression of strength during the isometric exercise programmes in PWH, in spite of its difficult applicability during clinical practice. Another important variable to consider during strength exercise prescription is rest between exercises, especially because it can affect exercise volume and intensity and thus, adaptations.[57] In PWH, the rest interval used in studies is usually 5-10 seconds between repetitions and 1 minute between sets. Rest intervals between sets of 3-5 minutes may be safer and more reliable. However, a short rest interval (30-60 seconds),[57] in combination with moderate intensity is usually recommended when the goal is muscle hypertrophy because of its greater acute effect on growth hormone levels than >3 minutes of rest.[57] The therapist experience was scarcely mentioned in the studies selected. Therapist experience, patient preferences, and education are also critical aspects to consider in clinical practice in PWH. If patients feel that the prescribed exercise is not acceptable or safe, clinical benefit or adherence to strength exercise may be limited.

Furthermore, assessment of adherence was under-reported in included studies. Recording exercise adherence through book events or digital systems, plus the inclusion of feedback (graphic, visual or verbal cues) on progression,[16] may help clinicians and researchers encourage PWH to complete programs and compare the adherence of different strength protocols in future studies.

All the above mentioned strength variables need to be further reported in order to be able to compare different exercise programmes in future systematic reviews and meta-analyses.

Recommendations for future studies and clinical practice in PWH

Only four studies evaluated the effect of isolated strength training [27,33,34,37] and thus most of the studies combined strength training with other modalities or treatments (e.g., manual therapy).[24,26,31,32,35] Understanding the physiological and functional effects of individual and combined strength variables may help to improve exercise protocols and maximise the effectiveness of strength training in PWH.

The perception of pain during exercise is relevant for the safety and adherence to strength exercises in PWH. While exercises are relevant for PWH, barriers remain regarding the perception of overall safety and effectiveness.[58] PWH may consider exercise therapy part of a pain management strategy if it is individualized.[58] The recommendation for musculoskeletal rehabilitation (e.g., osteoarthritis) is to use safety thresholds based on the visual analog scale (VAS).[16,59] Pain perception up to 2/10 is considered "safe" (green zone), pain up to a level of 5/10 is considered "acceptable" (yellow zone), and pain above 5/10 is considered "high risk" (red zone) (see figure 4).[16,59] Considering that there is no consensus on how pain perception during strength exercises should be used in PWH, the safety thresholds based on the VAS (0-10) may be an alternative for future studies and clinical practice. The pain-free or safe zone (VAS 0-2) may be helpful to prevent adverse events (joint and muscle bleeding), mainly in those PWH without access to prophylaxis treatment and severe haemophilia. The acceptable zone (VAS 3-5) may be individualised based on haemophilia severity (e.g., moderate and mild), access to prophylaxis treatment, joint damage severity, the experience of PWH with strength training and the experience of the therapist in haemophilia care. However, future studies are needed to find a consensus about selecting pain-free exercises or pain zones to prescribe strength training in PWH.

372 Another key issue in prescribing strength exercise in PWH is prophylactic factor
373 coverage during and after exercise, especially in those with a severe deficit in clotting
374 factor level (i.e., <1%). Information on how studies have prescribed factor replacement
375 (e.g., within 24 hours of exercise or 24-48 hours) may help future studies aimed at
376 restoring muscle strength in PWH. In our systematic review, only two studies [34,35]
377 reported whether exercise coincided with the day on which prophylactic treatment was
378 performed. It is relevant to take into account the weekly frequency of exercise in PWH,
379 especially due to the limitation of homeostatic coverage that is usually prescribed two
380 or three times per week. Adequate prophylactic treatment is essential to ensure a safe
381 exercise program and improve exercise adherence in PWH. In the included studies,
382 the assessment of adverse events during training was considered in most of the
383 studies (77.8%) and bleeding was only reported in isolated cases without major
384 complications. The recommendation is to encourage patients to inform the medical
385 and clinical team of adverse events (joint or muscle bleeding) in order to study possible
386 changes in training variables and/or prophylactic treatment. Future studies in PWH
387 need to improve information on the treatment regimen, especially how prophylaxis is
388 coordinated with the strength training day in PWH. Regarding supervision, this variable
389 was well reported among the studies, and the most common modality was supervised
390 exercise. Hybrid and unsupervised modalities are potential modalities to be included
391 in clinical practice. For example, home exercises and telerehabilitation was perceived
392 by PWH as a safe and effective intervention to improve physical condition.[31,60]
393 However, more literature is needed to know the effectiveness of supervised modalities.

394

395 Finally, we recommend a checklist of the variables considered in this systematic
396 review (Figure 5). This checklist may assist clinicians and researchers seeking to

develop programmes to improve muscle strength in PWH. We encourage clinicians and investigators to report strength exercise variables in future RCTs in PWH.

Limitations

The sample size of the included studies was relatively small. Additionally, most of the studies were at high or uncertain risk of bias in some of the domains assessed, with the most critical being allocation concealment, blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data. Also, we did not contact the authors of the studies to request additional information, we assumed that the information appearing in the studies on exercise protocols was reliable and our objective was to analyse compliance with the exercise variables as published.

Conclusion

Future research on strength training for PWH should improve information on pain threshold and other important variables such as prophylactic factor coverage, intensity, range of motion, time under tension, cognitive focus of attention and therapist experience in PWH and adherence assessment. These variables are relevant for improving muscle strength, structural adaptations and physical function. In contrast, strength training prescription variables such as weekly frequency, duration (weeks), number of repetitions, repetitions to failure/not to failure, types of contraction, rest duration between sets, supervision, exercise equipment and adverse event recording were reported to a greater extent in the included studies. However, all these variables should be further reported to improve clinical practice and comparison of different protocols in future systematic reviews and meta-analyses in PWH.

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

AUTHOR CONTRIBUTION

Concept and design: C.C-M, R.N-C, J.C; Writing: C.C-M, R.N-C, A.C-H, R.L-B, LL.A, G.M-R, S.P-A, J.C; Data analysis: C.C-M, R.N-C, A.C-H; Consultation: C.C-M, R.N-C, A.C-H, R.L-B, LL.A, G.M-R, S.P-A, J.C. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Legends

Figure 1. Study selection process.

Figure 2. Main results of the strength prescription variables among the included studies. The dashed black line indicates the 50% threshold value. Black bars indicate underreported strength prescription variables.

Figure 3. Risk of bias assessment.

Figure 4. Recommendation for safety thresholds based on the visual analog scale (VAS). Pain perception up to 2/10 is considered "safe" (green zone), pain up to a level of 5/10 is considered "acceptable" (yellow zone), and pain above 5/10 is considered "high risk" (red zone).

Figure 5. Exercise and pain threshold reporting checklist for strength training in PWH.

Table 1. Characteristics of the studies.

Author, year	Country	Design	n	Age (year)	Type of Haemophilia	Severity	Hemostatic treatment régimen	Prophylactic factor coverage	Strengthening exercise
Hilberg 2003	Germany	Before-After	9	32.4 ± 9.4	A: 9	Severe: 9	Prophylaxis: 9	NR	Specific muscle-strengthening programme
Hill 2010	Australia	Before-After	12	39.4 (95%CI: 33.7–45.1).	A: 11 B: 1	Severe: 9 Moderate: 2 Mild:1	NR	NR	Individualized balance and strength home exercise programme
Vallejo 2010	Spain	Before-After	13	32.27 ± 1.5	A: 13	Severe: 12 Moderate: 1	Inhibitors: 1 On-demand: 9 Prophylaxis: 4	NR	Aquatic muscular endurance and muscle strengthening exercises
Von Mackensen 2012	Germany	Prospective (non-randomized)	28	IG: 42.54 ± 13.5 CG 39.07 ± 12.3	A: 22 B: 6	NR	Prophylaxis: 8 On-demand: 19 Both: 1	NR	Specific aqua-training programme (strengthening exercises in the full range of motion)
Czepa 2013	Germany	Before-After	44	IG: 45±5 CG: 39 ± 11	A: 24 B: 1	Severe: 25	Prophylaxis: 12 On demand: 13	NR	Home training (muscle activation with elastic resistance exercises)
Goto 2014	Japan	RCT	32	IG: 41.8 ± 8.6 CG: 43.9 ±10.7	A: 26 B: 6	Severe: 27 Moderate: 5	Prophylaxis: 25 On demand: 7	NR	Home exercise program (knee extension strengthening, static stretching for the knee flexor muscles, and standing balance training)
Cuesta-Barriuso 2014	Spain	RCT	31	35.29 ± 2.877	A: 26 B: 5	Severe: 19 Moderate: 12	Prophylaxis: 17 On demand: 14	NR	Isometric and resisted exercises, in submaximal ranges, of dorsal and plantar flexion
Parhampour 2014	Iran	RCT	43	NR	A: 43	NR	Prophylaxis: 43	NR	Strength-training exercises consisted of hip flexion/ abduction/extension, knee extension, shoulder press, chest press, scapula retraction, leg press, back

									extension, and squat
Runkel 2016a	Germany	RCT	64	IG: 41.9 ± 10.6 CG: 40.3 ± 8.8	A: 57 B: 7	Severe: 59 Moderate: 5	Prophylaxis: IG: 92%, CG: 86% On demand: CG:7% Without specification: IG: 8%, CG: 7%	NR	Programmed sports therapy (supervised group therapy supplemented by individual training) with strength training equipment.
Runkel 2016b	Germany	RCT	64	IG: 41.9 ± 10.6 CG: 40.3 ± 8.8	A: 57 B: 7	Severe: 59 Moderate: 5	NR	NR	Programmed sports-specific therapy training (supervised group instruction supplemented by individual training at home)
Runkel 2017	Germany	Before-After	28	39.6 ± 9.0 to 41.9 ± 8.6	NR	NR	NR	NR	Specific training program in strength, coordination and endurance.
Cuesta-Barriuso 2017	Spain	RCT	20	30.95 ± 11.9	A: 14 B: 7	Severe: 10 Moderate: 4 Mild: 7	Prophylaxis: 7 On demand: 13	NR	Isometric exercises of quadriceps, hamstrings, biceps, triceps, and calves
Cuesta-Barriuso 2018	Spain	RCT	27	34.48 ± 12.99	A: 22 B: 5	Severe: 17 Mild: 10	Prophylaxis: 15 On demand: 12	NR	Isometric and isotonic exercises of elbow
Parhampour 2019	Iran	RCT	48	RT: 46.42 ± 4.68	A: 48	Moderate: 48	Prophylaxis: 48	NR	Core, upper limb and lower limb exercises. (knee ext-flex, calf raise, leg press, shoulder press, chest press and squat)
Calatayud 2020	Spain	RCT	20	IG: 36.3 ± 10.5 CG:39.1 ± 8.4	A:18 B:2	Severe: 17 Moderate: 1 Mild: 2	Prophylaxis: 17 On demand: 3	1 to 26 hours before each training session	Progressive Moderate-to-Vigorous Intensity Elastic Resistance Training
María García-Dasí 2021	Spain	Controlled trial study	19	IG: 45 ± 8.46 CG: 37.89 ± 13.31	A: 18 B: 1	Severe: 19	Prophylaxis: 19	NR	Resistance training with elastic bands

Tat 2021	Turkey	RCT pilot study	17	24 ±9	A: 15 B: 2	Severe: 16 Mild: 1	Prophylaxis: 16 On demand: 1	Interventions coincided with the day they received factor treatment (3 times per week).	Strengthening Exercises (with medium or mild resistance band)
Parhampour 2022	Iran	RCT	42	RT:46.79 ± 4.42	A: 42	Moderate: 42	Prophylaxis: 42	NR	Resistance training (Squat and leg press, shoulder and shoulder press, knee ext/knee flex and calf raise

Abbreviations: CG: control group, IG: interventional group, NR: not reported, RCT: Randomized controlled trials, RT: resistance training.

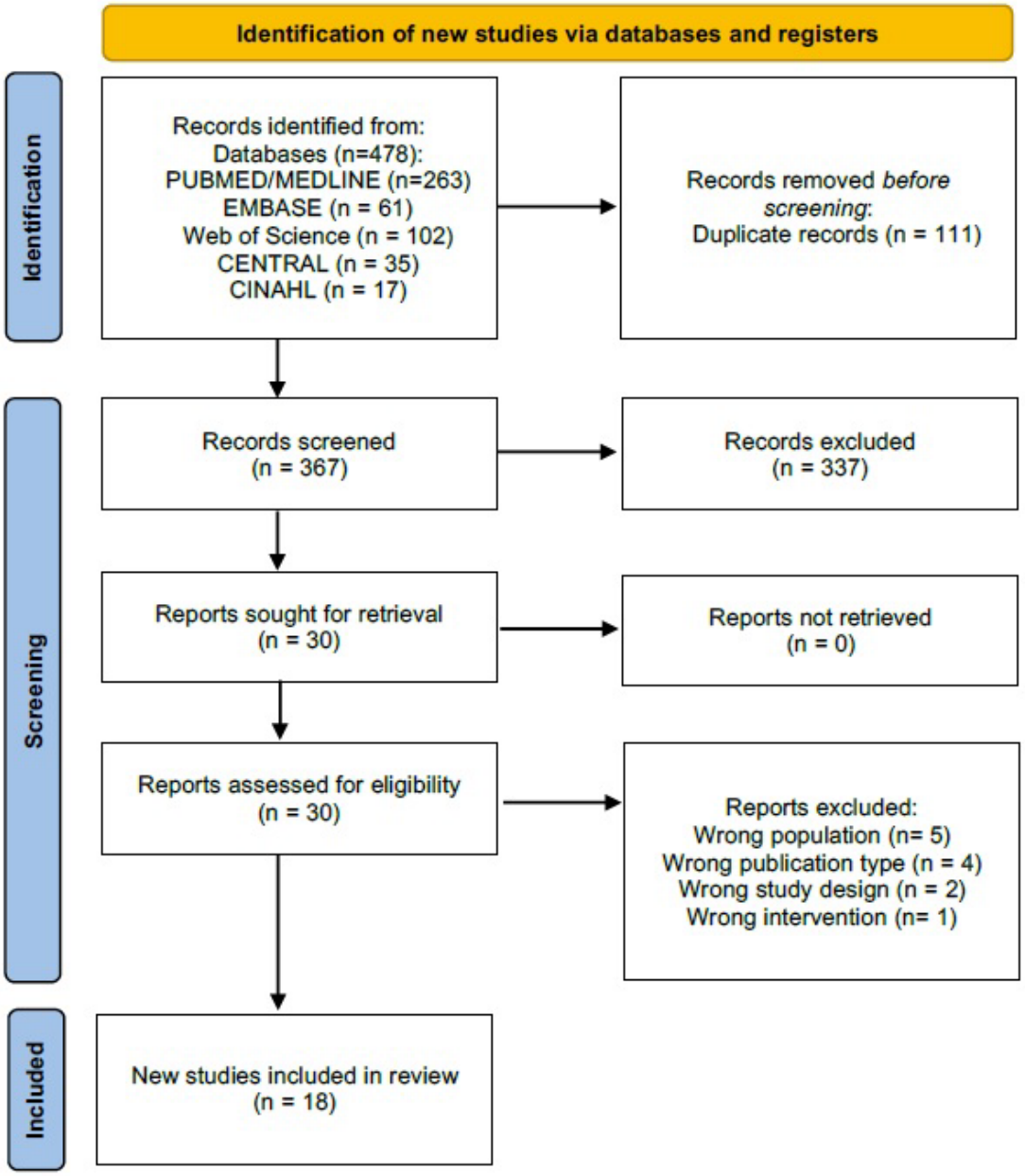
684 **Table 2. Exercise Variables in the strength exercise protocols**

Study	Tolerability or Pain threshold	Frequency	Duration	Intensity	Number of sets and repetitions	Repetitions to failure/not to failure	Full vs partial ROM	Type of muscle contraction	Tempo for each phase	Internal or external focus	Inter-set rest duration	Exercise progression	Supervised or unsupervised	Exercise equipment	Therapist experience in PWH	Adherence assessment	Adverse events record
Hilberg 2003	NR	Twice a week	6 months	NR	20–25 reps	Not to failure	NR	NR	NR	NR	NR	NR	NR	Elastic resistance band	NR	NR	Yes
Hill 2010	NR	5–7 days each week	4 months	NR	NR	NR	NR	NR	NR	NR	NR	NR	Hybrid	NR	NR	Exercise diary	Yes
Vallejo 2010	NR	3 days per week	9 weeks	Perceived exertion scale: 2-3 to 6-7	2 series of 20 reps	Not to failure	NR	Dynamic	NR	NR	Pause between series: 30 s	Yes	Supervised	Alter-gim, silicone, gloves/circles, circles/fist/hydrobells	NR	NR	Yes
Von Mackensen 2012	NR	Once a week	12 month	NR	≈ 20 reps	Not to failure	Full ROM	NR	NR	NR	NR	NR	Supervised	Aqua-dumbbells, pool-noodles and boards	NR	% of training units	Yes
Czepa 2013	NR	At least 2 times per week	1-year	NR	NR	Not to failure	NR	Isometric and dynamic	NR	NR	NR	NR	Supervised	Elastic resistance band	NR	Compliance with protoco	Yes
Goto 2014	NR	NR	8 weeks	NR	10 times per day.	NR	NR	Isometric and isotonic	NR	NR	NR	NR	Unsupervised	NR	NR	% of adherence	Yes
Cuesta-Barriuso 2014	NR	2 sessions per week	12 weeks	NR	20 reps	NR	NR	Isometric and isotonic	20 s	NR	10-s rest between each rep	NR	NR	NR	Yes	NR	Yes
Parhampour 2014	NR	3 days per week	6 weeks	50%-60% 1RM	10-15 reps	Not to failure	Partial ROM	Dynamic	NR	NR	10 s between reps, 1-2 minutes between muscle groups	Yes	Supervised	Free weights, dumbbells and halter	NR	NR	Yes
Runkel 2016a	NR	2 days per week	6-month	10–30% to 50-70% (rate of perceived exertion)	3 rates with 15 reps	Not to failure	NR	Dynamic	NR	NR	NR	Yes	Supervised	Exercise machine (leg press or cable pull).	Yes	Sign in attendance	Yes
Runkel 2016b	NR	2 days per week	6-month	10–30% to 50-70% (rate of perceived exertion)	3 rates with 15 reps	Not to failure	NR	Dynamic	NR	NR	NR	Yes	Supervised	Exercise machine (leg press or cable pull).	Yes	Sign in attendance	NR
Runkel 2017	NR	2 days per week	6-month	10–30% to 50-70% (rate of perceived exertion)	3 rates with 15 reps	Not to failure	NR	Dynamic	NR	NR	NR	Yes	Supervised	Exercise machine (leg press or cable pull).	Yes	NR	NR

Cuesta-Barriuso 2017	NR	6 days a week	15-week	NR	2 sets of 10 reps	Not to failure	NR	Isometric	20 s	NR	10-s rest between sets	NR	NR	NR	Yes	NR	NR
Cuesta-Barriuso 2018	NR	2 sessions weekly	12 weeks	NR	2 sets of 10 reps	NR	NR	Isometric and dynamic	20 s	NR	10-s rest between sets	NR	NR	NR	Yes	Daily register	Yes
Parhampour 2019	NR	3 days per week	6 weeks	65%-75% 1RM	10-12 reps	Not to failure	NR	Dynamic	NR	NR	10 s between reps, 1-2 minutes between muscle groups	Yes	Supervised	Free weights, dumbbells and halter	NR	NR	Yes
Calatayud 2020	NR	2 days per week	8 weeks	20RM and increased progressively toward 15, 12, and finally 10RM.	3 sets, 1 reps below muscle failure	Not to failure	Full ROM	Dynamic	Approximately 1 s	NR	1 min between sets and exercises	Yes	Supervised	Elastic resistance band	NR	% attendance	Yes
María García-Dasí 2021	NR	3 days per week	4 months.	Perceived exertion (level of 3–4)	3 sets of 10 reps each	Not to failure	Full ROM	Dynamic	NR	NR	1-minute rest intervals between each set	Yes	Hybrid	Elastic resistance band	NR	Exercise diary	NR
Tat 2021	"exercise within the limits of mobility and pain, slowly done"	3 days per week	5 weeks.	NR	10 reps, 1-2 times	Not to failure	NR	NR	10 sec of contraction	NR	5 sec intervals between each rep	Yes	Hybrid	Elastic resistance band	NR	NR	Yes
Parhampour 2022	NR	3 days per week	6 weeks	65%-75% 1RM	10-12 reps	Not to failure	Partial ROM	Dynamic	NR	NR	10-s between reps and a 1–2 min between two consecutive exercises	Yes	Supervised	Dumbbells, barbells and free weights	NR	NR	Yes

Abbreviations: NR, not reported; RM, repetition maximum; ROM, Range of motion.

Figura 1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Records excluded
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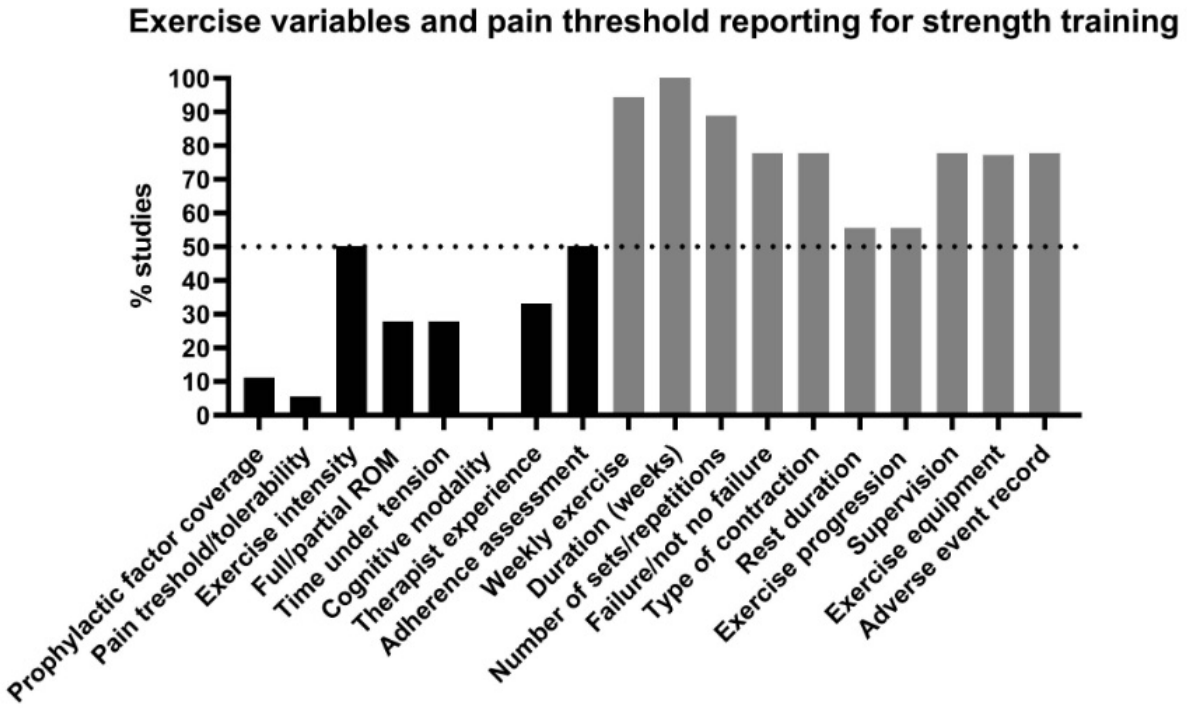
Figura 2


Exercise variables and pain threshold reporting for strength training
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80
70
60
50
40
30
20
10
0
Prophylactic factor coverage
Pain treshold/tolerability
Exercise intensity
Full/partial ROM
Time under tension
Cognitive modality
Therapist experience
Adherence assessment
Weekly exercise
Duration (weeks)
Number of sets/repetitions
Failure/not no failure
Type of contraction
Rest duration
Exercise progression
Supervision
Exercise equipment
Adverse event record

Figura 3

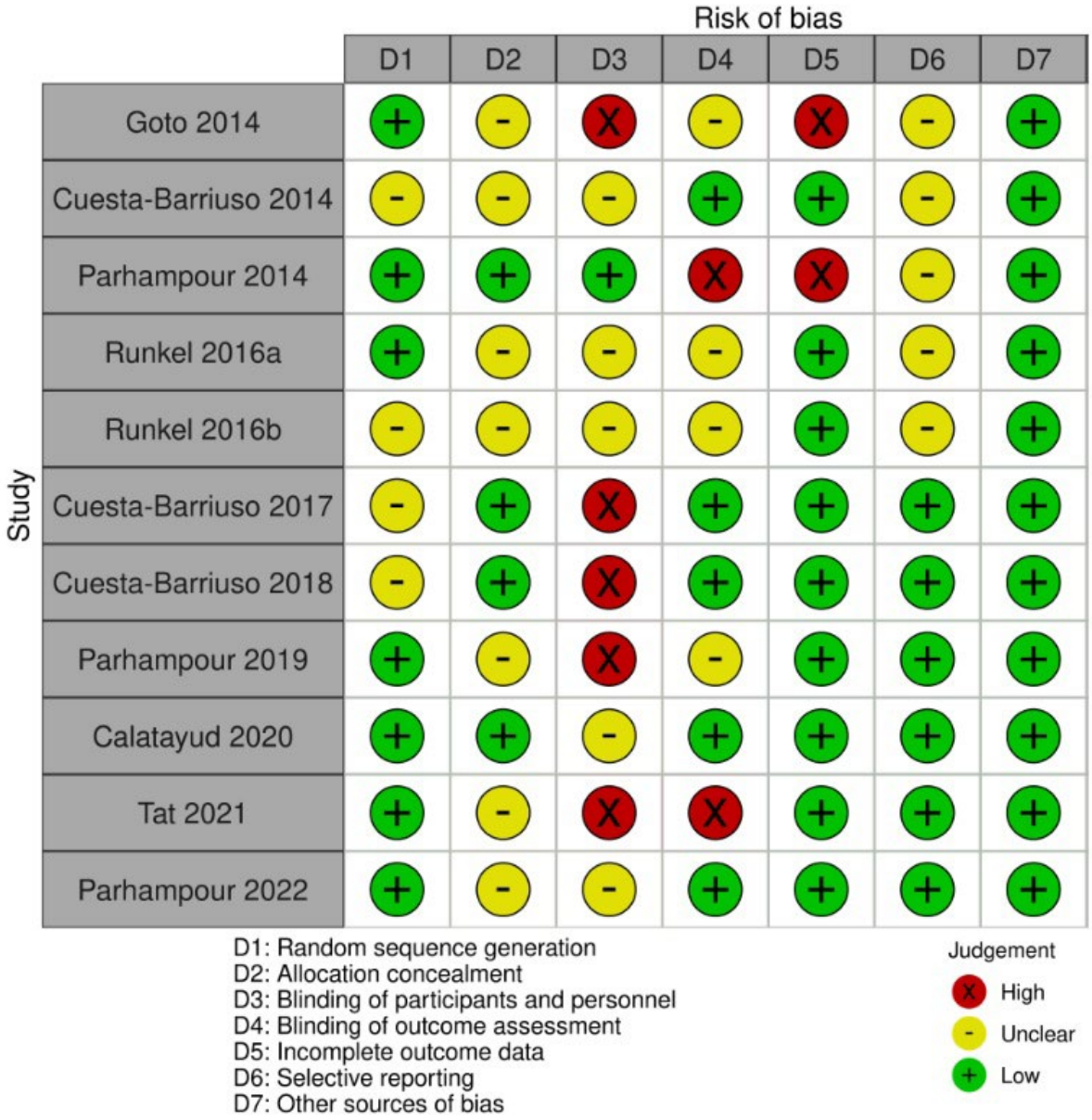
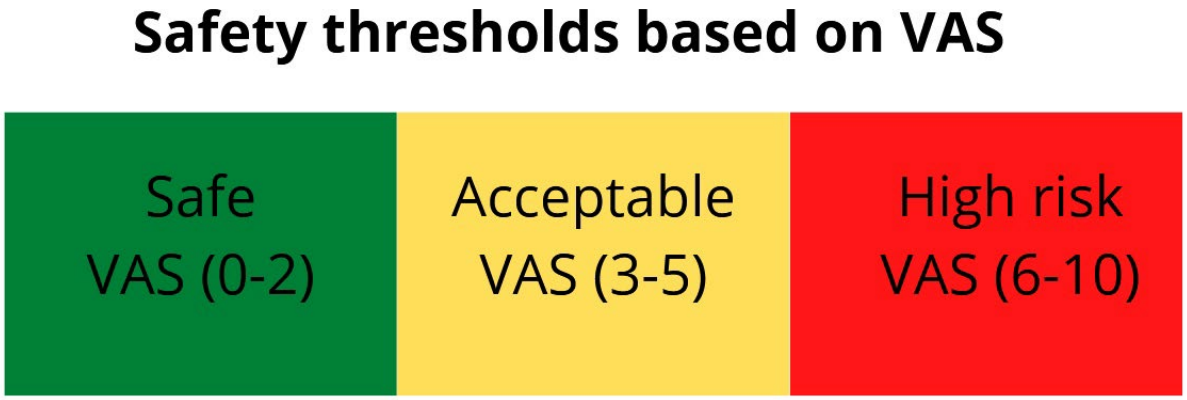

Risk of bias
D1
D2
D3
D4
D5
D6
D7
Study
Goto 2014
Cuesta-Barriuso 2014
Parhampour 2014
Runkel 2016a
Runkel 2016b
Cuesta-Barriuso 2017
Cuesta-Barriuso 2018
Parhampour 2019
Calatayud 2020
Tat 2021
Parhampour 2022
D1: Random sequence generation
D2: Allocation concealment
D3: Blinding of participants and personnel
D4: Blinding of outcome assessment
D5: Incomplete outcome data
D6: Selective reporting
D7: Other sources of bias
Judgement
High
Unclear
Low

Figura 4


Safety thresholds based on VAS
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Acceptable
VAS (3-5)
High risk
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