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INEQUITY IN EXERCISE-BASED INTERVENTIONS FOR ADULTS WITH RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: This systematic review described the extent to which PROGRESS-Plus equity factors were considered in the eligibility criteria of trials of exercise interventions for adults with rheumatoid arthritis.

Methods: Electronic databases were searched for published (Cinahl, Embase, Medline, Physiotherapy Evidence Database), unpublished (Opengrey) and registered ongoing (International Standard Randomised Controlled Trial Number registry) randomised controlled trials (RCTs) of exercise interventions for adults with rheumatoid arthritis. Two authors independently performed study selection and quality assessment (Cochrane Risk of Bias Tool).

Results: 9696 records were identified. Following screening 50 trials were included. All trials had either some concerns or high risk of bias and reported at least one PROGRESS-Plus equity factor within the eligibility criteria. This comprised place of residence, personal characteristics (age and disability), language, sex, social capital, time dependent factors or features of relationship factors. Where reported, this equated to exclusion of 457 of 1337 potential participants (34%) based on equity factors.

Conclusion: This review identified the exclusion of potential participants within exercise-based interventions for people with rheumatoid arthritis based on equity factors that may affect healthcare opportunities and outcomes. This will limit generalisability of results and yet this evidence is used to inform management and service design. Trials need to optimise participation in trials, particularly for people with cardiovascular conditions, older adults and cognitive impairments. Reasons for exclusions need to be justified. Further research needs to address health inequalities to improve treatment accessibility and generalisability of research findings. PROSPERO registration: CRD42021260941

KEY WORDS

Rheumatoid Arthritis, Systematic Review, Exercise, Equity factors,

KEY MESSAGES

- People with rheumatoid arthritis may not have equal opportunity to participate in exercise trials.
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- All included trials excluded potential participants based on at least one equity factor.
- Few studies justified the exclusion of potential participants based on equity factors.

PLAIN ENGLISH SUMMARY

This review summarises whether trials that investigated the effect of exercise programmes in people with rheumatoid arthritis included everyone with rheumatoid arthritis or whether some people were not invited to participate in exercise studies for reasons that could be considered unfair. These reasons are called equity factors and may be due to social, environmental or health related factors (e.g. where people live, their sex or disability level). We searched for and identified published and unpublished exercise trials and collected information on the criteria that researchers used to enrol people into their trials. We also collected details of the people enrolled onto the study and whether the results of the trials looked at the effect of exercise in different groups of people. We included 50 trials in our review. All trials did not enrol some people with rheumatoid arthritis due to at least one equity factor. The reasons were varied (e.g. where people lived, their age, level of disability, language or sex) and some of these reasons may be considered unjust. It is crucial that everyone can participate in exercise trials if they wish to because the findings of these trials are used to design treatments and healthcare services. If trials are not inclusive, then treatments and services may not be acceptable or accessible for everyone with rheumatoid arthritis.

INTRODUCTION

Access to healthcare is defined as the chance, or ease with, which individuals can use the services they need in proportion to their requirements[1]. Guidelines recommend that adults with rheumatoid arthritis have ongoing access to multidisciplinary team members for rehabilitation and advice. This includes support for and prescription of exercises to improve fitness, enhance range of movement, strength and maintain or restore function. However, access to exercise interventions is highly variable, in part due to social, environmental and/or health related factors[2]. Addressing systematic inequities in access to suitable services is a public health priority[3].

Healthcare services are commissioned based on evidence of clinical efficacy and cost utility, often from randomised controlled trials or systematic reviews of trials, with or without meta-analyses. However, only a small proportion of people with rheumatoid arthritis screened for eligibility are reported to take part in exercise trials[4]. It may be people with similar needs are not equally able to take part due to factors such as time or financial resources. On the other hand, it may be that some people with rheumatoid arthritis are not invited to participate in studies because they do not meet the eligibility criteria. Systematic exclusion of subgroups of people from trials may lead to the development of exercise interventions that are not suitable for everyone with rheumatoid arthritis. This may exacerbate inequities, particularly where those excluded from contributing to the evidence may bear a disproportionate disease burden and may differentially benefit from exercise.

Subgroups of people with rheumatoid arthritis may respond in a different way to exercise interventions due to differences in equity factors related to social, environmental, physiology or disease states. The PROGRESS-Plus guidance framework (place of residence, race/ethnicity, occupation, gender, religion, education, social capital, socioeconomic status and other factors such as personal characteristics (e.g. disability), features of relationships and time dependent relationships[5] helps summarise the factors that influence health opportunities and outcomes, such as the chance to participate in exercise interventions[3, 6]. Once subgroups have been identified, a failure to describe them in the baseline characteristics of trial participants or in trial subgroup analyses means clinicians and decision-makers lack evidence for appropriate management or service commissioning[7]. This may inadvertently perpetuate inequity of access to exercise interventions and health outcomes in adults with rheumatoid arthritis.

Therefore, the primary objective of this review was to describe the extent to which PROGRESS-Plus equity factors were considered in the eligibility criteria of trials of exercise interventions for adults with rheumatoid arthritis. Secondary objectives were to describe the extent to which equity factors were considered in baseline characteristics and sub-group analyses in trials of exercise interventions for people with rheumatoid arthritis.

METHOD

The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021260941)[8]. This review was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Equity extension[9].

Search Strategy

Electronic databases were searched from 1st January 2000 to 16th July 2021 for published (Cinahl, Embase, Medline, Physiotherapy Evidence Database, unpublished (Opengrey) and registered ongoing (International Standard Randomised Controlled Trial Number registry) randomised controlled trials (RCTs). The search strategy was based on previously published terms for the population (rheumatoid arthritis), intervention (exercise) and study design (RCTs)[10, 11] (Supplementary File 1).

Eligibility Criteria

This systematic review included RCTs of adults (aged 18 years and older) with an established classification criterion of rheumatoid arthritis [12-14]. Exercise interventions were defined as a “supervised and/or unsupervised programme conducted in an inpatient, outpatient, community, or home-based setting, including any type of exercise training”[15]. Multimodal interventions (e.g., exercise and diet) were also included. Eligible study designs included pilot, feasibility or full RCTs. Trials were included irrespective of comparator group or outcome. Non-randomised controlled studies and randomised controlled trials published before 1st January 2000 were excluded so that contemporary management of rheumatoid arthritis was captured[16].

Study Selection

Records were exported and de-duplicated in Endnote[17] prior to importing to Covidence for screening[18]. Disagreements were resolved by a third reviewer. Two of three reviewers independently screened titles, abstracts and full texts based on the eligibility criteria (NJ, PR, NiJ). A third reviewer (LB or KS) arbitrated, if necessary.

Data Extraction

Data from included RCTs was extracted by one of three reviewers (NJ, PR, NiJ) into a template modified from published extraction templates[19, 20]. Data was checked for accuracy by a third reviewer (LB). Data included author, year, location, total sample size, eligibility criteria, population, intervention, control, primary and secondary outcome measures, intervention effectiveness for primary outcome and PROGRESS-Plus factors reported in eligibility criteria, baseline characteristics, and subgroup analysis. Where available, the number of potential participants excluded based on PROGRESS-Plus factors and justification for exclusion based on PROGRESS-Plus were also extracted.

Quality Assessment

Quality was assessed using the Cochrane Risk of Bias Tool version 2 which enables reviewers to identify bias arising from the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and overall bias. Quality assessment was piloted by three reviewers (NJ, PR, NiJ) for three RCTs. Uncertainties were resolved by consensus. The remaining RCTs were assessed by one of the three reviewers and checked for accuracy by a fourth reviewer (LB).

Data Synthesis

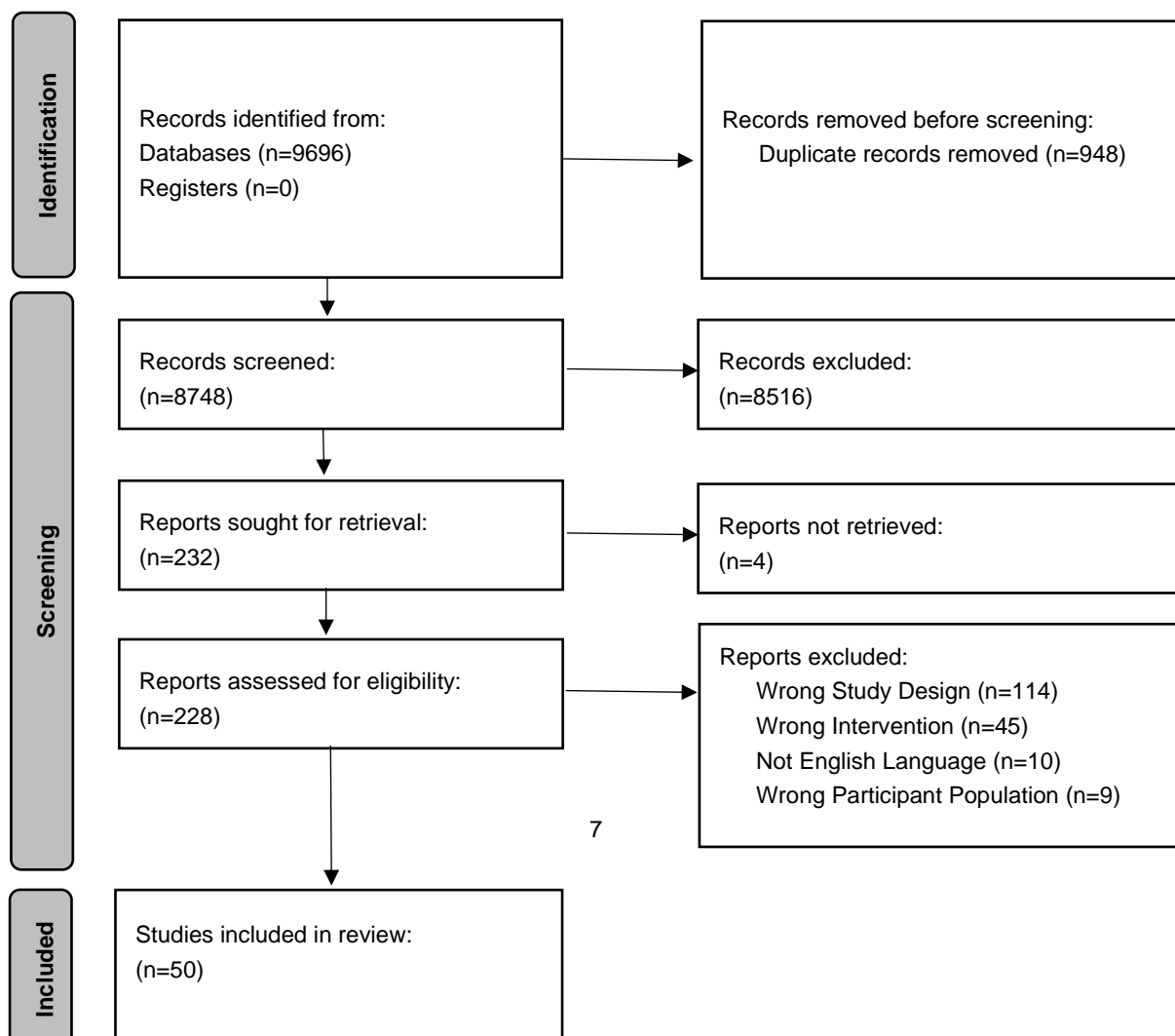
Trial characteristics were summarised descriptively. Counts and proportions were used to summarise study characteristics and the extent to PROGRESS-Plus factors were considered in 1) eligibility criteria, 2) baseline characteristics and 3) subgroup analyses in text, tables and figures. Justifications for exclusion criteria based on PROGRESS-Plus factors were summarised in text, if reported.

RESULTS

Study Selection

In total 8,748 records were identified after de-duplication. A total of 228 full texts were screened. Fifty studies met the eligibility criteria and were included in this systematic review (Figure 1).

Figure 1 Flow diagram for a systematic review of equity factors in randomized controlled trials of exercise interventions for adults with rheumatoid arthritis.



Study Characteristics

Overall, this review included 48 full trials[21-68], one feasibility trial[69] and one pilot trial[70]. A total of 4,382 participants were included (sample size ranged from 20[66] to 490[46] participants). Participant ages ranged from 18[27, 32, 33, 36, 38, 45, 55, 67, 70] to 87 years[22]. The majority of participants were female (n=3,431)[21-70].

Interventions included strengthening exercise (n= 26)[21, 23-25, 27, 30, 31, 35, 36, 38, 42, 43, 45-48, 50, 51, 54, 55, 58, 59, 61, 63, 64, 68], aerobic exercise (n= 17)[21, 23-25, 27, 29, 36, 38, 44, 45, 47, 55, 59, 61, 63, 64, 68], flexibility exercises (n=10)[25, 30, 31, 35, 36, 46, 51, 54, 63, 64], yoga (n=8)[37, 39-41, 52, 56, 62, 67], walking (n=5)[30, 36, 57, 69, 70], hydrotherapy (n=4)[26, 27, 33, 60], proprioception (n=3)[25, 28, 51], tai chi (n=1)[66] and non-specified exercise-based interventions (n=6)[22, 32, 34, 49, 53, 65]. Comparators included usual care (n=22)[22, 27-29, 32, 34, 36-41, 45, 46, 50, 52, 53, 57, 58, 62, 64, 68], an alternative exercise intervention (n=18)[21, 25, 26, 31, 33, 35, 42-44, 47-49, 51, 59-61, 63, 67], education and advice (n=10)[23, 24, 30, 54-56, 65, 66, 69, 70], or diet (n=2)[38, 55].

Quality Appraisal

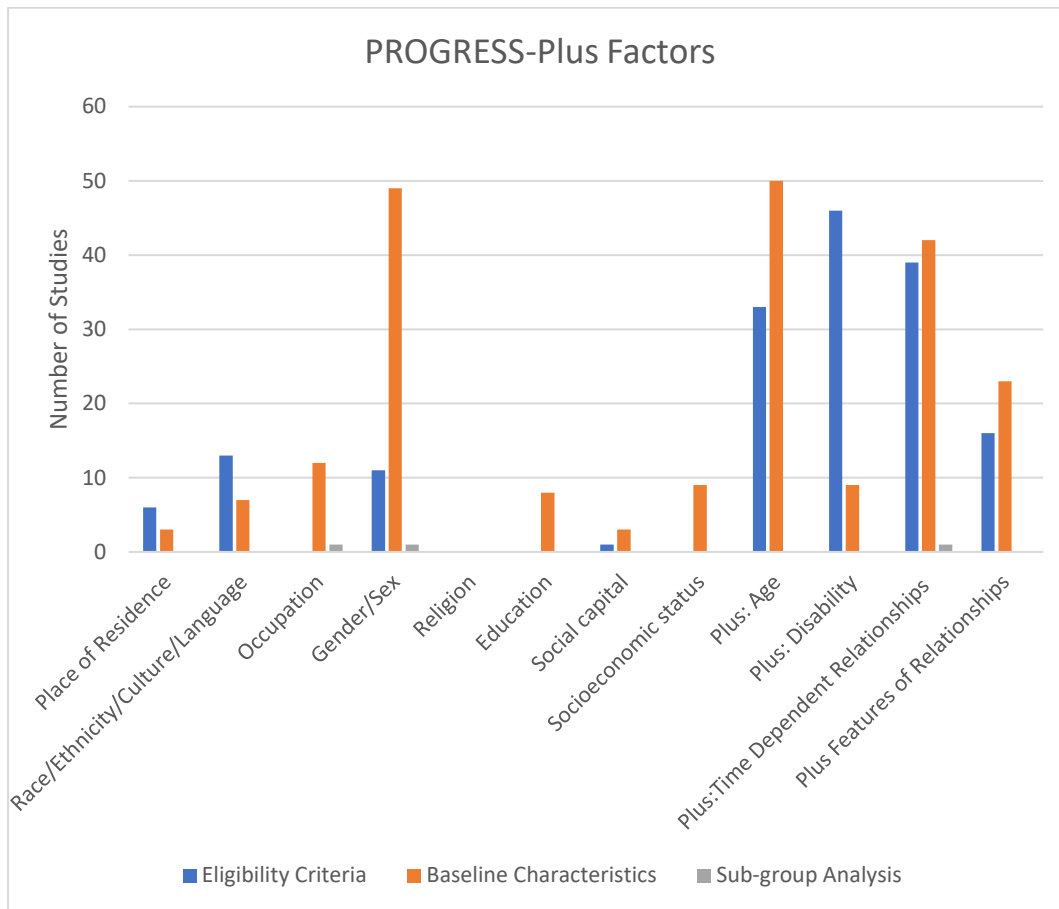
Thirty-five studies were considered to be at high risk of bias[21-24, 26, 29, 31, 34-43, 45, 48, 49, 51-53, 55, 57-61, 63-67, 69]. The most common reason for high bias assignment was the selection of the reported results (n=17)[22, 26, 29, 31, 35-43, 48, 49, 53, 69]. Fifteen studies had an overall judgement of some concerns[25, 27, 28, 30, 32, 33, 44, 46, 47, 50, 54, 56, 62, 68, 70] and no studies were deemed low risk of bias (Supplementary File 2).

Synthesis

Eligibility criteria

At least one PROGRESS-PLUS factor contributed to eligibility criteria in all 50 studies (Figure 2, Table 1 and 2). PROGRESS-Plus factors reported in the eligibility criteria included: place of residence (n=6)[21, 22, 30, 43, 53, 59], race/ethnicity/culture/language (n=13)[21, 24, 30-34, 47, 50, 59, 66, 67, 69], gender/sex (n=11)[22, 31, 38, 55, 57, 58, 60, 64, 65, 67, 68], social capital (n=1) [57], plus factor age (n=33%)[21, 23, 24, 26-29, 31-41, 44, 47, 50-52, 55-58, 60-62, 64-66], plus factor disability (n=46)[21-31, 33-41, 44-48, 50-70], plus factor time dependent (n=39)[21, 23, 25, 26, 28, 31, 33-42, 44-49, 51, 52, 54-60, 62-64, 66-70], plus factor features of relationship (n=16)[29, 35, 37-42, 48, 55-57, 59, 60, 62, 64]. Occupation, religion, education and socioeconomic status did not contribute to eligibility criteria.

Figure 2 Reporting of PROGRESS-Plus factors in eligibility criteria, baseline characteristics, and sub-group and sub-group analysis



Justification for eligibility criteria

Nineteen studies included justification for at least one eligibility criteria[21-23, 30, 33, 38, 39, 44, 47, 50, 53, 55, 57, 58, 60-62, 68, 69]. One trial excluded potential participants based on language due to the financial costs of a translator[69]. One trial excluded participants due to the potential influence that sex[55] may have on the outcome measure. Three studies provided justification for excluding participants due to age[21, 57, 58].

Fourteen studies excluded participants based on disability. Where provided, the justification for excluding people with disabilities were: unable to participate in the intervention due to safety (e.g. contraindication, infection control, cognitive impairment) (n=10)[21-23, 33, 47, 50, 58, 60, 61, 69], unable to complete an outcome measurement (n=1) [44] and participants' comorbidities may influence the results (n=3)[39, 62, 68]. Five studies provided justification details on why participants were excluded based on type of medication[33, 38, 57, 62, 68].

Potential participant exclusion counts and proportions

Seven studies provided counts of potential participants excluded[29, 30, 52, 55, 59, 60, 67] . Two studies excluded 243 out of 791 potential participants because they lived outside the catchment area[30, 59].

Of the 46 studies[21-31, 33-41, 44-48, 50-70]which excluded participants due to disability (Table 2), only five studies[52, 55, 59, 60, 67] provided counts of potential participants: 3 out of 103 potential participants were excluded because they required assistive devices[52], 3 out of 133 potential participants were excluded due to cognitive/visual impairments and 5 out of 133 potential participants were excluded because they used limb prosthetics[60]. Eleven out of 233 potential participants were excluded due to the severity of their disability (Steinbocker functional class IV), 39 out of 233 potential participants were excluded due to the presence of other autoimmune diseases and 28 out of 233 due to contraindications to exercise[55]. Two studies excluded 18 out of 310 potential participants due to acute/chronic comorbidities[55, 67], one study excluded 2 out of 391 potential participants due to hospitalisation[59], one study excluded 10 participants out of 281 due to malignancy, intestinal perforation, manic episode and substance abuse[29]. Two studies excluded 26 out of 414 potential participants due to cardiovascular conditions[29, 60]. Three studies reported exclusion of 9 out of 571 potential participants due to recent/planned surgery[52, 59, 67]. One study reported exclusion of 21 out of 391 potential participants due to drug treatment[59]. One study excluded 11 out of 103 potential participants because they were already taking part in regular exercise[52] and one study excluded 17 out of 77 potential participants due to sleep and pain issues[67]. One study excluded 11 out of 233 potential participants due to medication[55].

Baseline characteristics

At least one PROGRESS-PLUS factor was reported in the baseline participant in all 50 studies (Figure 2, Table 1 and 2). Religion was the only PROGRESS-PLUS factor not reported.

Sub-group analysis

PROGRESS-Plus factors were investigated in subgroup analyses in three trials[21, 43, 46]. One study reported a differential effect of exercise on inflammatory markers based on sex (females versus males). In this trial females had reduced inflammatory markers compared to males following the exercise intervention[21]. Another study reported no difference in hand function following an exercise intervention between participants with <5years compared to ≥5years disease duration (years/months) or various baseline drug regimens[46]. One study reported that functional capacity and disability were greater following exercise in employed participants compared to participants who retired preterm during follow up[43].

DISCUSSION

This systematic review described the extent to which equity factors were considered within the eligibility criteria, baseline characteristics and subgroup analysis of RCTs evaluating the efficacy of exercise-based interventions for people with rheumatoid arthritis. All included trials had either some concerns or high risk of bias and reported at least one PROGRESS-Plus equity factor within the eligibility criteria and baseline characteristics. These included place of residence, personal characteristics (age and disability), language, sex, social capital, time dependent factors and features of relationship factors. No studies excluded participants due to occupation, religion, education, and socioeconomic status. When reported, a total of 457 from 1337 potential participants (34.2%) were excluded based on an equity factor. Of the 457 participants excluded: 243 were due to place of residence, 162 due to disability factors, 32 due to features of relationships and 20 due to time-dependent factors.

Eligibility criteria are often not justified in published manuscripts due to word limits. The rationale for excluding adults with rheumatoid arthritis from participating in exercise-based interventions is often unclear. It may be that exclusions are due to perceived (i) perceived potential for benefit, (ii) target population or (iii) feasibility of participation.

Perceived Potential for Benefit

In this review, 46 studies (92%) excluded potential participants based on disability or co-morbidities, particularly cardiovascular conditions. Some studies excluded people with uncontrolled cardiovascular conditions such as unstable hypertension, presence of cardiac conditions (e.g. angina, arrhythmia) and recent myocardial infarctions. Excluding potential participants based on unstable or acute cardiovascular conditions may be appropriate due to the potential for harm. However, other trials excluded participants with common long-term or stable cardiovascular conditions such as hypertension and chronic heart failure. Whilst justification for these exclusions were seldom provided, they may be related to an increased risk of myocardial infarction or coronary death for adults with rheumatoid arthritis when compared to the general population[71].

The prevalence of cardiovascular events in people with rheumatoid arthritis is declining due to advancements in drug therapy[72] and there is evidence that demonstrates the benefits of exercise for individuals with stable cardiovascular disease and other co morbidities[73, 74]. Consequently, exclusions based on the increased risk of adverse events in people with stable cardiovascular disease may be unjustified, and inequitable. From the current review, Lange *et al.* (2019) examined the effects of a 20-week personalised moderate-to-high intensity aerobic and resistance programme compared to a low-intensity home exercise programme in older adults (65 years-old) with rheumatoid arthritis. This study appropriately excluded people with unstable cardiovascular conditions (unstable ischaemic heart disease, arrhythmia) which may preclude participation in moderate-intensity exercises but included participants with stable cardiovascular conditions[47]. The only adverse events reported were due to generalised pain which resolved after reducing exercise for one week. No cardiac-related adverse events occurred, and participants exhibited greater aerobic capacity, muscle strength and endurance[47]. This highlights that older adults with stable cardiovascular conditions and

rheumatoid arthritis have potential to benefit from participation in exercise programmes, including interventions being investigated in trials, if given the opportunity. Carefully prescribed and monitored exercise interventions are safe in people with rheumatoid arthritis and so exclusion based on exercise safety should be minimised, where possible or justification for exclusions provided.

Target Population

Age

Trials of exercise-based interventions define homogenous populations to reduce variance and the sample size needed. For example, in the trials included in this review, the majority of participants were middle-aged and nearly half of the RCTs excluded older adults above the age of 60 years. Some trial designs specifically recruited a target population defined by age or life stage such as pre-menopausal women[57] or post-menopausal women[44] to answer their research question. Focussing on these subgroup may be justified because the peak age of rheumatoid arthritis onset is middle age[75] and identifying appropriate management in this population may minimise disability, healthcare costs and work absence[76, 77]. Where the research does not target a specific age group, excluding older adults may not be justified and people of all ages should be included so that the findings can be generalised to everyone with rheumatoid arthritis.

Late-onset disease

It is important to include older people with rheumatoid arthritis in exercise trials because large joint disease contributes to substantial disability in people with late-onset rheumatoid arthritis[78]. Identifying effective exercise interventions in this subgroup of people with rheumatoid arthritis is crucial to optimise management. Interestingly, some trials performed more recently addressed this challenge and included only older adults[21, 22, 47]. For example, Anvar *et al.*, (2018) included female participants aged 60-87 years old, while Andersson *et al.*, (2020) included participants above the age of 65 years old[21, 22]. Exercise in these older adults with rheumatoid arthritis were found to be safe[21, 22, 47], improved aerobic capacity[21], muscle strength[21], inflammatory markers[21] and self-efficacy[22]. Furthermore, older adults with rheumatoid arthritis who participated in moderate-to-high intensity exercise programmes maintained significantly higher physical activity levels at 12 months compared to age-matched population who participated in a home-based low-intensity exercise programme[47]. As physical activity levels tend to be low in older adults and people with rheumatoid arthritis[79], exercise interventions could provide a wide range of health benefits amongst older adults with rheumatoid arthritis. Indeed, trial designs should optimise accessibility and acceptability to maximise participation and ensure potential health benefits of exercise are available to everyone.

Feasibility of Participation

Language

Another potential reason for excluding people from trials may be the feasibility of participation. In the current review, participants were excluded because they could not speak the native language and there was the potential for misunderstanding the trial processes and non-adherence to the intervention[21, 33]. There was a lack of funding for translators and alternative solutions to facilitate the inclusion of non-native language speakers were not considered. Researchers should maximise participation by providing translators where possible. However, these options may not be available and eligibility may be limited to meet time and funding restrictions. As randomised controlled trials are often publicly funded, if time and funding constraints limit the generalisability of a trial, the potential cost-benefit of conducting the trial at all should be questioned.

Cognitive Impairment

In this review, RCTs excluded participants with cognitive impairment due to concerns regarding capacity to consent and their ability to effectively participate in the study[21-23, 33, 47, 50, 58, 60, 61, 70]. However, people with mild cognitive impairments (including dementia) can adhere to strengthening and endurance-based exercise-based with appropriate adaptations[80]. The RCTs within this review did not specify the level of cognitive impairment that resulted in exclusion and did not provide solutions to overcome this exclusion such as using carers, memory books or adapting intervention delivery. Consequently, these vulnerable populations were denied access to exercise trials that may improve their health outcomes.

The Marmot Report (2010) recommended the use of health equity filters within health-based research and guidelines to identify avoidable health inequities[6]. More recently, the National Institute for Health Research (2020) published guidance to address the inclusion of underrepresented groups, such as non-native language speakers or cognitive impairment, within clinical research[81]. Systematically excluding those who are likely to incur the greatest healthcare costs will fail to generate the health economic evidence base required to change healthcare funding for these individuals. Collaborative decision making between researchers and key stakeholders throughout the research process may also help to identify inequitable practice and feasible solutions to facilitate participation from under-served groups [81].

Methodological Considerations

Firstly, to our knowledge, this was the first systematic review that used an established health equity framework to identify potential inequity within exercise-based trials for people with rheumatoid arthritis. Secondly, the protocol for this study was registered on PROSPERO to ensure transparency of our objectives and review methods. Thirdly, the search strategy included published, unpublished and ongoing trials. Finally, screening, selection, and quality appraisal were completed in duplicate. However, data extraction was completed by one

reviewer and checked for accuracy by a second reviewer; this may have led to some errors in extraction. Further, trials not published in English language and those published prior to 2000 were excluded which may have led to the exclusion of potentially relevant RCTs and an underestimation of the extent to which equity factors were considered by RCTs of exercise interventions for adults with rheumatoid arthritis.

CONCLUSION

This review identified the exclusion of potential participants within exercise-based interventions for people with rheumatoid arthritis based on equity factors that may affect healthcare opportunities and outcomes. It is crucial that participation in exercise-based trials are optimised as this evidence is used to inform management and service design. Where exclusion criteria are applied, an evidence-informed justification or reasons that participation could not be supported should be stated. All people with rheumatoid arthritis should be offered an equitable opportunity to improve their health, including participating in research design and delivery, where possible.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest

Table 1 - PROGRESS-Plus factors reported in eligibility criteria, baseline characteristics and subgroup analysis

	Eligibility Criteria	Baseline characteristics	Subgroup Analysis
	n (%)		
PROGRESS			
Place of Residence	6 (12%) ^[21, 22, 30, 43, 53, 59]	3 (6%) ^[57, 59, 67]	
Race/Ethnicity/Culture/Language	13 (26%) ^[21, 24, 30-34, 47, 50, 59, 66, 67, 69]	7 (14%) ^[44, 46, 50, 52, 66-68]	
Occupation		12 (24%) ^[22, 23, 26, 34, 43, 45, 46, 50, 53, 57, 67, 70]	1 (2%) ^[43]
Gender/Sex	11 (22%) ^[22, 31, 38, 55, 57, 58, 60, 64, 65, 67, 68]	49 (98%) ^[21-24, 26-70]	1 (2%) ^[21]
Religion			
Education		8 (16%) ^[22-24, 45, 52, 57, 67, 70]	
Social capital	1 (2%) ^[57]	3 (6%) ^[45, 49, 62]	
Socioeconomic status		9 (18%) ^[22, 23, 26, 34, 39, 47, 49, 62, 63]	
Plus: Personal Characteristics			
Age	33 (66%) ^[21, 23, 24, 26-29, 31-41, 44, 47, 50-52, 55-58, 60-62, 64-66]	50 (100%) ^[21-70]	
Disability	46 (92%) ^[21-31, 33-41, 44-48, 50-70]	9 (18%) ^[21, 23, 38, 47, 55, 58, 59, 63, 65]	
Plus: Time-dependent Relationships			
Disease Duration (years/ months)	10 (20%) ^[21, 25, 26, 34, 35, 37, 42, 47, 59, 69]	42 (84%) ^[21, 23, 24, 26-36, 38, 40-54, 56-58, 60, 61, 63-69]	1 (2%) ^[46]
Previous/ Upcoming Surgery/ joint injection	21 (42%) ^[21, 23, 31, 33, 35, 39-41, 44, 45, 47, 48, 51, 52, 54, 56, 59, 60, 62, 67, 68]		
Duration of medication	12 (24%) ^[23, 26, 31, 33-36, 45, 46, 54, 58, 68]	1 (2%) ^[36]	1 (2%) ^[46]

Current Exercise Participation	21 (42%) ^[28, 33, 36-40, 45, 47-49, 52, 55-57, 59, 62-64, 66, 70]	2 (4%) ^[44, 67]	
Plus: Features of Relationships			
Type of Medication/Supplements	15 (30%) ^[35, 37-42, 48, 55-57, 59, 60, 62, 64]	23 (46%) ^[21, 23, 26, 27, 29, 30, 32, 33, 35, 38, 42, 44, 46, 47, 49, 56, 58, 60, 63, 66-68, 70]	
Living alone	1 (2%) ^[29]		

Table 2 - PROGRESS-Plus disability factors reported within the eligibility criteria, baseline characteristics and sub-group analysis.

Disability Factor	Eligibility Criteria	Baseline Characteristics
	n (%)	
Smoking Status	1 (2%) ^[64]	8 (16%) ^[21, 23, 30, 42, 47, 58, 59, 63]
History of Alcoholism or Drug Abuse	1 (2%) ^[37]	
Contraindications to Exercise	13 (26%) ^[23, 26, 27, 31, 33, 38, 41, 48, 51, 60, 65, 68, 69]	
Mobility Limitations	10 (20%) ^[23, 28, 30, 31, 35, 52, 55, 56, 60, 70]	
Auditory or Visual Deficits	1 (2%) ^[60]	
Poor Skin Integrity	1 (2%) ^[60]	
Frailty	1 (2%) ^[22]	
Falls Risk	1 (2%) ^[30]	
Incontinence	2 (4%) ^[33, 60]	
Rheumatoid Arthritis Disease Severity	4 (8%) ^[27, 45, 58, 70]	
Limb loss	3 (6%) ^[29, 53, 60]	
Pregnancy	2 (4%) ^[23, 33]	
Co-morbidities		
Cardiovascular Conditions - total	39 (78%)	10 (26%)
-Chronic/Congestive Heart Failure	4 (8%) ^[30, 38, 55, 56]	
-Cardiac Arrhythmia	3 (6%) ^[21, 28, 61]	
-Myocardial Infarction	3 (6%) ^[23, 59, 61]	
-Ischemic Heart Disease	3 (6%) ^[28, 47, 56]	

-Thoracic/Chest Pain	3 (6%) ^[28, 30, 59]	
-Cardiovascular Disease	9 (18%) ^[21, 36, 44, 53, 58, 63, 64, 66, 68]	3 (6%) ^[21, 47, 65]
-Circulatory Problems	1 (2%) ^[60]	
-Cardiovascular Risk Factors	6 (12%) ^[25, 28, 33, 37, 59, 61]	4 (8%) ^[38, 55, 58, 59]
Respiratory/ Lung Diseases	7 (14%) ^[28, 30, 44, 53, 56, 59, 64]	2 (4%) ^[21, 47]
Neuromuscular Disorders	1 (2%) ^[37]	
Autoimmune Disorders	8 (16%) ^[37-41, 48, 55, 62]	
Musculoskeletal Conditions	6 (12%) ^[33, 35, 44, 50, 54, 58]	1 (2%) ^[58]
Malignancy	6 (12%) ^[23, 30, 38, 48, 56, 61]	1 (2%) ^[21]
Neurological Disorders	7 (14%) ^[23, 33, 51, 54, 60, 61, 64]	
Kidney/Liver Disease	4 (8%) ^[38, 55, 60, 64]	
Diabetes Mellitus	5 (10%) ^[25, 28, 33, 37, 64]	4 (8%) ^[38, 47, 55, 58]
Other Chronic or Acute Comorbidities	3 (6%) ^[57, 60, 67]	1 (2%) ^[23]
Thyroid Disease	4 (8%) ^[28, 30, 55, 56]	3 (6%) ^[38, 47, 55]
Non-specified Comorbidities	1 (2%) ^[34]	2 (4%) ^[47, 63]
Other Inflammatory Conditions	1 (2%) ^[52]	
Reproductive Diseases	1 (2%) ^[57]	
Serious Mental Health Conditions	7 (14%) ^[22-24, 48, 51, 60, 69]	1 (2%) ^[23]

Supplementary File 1 Database search strategies

Embase Search Strategy via OVID: (7824 Studies)

- 1) exp exercise/
- 2) (exercis* or aerobic* or cardiovascular* or Walk* or endurance* or Physical activit*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 3) (strength* or resistance*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 4) (aqua* or hydrotherap* or swim* or yoga* or tai chi*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 5) (Flexib* or stretch* or range motion or movement).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 6) (balance* or proprio*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 7) exp rheumatoid arthritis/
- 8) (Rheumatoid arthriti* or ra or rheumatoid nodule* or felty* syndrome or caplan* syndrome or Sjogren* syndrome or still* disease).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 9) exp randomized controlled trial/
- 10) (randomized controlled trial or clinical trial* or rct).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 11) 1 or 2 or 3 or 4 or 5 or 6
- 12) 7 or 8
- 13) 9 or 10
- 14) 11 and 12 and 13

Search Strategy for Medline via OVID: (2429 Studies)

1. Exp Exercise/

2. (Exercise* or aerobic* or cardiovascular* or walk* or endurance* or physical activit*).mp.
3. (strength* or resistance*).mp.
4. (aqua* or hydrotherapy* or swim* or yoga* or tai chi* or flexib* or stretch* or range of motion or movement* or balance* or proprio*).mp.
5. Exp rheumatoid arthritis/
6. (rheumatoid arthritis or ra or rheumatoid nodule* or felty* syndrome or caplan* syndrome or Sjogren* syndrome or still* disease).mp.
7. Exp randomized controlled trial/
8. (randomized controlled trial or randomi?ed controlled trial* or clinical trial* or rct).mp.
9. 1 and 2 and 3 and 4
10. 5 and 6
11. 7 and 8
12. 9 and 10 and 11

CINAHL Search Strategy: (324 studies)

- S1. (MH "Exercise+")
- S2. Exercise*
- S3. Physical activit*
- S4. Aerobic*
- S5. Cycling
- S6. Cardiovascular*
- S7. Walk*
- S8. Endurance*
- S9. Strength*
- S10. Resistance*
- S11. Flexib*
- S12. Stretch*
- S13. "range of motion"
- S14. Movement*
- S15. Hydrotherapy*
- S16. Aquatic*
- S17. Swim*
- S18. Balance*
- S19. Propriocep*
- S20. Yoga*
- S21. Tai chi*
- S22. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
- S23. (MH "Arthritis, Rheumatoid")
- S24. Rheumatoid nodule*
- S25. Felty* syndrome
- S26. Caplan syndrome*
- S27. Sjogren* syndrome

- S28. Still* disease
- S29. S23 OR S24 OR S25 OR S26 OR S27 OR S28
- S30. (MH “Randomized Controlled Trials”)
- S31. Randomi?ed control
- S32. Control clinical trial*
- S33. Clinical trial*
- S34. Rct
- S35. S30 OR S31 OR S32 OR S33 OR S34
- S36. S22 and S29 AND S35

PEDro Search Strategy – (315 studies)

PEDro Search Strategy (available at pedro.org.au) - 127 results

- Abstract & title: Exercis* AND Rheumatoid Arthritis
- Method: clinical trial

PEDro Search Strategy (available at pedro.org.au) - 75 results

- Abstract & title: Rheumatoid Arthritis
- Therapy: Fitness Training
- Method: clinical trial

PEDro Search Strategy (available at pedro.org.au) - 28 results

- Abstract & title: Rheumatoid Arthritis
- Therapy: Hydrotherapy , balneotherapy
- Method: clinical trial

PEDro Search Strategy (available at pedro.org.au) - 85 results

- Abstract & title: Rheumatoid Arthritis
- Therapy: Strength training
- Method: clinical trial

OpenGrey – 11 results

Exercis* AND rheumatoid arthritis

ISRCTN Registry – 14 results

rheumatoid arthritis AND exercise

Categories selected were: (condition) and (intervention)

Supplementary file 2: Risk of Bias Assessment

	Domain 1: Randomisation Process	Domain 2: Deviations from Intended Interventions	Domain 3: Missing Outcome Data	Domain 4: Measurement of the Outcome	Domain 5: Selection of the Reported Result	Overall Judgement
Anvar, 2018	Yellow	Red	Red	Red	Red	Red
Andersson, 2020	Green	Red	Red	Green	Yellow	Red
Azeez, 2020	Yellow	Green	Green	Red	Yellow	Red
Baillet, 2009	Green	Green	Green	Red	Yellow	Red
Bearne, 2002	Yellow	Green	Green	Yellow	Yellow	Yellow
Bilberg, 2005	Yellow	Green	Green	Green	Red	Red
Breedland 2011	Yellow	Green	Green	Green	Yellow	Yellow
DaSilva, 2013	Green	Green	Green	Green	Yellow	Yellow
Dejong, 2004	Yellow	Green	Green	Green	Red	Red
Durcan, 2014	Yellow	Green	Green	Green	Yellow	Yellow
Ellegaard, 2019	Red	Green	Green	Green	Red	Red
Eurenius, 2008	Yellow	Green	Green	Green	Green	Yellow
Eversden, 2007	Yellow	Green	Green	Green	Yellow	Yellow
Feldthusen, 2016	Red	Green	Red	Green	Yellow	Red
Figen, 2011	Red	Green	Green	Green	Red	Red
Flint-Wagner, 2009	Yellow	Red	Red	Yellow	Red	Red
Ganesan, 2020	Green	Red	Red	Green	Red	Red
Garcia-Morales, 2020	Yellow	Red	Red	Green	Red	Red
Gautam, 2020	Green	Green	Green	Green	Red	Red
Gautam, 2021	Green	Green	Green	Green	Red	Red
Gautam, 2019	Green	Green	Green	Green	Red	Red
Hakkinen, 2004	Green	Green	Green	Red	Red	Red

Hakkinen, 2003						
Hale, 2016						
Hsieh, 2009						
Jahanbin, 2014						
Lamb, 2015						
Lange, 2019						
Lemmey, 2009						
Lineker, 2001						
Lourenzi, 2017						
McKenna, 2021						
Mohanty, 2018						
Moonaz, 2015						
Munneke, 2003						
O'Brien, 2006						
Ogata-Medal, 2018						
Puksic, 2021						
Rezaei, 2020						
Rodrigues, 2020						
Seneca, 2015						
Siqueira, 2017						
Strasser, 2011						
Surabhi, 2018						
Van Rensburg, 2012						
Vandenberg, 2006						
Veldhunjzen, 2021						
Wang, 2008						
Ward, 2014						

Westby, 2000						
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