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Title:

Exercise or Physical Activity-Related Adverse Events in People Receiving Peritoneal Dialysis: A Systematic Review

Running Title:

Exercise and Adverse Events in Peritoneal Dialysis

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Abstract:

People receiving peritoneal dialysis may benefit from participation in exercise or physical activity. However, exercise therapy for people receiving peritoneal dialysis is not typically included in routine care, in-part, due to on-going uncertainties about risk. The aim of this review was to systematically collate and explore data on adverse events experienced by people receiving peritoneal dialysis whilst undertaking an exercise or physical activity intervention. Searches yielded 25 exercise or physical activity intervention studies involving people receiving peritoneal dialysis. Of these 25 studies, 17 studies provided adverse event data and were included in the final review. No serious adverse events (e.g. death, hospitalisation) were found attributable to the intervention. From 50 reported adverse events during the intervention period, 32 were attributable to the exercise or physical activity intervention with most being musculoskeletal (e.g. muscle / joint pain etc.) followed by fatigue. Most events were mild to moderate in severity and resolved by exercise program modification, education, rest or medication. The results from this review did not uncover signals of harm for people receiving peritoneal dialysis who engage in exercise with risk of adverse events appearing to be low, however, improved adverse events reporting and further interventional studies are required before robust guidelines can be produced.

Keywords:

Adverse events, end stage kidney disease, exercise peritoneal dialysis, physical activity

1.0 Introduction:

People receiving peritoneal dialysis are often physically inactive and sedentary (1, 2), with lower activity levels associated with poorer quality of life and increased risk of mortality (3). Exercise therapy has consistently been shown to elicit positive health benefits for chronically ill and frail populations (4, 5). Despite this, exercise therapy is not embedded in the routine care for people receiving peritoneal dialysis, in-part, due to the limited evidence of benefit and on-going uncertainties about risks (6), such as dialysis catheter problems (e.g. leaks) and hernia (7). Consequently, clinicians may be reluctant to provide exercise or physical activity-related advice to patients (7). This reluctance is exacerbated by a varied level of confidence reported by nephrology clinicians to recommend exercise or physical activity (8). The lack of exercise or physical activity counselling may increase physical inactivity (9) and thereby decrease a patients' potential to achieve the benefits of an active lifestyle (10, 11).

Exercise guidelines, prescription advice and safety considerations for people receiving peritoneal dialysis are yet to be developed, primarily due to the small number of exercise-based interventions and inconsistent reporting of adverse events (12, 13). A recent review (including 27 studies) exploring the safety and efficacy of intra-dialytic exercise for people receiving haemodialysis concluded that the risk of adverse event was no higher between exercisers and controls (14). However, a similar review has not yet been performed for people receiving peritoneal dialysis. Given the key differences between dialysis modalities (e.g. peritoneal dialysis involving a catheter in the lower abdomen, clinical condition of the patient etc.), it is unlikely haemodialysis findings can be directly translated to peritoneal dialysis.

To enhance patient and clinician confidence, it is vital to understand risks associated with exercise and physical activity for people receiving peritoneal dialysis. Thus, the aim of this review is to address this knowledge gap by exploring the characteristics and frequency of adverse health event data reported for people receiving peritoneal dialysis while undertaking exercise or

physical activity-based interventions. This evidence synthesis is essential for understanding whether exercise or physical activity can be safely encouraged and prescribed. Findings from this systematic review will inform future guidelines and may change exercise-related approaches for people receiving peritoneal dialysis.

2.0 Methods

2.1 Search Strategy

Electronic searches were performed in Medline, Embase, Ovid Emcare, The Cochrane Library and SPORTDiscus from their respective inceptions through May 2021. Published theses, conference abstracts and clinical trial records were searched through ProQuest, Web of Science and online clinical trial registries (Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, EU Clinical Trials Register and World Health Organization International Clinical Trials Registry Platform), respectively. A comprehensive search strategy was developed reflecting terms and key words related to end stage kidney disease, peritoneal dialysis, exercise and physical activity. Search strategies for respective databases are presented in the Supplementary Files. Reference lists of identified full text articles were examined. Additionally, exercise experts from the Global Renal Exercise Network (GREX) were consulted for any further studies or data sets not discovered through searches.

2.2 Study Screening

Electronic references were compiled in Endnote X9.2 (Clarivate Analytics, Boston, USA) with duplicates removed prior to screening. References were uploaded into Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia) for screening. Titles, abstracts and subsequent full text screening was completed by two independent reviewers with conflicts resolved by consensus.

2.3 Inclusion Criteria

Exercise or physical activity-based intervention studies (any study design) with adults (aged ≥18 years) receiving peritoneal dialysis (either automated peritoneal dialysis or continuous ambulatory peritoneal dialysis) were eligible for inclusion if they reported adverse event data. Mixed cohort studies (e.g. haemodialysis and peritoneal dialysis participants) were included only if adverse event data were stratified by dialysis modality. The exercise or physical activity intervention components could be educational, psychological (e.g. cognitive behavioural therapy) or exercise delivery-based to qualify. Combined therapy interventions (e.g. psychological and exercise-based) were included if the exercise or physical activity component was deemed by the research team to constitute a key aspect of the intervention. Peer reviewed and grey literature (e.g. ProQuest) were included, but commentaries and systematic or narrative reviews were excluded.

Studies that reported detail in full, in-text, were defined as those that reported all adverse events and classified whether they were related to the intervention and how they were managed (i.e. the outcome). Studies that provided partial adverse event data were defined as those that reported adverse events but did not provide any one or more or the following: stratification of adverse events by dialysis modality, classify whether they were related to the intervention and/or, how they were managed. If data were not reported in-full, in-text, requests for data and/or further clarification were sent to the authors.

2.4 Primary Outcome

The primary outcome was adverse events for people receiving peritoneal dialysis that occurred during an intervention. The definition of an adverse event was adapted from previous literature as any adverse change in health status or a side-effect that may or may not have been caused by the exercise or physical activity intervention (15). Serious adverse events were defined as any event requiring hospitalisation, or resulting in disability or death (16). Equivalent terminology for adverse event was accepted in lieu of the specific term, this included data reported as a

complication or problem experienced during the intervention period. In the absence of adverse event data being reported, withdrawal data were included if the research team deemed the withdrawal reason to be potentially related to exercise or physical activity (physical or mental related adverse event). Additionally, if reported, the details regarding whether the event was intervention related, the severity (e.g. mild, severe) and the outcome (e.g. action taken to mitigate / resolve the adverse event) were extracted.

2.5 Data Extraction

Data were extracted by two independent reviewers with a third reviewer performing random checks and any conflicts resolved through consensus. Data pertaining to study identification (first author and year of publication), participant characteristics (for people receiving peritoneal dialysis only), intervention description, adverse event definition, adverse event data, severity of each adverse event, event outcomes, event attribution to the intervention, method of capturing adverse events and withdrawal data were extracted. Corresponding authors for studies that did not provided full adverse event details in-text were contacted via e-mail for further data and given three weeks to respond.

2.6 Quality Assessment

Two independent reviewers assessed the quality of the included studies using the Joanna Briggs Institute Critical Appraisal Tool for both randomised controlled trials (including randomised trials) and quasi-experimental studies (including non-randomised controlled trials and pre-post studies) (17). Each study was assigned a yes (assigned one mark), no or unclear (both assigned a zero mark) for each criteria. Unclear was assigned if the information wasn't presented in-text. Studies were then given a score out of 13 or nine for randomised controlled trials and quasi-experimental studies, respectively.

2.7 Data Analysis

Studies were pooled into three adverse event reporting categories; 1) studies that reported adverse events and categorised them based on intervention attribution, 2) studies that reported adverse events but failed to report based on intervention attribution and, 3) studies that did not report adverse event data, but provided withdrawal data that could potentially be deemed an adverse event related to exercise or physical activity (physical, physiological or psychological related adverse event). Adverse event data were converted to a rate of adverse events per person, per week by taking the total number of adverse events (including adverse events experienced multiple times by a single person) and dividing this by the total number of participants and the total amount of intervention weeks of exercise or physical activity. This rate was calculated at the study, adverse event reporting category and total study level.

3.0 Results

3.1 Study Selection

Database and trial registry searches identified 6546 unique studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses(18) flow diagram is presented in Figure 1. From 25 studies that reported on an exercise or physical activity intervention involving people receiving peritoneal dialysis, 11 (44%) did not report adverse events. From the 11, two studies (19, 20) (8%) provided data upon request, one study (13) (4%) did not respond to a request for data however reported withdrawal data was accepted in lieu of adverse event data and, eight studies did not respond to requests for adverse event data (and did not have reported withdrawal data that could be used in lieu). Eight studies (21-28) (32%) reported full adverse event data in-text; four studies (12, 29-31) (16%) provided partial adverse event data in-text, with authors providing further data and/or clarification on request, two studies (32, 33) (8%) reported partial adverse event data in-text, but did not provide additional details on request to enable proper classification. This resulted in 17 studies being included in the final review.

3.2 Study Characteristics

Table 1 summarises the details of the included studies. Most were randomised controlled trials (59%), followed by pre-post studies (29%) and non-randomised controlled trials (12%). A total of 287 people receiving peritoneal dialysis participated in an exercise or physical activity intervention. Most studies involved only people receiving peritoneal dialysis (71%) with five studies (12, 20, 29-31) recruiting a mixed cohort (i.e. people receiving peritoneal dialysis or haemodialysis). The reported mean (SD) participant age of people receiving peritoneal dialysis ranged from 46.5 ± 12.8[SD] (22) to 67.3 ± 8.6[SD] (19) years.

3.3 Exercise or Physical Activity Intervention Details

Intervention details, stratified by the adverse event reporting category, are summarised in Table 2. Intervention durations ranged from four weeks (21, 33) to 52 weeks (32), with most (47%) being 12-13 weeks. The most prescribed modality was aerobic exercise alone (35%), followed by aerobic exercise with resistance training (23%), resistance training alone (12%), flexibility training (12%), general exercise (i.e. increase physical activity levels) (12%) and anaerobic exercise alone (6%). Three studies (12, 20, 27) included an exercise or physical activity intervention for both study groups (i.e., intervention and control group). Four studies involved additional (to exercise or physical activity) intervention components, including; psychological and education elements to increase knowledge surrounding peritoneal dialysis (e.g. nutrition, condition-related, machine operating procedure etc.) (32), dietary supplementation (protein) (20), neuromuscular electrical stimulation (24) and tools to enhance sleep quality (e.g. mattress, sleep hygiene etc.) (33). Four studies (22-24, 29) reported dialysate in the peritoneal cavity during exercise, one study encouraged participants to exercise with dialysate but to drain if uncomfortable (27), one study did not discourage participants from exercising with dialysate (28) and one study (21) advised participants to drain the dialysate prior to exercise. Ten studies did not report if exercise or physical activity was completed with or without dialysate in the peritoneal cavity.

3.4 Adverse Event or Withdrawal Characteristics

Adverse event and withdrawal details are summarised in Table 2. In total, there were 50 individual adverse events reported from 263 intervention weeks (rate of 0.06 adverse events, per 100 people, per week). Five studies reported no adverse events occurring during the intervention (19, 21, 23, 25, 27) and one reported no serious adverse events (26). Palanova and colleagues (24) reported no adverse events occurring, but it was unclear whether this applied specifically to the flexibility component of their intervention or not.

There were 32 individual adverse events attributed to the intervention reported from 206 participants and 199 intervention weeks (rate of 0.08 adverse events, per 100 people, per week). Fifteen individual adverse events that were not explicitly classified as intervention related from 73 participants and 56 intervention weeks (rate of 0.37 adverse events, per 100 people, per week). Three withdrawals that were potentially intervention related but reported as a withdrawal reason (not adverse events per se) from eight participants and eight intervention weeks (rate of 4.69 adverse events, per 100 people, per week).

Of the 32 adverse events attributed to exercise or physical activity interventions, musculoskeletal adverse events (e.g. joint or muscle pain / discomfort) were the most frequently reported (n=15) followed by fatigue (n=6), dyspnoea (n=4), hypotension (n=3), chest pain (n=3) and dizziness (n=1). All three episodes of chest pain were experienced by a single participant (29) whilst another participant reported both a musculoskeletal adverse event and an episode of fatigue (34). Severity was reported for five instances of fatigue (all moderate), four instances of dyspnoea (all moderate), three instances of chest pain (all mild) and single instances of abdominal discomfort and dizziness (both mild). A single intervention related adverse event (exercise hypotension) (29) resulted in the withdrawal of a participant from a study, with all other adverse events resolved by either exercise program modification, exercise education, prescribed medication and/or rest.

From the four studies that reported participants exercising with dialysate in the peritoneal cavity, two studies (23, 24) reported no adverse events occurred whilst the remaining two (22, 29) reported chest pain (n=3) and hypertension (n=3). The single study (21) that advised participants to drain the dialysate reported no adverse events. It is unclear in one study (28) if adverse events occurred whilst participants exercised with or without dialysate. Furthermore, in one study (27) where there were no adverse events reported, it is unclear if participants exercised with or without dialysate.

Of the 15 adverse events that were not explicitly classified as intervention related, infection was the most frequently reported (n=12) with two participants experiencing two episodes of peritonitis during the intervention period each (32). No details were reported regarding the severity or the outcome.

The withdrawal data related to single instances of infection, foot sores and chest pain. No details were reported regarding the severity.

No studies reported if adverse events led to any compromises in peritoneal dialysis treatment (e.g. delays).

3.4 Adverse Event Reporting Practices

Three studies (24, 30, 31) gathered adverse event data through weekly phone calls facilitated by the research team to participants. These calls asked participants to report any difficulties or incidents that had arisen and, provided opportunity for participants to ask questions or provide feedback about the intervention and / or study protocol. One study provided participants a phone number to contact to report if an adverse event occurred (12). The remaining studies did not report how adverse event data were collected. Only two studies (28, 30) provided their definition of adverse events. Bennett and colleagues (28) reported all adverse events from both the intervention and control arm, and defined exercise-program related adverse events as any occurrence of injury, impairment, or medical condition that was directly, or suspected to be, due

to performing the prescribed exercise. Their reporting protocol captured details regarding the severity of the adverse event, relationship to study, action taken to resolve, if they were withdrawn and any additional comments about the incident (e.g. patient history, provoking factors etc.). de Souza and colleagues (30) included the definition of an adverse event as an adverse symptom that occurred during the study. Adverse events that occurred during the exercise period were categorised as related to the intervention if they pertained to joint pain or severe muscle soreness during the exercises or severe muscle soreness up to two days after the exercises. Otherwise, all other adverse events were classified as unrelated to the intervention. Their reporting protocol captured the number, type (e.g. serious or non-serious; expected or unexpected) and severity of adverse events that occurred during the study.

3.5 Quality Assessment

All quality appraisal ratings are presented in Table 3. Mean percentages were 51% for randomised controlled trial (including randomised trials) and 60% for quasi-experimental studies (including non-randomised controlled trials and pre-post studies).

4.0 Discussion

The findings from this review suggest, based on the current literature available, exercise appears equally safe for people receiving peritoneal dialysis as other seriously ill, chronic disease populations (35). Overall, there were few adverse events reported, with 32 individual adverse events attributed to exercise or physical activity interventions at a rate of 0.08 adverse events, per 100 people, per intervention week. No serious adverse events were reported as being caused by participation in the exercise or physical activity interventions. This finding is consistent with other reviews exploring adverse events in cancer (36), heart failure (37) and pulmonary hypertensive populations (38) Furthermore, the low rate of adverse events in this review is consistent (when applying the same metric) with comparable clinical populations when

participating in exercise or physical activity interventions (35, 36, 39). Thirty-two percent of all intervention studies did not report or provide adverse event data.

Musculoskeletal adverse events were the most frequent accounting for 14 (47%) of 32 reported intervention-related adverse events. This finding is not unexpected as these events account for the majority of adverse events resulting from exercise and physical activity in both healthy and chronic disease populations (40-42). The effects of kidney failure on muscle and bone strength are well known (e.g. muscle wasting, renal osteodystrophy etc.). It is plausible that these may increase the risk of exercise-related musculoskeletal injury, but the findings from this study suggests musculoskeletal injury rates are consistent with other populations. No intervention-related musculoskeletal adverse events were serious or resulted in the withdrawal of a participant. Hence, although PD clinicians need to consider underlying disease physiology, this may not translate to increased exercise-related risk for people receiving peritoneal dialysis. As is best practice, exercise or physical activity counselling and prescription should be tailored based on the history, condition, capacity and preferences of the person at the time (43).

It has been hypothesised that exercise increases the risk of catheter exit site complications (e.g. infection, pulling trauma, leaks) or abdominal hernia (7). Consistent with a similar review (6), these complications were not reported in any of the included studies, with only a single, intervention related adverse event identified that pertained to mild abdominal discomfort (28). This was reported when the participant was performing an abdominal muscle strengthening exercise and was alleviated by ceasing the particular exercise. No details of the location or type of abdominal discomfort was provided; hence it is unclear whether the discomfort may have been a typical sensation when participating in abdominal strength exercises or a peritoneal dialysis-specific issue. Two studies (21, 28) in this review prescribed abdominal muscle strengthening exercises with Derici and colleagues (21) reporting that they have potential to reduce catheter leaks. The findings from this review indicate that catheter site or abdominal injury are rare and

that abdominal muscle strengthening exercises appear safe and can be considered when designing exercise programs for people receiving peritoneal dialysis.

Fatigue was the second most frequently reported adverse event (n=6) attributed to exercise or physical activity interventions. This is unsurprising given fatigue, a pathological symptom that is chronic and debilitating (44), is a highly prevalent symptom in patients receiving peritoneal dialysis (55-89%) (45). The high prevalence may be due to one or a combination of factors including treatment (schedule) burden, physical deconditioning and end stage kidney disease complications such as anaemia (13). Reporting of fatigue as a result of exercise or physical activity is not unique to this population as evident from other clinical populations (42, 46). Whilst fatigue can be a debilitating symptom, the literature supports that participation in exercise and physical activity can reduce feelings of fatigue in people living with cancer and multiple sclerosis (47, 48). Anecdotally, people receiving peritoneal dialysis regard exercise as necessary and beneficial to reduce feelings of fatigue (49). Exercise trials are currently underway to explore the impact on fatigue and boost the current low volume of interventional data (50). Techniques to manage fatigue may need to be incorporated when designing exercise or physical activity programs. One such technique is the concept of pacing, which encourages people to be as active as possible within the limits imposed by the condition and requires an individual determination as to what level they can function that does not lead to marked increase in symptom (i.e. fatigue) experience (51). Additionally, consistent monitoring of fatigue should be encouraged with the use of quick, low burden tools appropriate to people receiving dialysis such as the Standardized Outcomes in Nephrology-Haemodialysis instrument (52).

Whilst the majority of reported adverse events were classified as intervention related, 15 events were not explicitly classified, 12 of which were peritonitis. Peritonitis is defined as an inflammation of the membrane lining the abdominal wall usually as a result of infection (53). The prevalence of peritonitis for people receiving peritoneal dialysis is higher than general population

due to the treatment (e.g. catheter in the lower abdomen) (54). No study has explored whether there is an association between exercise or physical activity and peritonitis. However, as it has many contributing factors, it is unlikely that exercise or physical activity plays a causal role in the development of peritonitis. Luo and colleagues (32) reported the total number of peritonitis cases was less in the physical activity, condition education and nutrition-based intervention group compared with the control group receiving usual care, suggesting the intervention may have reduced peritonitis, or at the very least not increased the risk of it.

This review has highlighted suboptimal reporting practices of adverse events in exercise or physical activity trials involving people receiving peritoneal dialysis. Of the intervention studies that were assessed for eligibility, eleven studies (56%) provided no adverse even data and just under a third (32%) providing details in-full, in-text. Furthermore, adverse event definitions were reported in only two studies (28, 30). The Consolidated Standards of Reporting Trials (CONSORT) 2010 (55) statement identifies in checklist item 19, the reporting of all important harms or unintended effects in each group is required so that readers may make rationale and balanced decisions. Future exercise and physical activity trials involving people receiving peritoneal dialysis must improve their reporting practices for the development of robust exercise guidelines weighing risk and benefit.

4.1 Strengths and Limitations

This review was strengthened by the comprehensive search strategy that involved many data sources including databases, grey literature and, clinical and research networks. Furthermore, the inclusion of non-English articles broadened the number of studies initially captured for screening. However, synthesis of the studies included, or any subsequent statistical analyses, was difficult to complete due to the heterogeneity of studies (e.g. intervention components, exercise modalities / prescription, varied reporting of outcomes etc.). There were eight studies that did not provide adverse event data in-text (author requests for further data were unsuccessful) hence, did not meet

the criteria of the three reporting categories (outlined in Section 2.7). Therefore, the absolute number and rate of adverse events is unable to be determined, however, based on the frequency of adverse events across studies in this review and the diversity of exercise programs, there is nothing to suggest the rate would greatly increase.

Due to limited reporting of abdominal fluid status, it is unclear if participants being full or empty increases adverse event risk. Recently developed exercise guidelines for peritoneal dialysis have highlighted that the effect dialysate in the peritoneal cavity has on an individual varies dependent on the type of exercise (e.g. running, walking) and body position (e.g. standing, sitting, supine etc.) however there is no conclusive evidence to support that this leads to increased adverse event risk (56). It is possible that the intervention durations were too short to see the impact of exercise on hernia formation or catheter leaks. The perceived mechanism for this is that exercise or physical activity may interplay with increased diaphragmatic pressure from peritoneal dialysis therefore clinicians should aim to educate on techniques to mitigate pressure (e.g. controlled breathing) while undertaking exercise or physical activity (56). Furthermore, due to unclear or absent reporting; 1) it is possible that multiple adverse events were experienced by a single person, 2) how adverse data were collected for the majority of studies is not known, 3) any effect on peritoneal dialysis treatment as a result of an adverse event is not known and, 4) inconsistent presentation of adherence rate data precluded the research team from producing more specific rates of adverse events (e.g. per episodes of care, per hour of exercise participation etc.)

4.2 Reporting Recommendations

Future exercise or physical activity trials involving people receiving peritoneal dialysis should adopt the full recommendations outlined in the CONSORT related to Harms (55). Authors at the very least should provide; 1) a definition of what qualifies as an adverse event, 2) information about how adverse event data were collected, 3) a description of each individual adverse event (and if a participant experienced multiple adverse events), 4) information about whether an

adverse event was related to participation in the intervention, 5) detail about the severity of the adverse event (e.g. mild, moderate, severe), and 6) the outcome or method taken to resolve the adverse event (and if this event led to any compromises in standard treatment (e.g. halting of peritoneal dialysis). Studies should also stratify adverse events by dialysis type or chronic kidney disease stage if mixed cohorts are sampled, report adherence (definition and data) to the exercise intervention. Finally, authors must report whether people receiving peritoneal dialysis exercised with or without dialysate in the peritoneal cavity so that clinicians can accurately examine the impact of fluid status on adverse events.

4.2 Conclusion

People receiving peritoneal dialysis are likely to benefit from participation in exercise or physical activity. Exercise and physical activity-related adverse events are mild to moderate in severity and, no serious adverse events have been reported, suggesting that the risk for people receiving peritoneal dialysis is low. None of the commonly held perceptions regarding exercise risk (catheter leak, hernia or infection) have been confirmed. This review highlights that adverse event data reporting requires significant improvement and findings should be interpreted with some caution due to missing or inadequate data. Nevertheless, the available data does not indicate increased risk of harm for people receiving peritoneal dialysis who engage in physical activity or exercise, and it should be considered when developing management plans with the predicted benefits outweighing any risks.

5.0 Other

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (18). A complete protocol was registered with PROSPERO (CRD42021194238).

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7.0 Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this review. No funding was received for this research

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Table 1 – Participant Characteristics for People Receiving Peritoneal Dialysis in Included Studies

Author/s	Year	Country	Study Design	Multi-Component Intervention		Participants receiving PD (n)	Age (mean ± SD) (years)*	Duration of PD (mean ± SD) (months)*	PD Modality (% APD)	Sex (% m)
Bennett et al.(28)	2020	USA	RCT	No		13	57.7 ± 16.3	18 (8 - 28) [c]	100	61.5
Derici et al.(21)	2005	Turkey	Pre-Post	No		3	52.6 ± 5.2	16.3 ± 7.4	0	0
de Souza et al.(30) [a]	2020	Canada	Pre-Post	No		3	57.3 ± 2	22 ± 13.4	NR	66.6
Koufaki et al.(29) [a]	2002	UK	RCT	No		12	52.9 ± 12.8	46.8 ± 53.1	0	NR
Lo et al.(22)	1998	Hong Kong	NRCT	No		13	46.5 ± 12.8	57.6 ± 45.6	0	33.3
Luo et al.(32)	2019	China	RCT	Yes		64	53.2 ± 12.4	3-12 (n=17) 12-36 (n=31) >36 (n=16)	0	46.9
Manfredini et al.(12) [a]	2017	Italy	RT	No	Intervention	14	66 ± 11**	32.5 ± 17.2	0	NR
					Control [b]	21	63 ± 11**	42.9 ± 24.5	0	NR
Molsted at al.(20) [a]	2013	Denmark	RT	Yes	Intervention	3	58.7 ± 9.2	40.8 ± 1.2	NR	33.3
					Control [b]	2	67 ± 1	30 ± 9.6	NR	50
Mustata et al.(23)	2005	Canada	Pre-Post	No		6	53 ± 13**	24 ± 12**	66.6	66.6
Palanova et al.(24)	2018	Czech Republic	Pre-Post	Yes		14	61.9 ± 8.7	54 ± 32.4	0	42.8
Rouchon et al.(19)	2016	France	RCT	No		8	67.3 ± 8.6	22.8 ± 14.4	62.5	100
Shahgholian et al.(25)	2015	Iran	RCT	No		11	50.5 ± 14.3	12.1 ± 8.1	0	81.8
Sheshadri et al.(31) [a]	2020	USA	RCT	No		6	60.1 ± 5.3	43.2 ± 30	NR	50

Straub et al.(13)	2008	USA	NRCT	No		5	30-50 (n=1) 50-65 (n=2) >65 (n=2)	<12 (n=1) 12-60 (n=3) >60 (n=1)	80	80
Uchiyama et al.(26)	2019	Japan	RCT	No		24	64.9 ± 9.2	43.2 ± 32.4	30.4 [d]	79.1
Watanabe et al.(27)	2021	Japan	RT	No	Intervention Control [b]	26 27	66.2 ± 13.1 64 ± 13	60 ± 37.2 61.2 ± 46.8	42.3 [d] 74.1 [d]	76.9 77.8
Yngman-Uhlin et al.(33)	2012	Sweden	Pre-Post	Yes		9	65.4 ± 11.7	24.5 ± 24.8	33.3 [d]	77.8

* Rounded to one decimal point unless otherwise stated **Reported as whole numbers by authors

[a] Intervention cohort involved both people receiving haemodialysis and peritoneal dialysis (data presented pertains to the participants receiving peritoneal dialysis)

[b] Control group demographics reported when control group was given a form of exercise or physical activity intervention

[c] Median (Interquartile Range);

[d] Including participants who were receiving both continuous ambulatory peritoneal dialysis and automated peritoneal dialysis

APD – Automated peritoneal dialysis; PD – peritoneal dialysis; NRCT – non-randomised controlled trial; RCT – randomised controlled trial; RT – randomised trial; NR – not reported; SD – standard deviation; UK – United Kingdom; USA – United States of America

Table 2 – Intervention Details and Adverse Event / Withdrawal Data

Intervention Details					Adverse Event Details			
Author/s	Exercise Modality	Intervention Description	Delivered By	Duration (weeks)	Adverse Events	Related to Intervention	Outcome	Rate of AEs*
Group 1 – Adverse Event Data with Full Details								
Bennett et al.(28) †	Aerobic + Resistance	Monthly exercise consultation and prescription (using exercise bands) + 4 exercise support telephone calls	Exercise physiologist	12	Mild abdominal discomfort (n=1) Mild dizziness (n=1)	Yes Yes	Program modified Sat then continued	1.3
Derici et al.(21) †	Resistance	Abdominal strengthening exercises for 10mins followed by 10-15mins rest repeated over one hour Prolonged standing and sitting discouraged	Not reported	4	No adverse events related to intervention			-
de Souza et al.(30) ††	Aerobic + Resistance	Home exercise program including walking, squats and push ups	Physiotherapist	12	Knee pain (n=2)	Yes	Exercise technique education	5.6
Koufaki et al.(29) ††	Aerobic	Cycle ergometer 3x per week in a gym Baseline exercise intensity 90% of ventilatory threshold	Exercise physiologist	13	Exercise hypotension (n=1) Mild chest pain (n=3) * **All episodes of chest pain reported for same individual*	Yes Yes	Withdrawn Medicated and continued	2.6

Lo et al.(22) †	Aerobic	Exercise class 3 times per week including treadmill, ski training machine and, upper limb and bike ergometers Target training zone 70-85% peak heart rate	Not reported	12	Symptomatic hypotension (n=2)	Yes	Occurred after exercise session and was alleviated by bed rest for 10–15mins, did not prevent further participation.	1.3
Manfredini et al.(12) ††	Aerobic	Home-based, low-intensity walking program (two daily 10min walking sessions)	Rehabilitation team at the University of Ferrara, Italy and, dialysis nurses	26	Moderate fatigue (n=5) Moderate dyspnoea (n=4) Leg pain (n=6) Joint pain (n=3)	Yes Yes Yes Yes	Fatigue, dyspnoea, leg/joint pain events did not limit the program execution	4.9
Molsted et al.(20) †††	Resistance	Progressive high-load strength training 3 x per week. Sessions involved warm-up on a stationary ergometer followed by leg press, leg extension, and leg curl	Physiotherapist and exercise instructors	16	Delayed-onset muscle soreness (n=2)	Yes	Did not prevent participation	4.2
Mustata et al.(23) †	Flexibility + Balance	Tai Chi in-hospital and at home	Certified Tai-Chi instructor	13	No adverse events related to intervention			-
Palanova et al.(24) †	Flexibility	Leg muscle stretches, pre and post quadriceps muscle neuromuscular stimulation	Research team (medical doctor, physiotherapist, nurses)	20	No adverse events related to intervention #			-

Rouchon et al.(19) †††	Anaerobic	2 x 20min stationary bicycle sessions per week of high intensity interval training (repeated 8secs of sprinting and 12secs of slow pedalling) 15mins of stretching to finish	Not reported	13	No adverse events related to intervention			-
Shahgholian et al.(25) †	Aerobic	2 cycle ergometer sessions per week (15-30mins of pedalling at RPE 4 on a modified Borg scale) with 5mins of lower limb static stretching pre and post cycling	Not reported	8	No adverse events related to intervention			-
Sheshadri et al.(31) ††	Aerobic	Pedometers to record step counts and weekly counselling session and step goal setting (walk at comfortable pace)	Medical doctors	13	Foot pain (n=1) * Fatigue (n=1) * ** Both events reported for same individual*	Yes Yes	Program modification Program modification	2.6
Uchiyama et al.(26) †	Aerobic + Resistance	Unsupervised walking 3 x per week (40–60% of the peak heart rate) Resistance training (upper and lower body) exercises 70% of 1RM using TheraBand (1 set	Medical doctors	12	No serious adverse events related to intervention			-

		of 10 repetitions 2 x per week)						
Watanabe et al.(27) †	Aerobic + Resistance	Walk 20–30mins, 3–5 x per week with a goal to increasing step count Resistance exercises for the upper body (TheraBand) Lower body exercises included squats, calf raises, hip abductions and, unipedal standing. One set of 10–15 repetitions initially	Nurse	26	No adverse events related to intervention			-
Group 2 – Adverse Event Data that has not been Categorised as Related to the Intervention								
Luo et al.(32) ††††	General	Part of a broader multi-disciplinary renal rehabilitation program, support re exercise-related goals	Physiotherapist	52	Peritonitis (n=12) * ** Two participants experienced two episodes of peritonitis*	Not stated	Not reported	0.4
Yngman-Uhlin et al.(33) ††††	General	Participants were encouraged to increase activity in general	Nurse and neurophysiologist	4	Lower leg joint pain (n=2) * Esophageal dysfunction (n=1) * **One participant experienced both a single instance of lower leg joint pain and esophageal dysfunction*	Not stated Not stated	Not reported Not reported	8.3
Group 3 – Withdrawal Data used in lieu of Adverse Event Data								

Straub et al.(13) ††††	Aerobic	Walking, riding a stationary bike or swimming 3-4 days per week for 30mins	Nurse	8	Infection (n=1) Foot sores (n=1) Chest pain (n=1)	Not stated Not stated Not stated	Withdrawn Withdrawn Withdrawn	4.7

* Number of adverse events / per 100 people / per intervention week (rounded to one decimal point)

† Adverse event data was reported in-full, in-text

†† Adverse event data was partially reported in-text with authors providing extra detail

††† Adverse event data was not reported in-text however author provided details

†††† Adverse event data was reported however authors did not provide extra details to classify appropriately

Unclear if reporting of no adverse events applied to the flexibility component of the intervention

AE – adverse event; mins – minutes; PA – physical activity; RM – repetition maximum; secs – seconds

Table 3 – Quality Appraisal Scores

Author/s	Bennett et al.(28)	Koufaki et al.(29)	Manfredini et al.(12)	Molsted at al.(20)	Luo et al.(32)	Rouchon et al.(19)	Shahgholian et al.(25)	Sheshadri et al.(31)	Uchiyama et al.(26)	Watanabe et al.(27)	Lo et al.(22)	Straub et al.(13)	Derici et al.(21)	de Souza et al.(30)	Mustata et al.(23)	Palanova et al.(24)	Yngman-Uhlin et al.(33)
Study Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	NRCT	NRCT	Pre-Post	Pre-Post	Pre-Post	Pre-Post	Pre-Post
Randomised Controlled Trials																	
Was true randomization used for assignment of participants to treatment groups?	Y	Y	N	Y	Y	U	U	Y	Y	N							
Was allocation to treatment groups concealed?	Y	U	Y	N	U	U	U	U	Y	U							
Were treatment groups similar at the baseline?	Y	Y	Y	N	Y	U	Y	N	Y	Y							
Were participants blind to treatment assignment?	U	U	U	N	U	U	U	U	N	U							
Were those delivering treatment blind to treatment assignment?	N	U	U	N	U	U	U	U	N	U							
Were outcomes assessors blind to treatment assignment?	N	U	N	Y	U	U	U	U	N	U							
Were treatment groups treated identically other than the intervention of interest?	Y	Y	Y	Y	Y	U	U	Y	Y	Y							
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	U	U	U	U	U	U	U	Y	U							
Were participants analyzed in the groups to which they were randomized?	Y	U	Y	U	U	U	U	U	U	U							
Were outcomes measured in the same way for treatment groups?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y							
Were outcomes measured in a reliable way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y							
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y							

Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y							
Non-Randomised / Pre-Post Trials																	
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?											Y	Y	Y	Y	Y	Y	Y
Were the participants included in any comparisons similar?											N	N	N	Y	Y	Y	U
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?											Y	Y	Y	N	Y	Y	Y
Was there a control group?											Y	Y	N	N	N	N	N
Were there multiple measurements of the outcome both pre and post the intervention/exposure?											Y	Y	U	Y	Y	Y	Y
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?											U	U	Y	U	U	U	U
Were the outcomes of participants included in any comparisons measured in the same way?											U	U	Y	U	U	U	U
Were outcomes measured in a reliable way?											Y	Y	U	Y	Y	Y	Y
Was appropriate statistical analysis used?											Y	Y	U	Y	Y	Y	Y
Total	77%	54%	62%	54%	54%	8%	39%	46%	69%	46%	67%	67%	44%	56%	67%	67%	56%

N – No (i.e. criteria not met); NRCT – non-randomised controlled trial; RCT – randomised controlled trial; Y – Yes; U – Unclear

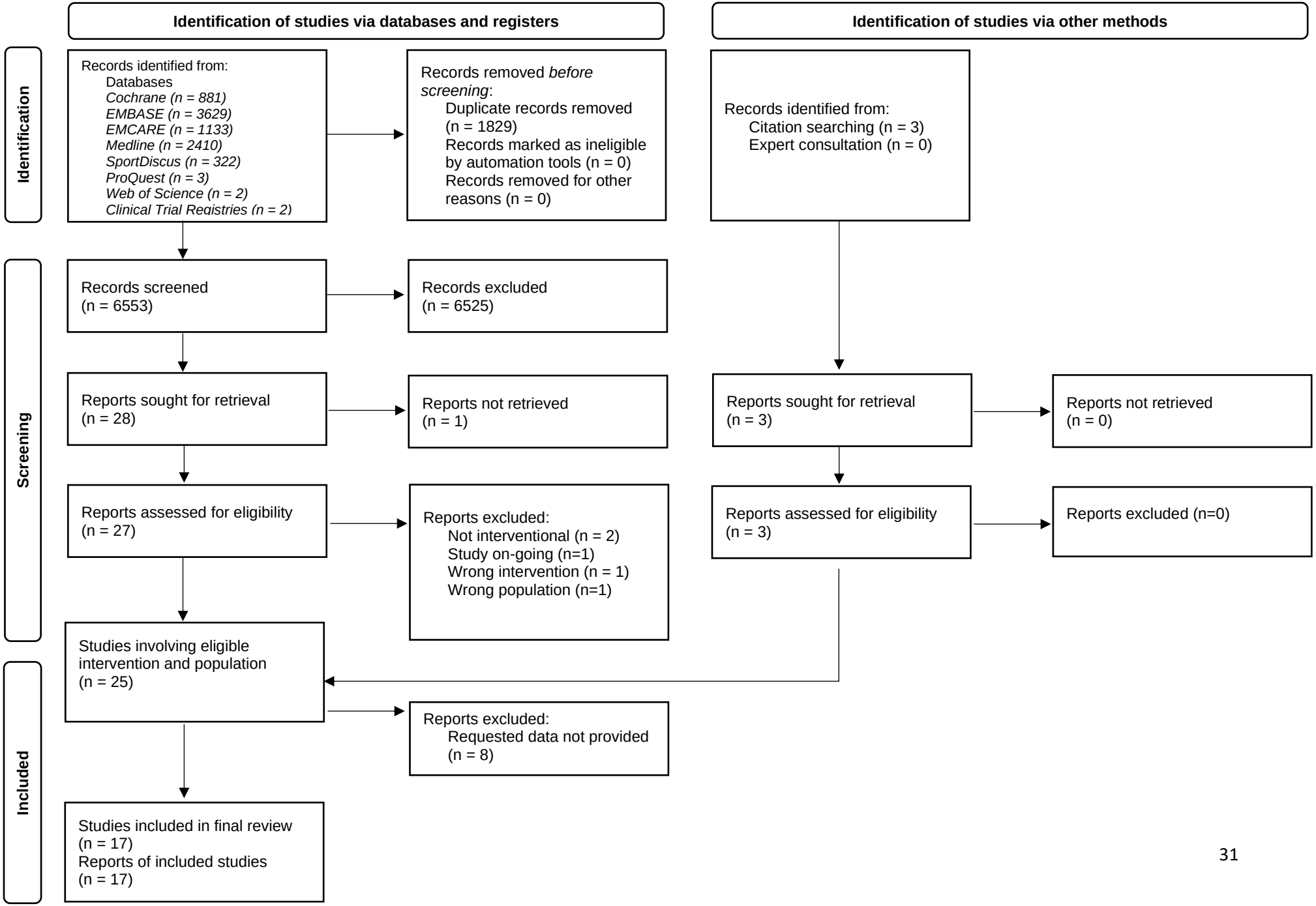


Figure 1 – PRISMA Study Selection Flowchart