Immersive virtual reality and psychological well-being in adult chronic physical illness: systematic review

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ABSTRACT

Introduction Individuals with chronic physical illness are at increased risk of negative psychological sequelae. Immersive virtual reality (VR) is an emerging treatment that might reduce these negative effects and increase quality of life in individuals with chronic physical illness.

Objective To systematically review literature examining the use of immersive VR in adult populations with chronic physical illness to understand: (1) how immersive VR is used to improve psychological well-being of adults with chronic physical illness (2) what effect this immersive VR has on the psychological well-being of adults with chronic physical illness.


Results 12,811 texts were identified; 31 met the inclusion criteria. Relieving and engaging immersive VR interventions were shown to be acceptable and feasible among adults with cancer, dementia, cardiovascular disease, kidney disease and multiple sclerosis. Many of the studies reviewed were feasibility or pilot studies and so the evidence about effectiveness is more limited. The evidence, mostly from studies of people with cancer, suggests that immersive VR can have a positive effect on anticipatory anxiety symptoms and pain.

Conclusions Environment-based and game-based relaxing immersive VR offer novel interventions, with beneficial effects among people with cancer and, potentially, beneficial effects in those with other long-term physical illness.

INTRODUCTION

Virtual reality (VR) refers to any system that allows an individual to experience being connected to a digital world outside their physical bodies, an experiential phenomenon referred to as presence.1 VR systems generate sensory impressions that can be categorised by the level of immersion offered to the user, ranging from non-immersive to fully immersive systems.2 Immersive systems use a head-mounted device to present a 360° digital environment, with an increased sense of presence for the user, where the VR is perceived as realistic and the user’s conscious perception of simulated mediation is reduced.3

The decrease in the physical and practical costs of VR technologies has generated a growing interest in their application to improve patient quality of life in health settings.4 VR systems can be classified by their contextual style: game-based VR interventions prompt the user to engage in goal-directed action, whereas environment-based VR interventions provide the user increased autonomy through self-directed action.5 VR systems may also be defined by their...
conceptual approach: relaxing VR programmes aim to improve a user’s adjustment reaction by inducing a positive emotional state, whereas engaging VR treatments immerse the user in a therapeutically orientated activity designed to improve their psychological state.6

Relaxing virtual realities often use a specific environment or experience, which may be combined with traditional relaxation techniques, to induce a positive effect or reduce emotional arousal in the user—for example, a relaxing nature walk with mindfulness meditation.7 Engaging VR programmes are more directive and aim to teach an individual to develop specific skills or behaviours that improve psychological adjustment. For anxiety disorders a VR intervention may deliver graded exposure therapy,8 whereas in mood disorders VR programmes might aim to teach emotional regulation strategies.6

There is considerable variability in which illnesses are termed ‘chronic disease’.9 The World Health Organization (WHO) detail four main categories of chronic disease: cardiovascular disease, cancer, chronic respiratory disease and diabetes.10 The Centre for Disease Control and Prevention (CDC) also include progressive neurological conditions and kidney disease within their categorisations of chronic physical illness.11 Despite the variability in aetiology across these illnesses, individuals diagnosed with a chronic physical illness generally require long-term treatments and are at increased risk of experiencing negative psychological sequelae, such as depression and anxiety, behavioural withdrawal and increased social isolation.12

Psychological adjustment refers to a healthy rebalancing to new circumstances across five core components: emotional balance, absence of psychological disorders, low negative affect, adequate functioning and satisfaction within life domains.12 A variety of different psychological models have been proposed to understand adjustment reactions to chronic disease, including the stress-coping model, the illness representation model and the adaptive tasks and coping model.13

The stress-coping and the adaptive tasks and coping models suggest that chronic physical illness generates acute and chronic illness stressors, which precipitate cognitive and behavioural responses that modulate individual health.13 The illness representation model and the adaptive coping model also incorporate emotional responses as a distinct pathway that regulates psychological adjustment.11 Overall, these models suggest that illness stressors produce cognitive, emotional and behavioural responses that result in either positive or negative adjustment reactions. The principal difference between models is their conceptualisation of the temporal relationship between these responses, although more recent literature suggests that these are parallel systems that probably interact with each other.13

The precise mechanism by which virtual realities improve individual adjustment is relatively unknown.15 It has been suggested that as immersive VR interventions offer access to virtual experiences with an increased sense of presence, they activate the same neural circuitry as embodied experience and thus can induce similar internal processes in the user.14 Accordingly, VR interventions probably moderate the user’s psychological state and improve psychological adjustment by either minimising the saliency of acute illness stressors or by altering behavioural and emotional responses to said stressors.

Emerging research consistently indicates that VR therapeutic interventions can be safely offered to mitigate the consequences of chronic physical illness and improve individual adjustment reactions. VR interventions have been shown to reduce distress during cancer treatments,15 induce positive states in patients with dementia,16 and promote positive postoperative outcome following cardiovascular surgery.17 VR interventions are promising methods to improve adjustment to chronic disease, but there is a need to evaluate how they are used in populations with chronic physical illness and the quality of the evidence supporting their use.18

A search of PROSPERO, Medline and the Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports, indicated no systematic reviews completed or currently in progress that have examined the effect of immersive VR interventions on psychological adjustment in adults with a chronic physical illness. Two reviews have examined the role of VR interventions in populations with cancer.15 19 However, these reviews did not specifically consider immersive interventions; they pooled studies across child and adult populations, and did not purposely examine adjustment outcomes. Additionally, a recently published review has examined the effectiveness of VR interventions in palliative care, again predominantly among people with cancer.20

Therefore, the aim of this review was to answer the following questions: (1) How are immersive VR interventions used to improve well-being in adults with chronic physical illness? (2) How effective are immersive VR interventions at improving psychological well-being or adjustment among adults with chronic physical illness?

METHOD

Design

A systematic literature review was conducted and reported in line with the Preferred Report Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.21 The review was preregistered in the PROSPERO register: CRD42019142611
Search strategy and study selection
The search strategy was developed in collaboration with a medical librarian (RF). The search was performed on 9 March 2023 across the following databases: Medline, PsycINFO, Embase, Web of Science and Scopus. It was limited to papers published since July 1993, which includes the entire lifespan of immersive VR systems.

The following keyword search was completed using medical subject headings and synonyms: ‘virtual reality’ OR ‘vr’ AND ‘quality of life’ OR ‘qol’ OR ‘mental health’ OR ‘emotions’ OR ‘mood’ OR ‘well-being’ OR ‘depression’ OR ‘depressive disorder’ OR ‘anxiety’ OR ‘anxiety disorders’ OR ‘stress’ OR ‘patient satisfaction’ OR ‘benefit’ OR ‘mood disorders’ OR ‘affective disorder’ OR ‘life change events’. An example of the Medline search strategy is provided in online supplemental appendix 1.

Owing to the variability in chronic illness characterisation,11 search terms relating to specific illnesses were not included in the search strategy, and records were manually screened to assess chronic illness, based on WHO and CDC definitions.12 13 This method enabled enhanced selectivity in the search strategy and ensured that no chronic illness conditions were inadvertently omitted from the study.

Similarly, no specific measure of adjustment was included in the search strategy. Based on the CDC definitions, a well-being or adjustment measure could assess: the presence of positive emotions and moods, absence of negative emotions, satisfaction with life and positive functioning.22 Identified records were manually screened to determine the presence of an appropriate pre–post measure of adjustment.

Inclusion and exclusion criteria
The review considered data in published articles, conference proceedings and abstracts. Studies were included if they met the following criteria: (a) adult population aged 18 years or older; (b) diagnosis of a chronic physical illness; (c) immersive VR intervention; (d) experimental, quasi-experimental or observational studies with a minimum of a pre–post design; (e) a minimum of one pre–post measure of adjustment.

Studies were excluded if they met any of the following criteria: (a) non-English language text; (b) non-immersive or semi-immersive VR intervention; (c) VR intervention was specifically designed to provide cognitive remediation or physical motor rehabilitation; (d) non-empirical research, such as expert reviews, opinion pieces etc; (e) qualitative research.

Once duplicate records were removed, the titles and abstracts of the remaining records were screened independently against the inclusion/exclusion criteria by two reviewers. Records identified for full-text review were then assessed independently by two reviewers. The reference lists of records identified for full-text review were also screened to find any additional records that met the inclusion/exclusion criteria, not detected through the search strategy. Any discrepancies between first and second reviewer, that could not be resolved independently, were resolved through a third reviewer.

Data extraction
Data were extracted from each study using the Cochrane Collaboration data collection form for intervention reviews for randomised controlled trials (RCTs) and non-RCTs.23 All data extractions were ratified by a second reviewer, with any disagreements resolved through a third reviewer.

Quality appraisal
Risk of bias was assessed following the Cochrane Collaboration recommendations,24 using either the ‘Cochrane risk-of-bias tool for randomised trials (RoB 2)’25 or the ‘Risk of Bias in Non-Randomised Studies – of Interventions’ (ROBINS-I) tool.26 Based on the results of these assessments, studies were rated as either at low risk of bias, some concerns of bias or at high risk of bias. Risk of bias assessments were not undertaken for feasibility or pilot studies or for published abstracts where information was not available to complete the assessment.

Data analysis
Where possible, effect sizes were reported or calculated using available data, with Cohen’s d and r values provided. Any transformations of effect sizes were completed using Psychometrica freeware.27 Variability in study designs and measures of outcome restricted the suitability for pooling data for meta-analysis. Accordingly, a narrative synthesis informed by the Template for Intervention Description and Replication (TIDieR) framework was undertaken.28

RESULTS
Figure 1 provides an illustration of the overall search and study selection process. A total of 31 studies were included in the review (see online supplemental table 1). The results that follow are structured by the type of VR examined in the studies. A summary of the findings is presented in online supplemental table 2.

Environment-based relaxing VR during medical treatments
Rationale
Overall seven studies investigated environment-based immersive VR as a non-pharmacological distraction intervention to reduce treatment distress and improve adjustment in patients undergoing medical treatment.29–35

Design
A total of three studies were defined as RCTs to assess efficacy,29 30 32 and another study was defined as a crossover design.33 The remaining three studies were
pre–post designs with no control conditions, with two of these studies aiming to measure effects of VR treatments, and the remaining study described as a feasibility study.

Samples
The studies ranged in size from 30 to 50 participants. The median age of participants was 50.8 years, with 75% identifying as female. In six studies, environment-based relaxing VR interventions were provided to 202 patients with cancer primarily undergoing chemotherapy treatments. A single study examined immersive VR as a distraction intervention in 58 patients with kidney disease undergoing haemodialysis.

VR intervention
Studies used a range of immersive headsets (Vuzix Wrap; ez Vision; Zeiss VR One; VR Box; Oculus Quest; unspecified systems) to allow participants to explore relaxing scenes of nature through several different VR software packages (Ocean Rift or Happy Place; Second Life; Nature Treks; unspecified software).

VR procedure
A total of five VR interventions examined single treatments delivered in clinical settings. One study provided daily VR treatment in a domestic setting, 5 days a week for 2 weeks. Another study delivered a single VR intervention weekly for 2 weeks. Only the intervention provided to patients undergoing haemodialysis was manualised, while in all other studies patients could choose their VR scenario. The median duration of VR interventions was 20 min.

In three studies interventions were offered by two intervention providers—either a psychologist and...
The interventions in the remaining studies were offered by either a nurse or an unspecified intervention provider. No study specified information on the intervention provider’s professional background, degree of expertise or level of training with the VR intervention.

**Findings**

Two RCTs suggested that VR significantly reduces anxiety symptoms, while improving pain and mood states. However, a single RCT and a crossover study found mild reductions in pain and distress that did not reach significance. A pre–post study suggested that VR significantly increases feelings of relaxation and provides a positive distraction during chemotherapy.

**Environment-based relaxing VR with integrated relaxation techniques during medical treatments**

**Rationale**

Three studies investigated environment-based immersive VR with integrated relaxation techniques, as a non-pharmacological distraction intervention to reduce treatment distress and improve adjustment in patients undergoing medical treatments. The proposal is that immersive VR with integrated relaxation techniques reduces saliency of illness stressors and engages patients in processes that increase emotional coping, which improves patient adjustment during medical treatments.

**Design**

A single study was classified as an RCT, comparing VR intervention with treatment as usual control conditions, whereas the other two studies were considered feasibility studies, with no control conditions.

**Population**

Study sample sizes ranged between 20 and 38 participants, with a median age of 50.3 years, and 55% of participants identifying as female. Overall, two studies investigated environment-based relaxing VR with integrated relaxation techniques across 73 patients with cancer receiving medical treatments, while one study examined these interventions in 20 patients with kidney disease receiving haemodialysis.

**Game-based relaxing VR during medical treatments**

**Rationale**

A total of four studies investigated game-based immersive VR as a non-pharmacological distraction intervention for distress and to improve adjustment in people with cancer and people with inflammatory bowel disease (IBD) undergoing medical treatments.

**Design**

All four studies in the cancer area were described as crossover studies, which were considered pre–post designs with treatment as usual control conditions. The study in IBD was a RCT where the control was treatment as usual.

**Population**

Study samples ranged between 16 and 137 individuals, with a median age of 52.4 years and 72% identifying...
as female. All participants who had a cancer diagnosis were receiving chemotherapy. The participants with IBD were receiving vedolizumab intravenous infusion.

**VR intervention**
Most studies used the Sony PC Glasstron PLM-S700 VR headset, with one using a Samsung VR headset. These headsets operated commercially available VR software, including: Oceans Below; A World of Art Timelapse; Titanic Adventure Out of Time.

**VR procedure**
All studies offered a single session VR intervention with a duration ranging between 10 and 180 min; median duration 67.5 min. All studies conducted among people with cancer offered participants the choice of VR scenario and duration of the VR scenario. The study conducted among people with IBD provided a specific gut healing game.

All interventions were delivered in clinic settings, by either a research nurse or an unspecified intervention provider. No study presented information on the provider’s professional background, degree of expertise or level of training needed to deliver the VR intervention.

**Outcomes**
All studies conducted among people with cancer used validated measures to assess pre–post changes in adjustment across a range of psychological constructs, including anxiety, symptom distress and fatigue. The study conducted in patients with IBD used a questionnaire that measured attitudes and feelings but no information on psychometric properties was provided.

**Findings**
One study noted that a game-based relaxing VR significantly reduced anticipatory anxiety, with further non-significant reductions in symptom distress and fatigue. Another study noted significant reduction in symptom distress, with non-significant decreases in anxiety and fatigue levels. Whereas another found game-based relaxing VR significantly altered time perception, with non-significant decreases in reported anxiety and symptom distress. For patients with IBD, significant improvements for the VR group were reported in well-being and psychological comfort, feeling of relaxation, improved positive attitude while waiting for the next administration of the drug and increased motivation for treatment.

**Environment-based relaxing immersive VR to improve adjustment in clinical settings**

**Rationale**
A total of 15 studies investigated immersive VR as a distraction intervention to improve patient adjustment. The studies are based on the assumption that providing patients with virtual access to natural environments can increase the availability of coping resources, which allows them to manage illness stressors and leads to improvements in adjustment.

**Design**
Study designs included a prospective single-arm study, a crossover study, four RCTs and two pilot studies following a RCT design. The remaining seven studies were described as feasibility studies.

**Population**
Sample sizes ranged between 8 and 77 participants, with a median age of 67 years and 57% identifying as female. Five studies examined the effect of immersive VR interventions on adjustment across 117 people with cancer. Another five studies explored the use of environment-based immersive VR to improve adjustment in a total of 60 people with dementia.

Three studies were conducted among people with coronary artery disease, one among people with heart failure and one among people with chronic obstructive pulmonary disease.

**VR intervention**
Four studies used the Samsung Headgear and three studies used the VR Tier One device. The remaining studies used a variety of immersive VR headsets operating a range of VR software allowing patients the opportunity to view and explore varying relaxing scenes of nature. Three studies used the therapeutic garden approach and one was based on compassionate mind training.

**VR procedure**
Nine studies offered a single VR session with a median duration of 20 min. The remaining studies offered a series of VR sessions, ranging in frequency from 3 to 10. Each of these VR sessions lasted a median time of 20 min.

Most studies offered a fixed-content VR session, whereas a few studies allowed participants to tailor their VR experience by choosing the viewing scenario or showing videos that were shot based on discussions with patients and carers.

**Outcomes**
Several studies used validated outcome measures to examine a range of psychological constructs, such as pain, symptom distress and other emotions. The remaining studies also used observer report measures assessing patient emotions and challenging behaviours.

**Findings**
A pre–post study suggested that a VR intervention significantly reduces pain and fatigue, while improving subjective anxiety and depression among inpatients with cancer. Comparably a crossover study indicated...
that environment-based-relaxing immersive VR can significantly improve emotional arousal and relaxation among patients with cancer in clinical research settings. A study among people with heart failure suggested that VR has beneficial effects on pain, and beneficial effects on anxiety, depression and stress were also found when VR was used as part of cardiac rehabilitation and pulmonary rehabilitation.

The feasibility studies examining environment-based relaxing VR determined that further controlled clinical studies are possible in this population. Preliminary analysis suggested that VR interventions are acceptable among patients and their caregivers.

**Mixed environment- and game-based relaxing VR**

**Rationale**
The included studies aimed to test feasibility of mixed environment and game-based relaxing immersive VR interventions with integrated relaxation techniques as a treatment to improve adjustment among patients with multiple sclerosis (MS) with frequently high symptom burden. These papers proposed that mixed environment and game-based VR interventions recruit attentional resources, which reduces the saliency of illness stressors and improves patient adjustment.

**Study design**
The included records consisted of two feasibility studies, considered pre–post designs with no control condition.

**Population**
The studies ranged in size from 4 to 8 patients, examining the use of immersive VR interventions in a total of 12 patients diagnosed with relapsing–remitting MS. Participant demographic variables were not reported in either study.

**VR intervention**
Both studies used HTC Vive Pro VR Headsets operating commercially available VR software. Patients with MS were randomly assigned to a game-based or environment-based relaxing VR programme, where participants were encouraged to engage in goal-based or self-directed activity to explore a VR environment designed on classic relaxation principles.

**VR procedure**
The VR intervention was delivered in either clinical or unspecified setting. Both interventions were delivered weekly for 8 weeks, facilitated by a single intervention provider. However, neither study provided information on the intervention provider’s professional background, degree of expertise or level of training. Both VR sessions were 35 min in duration and were manualised interventions.

**Outcome**
The studies measured pre–post changes in adjustment through a validated patient report measure of positive and negative affect.

**Findings**
These studies concluded that immersive VR interventions are acceptable in patients with MS. Neither study measured or reported adverse effects of the VR intervention

**DISCUSSION**
This review aimed to investigate how immersive VR interventions are used, and evaluated it as an intervention to improve psychological adjustment in adults diagnosed with chronic physical illness. Primarily, VR interventions consist of environment-based relaxing virtual realities, offered as a treatment to reduce side effects of medical procedures or as an intervention to reduce negative sequelae associated with chronic physical illness.

This systematic review and synthesis of findings indicated that immersive VR interventions are well tolerated and offer acceptable treatments with the aim of improving psychological adjustment in patients with cancer, dementia, cardiovascular disease, MS and kidney disease. However, 13 out of the 31 studies included in the review were feasibility or pilot studies and a further four studies were considered to have a high risk of bias. Therefore, any findings about effectiveness from these studies should be interpreted cautiously.

There was no evidence that different VR types offer any discernible benefit over each other. There was significant variability in the VR types and procedures used across studies. These methodological inconsistencies probably account for the variability in findings across studies and limit our ability to make detailed assessments of how virtual realities might be used in populations with chronic disease and understand the unique contribution different VR interventions might make to clinical practice. Accordingly, more robust studies of effectiveness are needed to establish the suitability of VR treatments as adjustment interventions in populations with chronic disease.

The precise mechanisms by which immersive virtual realities may exert physical and psychological effects on patients is unclear. Several hypotheses have been postulated to explain their impact; these generally suggest that immersive virtual realities modulate attentional and emotional resources in a manner that reduces the impact of negative sequelae in chronic physical illness.

**Immersive VR interventions, attentional modulation, nociception and pain**
Individuals diagnosed with chronic physical illness, may experience anxiety and depression as a direct
Immersive VR interventions and psychological coping

Alternatively, VR interventions may exert positive effects by modulating an individual’s capacity to cope with the negative consequences of chronic illness. Coping describes the changing cognitive and behavioural effort to manage external or internal demands that are appraised as stressful or beyond the resources of an individual. Lazarus and Folkman’s stress and coping framework states that emotion-focused coping strategies help an individual regulate their emotional responses to a challenging situation.

Immersive VR can be considered an emotion-focused strategy that facilitates emotional regulation in distressed patients with chronic disease. Immersive VR provides access to relaxing environments, while also promoting engagement in traditional relaxation techniques—for example, mindfulness. Therefore, the positive effects observed in patients with chronic disease may be a result of improved emotional regulation facilitated by immersive VR interventions.

Immersive VR and the therapeutic effects of nature

Lastly, the therapeutic benefits of immersive VR interventions may be a result of patients with chronic disease experiencing a simulated natural environment with increased presence. Access to nature has been shown to promote human health and adjustment reactions by mitigating adverse environmental stressors. This may be due to natural environments exerting a regenerative effect on attentional processes, which limits attention-directed fatigue and promotes adjustment among individuals.

Likewise, the visual perception of a natural environment may induce an immediate affective response that activates positive cognitive and emotional appraisal processes, which improves the physiological and psychological state of an individual. Therefore, the observed benefits of relaxing VR interventions could be related to the salutogenic nature of the VR environment.

Immersive VR as a platform to deliver therapeutic interventions

The physical and psychological consequences of chronic illness can have a debilitating effect on patients, which restricts their ability and motivation to engage in meaningful activity. A benefit of VR interventions is that it increases the availability of realistic experiences to patients. Thus, VR interventions could be particularly useful in populations with chronic disease by providing an innovative way for them to access equitable therapeutic experiences, which otherwise would be unavailable owing to the restrictive nature of their disease or inpatient treatments.

VR offers a unique platform to provide either classic relaxation techniques or complete therapeutic interventions, because it activates the same neurological circuitry as the embodied experience. A VR intervention may improve psychological adjustment as effectively as a face-to-face intervention; as was reported in some reviewed studies.

Limitations

Despite promising preliminary findings indicating that VR interventions may offer a novel method to improve psychological adjustment in certain chronic disease conditions, there were consistent methodological limitations across all studies that limited their general validity. These included: small samples, constrained recruitment methods, limited number of controlled studies, non-manualised treatment protocols and variability in outcome measures used.

Furthermore, the intrusive nature of immersive VR interventions also poses a unique methodological concern for any study examining their efficacy. VR equipment and programmes limit the opportunity for participant blinding in any study and this makes it difficult to determine whether any findings are a true treatment effect, or a placebo effect associated with expectancy bias generated by the captivating nature of VR treatment.

Future studies should aim to use RCT designs, with appropriate consideration given to unbiased recruitment and randomisation of participants. These studies should evaluate outcome using validated measures and clearly define their VR methodologies using a standardised framework—for example TIDieR, to allow for reliable replication and assessment of effect.

Clinical implications

Although a substantial portion of this review pertains to feasibility studies, the findings of this review...
highlight that immersive VR interventions may provide a safe and well-tolerated method with the potential to improve psychological adjustment among patients with cancer, dementia, MS and kidney disease, who require inpatient admission or undergo distressing medical procedures. These findings are promising in a population at risk of polypharmacy, and suggest immersive VR can offer a non-pharmacological intervention that is considered acceptable by clinicians, caregivers and patients.

As VR systems become progressively more accessible, immersive VR interventions may begin to offer cost benefits compared with conventional pharmacological and non-pharmacological treatments. One analysis found that VR interventions provide cost benefits in 89.2% of trials. Therefore, it is likely that VR platforms will be increasingly used to improve patient adjustment to chronic illness in non-clinical and clinical settings; particularly in the context of unforeseen events that restrict patient access to services and highlight the need for viable remote interventions.

Further research is needed to better understand the exact effect of VR interventions and the parameters that might determine VR efficacy, such as variations in VR hardware and software. Additionally, the long-term effects of immersive VR interventions remain unknown and this needs to be examined; particularly, whether immersive VR interventions demonstrate habituation in treatment effects and a reduction in long-term patient adherence, as noted in conventional pharmacological treatments used in patients with chronic health conditions.

CONCLUSION

In conclusion, our findings suggest that VR interventions are acceptable treatments that have the potential to improve physical and psychological consequences of physical illness. There is good-quality research to suggest that these VR interventions are effective in reducing pain and distress, particularly among people with cancer.

Contributors All authors contributed to the study design. WRGMG, CJD and RF designed and executed the search strategy. WRGMG, CJD, AA and MD screened abstracts, extracted data and assessed evidence quality. WRGMG and MD analysed and interpreted the data. All authors provided feedback and revisions to the manuscript. All authors approved the final version for submission. MD is the guarantor.

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