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Interventions for improving health literacy in people with chronic kidney disease (Protocol)

Campbell ZC, Stevenson JK, McCaffery KJ, Jansen J, Campbell KL, Lee VWS, Webster AC


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Interventions for improving health literacy in people with chronic kidney disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review aims to look at the benefits and harms of interventions for improving health literacy in patients with CKD.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a worldwide health problem, with an estimated 10% to 13% of the world’s population being affected (Couser 2011; Szczech 2009). CKD is classified into 5 stages; stage 1 and 2 are considered mild, stage 3 and 4 are considered moderate and stage 5 is referred to as end stage kidney disease (ESKD). Stages 1 to 4 CKD have been independently associated with diabetes, hypertension, cardiovascular disease, some cancers, increased hospitalisations and acute kidney injury (Hsu 2008). Specifically there is an increased cardiovascular related mortality even in very early disease (Hallan 2006). The aims of stage 1 to 4 CKD management include decreasing progression to ESKD and the risk of cardiovascular complications through management of kidney function and common factors of CKD progression such as hypertension and diabetes. Effective treatment methods include but are not limited to decreasing hypertension, decreasing proteinuria, increasing glycaemic control, encouraging weight loss and healthy-living behaviours, smoking cessation and treatment of other cardiovascular risk factors such as dyslipidaemia (James 2010).

Only a minority of stage 1 to 4 CKD patients go on to develop kidney failure or ESKD. This is partly because of the increased risk of mortality in earlier stages of kidney disease from other related comorbidities (Go 2004). ESKD can require renal replacement therapy (RRT) in the form of dialysis or kidney transplant, or can
be managed in a more conservative way usually in older patient with multiple co-morbidities. ESKD is associated with extremely high mortality, morbidity and a substantially low quality of life (Foley 1998). More than 2 million people worldwide are being kept alive by RRT however this is thought to only account for 10% of those who need it (Eggers 2011). The high financial and social cost of ESKD to both individuals and society place it as a significant health priority in the field of non-communicable diseases and it is considered a death sentence in many developing countries (De Vecchi 1999).

**Description of the intervention**

The long term management of both CKD requires a high level of patient involvement both in decision making and implementation of care. For patients to be effective at health decision making and self-management they must possess the ability to understand and utilise health information, a skill which is referred to as ‘health literacy’ (Nielsen-Bohlman 2004). The concept of health literacy can be approached in two ways, health literacy can be seen as a risk factor or as an asset, however these two ideas are not mutually exclusive. Health literacy as a risk factor - the idea that low health literacy is a risk for poorer health outcomes - has been widely investigated. Low health literacy has been associated with an increase in mortality and poorer overall health status (Berkman 2011). Those with lower general literacy are more likely to have a lower level of knowledge and comprehension regarding health related issues, have fewer immunisations and health screenings, have more hospitalisations and be admitted to emergency more frequently than those on the other end of the spectrum (Berkman 2011; Dewalt 2004). Some health literacy interventions aim to mitigate the negative effects of low health literacy, improve patients’ literacy or make it easier for those with low health literacy to understand and access health information. Health literacy can also be viewed as an asset, a skill that can be built through patient education, although this concept requires further solidification. Within this framework health literacy is seen as an outcome of health education and communication rather than a factor that may lead to poorer health outcomes. Health literacy interventions that are treating health literacy as an asset have a wider variety of aims including developing self-management abilities, improving patients’ ability negotiate or navigate within the health system, improving patients’ ability to understand and implement health-care information. These interventions are not necessarily aimed at those with low health literacy and could in theory help any patient. A more detailed appraisal of these two similar but distinct conceptualisations of health literacy can be found in the paper “The evolving concept of health literacy” (Nutbeam 2008). Both health literacy, the risk factor, and health literacy, the asset, impact on the ability for a patient to competently manage a health problem, especially in the context of chronic disease such as CKD which has an extremely high level of patient involvement in care. This study treats all interventions that fall under either category as a ‘health literacy intervention’ as the separation of the two types of intervention seems counter intuitive in this setting. The evidence about the effectiveness of specific health literacy interventions is still emerging. There is no standardised intervention to date, and there may never be, however some common design features have been found to improve health literacy (Sheridan 2011).

- Presenting written information in a different way (e.g. giving essential information first)
- Presenting numerical information in a different way (e.g. highest number is always better)
- Use of icons and symbols and graphs
- Presenting information pitched at a lower literacy level (e.g. that of primary school comprehension)
- Use of video tutorials
- Literacy training for physicians
- Implementing self-management plans.

**How the intervention might work**

There is evidence that health literacy interventions can reduce emergency department visits, hospitalisations and disease severity in other chronic diseases. Specifically within CKD low health literacy has been found to be associated with a higher risk of death (Cavanaugh 2010) and also a lower likelihood of being referred for transplant (Grubbs 2009). Low health literacy was found to be common among CKD patients in a systematic review in 2013, however the studies in this review predominately looked at patients with ESKD (Fraser 2013). Since then one study has investigated the prevalence of low health literacy specifically in those with stage 1 to 4 CKD and found that low health literacy is also common in this sub population of patients (Devraj 2015). This study also found a small but significant positive relationship between kidney function (estimated glomerular filtration rate (eGFR)) and health literacy. Due to the link between low health literacy and poorer health outcomes and the indication that it is prevalent in CKD and ESKD patients it follows that improving the health literacy of these patients could have a positive effect on their health outcomes.

Health literacy interventions are not just about reducing the risk for those with low health literacy, but also about improving the health management of any individual. This is most important in diseases which require a high level of patient involvement, such as CKD. The management of CKD is complex and requires patients to understand the impact many different things including but not limited to blood pressure, weight, cholesterol, fluid intake, diet, exercise, medications both adherence and interactions as well as navigate the health system and interact with many different health care providers. Health literacy interventions aimed at improving an individual’s self-management ability could be incredibly useful.
in the setting of stage 1 to 4 CKD or ESKD and this study will investigate both populations.

**Why it is important to do this review**

Health literacy and how to improve it has been identified as a central research priority both by Kidney Health Australia and The National Institute of Diabetes and Digestive and Kidney Diseases in Canada (Manns 2014; Tong 2015). It is now well accepted that a high proportion of patients with CKD do have low health literacy as measured by an array of health literacy measurement tools (Dageforde 2013; Kutner 2006). Those at higher risk for developing CKD may also be at high risk for having low health literacy as both low health literacy and CKD are disproportionally apparent in those who have low educational status, are from low socioeconomic backgrounds, are from minority groups and are of an older age (Dageforde 2013; Kutner 2006). Research into health literacy interventions thus far has been broad focusing on all chronic disease (Sheridan 2011) however patients with CKD have specific complications and outcomes that should be analysed separately. One example of this is the decrease in cognitive ability seen in CKD patients. CKD is an independent risk factor for the development of cognitive decline (Etgen 2012) and is thought to be related to cognitive impairment both directly through inflammation, toxins, and dialysis and indirectly through related complications such as hypertension and diabetes (Bugnicourt 2013). A review of health literacy interventions specifically targeted to patients with CKD will provide more focused information, as what works in one chronic disease may not work in another. Van Scoyoc 2010 completed a similar review analysing health literacy interventions in patients with diabetes. They highlighted the aspects of the interventions that had an impact on health outcomes, and the ones that had no effect, delivering information for future development of health literacy interventions in this population. This review expects similar results and hopes to forward the development of tools to improve healthcare for those with low health literacy in the CKD population.

**OBJECTIVES**

This review aims to look at the benefits and harms of interventions for improving health literacy in patients with CKD.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials (RCTs), quasi-RCTs (RCTs in which allocation to treatment where allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), cluster RCTs, cohort studies and non-randomised controlled studies looking at interventions for improving health literacy in patients with CKD.

**Types of participants**

**Inclusion criteria**

Patients with CKD defined by abnormalities of kidney structure or function, present for > 3 months, with implications for health (KDIGO 2012), with one or more markers of kidney damage.

- Albuminuria (albumin excretion ratio (AER) Z30 mg/24 h; albumin-creatinine ratio (ACR) Z30 mg/g (Z3 mg/mmol))
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation
- Decreased GFR: GFR < 60 mL/min/1.73 m² (GFR categories G3a to G5)

**Exclusion criteria**

- Children (< 18 years) or those under guardianship, proxies (carers).
- Studies with populations including people without CKD, perhaps another chronic disease, will only be included if the data for the CKD patients can be analysed separately.

**Types of interventions**

Any intervention that the authors report to be aimed at improving health literacy. This may include interventions that aim to:

- Mitigate the effects of low health literacy
- Facilitate literacy skill building
- Improve knowledge about disease and treatment
- Improving self care
- Improving comprehension skills.

The types of comparisons will include the following,

- Health literacy intervention versus placebo
- Health literacy intervention versus other intervention not aimed at improving health literacy
- Health literacy intervention versus another health literacy intervention.
Types of outcome measures

Primary outcomes
1. Progression of kidney disease (change in GFR, doubling of serum creatinine, progression of CKD stage)
2. Health literacy (improvement on an accepted health literacy measurement tool, knowledge, skills, self-management, involvement with care)

Secondary outcomes
1. Change in quality of life on a recognised quality of life scale either general (e.g. QoL, SF36) or disease appropriate (e.g. KDQOL)
2. Mortality (including cause-specific deaths, cardiovascular and kidney disease related death)
3. Hospitalisations including use of emergency care and length of stay
4. Complications of CKD (hypertension, diabetic control, metabolic bone disease, anaemia)
5. Adverse outcomes of health literacy intervention (depression, decreased self efficacy)

Search methods for identification of studies

Electronic searches
We will search the Cochrane Kidney and Transplant Specialised Register through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.
1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals

Data collection and analysis

Selection of studies
The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable; however studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Difference between authors in the screening will be reconciled by discussion and if needed inclusion of a third party.

Data extraction and management
Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies
The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).
- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?
For non-randomised studies the ACROBAT-NRSI will be used (Sterne 2014). Two authors will use this tool to independently assess the risk of bias of each included study.

**Measures of treatment effect**

For dichotomous outcomes (e.g. death, number of patients progressing to ESKD) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (health literacy measurement, length of hospital stay), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

**Unit of analysis issues**

Cluster RCTs will be analysed in one of two ways.

1. Using a statistical analysis that properly accounts for the cluster design. Some examples of these are based on a multi level model, a variance components analysis or may use ‘generalised estimating equations’ (Higgins 2011)

2. Conduct the analysis treating the sample size as the number of clusters and proceed as if the study were individually randomised, treating the clusters as individuals.

When considering cross-over studies we will only use data from the first period.

When considering studies with multiple treatment groups we will try to combine all relevant experimental intervention groups of the study into a single group and to combine all relevant control intervention groups into a single group to enable single pair wise comparison.

**Dealing with missing data**

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

**Assessment of heterogeneity**

Heterogeneity will be assessed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

**Assessment of reporting biases**

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

**Data synthesis**

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age, stage of CKD, underlying concurrent disease states (e.g. diabetes), severity of health literacy proficiency, English proficiency. Specifically we are interested in subgroup analysis of stage 1 to 4 CKD and ESKD. Heterogeneity in treatments could be related to the way the intervention is delivered (e.g. one-on-one, web based or in groups) or the duration of the intervention.

If meta-analysis is not possible, adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

**Sensitivity analysis**

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), delivery medium (paper versus electronic media versus other), stage of kidney disease (mild versus moderate versus ESKD).

**‘Summary of findings’ tables**

We will present the main results of the review in ‘Summary of findings’ tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The ‘Summary of findings’ tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.
The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b).

ACKNOWLEDGEMENTS

We wish to thank the referees for their comments and feedback during the preparation of this protocol.

REFERENCES

Additional references

Berkman 2011

Bugnicourt 2013

Cavanaugh 2010

Couser 2011

Dageforde 2013

De Vecchi 1999

Devraj 2015

Dewalt 2004

Eggers 2011
Eggers PW. Has the incidence of end-stage renal disease in the USA and other countries stabilized?. *Current Opinion in Nephrology & Hypertension* 2011;20(3):241–5. [MEDLINE: 21422925]

Etgen 2012

Foley 1998

Fraser 2013

Go 2004
Grubbs 2009

Hallan 2006

Higgins 2003

Higgins 2011

Hsu 2008

James 2010

KDIGO 2012

Kutner 2006

Manns 2014

Nielsen-Bohlman 2004

Nutbeam 2008

Schunemann 2011a

Schunemann 2011b

Sheridan 2011

Sterne 2014

Szczech 2009

Tong 2015

Van Scoyoc 2010
Van Scoyoc E, DeWalt D. Interventions to improve diabetes outcomes for people with low literacy and numeracy: a systematic literature review. *Diabetes Spectrum* 2010;23(4):228–37. [DOI: 10.2337/diaspect.23.4.228] * Indicates the major publication for the study
## Appendix 1. Electronic search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
</table>
| CENTRAL    | 1. MeSH descriptor: [Kidney Diseases] this term only  
2. MeSH descriptor: [Renal Replacement Therapy] explode all trees  
3. MeSH descriptor: [Renal Insufficiency] this term only  
4. MeSH descriptor: [Renal Insufficiency, Chronic] this term only  
5. hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched)  
6. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched)  
7. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched)  
8. kidney disease* or renal disease* or kidney failure or renal failure:ti,ab,kw (Word variations have been searched)  
9. ESRF or ESKF or ESRD or ESKD:ti,ab,kw (Word variations have been searched)  
10. CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched)  
11. CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched)  
12. predialysis or pre-dialysis:ti,ab,kw (Word variations have been searched)  
13. [or #1-#12]  
14. MeSH descriptor: [Health Literacy] this term only  
15. MeSH descriptor: [Health Education] this term only  
16. MeSH descriptor: [Consumer Health Information] this term only  
17. MeSH descriptor: [Patient Education as Topic] this term only  
18. MeSH descriptor: [Health Knowledge, Attitudes, Practice] this term only  
19. MeSH descriptor: [Comprehension] this term only  
20. MeSH descriptor: [Self Care] explode all trees  
21. MeSH descriptor: [Educational Status] this term only  
22. literacy or literate:ti,ab,kw (Word variations have been searched)  
23. patient education:ti,ab,kw (Word variations have been searched)  
24. self-management or self-car*:ti,ab,kw (Word variations have been searched)  
25. [or #14-#24]  
26. [and #13, #25] |

| MEDLINE    | 1. Health Literacy/  
2. Health Education/  
3. Consumer Health Information/  
4. (literacy or literate).tw.  
5. educational status/  
6. Patient Education as Topic/  
7. exp Self Care/  
8. Health Knowledge, Attitudes, Practice/  
9. Comprehension/  
10. patient education.tw.  
12. or/1-11  
13. Kidney Diseases/  
14. exp Renal Replacement Therapy/  
15. Renal Insufficiency/  
16. exp Renal Insufficiency, Chronic/ |
17. dialysis.tw.
18. (hemodialysis or haemodialysis).tw.
19. (hemofiltration or haemofiltration).tw.
20. (hemodiafiltration or haemodiafiltration).tw.
21. (kidney disease* or renal disease* or kidney failure or renal failure).tw.
22. (ESRF or ESKF or ESRD or ESKD).tw.
23. (CKF or CKD or CRF or CRD).tw.
24. (CAPD or CCPD or APD).tw.
25. (predialysis or pre-dialysis).tw.
26. or/13-25
27. and/12,26

EMBASE
1. health education/
2. health literacy/
3. health promotion/
4. psychoeducation/
5. patient education/
6. nutrition education/
7. consumer health information/
8. exp comprehension/
9. (literacy or literate).tw.
11. patient education$.tw.
12. or/1-11
13. exp renal replacement therapy/
14. kidney disease/
15. chronic kidney disease/
16. kidney failure/
17. chronic kidney failure/
18. mild renal impairment/
19. stage 1 kidney disease/
20. moderate renal impairment/
21. severe renal impairment/
22. end stage renal disease/
23. renal replacement therapy-dependent renal disease/
24. kidney transplantation/
25. (hemodialysis or haemodialysis).tw.
26. (hemofiltration or haemofiltration).tw.
27. (hemodiafiltration or haemodiafiltration).tw.
28. dialysis.tw.
29. (CAPD or CCPD or APD).tw.
30. (kidney disease* or renal disease* or kidney failure or renal failure).tw.
31. (CKF or CKD or CRF or CRD).tw.
32. (ESRF or ESKF or ESRD or ESKD).tw.
33. (predialysis or pre-dialysis).tw.
34. ((kidney or renal) adj (transplant* or graft* or allograft*)).tw.
35. or/13-34
36. and/12,35
### Appendix 2. Risk of bias assessment tool

<table>
<thead>
<tr>
<th>Potential source of bias</th>
<th>Assessment criteria</th>
</tr>
</thead>
</table>
| **Random sequence generation**  
Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence | **Low risk of bias:** Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)  
**High risk of bias:** Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention  
**Unclear:** Insufficient information about the sequence generation process to permit judgement |
| **Allocation concealment**  
Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment | **Low risk of bias:** Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)  
**High risk of bias:** Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unsealed procedure  
**Unclear:** Randomisation stated but no information on method used is available |
| **Blinding of participants and personnel**  
Performance bias due to knowledge of the allocated interventions by participants and personnel during the study | **Low risk of bias:** No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken  
**High risk of bias:** No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding  
**Unclear:** Insufficient information to permit judgement |
<table>
<thead>
<tr>
<th><strong>Blinding of outcome assessment</strong></th>
<th><strong>Low risk of bias:</strong> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken</th>
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<tbody>
<tr>
<td><strong>High risk of bias:</strong> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding</td>
<td></td>
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<td><strong>Unclear:</strong> Insufficient information to permit judgement</td>
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<th><strong>Incomplete outcome data</strong></th>
<th><strong>Low risk of bias:</strong> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods</th>
</tr>
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<tr>
<td><strong>High risk of bias:</strong> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ‘as-treated’ analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation</td>
<td></td>
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<tr>
<td><strong>Unclear:</strong> Insufficient information to permit judgement</td>
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<tr>
<th><strong>Selective reporting</strong></th>
<th><strong>Low risk of bias:</strong> The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)</th>
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</thead>
</table>
High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias
Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: ZC, JS, KM, JJ, KC, VL, AW
2. Study selection: ZC, JS
3. Extract data from studies: ZC, JS
4. Enter data into RevMan: ZC, JS
5. Carry out the analysis: ZC
6. Interpret the analysis: ZC, JS, KM, JJ, KC, VL, AW
7. Draft the final review: ZC, JS, KM, JJ, KC, VL, AW
8. Disagreement resolution: AW
9. Update the review: ZC
DECLARATIONS OF INTEREST

• Zoe C Campbell: none known
• Jessica K Stevenson: none known
• Kirsten J McCaffery: none known
• Jesse Jansen: none known
• Katrina L Campbell: none known
• Vincent WS Lee: none known
• Angela C Webster: none known