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Interventions to aid employment for people on dialysis and their families (Protocol)

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Interventions to aid employment for people on dialysis and their families

Rachael L Morton¹, Maria Da Silva-Gane², Alan Cass³, Keith Patterson⁴, Amy CW Yip¹, William A Handke⁵, Angela C Webster⁶, ⁷

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Editorial group: Cochrane Kidney and Transplant Group.


ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effectiveness of interventions aimed at assisting employment for people on dialysis, or their family caregivers.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a long-term illness where the functioning of the kidneys is progressively reduced. End-stage kidney disease (ESKD) occurs when kidney function is reduced to less than 15% of normal function, and affects about 5% of the population with CKD. ESKD is irreversible and renal replacement therapy with dialysis or kidney transplantation is usually undertaken. It is estimated that over 2 million people worldwide were receiving dialysis in 2010 (Liyanage 2015) and this figure is expected to double by 2030. Dialysis is an intensive and time consuming treatment, involving attachment to a dialysis machine or fluid exchange system either several times a week, or several times a day. People on dialysis may have other medical problems including cardiovascular disease, diabetes, bone disorders, anaemia, visual impairment, malnutrition, depression, and changes in cognition. Survival for people on dialysis aged between 40 to 44 years is approximately 8 years (USRDS 2013) however people who start dialysis in their late twenties can expect to live for another 20 years (UK Renal Registry 2009).

Employment for people on dialysis has been recently highlighted as a patient-important outcome in kidney management and research. People of working age managed on dialysis are much more likely to be unemployed than age-matched healthy individuals (Essue 2013; Helantera 2012; Kurner 2008; Molsted 2004; Muehrer 2011; van Manen 2001) although many indicate they would like to return to work in either a full-time or part-time capacity (Curtin 1996). The factors associated with job loss after starting
dialysis are older age (i.e. over 49 years); female gender; concurrent chronic diseases; haemodialysis rather than peritoneal dialysis as first treatment modality; poor health insurance coverage; and low or no erythropoietin usage before ESKD (Helantera 2012; Kutner 1991; Muehrer 2011). Family caregivers are also at risk of job loss, due to the time demands of caring for someone on dialysis (Morton 2011).

Description of the intervention

There are several different types of interventions that may assist an adult on dialysis to retain employment. These can include 1) vocational interventions such as flexible working hours, working from home arrangements; 2) workplace adjustments such as a private room for peritoneal dialysis exchanges; 3) government policies such as paid caregiver-assisted home dialysis; 4) skills training after extended time away from work due to hospitalisation; 5) psychosocial interventions to assist with re-adjustment to new roles; 6) drug interventions to reduce uraemic symptoms; 7) provision of nocturnal dialysis therapies such as automated peritoneal dialysis or nocturnal home haemodialysis may also be considered, as well as 8) dialysis machine adjustments to facilitate work-based tasks. The interventions may be delivered by the employer, the government, a kidney charity, dialysis industry, or the renal unit. Interventions that free up the time of a family caregiver such as the provision of patient transport to attend dialysis, or home assistance with dialysis-related duties may assist caregiver work retention.

How the intervention might work

A Cochrane review in oncology reported that multi-faceted interventions are likely to assist in return to work after cancer treatments (de Boer 2015). Multi-disciplinary interventions involving physical exercises combined with patient education, counselling, biofeedback assisted behavioural training and/or vocational counselling, led to higher return-to-work rates than care as usual (RR 1.15, 95% CI 1.01 to 1.30). It is anticipated that multi-faceted interventions will be most effective for dialysis patients.

Why it is important to do this review

“Large numbers of patients give up jobs or reduce work hours before or after initiating dialysis. Unemployment of working-age individuals is associated with greater physical and psychological problems such as anxiety, depression, and loss of self-esteem. Unemployment is also financially burdensome for the individual concerned and their family caregivers.” (Muehrer 2011). This review was undertaken because employment for people on dialysis was rated by kidney patients and carers, as the 4th highest research priority, in a 2014 national exercise hosted by Kidney Health Australia and the Australian Government. The findings from this Cochrane review will provide evidence of effectiveness of interventions aimed at employment for people on dialysis and their family members. This evidence can be used by stakeholders to support the implementation of effective interventions.

OBJECTIVES

To evaluate the effectiveness of interventions aimed at assisting employment for people on dialysis, or their family caregivers.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials (RCTs), quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), and cluster RCTs. We will also include cohort studies, controlled before and after studies, interrupted time series studies, qualitative studies and case studies.

Types of participants

The population was limited to people aged ≥ 15 years who had been diagnosed with CKD stage 5, or were in paid employment prior to starting dialysis; and family caregivers who were in paid employment prior to their family member starting dialysis. The review aims to include all types of dialysis treatment and study participants from low and middle income countries.

Inclusion criteria

• People aged between 15 and 80 years, diagnosed with CKD stage 5 or ESKD who have commenced dialysis
• Family caregivers of adults on dialysis.

Exclusion criteria

• People who are managed with pre-emptive kidney transplantation, or who have not had a period of chronic dialysis prior to transplantation
• People with ESKD < 15 years
• Caregivers of paediatric dialysis patients aged < 15 years.
Types of interventions
- Vocational interventions
- Workplace adjustments
- Government policies
- Skills training
- Psycho-social interventions
- Drug interventions
- Dialysis treatment interventions (e.g. dialysis modality: facility HD, home HD, PD)
- Dialysis equipment interventions.

Types of outcome measures
- Employment in a full-time or part-time capacity following dialysis initiation
- Unemployment, job loss or redundancy following dialysis initiation
- Time to return to work following dialysis initiation
- Durability - or length of time employed
- Sick leave, disability pension rates / or disability pension duration
- Carers' allowance rates / or carers' allowance duration
- Change in household equivalised income.

Primary outcomes
The main outcome is employment in a full-time or part-time capacity at any time point up to 5 years following initiation of chronic dialysis. This may be measured as a dichotomous outcome (i.e. Yes / No); as a rate (i.e. number of persons employed / number of persons of working age); or as a continuous variable (i.e. number of working hours per week).

Secondary outcomes
- Time to return to work following dialysis initiation, (e.g. measured in weeks or months)
- Days of sick leave, disability pension rates or disability pension duration, (e.g. measured in days, weeks or rates)
- Carers' allowance rates or carers' allowance duration (e.g. measured in monetary terms, a proportion of median income, or measured in weeks /months).
- Change in household income (e.g. measured in monetary terms, proportion increase or decrease, or income categories)
- Reasons for unemployment, job loss, redundancy or early retirement following dialysis initiation, (e.g. narrative report).

Search methods for identification of studies

Electronic searches
We will search the Cochrane Kidney and Transplant Specialised Register through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several 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 and transplant journals

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

For non-RCTs, we will also search MEDLINE, EMBASE, PsycINFO and NHS Economic Evaluation Database.
See Appendix 1 for search terms used in strategies for this review.

Searching other resources
1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. Conference proceedings, government reports and theses.

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.

**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 as required, to facilitate assessment. Where more than one publication of one study exists, reports will be grouped together and all relevant study data will be used in the analyses. Any discrepancy between published versions will be highlighted.

**Assessment of risk of bias in included studies**

**Randomised controlled trials**

The following items in studies of RCTs 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?

**Non-randomised controlled trials**

For non-randomised studies we will use the Newcastle-Ottawa scale (Wells 2015) that identifies issues of study quality according to three domains: (representativeness of cohorts); comparability (cohort design or analysis); and outcomes (assessment and follow-up). Domains are subdivided into eight questions, which will be represented in risk of bias tables in this review. A high-quality choice is represented by a star, with the selection, comparability and outcome domains having four, one and three possible stars respectively (see Appendix 3, Appendix 4).

For qualitative studies the Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups will be used (Tong 2007). Risk of bias assessments will be summarised at the outcome level.

**Measures of treatment effect**

For dichotomous outcomes (e.g. employment, unemployment) 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 (e.g. duration of employment or unemployment; household income) the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

**Unit of analysis issues**

The units of analysis in this review will vary depending on the outcome presented. We will adopt a person-centred analysis in that we will report effectiveness of employment interventions in terms of the numbers of people employed, or the number who incur job losses, rather than numbers of jobs created or retained, or productivity gains.

**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. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (e.g. last-observation-carried-forward) will be critically appraised (Higgins 2011).

**Assessment of heterogeneity**

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the $I^2$ statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of $I^2$ values will be as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of $I^2$ depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi$^2$ test, or a confidence interval for $I^2$) (Higgins 2011).

**Assessment of reporting biases**

If possible, funnel plots will be used to assess for the potential existence of publication bias (Deeks 2011).
Data synthesis

Data from RCTs will be pooled using random-effects. Data from non-randomised studies is expected to be heterogeneous, originating from different study designs and may not be suitable for pooling. In this case, effect estimates adjusted for confounding will be displayed in a forest plot. Data from qualitative studies, particularly regarding reasons for job loss will be reported using thematic synthesis following methods described by Thomas and Harden (Thomas 2008).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity. Sources of heterogeneity at study level could be type of dialysis, women or men, class of occupation, patients or carers, country of study or geographic region, social security or social insurance system, and employment interventions. Heterogeneity among participants could be related to age and co-morbid status (e.g. < 50 years, with concurrent heart disease or cancer). Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various interventions used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no employment intervention or usual care.

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: language of publication, source of funding (industry versus other), and country.

'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 (GRADE 2008). 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). We plan to present the following outcomes in the 'Summary of findings' tables.

- Employment in a full-time or part-time capacity following dialysis initiation
- Unemployment, job loss or redundancy following dialysis initiation
- Time to return to work following dialysis initiation
- Sick leave, disability pension rates / or disability pension duration
- Carers' allowance rates / or carers' allowance duration
- Change in household equivalised income.

Acknowledgements

We would like to thank Kidney Health Australia for highlighting this patient-important priority. We would like to thank Cochrane Kidney and Transplant's Information Specialist Gail Higgins for her invaluable assistance with the search strategy, and the referees for their comments and feedback.

We would also like to acknowledge the input of University of Sydney summer scholar, Samuel Herzog.

References

Additional references

Curtin 1996

De Boer 2015

Deeks 2011
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## Appendix 1. Electronic search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
</table>
| CENTRAL  | 1. MeSH descriptor: [Employment] explode all trees  
2. "return to work":ti,ab,kw (Word variations have been searched)  
3. "back to work":ti,ab,kw (Word variations have been searched)  
4. employ*:ti,ab,kw (Word variations have been searched)  
5. unemploy*:ti,ab,kw (Word variations have been searched)  
6. work* and (ability or status or retention or capacity):ti,ab,kw (Word variations have been searched)  
7. "workplace retention":ti,ab,kw (Word variations have been searched)  
8. MeSH descriptor: [Rehabilitation, Vocational] this term only  
9. MeSH descriptor: [Occupational Health Services] explode all trees  
10. MeSH descriptor: [Work] 1 tree(s) exploded  
11. MeSH descriptor: [Sick Leave] this term only  
12. MeSH descriptor: [Absenteeism] this term only  
13. MeSH descriptor: [Life Change Events] this term only  
14. MeSH descriptor: [Activities of Daily Living] this term only  
15. [or #1-#14]  
16. MeSH descriptor: [Renal Replacement Therapy] this term only  
17. MeSH descriptor: [Renal Dialysis] explode all trees  
18. MeSH descriptor: [Hemofiltration] explode all trees  
19. MeSH descriptor: [Kidney Failure, Chronic] this term only  
20. dialysis:ti,ab,kw (Word variations have been searched)  
21. hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched)  
22. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched)  
23. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched)  
24. CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched)  
25. end-stage kidney or end-stage renal or endstage kidney or endstage renal:ti,ab,kw (Word variations have been searched)  
26. ESKD or ESKF or ESRD or ESRF:ti,ab,kw (Word variations have been searched)  
27. [or #16-#26]  
28. [and #15, #27] |
| MEDLINE  | 1. exp Employment/  
2. "return to work".tw.  
3. "back to work".tw.  
4. employ$.tw.  
5. unemploy$.tw.  
6. Rehabilitation, Vocational/  
7. Occupational Health Services/  
8. exp Work/  
9. Occupations/  
10. (work$ and (ability or status or retention or capacity)).tw.  
11. workplace retention.tw.  
12. work capacity evaluation/  
13. Sick Leave/ |
14. Absenteeism/
15. Life change events/
16. “Activities of Daily Living”/
17. Rehabilitation/
18. or/1-17
19. exp Renal Dialysis/
20. exp Hemofiltration/
21. Kidney Failure, Chronic/ or Impairment
dialysis.tw.
22. (hemodialysis or haemodialysis).tw.
23. (hemofiltration or haemofiltration).tw.
24. (hemodiafiltration or haemodiafiltration).tw.
25. (CAPD or CCPD or APD).tw.
26. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw.
27. (ESKD or ESKF or ESRD or ESRF).tw.
28. or/19-28
29. and/18,29
30. Caregivers/
31. Family/
32. (carer$ or caregiver$).tw.
33. (family or families).tw.
34. or/31-34
35. or/30,36
36. and/18,30,35
37. or/30,36

EMBASE
1. exp employment/
2. employment discrimination/
3. work resumption/
4. exp work/
5. vocational rehabilitation/
6. work disability/
7. life event/
8. “return to work”.tw.
9. (work$ and (ability or status or retention or capacity)).tw.
10. workplace retention.tw.
11. unemploy$.tw.
12. or/1-11
13. renal replacement therapy/
14. extended daily dialysis/
15. hemodialysis/
16. home dialysis/
17. hemofiltration/
18. hemodiafiltration/
19. dialysis.tw.
20. (hemodialysis or haemodialysis).tw.
21. (hemofiltration or haemofiltration).tw.
22. (hemodiafiltration or haemodiafiltration).tw.
23. or/13-22
24. Peritoneal Dialysis/
25. Continuous Ambulatory Peritoneal Dialysis/
26. peritoneal dialysis.tw.
27. (CAPD or CCPD or APD).tw.
28. peritoneal dialysis fluid/
29. renal replacement therapy-dependent renal disease/
30. peritoneal dialysis catheter/
31. or/24-30
32. or/23,31
33. and/12,32
34. caregiver/
35. family/ or family health/ or exp family life/
36. and/12,31,35
37. or/33,36

PsycINFO
1. exp employment status/
2. employability/
3. exp reemployment/
4. exp vocational rehabilitation/
5. exp occupational status/
6. "quality of work life"/
7. unemployment/
8. "back to work".tw.
9. "return to work".tw.
10. (employment or employed or employability).tw.
11. or/1-10
12. exp dialysis/
13. dialysis.tw.
15. (hemofiltration or haemofiltration).tw.
16. (hemodialysis or haemodialysis).tw.
17. (hemodiafiltration or haemodiafiltration).tw.
18. (CAPD or CCPD or APD).tw.
19. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw.
20. (ESKD or ESKF or ESRD or ESRF).tw.
21. or/12-20
22. and/11,21
23. caregivers/
24. caregiver burden/
25. exp family socioeconomic level/
26. parental occupation/
27. exp family/
28. (family or families).tw.
29. (care$ or caregiver$).tw.
30. or/23-29
31. and/11,22,30
32. or/22,31
### Appendix 2. Risk of bias assessment tool for RCTs

<table>
<thead>
<tr>
<th>Potential source of bias</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random sequence generation</strong></td>
<td><strong>Low risk of bias:</strong> 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)</td>
</tr>
<tr>
<td>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence</td>
<td><strong>High risk of bias:</strong> 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</td>
</tr>
<tr>
<td></td>
<td><strong>Unclear:</strong> Insufficient information about the sequence generation process to permit judgement</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td><strong>Low risk of bias:</strong> 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)</td>
</tr>
<tr>
<td>Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment</td>
<td><strong>High risk of bias:</strong> 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 un concealed procedure</td>
</tr>
<tr>
<td></td>
<td><strong>Unclear:</strong> Randomisation stated but no information on method used is available</td>
</tr>
<tr>
<td><strong>Blinding of participants and personnel</strong></td>
<td><strong>Low risk of bias:</strong> 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</td>
</tr>
<tr>
<td>Performance bias due to knowledge of the allocated interventions by participants and personnel during the study</td>
<td><strong>High risk of bias:</strong> 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</td>
</tr>
<tr>
<td></td>
<td><strong>Unclear:</strong> Insufficient information to permit judgement</td>
</tr>
</tbody>
</table>
### Blinding of outcome assessment
Detection bias due to knowledge of the allocated interventions by outcome assessors

- **Low risk of bias:** 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.
- **High risk of bias:** 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.
- **Unclear:** Insufficient information to permit judgement.

### Incomplete outcome data
Attrition bias due to amount, nature or handling of incomplete outcome data

- **Low risk of bias:** 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.
- **High risk of bias:** 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.
- **Unclear:** Insufficient information to permit judgement.

### Selective reporting
Reporting bias due to selective outcome reporting

- **Low risk of bias:** 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).
### Appendix 3. Risk of bias assessment - Newcastle Ottawa Scale Form

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

#### Selection

1. Representativeness of the exposed cohort
   - i) truly representative of the average ... in the community *
   - ii) somewhat representative of the average ... in the community *
   - iii) selected group of users (e.g. nurses, volunteers)
   - iv) no description of the derivation of the cohort
2. Selection of the non-exposed cohort
   - i) drawn from the same community as the exposed cohort *
   - ii) drawn from a different source
   - iii) no description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
   - i) secure record (e.g. surgical records) *
   - ii) structured interview *
   - iii) written self-report
   - iv) no description
4. Demonstration that outcome of interest was not present at start of study
   - i) yes *

#### Other bias

Bias due to problems not covered elsewhere in the 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.

**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.
ii) no

Comparability
1. Comparability of cohorts on the basis of the design or analysis
   i) study controls for … (select the most important factor) *
   ii) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second
   important factor.)

Outcome
1. Assessment of outcome
   i) independent blind assessment *
   ii) record linkage *
   iii) self-report
   iv) no description
2. Was follow-up long enough for outcomes to occur
   i) yes (select an adequate follow up period for outcome of interest) *
   ii) no
3. Adequacy of follow-up of cohorts
   i) complete follow-up - all subjects accounted for *
   ii) subjects lost to follow-up unlikely to introduce bias - small number lost - <15 % follow-up, or description provided of those
   lost) *
   iii) follow-up rate < 85% and no description of those lost
   iv) no statement

Appendix 4. Risk of bias assessment - Newcastle Ottawa Scale

Coding manual for cohort studies

Selection

1. Representativeness of the exposed cohort
Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal oestrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of oestrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of oestrogen).
Allocation of stars as per rating sheet

2. Selection of the non-exposed cohort
Allocation of stars as per rating sheet.

3. Ascertainment of exposure
Allocation of stars as per rating sheet.
4. Demonstration that outcome of interest was not present at start of study
In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

Comparability

1. Comparability of cohorts on the basis of the design or analysis
A maximum of 2 stars can be allotted in this category. Either exposed or non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note; If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever versus never, current versus previous or never) Age = , Other controlled factors =

Outcome

1. Assessment of outcome
For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to X-rays would be required.
   1. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (X-rays, medical records, etc.)
   2. Record linkage (e.g. identified through ICD codes on database records)
   3. Self-report (i.e. no reference to original medical records or X-rays to confirm the outcome)
   4. No description.

2. Was follow-up long enough for outcomes to occur
An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3. Adequacy of follow-up of cohorts
This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.
Allocation of stars as per rating sheet

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: RM, AW, AC, WH, AY
2. Study selection: RM, KP, MDSG, AY
3. Extract data from studies: AY, RM, KP, MDSG
4. Enter data into RevMan: AY, RM, KP, MDSG
5. Carry out the analysis: RM, MDSG, AY
6. Interpret the analysis: RM, MDSG, WH
7. Draft the final review: RM, KP, MDSG, AW, AC, WH, AY
8. Disagreement resolution: MDSG, AW
9. Update the review: RM, AW, AC
DECLARATIONS OF INTEREST

None known

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