Is socioeconomic status associated with biological aging, as measured by telomere length?

Tony Robertson*, G David Batty, Geoff Der, Candida Fenton, Paul G. Shiels and Michaela Benzeval.

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A. Background

Throughout the world there are socially-derived inequalities in health. (1) Not only do the poorest members of society suffer the worst health, but there is also a social gradient, whereby each step up the social ladder is associated with improved health. However, the pathways and mechanisms by which socioeconomic status (SES) ‘gets under the skin’ are less well understood. One possible pathway is through a process referred to as ‘biological ageing’. Here, lower SES individuals would suffer greater degeneration of both physical functioning and the ability of the body to meet its physiological demands, compared to higher SES individuals of the same chronological age. (2-4) This biological ageing works via the accumulation of damage to macromolecules (DNA, RNA, proteins, lipids), (5) with this damage driven by exposure to physical, mental and behavioural insults. Importantly, all of these insults are more prevalent with lower SES. (6) Understanding the relationship between SES and biological ageing is important to aid our understanding of not only how social circumstances get under the skin to increase rates of early morbidity and mortality, but also so that we can attempt to minimise these detrimental effects and promote the need for a narrowing of the social inequality gap that presides currently.

Telomeres are nucleoprotein structures (proteins associated with DNA) present at the ends of chromosomes that erode over time through various processes of genetic damage and cell proliferation. This gradual shortening of telomeres has made telomere length a potential measure of an individual’s biological age. (7) If socioeconomic disadvantage does lead to greater cellular damage and more rapid biological ageing, this should be reflected in shorter telomeres. (2)

The evidence for an association between SES and telomere length has thus far been mixed. This myriad of results includes disadvantaged SES being associated with shorter telomeres, (8-9) disadvantaged SES being associated with longer telomeres (10) and SES not being associated with telomere length. (11-13) Therefore, there is a need to quantitatively assess this relationship. To our knowledge, this is the first such systematic review with meta-analysis in this field.
B. Review Aims

To systematically review and quantitatively assess the evidence (using meta-analysis) for the association between SES and telomere length.

Our objectives, in terms of the PICOS statement, were as follows:

**Population:** Adult men and women (18+)

**Intervention:** N/A

**Comparator:** Socioeconomic Status

**Outcome:** Telomere length differences between high and low socioeconomic status groups

**Study design:** Longitudinal, cross-sectional and repeat-cross sectional studies. Population/community-based studies. Population/community-based studies sampling from specific occupation, hospital admission or disease state groups. Case-control studies.
C. Search strategy

Author abbreviations: Tony Robertson (TR), G David Batty (DB), Geoff Der (GD), Candida Fenton (CF), Paul Shiels (PS) & Michaela Benzeval (MB).

Date of Search: 24/10/11
Authors involved: CF & TR

2. For telomere, these terms included: telomere; telomere binding-proteins; cell aging; cell ageing; biological aging; biological ageing; cellular aging; cellular ageing; nucleoprotein structure. For socioeconomic status, these terms included: socioeconomic; socioeconomic; education; income; area deprivation; neighbourhood; neighborhood; employment; housing; financial difficulties; car ownership; class; poverty; social; status; income; tenure.
3. All publications identified by electronic searches were stored in EndNote.
4. All authors contacted experts in the field
5. A cited-reference search of all articles included in the systematic review following exclusion/inclusion (see section D below) was carried out (followed by identical exclusion/inclusion review as before).
6. Reference sections of identified and relevant articles were scrutinised.
D. Selection criteria

Inclusion criteria
1. A full report in a peer-reviewed journal (excludes interviews, book reviews,
meeting summaries & conference presentations/abstracts).
2. Published in English.
3. Abstract available.
4. A human study population (not animal or plant).
5. Community, not laboratory based.
6. An empirical article (excludes reviews and cohort profiles).

Exclusion criteria
1. No evidence of telomere length.
2. No evidence of SES measures.
3. No evidence of telomere-SES analyses with telomere measured at a single point in time.
4. SES-telomere analysis, but no results presented. This includes where SES was used as a covariate, but no results presented or significance reported.
5. Telomere length measured in childhood (18+).

Selection process
1. Articles were assessed to confirm they met the inclusion criteria by TR and MB independently.
2. Results were combined and compared. For those that did not match TR & MB discussed and when a consensus was reached, the articles were included/excluded accordingly. Where a consensus was not reached a third author (GD) was available for their opinion and the majority view to be taken. This was not necessary.
3. TR identified any duplicate articles and these were verified by MB.
4. Articles that remained were scrutinised by TR & MB independently, with articles excluded if any of the above exclusion criteria were met.
5. Results were combined and compared. For those that did not match TR & MB discussed and where a consensus was reached, the articles were included/excluded accordingly. If a consensus was not reached a third author (GD) was available for their opinion and the majority view to be taken. This was not necessary.
E. Study quality assessment

1. Checklist defined by TR & MB (Table 1).
2. TR and MB independently assessed each article and assigned a score for each criterion using the data extracted (see section F). Any discrepancies were discussed and a final score agreed. All authors also checked during the draft paper stage using the extracted data.
3. Any disagreements on scores assigned could be discussed by all authors until a consensus was reached, although this was not necessary.
F. Data extraction

1. Data required for the systematic review agreed by all authors:
   Information on study participants (sample size, age range, sex, study design), telomere measure (technique and measurement units), SES dimensions, main results and adjustments in analysis.

2. TR extracted the data for each article according to the above features of each article and entered the data in a Microsoft Word table.

3. MB verified.

4. All authors checked data extraction had been completed properly during draft paper stage.
G. Synthesis

1. Extracted data were assessed for their suitability for quantitative analysis using meta-analysis by TR, MB and GD in order to perform a high-low SES comparison and a linear trend comparison (using a Relative Index of Inequality), with data required:
   - Mean telomere length (sex and age adjusted) for each category, error measurement (SD/SE/CI) and sample size.

2. Inclusion criteria:
   - Telomere was analyzed as a continuous measure.
   - SES measures were available as ordinal categories.
   - Results were available as mean telomere length, SD and the sample size for each SES category.

3. Where full results that meet the above criteria were not presented in the articles, authors were contacted by TR and requests made for the necessary summary statistics.

4. Quality scores were adjusted for the meta-analysis based on the complete data provided.

5. If more than one article presented identical analysis, the earliest-published article was used.

6. If telomere was measured more than once, baseline telomere length was used/sought.

7. TR summarised the available data according to three categories for the most consistent SES measures across studies:
   - Childhood SES, Contemporaneous SES and Education

8. For contemporaneous and childhood SES where social class (own/parental) was not available, income was used. Where income was available, employment status was used. For education, where attainment was not available, years of full-time education were used.

9. Separate meta-analyses were run for childhood SES, contemporaneous SES and education, using both the low-high and the RII comparison (as a sensitivity measure).

10. Comprehensive Meta-Analysis (CMA, version 2.2.064, Biostat, New Jersey, USA) was used for all analyses and for the production of forest plots / publication bias plots.

11. Heterogeneity between studies was considered by estimating a random-effects model, with the inverse variation method used to weight studies’ effect sizes. Meta-regression against quality score was used where heterogeneity identified. The sensitivity analyses below was also used to ascertain if the heterogeneity identified in any meta-analysis was linked to any subgroups or individual articles by calculating the same heterogeneity statistics for each sensitivity analysis.

12. The robustness of the results were checked in six ways:
   - i. By applying a fixed-effects model.
   - ii. By limiting articles to those where adjustments were made for only age, sex and assay plate (i.e. excluding those with a range of possible mediators).
   - iii. By removing articles that did not adjust for age/sex (where applicable).
   - iv. By removing poorer quality (lower and intermediate ranking) articles.
   - v. By repeating the meta-analyses with each article removed.
vi. By re-running the meta-analyses using the ordinal RII measure of SES (to allow for more gradated associations between SES and telomere length).

10. Publication bias was considered using the Begg and Mazumdar rank correlation test, as well as using a funnel plot in which the standardized mean differences are plotted against the sample sizes. (14-15)
I. Search Diary

**Medline 25.10.11**

Ovid MEDLINE(R) 1948 to October Week 2 2011

1. exp Telomere-Binding Proteins/ or exp Telomere/ or telomere.mp.  
   13906
2. Cell Aging.mp. or exp Cell Aging/  
   12871
3. biological aging.ti. or biological aging.ab. or biological ageing.ti. or biological ageing.ab. or Cellular aging.ti. or Cellular aging.ab. or Cellular ageing.ti. or Cellular ageing.ab. or Nucleoprotein structure*.ti. or Nucleoprotein structure*.ab.  
   1652
4. Social Class.mp. or exp Social Class/  
   31591
5. Socioeconomic Factors.mp. or exp Socioeconomic Factors/  
   298068
6. exp Employment, Supported/ or exp Employment/ or Employment.mp.  
   68363
7. Educational Status.mp. or exp Educational Status/  
   34621
8. exp Income/ or Income.mp. or exp Employee Retirement Income Security Act/  
   81867
9. Housing.mp. or exp Housing/ or exp Public Housing/ or exp Housing for the Elderly/  
   32333
10. exp Poverty Areas/ or exp Poverty/ or Poverty.mp.  
    32659
11. socio-economic.ti. or socio-economic.ab. or socioeconomic.ti. or socioeconomic.ab. or Education*.ti. or Education*.ab. or Income.ti. or Income.ab. or Area deprivation.ti. or Area deprivation.ab. or Social status.ti. or Social status.ab. or neighborhood.ti. or neighborhood.ab. or neighbourhood.ti. or neighbourhood.ab. or Employment.ti. or Employment.ab. or Housing.ti. or Housing.ab. or Financial difficulties.ti. or Financial difficulties.ab. or Car ownership.ti. or Car ownership.ab. or social class.ti. or social class.ab. or poverty.ti. or poverty.ab. or social.ti. or social.ab. or income.ti. or income.ab. or housing tenure.ti. or housing tenure.ab.  
    582121
12. 1 or 2 or 3  
    26423
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11  
    774067
14. 12 and 13  
    128

**Embase 24.10.11**

Embase 1980 to 2011 Week 42 via Ovid

1. exp telomere binding protein/ or exp telomere/ or telomere.mp.  
   16205
2. Cell Aging.mp. or exp cell aging/
3. biological aging.ti. or biological aging.ab. or biological ageing.ti. or biological ageing.ab. or Cellular aging.ti. or Cellular aging.ab. or Cellular ageing.ti. or Cellular ageing.ab. or Nucleoprotein structure*.ti. or Nucleoprotein structure*.ab.

4. Social Class.mp. or exp social class/

5. Socioeconomic Factors.mp. or exp socioeconomics/

6. exp temporary employment/ or exp employment discrimination/ or exp parttime employment/ or exp employment/ or exp employment status/ or employment.mp. or exp "employment of women"/ or exp self employment/

7. educational status.mp. or exp educational status/

8. exp lowest income group/ or income.mp. or exp income/

9. Poverty.mp. or exp poverty/

10. socio-economic.ti. or socio-economic.ab. or socioeconomic.ti. or socioeconomic.ab. or Education*.ti. or Education*.ab. or Income.ti. or Income.ab. or Area deprivation.ti. or Area deprivation.ab. or Social status.ti. or Social status.ab. or neighborhood.ti. or neighborhood.ab. or neighbourhood.ti. or neighbourhood.ab. or Employment.ti. or Employment.ab. or Housing.ti. or Housing.ab. or Financial difficulties.ti. or Financial difficulties.ab. or Car ownership.ti. or Car ownership.ab. or social class.ti. or social class.ab. or poverty.ti. or poverty.ab. or social.ti. or social.ab. or income.ti. or income.ab. or housing tenure.ti. or housing tenure.ab.

11. work schedule.mp. or exp work schedule/

12. exp housing/

13. 1 or 2 or 3

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

15. 13 and 14

16.

**ISI Web of Knowledge 24.10.11**

All years

1. Topic=(Telomere*) OR Topic=("Cell Aging") OR Topic=("Cell Ageing") OR Topic=("biological aging") OR Topic=("biological ageing") OR Topic=("Cellular aging") OR Topic=("Cellular ageing") OR Topic=("Nucleoprotein structure*")

Timespan=All Years

Search language=English   Lemmatization=Off

2. Topic=("Social Class") OR Topic=(Socioeconomic) OR Topic=("Socio-economic") OR Topic=(Employment) OR Topic=("Educational Status") OR Topic=(Income) OR
Topic="Housing tenure" OR Topic=(Poverty) OR Topic=(Education) OR Topic=(Income) OR Topic="Area deprivation" OR Topic="Social status" OR Topic=(neighborhood) OR Topic=(neighbourhood) OR Topic=(Employment) OR Topic="Financial difficulties" OR Topic="Car ownership" OR Topic="social class" OR Topic=(poverty) OR Topic=(social) OR Topic=(income)
Timespan=All Years
Search language=English Lemmatization=Off
4,134,334
3. #2 AND #1
Timespan=All Years
Search language=English Lemmatization=Off
256
## Table 1. Strengths and Limitations Criteria for Review Quality Score

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Community/population-based study (+1)</strong></td>
<td><strong>A. Other study</strong></td>
</tr>
<tr>
<td>- Sampled from the population of the geographic/demographic area of interest.</td>
<td>- Includes case-control studies and those sampling population groups based on occupation, hospital admissions or disease state.</td>
</tr>
<tr>
<td><strong>A. Representative sample (+1)</strong></td>
<td><strong>A. Non-representative sample</strong></td>
</tr>
<tr>
<td>- Generalisable to the wider population of the geographic/demographic area of interest (i.e. sex, age, ethnic-specific groups).</td>
<td>- A subset of the population that does not reflect the members of the wider population of the geographic/demographic area of interest. This includes exclusions based on disease state/health, socioeconomic group, behaviours or socio-demographic factors (e.g. marital and parenting status).</td>
</tr>
<tr>
<td><strong>B. More than one SES dimension (+1)</strong></td>
<td><strong>B. Only one SES dimension</strong></td>
</tr>
<tr>
<td>- More than one SES dimension tested for their respective associations with telomere length, including reporting of the significance of the association.</td>
<td>- One SES dimension used and tested for its association with telomere length, including reporting of the significance of the association.</td>
</tr>
<tr>
<td><strong>B. Hierarchical, graded SES categories (+1)</strong></td>
<td><strong>B. Binary SES variables</strong></td>
</tr>
<tr>
<td>- Ordinal categories or continuous SES measure</td>
<td>- Dichotomized SES measure, either formed from the original question (e.g. yes/no) or reduced to a binary measure from a multiple-category ordinal measure (e.g. 6-category Registrar General social class based on occupation reduced to manual/non-manual)</td>
</tr>
<tr>
<td><strong>B. SES-telomere results adjusted for age and/or sex (where applicable) (+1)</strong></td>
<td><strong>B. No adjustment for age and/or sex in SES-telomere analysis (where applicable)</strong></td>
</tr>
<tr>
<td>- Adjusting for the potential confounding effects of age and sex in the model of the association between SES and telomere length. Where age/sex have been tested and found non-significant (P&gt;0.05), this is regarded as equivalent to statistical</td>
<td>- Not adjusting for the potential confounding effects of age and sex in the model of the association between SES and telomere length, unless it has been clearly stated that neither variable is a confounder of the association of interest.</td>
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</tbody>
</table>
adjustment of the model. Studies that only include one sex and/or a fixed year age group are exempt and will receive a ‘+1’. This is irrespective of adjustment for other variables.

C. SES-telomere results presented in the form of beta-coefficients/means with SD/SE/CI & P value (+1)
- SES-telomere results presented in the form of beta-coefficients/means for telomere length by SES group with SD/SE/CI for at least one SES dimension. P-values are acceptable when included with the other summary statistics listed previous

C. Incomplete results presented for SES-telomere analysis
- SES-telomere results missing beta-coefficients/means with SD/SE/CI. P-values are not acceptable unless included with the other summary statistics listed previous
J. References

<table>
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<tr>
<th>Section/topic</th>
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<th>Checklist item</th>
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<tbody>
<tr>
<td><strong>TITLE</strong></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td><strong>ABSTRACT</strong></td>
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<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives;</td>
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<td></td>
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<td>study eligibility criteria, participants, and interventions; study appraisal</td>
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<td>and synthesis methods; results; limitations; conclusions and implications of</td>
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<td>key findings; systematic review registration number.</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>1-2</td>
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<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to</td>
<td>2</td>
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<td></td>
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<td>participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<td><strong>METHODS</strong></td>
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<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g.,</td>
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<td>Web address), and, if available, provide registration information including</td>
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<td>registration number.</td>
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<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report</td>
<td>2</td>
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<td>characteristics (e.g., years considered, language, publication status) used</td>
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<td>as criteria for eligibility, giving rationale.</td>
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<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage,</td>
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<td></td>
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<td>contact with study authors to identify additional studies) in the search and</td>
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<td>date last searched.</td>
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<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including</td>
<td>2</td>
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<td></td>
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<td>any limits used, such that it could be repeated.</td>
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<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included</td>
<td>2</td>
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<td></td>
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<td>in systematic review, and, if applicable, included in the meta-analysis).</td>
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<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms,</td>
<td>2</td>
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<td>independently, in duplicate) and any processes for obtaining and confirming</td>
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<td>data from investigators.</td>
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<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding</td>
<td>2</td>
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<tr>
<td></td>
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<td>sources) and any assumptions and simplifications made.</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including</td>
<td>7</td>
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<td></td>
<td></td>
<td>specification of whether this was done at the study or outcome level), and</td>
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<td>how this information is to be used in any data synthesis.</td>
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<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>73</td>
</tr>
<tr>
<td>Section/topic</td>
<td>#</td>
<td>Checklist item</td>
<td>Reported on page #</td>
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<tr>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td>3-7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section/topic</th>
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<th>Checklist item</th>
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<tbody>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>7</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>3-7</td>
</tr>
</tbody>
</table>

**RESULTS**

<table>
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<tr>
<th>Section/topic</th>
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<th>Checklist item</th>
<th>Reported on page #</th>
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</thead>
<tbody>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td>7-8</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>4-6</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>Suppl. data</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>8-11</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>8-11</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>8-11</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>8-11</td>
</tr>
</tbody>
</table>

**DISCUSSION**

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>11-12</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>11-12</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>11-12</td>
</tr>
</tbody>
</table>

**FUNDING**

<table>
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<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>12</td>
</tr>
</tbody>
</table>
