# Supplementary Material

Supplemental Table 1 – PRISMA checklist.

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

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| --- | --- | --- | --- |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 8 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 8 |
| **RESULTS**  |  |
| Study selection  | 17 | 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.  | 9 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Table 1 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | Appendix |
| Results of individual studies  | 20 | 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.  | Figure 1, 2, 3 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 11 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 10, Appendix |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | 11, 12 |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | 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).  | 13-17 |
| Limitations  | 25 | 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).  | 13-17 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 13-17 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | 17 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplemental Table 2 – EMBASE and MEDLINE search strategy (searches conducted in April, 2018).

|  |  |
| --- | --- |
| No. | Query |
| #1 | 'thyroid disease'/de |
| #2 | 'hypothyroidism'/exp |
| #3 | 'thyroid disease'/de OR 'hypothyroidism'/exp |
| #4 | 'case control study'/exp |
| #5 | 'cohort analysis'/exp |
| #6 | 'cross-sectional study'/exp |
| #7 | 'incidence'/exp |
| #8 | 'prevalence'/exp |
| #9 | incidence:ti,ab |
| #10 | prevalence:ti,ab |
| #11 | 'register' |
| #12 | 'questionnaire' |
| #13 | questionnaire:ab,ti |
| #14 | survey:ab,ti |
| #15 | 'case control study'/exp OR 'cohort analysis'/exp OR 'cross-sectional study'/exp OR 'incidence'/exp OR 'prevalence'/exp OR incidence:ti,ab OR prevalence:ti,ab OR 'register' OR 'questionnaire' OR questionnaire:ab,ti OR survey:ab,ti |
| #16 | ('thyroid disease'/de OR 'hypothyroidism'/exp) AND ('case control study'/exp OR 'cohort analysis'/exp OR 'cross-sectional study'/exp OR 'incidence'/exp OR 'prevalence'/exp OR incidence:ti,ab OR prevalence:ti,ab OR 'register' OR 'questionnaire' OR questionnaire:ab,ti OR survey:ab,ti) |
| #17 | 'animal' NOT 'human' |
| #18 | (('thyroid disease'/de OR 'hypothyroidism'/exp) AND ('case control study'/exp OR 'cohort analysis'/exp OR 'cross-sectional study'/exp OR 'incidence'/exp OR 'prevalence'/exp OR incidence:ti,ab OR prevalence:ti,ab OR 'register' OR 'questionnaire' OR questionnaire:ab,ti OR survey:ab,ti)) NOT ('animal' NOT 'human') |
| #19 | (('thyroid disease'/de OR 'hypothyroidism'/exp) AND ('case control study'/exp OR 'cohort analysis'/exp OR 'cross-sectional study'/exp OR 'incidence'/exp OR 'prevalence'/exp OR incidence:ti,ab OR prevalence:ti,ab OR 'register' OR 'questionnaire' OR questionnaire:ab,ti OR survey:ab,ti)) NOT ('animal' NOT 'human') AND [2008-2018]/py |

Supplemental Table 3 – COCHRANE CENTRAL search strategy (searches conducted in April, 2018).

|  |  |
| --- | --- |
| No. | Query |
| #1 | MeSH descriptor: [Thyroid Diseases] this term only |
| #2 | MeSH descriptor: [Hypothyroidism] explode all trees |
| #3 | #1 or #2  |
| #4 | MeSH descriptor: [Case-Control Studies] explode all trees |
| #5 | MeSH descriptor: [Cohort Studies] explode all trees |
| #6 | MeSH descriptor: [Cross-Sectional Studies] explode all trees |
| #7 | MeSH descriptor: [Registries] explode all trees |
| #8 | MeSH descriptor: [Surveys and Questionnaires] explode all trees |
| #9 | MeSH descriptor: [Incidence] explode all trees |
| #10 | MeSH descriptor: [Prevalence] explode all trees |
| #11 | survey:ti,ab  |
| #12 | questionnaire\*:ti,ab  |
| #13 | incidence:ti,ab  |
| #14 | prevalence:ti,ab  |
| #15 | #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14  |
| #16 | #3 and #15  |

Supplemental Table 4 – Quality assessment results for cohort studies included in the systematic review.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|    | Selection | Comparability | Exposure | Total score |
| **Representativeness of the exposed cohort** | **Selection of the non-exposed cohort** | **Ascertainment of exposure** | **Outcome of interest not present at start** | **Comparability: age and sex** | **Comparability: additional factors** | **Ascertainment of outcome** | **Follow-up long enough** | **Adequacy of follow-up** |
| Heeringa 2008 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Hogervorst 2008 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Ittermann 2010 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Schultz 2011 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| de Jongh 2011 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Formiga 2014 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |
| Kovar 2015 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| Pfister 2015 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |
| Veltri 2017 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |

Supplemental Table 5 – Quality assessment results for case-control studies included in the systematic review.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Selection | Comparability | Exposure | Total score |
| **Case definition adequate** | **Representativeness of cases** | **Selection of controls** | **Definition of controls** | **Comparability: age and sex** | **Comparability: additional factors** | **Ascertainment of exposure** | **Case and controls: same ascertainment method** | **Case and controls: same nonresponse rate** |
| Dişel 2012  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Diez 2012 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 6 |
| Elenkova 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |

Supplemental Table 6 – Quality assessment results for cross-sectional studies included in the systematic review.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Selection  | Comparability | Outcome | Total score |
|   | **Representativeness of the sample**  | **Sample size** | **Non-respondent** | **Ascertainment of exposure** | **The subjects in different outcome groups are comparable, based on the study design or analysis; confounding factors are controlled (i.e. age, gender)** | **The study control for any additional factor** | **Ascertainment of outcome** | **Statistical test** |
| Resta 2012 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 5 |
| Ceresini 2009 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Lucas 2010 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 6 |
| Asvold 2011 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Asvold 2013 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Delitala 2014 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 5 |
| Ludwig 2015 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 6 |
| Valdes 2017 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 6 |

Supplemental Figure 1 – Funnel plot of the studies included in the meta-analysis of subclinical hypothyroidism.



Supplemental Figure 2 – Funnel plot of the studies included in the meta-analysis of overt hypothyroidism.



Supplemental Figure 3 – Funnel plot of the studies included in the meta-analysis of total hypothyroidism.

