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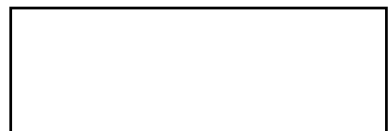
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## Hormone replacement therapy and women's health: umbrella review of interventional and observational studies

*Siew Hwa Lee, Ulugbek Nurmatov, Madar Talibov, Catherine Hawrylowicz, Hilary Critchley, Aziz Sheikh, Bright I Nwaru*

### Citation

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### Review question

To undertake an umbrella review of systematic reviews and meta-analyses of observational and interventional studies investigating the role of hormone replacement therapy in the primary and secondary prevention of multiple health and disease outcomes in menopausal women.

### Searches

We will search MEDLINE, EMBASE, Cochrane Library, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), ISI Web of Science, CINAHL, Google Scholar, AMED, PsycINFO, CAB International, and WHO Global Health Library. The databases will be searched for studies published from inception until year 2017. Additional references will be manually located through searching the references cited in identified studies; and contacting international experts in the field. We will use the following keywords and MeSH headings to identify eligible studies: ("hormone replacement therapy" OR "hormone therapy" OR "estrogen therapy" OR "estrogen-progestin therapy" OR "combined hormone therapy") AND ("systematic review" OR "meta-analysis").

### Types of study to be included

We will include all systematic reviews and meta-analyses of analytical epidemiological studies and clinical trials

### Condition or domain being studied

Any health or disease outcome: for example neoplasm, cardiovascular conditions, mortality, respiratory, metabolic, and allergic outcomes, and symptoms of menopause.

### Participants/population

We will include all systematic reviews and meta-analyses of analytical epidemiological studies and clinical trials that have investigated the associations and effect of hormone replacement therapy given for perimenopausal, menopausal and postmenopausal women on any disease outcome or health indicator in women, including symptoms resulting from menopause. We will include only human studies in which authors performed a systematic search to identify studies. There will be no language restriction and will translate any study not published in English language. We will exclude meta-analyses lacking sufficient data from individual studies, such as relative risks, 95% confidence intervals, number of cases and controls, or total population. If more than one systematic review/meta-analysis exists for the same exposure/intervention-outcome relationship, we will select the study with the largest number of studies in order to avoid any duplication. For observational studies, we will focus on cohort studies as these are considered the strongest study designs within observational evidence in judging the strength of cause-effect relationships. However, for studies with case-control design, we will undertake sensitivity analyses to evaluate their influence on the effect estimates and overall conclusion.

## PROSPERO

### International prospective register of systematic reviews

#### Intervention(s), exposure(s)

Hormone replacement therapy prescribed for perimenopausal, menopausal and postmenopausal women

#### Comparator(s)/control

No hormone replacement therapy

#### Primary outcome(s)

Any chronic condition subjectively or objectively measured

#### Secondary outcome(s)

All non-chronic conditions subjectively or objectively measured

#### Data extraction (selection and coding)

The papers retrieved from the databases will be exported to a relevant literature management platform and will be independently screened by at least two members of the project team. First stage of screening will be at the level of article titles and abstracts. Full text of papers potentially meeting the eligibility criteria at this stage will be further independently screened by at least two team members. Any discrepancies in the screening process will be resolved by discussion or arbitrated by at least one of the team members. We will use a customized data extraction form to retrieve relevant data from included studies: from systematic reviews/meta-analyses, we will extract the name of the first author, year of publication, outcomes, exposure/intervention, and number of studies included. From the primary studies included in a systematic review/meta-analysis, we will extract the name of the first author, year of publication, study design, number of cases and controls for case-control studies, events and participants/person-years of follow-up for cohort studies, and numbers in intervention and control groups in clinical trials, type of risk estimates used in meta-analysis, effect estimates and their corresponding 95% confidence intervals, and type of meta-analysis model (fixed or random effects). Any discrepancies in data extraction and quality appraisal will be resolved by discussion or arbitrated by at least one of the team members.

#### Risk of bias (quality) assessment

We will use the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool to appraise the quality of included studies.

#### Strategy for data synthesis

For the association between HRT (or effect on) and specific outcomes, we will compute the effect estimates and their corresponding 95% confidence intervals using fixed and random effects approaches, depending on the assumption made on each specific estimate. We will evaluate heterogeneity between studies by using Cochran's Q test and the  $I^2$  statistic. We will also estimate the 95% prediction interval, which takes into account the overall uncertainty surrounding the summary effect and heterogeneity across studies to provide a range for which we are 95% confident that the effect of HRT on specific outcomes in new studies would lie. We will evaluate small study effect (as an indication of publication bias) by plotting funnel plots and computing the Egger's regression asymmetry test. We will assess excess significance bias and calculate the credibility ceilings, which provides sensitivity evaluation of the results by accounting for possible methodological limitations of observational studies.

#### Analysis of subgroups or subsets

We will evaluate the role of different types of HRT (estrogen vs estrogen-progestin hormone therapies). Where possible, we will stratify the analyses by age of women (e.g. younger women < 55 years vs older women ≥55 years), and by menopausal status (perimenopausal, menopausal, postmenopausal). We will also analyze the data with regards to the effect of HRT for primary prevention vs secondary prevention of outcomes in women.

### Contact details for further information

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07 December 2017

### Anticipated completion date

12 December 2018

### Funding sources/sponsors

None

### Conflicts of interest

None declared

### Language

(there is not an English language summary)

### Country

England, Scotland, Sweden, Finland

### Stage of review

Review\_Ongoing

### Subject index terms status

Subject indexing assigned by CRD

### Subject index terms

Female; Hormone Replacement Therapy; Humans; Peer Review; Women's Health

### Date of registration in PROSPERO

18 December 2017

### Date of publication of this version

18 December 2017

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

<b>Stage</b>	<b>Started</b>	<b>Completed</b>
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

### Versions

18 December 2017

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#### PROSPERO

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