Supplementary Table D - The Cochrane Collaboration's tool for assessing risk of bias in Intervention Studies

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	The researcher describes methods used to generate the allocation sequence such that, an assessment can be made to determine they are comparable.	Was any selection bias present (biased allocation to interventions) as a result of a poor randomisation sequence? **YES** **NO** **UNCLEAR**
Comments:		
Allocation concealment	The researcher describes the method used to conceal the allocation sequence in enough detail to determine whether intervention allocations could have been foreseen prior to, or during enrolment.	Was there any selection bias (biased allocation to interventions) based on inadequate concealment of allocations prior to assigning? **YES** **NO** **UNCLEAR**
Comments:		
Performance Bias		
Blinding of participants and personnel. Assessment should be made for each main outcome (or class of outcomes)	The researcher describes all methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. The research should also give information as to whether the blinding was effective.	Was there any performance bias due to awareness of allocated interventions by participants and personnel during the study? **YES** **NO** **UNCLEAR**
Comments:		
Detection Bias		
Blinding of an outcome assessment. Assessment should be made for each main outcome (or class of outcomes)	Describe all measures used (if any) to blind outcome assessors from knowledge of which intervention a participant has received. Give information relating to whether this blinding was successful.	Was there any detection bias due to knowledge of the allocated interventions by outcome assessors? **YES** **NO** **UNCLEAR**

Attrition Bias		
Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes)	Does the researcher describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis?	Was there any attrition bias due to amount, nature or handling of incomplete outcome data? **YES** **NO** **UNCLEAR**
Comments:		
Reporting Bias		
Selective reporting	Does the research state how the possibility of selective outcome reporting was examined by the review authors and what the findings were? Intention to treat or Per protocol	Was there any reporting bias due to selective outcome reporting? **YES** **NO** **UNCLEAR**
Comments:		
Other sources of bias:		
Hormonal treatments	Does the researcher adjust for (or consider) compatibility of control and intervention groups, such as hormonal treatments, including the following? - Hormonal replacement therapy (HRT)[1] - 5 alpha reductase inhibitors[2, 3] - Adrenal cortical steroids (corticotrophin, glucocorticoids, mineralocorticoids)[4] - Adrenal corticosteroid inhibitors[4] -Anti-androgens[5] - Anti-gonadotropic agents[6] - Anti-thyroid hormones / thyroid medication[7] - Aromatase inhibitors[8] - Calcitonin[9] - Oestrogen receptor antagonists / Selective oestrogen receptor modulators [10] - Gonadotrophin releasing hormone antagonists[11, 12] - Growth hormone receptor blockers[13] - Growth hormones[14, 15] - Insulin like growth factor[16] - Parathyroid hormone and analogues[17]. - Prolactin inhibitor[18] - Sex hormones: androgens and anabolic steroids, hormonal contraception (combined pill, progesterone only pill, IUS coil, injection, patch, creams), gonadotrophin releasing hormones, gonadotrophins, progestins, sex hormone combinations. - Somatostatin and somatostatin analogues[19]. - Synthetic ovulation stimulants[20]	Was there any evidence of hormonal medication confounding results of the study? This may include the researcher including results from individuals who may have: **started/stopped/changed dose of existing or new hormonal medication.** **YES** **NO** **UNCLEAR**

Dietary influences	Does the researcher consider the impact of certain dietary components influencing sex hormones? This specifically addresses participants **changing current dietary behaviours** during the study (including: starting, stopping, increasing or decreasing particular foods). Types of foods to consider include: - Soy protein isolate[21] - Licorice root[22, 23] - Hemp, flax and chia seeds[24] - Green tea catechins[22, 25] - Chaste tree (vitex angus)[22, 26] - Reishi mushroom [22, 27-29] - Fenugreek[30] - Saw palmetto[22] - Bitter melon[31] - White peony[22] - ATD (1,4,6-androstatrience-3,17-dione)[32]	Was there any evidence of dietary changes in participants that may influence the results of the study? This may include the researcher including results from individuals who may have: **Started, stopped, increased, or decreased** amounts of food/supplements that enhance or attenuate sex hormones. **YES** **NO** **UNCLEAR**
Comments:		
Micronutrient extraction	Bias through inaccuracy of micronutrient extraction can influence the true findings of the study. Common methods of micronutrient extraction in epidemiological studies, include the use of "food frequency questionnaires (FFQs)". Evidence suggests that, if FFQs are administered by the interviewer they are more likely to produce stronger linear correlation coefficients when compared to reference methods. Furthermore, if the researchers include or state whether dietary supplements were used, this would further minimise bias associated with micronutrient extraction[33]. Extraction of micronutrient through blood measurement will be analysed separately (sub-group), however analysis by plasma will include coagulants and other trace elements which may skew true biochemical values. However, research suggests the variability between the two methods is very small[34], and reproducibility is good in both plasma and serum[35].	Is there any evidence of bias that can be drawn from the methodology of the paper? **YES** (measurements other than FFQs, OR measurements using FFQs with no reference to supplemental use) **NO** (measurements that used FFQs, with some regard/ acknowledgement for dietary supplements **UNCLEAR** (The paper does not provide enough detail to work out micronutrient extraction method).
Comments:		

Outcome measurement and bias associated with measures used.	Bias through inaccuracy of hormonal extraction can influence the true findings of the study. Measurements of sex hormones using "mass spectrometry" (gas or liquid) will convey the highest accuracy, and therefore lowest amount of bias. Studies that use other (less reliable) methods of hormone extraction e.g. direct immunoassay[i] or Electro chemiluminescent assay[ii], will still be eligible in the systematic review, however the reliability of methodology will reflect in conclusions drawn from that study.	Is there any evidence of bias that can be drawn from the methodology of the paper? **YES** (measurements other than "mass spectrometry") **NO** (measurements that only included "mass spectrometry") **UNCLEAR** (no mention of hormone extraction method).
Sponsorship bias	Does the researcher address the possibility of sponsorship bias through the funding of the study?	Was there any evidence of funding bias in any part of the methodology, results or conclusions? **YES** **NO** **UNCLEAR**

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