Effect of weight loss interventions on the symptomatic burden and biomarkers of polycystic ovary syndrome: a systematic review of randomised controlled trials

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Abstract

Background:

Polycystic ovary syndrome (PCOS) is common in women of reproductive age and is associated with obesity. Clinical guidelines recommend weight loss, but the impact on the clinical manifestations of PCOS is unclear.

Purpose:

To quantify the effect of weight-loss interventions on clinical features of PCOS, compared with usual care.

Data Sources:

MEDLINE, Embase, PsycINFO, CINAHL, Cochrane, Web of Science and trial registries were searched from inception through June 2024.

Study Selection:

Randomised controlled trials comparing interventions aiming to reduce weight against usual care, including lower-intensity weight-loss interventions in people with PCOS. Conversations with people with PCOS informed the outcomes.

Data Extraction:

Pairs of independent reviewers screened studies, extracted data, and assessed risk of bias (RoB). Outcomes included glycaemic control (HOMA-IR, fasting insulin and glucose), hormonal markers (free androgen index (FAI) and other sex hormones), menstrual frequency, hirsutism and PCOS-related quality of life (QoL). Pooled mean differences were obtained from random effects meta-analysis-with Knapp-Hartung adjustment

Data Synthesis:

Primary analyses included 29 comparisons with 1529 participants. 13, 12 and 4 comparisons were judged as high, some or low RoB, respectively. 12 used behavioural interventions, 9 used GLP1-agonists and 8 used other weight loss medications. Weight loss interventions were associated with significantly greater improvements in HOMA-IR (mean difference -0.45, -0.75;-0.15; I^2=24%), FAI (mean difference -2.03, -3.0;-1.07; I^2=48%) and menstrual frequency (mean difference 2.64; 0.65;4.63, I^2=43%). There was no evidence that weight-loss interventions were associated with clinically or statistically significant improvements in hirsutism, QoL or other sex hormones, which may be due to the limited power of the available data.

Limitations:

There was high statistical heterogeneity in the interventions, comparators and outcomes, largely unexplained by sensitivity and subgroup analyses.

Conclusion:

Weight-loss interventions were ~~generally~~ associated with improvements in some important features of PCOS and should be considered as a routine treatment option for people with PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. While prevalence varies depending on diagnostic criterion used, it is estimated that around 10% of women are diagnosed with PCOS (1). Estimates suggest that over 50% of women with PCOS have overweight or obesity (2), 65-80% have insulin resistance and 80% have elevated blood androgens (3). Women with PCOS and overweight or obesity have significantly worse metabolic, hormonal and reproductive outcomes than women with PCOS and a healthy weight (4). PCOS is a heterogenous condition, and the symptoms that people may experience vary, although most women with PCOS report anovulation, menstrual cycle irregularity and hyperandrogenism.

There are no reference biomarkers to characterise the progression and severity of symptoms associated with PCOS. International multi-stakeholder groups advise that BMI, quality of life (QoL) and treatment satisfaction, should be considered as core outcomes in the management of PCOS (5).

Clinical guidelines, including from the 2023 International Evidence for the Management of PCOS and the Royal College of Obstetricians and Gynaecologists within the UK, advise that 5% weight loss may reduce testosterone levels and markers of insulin resistance, but do not reference changes in other markers or symptoms such as hirsutism or FAI. This guidance is underpinned by systematic reviews of case-control or cohort studies, but not of clinical trials (6). They recommend that women with PCOS living with overweight are offered advice on lifestyle modification, typically including weight loss through hypoenergetic diets and increased physical activity (7) and that metabolic surgery be considered to improve hirsutism, menstrual regularity and ovulation. However, our patient and public involvement (PPI) advisors explained that in their experience, support for weight management is uncommon, and they found it hard to achieve weight loss. Furthermore, evidence shows that encouragement to lose weight without support is largely ineffective (8).

Previous reviews have shown that low energy dietary interventions or weight loss pharmacotherapy achieve weight loss and lead to greater improvements in insulin resistance, fasting glucose and HbA1c than metformin or no intervention (9). Dietary interventions, not focused on weight loss (10, 11), or exercise (12), have shown improvements in menstrual frequency and improved glycaemic control. However, no reviews have considered the full range of weight loss interventions, and often have insufficient data to meta-analyse the broad range of symptoms and markers that are clinically relevant for the management of PCOS, and identified as important by our PPI panel, such as menstrual frequency, hirsutism and FAI. There is currently limited evidence to quantify the impact of weight loss which makes it challenging for clinicians to recommend weight loss interventions specifically for the management of PCOS.

This review aimed to address this evidence gap, through synthesising and quantifying the impact of any weight-loss intervention on metabolic markers (homeostasis model assessment for insulin resistance (HOMA-IR), fasting glucose and fasting insulin), hormonal markers (androgen and sex hormone profiles), gynaecological markers (menstrual frequency, ovulation) and QoL as compared to comparators offering no additional care, usual care or a lower-intensity weight loss intervention.

Methods

The review protocol was registered prospectively and we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (13-15).

Search Strategy

We searched MEDLINE, Embase, PsycINFO, CINAHL, Cochrane, Web of Science, and trial registries for randomised controlled trials (RCTs) from database inception until June 2024. The search strategy was created by an experienced librarian, and not restricted by language or country (supplementary table 1). Databases were hand-searched for systematic reviews, to identify other relevant studies.

Study Selection

The review included RCTs of interventions aiming to reduce weight in adults diagnosed with PCOS. Given the variable definition of PCOS, we used the criteria for PCOS diagnosis presented in each study. Interventions had to explicitly aim to reduce weight, and included behavioural interventions (diet or physical activity), current or previously licenced weight loss pharmacotherapy, bariatric surgery, or combinations of such interventions.

The comparator intervention was usual care (metformin, oral contraceptives, standard advice) or a minimal intervention aimed at weight loss (such as advice for weight loss without support) or placebos. To maximise available data, we also included trials that compared a higher and lower-intensity weight loss intervention, using the latter as the comparator, recognising that weight loss is recommended in clinical guidelines, representing recommended usual care. Trials comparing interventions of similar intensity were excluded, such as comparisons between diets with the same energy deficit but different macronutrient content. In trials that compared pharmacological and behavioural interventions, pharmacotherapy was *a priori* deemed the intervention and behavioural intervention the comparator, since pharmacotherapy interventions routinely offer behavioural support. Metformin was not considered as an intervention as it has never been licenced for weight loss and evidence for weight loss is inconsistent (16, 17). It was considered as a potential component of usual care given the high prevalence of insulin resistance in this patient group.

Primary outcomes included biological markers and symptoms of PCOS. Important outcomes were selected in consultation with patients with PCOS and clinicians with expertise in PCOS management. Included trials reported data to allow weight change to be calculated, as a process measure, indicating the effectiveness of the weight loss interventions, and reported at least one biomarker or symptom marker of PCOS, including HOMA-IR, fasting insulin, fasting glucose, total testosterone, free androgen index (FAI), sex hormone binding globulin (SHBG), luteinising hormone (LH), follicular stimulating hormone (FSH), LH:FSH, menses frequency, ovulation, acne, hirsutism, and PCOSQoL. Key primary outcomes, informed through consultation with clinicians and our PPI advisory panel, were HOMA-IR, FAI and menses frequency, to best address improvements in glycaemic, androgenic and symptomatic features of PCOS. Secondary outcomes included adverse events. Trials were included irrespective of the length of intervention or follow-up. We used the outcomes as reported at final follow-up in each trial. All outcomes are detailed in Table 1.

Data Collection and Quality Assessment

Studies were independently screened by pairs of researchers and data extracted using Covidence (18) based on the Template for Intervention Description and Replication checklist (19). Disagreements were resolved by discussion or a third reviewer. Authors were contacted for missing data, full texts or clarifications as required.

We used the Cochrane risk of bias (RoB) 2 tool to assess bias arising from randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome assessment and selection of the reported result. Detailed description of how RoB was assessed is available in the supplementary material. We assessed funnel plots for asymmetry to evaluate the

presence of small study effect and the possibility of reporting bias, where sufficient studies (≥10) were available (20).

Data Synthesis and Analysis

We estimated the change in outcomes for all relevant trial groups. We extracted the mean difference in the change in outcomes between groups and the accompanying SD, using Cochrane Handbook guidelines (21). Meta-analyses and meta-regression were conducted using the 'meta' package in R v4.2.2 for outcomes in which at least two studies were available.

For each outcome measure, our primary meta-analysis included comparisons where more intense weight loss interventions were compared with lesser-intensity weight loss interventions. Where there was simultaneous use of pharmacotherapy (metformin or OCPs) for the management of PCOS symptoms, these medications were used in both groups, reducing any confounding. Our secondary analyses were broader, comprising any comparisons that compare weight loss interventions to any lesser-intensity intervention, where other treatments weren't necessarily balanced between arms, to better assess the implications of weight loss interventions in routine clinical care. The random effects model was defined a priori given the heterogeneity in the context and nature of the interventions, study populations, and assessment of outcomes. We used inverse variance random-effects models based on the DerSimonian and Laird method, with the Knapp-Hartung adjustments, to obtain less biased estimated effects and 95% CIs (22).

Studies varied in whether and how they imputed data for participants lost to follow-up, and we used the data as reported for analysis. Where a study contributed more than one intervention arm to the analysis, the control group was divided equally between arms to avoid double counting. We evaluated the consistency of the evidence based on the direction of the effects in each study, and the precision of the evidence based on the size of the confidence intervals. All outcomes are summarised as mean difference with 95% CIs. Statistical heterogeneity was assessed with the I^2 statistic (23). The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess certainty of evidence (24).

To assess sources of heterogeneity, we conducted subgroup analyses to examine four types of intervention: behavioural, GLP1 receptor agonists, other weight-loss medications, and combined pharmacotherapy/behavioural programmes and exploratory meta-regression investigated mean difference in weight loss as a moderator, where sufficient studies were available.

Sensitivity Analyses

We conducted five separate sensitivity analyses. Those prespecified excluded; i) studies at high RoB and ii)comparisons involving a pharmacological weight loss agent no longer licenced for weight loss (sibutramine and rimonabant). Post-hoc analyses excluded; iii)comparisons including OCPs in analyses of hormonal outcomes iv) studies with metformin used in either arm, as the evidence for metformin to achieve weight loss is uncertain v) comparisons with greater weight loss in the comparator arm vi)comparisons contributing to significant asymmetry on funnel plots

Presentation of results

Data in forest plots are presented in descending order according to the mean difference of weight change achieved. Secondary analyses are reported in supplementary material.

Public involvement

This project was conducted in partnership with patient and public involvement advisors (25). We spoke with 36 women with PCOS throughout the project. These conversations informed

prioritisation of the outcomes explored within the review, and guided how we presented outcomes. They explained that symptoms and markers relating to menses, hirsutism, PCOS-related QoL and wellbeing were priorities for them, but that they felt there was little information about how weight loss could influence these. They identified the value of using 'woman' forward language. When discussing participants within trials, gendered language is used, reflecting the inclusion criteria.

Results

From 3760 studies, 39 (48 comparisons) were included in this review, of which 26 studies (29 comparisons) were included in the primary analysis (Figure 1).

Characteristics of included studies

Supplementary table 2 shows summary data for included comparisons, describing the nature of the intervention and comparator for each. Supplementary table 3 describes the aggregate study characteristics for comparisons included in the primary and secondary analyses. Briefly, 1624 participants were randomised and 1529 contributed data to our primary analyses. 2696 participants were randomised and 2308 contributed data to our secondary analyses.

Risk of Bias

In our primary analyses, 13 studies were judged at high RoB in at least 1 domain, 12 studies with some concerns of RoB in at least 1 domain and 4 at low RoB in all domains. Visual inspection of funnel plots indicated asymmetry for fasting insulin and SHBG. For the other outcomes, there was no substantial asymmetry though this cannot rule out the possibility of publication bias (supplementary figures 1-8) (20). For studies included in the secondary analyses, 19 studies were judged at high RpB in at least 1 domain, 24 studies with some concerns of RoB in at least 1 domain and 5 at low RoB in all domains (supplementary table 4).

GRADE certainty of evidence

For all primary meta-analyses, HOMA-IR, fasting insulin and FAI were judged to have a high certainty of evidence. Fasting glucose, testosterone, SHBG, LH, FSH and menstrual frequency were judged to be of moderate certainty. LH:FSH, hirsutism and QoL were judged to be of very low certainty (supplementary table 5).

Process measure: weight change

In our primary analysis, the mean difference in weight change was -3.78kg (-4.61;-2.94); I^2=78%, based on 29 comparisons (1529 participants) (supplementary figure 9 and table 6).

In our secondary analyses, the mean difference in weight change was -4.31kg (-5.98;-2.64); I^2=98%, based on 48 comparisons (2288 participants) (supplementary figure 10). One comparison used bariatric surgery to achieve weight loss, losing ~38kg, substantially larger than weight loss achieved by any other intervention. Excluding this comparison, the summary estimates were -3.43kg (-4.08;-2.77), I^2=78%.

HOMA-IR

19 comparisons, comprising 1016 participants (521 intervention, 495 comparator) were included in our primary analyses. Mean follow-up was 18±11 weeks and the mean length of weight loss intervention was 16 weeks. The mean age of participants allocated to receive both the weight loss intervention and the comparator was 29±3 years. The mean BMI of those allocated to receive the weight loss interventions and comparators were 34.1±4.8kg/m^2 and 33.4±5kg/m^2, respectively. 6

comparisons used a behavioural intervention (26-30), 8 used a GLP1 agonist (31-38) and 5 used orlistat or sibutramine (39-43) (figure 2).

7 comparisons were judged to be at a high RoB in at least one domain. Weight loss interventions were associated with greater reductions in HOMA-IR; -0.45 (-0.75; -0.15; I^2=24%) (figure 2). Excluding studies at a high RoB did not meaningfully change the summary estimates; -0.36 [-0.73; -0.01], I^2=38%) (supplementary figure 10).

In our secondary analysis, data from 34 comparisons with 1545 participants reported on HOMA-IR. The weight loss interventions were associated with greater reductions in HOMA-IR; -0.56 (-0.9; -0.23; I^2= 68%) (supplementary table 6).

FAI

15 comparisons, comprising 844 participants (477 intervention, 367 comparator), were included in our primary analyses. Mean follow-up was 25±13 weeks, and the mean length of the weight loss intervention was 23 weeks. The mean age of participants allocated to receive both the weight loss intervention and the comparator was 30±2 and 28±2 years, respectively. The mean BMI those allocated to receive the weight loss interventions and comparators, respectively were 35.1±5.1 and 34.8±5.3. 6 comparisons used a behavioural intervention (27, 29, 44-46), 4 used a GLP1-agonist (33-35, 47) and 5 used either orlistat or sibutramine (40-42, 48)(figure 3).

6 comparisons were judged to be at a high RoB in at least one domain. Weight loss interventions were associated with greater reductions in FAI; -2.03 (-3.0;-1.07; I^2=48%) (figure 3). Excluding studies judged at a high RoB did not meaningfully change the summary estimates; -1.6 [-2.9;-0.33] I^2=57%) (supplementary figure 11). The meta-regression showed there was 0.7 [0.34;1.06] unit reduction in the effect measure (mean difference in FAI change) for every kg decrease in the moderator (mean difference in weight change) (supplementary figure 12).

In our secondary analysis, data from 27 comparisons (1344 participants) reported on FAI. Weight loss interventions were associated with greater reductions in FAI; -1.37(-2.43;-0.31; I^2=60%) (supplementary table 6).

Menstrual frequency

Our primary analysis included 5 comparisons of menstrual frequency, comprising 218 participants (130 intervention, 88 comparator).The mean length of both the intervention and follow-up was 24±8 weeks. The mean age of participants allocated to receive both the weight loss intervention and the comparator was 31±1 and 29±3 years, respectively. The mean BMI of those allocated to receive the weight loss interventions and the comparators were 37.2±4.6 and38.5±5.1, respectively. All bar 1 comparison used a GLP1 agonist (32-34, 47), with the other using sibutramine (40).

1 comparison was judged at high RoB in at least 1 domain. Weight loss interventions were associated with greater increases in menstrual frequency; 2.64 menses/year (0.65;4.63; I^2=43%) (figure 4). Excluding studies at high RoB did not meaningfully change the summary estimates; 2.49 menses/year [-0.43;5.41] I^2=57%) (supplementary figure 13).

12 comparisons involving 582 participants were included in our secondary analysis of menstrual frequency. Weight loss interventions were associated with greater increases in menstrual frequency; 1.88 (0.84;2.93; I^2=59%) (supplementary table 6).

Other primary outcomes

Mean follow-up time (weeks) for the remaining outcomes were as follows: fasting insulin (18±11), FPG (21±13), FSH and LH (18±12), LH:FSH (18±8), hirsutism (30±18) and QoL (16±0).

Weight loss interventions were associated with greater reductions in fasting insulin (-1.28 [-2.24;-0.31], I^2=0%, 17 comparisons, n=932), total testosterone (-0.16 [-0.26;-0.05], I^2=80%, 25 comparisons, n=1459) and SHBG (7.46 [2.26;12.67], I^2=63%, 21 comparisons, n=1156).

There was no evidence of clinically significant changes in fasting glucose (-0.11 [-0.22 0], I^2=89%, 20 comparisons, n=1111), FSH (-0.19 [-0.41;0.02] I^2=7%, 14 comparisons, n=1012), LH (-0.61 [-1.61;0.38] I^2=45%, 14 comparisons, n=1012), LH:FSH (-0.06 [-0.17;0.05] I^2=0%, 3 comparisons, n=148), hirsutism (-1.50 [-4.9;1.19], I^2=51%, 4 comparisons, n=110) and PCOS-QoL (supplementary table 6, figures 14-29).

There was insufficient data to meta-analyse changes in ovulation or acne. In trials that did report these outcomes, there was no clinically significant differences between arms.

Sensitivity analyses

Our conclusions were generally robust to sensitivity analysis. Notable differences were that after excluding studies at high RoB the differences HOMA-IR, fasting insulin and menstrual frequency were no longer statistically significant. Likewise, after excluding studies using metformin there was no significant difference in SHBG and menstrual frequency. However, the summary estimates remained clinically meaningful (supplementary table 6).

Adverse events

Fifteen studies reported information on adverse events (supplemental table 7). Adverse events were more common in the intervention arms, especially for interventions involving pharmacotherapy and were mostly related to gastrointestinal symptoms such as nausea, diarrhoea or vomiting. Due to variability in reporting adverse events, it was not possible to pool data.

Discussion

For women with PCOS, our systematic review suggests weight loss interventions ~~generally~~ led to improvements in some important clinical ~~symptoms~~features of PCOs. HOMA-IR, fasting insulin and FAI all decreased and there was an increase the number of menstrual periods per year. There was no conclusive evidence that weight loss interventions were associated with clinically meaningful changes in fasting glucose, testosterone, SHBG, FSH, LH, LH:FSH, hirsutism or PCOS-QoL, though the findings were limited by a small number of studies, high heterogeneity and are likely to reflect the clinical variability in the populations sampled within this review. There were insufficient data to meta-analyse ovulation and acne. The interpretation of the impact of weight loss interventions was largely unchanged in sensitivity analyses. There was a high certainty of evidence of the association between weight loss interventions on HOMA-IR, fasting insulin and FSH and moderate certainty for fasting glucose, FAI, testosterone and menstrual frequency. Evidence for other outcomes was of low or very low certainty.

Our secondary analyses included a larger number of studies with more pragmatic inclusion criteria comparing any weight loss intervention to usual care, including lesser-intensity weight loss intervention such as dietary advice. This included direct comparisons between weight loss interventions and other treatments for PCOS, such as metformin and OCPs. Results were similar to the primary analysis, though there was greater heterogeneity, some of which was attributable to one study involving bariatric surgery. Weight loss interventions were associated with clinically significant improvements in HOMA-IR, fasting insulin, FAI and menstrual frequency.

This is the first review to show a clinically significant association in improvement in menstrual frequency with weight-loss interventions, an important indicator of subsequent fertility, an important outcome for women. Previous systematic reviews have reported that weight loss in women with PCOS is associated with improvements in glycaemic control (9, 49), consistent with the well-established effects of weight loss in people living with excess weight. For HOMA-IR, the effect estimates for weight loss are consistent with previous meta-analyses (50). Estimates for other measures of glycaemia tended to be lower than in previous reviews, particularly for fasting glucose. This may be because our comparators often included metformin and weight-loss interventions of lesser-intensity, both associated with some improvements in glycaemic control. Our meta-regression suggests that the greater the difference in weight-loss between arms, the greater the reduction in FAI, relative to the comparator, consistent with evidence that excess weight is associated with elevated FAI (4). FAI is the primary clinical indicator of biochemical hyperandrogenism, one of the three diagnostic criteria for PCOS. High FAI is consistently associated with elevated cardiovascular risk (51). There was no evidence of associations between weight change and other hormones.

One trial of bariatric surgery was included, which achieved a mean weight-loss of 38kg and substantial improvements in the clinical features of PCOS. Nonrandomised trials of bariatric surgery support this, suggesting improvements in menstrual irregularity and hirsutism for women living with PCOS (52, 53). Other findings from this review are also supported by observational and cohort analyses of other weight-loss interventions (54, 55).

Our review extends prior reviews by including RCTs including all types of weight loss interventions in women with PCOS with comparators spanning a range of other treatment modalities, or none. No perfect measure of PCOS exists, and we worked with patients with PCOS to inform the outcomes we reported, alongside markers which may be used in clinical care. We did not aim to report on conception rates or pregnancy-related outcomes. However, re-instatement of menstruation has been identified as important for those living with PCOS, and clinically relevant as an indicator of fertility (56).

The main limitation is high statistical heterogeneity which was not eliminated by categorising studies by different types of intervention and this sub-division means many subgroups include only a small number of comparisons. The included interventions and comparators were heterogenous and our conclusions may not extend to all interventions that produce weight loss. More detailed network meta-analysis is needed to compare different weight loss interventions. Several analyses were limited by imprecision and inconsistency of the CIs and the inconclusive nature of these analyses reflects clinical uncertainty. Methods to handle missing data were often not sufficiently reported and the variability may have introduced spurious differences between comparisons. Thirteen comparisons were judged to be at high RoB, predominantly due to a high risk of attrition bias due to large drop-out rates, but removing these studies did not meaningfully affect the results. The quality of the evidence was only judged to be high for HOMA-IR, fasting insulin and FAI. Due to broad confidence intervals, the summary estimates for SHBG, LH, LH:FSH, hirsutism and PCOS-QoL were imprecise, and are not conclusive. Most studies were less than 6 months, so the long-term effectiveness of these interventions for the management of PCOS is unclear. No trials were conducted in primary care or community settings where populations may differ.

Patients offered access to weight loss interventions in routine care can expect to lose ~4kg after one year (57). This is close to the mean weight losses reported in the weight loss interventions in this review and implies that referral to these services could bring improvements in the symptomatic burden to women affected by PCOS. Advice without referral to support services is much less

effective with weight losses of around 1kg after 1 year (8, 58, 59). The magnitude of weight lost in formal programmes is highly dependent on the nature of the intervention.

Behavioural interventions for weight loss in this review were predominately based on modest energy deficit diets, with a mean difference in weight of ~3kg. However, interventions such as total dietary replacements are increasingly offered, typically achieving weight losses of ~10kg after 1 year, with large reductions in insulin resistance. Interventions included here using GLP-1 agonists used doses generally similar to dosages for glycaemic control (eg. 1.8mg/day for liraglutide), rather than weight management (3mg/day), and weight loss was correspondingly lower than recent reported outcomes for the treatment of obesity (60). These recent changes in obesity management are not reflected in this review and it is plausible that more effective treatments which led to greater weight loss will further improve clinical outcomes for women with PCOS (61).

Clinicians may use these findings to counsel women with PCOS on the expected improvements in PCOS markers after weight loss and direct patients towards interventions, though our findings may not extend to all weight loss interventions especially if they target specific metabolic pathways. However, our secondary analyses show that weight loss interventions in general may be an effective tool for PCOS management in applied clinical settings, suggesting advantages above or similar to management strategies already used, such as metformin or OCPs. Since weight-loss programmes are cost-effective interventions to improve cardio-metabolic risk they may be particularly valuable for this population at elevated risk (57).

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Reproducible research statement:

Protocol: available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=367488

Statistical code: Available on request to interested readers by contacting Dr Jadine Scragg at jadine.scragg@phc.ox.ac.uk

Data: Data are from published research and therefore are in the public domain. Aggregate data may be available on request to Dr Jadine Scragg at jadine.scragg@phc.ox.ac.uk (jadine.scragg@phc.ox.ac.uk).

Footnotes: Contributors: JS, SD, KT and SAJ conceived and designed the review. JS, GT, LW and AH conducted the screening. JS, LW, AH, YA and IVH conducted the data extraction and assessed studies for risk of bias. JS and AH conducted the main statistical analyses, with input from KT. JS and AH

prepared the first draft of the review with further input from SD, KT and SAJ. All authors contributed to the interpretation and final write up. All authors had direct access to the data, or access was provided as requested. JS is the guarantor and SAJ is the senior author. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Potential Conflicts of Interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare JS was involved with a Nestle Health Sciences advisory board and was an invited speaker at a Nestle Health Sciences webinar, for which a personal honorarium was received. SAJ reports being an investigator in 2 investigator-led publicly funded (National Institute for Health Research) trials where the weight loss intervention was donated by Nestle Health Science and Oviva to the University of Oxford outside the submitted work. JS and SAJ report being investigators in a trial where Second Nature is delivering a weight loss intervention and they both supervise a doctoral student who is funded by an MRC industrial collaborative award in science and engineering studentship, where Second Nature is the collaborative partner.

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