

BMJ Open Dietary and/or physical activity interventions in women with overweight or obesity prior to fertility treatment: protocol for a systematic review and individual participant data meta-analysis

Emily Evans-Hoeker,^{1,2} Zheng Wang ,³ Henk Groen ,⁴ Astrid E P Cantineau,³ Ann Thurin-Kjellberg,^{5,6} Christina Bergh,^{5,6} Joop S E Laven,⁷ Alexandra Dietz de Loos,⁷ Geranne Jiskoot,⁷ Jean-Patrice Baillargeon ,⁸ Stefano Palomba ,⁹ Kyra Sim,¹⁰ Lisa J Moran,¹¹ Juan J Espinós,¹² Trine Moholdt ,^{13,14} Amy E Rothberg ,^{15,16} Donna Shoupe,¹⁷ Annemieke Hoek ,³ Richard S Legro,¹⁸ Ben W Mol ,^{19,20} Rui Wang ,¹⁹ On behalf of the Venus-IPD Collaboration

To cite: Evans-Hoeker E, Wang Z, Groen H, *et al*. Dietary and/or physical activity interventions in women with overweight or obesity prior to fertility treatment: protocol for a systematic review and individual participant data meta-analysis. *BMJ Open* 2022;**12**:e065206. doi:10.1136/bmjopen-2022-065206

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-065206>).

Received 27 May 2022
Accepted 10 October 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Rui Wang;
r.wang@monash.edu

ABSTRACT

Introduction Dietary and/or physical activity interventions are often recommended for women with overweight or obesity as the first step prior to fertility treatment. However, randomised controlled trials (RCTs) so far have shown inconsistent results. Therefore, we propose this individual participant data meta-analysis (IPDMA) to evaluate the effectiveness and safety of dietary and/or physical activity interventions in women with infertility and overweight or obesity on reproductive, maternal and perinatal outcomes and to explore if there are subgroup(s) of women who benefit from each specific intervention or their combination (treatment-covariate interactions).

Methods and analysis We will include RCTs with dietary and/or physical activity interventions as core interventions prior to fertility treatment in women with infertility and overweight or obesity. The primary outcome will be live birth. We will search MEDLINE, Embase, Cochrane Central Register of Controlled Trials and trial registries to identify eligible studies. We will approach authors of eligible trials to contribute individual participant data (IPD). We will perform risk of bias assessments according to the Risk of Bias 2 tool and a random-effects IPDMA. We will then explore treatment-covariate interactions for important participant-level characteristics.

Ethics and dissemination Formal ethical approval for the project (Venus-IPD) was exempted by the medical ethics committee of the University Medical Center Groningen (METc code: 2021/563, date: 17 November 2021). Data transfer agreement will be obtained from each participating institute/hospital. Outcomes will be disseminated internationally through the collaborative group, conference presentations and peer-reviewed publication.

PROSPERO registration number CRD42021266201.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This, to our knowledge, is the first individual participant data meta-analysis (IPDMA), which evaluates the effectiveness and safety of dietary and/or physical activity interventions in women with infertility and overweight or obesity on reproductive, maternal and perinatal outcomes.
- ⇒ An IPDMA allows us to explore treatment-covariate interactions for important participant-level characteristics, which are usually impossible in meta-analyses based on study-level data due to various reporting and analysis strategies.
- ⇒ Venus-IPD collaboration provides a unique opportunity to harmonise outcome reporting in this IPDMA by collaborating with trial investigators.
- ⇒ The various intervention strategy and follow-up periods may limit the available subgroup analyses.

INTRODUCTION

The prevalence of obesity continues to rise worldwide, with around half of women of reproductive age having overweight or obesity.¹ Obesity is negatively associated with reproductive outcomes, including increased risks of miscarriage and obstetric complications and decreased spontaneous pregnancy rate.²⁻⁴ In addition, risks of congenital anomalies and perinatal and neonatal death are also increased.^{5,6} The mechanism behind the adverse effect of obesity on inferior reproductive performances in women remains unclear, although impaired ovarian folliculogenesis, oocyte quality, embryo quality and uterine receptivity have been implicated.⁷⁻¹¹

Box 1 Outcome measures

Primary outcome:

Live birth*

Secondary outcomes:

Body mass index: amount of weight loss in kg.

Dropout.

Fertility outcomes

Spontaneous resumption of ovulation.

Spontaneous pregnancy.

Ongoing pregnancy (>12 weeks).

Biochemical pregnancy.

Clinical pregnancy (viable intrauterine pregnancy confirmed by ultrasound)*, accounting for singleton pregnancy, twin pregnancy and higher multiple pregnancy.

Pregnancy loss* accounting for ectopic pregnancy, miscarriage, still-birth and termination of pregnancy.

Gestational age at delivery*

Time to pregnancy leading to live birth*.

Preterm birth (<37 weeks).

Obstetric outcomes†

Hypertensive disorders of pregnancy.

Gestational diabetes.

Antepartum haemorrhage.

Postpartum haemorrhage.

Other maternal safety outcomes‡

Ovarian hyperstimulation syndrome (mild; moderate; severe).

Pulmonary embolism.

Endometritis.

Neonatal outcomes

Birth weight*

Large for gestational age; small for gestational age.

Neonatal mortality*.

Major congenital anomaly*.

Admission to neonatal intensive care unit.

Cardiometabolic outcomes after the intervention (if available)

Waist circumference; hip circumference (cm).

Waist-hip ratio.

Blood pressure (mm Hg).

Serum testosterone (ng/dL).

Triglycerides (mmol/L).

Total cholesterol (mmol/L).

Low-density lipoprotein cholesterol (mmol/L).

High-density lipoprotein cholesterol (mmol/L).

Glucose (mmol/L).

Insulin (mmol/L).

Insulin sensitivity index.

Haemoglobin A1c (mmol/mol).

C reactive protein (mg/L).

Metabolic syndrome.

Note: Definitions not specifically stated will take into account the various definition criteria between countries and regions.

†Definitions are based on International Statistical Classification of Diseases and Related Health Problems (ICD-10).

*The core outcome set for infertility.^{25 26}

Various guidelines recommend lifestyle interventions based on dietary and/or physical activity targeting at a 5%–10% reduction in body weight as an initial step prior to fertility treatment for women with infertility and overweight or obesity.^{12 13} However, evidence supporting such a treatment strategy is limited, and randomised controlled trials (RCTs) assessing the effect of lifestyle interventions prior to fertility treatments have not consistently demonstrated an improvement in live birth rate.^{14–16} Existing systemic reviews and/or meta-analyses of study level data have demonstrated inconsistent results on live birth rate and miscarriage, partly due to varying inclusion criteria.^{17–20} Additionally, these systemic review and meta-analyses are limited in the analysis of subgroup effects and time-to-event outcomes due to inadequate reporting or different reporting and analytical strategies in the primary trials. These issues can potentially be addressed through evidence synthesis using individual participant data (IPD) from relevant studies.^{21 22} The overall objective of this individual participant data meta-analysis (IPDMA) (Venus-IPD project) is to better inform current practice regarding the effectiveness and safety of dietary and/or physical activity interventions in women with overweight or obesity prior to initiating fertility treatments.

The specific objectives of the Venus-IPD project are:

1. To identify whether dietary and/or physical activity interventions in women with infertility and overweight or obesity seeking fertility treatment improves live birth and/or other reproductive, maternal and perinatal outcomes.
2. To explore if there are subgroup(s) of women who benefit from dietary and/or physical activity interventions (treatment–covariate interactions).
3. To evaluate attrition with dietary and/or physical activity interventions.
4. To explore the association between the magnitude of preconception weight change and reproductive and perinatal outcomes.
5. To explore the effect of dietary and/or physical activity interventions on cardiometabolic outcomes.

METHODS

This systematic review and IPDMA is registered on PROSPERO (CRD42021266201). The protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis of IPD and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.^{23 24}

Eligibility criteria

Study type

Only RCTs are considered eligible. Quasi-RCTs will be excluded.

Study populations

Women with infertility and overweight or obesity, who are eligible for fertility treatments.

Study intervention

Any intervention consisting of dietary, physical activity interventions or a combination of both. Optional elements are medication, psychological counselling and supportive non-surgical weight management interventions. Bariatric surgery will be excluded.

Study comparator

Regular or standard advice with respect to healthy diet and physical activity, routine care or no intervention.

Outcomes

All outcomes in the core outcomes set for infertility research will be included and the definition of these outcomes will be used.^{25 26}

Primary outcome

The primary outcome will be live birth (counted as birth events, eg, twin live birth is counted as one live birth event).^{25 26}

Secondary outcomes

Secondary outcomes will include viable intrauterine pregnancy confirmed by ultrasound (accounting for singleton, twin and higher order multiple pregnancies); pregnancy loss (accounting for ectopic pregnancy, miscarriage, still-birth and termination of pregnancy); gestational age at delivery; birth weight; neonatal mortality; major congenital anomaly; and time to pregnancy leading to live birth. In addition to the core outcome set, we will assess live birth resulting from spontaneous pregnancies, resumption of ovulation, maternal and perinatal complications, dropout, amount of weight loss and cardiometabolic outcomes. Detailed outcome measures are presented in [box 1](#). The final outcomes reported will be determined by the availability of data on these outcomes and some parameters may be used for future analysis.

Setting

There will be no restriction on setting.

Identification of studies

The following electronic databases will be used to identify potentially eligible studies: MEDLINE, Embase and Cochrane Central Register of Controlled Trials (CENTRAL). Key authors in the area of fertility treatment will be consulted for additional literature and unpublished manuscripts. Citations in identified studies and previously published meta-analyses will be reviewed. In addition, clinical trial registries including International Clinical Trials Registry Platform and ClinicalTrials.gov will be searched. The grey literature including Google Scholar and any other relevant sources will be reviewed. No language, time period or publication status restrictions will be applied. The search strategy is presented in a online supplemental file.

Inclusion of studies

Study selection process

Two reviewers (EE-H and ZW) will perform independent screening and determination of the eligibility and

inclusion using COVIDENCE. Additional reviewer(s) will solve conflicts or disagreements. The screening process will begin with title/abstract review and will be followed by full text review.

Risk of bias assessment

Study risk of bias will be assessed by two reviewers (EE-H and ZW) independently based on the Risk of Bias 2 tool.²⁷ The following five domains will be assessed: (1) risk of bias arising from the randomisation process; (2) risk of bias due to deviations from the intended interventions effect of adhering to intervention); (3) missing outcome data; (4) risk of bias in measurement of the outcome; and (5) risk of bias in selection of the reported result. Studies will be rated on each criterion with either 'low risk of bias', 'some concerns' or 'high risk of bias'. Trial authors will be contacted when further information is needed for the assessments.

Development of the database

Establishing the Venus-IPD collaboration

We have established the Venus-IPD collaboration by inviting leading authors of eligible trials identified in our search in 2021. Leading authors of new trials identified in future search before project completion will be invited via email to join the collaboration. The protocol for the IPDMA will be shared with new authors who wish to participate in the project.

Data management

In accordance with the study objectives, IPD will be requested. Leading authors of included RCTs will be provided with a list of data items requested. Deidentified raw data can be transferred by a variety of secure methods (courier, secure email or secure electronic transfer) depending on the authors' institutional regulations and preference. All authors will be asked to sign a Data Sharing Agreements detailing the conditions for data release. IPD will be stored on a secure server at the University Medical Center Groningen.

Data checking and cleaning

Data consistency between the IPD and the trial publications will be verified, and possible data errors, duplications and missing values will be identified and investigated. The trial investigators will be asked to solve discrepancies or concerns about the dataset. Data will be harmonised across studies, for example, in terms of uniform cut-offs and units where applicable. Cleaned IPD will be collated into a single database.

Data analysis

Individual participant data meta-analysis

After data checking and harmonisation, the analytical approach for the IPDMA will be determined. For outcomes where multiple included studies are small or have rare events (including zero event), we will perform a one-stage IPDMA. Otherwise, a two-stage random effects IPDMA will be preferable.²⁸ The first stage will involve analysing the IPD in each study separately, to account for

the clustering of participants within trials and to obtain the estimates of interest and their variances. The primary outcome will be analysed by logistic regression models. OR with 95% CIs will be calculated with adjustment for baseline covariates (age and baseline body mass index (BMI)). Secondary outcome measures will be estimated using ORs for binary outcomes, mean difference for continuous outcomes and HR for time-to-event outcomes. To assess potential effect modifiers, treatment–covariate interaction terms between participant level covariates and the intervention will be added to the analyses.

In the second stage, the derived effect estimates, that is, treatment effects or treatment–covariate interactions, will be pooled across studies using a random effects model based on the assumed differences in treatment effect due to between-study heterogeneity. Restricted maximum likelihood will be used for these models. Heterogeneity will be summarised using τ^2 and I^2 .²⁹ The results will be presented in forest plots. Only within-study interaction will be considered as recommended by current guidance on IPDMA.³⁰

The main analysis will be based on the intention-to-treat principle. We will conduct this IPDMA using Stata V.17 (StataCorp, College Station, Texas, USA). A detailed statistical analysis plan will be developed before commencing the analysis.

Unavailable IPD data

Studies without IPD will not be pooled with studies with IPD in this IPDMA. The aggregate data of RCTs without IPD will be synthesised separately, and the results will be compared with the those based on IPDMA.

Missing data

The percentage of individual participant missing data will be recorded. Missing data in each study will be dealt with separately using multiple imputation when missing at random assumption is not violated.^{31–33}

Treatment–covariate interaction analysis

Treatment–covariate interaction analysis will be performed for the primary outcome by exploring the following treatment–covariate interactions.

- ▶ Baseline BMI.
- ▶ Intervention type (dietary, physical activity, their combination).
- ▶ Magnitude of weight loss (or BMI points change).
- ▶ Polycystic ovary syndrome (PCOS) versus non-PCOS.
- ▶ Age.

Continuous variables will be treated as continuous without categorisation. Non-linear association will be explored using restricted cubic spline according to current practice.³⁰

Sensitivity analysis

Sensitivity analysis will test the robustness of our conclusions for the analysis of the primary outcome. This will be explored by limiting the analysis to:

- ▶ Studies with overall low risk of bias.

- ▶ Women with obesity (BMI ≥ 30).
- ▶ Women adherent to the intervention (as per-protocol analysis).
- ▶ Using a one-stage IPDMA (if two stage is used in the main analysis).

Publication bias

A contour enhanced funnel plot will be used to investigate potential publication bias (small study effects) when more than 10 studies are included. Data availability bias will be evaluated by incorporating evidence from studies without IPD.

Overall certainty of evidence

We will evaluate the overall certainty of the body of evidence by considering risk of bias, inconsistency, indirectness, imprecision and publication bias using the GRADE framework.³⁴

Ethics and dissemination

Formal ethical approval for the Venus-IPD project was exempted by the medical ethics committee of the University Medical Center Groningen (METc code: 2021/563, date: 17 November 2021). Contributors will be asked to submit only de-identified datasets (ie, specific identifiable information will be erased before sharing). Additional restrictions on data use or storage may apply to some IPD when applicable. Findings will be disseminated internationally through the collaborative group, conference presentations and peer-reviewed publication.

Patient and public involvement

Patient and public representatives have acknowledged the importance of the Venus-IPD project and will be involved in the interpretation and reporting of the findings as well as wider disseminations.

DISCUSSION

The Venus-IPD project has the potential to inform clinicians, healthcare providers and women with overweight or obesity seeking fertility treatment regarding whether postponing fertility treatment to receive dietary and/or physical activity interventions would be helpful to improve reproductive, maternal and perinatal outcomes. In addition, by collecting the IPD, specific subsets of women for whom these interventions provide the greatest benefit may be identified. Meanwhile, we acknowledge that the classification of intervention type can only be limited to broad categories in this IPDMA. Lastly, the findings of this study may identify the minimum amount of weight loss required to observe a benefit. The findings can then be used to inform fertility treatment strategies and decisions regarding the design of future studies.

Author affiliations

¹Department of Obstetrics and Gynaecology, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA

²Shady Grove Fertility, Roanoke, Virginia, USA

- ³Department of Obstetrics and Gynaecology, University Medical Centre Groningen, Groningen, The Netherlands
- ⁴Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands
- ⁵Department of Obstetrics and Gynaecology, University of Gothenburg Sahlgrenska Academy, Gothenburg, Sweden
- ⁶Department of Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
- ⁷Department of Obstetrics and Gynaecology, Erasmus University Medical Center, Rotterdam, Zuid-Holland, Netherlands
- ⁸Department of Medicine, Université de Sherbrooke, Sherbrooke, Quebec, Canada
- ⁹Department of Obstetrics and Gynaecology, University "Magna Graecia" of Catanzaro, Catanzaro, Italy
- ¹⁰Metabolism & Obesity Service, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
- ¹¹Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Victoria, Australia
- ¹²Clínica Fertty, Universidad Autónoma de Barcelona, Universidad Autónoma de Barcelona, Barcelona, Spain
- ¹³Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Trøndelag, Norway
- ¹⁴Department of Obstetrics and Gynaecology, St Olavs Hospital Trondheim University Hospital, Trondheim, Trøndelag, Norway
- ¹⁵Department of Internal Medicine, Division of Metabolism, Endocrinology & Diabetes, University of Michigan, Ann Arbor, Michigan, USA
- ¹⁶Department of Nutritional Sciences, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA
- ¹⁷Department of Obstetrics and Gynaecology, University of Southern California Keck School of Medicine, Los Angeles, California, USA
- ¹⁸Department of Obstetrics and Gynaecology, Penn State College of Medicine, Hershey, Pennsylvania, USA
- ¹⁹Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia
- ²⁰Aberdeen Centre for Women's Health Research, Institute of Applied Health Sciences, University of Aberdeen School of Medicine Medical Sciences and Nutrition, Aberdeen, UK

Twitter Henk Groen @Groen62H and Trine Moholdt @trinemoholdt

Acknowledgements We thank all participating hospitals and their patients and staff for their contribution to this IPDMA.

Collaborators The Venus-IPD Collaboration.

Contributors Study conception and/or design: EE-H, ZW, HG, AEPC, AH, RSL, BWJM and RW. Acquisition of data: AT-K, CB, JSEL, ADdL, GJ, J-PB, SP, SK, LM, JJE, TM, AER, DS, AH, and RSL. Analysis: ZW, RW, and HG. Drafting of the manuscript: EE-H, ZW, HG and RW. Interpretation and critical revision of the article: AEPC, AT-K, CB, JSEL, ADdL, GJ, J-PB, SP, SK, LM, JJE, TM, AER, DS, AH, RSL, and BWJM.

Funding This project is partly supported by the Centre for Research Excellence in Women's Health in Reproductive Life (app1171592) through a project support grant. RW is supported by a National Health and Medical Research Council (NHRC) Investigator grant (2009767). LM is supported by a Heart Foundation Future Leader Fellowship.

Competing interests AH reports consultancy for Ferring with respect to the development of a lifestyle app. BWM is supported by an NHMRC Investigator grant (GNT1176437). BWM reports personal fees from ObsEva and Merck, and travel support from Merck, outside the submitted work. RW reports grants from the NHMRC. TM is supported by a Future Leader in Diabetes Award from the European Foundation for the Study of Diabetes/Novo Nordisk Foundation (NNF19SA058975) and grants from the regional health authority in Central Norway. ATK reports personal fees from Merck for lectures. The other authors do not have competing interest to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Formal ethical approval for the project (Venus-IPD) was exempted by the medical ethics committee of the University Medical Center Groningen (METC code: 2021/563, date: 17 November 2021).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No datasets were generated for this publication as this is a protocol.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Zheng Wang <http://orcid.org/0000-0003-1592-6765>
 Henk Groen <http://orcid.org/0000-0002-6629-318X>
 Jean-Patrice Baillargeon <http://orcid.org/0000-0002-1336-081X>
 Stefano Palomba <http://orcid.org/0000-0003-2767-8295>
 Trine Moholdt <http://orcid.org/0000-0003-1024-8088>
 Amy E Rothberg <http://orcid.org/0000-0002-0243-9135>
 Anemiek Hoek <http://orcid.org/0000-0003-4441-7142>
 Ben W Mol <http://orcid.org/0000-0001-8337-550X>
 Rui Wang <http://orcid.org/0000-0002-6622-8134>

REFERENCES

- Vahratian A. Prevalence of overweight and obesity among women of childbearing age: results from the 2002 national survey of family growth. *Matern Child Health J* 2009;13:268–73.
- van der Steeg JW, Steures P, Eijkemans MJC, *et al*. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod* 2008;23:324–8.
- Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril* 2017;107:840–7.
- Ramlau-Hansen CH, Thulstrup AM, Nohr EA, *et al*. Subfecundity in overweight and obese couples. *Hum Reprod* 2007;22:1634–7.
- Johansson S, Villamor E, Altman M, *et al*. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. *BMJ* 2014;349:g6572.
- Persson M, Cnattingius S, Villamor E, *et al*. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. *BMJ* 2017;357:j2563.
- Brannian JD, Hansen KA. Leptin and ovarian folliculogenesis: implications for ovulation induction and art outcomes. *Semin Reprod Med* 2002;20:103–12.
- Purcell SH, Moley KH. The impact of obesity on egg quality. *J Assist Reprod Genet* 2011;28:517–24.
- Leary C, Leese HJ, Sturme RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. *Hum Reprod* 2015;30:122–32.
- Shah DK, Missmer SA, Berry KF, *et al*. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. *Obstet Gynecol* 2011;118:63–70.
- Bellver J, Pellicer A, García-Velasco JA, *et al*. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. *Fertil Steril* 2013;100:1050–8.
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Obesity in pregnancy: ACOG practice Bulletin, number 230. *Obstet Gynecol* 2021;137:e128–44.
- Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: a Committee opinion. *Fertil Steril* 2015;104:1116–26.
- Espinós JJ, Polo A, Sánchez-Hernández J, *et al*. Weight decrease improves live birth rates in obese women undergoing IVF: a pilot study. *Reprod Biomed Online* 2017;35:417–24.



- 15 Sim KA, Dezarnaulds GM, Denyer GS, *et al.* Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clin Obes* 2014;4:61–8.
- 16 Einarsson S, Bergh C, Friberg B, *et al.* Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. *Hum Reprod* 2017;32:1621–30.
- 17 Lan L, Harrison CL, Misso M, *et al.* Systematic review and meta-analysis of the impact of preconception lifestyle interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women. *Hum Reprod* 2017;32:1925–40.
- 18 Hunter E, Avenell A, Maheshwari A, *et al.* The effectiveness of weight-loss lifestyle interventions for improving fertility in women and men with overweight or obesity and infertility: a systematic review update of evidence from randomized controlled trials. *Obes Rev* 2021;22:e13325.
- 19 Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev* 2014;15:839–50.
- 20 Boedt T, Vanhove A-C, Vercoe MA, *et al.* Preconception lifestyle advice for people with infertility. *Cochrane Database Syst Rev* 2021;4:Cd008189.
- 21 Riley RD, Lambert PC, Abo-Zaid G. Meta-Analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;340:c221.
- 22 Broeze KA, Opmeer BC, van der Veen F, *et al.* Individual patient data meta-analysis: a promising approach for evidence synthesis in reproductive medicine. *Hum Reprod Update* 2010;16:561–7.
- 23 Stewart LA, Clarke M, Rovers M, *et al.* Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA* 2015;313:1657–65.
- 24 Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- 25 Duffy JMN, AlAhwany H, Bhattacharya S, *et al.* Developing a core outcome set for future infertility research: an international consensus development study† ‡. *Hum Reprod* 2020;35:2725–34.
- 26 Duffy JMN, Bhattacharya S, Bhattacharya S, *et al.* Standardizing definitions and reporting guidelines for the infertility core outcome set: an international consensus development study† ‡. *Hum Reprod* 2020;35:2735–45.
- 27 Sterne JAC, Savović J, Page MJ, *et al.* Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
- 28 Burke DL, Ensor J, Riley RD. Meta-Analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017;36:855–75.
- 29 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- 30 Riley RD, Debray TPA, Fisher D, *et al.* Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. *Stat Med* 2020;39:2115–37.
- 31 Mavridis D, White IR. Dealing with missing outcome data in meta-analysis. *Res Synth Methods* 2020;11:2–13.
- 32 Sullivan TR, Yelland LN, Lee KJ, *et al.* Treatment of missing data in follow-up studies of randomised controlled trials: a systematic review of the literature. *Clinical Trials* 2017;14:387–95.
- 33 Jakobsen JC, Gluud C, Wetterslev J, *et al.* When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017;17:162.
- 34 Schünemann H, Brożek J, Guyatt G. *Grade Handbook for grading quality of evidence and strength of recommendations. updated October, 2013.*

Supplementary file

Search strategy

Ovid MEDLINE(R)

- 1 exp infertility/
- 2 infertil\$.tw.
- 3 subfertil\$.tw.
- 4 fertility.tw.
- 5 exp reproductive techniques, assisted/
- 6 exp ovulation induction/
- 7 exp insemination, artificial/
- 8 exp embryo transfer/
- 9 exp fertilization in vitro/
- 10 exp sperm injections, intracytoplasmic/
- 11 ART.tw.
- 12 assisted reproduct\$.tw.
- 13 ovulat\$ induc\$.tw.
- 14 (ovar\$ adj2 stimulat\$.tw.
- 15 superovulat\$.tw.
- 16 ovarian hyperstimulation.tw.
- 17 COH.tw.
- 18 intrauterine insemination\$.tw.
- 19 artificial insemination\$.tw.
- 20 IUI.tw.
- 21 vitro fertili?ation.tw.
- 22 ivf.tw.

- 23 icsi.tw.
- 24 intracytoplasmic sperm injection\$.tw.
- 25 exp polycystic ovary syndrome/
- 26 polycystic ovar\$.tw.
- 27 PCOS.tw.
- 28 PCO.tw.
- 29 exp anovulation/
- 30 anovulat\$.tw.
- 31 oligo ovulat\$.tw.
- 32 or/1-31
- 33 exp obesity/
- 34 exp overweight/
- 35 exp body weight/
- 36 (obese or obesity).tw.
- 37 overweight.tw.
- 38 or/33-37
- 39 exp body weight changes/
- 40 exp weight loss/
- 41 exp body weight/
- 42 weight loss.tw.
- 43 weight reduc\$.tw.
- 44 exp weight reduction programs/
- 45 exp diet, reducing/
- 46 exp diet therapy/
- 47 exp food, formulated/

- 48 exp diet, carbohydrate-restricted/
49 exp diet, healthy/
50 exp dietary supplements/
51 exp energy intake/
52 exp caloric restriction/
53 exp fasting/
54 diet.tw.
55 calorie controlled.tw.
56 calorie restrict\$.tw.
57 exp nutrition therapy/
58 meal replacement\$.tw.
59 exp exercise/
60 exp exercise therapy/
61 physical activit\$.tw.
62 exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/
63 fitness.tw.
64 or/39-63
65 clinical trials as topic.sh.
66 exp randomized controlled trial/
67 exp randomization/
68 randomi?ed controlled trial\$.tw.
69 rct.tw.
70 controlled clinical trial.pt.
71 random allocation.tw.
72 randomly.tw.

- 73 (allocated adj2 random).tw.
74 or/65-73
75 exp animals/ not humans.sh.
76 74 not 75
77 32 and 38 and 64 and 76