Methods and Results

# Methods

This systematic review and meta-analysis was pre-registered on PROSPERO ([CRD42024601434](https://www.crd.york.ac.uk/PROSPERO/view/CRD42024601434)) initially on the of December 2024. The primary aim of this review was to examine the descriptive question “Does resting energy expenditure (REE) differ between women with and without polycystic ovary syndrome (PCOS)?”.

## Search Strategy

PubMed, Web of Science, and MEDLINE databases were searched using the following Boolean search string: ((“Basal Metabolic Rate”[MeSH] OR “Energy Metabolism”[MeSH] OR “Resting Metabolic Rate” OR RMR OR “Resting Energy Expenditure” OR REE OR “Basal Metabolic Rate” OR BMR OR “resting energy” OR “basal energy expenditure”) AND (“Polycystic Ovary Syndrome”[MeSH] OR “Polycystic Ovary Syndrome” OR PCOS OR “Polycystic Ovarian Disease” OR “Stein-Leventhal Syndrome”)). Searches were limited to publications up until May 2025 when the search was completed, limited to English language articles, and Rayyan was used to manage the search and screening process.

## Eligibility Criteria

The condition being studied was PCOS and we included observational cross-sectional design studies, in addition to studies of intervention where REE was reported for the population (and if included, the comparator) condition of interest. Following the PICO framework our eligibility criteria were as follows:

* Population
  + Inclusion criteria:
    - Women
    - 18-65 y
    - With or without insulin resistance (IS)
  + Exclusion criteria: -Studies using invalid or non-standard methods for measuring REE (e.g., predicted REE from body composition)
* Intervention(s) or exposure(s)
  + Otherwise healthy women with PCOS
* Comparator(s) or control(s)
  + Otherwise healthy control women without PCOS
* Outcome
* Resting energy expenditure (REE) measured via multiple methods including direct/indirect calorimetry, doubly labelled water.

Studies using invalid or non-standard methods for measuring BMR (e.g., predicted BMR from body composition) were excluded.

## Data extraction (selection and coding)

Bibliometric data including authors, journal, and title of article were extracted. Descriptive statistics for age, body mass, fat mass, fat free mass, height, BMI, race, physical activity levels, country of investigation, information regarding glucose/insulin regulation and insulin resistance status (where available) were extracted for each arm within each study in addition to sample size. Descriptive characteristics were then tabulated across studies for reporting.

The method of measuring REE was extracted and the units of measurement for which REE was reported. For each arm, and observation time point if multiple observations reported (e.g., before and after an intervention), depending on what was reported by the authors we extracted the means, medians, standard deviations, standard errors, lower and upper range values, and interquartile range for the unadjusted and/or body mass adjusted and/or fat free mass adjusted REE values. Where REE values adjusted for body mass and/or fat free mass were reported we used the reported body mass and/or fat free mass mean values for that arm to convert them to unadjusted REE values (i.e., multiplied them by body mass and/or fat free mass mean values). Where means and/or standard deviations were missing the latter were either calculated from standard errors and sample size, or all both were estimated from lower and upper range, interquartile range, median, and sample size depending on the information available using the methods of Wan et al. (2014). All REE values were converted to kcal/day.

## Statistical Analysis

Statistical analysis of the data extracted was be performed in R, (v 4.3.3; R Core Team, https://www.r-project.org/) and RStudio (v 2023.06.1; Posit, https://posit.co/). All code utilised for data preparation, transformations, analyses, plotting, and reporting are available in the corresponding GitHub repository <https://github.com/jamessteeleii/pcos_ree_meta>. We cite all software and packages used in the analysis pipeline using the grateful package (Rodriguez-Sanchez et al., 2023) which can be seen here: <https://github.com/jamessteeleii/pcos_ree_meta/blob/main/grateful-report.pdf>. The statistical analysis plan was linked in our pre-registration (PROSPERO: [CRD42024601434](https://www.crd.york.ac.uk/PROSPERO/view/CRD42024601434)) and available at the accompanying github repository. Any deviations from the pre-registration are noted below.

Given our research question our analysis was aimed at parameter estimation (Cumming, 2014) within a Bayesian meta-analytic framework (Kruschke & Liddell, 2018). For all analyses model parameter estimates and their precision, along with conclusions based upon them, are interpreted continuously and probabilistically, considering data quality, plausibility of effect, and previous literature, all within the context of each model. The renv package (Ushey et al., 2023) was used for package version reproducibility and a function based analysis pipeline using the targets package (Landau et al., 2023) was employed (the analysis pipeline can be viewed by downloading the R Project and running the function targets::tar\_visnetwork()). Effect sizes and their variances were all calculated using the metafor packages escalc() function (Viechtbauer, 2023). The main package brms (Bürkner et al., 2023) was used in fitting all the Bayesian meta-analysis models. Prior and posterior draws were taken using marginaleffects (Arel-Bundock et al., 2023) and tidybayes (Kay & Mastny, 2023) packages. All visualisations are created using ggplot2 (Wickham et al., 2023), tidybayes, and the patchwork (Pedersen, 2023) packages.

### Main Pre-registered Models

We adopted an arm-based multiple condition comparison (i.e., network) type model given that the studies included had arms of women with PCOS both with, and without, a non-PCOS control arm (Hong et al., 2016), and also in some cases multiple observations of REE in the different arms included in the study. In typical contrast-based meta-analyses data is limited to the effect sizes for paired contrasts between arms and thus studies that include both arms (i.e., relative effects between non-PCOS control vs PCOS arms); however, in arm-based analyses the data are the absolute effects within each arm and information is borrowed across studies to enable both within condition absolute, and between condition relative contrasts to be estimated. From this model we focus on reporting the global grand mean estimate for the fixed between condition relative contrast for non-PCOS control vs PCOS arms as our primary estimand of interest (i.e., in both mean and standard deviation models). We examined both raw mean REE (i.e., the absolute mean REE in kcals per day for each arm) in addition to the between person standard deviation in REE (i.e., the absolute standard deviation in REE in kcals per day for each arm). Both models were multilevel in that they included nested random intercepts for both study, and arm within study, and in addition and in deviation from our pre-registration we also included lab as a random intercept as in some cases we had multiple studies from the same lab or research group included. Lastly, the inclusion of a random intercept for each effect size was also accidentally omitted from our pre-registration and so this is also included in the model.

#### Mean REE Model

The main model for mean REE with representing the condition (either control or PCOS) was as follows:

where is the mean REE estimate from the arm, for the study, conducted by the lab and is the corresponding sampling error for that estimate. The random intercepts for the lab, study, arm, and mean REE estimate are , , , and respectively each with standard deviation of , , , and . The parameter represents the fixed effect estimate of REE for control conditions and the fixed effect estimate for the offset from this for the PCOS conditions (i.e., the difference between conditions). The estimated offset was allowed to vary across both labs and studies each reflected by and respectively, and these effects were also modelled as correlated with the corresponding random intercepts with covariance and , and and correlation matrices.

The priors for this model were as follows:

$$
\beta\_0 \sim \text{Student-}t(3, 1441.81, 84.56) \\
\beta\_1 \sim \text{Student-}t(3, 0, 200)
$$

$$
\sigma^2\_{0,\mathrm{study}} \sim \text{Half-student-}t(3, 149.89, 82.91) \\
\sigma^2\_{0,\mathrm{lab}},\, \sigma^2\_{1,\mathrm{lab}},\,
\sigma^2\_{1,\mathrm{study}},\, \sigma^2\_{0,\mathrm{arm}},\, \sigma^2\_{0,\mathrm{effect}} \sim \text{Half-student-}t(3, 0, 112.4)
$$

$$
\mathrm{corr}\_{\mathrm{lab}} \sim \mathrm{LKJ}(1) \\
\mathrm{corr}\_{\mathrm{study}} \sim \mathrm{LKJ}(1)
$$

where the prior for , which corresponded to the model intercept and mean REE in the control condition, was set based on meta-analysis of the mean REEs for women from two large studies of healthy people (Pavlidou et al., 2023; Velasquez, 2011) though set with a conservative degrees of freedom for the distribution.The random intercept was set similarly to this. The prior for the fixed effect , reflecting the difference between control and PCOS conditions was set based on a wide range of possible values considering the minimum and and maximum values of the ranges reported in the two studies noted (i.e., 2492 - 908 = 1584). We then set a prior that permits values approximately across this range of values with the majority of it’s mass centred around zero. The remaining random effects were set based on the default weakly regularising priors for brms and scaled to the expected response values using a distribution with 3 degrees of freedom and , and both correlation matrices and were set with an distribution.

#### Standard Deviation of REE Model

The main model for the standard deviation of REE with representing the condition (either control or PCOS) was as follows:

where is the natural logarithm of the standard deviation of REE estimate from the arm, for the study, conducted by the lab and is the corresponding sampling error for that estimate. The random intercepts for the lab, study, arm, and standard deviation of REE estimate are , , , and respectively each with standard deviation of , , , and . The parameter represents the fixed effect estimate of standard deviation of REE for control conditions and the fixed effect estimate for the offset from this for the PCOS conditions (i.e., the difference between conditions). The estimated offset was allowed to vary across both labs and studies each reflected by and respectively, and these effects were also modelled as correlated with the corresponding random intercepts with covariance and , and and correlation matrices. Finally, represents the fixed effect of the natural logarithm of the corresponding mean REE estimate which is modelled as estimated with measurement error i.e., represents the point estimate for the natural logarithm of the mean REE estimate from the arm, for the study, conducted by the lab and is the corresponding sampling error for that estimate.

The priors for this model were as follows:

$$
\beta\_0 \sim \text{Student-}t(3, 5.54, 0.80) \\
\beta\_1 \sim \text{Student-}t(3, 0, 5.3) \\
\beta\_2 \sim \text{Student-}t(3, 0, 2.5)
$$

$$
\text{mean}(\tilde{m}) \sim \text{Half-student-}t(3, 7.28, 0.62) \\
\text{sd}(\tilde{m}) \sim \text{Half-student-}t(3, 0, 5)
$$

$$
\sigma^2\_{0,\mathrm{study}} \sim \text{Half-student-}t(3, 1.08, 1.06) \\
\sigma^2\_{0,\mathrm{lab}},\, \sigma^2\_{1,\mathrm{lab}},\,
\sigma^2\_{1,\mathrm{study}},\, \sigma^2\_{0,\mathrm{arm}},\, \sigma^2\_{0,\mathrm{effect}}
\sim \text{Half-student-}t(3, 0, 2.5)
$$

$$
\mathrm{corr}\_{\mathrm{lab}} \sim \mathrm{LKJ}(1) \\
\mathrm{corr}\_{\mathrm{study}} \sim \mathrm{LKJ}(1)
$$

where the prior for , which corresponded to the model intercept and standard deviation of REE in the control condition, was again set based on meta-analysis of the standard deviation of REEs for women from two large studies of healthy people (Pavlidou et al., 2023; Velasquez, 2011) though set with a conservative degrees of freedom for the distribution.The random intercept was set similarly to this. The prior for the fixed effect , reflecting the difference between control and PCOS conditions was set based on a wide range of possible values. Given that in many cases of variables in the field there is an approximate relationship of ~1 for the natural logarithm of the standard deviation conditioned upon the natural logarithm of the mean (Steele et al., 2023) we set this prior to reflect the range of differences on the on the log scale (i.e., ). We then set a prior that permits values approximately across this range of values with the majority of it’s mass centred around zero. The prior for the fixed effect , reflecting the relationship between the natural logarithm of the mean REE with the natural logarithm of the standard deviation of REE, was set it to be weakly informative centred on zero with a wide scale to indicate uncertainty in this outcome specifically despite the typical relationship close to ~1. Priors for the measurement error of the natural logarithm of the mean REE estimate were again based upon meta-analysis of the aforementioned studies, though measurement error has to be positive, as does the corresponding standard deviation of this error, so we set these to conservative wide distributions. The remaining random effects were set based on the default weakly regularising priors for brms and scaled to the expected response values using a distribution with 3 degrees of freedom and , and both correlation matrices and were set with an distribution.

#### Post-processing of models

For both models we examined trace plots along with values to examine whether chains have converged, and posterior predictive checks for each model to understand the model implied distributions. From each model we took draws from the posterior distributions for the conditional absolute estimates for each condition (i.e., controls and PCOS) by study incorporating random effects, the global grand mean absolute estimates for each condition ignoring random effects, and the global grand mean between condition relative contrast for controls vs PCOS conditions ignoring random effects. The between condition relative contrast for controls vs PCOS conditions corresponded to in each model and was our primary estimand of interest; for the mean REE model this corresponded to the absolute difference in mean REE, and for the standard deviation of REE model this corresponded to the natural logarithm of the ratio of standard deviations of REE which was exponentiated (note, all log standard deviation of REE model estimates were exponentiated back to the original scale to aid interpretibility). We present the full probability density functions for posterior visually, and also to calculate mean and 95% quantile intervals (QI: i.e., ‘credible’ or ‘compatibility’ intervals) for each estimate providing the most probable value of the parameter in addition to the range from 2.5% to 97.5% percentiles given our priors and data.

### Sensitivity analysis using pairwise contrast based models

By way of sensitivity analysis we also conducted pairwise contrast based models where we limited the included effects to those extracted from studies including only a directly comparable control and PCOS arm at baseline. These models were both as follows:

where is the pairwise effect size, either the mean difference in REE or the log coefficient of variation ratio (calculated as PCOS vs control), for the study, conducted by the lab and is the corresponding sampling error for that effect size estimate. The random intercepts for the lab, study are and respectively each with standard deviation of , . The parameter represents the fixed effect estimate of the pairwise effect size i.e., the pooled estimate of the contrast between conditions. The priors for in these models were set as default weakly regularising which is set on an intercept that results when internally centering all population-level predictors around zero to improve sampling efficiency and scaled to the expected response values using a distribution; for the mean difference in REE this was and for the log coefficient of variance ratio this was . The random effects were set similarly scaled to the expected response values but using a distribution centred on zero. From these models we calculated the mean and 95% quantile intervals (i.e., ‘credible’ or ‘compatibility’ intervals) for the (comparable to the from the corresponding mean and standard devation of REE arm-based models) for each effect size providing the most probable value of the parameter in addition to the range from 2.5% to 97.5% percentiles given our priors and data.

# Results

A total of 17 studies from 13 labs including 33 arms (Control arms = 9, PCOS arms = 15) and a total of 918 participants (Controls: minimum n = 9, median n = 29, maximum n = 54; PCOS: minimum n = 5, median n = 28, maximum n = 266). Descriptive characteristics of the arms and participants in these studies are reported in Table 1.

## Mean REE Model Results

The main model for mean REE resulted in a posterior distribution for the contrast between control and PCOS conditions with a mean point estimate of 37 kcal/day with a 95% quantile interval ranging from -39 kcal/day to 129 kcal/day suggesting there is a 95% probability that the true difference lies between these values given our priors and the data from included studies. The corresponding conditional estimates for the control condition and PCOS condition respectively were 1479 kcal/day [95%QI:1375 kcal/day to 1591 kcal/day] and 1516 kcal/day [95%QI:1409 kcal/day to 1625 kcal/day]. These results including the full visualisation of the posterior distribution, in addition to the conditional estimates by study, can be seen in [Figure 1](#fig-mean-REE).

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| Figure 1: Posterior distribution, mean point estimates, and 95% quantile intervals for conditional estimates by study, global grand mean estimates by condition, and the contrast between conditions for mean resting energy expenditure of control women without PCOS and women with PCOS. |

## Standard Deviation of REE Model Results

The main model for the between participant standard deviation of REE resulted in a posterior distribution for the contrast ratio between control and PCOS conditions with a mean point estimate of 1.05 with a 95% quantile interval ranging from 0.75 to 1.47 suggesting there is a 95% probability that the true ratio of standard deviations lies between these values given our priors and the data from included studies. The corresponding conditional estimates for the standard deviations of the control condition and PCOS condition respectively were 247 kcal/day [95%QI:182 kcal/day to 333 kcal/day] and 254 kcal/day [95%QI:188 kcal/day to 335 kcal/day]. These results including the full visualisation of the posterior distribution, in addition to the conditional estimates by study, can be seen in [Figure 2](#fig-variance-REE).

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| --- |
| Figure 2: Posterior distribution, variance point estimates, and 95% quantile intervals for conditional estimates by study, global grand variance estimates by condition, and the contrast ratio between conditions for the standard deviation of resting energy expenditure of control women without PCOS and women with PCOS. |

## Sensitivity Analysis with Pairwise Models

For mean REE the pairwise model resulted in qualitatively similar inferences suggesting little difference between control and PCOS conditions with mean point estimate of 16 kcal/day with a 95% quantile interval ranging from -36 kcal/day to 70 kcal/day. This was similar for the standard deviation of REE with the pairwise model resulting in a contrast ratio between control and PCOS conditions with a mean point estimate of 0.9 with a 95% quantile interval ranging from 0.6 to 1.35.

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