Supplementary material

Material and methods

The study protocol was registered with PROSPERO (CRD42023460206). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed as a guideline for this study (**Figure S1**). The research question was defined using the PICOS framework.

Study selection

The following criteria had to be met for the study to be eligible: (i) patients must have a cancer undergoing active cancer therapy; (ii) patients must be on one of the three restrictive diets (CR, a FMD, or STF); (iii) duration of diet ≥48 h; (iv) study involving only human subjects; (v) language of the publication must be in English; and (vi) study designs included randomised controlled trials (RCTs), cohort studies, case-control studies, case reports or series. The minimum duration of 48 h was chosen based on previous literature indicating that metabolic changes relevant to cancer therapy, such as reductions in insulin and IGF-1, typically become evident after this threshold[1]. This duration also aligned with commonly used STF and FMD protocols in included trials.

Identification and selection of studies

We searched PubMed, CINAHL, and Embase (search terms can be found in the supplementary material), spanning from June 1973 to October 2025. We further supplemented our

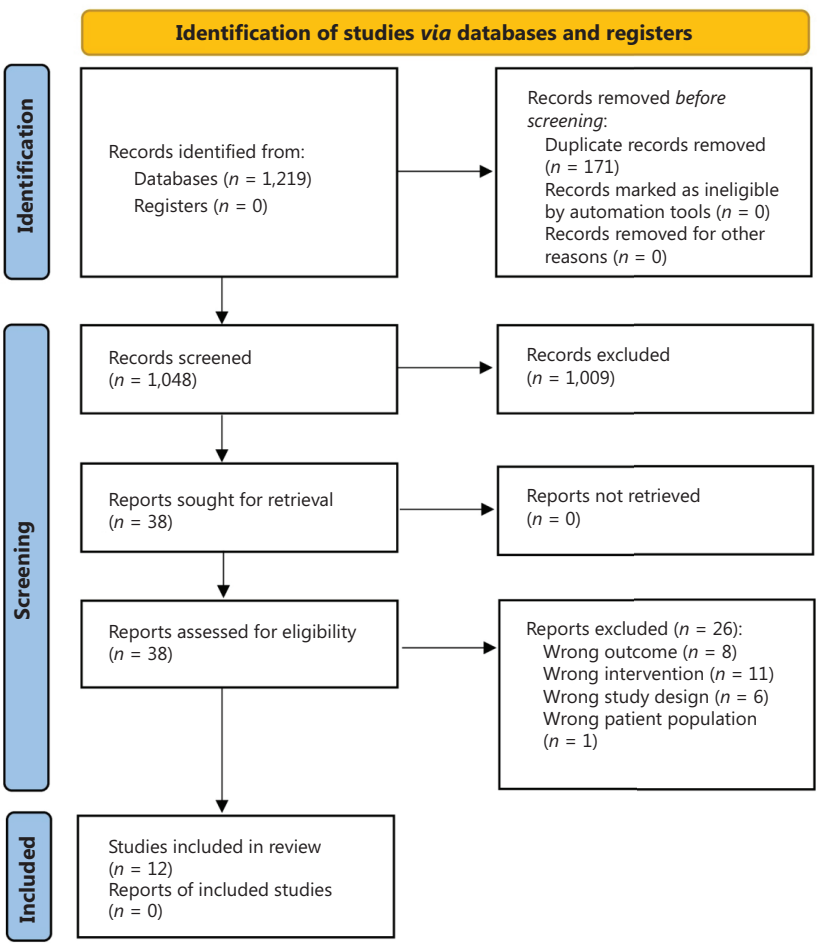

Figure S1 PRISMA 2020 flow diagram for study selection: this figure outlines the study selection process based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. The flow diagram illustrates the number of records identified, screened, assessed for eligibility, and ultimately included in the systematic review.

search using relevant web resources. The search was updated to include publications up to October 2025. One additional study published between August 2023 and October 2025 met the inclusion criteria and was included in the analysis. The retrieved studies were uploaded to Covidence, a systematic review platform, and duplicates were eliminated using the Covidence deduplication algorithm. The processes of screening titles and abstracts, as well as conducting full-text reviews, were carried out independently by two reviewers (ECN and DSYG). At each stage, the reviewers excluded studies that did not meet the inclusion criteria. Any disagreements were resolved through consensus between the two reviewers. In the event of an unresolved conflict, a third reviewer (SHW) was consulted.

Data extraction

Two independent reviewers (ECN and DSYG) performed data extraction from the final list of studies using a predefined, standardised data extraction form. The extracted data included study details (journal, study design, and country), population demographics (population size, gender, age, and race), intervention characteristics (type of dietary restriction, duration of dietary restriction, and additional interventions given), outcomes of interest [treatment response, metabolic markers (IGF-1, insulin, and glucose), QOL, and adverse outcomes] and mean difference and standard deviation (SD) of outcomes from baseline when applicable. The treatment response was evaluated based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, a standardized system applied across many cancer types. For the purposes of the meta-analysis, responses were categorized into 'favourable' (complete or partial response) and 'non-favourable' (stable or progressive disease) to harmonize results across studies. A complete response was defined as the disappearance of all target lesions. Partial response was defined as a minimum of a 30% decrease in the sum of target lesions from the baseline sum of the longest diameter. Progressive disease was defined as a minimum of a 20% increase in the sum of the longest diameter of target lesions compared to the smallest sum of the longest diameter recorded[2].

Risk of bias assessment

Two independent reviewers (ECN and DSYG) utilised three different tools to assess the risk of bias in the studies included in this systematic review. Any disagreement was resolved by consensus. A third party (SHW) was consulted to resolve any disagreements. The Cochrane Risk-of-Bias 2 Tool[3] was used to assess the risk of bias for randomised controlled trials. Studies were deemed to have a low risk of bias if the study exhibited "low risk" across all domains. Studies were deemed to have a high risk of bias if at least one domain exhibited "high risk." Studies with "some concerns" in at least one domain but were not "high risk" were considered to have a moderate risk of bias[4]. The Joanna Briggs Institute Critical Appraisal Tool[5] was used to evaluate the risk of bias of the case report by Zuccoli et al.[4] The Risk of Bias in non-randomized studies of intervention (ROBINS-I) tool[6] was used to evaluate the risk of bias of the single-arm prospective trial by Vernieri et al.[7] This tool assessed the study through seven domains and judgment of each domain determined the overall risk of bias for the outcome being assessed.

Statistical analysis

In the current study research findings were categorized based on predefined primary and secondary outcomes. Continuous data outcomes were analysed using the standardized mean difference (SMD) and accompanying 95% confidence intervals (CIs). To assess heterogeneity, forest plots and the I^2 statistic were used and findings were interpreted with caution and supported by narrative synthesis. A meta-analysis was conducted to combine data from studies with three or more assessments of the same outcome utilizing a random-effects model. To ensure uniformity, data were inverted when higher values indicated better outcomes. Any data presented in formats unsuitable for meta-analysis, such as median and interquartile ranges, were described narratively.

Changes in SD from baseline were calculated according to the formula in the Cochrane Handbook for Systematic Reviews of Intervention.[8] We assumed a correlation coefficient of 0.5 for the change from baseline calculations, following standard practice in systematic reviews as the raw data in the trials were unavailable[8]. SMD was calculated by dividing the difference in mean outcome between the intervention and control groups by the standard deviation of outcomes among participants.

To assess statistical heterogeneity, forest plots and the I^2 statistic were used and findings were interpreted in conjunction with a narrative synthesis. Due to the small number of studies available per subgroup, subgroup analyses (e.g., by cancer type or type of dietary restriction) and meta-regression were not performed to avoid underpowered and potentially misleading estimates. Similarly, publication bias was not assessed using funnel plots or Egger's test because <10 studies were available per outcome. Two sensitivity analyses were performed to evaluate the robustness of our findings: excluding studies at high risk of bias; and excluding statistical outliers, defined as studies with effect sizes outside the 95% confidence bounds of the overall effect estimate. All statistical analyses were performed using R software (version 4.3.1) with the metafor package (version 4.2-0). Statistical significance was defined as a $P < 0.05$ (two-sided). Supplementary Material includes full results of the sensitivity analyses.

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