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REVIEW

Weight management / Intervention

Weight management using meal replacements and cardiometabolic risk reduction in individuals with pre-diabetes and features of metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials

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Summary

This review synthesized the evidence from randomized controlled trials comparing the effect of meal replacements (MRs) as part of a weight loss intervention with conventional food-based weight loss diets on cardiometabolic risk in individuals with pre-diabetes and features of metabolic syndrome. MEDLINE, EMBASE, and Cochrane Library were searched through January 16, 2024. Data were pooled using the generic inverse variance method and expressed as mean difference [95% confidence intervals]. The overall certainty of the evidence was assessed using GRADE. Ten trials (n = 1254) met the eligibility criteria. MRs led to greater reductions in body weight

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(−1.38 kg [−1.81, −0.95]), body mass index (BMI, −0.56 kg/m^2 [−0.78, −0.34]), waist circumference (−1.17 cm [−1.93, −0.41]), HbA_{1c} (−0.11% [−0.22, 0.00]), LDL-c (−0.18 mmol/L [−0.28, −0.08]), non-HDL-c (−0.17 mmol/L [−0.33, −0.01]), and systolic blood pressure (−2.22 mmHg [−4.20, −0.23]). The overall certainty of the evidence was low to moderate owing to imprecision and/or inconsistency. The available evidence suggests that incorporating MRs into a weight loss intervention leads to small important reductions in body weight, BMI, LDL-c, non-HDL-c, and systolic blood pressure, and trivial reductions in waist circumference and HbA_{1c}, beyond that seen with conventional food-based weight loss diets.

KEYWORDS
meal replacements, metabolic syndrome, prediabetes, weight management

1 | INTRODUCTION

Overweight/obesity is the main reversible risk factor for diabetes and cardiovascular disease.[1] This makes weight loss a critically important therapeutic target.[2–4] Meal replacements (also known as formula diet products) may aid in weight loss and improve weight-related cardiometabolic risk. For the purpose of this review, meal replacements were defined according to the European Food Safety Authority (EFSA) definition as distinct foods that served as substitutes for regular foods, typically consumed during one or more meals per day. These meal replacements had to be used as part of an energy-restricted diet aimed at weight reduction.[5]

Recent systematic reviews and meta-analyses support the use of meal replacements for weight loss.[6,7] A systematic review and meta-analysis of randomized controlled trials (RCTs) in individuals who were overweight or living with obesity found that programs incorporating meal replacements led to greater weight loss at 1 year than comparator weight loss programs.[6] Another systematic review and meta-analysis of RCTs in individuals with type 2 diabetes showed that use of meal replacements leads to moderate reductions in body weight, body mass index (BMI), systolic blood pressure, and small but significant reductions in body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, and diastolic blood pressure compared with conventional weight loss diets.[7] These findings were relevant in informing the European recommendations for the dietary management of diabetes,[8] but the previous evidence syntheses do not extend to individuals with pre-diabetes and features of metabolic syndrome.

To help inform future dietary recommendations for patients at risk of diabetes, the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) commissioned this systematic review and meta-analysis of RCTs to summarize the effect of meal replacements as part of a weight loss intervention compared with conventional food-based weight loss diets on cardiometabolic risk in individuals with pre-diabetes and features of metabolic syndrome.

2 | METHODS

The present systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions,[9] and results were reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The study protocol was registered on ClinicalTrials.gov under the following identification number: NCT02779790. This analysis represents a subset of a larger systematic review and meta-analysis investigating the effects of meal replacements on cardiometabolic risk in individuals who are overweight or living with obesity (all-comers).

2.1 | Data sources

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through to January 16, 2024, for eligible trials. Electronic database searches were supplemented with manual searches of references from included trials. The detailed search strategy is outlined in Table S1.

2.2 | Study selection

Table S2 shows our PICOTS (population, intervention, comparator, outcome, time, and settings) framework. We selected RCTs that investigated the effect of meal replacements (also known as formula diet products) as part of a weight loss intervention compared with conventional food-based weight loss diets (not including meal replacements) in individuals with at least one feature of metabolic syndrome.[11] These features included: (1) elevated waist circumference (men: ≥102 cm, women: ≥88 cm), (2) elevated triglycerides (≥1.7 mmol/L), (3) reduced high-density lipoprotein-cholesterol (HDL-c) (men: <0.9 mmol/L, women: <1.1 mmol/L), (4) elevated blood pressure (≥130/≥85 mmHg), and (5) elevated fasting glucose (≥5.6 mmol/L). To be included, studies had to be ≥2 weeks in duration, contain an intervention arm utilizing partial meal replacements (1–2 main meals per day) or total diet replacement with formula diet products (replacing all meals), contain an appropriate comparator arm, and provide viable outcome data. Studies that assessed enteral nutrition formulas and/or contained co-interventions (e.g., medications/surgery) in one arm but not the other were excluded.

2.3 | Data extraction

Two independent reviewers (J.C.N and S.K.N.) extracted relevant data from each included report. These data included study setting, design, duration, blinding, sample size, participant characteristics, (i.e., age, sex, BMI), intervention diet characteristics (i.e., energy content of meal replacement and frequency and duration of use), control diet characteristics (energy content and diet type), drop-out rate, adverse events, funding, and outcome data. The authors were contacted for missing outcome data. In the absence of numerical values for outcome measurements or the inability to contact study authors, values were extracted from graphically presented data using Plot Digitizer, version 2.5.1 (Free Software Foundation, Boston, MA).

2.4 | Risk of bias assessment

The same investigators also assessed risk of bias from each included report using the Cochrane risk of bias tool, which categorizes studies as having high, low, or unclear risk of bias on the basis of criteria pertaining to selection bias, blinding, incomplete outcome data, and reporting bias.[10] Any discrepancies in risk of bias assessments were reconciled by consensus.

2.5 | Outcomes

Outcomes included markers of adiposity (body weight, BMI, body fat, and waist circumference), glycemic control (HbA_{1c}, fasting glucose, and fasting insulin), blood lipids (low-density lipoprotein-cholesterol [LDL-c], HDL-c, non-HDL-c, apolipoprotein [apo]-B, and triglycerides), and blood pressure (systolic and diastolic blood pressure).

2.6 | Data synthesis and analysis

Pooled analyses were conducted using the generic inverse variance method in Stata, version 16.1 (StataCorp LLC). Random effects models were used even in the absence of statistically significant heterogeneity, as they typically yield more conservative estimates. Fixed effects models were only used when fewer than five trials were present for an outcome. The pooled effect estimate for each outcome was expressed as mean difference (MD) with 95% confidence intervals (CIs) and, for visualization purposes, as standardized mean difference (SMD) with 95% CIs.

Change-from-baseline values were preferred and differences in change-from-baseline values were used when provided. If these data were not available, we used end-difference values, if reported, or calculated the differences from available data. If no variance data were available, the average SD of the MDs across all other included trials was used to derive the SE of the MD based on the respective trial's sample size. When non-HDL-c values were not directly reported, they were calculated by subtracting HDL-c from total cholesterol values. The variance sum law was used to derive SDs for non-HDL-c from total cholesterol and HDL-c variance data.[12]

Interstudy heterogeneity was assessed using the Cochran Q statistic and quantified using the I^2 statistic, where $I^2 \geq 50\%$ and $P_Q < 0.10$ was considered evidence of substantial heterogeneity.[9] Potential sources of heterogeneity were investigated by sensitivity and subgroup analyses. For determination of whether a single trial exerted an undue influence, sensitivity analyses were performed in which we recalculated the pooled effect estimates and heterogeneity after removing each individual trial. A trial whose removal explained the heterogeneity or changed the significance, direction, or magnitude of the effect by more than the minimally important difference (MID) for each outcome (prespecified as: 1 kg for body weight, 0.4 kg/m^2 for BMI, 2% for body fat, 2 cm for waist circumference, 0.3% for HbA_{1c}, 0.5 mmol/L for fasting glucose, 5 pmol/L for fasting insulin, 0.1 mmol/L for all blood lipids, and 2 mmHg for systolic and diastolic blood pressure) was considered an influential trial. If 10 or more trials were available per outcome, then potential sources of heterogeneity were also explored through *a priori* subgroup analyses in Stata, version 16.1 (StataCorp, College Station, TX) using meta-regression by health status, type of meal replacements, follow-up duration, type of comparator, and funding.

If 10 or more trials were available, then we assessed publication bias in Stata, version 16.1 (StataCorp, College Station, TX) by visual inspection of funnel plots and formal testing by the Egger and Begg tests. If publication bias was suspected, Duval and Tweedie nonparametric "trim and fill" analyses were applied to assess the effect of the imputed "missing" studies.[13]

2.7 | Certainty of the evidence

The certainty of the evidence was assessed using the GRADE approach.[14] The evidence was rated as high, moderate, low, or very low certainty. The included RCTs were initially rated as high certainty by default and then downgraded or upgraded based on prespecified criteria. Reasons for downgrading the evidence included risk of bias (assessed by the Cochrane risk of bias tool[13]), inconsistency (substantial unexplained interstudy heterogeneity: $I^2 \geq 50\%$ and $P_Q < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision (the 95% CI for effect estimates overlap the MID for benefit or harm), and publication bias (significant evidence of small-study effects). The importance of the magnitude of the pooled estimates was assessed using our prespecified MIDs and the effect

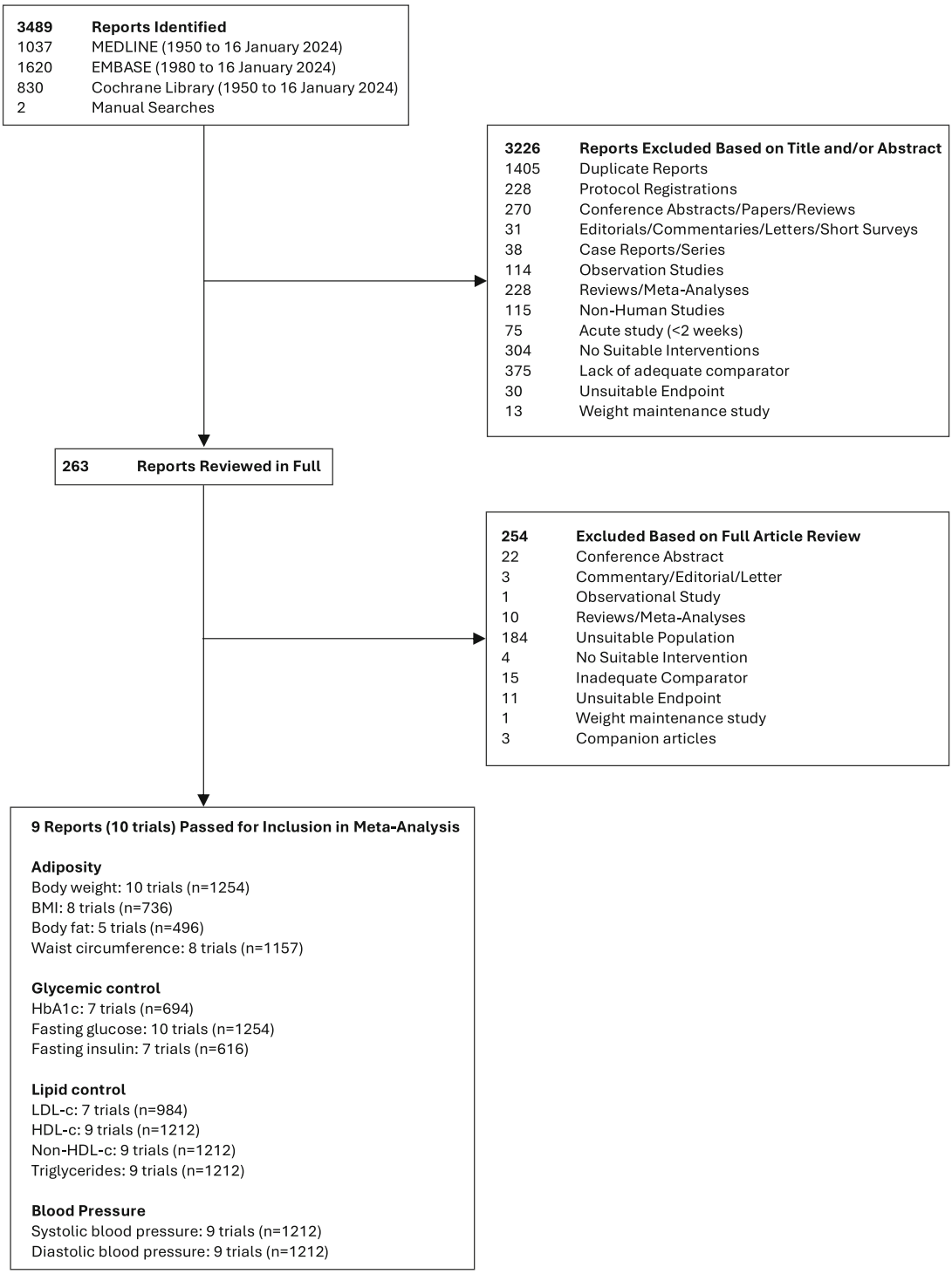

FIGURE 1 Flow of literature.

size categories according to the GRADE guidance[14–17] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1× MID).

3 | RESULTS

3.1 | Search results

Figure 1 shows the literature search and selection process. We identified a total of 3489 reports, of which 3226 were excluded based on review of titles and/or abstracts. The remaining 263 reports were retrieved and reviewed in full, of which 254 were excluded. A total of nine reports containing data for 10 trial comparisons involving 1254 individuals with pre-diabetes and/or features of metabolic syndrome met the eligibility criteria and were included in the final analyses.[18–26]

3.2 | Trial characteristics

Tables 1 and S3 show the characteristics of all included trials assessing the effect of meal replacements in weight loss interventions compared with conventional food-based weight loss diets. The median follow-up duration across all trials was 12 weeks (range 6–52). All trials had a parallel design and were conducted in outpatient settings in Europe (4 trials), Asia (4 trials), Australia (1 trial), and North America (1 trial). Most participants were middle-aged (median age 50 years [range 42–59]) and women (69%). The median BMI of participants was 32 kg/m^2 (range 26.3–36.3).

The type of meal replacements used in the trials were high-protein meal replacements (4 trials), balanced meal replacements (4 trials), and low glycemic index meal replacements (3 trials). Brands of meal replacements included Herbalife®, Almased®, SlimFast™, Slim-well®, Pure Grain Company, and FormMed HealthCare AG. The meal replacements included a liquid component in all trials, with additional snack bars and/or soups in four trials.[18–20,24] The meal replacements represented a median ~28% of total energy intake (range ~11–42%) across all trials. The comparators were conventional energy-restricted diets (5 trials), conventional energy-restricted diets plus lifestyle education (3 trials), structured low-fat, high-carbohydrate energy-restricted diet (1 trial), and standard medical therapy (1 trial). Median daily caloric intake and macronutrient compositions (% energy as carbohydrate: fat: protein) of the intervention and comparator arms were similar across trials (intervention: ~1362 kcal/day [54:27:25]; comparator: ~1329 kcal/day [53:28:17]).

The median dropout rates in the intervention and comparator arms were similar at 11% (0–21) and 12% (0–19), respectively. Most trials were funded by industry sources (4 trials) and a combination of agency and industry sources (3 trials). Two trials were funded by agency sources, and one trial did not report funding information.

TABLE 1 Summary of trial characteristics.

Number of trials	10
Number of participants	1254
Follow-up duration, weeks	12 (6–52)
Design, number of trials	
Parallel	10
Setting, number of trials	
Europe	4
Asia	4
Australia	1
North America	1
Participant characteristics at baseline	
Age, years	50 (42–59)
Male: female	31:69
BMI, kg/m^2	32 (26.3–36.3)
Health status, number of trials	
Pre-diabetes	2
At least one feature of MetS	3
MetS	5
Intervention characteristics	
Meal replacement (MR) type	
High-protein MR	4
Balanced MR	3
Low GI MR	3
Meal replacement dose, %E	28 (11–42)
Estimated total caloric intake, kcal/day	1362 (1100–1850)
Macronutrient composition, C: F: P (median)	54: 27: 25
Comparator characteristics	
Comparator type, number of trials	
Conventional energy-restricted diet	5
Conventional energy-restricted diet plus lifestyle education	3
Structured energy-restricted diet (low-fat, high-carbohydrate)	1
Standard medical therapy	1
Estimated total caloric intake, kcal/day	1329 (1100–1850)
Macronutrient composition, C: F: P (median)	53: 28: 17
Dropout rate, %	
Intervention	11 (0–21)
Comparator	12 (0–19)
Funding source, number of trials	
Agency	2
Industry	4
Agency & Industry	3
N/A	1

Note: Data are median (range) unless otherwise indicated.
Abbreviations: % E, % energy; BMI, body mass index; C, carbohydrate; F, fat; GI, glycemic index; MetS, metabolic syndrome; P, protein.

3.3 | Risk of bias

Figures S1 and S2 show the individual and summary Cochrane risk of bias assessments of the included trials, respectively. The majority of trials were assessed as having low or unclear risk of bias across domains.

3.4 | Effect of weight management programs including meal replacements on adiposity

Figures 2 and S3–S6 show the effect of weight management programs including meal replacements on markers of adiposity. Compared with conventional food-based weight loss diets, weight management programs that included meal replacements significantly reduced body weight (MD −1.38 kg [95% CI −1.81 to −0.95], $P < 0.001$, no evidence of heterogeneity [$I^2 = 4\%$, $P_Q = 0.40$]), BMI (MD −0.56 kg/m^2 [−0.78 to −0.34], $P < 0.001$, no evidence of heterogeneity [$I^2 = 0\%$, $P_Q = 0.73$]), and waist circumference (MD −1.17 cm [−1.93 to −0.41], $P = 0.003$, no evidence of heterogeneity [$I^2 = 0\%$, $P_Q = 0.56$]). A 5% reduction in body weight was estimated to have been achieved by ~54% in the meal replacement group and ~41% in the control group. There was no significant effect on body fat.

3.5 | Effect of weight management programs including meal replacements on glycemic control

Figures 2 and S7–S9 show the effect of weight management programmes including meal replacements on glycemic control. Compared with conventional food-based weight loss diets, weight management programs that included meal replacements reduced HbA_{1c} (MD −0.11% [−0.22 to 0.00], $P = 0.05$, no evidence of heterogeneity [$I^2 = 47\%$, $P_Q = 0.08$]). There was no significant effect on fasting glucose and fasting insulin.

3.6 | Effect of weight management programs including meal replacements on blood lipids

Figures 2 and S10–S13 show the effect of weight management programs including meal replacements on blood lipids. Compared with

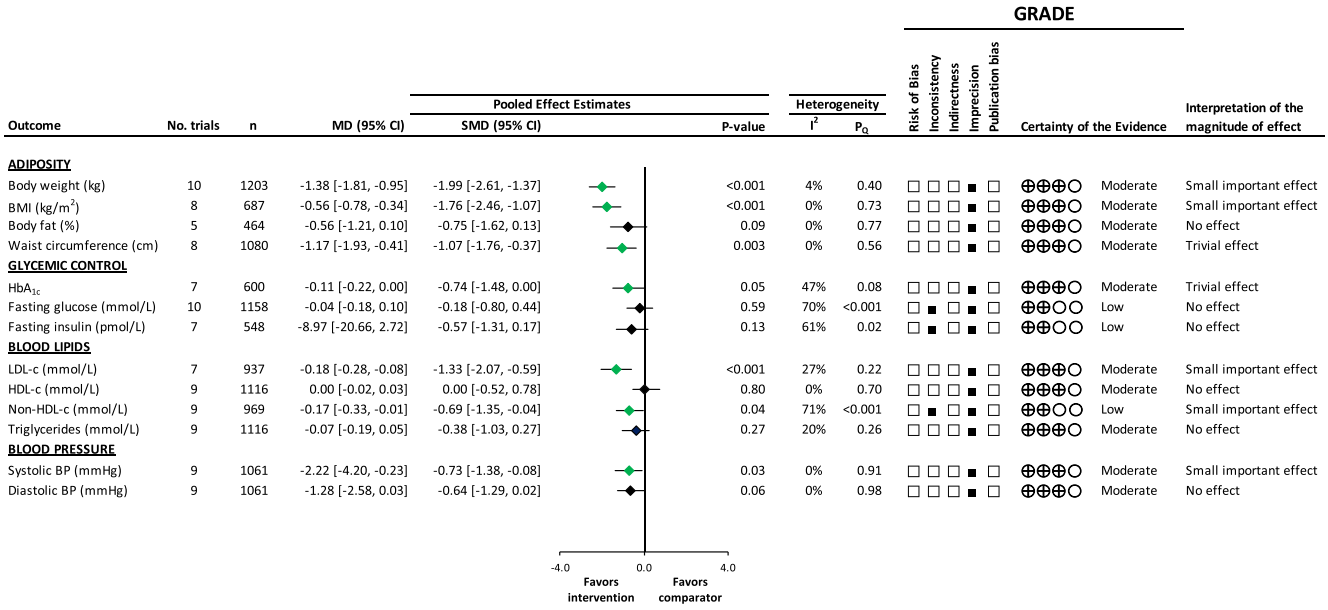

FIGURE 2 Summary of pooled effect estimates from randomized controlled trials (RCTs) investigating the effect of meal replacements as part of a weight loss intervention (intervention) compared with conventional food-based weight loss diets (comparator) on cardiometabolic risk factors in individuals with pre-diabetes and features of metabolic syndrome. Pooled effect estimates are expressed as mean differences (MDs) with 95% confidence intervals (CIs) and, for visualization purposes, as standardized mean differences (SMDs) with 95% CIs. SMDs are represented by the diamonds and 95% CIs by the line through the diamonds. Any statistically significant reductions are highlighted in green. Analyses were conducted using the generic inverse variance method with random effects models. Interstudy heterogeneity was assessed using the Cochran *Q* statistic and quantified using the I^2 statistic, where $I^2 \geq 50\%$ and $P_Q < 0.10$ were considered evidence of substantial heterogeneity. The GRADE approach was used to evaluate the certainty of the evidence. Evidence was graded as high, moderate, low, or very low certainty. RCTs were graded as high-certainty evidence by default and downgraded on the basis of risk of bias, inconsistency, indirectness, imprecision, and publication bias. We used minimally important differences (MIDs) to assess the magnitude of our point estimates. The MIDs were prespecified as 1 kg for body weight, 0.4 kg/m^2 for BMI, 2% for body fat, 2 cm for waist circumference, 0.3% for HbA_{1c}, 0.5 mmol/L for fasting glucose, 5 pmol/L for fasting insulin, 0.1 mmol/L for all blood lipids, and 2 mmHg for systolic and diastolic blood pressure. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance as follows: a large effect (≥5× MID); moderate effect (≥2x MID); small important effect (≥1x MID); and trivial/unimportant effect (<1 MID).

conventional food-based weight loss diets, weight management programs that included meal replacements significantly reduced LDL-c (MD −0.18 mmol/L [−0.28 to −0.08], $P < 0.001$, no evidence of heterogeneity [$I^2 = 27\%$, $P_Q = 0.22$]) and non-HDL-c (MD −0.17 mmol/L [−0.33 to −0.01], $P = 0.04$, evidence of substantial heterogeneity [$I^2 = 71\%$, $P_Q < 0.001$]). There was no significant effect on HDL-c and triglycerides. No trials were identified examining apo-B.

3.7 | Effect of weight management programs including meal replacements on blood pressure

Figures 2, S14, and S15 show the effect of weight management programmes including meal replacements on blood pressure. Compared with conventional food-based weight loss diets, weight management programs that included meal replacements significantly reduced systolic blood pressure (MD −2.22 mmHg [−4.20 to −0.23], $P = 0.03$, no evidence of heterogeneity [$I^2 = 0\%$, $P_Q = 0.91$]). There was no significant effect on diastolic blood pressure.

3.8 | Adverse events

Five trials reported information on adverse events.[19,20,23,26] No serious adverse events were reported in three trials.[19,23] One trial reported diarrhea in one participant in the meal replacement group but noted that meal replacements were well-tolerated by most participants.[20] Another trial reported one health issue leading to a dropout (although details were not described).[26]

3.9 | Sensitivity analyses

Figures S16–S28 show the individual trial influence analyses on the effect of weight management programs including meal replacements across all outcomes. For HbA_{1c}, individual removal of Lee et al.[23] and Metzner et al.[20] changed the evidence from non-significant to statistically significant ($P < 0.05$). In the case of non-HDL-c, individual removal of Chaiyasoot et al.,[25] Flechtner-Mors et al.,[19] Halle et al.,[26] Lee et al.,[23] Metzner et al.,[20] and Xu et al.[21] changed the evidence from statistically significant to non-significant ($P > 0.05$). Removal of Lee et al.[23] explained all of the substantial heterogeneity ($I^2 = 0\%$, $P_Q = 0.485$) without altering the significance or direction of the effect observed in non-HDL-c. For systolic blood pressure, individual removal of Flechtner-Mors et al.[19] and Xu et al.[21] changed the evidence from statistically significant to non-significant ($P > 0.05$). Lastly, the removal of Metzner et al.[20] changed the evidence from non-significant to statistically significant ($P < 0.05$) for diastolic blood pressure.

3.10 | Subgroup analyses

Figures S29–S33 and 34–38 show subgroup analyses of the effect of weight management programs including meal replacements on body weight and fasting glucose, respectively. For body weight, there was no significant effect modification by participants' health status, type of meal replacement used, duration of follow-up, type of comparator, and source of trial funding. Similar findings were observed for fasting glucose except for a significant effect modification ($P < 0.05$) by type of comparator (Figure S37). Subgroup analyses were not conducted for the remaining outcomes because <10 trials were available.

3.11 | Publication bias analyses

There was no evidence of small-study effects on body weight or fasting glucose (Figures S39 and S40). Publication bias was not assessed for the remaining outcomes because <10 trials were available.

3.12 | GRADE assessment

Figure 2 and Table S4 summarize the GRADE assessments. The evidence supporting the small important reductions in body weight, BMI, LDL-c, and systolic blood pressure was graded as moderate owing to downgrades in imprecision. Similarly, the evidence for the trivial reductions in waist circumference and HbA_{1c} was also graded as moderate owing to downgrades in imprecision. Lastly, the evidence for the small important reduction in non-HDL-c was graded as low owing to downgrades for both inconsistency and imprecision.

4 | DISCUSSION

4.1 | Summary of findings

The present systematic review and meta-analysis of 10 RCTs included 1254 participants with prediabetes and/or features of metabolic syndrome. Weight management programs incorporating meal replacements led to small important reductions in body weight, BMI, LDL-c, non-HDL-c, and systolic blood pressure, as well as trivial reductions in waist circumference and HbA_{1c}, beyond those achieved with conventional food-based weight loss diets, over a median follow-up duration of 12 weeks.

4.2 | Results in relation to previous studies

Our findings align with previous systematic reviews and meta-analyses investigating the effect of meal replacements as part of an intended weight loss intervention in adults who were overweight or living with obesity.[6,27,28] A systematic review and meta-analysis of 23 studies involving 7884 adult participants who were overweight or living with obesity found that incorporating meal replacements led to greater weight loss at 1 year than control weight loss programs. Notably, when the meal replacement diet was provided with enhanced levels of support, even more substantial weight reductions were observed (ranging from −2.22 kg to −6.13 kg) when compared with

alternative diets and regular support.[6] Regarding biochemical outcomes, the authors found that results consistently favored meal replacement groups for HbA_{1c}, and the results for other outcomes (glucose, insulin, lipids, and blood pressure) were mixed and rarely reached statistical significance.[6] Another systematic review and meta-analysis of 22 studies involving 1982 adult participants who were overweight or living with obesity reported that meal replacement-based low-energy diets were superior to that of food-based low-energy diets in the context of weight loss.[27] Additionally, they found that receiving more than 60% of total daily energy intake from meal replacements had the greatest effect on weight loss.[27] In our analysis, the median dose of meal replacements represented ~28% (range 11–42%) of total daily energy intake across all included trials. Therefore, we were unable to make a direct comparison with the >60% dose threshold. Lastly, a systematic review and meta-analysis of 9 studies involving 934 adult participants who were overweight or living with obesity found that high-protein meal replacements led to greater reductions in body weight, BMI, and fat mass compared with individuals consuming control diets.[28] In our subgroup analysis, where more than 10 trials were available, the type of meal replacement used, which included high-protein meal replacements, did not modify the effects on body weight or fasting glucose.

Our findings also align with studies conducted in patients with type 2 diabetes. In our previously published systematic review and meta-analysis of 9 trials involving 961 patients with type 2 diabetes, we found that meal replacements in weight loss diets lead to modest reductions in body weight (−2.37 kg), BMI (−0.87 kg/m^2), and systolic blood pressure (−4.97 mmHg) when compared with traditional weight loss diets.[7] However, the reductions in body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, and diastolic blood pressure were of marginal clinical significance, and there was no effect of meal replacements on blood lipids. Generally, the reductions we found in participants with pre-diabetes and features of metabolic syndrome were smaller than in those with type 2 diabetes (body weight, −1.38 kg vs. −2.37 kg; BMI −0.56 kg/m^2 vs. −0.87 kg/m^2; and systolic blood pressure −2.22 mmHg vs. −4.97 mmHg). Evidence from large-scale RCTs, such as the Look AHEAD (Action for Health in Diabetes) study,[29] the Why WAIT (Weight Achievement and Intensive Treatment) program,[30,31] the DiRECT (Diabetes Remission Clinical Trial) trial,[32,33] and the DIADEM-I (Diabetes Intervention Accentuating Diet and Enhancing Metabolism-I) trial,[34] also supports the use of meal replacements as an effective strategy for weight management and improving cardiometabolic outcomes. These trials have consistently demonstrated that incorporating meal replacements into comprehensive interventions leads to substantial reductions in body weight, improvements in glycemic control including remissions, and favorable changes in cardiovascular risk factors in patients with type 2 diabetes.

4.3 | Strengths and limitations

The strengths of our systematic review and meta-analysis include (1) a comprehensive and reproducible search and selection process of the literature examining the effect of meal replacements as a weight loss strategy on cardiometabolic risk factors, (2) inclusion of RCTs (provides the best protection against bias), and (3) use of the GRADE approach to evaluate the overall certainty of the evidence. However, there are some possible limitations as well. We downgraded the certainty of the evidence for serious imprecision in the pooled estimates for body weight, BMI, waist circumference, HbA_{1c}, LDL-c, non-HDL-c, and systolic blood pressure, as the 95% CIs overlapped the MIDs for clinical benefit. Second, we downgraded the certainty of the evidence for non-HDL-c due to serious inconsistency as there was presence of unexplained heterogeneity. Although generally there was no significant effect modification by pre-specified subgroups or presence of small study effects for body weight and fasting glucose, we were unable to conduct subgroup and publication bias analyses for the majority of outcomes owing to the small number of available trials (<10 trials). Balancing these strength and limitations, we graded the certainty of the evidence as moderate for body weight, BMI, waist circumference, HbA_{1c}, LDL-c, and systolic blood pressure, and low for non-HDL-c.

4.4 | Potential mechanism(s) of action

The mechanism of action of meal replacements in exerting cardiometabolic effects is likely multifaceted, involving nutritional, behavioral, and physiological aspects. Meal replacements contain a mix of carbohydrates, proteins, fats, vitamins, and minerals. Although compositions vary by formulation, meal replacements tend to be high in protein. Proteins in meal replacements can stimulate satiety through various mechanisms, including the induction of satiety hormones like cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1), thus aiding in appetite control. Additionally, meal replacements typically have a low glycemic index (GI), beneficial for insulin sensitivity and glucose metabolism—key factors in managing metabolic syndrome.[35]

Furthermore, meal replacements facilitate controlled caloric intake, which aids individuals in maintaining a caloric deficit that is conducive to weight loss. While the impact of meal replacements on eating behaviors has not been extensively studied, integrating meal replacements into regular dietary patterns may potentially curb the consumption of unhealthy foods and improve the intake of essential nutrients. The consequent weight loss associated with the use of meal replacements can result in favorable changes in body composition, such as reductions in waist circumference. These changes are especially beneficial for individuals with features of metabolic syndrome, as they can lead to reduced blood pressure and more favorable lipid profiles.

4.5 | Implications

The use of meal replacements for weight management in individuals with prediabetes and features of metabolic syndrome presents promising clinical and service implications. As a short-term, temporary

strategy within a comprehensive lifestyle intervention, meal replacements can help individuals achieve improvements in adiposity and various cardiovascular health markers. This initial success can then facilitate a transition to a sustainable and healthier dietary pattern, such as the Mediterranean or Portfolio diet, for long-term weight management. Adherence is the most important determinant for attaining the benefits of any diet. Therefore, healthcare professionals should recommend evidence-based dietary patterns (including meal replacements) that align with the patient's individual values, preferences, and treatment goals. While several studies, including DiRECT,[32,33] DIADEM-I,[34] and PREVIEW,[36] have explored this approach in individuals with type 2 diabetes, further research specifically in individuals with prediabetes and features of metabolic syndrome is needed.

5 | CONCLUSIONS

Our analysis of the available evidence suggests that incorporating meal replacements into a weight loss intervention for individuals with prediabetes and/or features of metabolic syndrome for a median 12 weeks leads to small important reductions in body weight, BMI, LDL-c, non-HDL-c, and systolic blood pressure, and trivial reductions in waist circumference and HbA_{1c}, beyond what is achieved with conventional food-based weight loss diets. Our certainty in the pooled effect estimates were moderate for body weight, BMI, waist circumference, HbA_{1c}, LDL-c, and systolic blood pressure, and low for non-HDL-c. More high-quality RCTs are needed to investigate the longer-term effects of meal replacements as part of a weight loss intervention on cardiometabolic risk factors in individuals with prediabetes and features of metabolic syndrome.

AUTHOR CONTRIBUTIONS

Study concept and design: J.C.N. and J.L.S. Acquired data: J.C.N. and S.K.N. Analyzed and interpreted data: J.C.N., S.K.N., T.A.K., S.B.M., C.W.C.K., H.K., D.R., J.S.-S., L.A.L., M.E.J.L., J.L.S. Drafted the manuscript: J.C.N. Critically revised the manuscript for important intellectual content: J.C.N., S.K.N., T.A.K., S.B.M., C.W.C.K., H.K., D.R., J.S.-S., L.A.L., M.E.J.L., and J.L.S. Final approval of the version to be published: J.C.N., S.K.N., T.A.K., S.B.M., C.W.C.K., H.K., D.R., J.S.-S., L.A.L., M.E.J.L., and J.L.S. Study guarantor: J.L.S.

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DECLARATION OF INTERESTS

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Departament de Salut Pública de la Generalitat de Catalunya, Catalonia, Spain; the European Commission; the California Walnut Commission, USA; Patrimonio Comunal Olivarero, Spain; La Morella Nuts, Spain; and Borges, Spain. He reports receiving consulting fees or travel expenses from Danone, the California Walnut Commission, the Eroski Foundation, and the Instituto Danone Spain. He is on the Clinical Practice Guidelines Expert Committee of the EASD and served on the Scientific Committee of the Spanish Agency for Food Safety and Nutrition and the Spanish Federation of the Scientific Societies of Food, Nutrition and Dietetics. He is a member of the International Carbohydrate Quality Consortium (ICQC) and an Executive Board Member of the Diabetes and Nutrition Study Group of the EASD. He is member of the Institute Danone International and reports receiving travel expenses of this organization. **M.E.J.L** has had departmental research funding from Diabetes UK, NIHR, and Novo Nordisk and has received personal fees for lecturing and consultancy from Novo Nordisk, Merck, Eli Lilly, Sanofi, Nestle, Oviva, and Counterweight Ltd. **J.L.S** has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of health Research (CIHR), Diabetes Canada, American Society for Nutrition (ASN), International Nut and Dried Fruit Council (INC) Foundation, National Honey Board (U.S. Department of Agriculture [USDA] honey "Checkoff" program), Institute for the Advancement of Food and Nutrition Sciences (IAFNS), Pulse Canada, Quaker Oats Center of Excellence, The United Soybean Board (USDA soy "Checkoff" program), Protein Industries Canada (a Government of Canada Global Innovation Clusters), Almond Board of California, The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), The Plant Protein Fund at the University of Toronto (a fund which has received contributions from IFF among other donors), The Plant Milk Fund at the University of Toronto (a fund established by the Karuna Foundation through Vegan Grants), and The Nutrition Trialists Network Fund at the University of Toronto (a fund established by donations from the Calorie Control Council and Physicians Committee for Responsible Medicine). He has received food donations to support randomized controlled trials from the Almond Board of California, California Walnut Commission, Peanut Institute, Barilla, Unilever/Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, Danone, Nutrartis, Soylent, and Dairy Farmers of Canada. He has received travel support, speaker fees and/or honoraria from Danone, Dairy Farmers of Canada, FoodMinds LLC, Nestlé, Abbott, General Mills, Nutrition Communications, International Food Information Council (IFIC), Calorie Control Council, International Sweeteners Association, International Glutamate Technical Committee, Arab Beverages Association, and Phynova. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, Ingredion, and Brightseed. He is a former member of the European Fruit Juice Association Scientific Expert Panel and Soy Nutrition Institute (SNI) Scientific Advisory Committee. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada/Canadian Association of Bariatric Physicians and Surgeons. He serves as an unpaid member of the Board of Trustees of IAFNS. He is a Director at Large of the Canadian Nutrition Society (CNS), founding member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His spouse is an employee of AB InBev. **J.C.N, S.B.M, H. K, and L.A.L** have no conflicts of interest to report.

PRIOR PRESENTATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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