The Effect of Liquid Meal Replacements on Cardiometabolic Risk Factors in Overweight/Obese Individuals With Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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OBJECTIVE

The evidence for liquid meal replacements in diabetes has not been summarized. Our objective was to synthesize the evidence of the effect of liquid meal replacements on cardiometabolic risk factors in overweight/obese individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data sources included MEDLINE, EMBASE, and the Cochrane Library through 10 December 2018. We included randomized trials of ≥2 weeks assessing the effect of liquid meal replacements in weight loss diets compared with traditional weight loss diets on cardiometabolic risk factors in overweight/obese subjects with type 2 diabetes. Two independent reviewers extracted relevant data and assessed risk of bias. Data were pooled using the inverse variance method. The overall certainty of the evidence was evaluated using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

RESULTS

Nine trial comparisons (N = 961 [median follow-up 24 weeks]) met eligibility criteria. Mean differences were for body weight −2.37 kg (95% CI −3.30 to −1.44), BMI −0.87 kg/m^2 (−1.31 to −0.42), body fat −1.66% (−2.17 to −1.15), waist circumference −2.24 cm (−3.72 to −0.77), HbA_{1c} −0.43% (−0.66 to −0.19) (−4.7 mmol/mol [−7.2 to −2.1]), fasting glucose −0.63 mmol/L (−0.99 to −0.27), fasting insulin −11.83 pmol/L (−23.11 to −0.54), systolic blood pressure −4.97 mmHg (−7.32 to −2.62), and diastolic blood pressure −1.98 mmHg (−3.05 to −0.91). There was no effect on blood lipids. The overall certainty of the evidence was low to moderate owing to imprecision and/or inconsistency.

CONCLUSIONS

Liquid meal replacements in weight loss diets lead to modest reductions in body weight, BMI, and systolic blood pressure, and reductions of marginal clinical significance in body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, and diastolic blood pressure. More high-quality trials are needed to improve the certainty in our estimates.

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Modest and sustained weight loss has been shown to reduce the need for glucose-lowering medications and improve glycemic control in overweight/obese individuals with type 2 diabetes (1–3). However, many overweight/obese individuals with type 2 diabetes face challenges in achieving weight loss. Metabolic, psychological, and behavioral factors affect the ability of people with diabetes to lose weight (4,5). Many pharmacological agents used in the treatment of diabetes also directly contribute to weight gain through their glucose-lowering mechanisms (i.e., sulfonylureas, meglitinides, and thiazolidinediones) (6). The use of liquid meal replacements within a structured dietary plan may offer a viable solution. Liquid meal replacements provide a mixture of carbohydrates, fat, and protein, along with added vitamins and minerals, in ready-to-drink form or powder formulas that require mixing. They are frequently used to replace one or two main meals each day and are often supplemented with fruits, vegetables, and nuts during or between meals to achieve the targeted daily caloric intake.

The American Diabetes Association, Diabetes Canada, and Diabetes UK clinical practice guidelines include recommendations for the use of meal replacements for diabetes management (7–9). However, the European Association for the Study of Diabetes (EASD) has not made any specific recommendations for the use of liquid meal replacements. To update the recommendations for the role of liquid meal replacements in diabetes management, the Diabetes and Nutrition Study Group (DNSG) of the EASD commissioned this systematic review and meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the available evidence from randomized controlled trials (RCTs) investigating the effect of liquid meal replacements as part of a weight loss diet in comparison with traditional low-calorie weight loss diets on cardiometabolic risk factors in overweight/obese individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (10). Data were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). 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 aimed at investigating the effect of liquid meal replacements on cardiometabolic risk factors in overweight/obese individuals (all comers).

Data Sources

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through 10 December 2018 for eligible trials. Electronic searches were supplemented with manual searches of references from included studies. Supplementary Table 1 shows our detailed search strategy.

Study Selection

We included RCTs that investigated the effect of liquid meal replacements as part of a weight loss diet compared with traditional low-calorie weight loss diets on cardiometabolic risk factors in overweight/obese individuals with type 2 diabetes. To be included, studies had to be $\geq$2 weeks in duration, contain an intervention arm that replaced one to three main meals with liquid meal replacements, contain an appropriate comparator arm, and provide viable outcome data. Studies that assessed weight maintenance and enteral nutrition formulas and contained cointerventions (i.e., drugs, exercise, or surgery) in one arm but not the other were excluded.

Data Extraction

Two investigators (J.C.N. and either S.K.N. or C.R.B.) independently reviewed and extracted relevant data from each included report. Extracted data included study setting, design, duration, blinding, sample size, participant characteristics (i.e., age, sex, BMI, and HbA_{1c}), intervention diet characteristics (i.e., energy content of liquid meal replacement and frequency and duration of use), control diet characteristics (energy content and diet type), dropout rate, and funding and outcome data. Authors were contacted for missing outcome data. 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). In the absence of numerical values for outcome measurements or the inability to contact study authors, values were extracted from figures using Plot Digitizer, version 2.5.1 (Free Software Foundation, Boston, MA). Any discrepancies in data extraction or risk of bias assessments were reconciled by consensus.

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 (LDL [LDL-c] and HDL [HDL-c] cholesterol, non-HDL-c, apolipoprotein [apo]-B, and triglycerides), and blood pressure (systolic and diastolic blood pressure).

Data Synthesis and Analysis

Pooled analyses were conducted on Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) using the generic inverse variance method. 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% CI and, for visualization purposes, as standardized MD (SMD) with 95% CI.

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. Paired analyses were applied to all crossover trials (12). 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 (13).

Interstudy heterogeneity was assessed using the Cochran Q statistic and quantified using the I^2 statistic, where $I^2 > 50\%$ and $P_Q < 0.10$ was considered evidence of substantial heterogeneity (10). Potential sources of heterogeneity were investigated by sensitivity 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. Sensitivity analyses were also conducted based on certain trial characteristics (i.e., study duration and type of liquid meal replacement). Studies whose removal explained the heterogeneity, changed the significance of the effect, or altered the effect size by 10% or more were considered influential. If 10 or more trials were available per outcome, then potential sources of heterogeneity were also explored through a priori subgroup analyses using meta-regression by baseline values, study design, follow-up, type of liquid meal replacement, comparator arm, risk of bias, and diabetes duration. If 10 or more trials were available, then we assessed publication bias 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 (14). Subgroup and publication bias analyses were conducted on Stata, version 13 (StataCorp, College Station, TX).

Grading of the Evidence

The overall certainty of the evidence was evaluated using the GRADE approach (https://gradepro.org/) where evidence was graded as high, moderate, low, or very low certainty (15). RCTs are graded as high-certainty evidence by default and then downgraded on the basis of the following prespecified criteria: risk of bias (weight of studies shows important risk of bias as assessed by the Cochrane risk of bias tool), inconsistency (substantial unexplained interstudy heterogeneity, $I^2 > 50\%$, $P_Q < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision (95% CIs for pooled effect estimates are wide or overlap minimally important differences of 0.5 kg for body weight [16], 0.2 kg/m^2 for BMI, 2% for body fat, 2 cm for waist circumference, 0.3% for HbA_{1c} [17], 0.5 mmol/L for fasting glucose, 5 pmol/L for fasting insulin, 0.1 mmol/L for LDL-c, HDL-c, non-HDL-c, and triglycerides, 0.04 g/L for apo-B, and 2 mmHg for systolic and diastolic blood pressure [18]), and publication bias (significant evidence of small-study effects).

RESULTS

Search Results

Fig. 1 shows the literature search and selection process. We identified a total of 2,287 reports, of which 2,131 were excluded based on review of titles and/or abstracts. The remaining 156 reports were retrieved and reviewed in full, of which 148 were excluded. A total of eight reports containing data for nine trial comparisons involving 961 overweight/obese participants with type 2 diabetes met the eligibility criteria and were included in the final analyses (19–26).

Trial Characteristics

Table 1 and Supplementary Table 2 show the characteristics of all included trials assessing the effect of liquid meal replacements as part of a weight loss diet compared with traditional low-calorie weight loss diets. The median follow-up duration across all trials was 24 weeks (range 12–52). All trials had a parallel design except one that had a crossover design. All trials were conducted in outpatient settings with four trials conducted in Asia, three in North America, one in Europe, and one in Australia. Most participants were middle-aged (median age 55 years [range 51–62]) men and women (48% were men and 52% women). The median BMI and HbA_{1c} levels of participants across the trials were 30.5 kg/m^2 (range 26.8–35.5) and 7.6% (range 6.5–8.8) (60 mmol/mol [48–73]), respectively.

The type of liquid meal replacements used in the trials were Glucerna SR (4 of 9 trials), SlimFast (2 of 9 trials), Medifast (1 of 9 trials), Probiotec Formula WL (1 of 9 trials), and Microdiet (1 of 9 trials). The median estimated dose of liquid meal replacement represented ~20% of energy (% E) (range ~13–47% E). The comparators in the trials were low-calorie diets using food-exchange systems (4 of 9 trials), self-selected low-calorie foods (4 of 9 trials), and a diet book (1 of 9 trials). Total caloric intake and macronutrient composition of the intervention and control arms varied across trials. Across the intervention arms, the median intake values from available trials were as follows: total caloric intake, ~1,500 kcal/day (range ~1,195–1,659); carbohydrate, ~48% E (~46–52% E); fat, ~30% E (~20–35% E); and protein, ~20% E (~18–33% E). Across the comparator arms, the median intake values were as follows: total caloric intake, ~1,500 kcal/day (range ~1,350–1,737); carbohydrate, ~55% E (~45–60% E); fat, ~25% E (~18–31% E); and protein, ~17% E (~15–37% E). Of the nine trials, five trials involved group education or counseling and four trials received no additional support or resources.

The median dropout rate in the intervention and comparator arms was 18% (range 1–43%) and 20% (2–71%), respectively. Most of the trials were funded by industry sources (6 of 9 trials), with one by agency sources (government, not-for-profit health agency, or university sources) and one by both industry and agency sources. Funding information was not reported for one trial.

RISK OF BIAS

Supplementary Figs. 1 and 2 show the individual and summary Cochrane risk of bias assessments of the included trials. The majority of trials were assessed as having unclear or low risk of bias across domains.

Effect of Liquid Meal Replacements on Adiposity

Figure 2 and Supplementary Figs. 3–6 show the effect of liquid meal replacements on body weight, BMI, body fat, and waist circumference. Liquid meal replacements as part of a weight loss diet significantly reduced body weight (MD −2.37 kg [95% CI −3.30 to −1.44], $P < 0.001$, substantial heterogeneity [I^2 = 84%, $P_Q < 0.001$]), BMI (−0.87 kg/m^2 [−1.31 to −0.42], $P < 0.001$, substantial heterogeneity [I^2 = 89%, $P_Q < 0.001$]), body fat (−1.66% [−2.17 to −1.15], $P < 0.001$, moderate heterogeneity [I^2 = 50%, P_Q = 0.11]), and waist circumference (−2.24 cm [−3.72 to −0.77], P = 0.003, substantial heterogeneity (I^2 = 74%, P_Q = 0.004]).

Effect of Liquid Meal Replacements on Glycemic Control

Figure 2 and Supplementary Figs. 7–9 show the effect of liquid meal replacements on

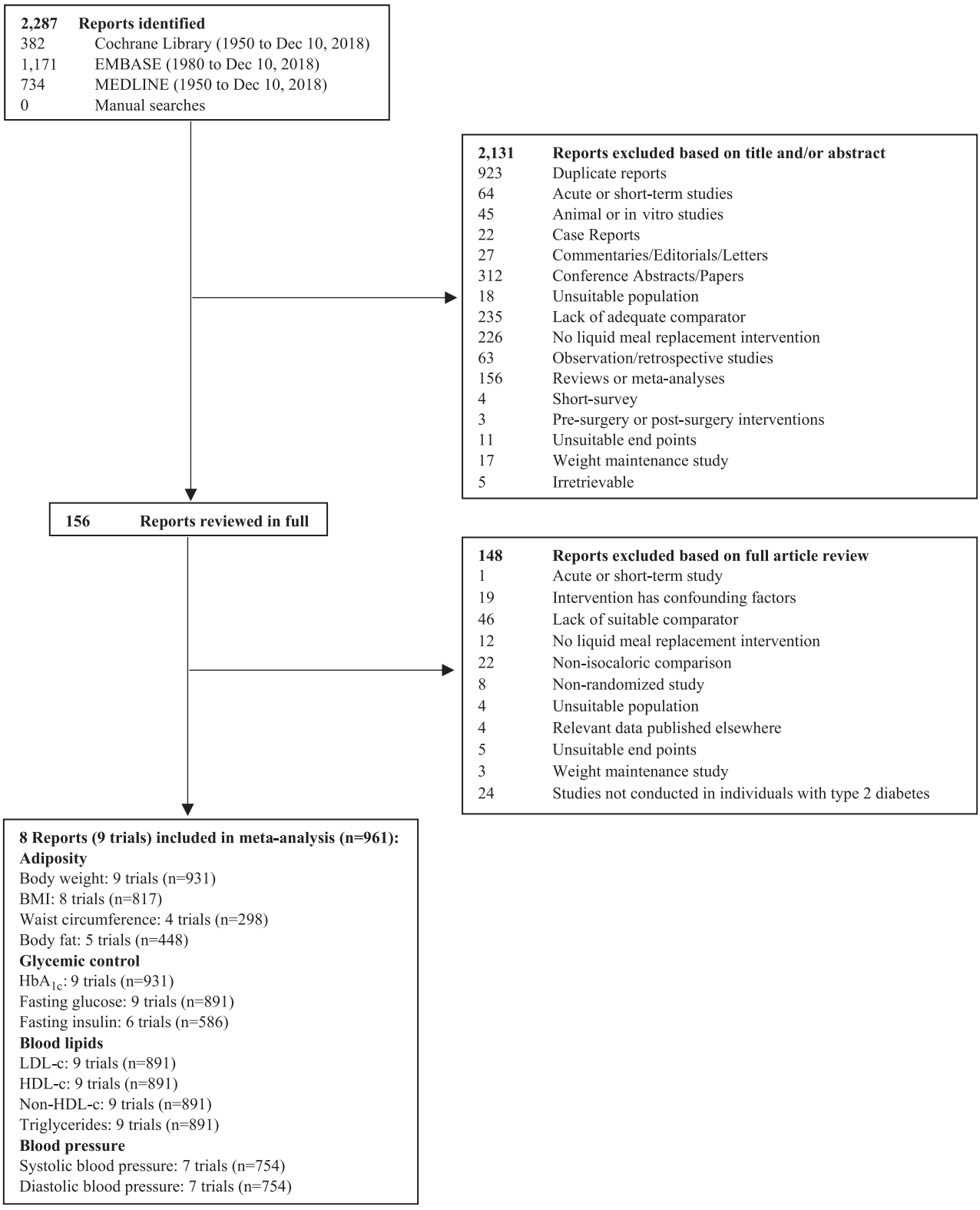

Figure 1—Search summary.

HbA_{1c}, fasting glucose, and fasting insulin. Liquid meal replacements as part of a weight loss diet significantly reduced HbA_{1c} (MD −0.43% [95% CI −0.66 to −0.19], −4.7 mmol/mol [−7.2 to −2.1], $P < 0.001$, substantial heterogeneity [I^2 = 87%, $P_Q < 0.001$]), fasting glucose (−0.63 mmol/L [−0.99 to −0.27], $P < 0.001$, substantial heterogeneity [I^2 = 70%, $P_Q < 0.001$]), and fasting insulin (−11.83 pmol/L [−23.11 to −0.54], P = 0.04, no evidence of heterogeneity).

Effect of Liquid Meal Replacements on Blood Lipids

Figure 2 and Supplementary Figs. 10–13 show the effect of liquid meal replacements on LDL-c, HDL-c, non-HDL-c, and triglycerides. Liquid meal replacements as part of a

Table 1—Summary of trial characteristics	
Number of trials	9
Number of participants	961
Follow-up duration, weeks	24 (12–52)
Design, number of trials	
Parallel	8
Crossover	1
Setting, number of trials	
Asia	4
North America	3
Europe	1
Australia	1
Participant characteristics at baseline	
Age, years	55 (51–62)
Male: female (%)†	48: 52
BMI, kg/m^2	30.5 (26.8–35.5)
HbA_{1c}, %	7.6 (6.5–8.8)
HbA_{1c}, mmol/mol	60 (48–73)
Intervention characteristics	
Liquid meal replacement type, number of trials	
Glucerna SR	4
SlimFast	2
Medifast	1
Probiotec Formula WL	1
Microdiet	1
Liquid meal replacement dose, % E‡	20 (13–47)
Estimated total caloric intake, kcal/day§	1,500 (1,195–1,659)
Macronutrient composition, C: F: P (median)¶	48: 30: 20
Comparator characteristics	
Comparator type, number of trials	
Food exchange system	4
Self-selected low-calorie foods	4
Diet book	1
Estimated total caloric intake, kcal/day§	1,500 (1,350–1,737)
Macronutrient composition, C: F: P (median)¶	55: 25: 17
Dropout rate	
Intervention, % dropout	18 (1–43)
Comparator, % dropout	20 (2–71)
Funding source, number of trials**	
Agency	1
Industry	6
Agency and industry	1
Not reported	1

Data are median (range) unless otherwise indicated. % E, % energy; C, carbohydrate; F, fat; P, protein. †Eight of nine trials provided data on sex. ‡If data were not provided, calculations were made under the assumption that an average individual consumes 2,000 kcal/day. For example, if participants consumed one serving of a 200-kcal liquid meal replacement per day and were recommended a caloric target by achievement of a 500-kcal deficit per day, then the dose was calculated as follows: ([200] / [2,000–500]) × 100% = ~13% E. §If data were not provided, calculations were made under the assumption that an average individual consumes 2,000 kcal/day. For example, if participants were recommended a caloric target by achieving a 500-kcal deficit per day, then the daily caloric intake was calculated as follows: 2,000 – 500 = 1,500 kcal/day. ¶Four of nine trials provided data for the intervention group and six of nine trials provided data for the comparator group from which macronutrient composition could be estimated. End-of-study values measuring energy from carbohydrates, fat, and protein were reported only if the study did not report or design diets to have a planned macronutrient composition. **Agency funding is that from government, university, or not-for-profit sources. Industry funding is that from trade organizations that obtain revenue from the sale of products.

weight loss diet did not have a significant effect on LDL-c (P = 0.78, substantial heterogeneity [I^2 = 68%, P_Q = 0.001]), HDL-c (P = 0.93, substantial heterogeneity [I^2=71%, P_Q<0.001]), non-HDL-c (P=0.69, no evidence of heterogeneity), and triglycerides (P = 0.86, substantial heterogeneity [I^2 = 68%, P_Q = 0.002]). No trials were identified assessing the effect of liquid meal replacements on apo-B.

Effect of Liquid Meal Replacements on Blood Pressure

Figure 2 and Supplementary Figs. 14 and 15 show the effect of liquid meal replacements on systolic and diastolic blood pressure. Liquid meal replacements as part of a weight loss diet significantly reduced systolic blood pressure (MD −4.97 mmHg [95% CI −7.32 to −2.62], P < 0.001, substantial heterogeneity [I^2 = 53%, P_Q = 0.05]) and diastolic blood pressure (−1.98 mmHg [−3.05 to −0.91], P<0.001, no evidence of heterogeneity).

Adverse Events

Six trials provided information on adverse events. No serious adverse events were reported in four of the six trials (19–21,24). One trial reported that a participant withdrew owing to gastrointestinal discomfort associated with the liquid meal replacement (22). Another trial reported presence of altered defecation and/or flatulence in 8 out of 20 participants (40%), nausea in 1 participant (5%), and a mild attack of gout in 1 participant (5%) (25).

Sensitivity Analyses

Supplementary Table 3 shows select sensitivity analyses in which systematic removal of individual trials altered the significance of the effects or the statistical significance of the interstudy heterogeneity. Removal of those of Li et al. (20), Cheskin et al. (21), Sun et al. (22), and Shirai et al. (24) changed the evidence for fasting insulin from significant to nonsignificant (P > 0.05) but not the direction of the effect. For waist circumference, removal of those of Sun et al. (22) and Chee et al. (motivational interviewing versus usual care [UC]) (26) changed the significance (P = 0.05) but not the direction of the effect or the evidence of substantial heterogeneity. Removal of those of Stenvers et al. (25) for waist circumference and Keogh and Clifton (23) for systolic blood pressure explained all of the substantial heterogeneity (I^2 = 0%, P_Q = 0.43, and I^2 = 0%, P_Q = 0.61, respectively) but did not change the significance or the direction of the effect. Removal of that of Li et al. (20) partially explained the substantial heterogeneity for LDL-c (I^2 = 37%, P_Q = 0.14) but did not change the significance or the direction of the effect. Removal of that of Sun et al. (22) partially

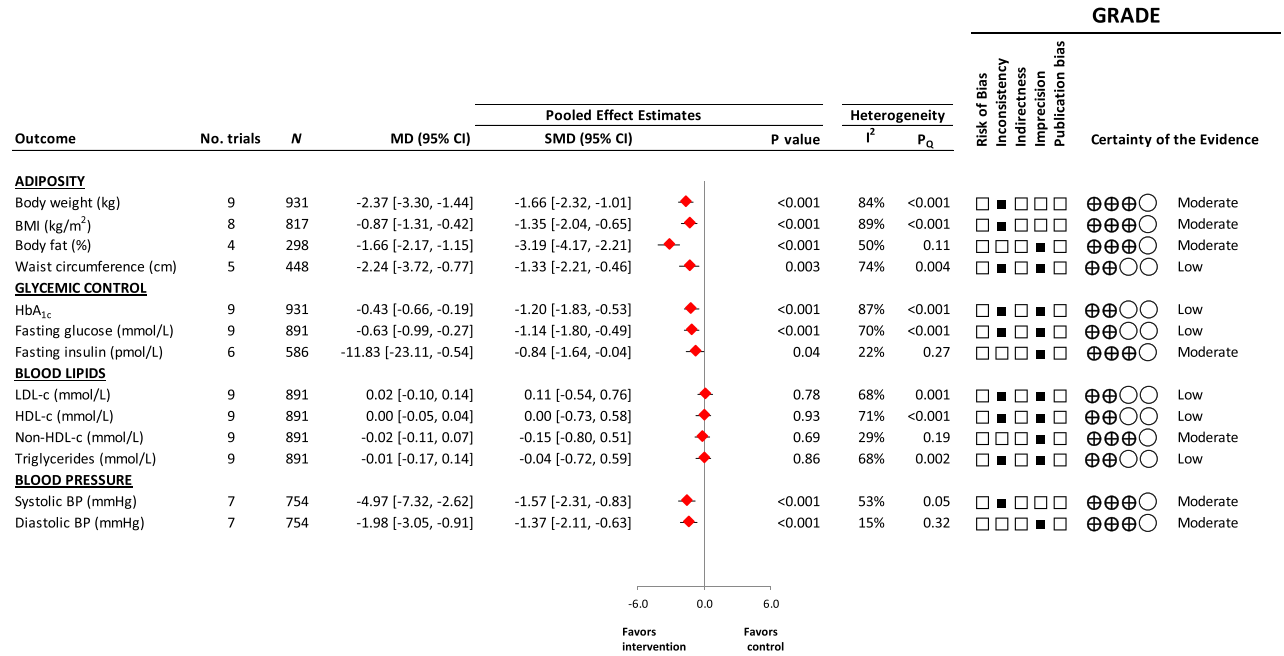

Figure 2—Summary of pooled effect estimates from RCTs investigating the effect of liquid meal replacements as part of a weight loss diet (intervention) compared with traditional low-calorie weight loss diets (comparator) on cardiometabolic risk factors. Pooled effect estimates are expressed as MDs with 95% CIs and, for visualization purposes, as SMDs with 95% CIs. SMDs are represented by the diamonds and 95% CIs by the line through the diamonds. Analyses were conducted using the generic inverse variance method with random effects models (at least 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested by the Cochran Q statistic (χ^2) at a significance level of $P_Q < 0.10$. The GRADE approach was used to evaluate the certainty of the evidence. Evidence was graded as high, moderate, low, or very low quality. RCTs were graded as high-quality evidence by default and downgraded on the basis of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

explained the substantial heterogeneity for HDL-c (I^2 = 47%, P_Q = 0.07), changing the direction but not the significance of the effect. Removal of that of Stenvers et al. (25) partially explained the substantial heterogeneity for triglycerides (I^2 = 37%, P_Q = 0.13) but did not change the significance or the direction of the effect. Removal of that of Chee et al. (motivational interviewing versus UC) (26) and Chee et al. (conventional counseling versus UC) (26) led to substantial heterogeneity for body fat but did not change the significance or the direction of the effect.

Supplementary Tables 4 and 5 show sensitivity analyses in which trials of <24 weeks in duration (19,25) were removed. Removal of these trials did not change the significance of any outcome but changed the direction of the effect estimate for HDL-c. Removal of these trials explained the substantial heterogeneity for waist circumference (I^2 = 0%, P_Q = 0.43) and partially explained the substantial heterogeneity for triglycerides (I^2 = 46%, P_Q = 0.09).

Supplementary Tables 6 and 7 show sensitivity analyses in which trials using non–diabetes-specific liquid meal replacements (19,20,23,24) were removed. Removal of these trials did not change the significance of any outcome except fasting insulin, where the evidence changed from significant to nonsignificant (P = 0.20). Removal of these trials did not change the direction of the effect estimate of any outcome except HDL-c, non-HDL-c, and triglycerides. Removal of these trials explained the substantial heterogeneity for systolic blood pressure (I^2 = 0%, P_Q = 0.62) and partially explained the substantial heterogeneity for HDL-c (I^2 = 37%, P_Q = 0.18).

Subgroup Analyses

No subgroup analyses were conducted for any outcome because <10 trials were available.

Publication Bias Analyses

Publication bias was not assessed for any outcome because <10 trials were available.

GRADE Assessment

A summary of the overall certainty of the evidence assessment of the effect of liquid meal replacements as part of a weight loss diet compared with traditional low-calorie weight loss diets on cardiometabolic risk factors is shown in Fig. 2 and Supplementary Table 8. The overall certainty of the evidence was graded as moderate for body weight, BMI, and systolic blood pressure owing to downgrades for serious inconsistency; moderate for body fat, fasting insulin, non-HDL-c, and diastolic blood pressure owing to downgrades for serious imprecision; and low for waist circumference, HbA_{1c}, fasting glucose, LDL-c, HDL-c, and triglycerides owing to downgrades for serious inconsistency and serious imprecision.

CONCLUSIONS

Summary of Findings

The present systematic review and meta-analysis of nine RCTs including 961 predominantly middle-aged, overweight/obese participants with type 2 diabetes showed that liquid meal replacements as part of a weight loss lead to modest reductions in body weight, BMI, and systolic blood pressure in comparison with traditional low-calorie weight loss diets over a median follow-up duration of 24 weeks. The reductions in body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, and diastolic blood

pressure were of marginal clinical significance. No significant effects were observed for blood lipids (LDL-c, HDL-c, non-HDL-c, and triglycerides).

Results in Relation to Previous Studies

Our findings extend those of a previous systematic review and meta-analysis of six studies that showed that partial meal-replacement plans lead to significantly greater weight loss and improvements in fasting insulin levels compared with conventional reduced-calorie diets at 3-month and 1-year time points in a mixed population of overweight/obese individuals with (~20%) and without (~80%) type 2 diabetes (27).

Our findings are also partly in alignment with RCTs that did not meet our inclusion/exclusion criteria but assessed the effect of liquid meal replacements as part of a multimodal intervention. In the Look AHEAD (Action for Health in Diabetes) study, 5,145 overweight/obese participants with type 2 diabetes were randomized to an intensive lifestyle intervention that included the possible use of meal replacements (intervention) as part of a multidisciplinary weight management approach or a standard diabetes support and education group (control). Participants in the intervention group had significantly greater reductions in body weight, waist circumference, HbA_{1c}, and systolic blood pressure compared with the control group. However, LDL-c and HDL-c levels were significantly lower in the control group than in the intervention group (28). In the Diabetes Remission Clinical Trial (DiRECT), 49 primary care practices were randomly assigned to provide either a weight management program, which included total diet replacement with liquid meal replacements for 3–5 months with stepped food introduction and structured support for long-term weight loss maintenance (intervention), or best-practice care by guidelines (control). An intention-to-treat analysis of 149 overweight/obese participants with type 2 diabetes in each group at 12 months showed that the intervention group had significantly greater reductions in body weight, HbA_{1c}, and serum triglycerides compared with the control group. There were no significant differences in total cholesterol, HDL-c, and systolic blood pressure between groups (29). In the Why WAIT (Weight Achievement and Intensive Treatment) program designed by the Joslin Diabetes Center, participants were instructed to consume two liquid meal replacements plus two snacks for their breakfast and lunch and natural food for their dinner as part of a structured modified dietary intervention for 12 weeks. Other principals included intensive and interactive medication adjustments; a graded, balanced, and individualized exercise intervention; cognitive behavioral intervention; and group education. After 12 weeks, 62 participants who were enrolled in the program lost an average of 9.8% of their initial body weight and demonstrated significant reductions in HbA_{1c} levels (from 7.26% to 6.37%) (30,31).

Modest weight loss has been shown to improve glycemic control and blood pressure; however, greater amounts of weight loss may be needed to improve dyslipidemia (2,32–36). This aligns well with our findings, as the improvements in glycemic control and blood pressure may be explained by the greater weight reduction observed in the intervention arms using liquid meal replacements. However, this weight reduction may not have been sufficient to improve levels of blood lipids (LDL-c, HDL-c, non-HDL-c, and triglycerides).

Strengths and Limitations

The strengths of the present systematic review and meta-analysis include that it is comprehensive, includes RCTs (provides the best protection against bias), and uses the GRADE approach to evaluate the certainty of the evidence. However, there are some limitations. First, we downgraded the certainty of the evidence for serious imprecision in the pooled estimates for body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, LDL-c, HDL-c, non-HDL-c, triglycerides, and diastolic blood pressure, as the 95% CIs overlap the minimally important difference for clinical benefit. Although the mean reductions in HbA_{1c} met established thresholds for clinical significance (17), the 95% CIs contained trivial effects and so were assessed as imprecise for clinical benefit. Second, we downgraded the certainty of the evidence for serious inconsistency in the pooled estimates for body weight, BMI, waist circumference, HbA_{1c}, fasting glucose, LDL-c, HDL-c, triglycerides, and systolic blood pressure, as there was presence of unexplained heterogeneity ($I^2 > 50\%$ and $P_Q < 0.10$). Lastly, we were unable to conduct subgroup and publication bias analyses for any outcome owing to the small number of available trials (<10 trials). Balancing these strengths and limitations, we graded the certainty of the evidence as low to moderate.

Implications

Weight reduction is an important therapeutic target for overweight/obese patients with type 2 diabetes. Several international diabetes guidelines have recommended a modest weight loss of 5–10% to improve glycemic control and other cardiovascular risk factors (7,9,32,37). However, overweight/obese individuals with type 2 diabetes tend to have greater difficulty losing weight and are at a greater risk for developing complications compared with overweight/obese individuals without type 2 diabetes (32,38). A variety of dietary patterns and popular weight loss programs of varying macronutrient compositions including the vegetarian diet, DASH (Dietary Approaches to Stop Hypertension) diet, Atkins diet, Weight Watchers diet, and the Zone diet have been shown to be of benefit in overweight/obese individuals with type 2 diabetes (8,16). In addition to these weight reduction strategies, our findings provide some support for the use of liquid meal replacements as part of a weight loss diet in diabetes management.

Our findings also suggest that the use of liquid meal replacements as part of a weight loss diet may be effective as a temporizing strategy in diabetes management, given that the median follow-up duration of the included trials was 24 weeks. Liquid meal replacements are often used to reduce daily caloric intake by controlling portions and limiting the possibility of selecting calorie-dense foods. Although weight loss can be achieved by restricting food intake in the short-term, weight is typically regained over the long-term (39). For long-term weight maintenance, using liquid meal replacements in combination with exercise, behavioral therapy, social support, and counseling may help patients if they start to regain weight. Adherence is one of the most important determinants for attaining the benefits of any diet. Patients should choose the diet that best fits with their values and preferences, allowing them to achieve the greatest adherence over the long-term. Although

there was no evidence of hypoglycemic events in the included trials, monitoring of blood glucose levels and adjustment of diabetes medications are needed, as with any other weight reduction approach.

Conclusion

Liquid meal replacements as part of a weight loss diet lead to modest reductions in body weight, BMI, and systolic blood pressure compared with traditional low-calorie weight loss diets in predominantly middle-aged, overweight/obese men and women with type 2 diabetes. The reductions in body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, and diastolic blood pressure were of marginal clinical significance. No significant effects were observed for blood lipids (LDL-c, HDL-c, non-HDL-c, and triglycerides). Our confidence in the pooled effect estimates is low to moderate for markers of adiposity, glycemic control, blood lipids, and blood pressure. Sources of uncertainty include serious imprecision in the pooled effect estimates for body fat, waist circumference, HbA_{1c}, fasting glucose, fasting insulin, LDL-c, HDL-c, non-HDL-c, triglycerides, and diastolic blood pressure and serious inconsistency for body weight, BMI, waist circumference, HbA_{1c}, fasting glucose, LDL-c, HDL-c, triglycerides, and systolic blood pressure. More high-quality RCTs investigating the effect of liquid meal replacements as part of a weight loss diet on cardiometabolic risk factors are needed to address the uncertainties and assess whether there are differences among different types of liquid meal replacements.

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Duality of Interest. J.C.N. has worked as a clinical research coordinator at Glycemic Index Laboratories, Toronto, Canada. C.R.B. has worked as a clinical research assistant at Glycemic Index Laboratories, Toronto, Canada. C.W.C.K. has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, Barilla, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, INC International Nut and Dried Fruit Council Foundation, International Tree Nut Council Research & Education Foundation, Loblaw Brands Ltd., National Dried Fruit Trade Association, Pulse Canada, and Unilever. He has received in-kind food donations to support an RCT from the Almond Board of California, American Peanut Council, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Quaker (Pepsico), Primo, Unico, Unilever, and WhiteWave Foods. He has received travel support and/or honoraria from the American Peanut Council, International Nut and Dried Fruit Council, International Pasta Organization, Oldways Preservation Trust, and Peanut Institute. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute, Oldways Preservation Trust, Paramount Farms, and Pulse Canada. He is a member of the International Carbohydrate Quality Consortium (ICQC) and an Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD); is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD, and is a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. D.R. is the president of the Croatian Society for Diabetes and Metabolic Disorders of the Croatian Medical Association and serves as an Executive Committee member for the Croatian Endocrine Society, Croatian Society for Obesity, and the Croatian Society for Endocrine Oncology. He was a board member and secretary of International Diabetes Federation (IDF) Europe and currently is the chair of IDF Young Leaders in Diabetes Programme. He has served as an Executive Committee member of the Diabetes and Nutrition Study Group of EASD and currently serves as an Executive Committee member of the Diabetes and Cardiovascular Disease Study Group of EASD. He has served as a principal investigator or co-investigator in clinical trials of AstraZeneca, Eli Lilly, Merck Sharp & Dohme (MSD), Novo Nordisk, Sanofi Aventis, Solvay, and Trophos and has received honoraria for speaking or advisory board engagements and consulting fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, LifeScan – Johnson & Johnson, Novartis, Novo Nordisk, MSD, Pfizer, Pliva, Roche, Salvus, Sanofi Aventis, and Takeda. 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He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, EASD, Canadian Cardiovascular Society (CCS), and Canadian Obesity Network. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the ICQC, Executive Board Member of the DNSG of the J.L.S. has received research support from the Canadian Institutes of Health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, 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), and the Nutrition Trialists Fund at the University of Toronto (a fund established by the Calorie Control Council). He has received in-kind food donations to support an RCT from the Almond Board of California, California

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