

Impact of Meal Frequency on Anthropometric Outcomes: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

The relation between meal frequency and measures of obesity is inconclusive. Therefore, this systematic review and network meta-analysis (NMA) set out to compare the isocaloric effects of different meal frequencies on anthropometric outcomes and energy intake (EI). A systematic literature search was conducted in 3 electronic databases (Medline, Cochrane Library, Web of Science; search date, 11 March 2019). Randomized controlled trials (RCTs) were included with ≥ 2 wk intervention duration comparing any 2 of the eligible isocaloric meal frequencies (i.e., 1 to ≥ 8 meals/d). Random-effects NMA was performed for 4 outcomes [body weight (BW), waist circumference (WC), fat mass (FM), and EI], and surface under the cumulative ranking curve (SUCRA) was estimated using a frequentist approach (P-score: value is between 0 and 1). Twenty-two RCTs with 647 participants were included. Our results suggest that 2 meals/d probably slightly reduces BW compared with 3 meals/d [mean difference (MD): -1.02 kg; 95% CI: $-1.70, -0.35$ kg] or 6 meals/d (MD: -1.29 kg; 95% CI: $-1.74, -0.84$ kg; moderate certainty of evidence). We are uncertain whether 1 or 2 meals/d reduces BW compared with ≥ 8 meals/d (MD_{1 meal/d vs. ≥ 8 meals/d}: -2.25 kg; 95% CI: $-5.13, 0.63$ kg; MD_{2 meals/d vs. ≥ 8 meals/d}: -1.32 kg; 95% CI: $-2.19, -0.45$ kg) and whether 1 meal/d probably reduces FM compared with 3 meals/d (MD: -1.84 kg; 95% CI: $-3.72, 0.05$ kg; very low certainty of evidence). Two meals per day compared with 6 meals/d probably reduce WC (MD: -3.77 cm; 95% CI: $-4.68, -2.86$ cm; moderate certainty of evidence). One meal per day was ranked as the best frequency for reducing BW (P-score: 0.81), followed by 2 meals/d (P-score: 0.74), whereas 2 meals/d performed best for WC (P-score: 0.96). EI was not affected by meal frequency. In conclusion, our findings indicate that there is little robust evidence that reducing meal frequency is beneficial. *Adv Nutr* 2020;11:1108–1122.

Keywords: network meta-analysis, meal frequency, snacking, obesity, weight loss

Introduction

Across the globe, dietary habits include the consumption of foods (snacking) and calorie-containing beverages between main meals (1). It has been hypothesized that eating small,

frequent meals instead of few larger meals enhances fat loss and helps to achieve better weight maintenance (2). A number of observational studies provided support for this hypothesis, with an inverse relation noted between the frequency of eating and obesity (3, 4). For example in the Malmö Diet and Cancer Study, lower meal frequencies (≤ 3 meals/d) were associated with a higher risk of (abdominal) obesity compared with a higher meal frequency (≥ 6 meals/d) (4). These findings are in line with a meta-analysis of randomized controlled trials (RCTs), indicating that a higher meal frequency was effective in reducing fat mass (5). Controversially, another prospective cohort study indicated that increasing the number of eating occasions beyond 3 meals/d is associated with a higher risk for weight gain (6). Similarly, a recent pairwise meta-analysis of 13 RCTs

The authors reported no funding received for this work. SL participated in this project during her research stay at the Institute for Evidence in Medicine, University of Freiburg, supported by the Alexander von Humboldt Foundation, Germany.

Author disclosures: LS is a member of the Editorial Board of *Advances in Nutrition*. The other authors report no conflicts of interest.

Supplemental Appendixes 1 and 2, Supplemental Figures 1–35, and Supplemental Tables 1–3 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances>.

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Abbreviations used: BW, body weight; EI, energy intake; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; NMA, network meta-analysis; RCT, randomized controlled trial; RoB, risk of bias; T2D, type 2 diabetes; WC, waist circumference.

suggested that lowering meal frequency through skipping breakfast and thereby prolonging fasting times may help to reduce weight in adults (7).

Given these contradictions, it is also still unclear whether an increased meal frequency through snacking between main meals influences anthropometric outcomes. Generally, there are healthy (e.g., fruit, salads, or nuts) and unhealthy (e.g., sweets or crisps) snacks that have a different effect on health and anthropometric outcomes as well (1). Yet, no consensus on the relation between meal frequency—by spreading main meals over more eating occasions or through healthy snacking—and obesity has been reached (8).

Compared with the above-described pairwise meta-analyses, the methodological approach of network meta-analysis (NMA) offers the possibility to combine direct (i.e., from trials comparing 2 meal frequency interventions directly: e.g., 3 meals/d vs. 6 meals/d) and indirect (i.e., from a connected root via ≥ 1 intermediate comparators) evidence in a network of trials. To the best of our knowledge, no NMA has been conducted to date that simultaneously compared the isocaloric effects of different meal frequencies on anthropometric outcomes and energy intake. Therefore, the aim of the present research project was to investigate the impact of different meal frequencies, combine the direct and indirect evidence, and rank the different dietary approaches for effects on anthropometric outcomes (body weight, waist circumference, fat mass) and energy intake using NMA methodology.

Methods

This NMA was registered in PROSPERO (International Prospective Register of Systematic Reviews; www.crd.york.ac.uk/prospero/index.asp, identifier CRD42019138572) and is being reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards for reporting NMAs (9, 10).

Search strategy

The systematic literature search was performed in the electronic databases Medline (**Supplemental Appendix 1**), Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) up until 11 March 2019, with no restriction of language and calendar date. Furthermore, the reference lists from eligible studies were screened to identify additional relevant research. Screening and study selection were conducted by 2 authors independently (LS, KB).

Selection of studies

Studies were included in the NMA if they met the following criteria:

- 1) RCTs (with a parallel or crossover design) examining ≥ 2 dietary meal frequency interventions per day: 1 meal/d vs. 2 vs. 3 vs. 4 vs. 5 vs. 6 vs. 7 vs. ≥ 8 .
- 2) Isocaloric comparison (11):

- i) If the amount of energy intake was exchanged with an equal amount of energy intake for the different meal frequency interventions within a trial.
 - a) Hypo vs. hypocaloric energy intake within a trial
 - b) Eucaloric vs. eucaloric energy intake within a trial
 - ii) If the RCT involved overfeeding, such that excess energy was supplied, resulting in a positive energy balance, then the comparison was still considered isocaloric as long as the comparator was matched for the excess energy, resulting in the same positive energy balance.
 - a) Hyper vs. hypercaloric energy intake within a trial
- 3) Minimum duration of the intervention: ≥ 2 wk, in line with a recent meta-analysis on breakfast skipping (7).
 - 4) Participants with a mean age ≥ 18 y.

The following studies were excluded:

- 1) RCTs of acute (single meal) postprandial effects only.
- 2) RCTs with critically ill and hospitalized patients, patients undergoing bariatric surgery, patients with eating disorders.
- 3) RCTs based solely on liquid/formula diets, meal replacement interventions, or dietary supplements.
- 4) Co-intervention (e.g., drugs, supplements, diet, or physical activity) not applied in all intervention arms.

Data extraction

For included studies, 2 reviewers independently (KB, JZ) extracted the following characteristics to a piloted data extraction form: name of first author, year of publication, study origin (country), study design (RCT: parallel or crossover, including duration of washout period), comparison of meal frequency type, sample size, disease status (i.e., healthy, obese, type 2 diabetic, hypercholesterolemia), mean age, mean BMI, presence of type 2 diabetes (T2D; %), gender, duration of intervention (weeks), specification of the type of isocaloric comparison within an RCT (i.e., hypocaloric, eucaloric, hypercaloric), provision of food (yes/no), meals consumed in research center (yes/no), energy intake and macronutrient composition, outcomes extracted for the present NMA, and dietary adherence.

The preferred outcome data were change scores adjusted for baseline measurements with corresponding SDs, followed by postintervention values and change scores not adjusted for baseline measurements, as reported previously (12).

Risk-of-bias assessment

Risk of bias (RoB) was assessed by 2 authors independently (SL, GT) according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (13). The following domains were considered: selection bias (random-sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective

reporting), and other bias (carryover effect in crossover RCTs and potential conflict of interest).

Data synthesis

Statistical analysis.

Available direct comparisons between dietary interventions were illustrated using a network plot (14) for the following outcomes: body weight (kilograms), waist circumference (centimeters), fat mass (kilograms), and energy intake (kilocalories per day). Of note, in NMAs the size of the nodes is proportional to the sample size of each dietary intervention and the thickness of the lines proportional to the number of studies available.

Afterwards, the direct and indirect treatment effects across the RCTs were pooled, and weighted mean differences (MDs) for the outcome measures were calculated.

We performed NMAs in a contrast-based framework using the R package *netmeta*, version 6.6–6 (15). Treatments were ranked by P-scores, which are a frequentist version of the surface under the cumulative ranking curve (SUCRA) (16, 17). P-scores are values between 0 and 1, where a value of 1 means that a treatment ranks always best and a value of 0 means that a treatment ranks always worst.

Assessment of intransitivity.

To evaluate the assumption of transitivity (18), we compared the similarity of the included populations and study settings in terms of age, BMI, disease status, and study length for the available direct comparisons.

Assessment of inconsistency.

The effect estimate for each comparison was split into the contribution of direct and indirect evidence to see whether they differed and, therefore, we were able to assess potential inconsistency. We created a net heat plot by applying a full treatment-design interaction model (19). This model separates effects within and between different designs (19). A design is defined as the subset of treatments that are compared in a trial.

Secondary analyses and sensitivity analyses.

We planned a priori to conduct secondary analyses for gender, study duration (<6 vs. ≥6 mo), anthropometric status (e.g., lean vs. overweight vs. obese), provision of food (yes/no), meal consumed in research center (yes/no), energy intake (hypo- vs. eucaloric), breakfast skipping (yes/no), and by excluding RCTs rated for high RoB.

Dissemination bias.

To evaluate dissemination bias, a comparison-adjusted funnel plot (20) was created for each direct pairwise comparison, and Egger's linear regression test for funnel plot asymmetry was conducted to investigate small study effects (21).

Grading of recommendations assessment, development, and evaluation (certainty of the evidence)

We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of evidence derived from NMA. For all outcomes, 2 authors independently (LS, CS) rated the certainty of evidence in each of the direct, indirect, and network estimates (22). Direct estimates were evaluated with the following GRADE criteria: RoB, indirectness, inconsistency, and publication bias. As suggested recently by the GRADE working group, consideration of imprecision is not necessary when rating the direct and indirect estimates to inform the rating of NMA estimates (22). The indirect estimate assessments were based on the direct estimate certainty and were rated down if intransitivity was judged as serious (i.e., disease status). The NMA certainty estimates were based on the direct and indirect estimates certainty (specifically, the higher certainty between direct and indirect was chosen as the certainty of the NMA estimate), and rated down if incoherence or imprecision were present (22). Overall, GRADE specifies 4 levels of certainty of evidence: high, moderate, low, and very low.

Results

Out of 1202 records identified by the literature searches, 42 records were assessed as full texts (Figure 1, Supplemental Appendix 2). Finally, 22 RCTs with a total of 647 participants published between 1971 and 2018 were included in the systematic review and NMA (23–44).

Eight RCTs were conducted in the United States (23, 25, 29, 32, 40–42, 44); 3 in New Zealand (26–28); 2 each in the Netherlands (36, 43), Canada (31, 34), and Greece (38, 39); and 1 each in France (24), Sweden (30), Japan (33), Czech Republic (35), and United Kingdom (37). The study duration ranged from 2 to 52 wk; the mean age of the participants ranged from 20 to 70 y, their BMI (kg/m²) ranged from 20.9 to 38.4. In 10 RCTs, the mean BMI of the included participants was ≥30 (23, 24, 29–31, 36, 39, 41, 43, 44), while in 5 RCTs (23, 24, 30, 31, 41) only participants with a BMI ≥30 were included and 3 RCTs included participants with T2D or impaired glucose tolerance, respectively (28, 35, 39). The study sample of 5 RCTs was described as healthy with no major diseases (26, 33, 36, 37, 42). The most common type of frequency comparison was 3 vs. 6 meals/d, assessed in 9 RCTs, followed by 2 vs. 6 meals/d and 3 vs. 9 meals/d evaluated in 3 RCTs, respectively. In 13 RCTs the intervention of different meal frequencies aimed to reduce body weight (prescription of a hypocaloric diet) (23–25, 29–33, 35, 36, 41, 43, 44). Nine of the 22 included RCTs (41%) provided information on the macronutrient distribution: the ranges were 15–35% for protein, 20–40% for fat, and 40–60% for carbohydrates (23, 25, 29, 32, 33, 35, 41, 42, 44). Eleven RCTs provided information on caloric intake, but not macronutrient distribution for single meals (26–28, 30, 34, 37–40, 43). Study and

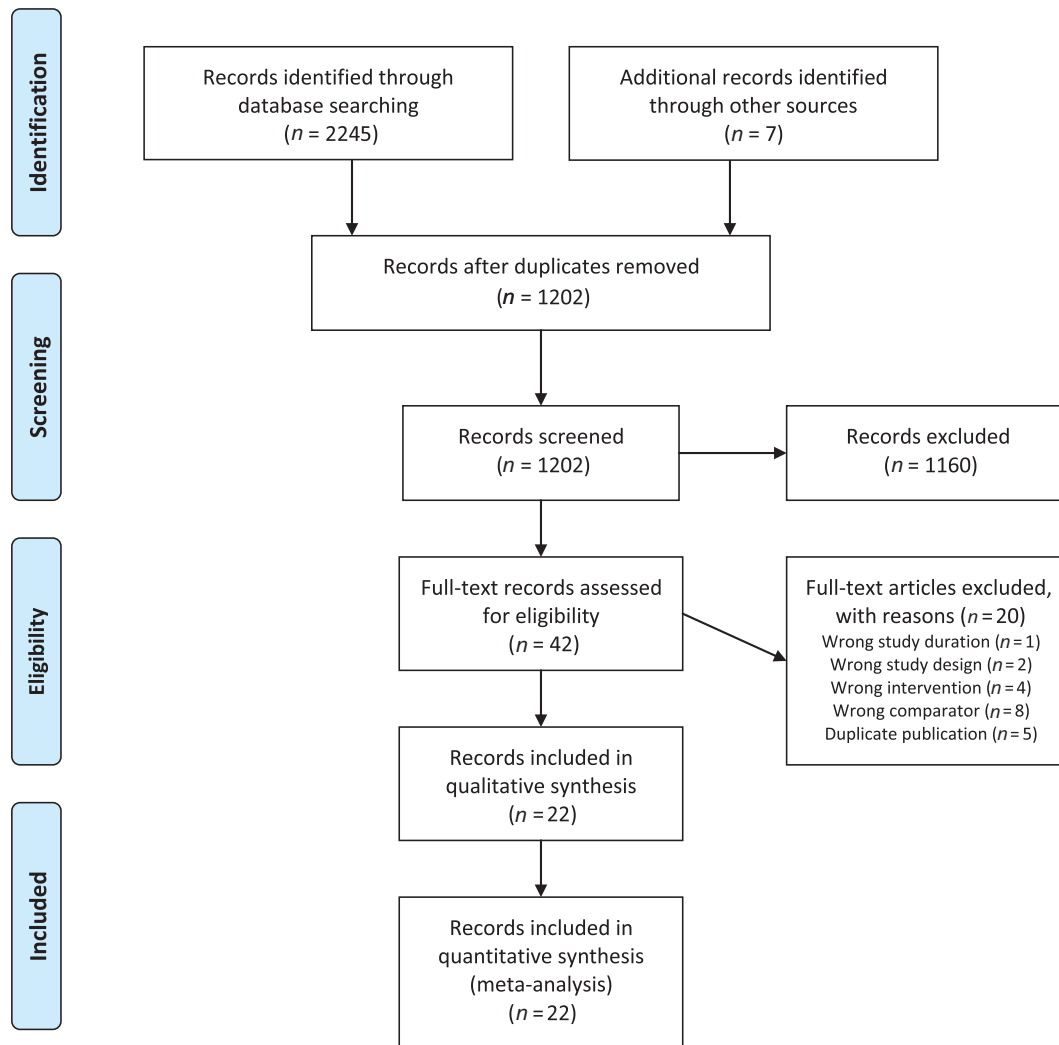


FIGURE 1 Flow diagram showing study selection process.

participant characteristics are summarized in [Tables 1](#) and [2](#), respectively.

RoB

The results of the RoB assessment are provided in [Supplemental Figure 1](#). No study was judged to have a low risk of selection bias. No RCT adequately performed blinding of participants and personnel; no RCT was judged as low RoB for blinding of outcome assessment; however, 13 RCTs (59%) were judged as low RoB for incomplete data outcome ([24](#), [25](#), [27](#), [29](#), [31](#), [32](#), [34–39](#), [41](#)). Twenty RCTs (91%) were judged to have a low RoB for selective reporting ([23–39](#), [41–43](#)), and 6 RCTs (26%) showed a low risk of other bias ([Supplemental Figure 1](#)) ([23](#), [25](#), [29–31](#), [34](#)). Overall, 15 RCTs (68%) were rated as high RoB for ≥ 1 domain ([23–30](#), [33](#), [35](#), [36](#), [38](#), [39](#), [42](#), [44](#)).

[Figure 2](#) shows the network diagrams for body weight ([Figure 2A](#)), waist circumference ([Figure 2B](#)), fat mass ([Figure 2C](#)), and energy intake ([Figure 2D](#)).

Body weight

We are uncertain whether 1 meal/d (MD: -2.25 kg; 95% CI: -5.13 , 0.63 kg) or 2 meals/d (MD: -1.32 kg; 95% CI: -2.19 , -0.45 kg) reduce body weight compared with ≥ 8 meals/d (very low certainty of evidence) ([Figure 3A](#)). Moreover, our results suggest that 2 meals/d probably slightly reduces body weight compared with 3 meals/d (MD: -1.02 kg; 95% CI: -1.70 , -0.35 kg) or 6 meals/d (MD: -1.29 kg; 95% CI: -1.74 , -0.84 kg; moderate certainty of evidence) ([Supplemental Figure 2](#)). No effects were observed when 3, 4, or 6 meals/d were compared with ≥ 8 meals/d.

Waist circumference

Two meals per day probably improve waist circumference compared with 6 meals/d (MD: -3.77 cm; 95% CI: -4.68 , -2.86 cm; moderate certainty of evidence) ([Figure 3B](#)), whereas no effects were detected comparing 3 vs. 6 meals/d (MD: -0.71 cm; 95% CI: -4.69 , 3.26 cm; low certainty of evidence).

TABLE 1 Study characteristics of the included RCTs¹

Author, year, reference	Study origin (country)	Study design (RCT; parallel or crossover)	Study length, wk	Washout (length)	Comparison of meal types or meal frequency	Sample size, n	Primary disease status	Mean age, y	Mean BMI, kg/m ²	T2D, %	Female, %
Alencar et al., 2015 (23)	USA	RCT, crossover	2	2 wk	6 vs. 2	11	Obesity	52	39.1	0	100
Antoine et al., 1984 (24)	France	RCT, crossover	2	None	6 vs. 3	10	Obesity	40.9	31.8	NR	100
Aiciero et al., 2013 (25)	USA	RCT, parallel	4	—	6 vs. 3	30	Overweight or obesity	46	29.9	0	86
Arnold et al., 1993 (26)	New Zealand	RCT, crossover	2	1–7 d	9 vs. 3	19	Healthy	32.1	23.1	0	50
Arnold et al., 1994 (27)	New Zealand	RCT, crossover	4	None	9 vs. 3	16	Hypercholesterolemia	49.9	26.5	0	31
Arnold et al., 1997 (28)	New Zealand	RCT, crossover	4	None	9 vs. 3	13	T2D, impaired glucose tolerance	46–70 (range)	29.9	85	69
Bachman and Raynor, 2012 (29)	USA	RCT, parallel	24	—	7–9 vs. 3	51	Overweight or obesity	51	35.5	0	58
Berteus Forslund et al., 2008 (30)	Sweden	RCT, parallel	52	—	6 vs. 3	140	Obesity	39.5	38.4	0	74
Cameron et al., 2010 (31)	Canada	RCT, parallel	8	—	6 vs. 3	18	Obesity	35.5	36	0	50
Finkelstein and Fryer, 1971 (32)	USA	RCT, parallel	9	—	6 vs. 3	8	Overweight	20–22	26.9	0	100
Iwao et al., 1996 (33)	Japan	RCT, parallel	2	—	6 vs. 2	12	Healthy	20	20.9	0	NR
Jenkins et al., 1995 (34)	Canada	RCT, crossover	2	3 wk	17 vs. 3	7	Normal weight and overweight	39.6	NR	0	0
Kahleova et al., 2014 (35)	Czech Republic	RCT, crossover	12	None	6 vs. 2	54	T2D	59.4	32.6	100	46
Koopman et al., 2014 (36)	Netherlands	RCT, parallel	6	—	6 vs. 3	36	Healthy	22	22.5	0	0
Murphy et al., 1996 (37)	UK	RCT, crossover	2	3 wk	12 vs. 2	11	Healthy	22	23.6	0	100
Papakonstantinou et al., 2016 (38)	Greece	RCT, crossover	12	None	6 vs. 3	45	PCOS	27	27	0	100
Papakonstantinou et al., 2018 (39)	Greece	RCT, crossover	12	None	6 vs. 3	53	Impaired glucose tolerance or T2D	49.3	32.4	26	53
Perrigue et al., 2017 (40)	USA	RCT, crossover	3	2 wk	8 vs. 3	15	Healthy and obesity	27.1	23.7	0	67
Schlundt et al., 1992 (41)	USA	RCT, parallel	12	—	3 vs. 2	52	Obesity	18–55 (range)	30.6	0	100
Store et al., 2007 (42)	USA	RCT, crossover	8	11 wk	3 vs. 1	21	Healthy	45	23.4	0	67
Verboeket-van de Venne and Westerterp, 1993 (43)	Netherlands	RCT, parallel	4	—	4 vs. 2	14	Overweight and obesity	46.1	30.2	NR	100
Young et al., 1971 (44)	USA	RCT, crossover	5	None	6 vs. 3 vs. 1	11	Overweight and obesity	22.2	33.5	NR	0

¹NR, not reported; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; T2D, type 2 diabetes.

TABLE 2 Specific study characteristics of the included randomized controlled trials¹

Author, year, reference	Specification of the intervention arms (meals/d)	Specification of the intervention arms (meals/d)	Provision of food	Meals consumed in research center	Energy intake during/after intervention, kcal/d	Adherence (method)
Alencar et al., 2015 (23)	6 meals/d: Hypocaloric, 1200 kcal/d with ~75 g/d of protein. Daily participant dietary macronutrients averaged per day 52% carbohydrates, 27% protein, and 21% fat, every 2 to 3 h.	2 meals/d: Hypocaloric, 1200 kcal/d with ~75 g/d of protein. Daily participant dietary macronutrients averaged per day 52% carbohydrates, 27% protein, and 21% fat, every 5 to 6 h.	Yes	No	NR	Assessed but not reported (reported during weekly meetings)
Antoine et al., 1984 (24)	6 meals/d: Hypocaloric, 1200 kcal/d (feeding study)	3 meals/d: Hypocaloric 1200 kcal/d (feeding study)	Yes	Yes	NR	Assessed but not reported (supervision during meals in clinic)
Arciero et al., 2013 (25)	6 meals/d: Eucaloric (28 d), hypocaloric (28 d); 35% protein, 45% carbohydrates, and 20% fat/d	3 meals/d: Eucaloric (28 d), hypocaloric (28 d); 35% protein, 45% carbohydrates, and 20% fat/d	Partly	No	6 meals/d: 1541; 3 meals/d: 1559	Assessed but not reported (monitored through daily subject-researcher contact)
Arnold et al., 1993 (26)	9 meals/d: Eucaloric; daily energy allowance was divided into early morning 8.3%, breakfast 8.3%, midmorning 8.3%, lunch 8.3%, midafternoon 8.3%, late afternoon 8.3%, dinner 16.6%, midevening 16.6%, and late evening 16.6%. Guidelines about how to allocate food into the meal or snack category were given and the nine meals were spaced between 1 and 2 h apart depending on the subject's schedule.	3 meals/d: Eucaloric; breakfast 25%, lunch 25%, dinner 50%, and a single small snack of 150 kcal to be consumed when desired	No	No	9 meals/d: 1995; 3 meals/d: 1934	9 meals/d: 8.3; 3 meals/d: 3.2 (3-d dietary records)
Arnold et al., 1994 (27)	9 meals/d: Eucaloric; daily energy allowance was divided into early morning 8.3%, breakfast 8.3%, midmorning 8.3%, lunch 8.3%, midafternoon 8.3%, late afternoon 8.3%, dinner 16.6%, midevening 16.6%, and late evening 16.6%. Guidelines about how to allocate food into the meal or snack category were given and the 9 meals were spaced between 1 and 2 h apart depending on the subject's schedule.	3 meals/d: Eucaloric; breakfast 25%, lunch 25%, dinner 50%, and a single small snack of 150 kcal to be consumed when desired	No	No	9 meals/d: 1972; 3 meals/d: 1898	9 meals/d: 7.9; 3 meals/d: 3.1 (dietary records)

(Continued)

TABLE 2 (Continued)

Author, year, reference	Specification of the intervention arms (meals/d)	Specification of the intervention arms (meals/d)	Provision of food	Meals consumed in research center	Energy intake during/after intervention, kcal/d	Adherence (method)
Arnold et al., 1997 (28)	9 meals/d: Eucaloric; daily energy allowance was divided into early morning 8.3%, breakfast 8.3%, midmorning 8.3%, lunch 8.3%, midafternoon 8.3%, late afternoon 8.3%, dinner 16.6%, midevening 16.6%, and late evening 16.6%. Guidelines about how to allocate food into the meal or snack category were given and the nine meals were spaced between 1 and 2 h apart depending on the subject's schedule.	3 meals/d: Eucaloric; breakfast 25%, lunch 25%, dinner 50%, and a single small snack of 150 kcal to be consumed when desired	No	No	NR	Assessed but not reported (regular contact between researchers and participants + dietary records)
Bachman and Raynor, 2012 (29)	7–9 meals/d: Hypocaloric (1200–1500 kcal/d, <30% from fat/d), consume at least 100 kcal every 2–3 h	3 meals/d: Hypocaloric (1200–1500 kcal/d, <30% of kcal from fat/d)	No	No	7–9 meals/d: 1314; 3 meals/d: 1217	Assessed but not reported (3-d food records)
Bertueso Forslund et al., 2008 (30)	6 meals/d: Hypocaloric (from the estimated total energy expenditure 30% was subtracted to get the prescribed energy intake). The minimum energy level prescribed was 1400 kcal/d. The prescribed energy level was divided into 3 meals and 3 snacks, daily energy intake was divided in breakfast 20%, lunch 25%, dinner 25% and 3 snacks, each snack 10% of daily energy; breakfast 20% + lunch 25% + dinner 25% + 3 x 10% = 100%.	3 meals/d: Hypocaloric (from the estimated total energy expenditure 30% was subtracted to get the prescribed energy intake). The minimum energy level prescribed was 1400 kcal/d. Recommended energy intake in the group of 3 meals was divided in breakfast, lunch 30% of daily energy intake, lunch 35%, and dinner 35% and no limited fruit intake and calorie-free drinks.	No	No	6 meals/d: 2150; 3 meals/d: 2098	Assessed but not reported (questionnaires, telephone interviews)
Cameron et al., 2010 (31)	6 meals/d: Hypocaloric: –700 kcal/d	3 meals/d: Hypocaloric: –700 kcal/d	No	No	NR	Data not collected
Finkelstein and Fryer, 1971 (32)	6 meals/d: Hypocaloric (period 1: 1700 kcal/d; period 2: 1400 kcal/d). All meals containing similar amounts of protein, carbohydrate, and fat.	3 meals/d: Hypocaloric (period 1: 1700 kcal/d; period 2: 1400 kcal/d). All meals containing similar amounts of protein, carbohydrate, and fat.	Yes	Partly	NR	Data not collected

(Continued)

TABLE 2 (Continued)

Author, year, reference	Specification of the intervention arms (meals/d)	Specification of the intervention arms (meals/d)	Provision of food	Meals consumed in research center	Energy intake during/after intervention, kcal/d	Adherence (method)
Iwao et al., 1996 (33)	6 meals/d: Hypocaloric (1200 kcal/d), intervals of 2 h, daily percentages of carbohydrates, protein and lipids in total sources of energy were 60%, 20%, and 20%	2 meals/d: Hypocaloric (1200 kcal/d), intervals of 12 h, daily percentages of carbohydrates, protein, and lipids in total sources of energy were 60%, 20%, and 20%	Yes	No	NR	Data not collected
Jenkins et al., 1995 (34)	17 meals/d: Eucaloric (2730 kcal/d). Equal macronutrient and caloric content per meal.	3 meals/d: Eucaloric (2730 kcal/d). Daily energy distribution: 30% breakfast, 30% lunch, and 40% dinner; 33% fat, 15% protein, and 52% carbohydrate.	Yes	Partly (for the 17-meals/d intervention: at least 1 portion/d was eaten in the study kitchen; for 3-meals/d intervention: at least 1 meal/d was eaten in the study kitchen)	NR	Assessed but not reported (food diary)
Kahleova et al., 2014 (35)	6 meals/d: Hypocaloric, energy requirements were based on the formula: (resting energy expenditure \times 1.5) – 500 kcal. Macronutrient distribution per day: 50–55% carbohydrates, 20–25% protein, and <30% from fat.	2 meals/d: Hypocaloric, energy requirements were based on the formula: (resting energy expenditure \times 1.5) – 500 kcal. Macronutrient distribution per day: 50–55% carbohydrates, 20–25% protein, and <30% from fat.	Partly (for one-half of the participants, equally in both groups)	No	6 meals/d: –380; 2 meals/d: –420	Assessed but not reported (dietary records)
Koopman et al., 2014 (36)	6 meals/d: Hypocaloric (40% caloric surplus on top of the ad libitum weight-maintaining diet)	3 meals/d: Hypocaloric (40% caloric surplus on top of the ad libitum weight-maintaining diet)	Partly (additional meal, liquid meal)	No	6 meals/d: 3614; 2 meals/d: 3474	Assessed but not reported (diet monitoring)
Murphy et al., 1996 (37)	12 meals/d: Eucaloric, ~2000 kcal/d, with a daily average 40% fat, 20% protein, and 40% carbohydrate; meals were eaten at hourly intervals from 8 h to 20 h.	2 meals/d: Eucaloric, ~2000 kcal/d, with a daily average 40% fat, 20% protein, and 40% carbohydrate; meals were split into 2 meals/d to be eaten at 12 h and 19:30 h.	No	No	12 meals/d: 2020; 2 meals/d: 2082	2 meals: 90%; 12 meals: 78%
Papakonstantinou et al., 2016 (38)	6 meals/d: Eucaloric, weight-maintenance diet; daily distribution: 40% carbohydrates, 25% protein, and 35% fat	3 meals/d: Eucaloric, weight-maintenance diet; daily distribution: 40% carbohydrates, 25% protein, and 35% fat	No	No	6 meals/d: 1916; 3 meals/d: 1859	Assessed but not reported (food records)

(Continued)

TABLE 2 (Continued)

Author, year, reference	Specification of the intervention arms (meals/d)	Specification of the intervention arms (meals/d)	Provision of food	Meals consumed in research center	Energy intake during/after intervention, kcal/d	Adherence (method)
Papakonstantinou et al., 2018 (39)	6 meals/d: Eucaloric, weight-maintenance diet; daily distribution: 40% carbohydrates, 25% protein, and 35% fat	3 meals/d: Eucaloric, weight-maintenance diet; daily distribution: 40% carbohydrates, 25% protein, and 35% fat	No	No	6 meals/d: 2081; 3 meals/d: 1917	Adherence to Mediterranean diet score: 32.1 from 55
Perrigue et al., 2017 (40)	8 meals/d: Eucaloric (providing all energy as evenly spaced eating occasions per day)	3 meals/d: Eucaloric (providing all energy as evenly spaced eating occasions per day)	No	No	NR	8 meals: 100%; 3 meals: 96%
Schlundt et al., 1992 (41)	3 meals/d: Breakfast: hypocaloric 1200 kcal/d. Daily distribution: 55% of energy from carbohydrates, 15–20% from protein, and 25–30% from fats.	2 meals/d: No breakfast; hypocaloric 1200 kcal/d. Daily distribution: 55% of energy from carbohydrates, 15–20% from protein, and 25–30% from fats.	No	No	NR	Whole study group: 71%
Stote et al., 2007 (42)	3 meals/d: Eucaloric (weight maintenance). Daily macronutrient distribution: 50% carbohydrates, 15% protein, 35% fats.	1 meal/d: Eucaloric (weight maintenance); minimum fast of 20 h/d. Daily macronutrient distribution: 50% carbohydrates, 15% protein, 35% fats.	Yes	Partly (only dinner in study center)	3 meals/d: 2429; 1 meals/d: 2364	Assessed but not reported (daily questionnaires)
Verboeket-van de Venne and Westerterp, 1993 (43)	4 meals/d: Hypocaloric, 1000 kcal/d; 300 kcal/d breakfast, 300 kcal/d lunch (with option of 100 kcal/d snack), 400 kcal/d dinner (with option 100 kcal/d snack)	2 meals/d: Hypocaloric, 1000 kcal/d, no breakfast, 400 kcal lunch, 600 kcal dinner.	No	No	4 meals/d: 1018; 2 meals/d: 1090	Data not collected
Young et al., 1971 (44)	6 meals/d: Hypocaloric, 1800 kcal/d. Daily macronutrient distribution: 115 g protein, 104 g carbohydrates, 103 g fat.	3 meals/d: Hypocaloric, 1800 kcal/d. Daily macronutrient distribution: 115 g protein, 104 g carbohydrates, 103 g fat. 1 meal/d: Hypocaloric, 1800 kcal/d. Daily macronutrient distribution: 115 g protein, 104 g carbohydrates, 103 g fat.	Yes	No	NR	Data not collected

¹NR, not reported.

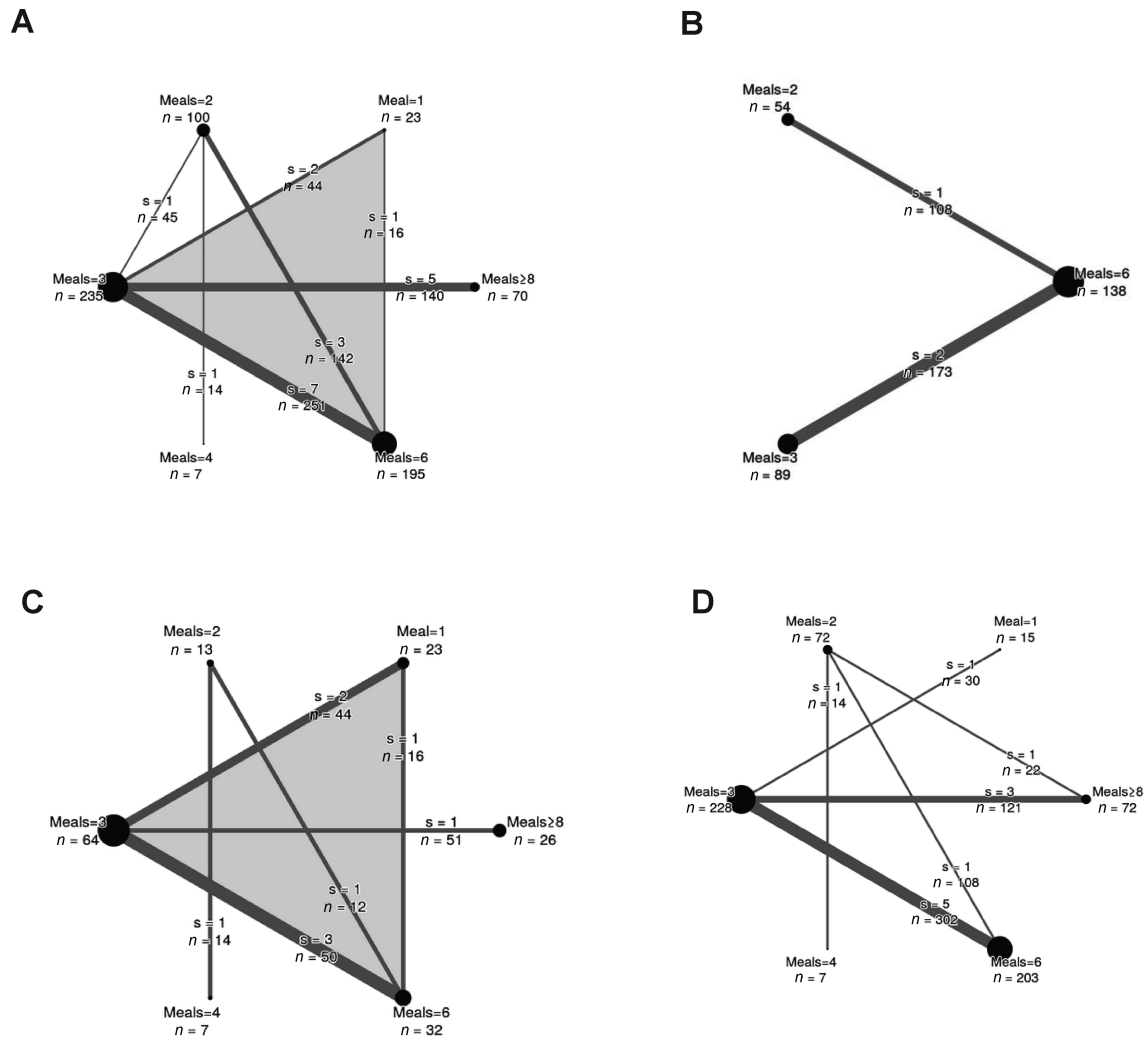


FIGURE 2 Network diagrams for body weight (A), waist circumference (B), fat mass (C), and energy intake (D). The size of the nodes is proportional to the total number of participants allocated to the intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison. Moreover, the total number of participants for each comparison is displayed (e.g., the body-weight comparison of 3 meals/d and 6 meals/d included 7 studies with a total of 251 participants). The number of multiarm studies for the interventions are indicated by the shade of gray of the background (white for none). s, studies.

Fat mass

Neither 1, 2, 3, 4, nor 6 meals/d were more effective in reducing fat mass compared with ≥ 8 meals/d (Figure 3C). We are uncertain whether 1 meal/d is more effective than 3 meals/d in reducing fat mass (MD: -1.84 kg; 95% CI: -3.72 , 0.05 kg; very low certainty of evidence) (Supplemental Figure 3).

Energy intake

No significant differences were observed comparing the different meal frequencies on energy intake (mainly very low certainty of evidence) (Figure 3D, Supplemental Figure 4).

Table 3 and Supplemental Tables 1–3 show the certainty of evidence assessment for the direct evidence, indirect evidence, and network estimates for all outcomes.

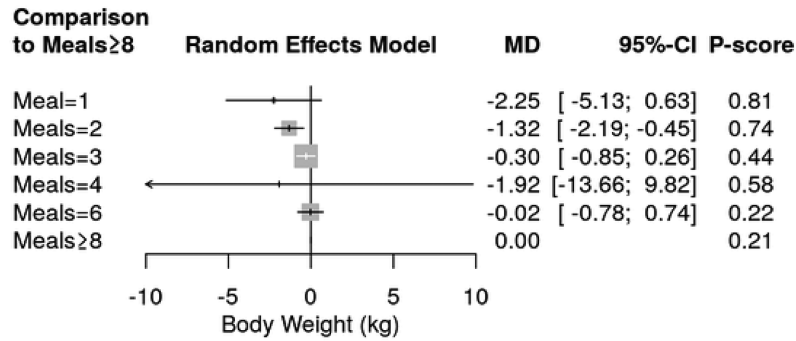
P-score and rankings

One meal per day was ranked as the best treatment for body weight (P-score: 0.81), followed by 2 meals/d (P: 0.74), whereas 2 meals/d performed best for waist circumference (P: 0.96). Rankings for fat mass and energy intake were inconclusive since none of the different meal frequencies investigated were “superior” when compared with each other (Figure 3).

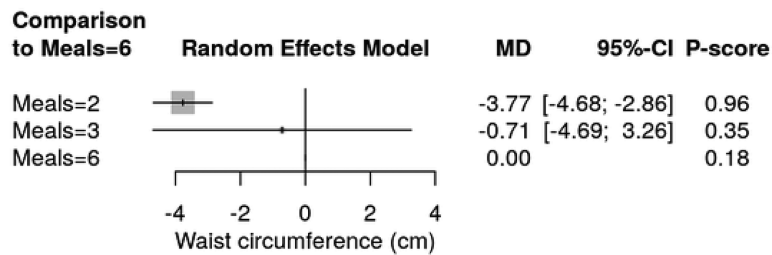
Inconsistency

The net heat plots are shown in Supplemental Figures 5–7. No relevant inconsistency between designs was observed for body weight and fat mass. Due to the low number of comparisons available for the outcome waist circumference, it was not possible to investigate inconsistency.

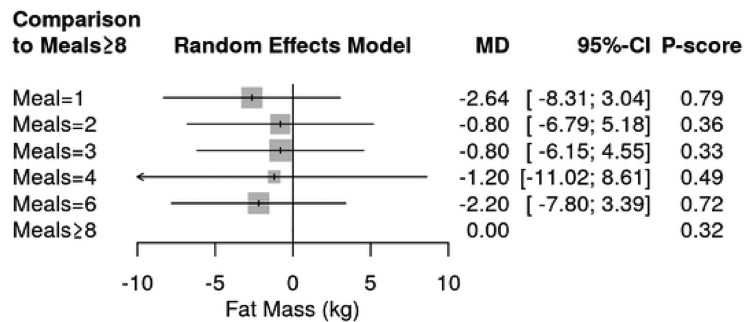
A



B



C



D

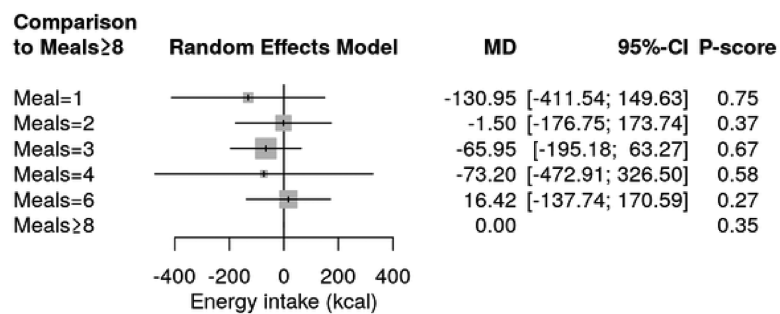


FIGURE 3 Summary effect estimates of different dietary approaches on body weight (A), waist circumference (B), fat mass (C), and energy intake (D). “ \geq 8” Meals (if available) is defined as the reference treatment. P-scores are defined, such that they are between 0 and 1, where 0 means that a treatment is always worst and 1 means that a treatment is always best compared with the other treatments in the network. For example, 2 meals/d (P-score: 0.96) was ranked best to improve waist circumference, followed by 3 meals/d (0.35), and 6 meals/d (0.18). MD, mean difference.

TABLE 3 GRADE evaluation for body weight (kg) and all comparisons¹

Comparison (meals/d)	Direct evidence		Indirect evidence		Network meta-analysis		
	No. of studies	MD (95% CI)	Certainty of evidence	MD (95% CI)	Certainty of evidence	MD (95% CI)	Certainty of evidence
1 vs. 2	0	—	—	−0.93 (−3.80, 1.94)	⊕⊕○○ ²	−0.93 (−3.80, 1.94)	⊕○○○ ³
1 vs. 3	2	−3.35 (−6.60, −0.09)	⊕⊕⊕○ ⁴	2.28 (−3.40, 7.96)	⊕⊕○○	−1.95 (−4.78, 0.87)	⊕⊕○○ ^{3,5,6}
1 vs. 4	0	—	—	−0.33 (−12.39, 11.73)	⊕⊕○○ ²	−0.33 (−12.39, 11.73)	⊕○○○ ^{3(↓↓)}
1 vs. 6	1	0.01 (−3.94, 3.96)	⊕⊕⊕○ ⁴	−4.61 (−8.68, −0.53)	⊕⊕○○ ²	−2.22 (−5.06, 0.61)	⊕⊕○○ ^{3,5,6}
1 vs. ≥8	0	—	—	−2.25 (−5.13, 0.63)	⊕⊕○○ ²	−2.25 (−5.13, 0.63)	⊕○○○ ³
2 vs. 3	1	−1.13 (−3.36, 1.10)	⊕⊕⊕⊕	−1.01 (−1.72, −0.31)	⊕⊕⊕○ ²	−1.02 (−1.70, −0.35)	⊕⊕⊕○
2 vs. 4	1	0.60 (−11.11, 12.31)	⊕⊕⊕⊕	—	—	0.60 (−11.11, 12.31)	⊕⊕○○ ^{3(↓↓)}
2 vs. 6	3	−1.29 (−1.75, −0.83)	⊕⊕⊕○ ⁴	−1.41 (−3.70, 0.89)	⊕⊕⊕○ ²	−1.29 (−1.74, −0.84)	⊕⊕⊕○ ⁵
2 vs. ≥8	0	—	—	−1.32 (−2.19, −0.45)	⊕⊕○○ ²	−1.32 (−2.19, −0.45)	⊕○○○ ³
3 vs. 4	0	—	—	1.62 (−10.11, 13.35)	⊕⊕○○ ²	1.62 (−10.11, 13.35)	⊕○○○ ^{3(↓↓)}
3 vs. 6	7	−0.28 (−0.81, 0.26)	⊕⊕⊕○ ⁴	−0.18 (−2.44, 2.09)	⊕⊕⊕○ ²	−0.27 (−0.79, 0.25)	⊕⊕⊕○ ⁵
3 vs. ≥8	5	−0.30 (−0.85, 0.26)	⊕⊕⊕⊕	—	—	−0.30 (−0.85, 0.26)	⊕⊕⊕○ ⁷
4 vs. 6	0	—	—	−1.89 (−13.61, 9.83)	⊕⊕○○ ²	−1.89 (−13.61, 9.83)	⊕○○○ ^{3(↓↓)}
4 vs. ≥8	0	—	—	−1.92 (−13.66, 9.82)	⊕⊕○○ ²	−1.92 (−13.66, 9.82)	⊕○○○ ^{3(↓↓)}
6 vs. ≥8	0	—	—	−0.02 (−0.78, 0.74)	⊕⊕○○ ²	−0.02 (−0.78, 0.74)	⊕⊕○○

¹Direct estimates were evaluated with the following GRADE criteria: risk of bias, indirectness, inconsistency, and publication bias. As suggested recently by the GRADE working group, consideration of imprecision is not necessary when rating the direct and indirect estimates to inform the rating of NMA estimates. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; NMA, network meta-analysis; ⊕⊕⊕⊕, high; ⊕⊕⊕, moderate; ⊕⊕○○, low; ⊕○○○, very low; ↓↓, downgraded twice due to very serious imprecision.

²Downgraded due to intransitivity (i.e., patients with obesity and healthy participants included).

³Downgraded due to imprecision (95% CI overlaps important benefit: −2 kg; or important harm: +2 kg).

⁴Downgraded due to risk of bias (≥1 RCT with high risk of bias).

⁵Direct evidence contributing more to the NMA estimate (>50%).

⁶Not downgraded due to incoherence (dominant estimate similar to network estimate).

⁷Downgraded due to imprecision (sample size: <400).

Secondary and sensitivity analysis

In sensitivity analyses including only patients with obesity, both 1 and 2 meals/d were slightly more effective than 6 meals/d (effect ranged between −1.31 and −2.31 kg) in reducing body weight. Considering only overweight participants, no further effects of different meal frequencies were observed (**Supplemental Figures 8–9**).

Sensitivity analyses for provision of food (yes/no), meals consumed in research center (yes/no), energy intake (hypo- vs. eucaloric), and breakfast skipping (yes/no) indicated no influence on the primary analysis (**Supplemental Figures 10–31**).

Due to the low number of studies it was not possible to conduct the additional a priori planned sensitivity analyses for gender differences (e.g., 3 RCTs including men only), study length (e.g., only 2 RCTs with an intervention duration ≥6 mo), and by excluding high RoB RCTs, since ~70% of the included studies were rated as high RoB.

Dietary adherence

Dietary adherence was only reported in 6 RCTs (22%) (26, 27, 37, 39–41), however assessed but not reported in 11 of the included RCTs through regular interviews and questionnaires (see **Table 2**). Especially where food was provided or even served in research facilities, adherence was considered as good. Moreover, as shown above, no significant differences were observed comparing the different meal frequencies on energy intake, which indicated substantial adherence.

Dissemination bias

For none of the outcomes, the funnel plots appeared obviously asymmetric, and the Egger’s test showed no evidence for small study effects (**Supplemental Figures 32–35**).

Discussion

This is the first NMA to evaluate the isocaloric effects of different meal frequencies on anthropometric outcomes (body weight, waist circumference, and fat mass) and energy intake in 647 participants.

In summary, a lower eating frequency (2 meals/d) seems to reduce body weight and waist circumference as compared with 6 meals/d in the short term. We are uncertain whether 1 or 2 meals/d reduce body weight compared with ≥8 meals/d, and whether 1 meal/d may reduce fat mass compared with 3 meals/d as the certainty of the evidence has been assessed as very low. No significant effects were observed for energy intake. Generally, for most of the comparisons, the present NMA yielded no important effects and the certainty of evidence was mainly rated as low or very low.

Comparison with other systematic reviews and possible mechanisms

Contrary to our findings, in a recent pairwise meta-analysis of 15 RCTs, ≥5 meals/d resulted in greater loss of fat mass (by −1.25 kg) than did 1–2 meals/d (5). However, these findings were highly driven by 1 RCT, and in a sensitivity analysis the observed effect became nonsignificant. For the outcome body weight, no significant effects were observed comparing 1–2 meals/d vs. 3–4 meals/d or vs. ≥5 meals/d.

The authors concluded from their findings a potential benefit of increased meal frequencies for enhancing body composition (5). In addition, observational studies reported an inverse association between the frequency of eating and BMI; however, underreporting of energy intake and eating frequency could be an important bias for this observation (45, 46). In contrast, our findings are more in line with a recent pairwise meta-analysis of RCTs, which examined weight change and energy intake in adults consuming or skipping breakfast and therefore reducing meal frequency (7). The meta-analysis found no evidence to support the notion that breakfast consumption (i.e., a higher meal frequency) promotes weight loss or that a lower meal frequency leads to weight gain (7). Moreover, the lower meal frequency group had a higher daily energy intake (~250 kcal/d) compared with the higher meal frequency group (7). Specifically in this meta-analysis, consumption of breakfast was associated with a clinically nonrelevant body weight increase of 0.5 kg (time frame up to 16 wk). Of note, all included RCTs in this systematic review were considered as high RoB. Discordance between studies could be driven by mixing isocaloric and nonisocaloric comparisons in the recent meta-analysis of RCTs (i.e., breakfast consumption leads to higher energy intake and therefore weight gain) (7). More than 20 y ago, Bellisle et al. (45) claimed that the reason for weight loss is not to be found in the frequency of meals but in general hypocaloric energy intake. To avoid this bias, we included only isocaloric comparisons in our NMA.

However, dietary adherence was not reported in all RCTs, but no differences were observed for energy intake comparing the different meal frequencies. Thus, if energy intake was similar between the comparison groups, the question arises if other mechanisms could explain these observations. There is no consensus yet, and we can only speculate about the mechanisms. The meal frequency could have different effects on metabolic rates, including energy expenditure and carbohydrate and fat oxidation (35, 42). In addition, in combination with timing of the meal (e.g., skipping of late-night meals), the frequency could have an influence on satiety hormones (ghrelin and leptin), circadian rhythms, and a beneficial effect on oxidative damage (47).

Relevance of our findings

Research has shown that, in adults with overweight and obesity, a reduction in body weight of 5–10% of initial body weight was associated with improvements in health risk factors (48). In our NMA, weight loss was not of sufficient magnitude to likely be associated with clinical benefits following lower meal frequencies compared with higher meal frequencies (–0.30 to –2.31 kg) in patients with obesity. However 2 meals/d reduced waist circumference by ~4 cm compared with 6 meals/d. This effect is considered clinically relevant, since evidence from observational studies has shown, that a 1-cm increase in waist circumference is associated with a 2% increased risk of cardiovascular disease (49). Again, the role of the length of fasting periods has

to be taken into consideration as longer fasting periods are inversely associated with fat-free mass (50).

Implications

In a recent scoping review, nearly 50 countries and 7 organizations were identified that referred to snacking between main meals (i.e., higher meal frequencies) (1). Most of them established quantitative recommendations most often related to frequency of meals (i.e., snacking throughout the day), often with a special focus on children. Of all of the recommendations, only 2 suggested avoidance of small meals between main meals. The findings of our NMA have important implications with respect to the prevailing recommendation that eating small, frequent meals is helpful for optimizing weight management in the general (adult) population. Increasing meal frequency is often promoted as a beneficial strategy for anthropometric outcomes (2). The results of our NMA do not support these recommendations, but rather point to a slight contrary effect. Our findings are more in line with a recent statement by the American Heart Association, where the authors concluded that altering meal frequency under eucaloric conditions may not be effective for decreasing body weight (51).

Strength and limitations

Our systematic review and NMA has several strengths and limitations that need to be considered. Among the strengths are the application of the NMA methodology, the a priori-deposited protocol, the comprehensive search strategy, RoB assessment, sensitivity analyses, and the GRADE certainty of evidence judgment.

Limitations of the current NMA include the absence of long-term RCTs (>52 wk); therefore, we were not able to provide data on the persistence of observed effects. Overall, only 2 out of 22 RCTs (9%) had a study duration >12 wk. Moreover, the certainty of evidence was rated as mainly low or very low. This was mainly driven by RoB and imprecision: overall, 15 RCTs (68%) were rated with a high RoB for ≥ 1 domain. Imprecision was driven by the low sample sizes of the various study arms; hence, the studies and also the meta-analyses may have lacked power to detect differences within or between groups. Due to the low number of RCTs, it was not possible to conduct several a priori-planned sensitivity analyses. Adherence was assessed and reported in only 6 RCTs. Moreover, only very few studies implemented a controlled-feeding protocol.

Conclusions

In conclusion, our findings indicate that there is little robust evidence that reduced meal frequency is a beneficial strategy for anthropometric outcomes. In addition, no significant effects were observed for energy intake. The currently available evidence is of low certainty and does not support current recommendations for increased meal frequencies. The findings should be, however, interpreted with caution. Further high-quality RCTs are needed to substantiate

whether individuals seeking to lose weight should skip or consume meals.

Acknowledgments

All authors substantially contributed to the concept, data collection and analysis, or preparation of the manuscript, and read and approved the final manuscript.

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