Effect of Intermittent Fasting on Weight Loss and Risk Factors for Cardiovascular Disease and Diabetes: A Systematic Review

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ABSTRACT

BACKGROUND: Obesity is a global pandemic associated with substantial morbidity, mortality, and economic costs, yet there are few effective clinical interventions for weight loss. One novel approach is intermittent fasting, a dietary pattern in which patients are allocated to a predetermined number of fasting days per week and are permitted to consume food *ad libitum* on non-fasting days.

OBJECTIVES*:* To conduct a systematic review of the efficacy of intermittent fasting versus daily caloric restriction on weight loss and improvement in risk factors associated with cardiovascular disease and diabetes.

SEARCH METHODS: We searched MEDLINE, Embase, and CINAHL for published studies and clinicaltrials.gov for unpublished results prior to June 28th, 2017. We also checked references lists from previous reviews for possible references to include in this review.

SELECTION CRITERIA: We selected randomized controlled trials of intermittent fasting interventions of ≥4 weeks' duration. We excluded studies that did not explicitly have one day of *ad libitum* feeding per week. We also excluded studies in cancer patients and in which weight loss was not the desired outcome, including Ramadan fasting studies.

DATA COLLECTION AND ANALYSIS: One author independently screened references, performed data extraction, risk of bias assessments, and used the GRADE tool to rate the strength of evidence underlying each of three Key Questions generated for this review.

RESULTS: We screened titles and abstracts of 1401 studies. Of these, we reviewed 63 full-text articles for inclusion in the systematic review. After application of inclusion criteria, 10 papers

reporting results from 9 studies and 11 intervention groups were identified for inclusion. In all 11 reported intermittent fasting groups, participants lost weight. Based on the reviewed data there is moderate strength of evidence in support of an association between intermittent fasting and weight loss. There is very low strength of evidence supporting a difference in efficacy between intermittent fasting and daily calorie restriction. There is also very low strength of evidence in support of an association between intermittent fasting and risk factors related to cardiovascular disease and diabetes. Few studies report intermittent fasting-associated harms, but those that did reported prevalence of headache and constipation to be 5-13% and 6.5-8% respectively, which was not significantly different from control groups.

CONCLUSION: Intermittent fasting is equally effective as, but not superior to, daily caloric restriction. Some patients may find intermittent fasting preferable to traditional weight loss strategies. Further research is needed regarding associations between intermittent fasting and risk factors for cardiovascular disease and diabetes, as well as adverse events related to this dietary pattern.

INTRODUCTION

Background

Obesity is a public health crisis that has grown in prevalence over the last four decades[1] and is associated with adverse health outcomes including various cancers, cardiovascular disease, respiratory disease, and musculoskeletal problems including osteoarthritis.[2] In addition, obesity disproportionately affects both rural and urban as well as racial and ethnic minorities.[1–3] Not only are these groups more likely to be obese, but they are also less likely to access or receive interventions that address obesity.[2] For this reason, interventions targeting these vulnerable populations are needed.

Obesity is also associated with significant healthcare expenditures both in the United States and worldwide. According to an analysis by Spieker and Pyzocha, obesity is responsible for 20 percent of all health care spending in the United States, with annual directly-associated medical costs of $209.7 billion and indirect costs of $66 billion.[4] This same analysis found that with optimal use of weight loss interventions, obesity-related costs may be reduced by $600 billion dollars over 20 years.

Obesity-associated economic impacts include direct medical costs, productivity costs, transportation costs, and human capital costs.[5] Estimates of direct medical costs include treatment for obesity-related diseases such as hypertension and diabetes as well as interventions specifically aimed at treating obesity, including bariatric surgery and intensive nutritional and educational counseling. Productivity costs associated with obesity include labor absenteeism, premature mortality, and disability as reflected by loss of quality-adjusted life years (QALYs).[5] Additionally, decreased productivity while working, deemed "presenteeism" by Hammond and Levine, is another source of obesity-related productivity cost.[5] Worker productivity may be

negatively impacted by obesity-associated pain, fatigue, and disability. Furthermore, transportation costs associated with obesity include higher fuel consumption in airplanes, trains, and automobiles, and the increased demand for larger vehicles to accommodate a greater range of passenger sizes. Finally, estimates of human capital costs are based on studies reporting associations between obesity and decreased levels of upward mobility as measured by academic performance, educational status, and socioeconomic status after adjustment for baseline factors.[5–7]

Despite the health and economic consequences of obesity, there is a paucity of effective and broadly implementable interventions, with one recent review suggesting that bariatric surgery is the most evidence-based option for treating obesity with associated comorbidities including diabetes, gastroesophageal reflux disease (GERD), hypertension, and hyperlipidemia.[8] However, access to bariatric surgery is dependent on health care coverage for the significant associated expense, as well as proximity to bariatric surgery services, which tend to be clustered in large, academic medical centers.[9] Furthermore, bariatric surgery in many cases is irreversible and carries the risk of severe adverse events such as bleeding, infection, and failure of anastamoses. Additionally, bariatric surgery is not recommended for individuals with overweight body mass index (BMI) of 25-30 or for obese individuals with BMI 30-35 without comorbidities, and use in adolescents is controversial.[9] For these reasons, bariatric surgery is not an ideal first-line treatment for overweight and obese patients.

Given limited access to bariatric surgery and the lack of highly effective and translatable outpatient interventions geared towards obesity, there has been increased attention on novel techniques to achieve weight loss. Interventions have sought to affect change at all levels of the Public Health Pyramid, a public health intervention framework that specifies levels of

intervention ranging from broad (socioeconomic factors) to specific (counseling and education).[10] Some of the most widely studied interventions for weight loss include restaurant menu labeling, office-based peer support groups, intensive nutritional counseling, excise taxes on sugar sweetened beverages, physical activity programs, pharmacotherapy, bariatric surgery, and a wide array of complementary and alternative therapies, yet overall evidence is mixed regarding the efficacy of these interventions.[11–14]Caloric restriction is another weight loss strategy that has been attempted with conflicting results. In caloric restriction diets, patients are asked to eat fewer than a pre-specified number of calories in a given day, based on basal metabolic rate, sex, age, and average daily physical activity level. Though caloric restriction is associated with weight loss, this finding is inconsistent, and there appears to be a significant propensity for patients to regain weight even after successful periods of weight loss.[13] Reasons that traditional caloric restriction diets may be limited in efficacy include the constant requirement to exercise self-control and track calories. The difficulty of losing weight by caloric restriction highlights the need for weight loss strategies that are both flexible for individual needs and that can be incorporated into patient lifestyles even after the weight loss phase of a dietary change.

Intermittent Fasting as a Weight Loss Intervention

One possible alternative to traditional caloric restriction is intermittent fasting. Intermittent fasting is similar to traditional caloric restriction in that it is designed to reduce the average number of calories consumed over a given time. However, unlike traditional caloric restriction, intermittent fasting employs techniques of limited meal skipping and fasting days, during which as few as 500 calories may be consumed.[15,16] These days are interspersed with *ad libitum* feeding days. Advantages of this approach include having days on which participants do

not feel like they are on a restrictive diet and disruption of the addictive neurochemical pathways that have been associated with hyperphagia.[15,16] Similarly, intermittent fasting may also encourage mindful and appreciative eating patterns that persist beyond the period of caloric restriction. Another advantage is that intermittent fasting can be maintained on a limited basis after the weight loss phase of a diet, possibly contributing to sustained weight loss, although studies of this outcome have not been described in the literature.

A wide variety of intermittent fasting approaches have been reported. In one specific strategy called alternate day fasting (ADF), participants consumed 25% of their baseline caloric intake on alternating days interspersed with *ad libitum* feeding days, with all caloric consumption on fast days occurring between 12:00pm and 2:00pm.[17] Other intermittent fasting regimens include daily meal skipping (skipping one meal per day, often breakfast) or abstaining from all caloric intake for at least 12 hours in a given 24 hour period.[18] This strategy of eating within a small window of time each day is also called time-restricted feeding. Other studies have been conducted in participants fasting daily during religious or spiritual events such as Ramadan.[19]

Recognizing that there may be an addictive component in overeating is an important factor in preventing and treating obesity.[20] Based on an addiction model of overeating, several mechanisms have been proposed by which fasting-based diets may lead to weight loss either differently or more effectively than daily caloric restriction diets. In one small trial central μ-opioid receptor characteristics were shown to change based on whether the participants were in fasting or fed states, suggesting that food intake may acutely increase addictive food-consuming behavior.[21] Similarly, food intake appears to activate the mesocorticolimbic dopamine system, which may contribute to feelings of pleasure and satiety.[22] In one study, Wang et al. found that dopamine D2 receptor expression was lower in obese participants, suggesting that obese

individuals may have to overeat to achieve a level of satiety sufficient to quell hunger.[23] Wang et al. also hypothesized that downregulation of D2 receptors in chronic overeaters may contribute to addictive eating behavior,[24] possibly illuminating a mechanism whereby periodic caloric deprivation as part of an intermittent fasting diet might re-sensitize the mesocorticolimbic dopamine system to postprandial stimulation. Similarly, decreased sensitivity to the satiety-promoting hormone leptin may play a role in obesity, as obese populations have elevated leptin concentrations relative to normal-weight controls despite lower satiety.[25] Calorie restriction and weight loss decrease leptin levels, which in turn causes hunger to increase. However, the breaking of short duration fasts in humans appears to return leptin levels to baseline,[26] which may promote satiety in individuals attempting to lose weight.

Several animal studies suggest that intermittent calorie restriction may alter expression of obesity-related genes and influence production of hormones involved in satiety and fullness. Long-term caloric restriction and fasting in rats suppresses adipose tissue expression of UCP-1, a thermoregulatory gene associated with obesity in humans.[27,28] Although suppression of UCP1 may decrease rate of weight loss, the effect of UCP1 suppression may be smaller with fasts of shorter duration such as those that comprise a regimen of intermittent fasting.[29] Similarly, the concentration of the satiety-promoting hormone leptin decreases in calorie-restricted rats, though Kim et al. showed this could be avoided by cycling fasting and feeding, which was found to increase leptin levels.[30]

Although it is plausible that intermittent fasting may cause weight loss either more rapidly or consistently than traditional daily calorie restriction, human trials suggest the difference between the two dietary patterns is equivocal.[17,31–33] In addition to weight loss, studies have reported associations between intermittent fasting and changes in fasting plasma

glucose, hemoglobin A1C, blood pressure, and lipid profile,[34–36] though no consistent associations between fasting and these outcomes have been reported.

Rationale for Systematic Review

Findings from clinical trials and observational studies have been summarized in three systematic reviews, all of which concluded that intermittent fasting and daily caloric restriction are similarly effective approaches to weight loss.[15,16,37] However, these reviews have included observational studies with high risk of bias or have applied inclusion criteria that do not effectively differentiate intermittent diet patterns with daily caloric restriction diets. For example, two systematic reviews included studies of very low calorie diets in which participants were asked to restrict caloric intake for up to five weeks in a row without days of non-fasting or ad libitum intake.[16,37] Although there are currently no clear criteria to define intermittent fasting, the appeal of this pattern of eating is to reduce the constant need for restriction often experienced by dieters. These same reviews also included pre-post observational studies with critically high risk of bias according to Cochrane Foundation guidelines.[38] In addition, it is unclear whether Horne et al. used a comprehensive literature search strategy. None of these reviews systematically addressed intermediate outcomes related to cardiovascular disease or diabetes, and none reported the occurrence of adverse events across included studies.

To facilitate addressing these data gaps we designed three key questions based on the populations, interventions, comparators, outcomes, and study designs of interest. Key Question 1 for this systematic review focused on weight loss: *"In overweight and/or obese adults, does intermittent fasting compared with traditional caloric restriction and/or non-intervention result in lower weight and/or BMI?"* Key Question 2 was focused on intermediate outcomes related to

type 2 diabetes mellitus: *"In overweight and/or obese adults, does intermittent fasting compared with traditional caloric restriction and/or non-intervention reduce hemoglobin A1c or fasting plasma glucose?"* Key Question 3 was focused on intermediate outcomes related to cardiovascular disease risk factors: *"In overweight and/or obese adults, does intermittent fasting compared with traditional caloric restriction and/or non-intervention increase high-density lipoprotein or decrease low-density lipoprotein, and/or triglycerides?"* For all of the key questions, we reviewed data from randomized controlled trials and observational longitudinal cohort studies.

METHODS

Protocol and Registration

A review protocol was developed for this systematic review but is currently unpublished. This review is not currently registered, although the review protocol is being prepared for possible submission to the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility Criteria

We only considered observational cohort studies and randomized controlled trials for inclusion in this review. Eligible populations for all three Key Questions included adults 18 year of age or older who were overweight and/or obese, defined as BMI $\geq$25 kg/m^2. We did not include studies if they reported outcomes in children (<18 years of age) or exclusively non-obese/overweight patients because results of such studies may have limited external validity in obese adult populations. For Key Questions 2 and 3, we did not limit the eligible study population to individuals with diabetes or cardiovascular disease, as the intermediate endpoints

of interest are readily measurable in individuals without these conditions, and there are scarce data on intermittent fasting in these patient populations. We excluded from this review studies reporting outcomes of fasting in cancer patients, as malignancy is a confounder of weight loss and fasting interventions in cancer patients are designed to slow cancer growth, not to decrease weight. We also excluded studies performed in populations observing Ramadan, as Ramadan fasting is not explicitly intended as a weight loss intervention. Furthermore, Ramadan lasts one full month, and the inclusion criteria for this review necessitate at least one non-fasting *ad libitum* feeding day per week.

For all three Key Questions, the intervention of interest was intermittent fasting, defined as at least 12 hours without caloric intake OR at least 24 hours w/ ≥50% reduction in baseline caloric requirement. We excluded studies that did not include *ad libitum* eating periods, as a fundamental component of intermittent fasting interventions is the ability to eat without restriction during non-fasting periods. Furthermore, we excluded studies that did not have an *ad libitum* feeding component at least once per week. This excluded studies of very low calorie diets (VLCDs) that do not necessitate alternating periods of caloric restriction and *ad libitum* intake, but nonetheless may have alternating components. For example, one VLCD diet regimen includes continuous eight week VLCD intervals,[39] and another includes alternating VLCD and *ad libitum* periods lasting five weeks.[40] Given that a major advantage of intermittent fasting is permitting participants to have "off days" during which they do not feel the pressure to limit their food intake, it is important to exclude studies of VLCDs that do not have an intermittent component at least once weekly. We did not specify a minimum frequency of fasting for inclusion in this review, as some interventions are based on monthly or semi-monthly fasting regimens.[41]

For all three Key Questions, the comparator groups were either traditional caloric restriction or non-intervention. We defined non-intervention as any intervention not designed directly to reduce weight, including education-only control groups, support groups, intensive dietary counseling, and treatment with placebo weight loss pills, or representative populations that did not undergo a form of intermittent fasting. We included any intervention-based comparator group if it did not meet the inclusion criteria for intermittent fasting as described above.

Studied outcomes for Key Question 1 included weight change (measured in pounds and/or kilograms) and BMI change (reported in kg/m^2). We only considered for inclusion time points inclusive of the active intervention, as some studies report continuing weight loss and weight maintenance during non-intervention follow-up periods, and the efficacy of dietary interventions in producing weight maintenance is beyond the scope of this review. For Key Question 2, intermediate outcomes related to diabetes included hemoglobin A1c and fasting plasma glucose (FPG). For Key Question 3 intermediate outcomes related to cardiovascular disease included levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG).

Given that our review is designed to assess the efficacy of intermittent fasting as a long-term weight loss intervention, we excluded studies of interventions lasting less than four weeks. For lipid profile outcomes and for hemoglobin A1c, we only included studies of ≥4 weeks duration, as changes in these outcomes require additional time to occur. Specific population, intervention, comparator, outcome, timing, setting, and study design (PICOTSS) criteria for each Key Question are listed in Table 1.

Table 1. Population, Intervention, Comparator, Outcome, Timing, Setting, and Study Design (PICOTSS) for the three Key Questions assessed in this systematic review of intermittent fasting

	Key Question 1: Weight Loss	**Key Question 2:** Intermediate Outcomes Related to Diabetes	**Key Question 3:** Intermediate Outcomes Related to Cardiovascular Disease
Population	Overweight/obese (BMI≥25 kg/m^2) adults (age≥18 years)	Overweight/obese (BMI≥25 kg/m^2) adults (age≥18 years)	Overweight/obese (BMI≥25 kg/m^2) adults (age≥18 years)
Intervention	Intermittent fasting (at least 12 hours without caloric intake OR at least 24 hours w/ ≥50% reduction in caloric intake)	Intermittent fasting (at least 12 hours without caloric intake OR at least 24 hours w/ ≥50% reduction in baseline caloric intake)	Intermittent fasting (at least 12 hours without caloric intake OR at least 24 hours w/ ≥50% reduction in baseline caloric intake)
Comparator	Traditional caloric restriction and/or non-intervention or other control group	Traditional caloric restriction and/or non-intervention or other control group	Traditional caloric restriction and/or non-intervention or other control group
Outcomes	Weight (lbs/kgs), BMI (Kg/m^2)	Hemoglobin A1c (HgbA1c), fasting plasma glucose (FPG)	High-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG)
Timing	≥4 weeks	≥4 weeks for fasting insulin, and/or insulin resistance. ≥4 weeks for HgbA1c	≥4 weeks for blood pressure, ≥ 4 weeks for cholesterol, high-density lipoprotein, low-density lipoprotein, and/or triglycerides
Setting	University research centers, outpatient clinics, community based interventions	University research centers, outpatient clinics, community based interventions	University research centers, outpatient clinics, community based interventions
Study Design	Randomized controlled trials, longitudinal cohort studies	Randomized controlled trials, longitudinal cohort studies	Randomized controlled trials, longitudinal cohort studies

Literature Search Strategy

We conducted formal literature searches via MEDLINE, EMBASE, and CINAHL, and additional queries were made with The Cochrane Database of Systematic Reviews and GoogleScholar between January 15th, 2017 and June 28th, 2017. We also searched clinicaltrials.gov on June 28th, 2017 for grey literature including unpublished studies and results. Literature published after June 28th, 2017 was therefore not included in this review. We considered additional sources based on review of references used in the papers discovered through the initial search. We designed search strings based on the PICO factors for each key question. The full search strings, including the list of synonyms used to search MEDLINE, EMBASE, and CINAHL are shown in Appendix 1.

Study Selection and Data Extraction

One author (RA) independently assessed all titles and abstracts identified by the literature search. For papers deemed potentially eligible by title/abstract review, RA obtained and reviewed the full text. All studies meeting the pre-specified eligibility criteria were included.

RA extracted data into Microsoft Word tables designed specifically for this review. Extracted data included sample size (N), study duration, post-intervention values for weight change (kg), HgbA1c, FPG, HDL, LDL, and triglycerides. Given that these values were continuous, we included means and standard deviations when reported by the included studies. When possible we also included prevalence (percent, or proportion converted to percent, and standard deviation) of adverse outcomes including headache, nausea, compensatory binge eating, hunger, fullness, and constipation in the intervention vs. nonintervention groups.

Risk of Bias in Individual Studies

One author (RA) assessed each included study for risk of bias. Bias assessments were conducted using the Cochrane Risk of Bias Tool as specified in the The Cochrane Handbook for Systematic Reviews and Interventions.[38] Risk of bias was assessed based on six domains, including: 1.) allocation sequence generation, 2.) concealment of allocation, 3.) blinding of participants and investigators, 4.) incomplete outcome data, 5.) selective outcome reporting, and 6.) other bias sources. Within each domain, we scored studies as having low, high, or unclear risk of bias. Pre-post studies or uncontrolled observational studies were excluded based on having critical risk of bias, in accordance with Cochrane guidance.[38]

Data Synthesis and Summary Measures

We did not perform imputations for missing data, and we did not contact authors of studies reporting missing data. Using the GRADE approach[42] we combined information on internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results, applicability to patient populations) to characterize the overall quality of evidence supporting the efficacy of intermittent fasting in changing each outcome variable.

RESULTS

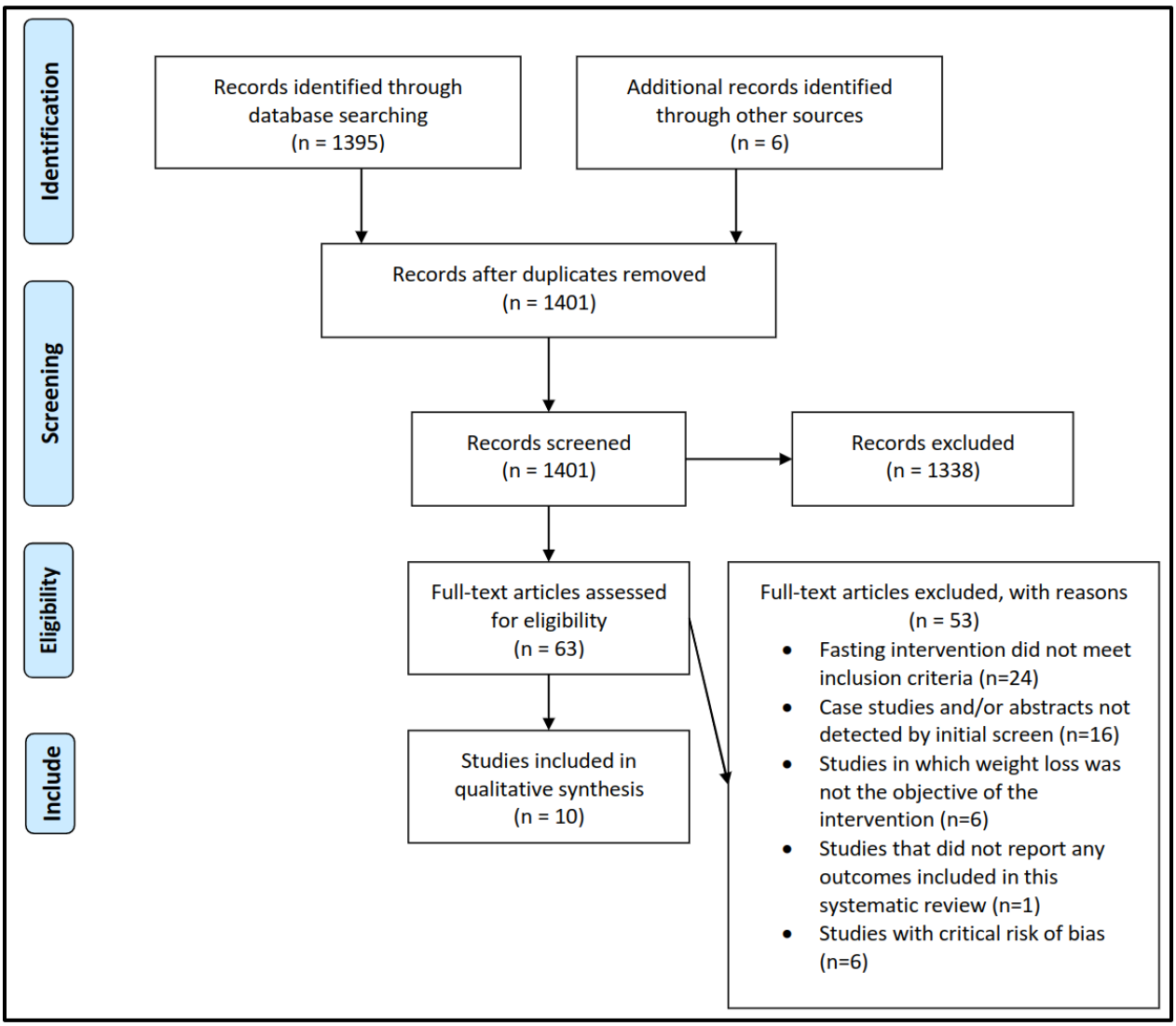
Study Selection

After removal of duplicates, our initial literature search identified 1395 titles and abstracts, and 6 additional references were added through reference review of the identified publications as well as literature searches conducted via GoogleScholar; in total 1401 references were identified for possible inclusion in this review. 1338 records were excluded on the basis of title and abstract, with reasons for exclusion being: acute study duration (n=19), animal studies

or studies of dietary interventions that did not meet inclusion criteria for this review based on frequency or duration of fasting (n=905), studies in children (n=10), non-English language publications (n=19), studies of Ramadan participants (n=36), and non-experimental references such as other reviews, case studies, or conference abstracts (n=349).

We reviewed 63 full-text articles for eligibility. Of these, we excluded studies on the basis of not meeting inclusion criteria for intermittent fasting (n=24); reviews, case studies, or conference abstracts that were not identified with the initial title/abstract screen (n=16); studies in which weight loss was not the objective of the intervention (n=6); studies that did not report the outcomes included in this systematic review (n=1) and; studies with critical risk of bias (n=6). Even though it did not explicitly violate inclusion criteria, we excluded a study by Lantz et al.[43] because the frequency of fast days in the "on-demand" weight loss group was not reported, and therefore it was not possible to ascertain whether there was at least one fasting day per week of intervention. After review by full text, we found 10 papers reporting on 9 randomized controlled trials that fully met inclusion criteria for this review. The PRISMA flow diagram outlining the results of our literature search is shown in Figure 1.

Figure 1. PRISMA flow diagram indicating identification and inclusion of references for systematic review



Characteristics and Results of Included Studies

Results from included studies are summarized herein, but full data extraction tables are available in Appendix 2. Ash et al.[44] conducted a randomized trial in overweight men with type 2 diabetes in which participants were randomized to one of three experimental groups. The two experimental groups included one intermittent energy restriction group and a group given

predetermined meals with a set number of calories. The latter group was not included in this systematic review, as the predetermined meal intervention did not fit the inclusion criteria for interventions or controls. The control group was allowed to self-select dietary pattern but was required to adhere to the same average caloric intake as the experimental groups. After twelve weeks, participants in the control group and the experimental group lost 6.4+/-4.6 Kg on average, and the difference between the two groups was not statistically significant. Triglycerides decreased by 3.6mg/dL across the two groups, and hemoglobin A1c decreased by 1.2%. Given that none of the differences were significant across groups, the study authors reported only mean changes in outcomes across both control and experimental groups.

Bhutani et al.[45,46] performed a randomized controlled trial in 41 obese adults between the ages of 25 and 65 examining the role of intermittent fasting and exercise interventions on weight loss. There were two experimental groups; both participated in an intermittent fasting regimen comprised of 25% of baseline calorie consumption on alternating days, with *ad libitum* feeding allowed on non-fasting days. In one of the two experimental groups, participants were also required to complete moderate-intensity endurance exercises three times per week. The fasting+exercise group was compared to an education+exercise control group, while the fasting-only group was compared to an education-only group. After 12 weeks, subjects in the intermittent fasting+exercise group lost -6+/-4 kg, compared to -1+/-0 kg in the exercise-only control group. The difference between the experimental and control exercise groups was not statistically significant. However, there was a significant difference between the intermittent fasting-only group and the group of education-only controls, with weight loss of 3+/-1 kg and 0+/-0 kg respectively. There was also a significant increase in HDL in the fasting+exercise group relative controls, but there were no other significant differences between experimental and

control groups. The authors also reported on diet-associated hunger, fullness, and uncontrolled eating. In fasting groups, hunger decreased and fullness increased over the 12 week study. Uncontrolled eating decreased in the fasting and fasting+exercise groups.

Carter et al.[34] randomized 63 overweight and obese adults with type 2 diabetes to either an experimental group that fasted twice per week or a control group that was administered a daily calorie restriction diet capped at 1200-1550 kcal/day. On fast days participants were permitted consumption of up to 400-600 calories, dependent on baseline calculated caloric need, while on non-fasting days participants were allowed to eat *ad libitum*. After 12 weeks, both groups lost 8 kg of weight. The study authors also reported change in HgbA1c, which decreased by 0.6% in the fasting group and 0.8% in the control group, though this difference was not statistically significant. Carter et al. also reported on diet-associated hunger and fullness; control and experimental groups both reported decreases in hunger and increased fullness over the twelve weeks of the study.

In one study of overweight and obese patients with family history of breast cancer, Harvie et. al.[33] randomized 107 women to one of two diets: a control diet of daily caloric restriction of 75% of calculated need and an experimental diet comprised of two fasting days per week. On fasting days, participants were asked to consume fewer than 645 calories and to aim for 50g of total protein consumption. At the end of 26 weeks, the intermittent fasting group had lost 5.7 kg compared to 4.5 kg in the control group, though this difference was not statistically significant. In the intermittent fasting group, LDL-c decreased by 11.6mg/dL and triglycerides by 18mg/dL. HDL cholesterol was unchanged, and none of these differences were significant between groups.

Harvie et al. conducted a second similarly designed study[47] in which 36 overweight and obese women between the ages of 20 and 69 and with positive family history of breast cancer were randomized to one of two diets. The control diet was comprised of standard caloric restriction of 75% of calculated daily energy requirement. The experimental group was asked to fast on two fasting days per week (a 5:2 regimen), with caloric intake on fast days capped at 30% of calculated daily caloric need. Furthermore, participants were limited to 40g of carbohydrates on fast days. After 12 weeks, the fasting group had lost 5.0 kg on average compared to 4.0 kg in the control group, though this difference was not statistically significant. Similarly, there were no statistically significant differences between any of the reported cardiovascular or diabetes risk-related endpoints.

The two included studies by Harvie et al. also reported on adverse events experienced during the course of the trial. Decreased energy was reported by 5% of the intermittent fasting group and 5% of the daily calorie restriction control group. Constipation occurred in 8% of intermittent fasters vs. 3% of controls. Headache occurred in 5% of the intermittent fast group and 0% of controls. Light-headedness occurred in 3 vs. 0% (fasting vs. controls) and mood instability was reported in 3% of intermittent fasting participants but 5% in the control group. Finally, halitosis was reported by 5% of participants in the fasting group vs. 3% in controls. Overall, there were more events reported in the fasting group, though none of these differences from controls reached statistical significance.

Hill et al.[48] performed a randomized controlled trial in which 40 moderately obese women were assigned to a regimen of alternate daily fasting intervention or daily caloric restriction. Both groups had a subgroup of participants who were asked to exercise by walking 5 days per week. All diets provided an average of 1200 kcal/day over a 12 week period, and all

participants also received an educational program. At the end of the study, all participants engaging in intermittent fasting had lost 7.6 kg, while the control group lost 7.6 kg also. Hill et. al did not report outcomes related to cardiovascular disease or diabetes.

Varady et al.[35] compared the effects of daily caloric restriction with those of alternate daily fasting on weight and cardiovascular disease risk factors. They performed a randomized controlled trial in 30 overweight and obese adults age 35-65 with no history of cardiovascular disease, diabetes, or smoking. Participants were randomized to an intervention group that fasted every other day for 84 days or to a control group that was prescribed a daily calorie restriction diet comprised of 75% of baseline daily caloric need. Absolute weight loss was not reported in this study; however, participants in the intervention group lost 5.2+/-1.1 percent of their baseline body weight, while participants in the control group lost 5.0+/1.4 percent, a difference that was not statistically significant. Varady et al. similarly reported cardiovascular disease risk factor changes as percent change instead of absolute change. The only statistically significant difference in cardiovascular disease risk factors for the control vs. intervention group was in LDL cholesterol, which decreased by 10+/-4 percent in the intervention group and by 8+/-4 percent in the control group. Differences in HDL and triglyceride change were not significant, though small improvements were seen in both groups. The study authors also reported adverse event rates in the fasting intervention group. Two out of 15 subjects (13%) experienced new-onset headaches during the course of the study. One out of 15 intervention subjects (6.5%) reported constipation; however, this had resolved by the third week after the participant was encouraged to increase fruit and vegetable intake.

Varady et al conducted a second randomized controlled trial[17] of intermittent fasting in 25 patients who were either normal or overweight (BMI 20-29.99 kg/m^2). Participants were

randomized to either an alternate daily fasting regimen on which 25% or fewer of baseline calorie needs were consumed between 12:00pm and 2:00pm or a non-intervention group in which participants were asked to maintain their regular food consumption habits but had regular meetings with nutritionists. At the end of the 12 week study period, body weight decreased in both groups, but the fasting group lost 5.2+/-0.9 kg more than the control group, a difference that was statistically significant. Participants in the alternate daily fasting arm also reported a statistically significant decrease in overall fullness over the course of the study, but there were no significant differences between the two groups in hunger or satisfaction. There also were no significant differences between the two groups in outcomes associated with cardiovascular disease or diabetes risk factors.

Williams et al.[41] performed a randomized controlled trial in 40 individuals with type 2 diabetes and who were at least 20 percent above ideal body weight. In this study, a control group was treated with standard diet-related behavioral therapy. There were two fasting interventions, both of which started with a period of fasting for five days in one week with 400-600 kcal permitted on fasting days. Then, in the first group, participants spent 15 weeks with one fasting day per week. In the second group, participants were asked to fast for five consecutive days at least four times over the remaining 15 weeks. By study's end, the group receiving the standard behavioral intervention had lost 5.4+/-5.9 kg, while the group that fasted one day per week lost 9.6+/-5.7 kg, and the group that engaged in four five-day fasting periods lost 10.4+/-5.4. Weight loss in both experimental groups was statistically significant in comparison to controls, but the difference in weight loss between the two fasting regimens was not. There also were no statistically significant differences in cardiovascular disease or diabetes-related outcomes.

Synthesis of Results

In summary there were 9 studies published in 10 papers reporting on 11 experimental fasting groups and their reported weight loss. Among the 11 fasting groups, 6 were compared to a daily calorie restriction group as the control, while 5 fasting groups were compared to an education-only control group. Overall, weight loss was reported in all 11 experimental groups, and 10 out of 11 control groups. There were no statistically significant differences in weight loss in fasting groups compared to daily calorie restriction control groups, however, when compared to education-only controls, 4 out of 5 experimental groups experienced statistically significant weight loss. It was not possible to calculate the average weight lost in experimental vs. control groups given the heterogeneity across studies in reporting weight loss values and estimates of precision

Regarding outcomes related to cardiovascular disease and diabetes, there were 8 studies published in 9 papers reporting on 10 experimental fasting groups and their reported changes in triglycerides, LDL, HDL, HgbA1c, and fasting plasma glucose. Only the study by Hill et al.[48] did not report these outcomes. There were few statistically significant differences found between intervention and control groups, including those control groups comprised of behavioral or education-only interventions. No trends were observed in changes in these parameters, with different studies reporting increases and/or decreases in the same parameters. Across studies, two statistically significant results were reported. Bhutani et al.[45,46] found a statistically significant increase in HDL in a fasting+exercise experimental group compared to fasting-only and exercise-only groups (+9 vs. +4 mg/dl). Varady et al.[35] reported statistically significant differences between fasters and controls in LDL (respectively, -10+/-4% vs. -8+/-4%) and triglycerides (respectively -15+/-12% vs. +10+/-12%) at the end of 12 weeks.

Adverse outcomes were reported in 4 of the 10 included publications, including Harvie et al.,[47] Bhutani et al.,[46] Carter et al.,[34] and Varady et al.[17] Outcomes described in more than one study include constipation, headache, and hunger. The rate of constipation in fasting groups ranged from 6.5%-8% vs. 0%-3% in controls, and for headache from 5%-13% in fasting groups vs. 0% reported in controls. Qualitative hunger was reported to decrease in two studies. Full data for adverse outcomes are available in Appendix 2

Based on our analysis using the GRADE instrument, the overall quality of evidence supporting a difference between intermittent fasting and education-only non-intervention groups is moderate. In all 9 randomized controlled trials including 244 participants, the intermittent fasting interventions produced weight loss. There was a consistent trend of statistical significance across studies supporting an association between intermittent fasting and weight loss in comparison to populations treated only with behavioral or educational interventions. The overall quality of evidence supporting a difference between intermittent fasting interventions and daily caloric restriction for weight loss is low due to small sample sizes and inconsistently observed effects. Similarly, the overall evidence for associations between intermittent fasting and changes in cardiovascular disease and diabetes endpoints is constrained by small sample sizes and inconsistently observed effects. A summary table describing our findings with the GRADE assessment is shown in Table 2.

Table 2. Summary of strength of evidence for selected outcomes of this review in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. +=Very low strength of evidence; ++=Low strength of evidence; +++=Moderate strength of evidence; +++++=High strength of evidence

Outcome	Fasting (n)	Daily Energy Restriction (n)	Non-intervention (n)	Total No. of participants (n)	Quality of Evidence (GRADE) Fasting vs. daily calorie restriction	Quality of Evidence (GRADE) Fasting vs. non-intervention
Change in weight	244	152	91	487	+	+++
Change in LDL	224	132	91	447	+	+
Change in HDL	224	132	91	447	+	+
Change in TG	224	132	91	447	+	+
Change in HgbA1c	224	132	91	447	+	+
Change in FPG	224	132	91	447	+	+

Assessment of Risk of Bias

We assessed the included studies for risk of bias using the Cochrane Risk of Bias Tool. Results are shown in Table 3. The overall risk of bias is unclear due insufficient reporting on blinding of outcome assessment and other potential sources of bias including conflicts of interest. All included studies had either a low or unclear risk of selection bias related to random sequence generation or allocation concealment. All included studies were considered high risk of performance bias due to the insufficient blinding of participants and personnel; in no studies were participants blinded to dietary intervention. Similarly, all but one study was rated an unclear level of detection bias. Study personnel performing assessments were blinded in one of the 9 included trials. The risk of attrition bias due to incomplete outcome data was deemed to be low in 8 of 9 of the included studies. The study that was rated as "unclear" risk of attrition bias did not report comparability of dropout between groups and did not use intention-to-treat analyses. Reporting bias due to selective reporting was difficult to assess because 7 of the 9 included trials did not have clinical trial registry data available for comparison. One study was deemed high risk of selective reporting bias because changes from baseline to 12-weeks of intervention were not reported for both groups; outcomes were pooled and average weight loss was reported. Justifications for our reported risk of bias for each included study are available in Appendix 3.

Table 3. Risk of bias in included studies. For each study, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias was rated as "High," "Low," or "Unclear." Full ratings with justifications are available in Appendix 3.

Reference	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Ash *et al.*	Low	Unclear	High	Unclear	Low	High	Unclear
Bhutani *et al.*	Low	Low	High	Unclear	Low	Unclear	Unclear
Carter *et al.*	Low	Low	High	Unclear	Low	Low	Unclear
Harvie *et al.* Study 1	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Harvie *et al.* Study 2	Unclear	Low	High	Low	Low	Unclear	Unclear
Hill *et al.*	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Varady *et al.* Study 1	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Varady *et al.* Study 2	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Williams *et al*	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear

DISCUSSION

Intermittent Fasting as a Dietary Intervention for Weight Loss

Key Question 1 for this systematic review focused on weight loss: *"In overweight and/or obese adults, does intermittent fasting compared with traditional caloric restriction and/or non-intervention alter weight and/or BMI?"* Based on the results of this systematic review there is moderate evidence supporting the efficacy of this intervention for weight loss in comparison to behavioral-only or education-only interventions. However, we found that the quality of evidence supportive of a difference between daily caloric restriction and intermittent fasting is very low overall. No studies reported statistically significant differences between the two diets and there was substantial heterogeneity, small sample size, and small effect sizes.

The finding that daily caloric restriction is comparable in efficacy to intermittent fasting is consistent with those of previous systematic reviews. The review by Davis et al.[16] found that all included studies reported significant weight loss in intermittent fasting groups and that intermittent energy restriction diets did not appear to differ in their efficacy for weight loss when compared to traditional caloric restriction diets. Similarly, Seimon et al.[37] found that intermittent fasting was equivalent, but not superior to traditional daily caloric restriction, and this relationship was true for both long-term interventions such as those included in this review and short term interventions lasting fewer than four weeks. Horne et. al.[15] also published a systematic review on intermittent fasting, however their literature search strategy was unclear and included only five studies, some of which were based on Ramadan fasts not explicitly intended to cause weight loss. Nonetheless, Horne et al. found results similar to those of this review, reporting that intermittent fasting appears to be efficacious for weight loss but is not significantly different from daily caloric restriction in this regard. All three of these systematic

reviews included studies reporting on very-low calorie diets, which were excluded in this systematic review based on lacking an intermittent component. Nonetheless, the results of this review add to a growing body of evidence that intermittent fasting diets may be an effective alternative to daily caloric restriction for patients attempting to lose weight.

The availability of alternative weight loss strategies for patients attempting weight loss is important clinically. In busy clinical settings, physicians tend to rely on simple, well-known dietary interventions such as daily caloric restriction, yet current success rates of these traditional dietary interventions for long-term weight loss are approximately 20%.[49] This highlights the importance of customizing dietary approaches to individual preference, particularly for patients with addictive patterns of eating for whom daily caloric restriction may not be an ideal strategy to lose weight. As an analogy, the "cold turkey" approach is considered an effective way to quit smoking,[50] and for many smokers the notion of reducing cigarette consumption but not quitting outright is more daunting than stopping altogether. For addictive eaters there may be some similarity in the sense that food consumption, which is necessary for survival, is itself a trigger for additional eating. For this reason, intermittent fasting may represent the best middle ground between the diet fatigue associated with daily calorie counting and a theoretical "cold turkey" method. In summary, the shortcomings of daily caloric restriction may be mitigated through use of an intermittent fasting diet. Regardless, of the intervention used, successful weight loss necessitates a comprehensive, multidisciplinary approach.[51]

Intermittent Fasting to Minimize Cardiovascular Disease and Diabetes Risk Factors

Key Question 2 for this systematic review focused on intermediate outcomes related to type 2 diabetes mellitus: *"In overweight and/or obese adults, does intermittent fasting compared*

with traditional caloric restriction and/or non-intervention alter hemoglobin A1c and/or fasting plasma glucose?" Similarly, Key Question 3 focused on intermediate outcomes related to cardiovascular disease risk factors: *"In overweight and/or obese adults, does intermittent fasting compared with traditional caloric restriction and/or non-intervention alter high-density lipoprotein, low-density lipoprotein, and/or triglycerides?"* Based on the results of this systematic review, the strength of evidence supporting a relationship between intermittent fasting and these outcomes is very low overall. This is primarily due to widespread heterogeneity of results, small sample sizes, and small effect sizes. The strength of evidence is similarly very low regarding a possible difference between intermittent fasting and daily caloric restriction in terms of these outcomes.

Of the three identified previous systematic review on intermittent fasting, only Horne et al.[15] reported on an association between intermittent fasting and cardiovascular disease risk factors. They included two observational studies on intermittent fasting and coronary artery disease risk factors, both of which were excluded from this review due to critical risk of bias. The authors conclude that further research is needed to determine whether intermittent fasting is associated with changes in risk factors for cardiovascular disease and diabetes. The evidence in our review is supportive of this conclusion; studies included reported small sample sizes that were likely insufficient to detect a significant effect on these outcomes. The systematic review by Davis et al. did not include outcomes related to diabetes or cardiovascular disease, however, the authors based their decision to exclude these data on the apparent lack of statistical power in existing studies.[16]

Intermittent Fasting and Adverse Outcomes

Of the 9 studies included in this review, four reported on adverse outcomes and events, although reporting was inconsistent and sample sizes were insufficient to detect significant differences. The most commonly reported adverse effects of intermittent fasting diets appear to be headache, constipation, and decreased energy, although these occur with similar frequency in the daily calorie restriction groups. Interestingly, hunger appears to decrease with intermittent fasting interventions. No studies reported on anorexia, binge eating, or bulimic behaviors in intervention arms, however, a previous study found an association between engaging in fasts and bulimia,[52] although the direction of causality was unclear based on the cross-sectional study design. Another systematic review found that daily caloric restriction reduced prevalence of binge-eating disorder in experimental groups.[53]. There are limited data specifically regarding the safety and tolerability of intermittent fasting as an intervention for weight loss. However, emerging expert opinion is supportive of the notion that intermittent fasting is comparable to daily caloric restriction in terms of adverse outcomes and that adverse outcomes are collectively uncommon unless a fasting intervention is implemented in normal weight participants attempting further weight loss.[32,54,55]

Limitations and Future Directions

This review has several limitations. Due to logistical limitations, studies of intermittent fasting that were published in other languages were not included in this review. These constitute a potentially important source of information on the efficacy and/or harms of intermittent fasting interventions, particularly given the rising prevalence of obesity in developing nations.[56] Additionally, only one author reviewed titles, determined inclusions, and assessed risk of bias.

Another limitation of this study was the limited inclusion of possible markers of cardiovascular disease and diabetes. Given that the results of this review might be used by clinicians to counsel patients about weight loss strategies, we did not include infrequently used or difficult-to-obtain laboratory measurements such as fasting insulin, insulin sensitivity, and LDL and HDL particle size. These may be significant markers of disease risk or progression but are not part of routine laboratory evaluation for these diseases and so were not included in this review. This review may also be limited in external validity, as it is unclear if these findings are externally valid to populations that may be vulnerable based on race, ethnicity, socioeconomic status, gender, sex, and/or geography. Finally, we were unable to perform a meta-analysis with included data due to heterogeneity of reporting and inadequate availability of measures of precision in the included studies.

In part, the limitations of this review are attributable to evidence gaps in the literature. Overall, sample sizes in the included studies are small, and there is a paucity of data on intermittent fasting as an intervention in specific subpopulations, particularly racial and ethnic minorities. In addition, all of the included studies took place in resource-rich university settings where participants had access to behavioral counseling, nutritionists, and high quality food sources. It is unclear if individuals attempting weight loss in underserved and/or rural areas, where the obesity epidemic is particularly problematic, would achieve similar weight loss outcomes, and future studies of intermittent fasting should assess interventions that may have greater external validity or are easier to implement. There may also be varied efficacy of intermittent fasting as an intervention in subgroups with specific patterns of overeating, such as addictive or binge eaters,[57] but efficacy of intermittent fasting in these groups has not been

reported in the literature. Future studies might better characterize the efficacy of intermittent fasting interventions by stratifying participants by eating behavior.

Overall, the strength of evidence supporting an association between intermittent fasting and outcomes related to cardiovascular disease and diabetes is very low. Several systematic reviews and meta-analyses support the notion that weight loss reduces morbidity and mortality in obese patients, possibly by 15%,[58,59] and much of this reduction is attributable to reductions in prevalence of diabetes and cardiovascular disease. However, there are few data reporting morbidity and mortality associated with specific weight loss interventions. Ideally, future studies of intermittent fasting and/or daily caloric restriction will be sufficiently powered and of sufficient duration to observe morbidity and mortality changes and to accurately measure adverse event rates. Absent morbidity and mortality data, it will be helpful for future studies of intermittent fasting to be sufficiently powered to detect significant differences in intermediate outcomes associated with cardiovascular disease and diabetes, the chief drivers of obesity-associated mortality.[60]

Adverse event reporting is inconsistent across studies, with the majority of studies included in this review omitting reporting on such outcomes. Future studies should include rates of constipation, headache, and fatigue in experimental and control groups, as based on this review these are the most commonly reported adverse events associated with intermittent fasting. Furthermore, studies are needed on the safety of this dietary intervention in groups with history of eating disorders such as anorexia, bulimia, and binge-eating disorder, as improper compliance with an intermittent fasting diet could contribute to first occurrence or relapse of these conditions. This is of particular importance given that the prevalence of eating disorders in obese populations may be increasing.[61]

CONCLUSION

In summary, the obesity pandemic is an international public health crisis, and novel interventions are needed to help obese patients lose weight. Intermittent fasting is one such intervention that affords dieters periods of indulgence interspersed with periods of strict caloric restriction, which may improve weight loss compliance for some patients. In this systematic review, we assessed the efficacy of intermittent fasting for weight loss in comparison to daily caloric restriction, which has long been a mainstay of dietary interventions for patients seeking to lose weight. We also reviewed the evidence supporting an association between intermittent fasting and changes in risk factors for cardiovascular disease and diabetes. In this review, which included nine randomized controlled trials, we found moderate strength evidence that intermittent fasting is effective for weight loss, though its efficacy for weight loss is approximately the same as that of daily caloric restriction. The overall strength of evidence supporting an association between intermittent fasting and changes in risk factors for cardiovascular disease and diabetes was very low. Intermittent fasting-associated adverse events reported across studies included headache and constipation, though reporting of adverse events is inconsistent across studies, and we found no reports of associations between intermittent fasting dietary interventions and unhealthy eating behaviors.

Collectively, these data support the hypothesis that intermittent fasting is an effective alternative to daily caloric restriction, though future studies should be sufficiently powered to detect changes in risk factors for cardiovascular diseases and diabetes as well as adverse event rates. Intermittent fasting as an intervention may be preferred by some patients, and clinicians should tailor dietary weight loss plans to individual needs. Like other dietary weight loss

interventions, intermittent fasting is most effective when combined with additional lifestyle modifications including exercise, counseling, and peer support.

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APPENDIX 1: Literature Search Strings

MEDLINE Search String (832 Results Identified)

("Overweight"[Mesh] OR "Obesity"[Mesh] OR ("obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields])) AND ((periodic[All Fields] AND ("fasting"[MeSH Terms] OR "fasting"[All Fields] OR "fast"[All Fields])) OR (periodic[All Fields] AND fasts[All Fields]) OR "periodic fasting"[All Fields] OR "intermittent calorie restriction"[All Fields] OR "intermittent fasting"[All Fields] OR "intermittent fasts"[All Fields] OR "intermittent fast"[All Fields] OR "intermittent energy restriction"[All Fields] OR "intermittent caloric restriction"[All Fields] OR "Very low calorie diet"[All Fields] OR "very low calorie diets"[All Fields] OR "continuous energy restriction"[All Fields] OR "time restricted feeding"[All Fields] OR (("time"[MeSH Terms] OR "time"[All Fields]) AND restricted[All Fields] AND feeds[All Fields]) OR (("time"[MeSH Terms] OR "time"[All Fields]) AND restricted[All Fields] AND feed[All Fields])) AND ("Body Mass Index"[Mesh] OR "Ideal Body Weight"[Mesh] OR "body weight"[All Fields] OR ("weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]) OR "ideal body"[All Fields] OR "normal body weight"[All Fields])

CINAHL Search String (166 Results Identified)

("periodic fasting" OR "periodic fasts" OR "periodic fast" OR "intermittent fasting" OR "intermittent fasts" OR "intermittent fast" OR "intermittent energy restriction" OR "intermittent calorie restriction" OR "intermittent caloric restriction" OR "very low calorie diet" OR "very low

calorie diets" OR "time restricted feeding") AND (BMI OR "body mass index" OR "weight" OR "mass")

Embase Search String (1287 Results Identified)

("periodic fasting" OR "periodic fasts" OR "periodic fast" OR "intermittent fasting" OR "intermittent fasts" OR "intermittent fast" OR "intermittent energy restriction" OR "intermittent calorie restriction" OR "intermittent caloric restriction" OR "very low calorie diet" OR "very low calorie diets" OR "time restricted feeding") AND (BMI OR "body mass index" OR "weight" OR "mass")

List of synonyms used in building literature searches

- *Intermittent fasting*
- *Alternate day fasting*
- *Very-low calorie diet*
- *Intermittent energy restriction*
- *Intermittent calorie restriction*
- *Periodic fasting*
- *Periodic calorie restriction*
- *5:2 diet*
- *Time restricted feeding*
- *Time restricted caloric intake*
- *Fasting diet*
- *Intermittent diet*

Appendix 2: Extracted Data from Included Studies

Table 1. RCTs reporting weight loss associated with intermittent fasting diets

	Study Characteristics				**Outcomes for Weight Loss**	
Study	Population	Interventions and Comparators	Sample Size	Duration of Follow Up (weeks)	Weight change (Kg)	Difference between groups?*
Studies with Daily Caloric Restriction as Control Group						
Ash *et al*.[2]	Overweight men with type 2 diabetes	I: 48 fasting days, 36 ad libitum days. On fasting days participants given 1000 kcal/day w/ liquid meal replacement	14 men	12	-6.4 ± 4.6 (sd[b])	No
		C: 1400-1700 kcal/day	17 men	12	-6.4 ± 4.6 (sd)[c]	
Carter *et al*.[9]	Overweight or obese adults with type 2 diabetes	I: 2 fast days per week, w/ 400-600 kcal on fast days and *ad libitum* on non-fast days	31 (17 women, 14 men)	12	-8	No
		C: Continuous energy restriction of 1200-1550 kcal/day	32 (16 women, 16 men)	12	-8	
Harvie *et al.* Study 1[5]	Overweight women between ages of 30-45 years, w/ family history of breast cancer	I: 2 fasting days per week. On fasting days total caloric intake <645 kcal/day and total protein intake goal was 50g	53 women	26	-5.7	No

		C: Standard daily caloric restriction (goal caloric intake 75% of calculated need)	54 women	26	-4.5	
Harvie *et al.* Study 2[6^]	Overweight women between ages of 20-69, w/ family history of breast cancer	I: 2 fasting days per week. On fasting days total caloric intake was capped at 30% of calculated daily caloric need. Also 40g carbohydrate limit on fast days.	19 women	12	-5.0	No
		C: Standard daily caloric restriction (goal caloric intake 75% of calculated need)	17 women	12	-4.0	
Hill *et al.*[10]	Obese women 130-160% of ideal body weight	I: Alternating fasting and non-fasting days: 600 kcal limit on fast days, 1800 kcal limit on non-fasting days. Half of participants required to walk 5 days/week.	20 women	12	-7.6	No
		C: Continuous energy restriction: 1200 kcal/day. Half of participants required to walk 5 days/week	20 women	12	-7.6	
Varady *et al* Study 1.[3]	Overweight and obese adults aged 35-65 with no history of cardiovascular disease, diabetes, or smoking	I: 42 days of 25% of normal caloric requirement alternated w/ 42 days of *ad libitum*	13 (10 women, 3 men)	12	PERCENT of BODY WEIGHT LOST -5.2 ± 1.1 (sem)	No
		C: 75% of normal caloric requirement/day	12 (10 women, 2 men)	12	PERCENT OF BODY WEIGHT LOST -5.0 ± 1.4 (sem)	

Studies with Non-interventional or Education-Only Control Groups						
Bhutani *et al*.[7,8] Group 1	Obese adults aged 25-65. Participants with history of diabetes, smoking, or cardiovascular disease were excluded	I: Fasts every other day. Fast days included 25% of baseline energy requirement, consumed between 12:00pm and 2:00pm	25 (24 women, 1 man)	12	-3 ± 1	Yes
		C: No intervention; participants asked to maintain regular food habits	16 (15 women, 1 man)	12	0 ± 0	
Bhutani *et al*.[7,8] Group 2	Obese adults aged 25-65. Participants with history of diabetes, smoking, or cardiovascular disease were excluded	I: Fasts every other day. Fast days included 25% of baseline energy requirement, consumed between 12:00pm and 2:00pm. Participants in this group also required to complete moderate-intensity endurance exercises 3x weekly	18 women	12	-6 ± 4	No
		C: No dietary intervention, but participants required to complete moderate-intensity endurance exercises 3x weekly	24 (23 women, 1 man)	12	-1 ± 0	
Varady *et al* Study 2.[11]	Normal and overweight (but not obese) subjects aged 35-65 years. Participants w/ history of diabetes or cardiovascular disease excluded.	I: Fasts every other day. Fast days included 25% of baseline energy requirement, consumed between 12:00pm and 2:00pm	15 (10 women, 5 men)	12	Both groups lost weight. Fasting group lost 5.2 ± 0.9 kg more than non-fasting group	Yes
		C: No intervention; participants asked to maintain regular food habits	15 (12 women, 3 men)	12		

Williams *et al.*[4] Group 1	Individuals w/ Type 2 diabetes and ≥20% over ideal body weight	I: 5 fasting days in one week followed by 15 weeks with one fasting day per week (fast=400-600 kcal/day)	18 (9 women, 9 men)	20	-9.6 ± 5.7 (sem)	Yes
		C: Standard behavioral therapy	18 (11 women, 7 men)	20	-5.4 ± 5.9 (sem)	
Williams *et al.*[4] Group 2	Individuals w/ Type 2 diabetes and ≥20% over ideal body weight	I: 5 fasting days in one week followed by four 5-day fasting periods over the remaining 19 weeks	18 (11 women, 7 men)	20	-10.4 ± 5.4 (sem)	Yes
		C: Standard behavioral therapy	18 (11 women, 7 men)	20	-5.4 ± 5.9 (sem)	

[a] Standard error of the mean

[b] Standard deviation

[c] In this study authors reported pooled weight loss for both groups

[d] For these studies, no estimate of precision was included in the value for weight loss

*Defined as $p<0.05$ by pairwise t-tests or ANOVA

^ In this study we excluded the intermittent fasting + *ad libitum* protein and fat group because the unrestricted consumption of fat and protein violated the inclusion criteria of this systematic review

Table 2. RCTs reporting intermediate outcomes related to cardiovascular disease and diabetes following implementation of intermittent fasting diet

	Study Characteristics				Cardiovascular Disease and Diabetes Outcomes					
Study	Population	Interventions and Comparators	Sample Size	Duration of Follow Up (weeks)	LDL	HDL	Triglycerides	HgbA1c (%)	FPG	Difference between groups?*
Studies with Daily Caloric Restriction as Control Group										
Ash *et al.*[2]	Overweight men with type 2 diabetes	I: 48 fasting days, 36 ad libitum days. On fasting days participants given 1000 kcal/day w/ liquid meal replacement	14 men	12	--	--	-0.3	-1.2	--	No
		C: 1400-1700 kcal/day	17 men	12						
Carter *et al.*[9]	Overweight or obese adults with type 2 diabetes	I: 2 fast days per week, w/ 400-600 kcal on fast days and *ad libitum* on non-fast days	31 (17 women, 14 men)	12	-	-	-	-0.6+/- 0.8%	-	No
		C: Continuous energy restriction of 1200-1550 kcal/day	32 (16 women, 16 men)	12	-	-	-	-.8+/- 1.0%	-	
Harvie *et al.*[5]	Overweight women between	I: 2 fasting days per week. On fasting days total caloric	53 women	26	-0.3 (mm	0 (mm	-0.2 (mmol/L)	-	-0.1 (mmol/	No

	ages of 30-45 years, w/ family history of breast cancer	intake <645 kcal/day and total protein intake goal was 50g			ol/L)	ol/L)			L)	
		C: Standard daily caloric restriction (goal caloric intake 75% of calculated need)	54 women	26	-0.3 (mmol/L)	-0.1 (mmol/L)	-0.3 (mmol/L)	-	-0.1 (mmol/L)	
Harvie *et al.*[6]	Overweight women between ages of 20-69, w/ family history of breast cancer	I: 2 fasting days per week. On fasting days total caloric intake was capped at 30% of calculated daily caloric need. Also 40g carbohydrate limit on fast days.	19 women	16	-0.14 (mmol/L)	-0.03 (mmol/L)	-	+0.3mmol/l[$]	-0.1	No
		C: Standard daily caloric restriction (goal caloric intake 75% of calculated need)	17 women	16	-0.10 (mmol/L)	+0.03 (mmol/L)	-	--0.1mmol/l	-0.1	
Varady *et al* Study 1.[3]	Overweight and obese adults aged 35-65 with no history of	I: 42 days of 25% of normal caloric requirement alternated w/ 42 days of *ad libitum*	13 (10 women, 3 men)	12	-10+/-4%	2+/-3%	-15+/-12%	--	--	Statistically significant difference between fasting

	cardiovascular disease, diabetes, or smoking	C: 75% of normal caloric requirement/day	12 (10 women, 2 men)	12	-8+/-4%	4+/-3%	10+/-12%	--	--	group and caloric restriction group for LDL and triglycerides
Studies with Non-interventional or Education-Only Control Groups										
Bhutani *et al.*[7,8] Group 1	Obese adults aged 25-65. Participants with history of diabetes, smoking, or cardiovascular disease were excluded	I: Fasts every other day. Fast days included 25% of baseline energy requirement, consumed between 12:00pm and 2:00pm	25 (24 women, 1 man)	12	-1mg/dl	0	+5mg/dl	-	-3mg/dl	No
		C: No intervention; participants asked to maintain regular food habits	16 (15 women, 1 man)	12	+4mg/dl	+4mg/dl	+5mg/dl	-	+2mg/dl	
Bhutani *et al.*[7,8] Group 2	Obese adults aged 25-65. Participants with history of diabetes, smoking, or cardiovascular disease were excluded	I: Fasts every other day. Fast days included 25% of baseline energy requirement, consumed between 12:00pm and 2:00pm. Participants in this group also required to complete	18 women	12	-16mg/dl	+9mg/dl	+10mg/dl		-2mg/dl	HDL increased significantly in fasting+exercise group

		moderate-intensity endurance exercises 3x weekly								
		C: No dietary intervention, but participants required to complete moderate-intensity endurance exercises 3x weekly	24 (23 women, 1 man)	12	+4mg/dl	+4mg/dl	+5mg/dl	-	+2mg/dl	
Varady *et al* Study 2.[11]	Normal and overweight (but not obese) subjects aged 35-65 years. Participants w/ history of diabetes or cardiovascular disease excluded.	I: Fasts every other day. Fast days included 25% of baseline energy requirement, consumed between 12:00pm and 2:00pm	15 (10 women, 5 men)	12	-18+/-6mg/dl	-2+/-3mg/dl	-22+/-11	-	-	No
		C: No intervention; participants asked to maintain regular food habits	15 (12 women, 3 men)	12	-9+/-5mg/dl	+1+/-2mg/dl	+10+/-7	-	-	
Williams *et al.*[4] Group 1	Individuals w/ Type 2 diabetes and ≥20% over ideal body weight	I: 5 fasting days in one week followed by 15 weeks with one fasting day per week (fast=400-600 kcal/day)	18 (9 women, 9 men)	20	-0.15 (mmol/L)	.03 (mmol/L)	-1.15 (mmol/L)	-0.65+/-1.35%	-	No

		C: Standard behavioral therapy	18 (11 women, 7 men)	20	-0.19 (mmol/L)	-0.15 (mmol/L)	-0.66 (mmol/L)	-0.71+/- 1.59%	-	
Williams *et al.*[4] Group 2	Individuals w/ Type 2 diabetes and ≥20% over ideal body weight	I: 5 fasting days in one week followed by four 5-day fasting periods over the remaining 15 weeks	18 (11 women, 7 men)	20	-0.19 (mmol/L)	-0.01 (mmol/L)	-0.22 (mmol/L)	-0.97+/- 1.70%	-	No
		C: Standard behavioral therapy	18 (11 women, 7 men)	20	-0.19 (mmol/L)	-0.15 (mmol/L)	-0.66 (mmol/L)	-0.23+/- 1.04%	-	

[a] Standard error of the mean

[b] Standard deviation

[c] In this study authors reported pooled weight loss for both groups (which is why the values are the same)

[d] For these studies, no estimate of precision was included in the value for weight loss

*Defined as $p<0.05$ by pairwise t-tests or ANOVA

^Subdivide Table By: Studies w/ education/*ad libitum*-only control groups OR Studies in which control group is some type of caloric restriction

$ For the study by Harvie *et al.* HgbA1c was reported at 12 weeks but not at 16 weeks

Table 3. Adverse events and outcomes reported in randomized-controlled trials of intermittent fasting

Study	Adverse Events and Outcomes
Harvie *et al.* Study 2[6]	● Decreased Energy ○ 5% in intermittent fasting group vs 5% in daily energy restriction (control) group ● Constipation ○ 8% in intermittent fasting group vs. 3% in controls ● Headache ○ 5% in intermittent fasting group vs. 0% in controls ● Halitosis ○ 5% in intermittent group vs. 3% in control group ● Light-headedness ○ 3% in fasting group vs. 0% in control group ● Mood instability ○ 3% in fasting group vs. 5% in control (daily energy restriction) group
Bhutani *et al.*[8]	● In fasting group hunger decreased and fullness increased over the 12 week study. Uncontrolled eating decreased in the fasting and fasting+exercise groups.
Carter *et al.*[9]	● Intermittent fasting group and daily caloric restriction group reported decrease in hunger and increase in fullness
Varady *et al.*[11]	● Headaches ○ 2/15 intervention subjects (13%) ● Constipation ○ 1/15 (6.5%) ■ This resolved by week 3 after participant was encouraged to increase fruit and vegetable intake

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Appendix 3: Risk of Bias with Support for Judgement

Table 1. Risk of bias in included studies, with support for judgement. Assessment performed with Cochrane Risk of Bias Tool.[11]

Ash et al.[1]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Low	Quote from article: "Following the dietary stabilization period subjects were randomized, using a random number table, into one of three dietary intervention groups for the 12-week intervention period: intermittent energy restriction (IER), pre-portioned meals (PPM) and self-selected meals (SSM)."
Allocation Concealment (Selection Bias)	Unclear	Comment: Allocation concealment is not discussed in the article
Blinding of Participants and Personnel (Performance Bias)	High	Comment: Blinding is not discussed in the article
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Blinding of outcome assessment was not performed; however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Quote from article: "Although loss to follow-up was high, subjects studied at 18 months were comparable in every respect to the original study population." Comment: Loss to follow up was not significantly different in the three experimental groups.
Selective Reporting (Reporting Bias)	High	Comment: Change from baseline to 12-weeks of intervention were not reported for both groups; outcomes were pooled and average weight loss was reported. No protocol or clinical trial

		registry entry available.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias
Bhutani *et al*. (reported in two papers)[6,7]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Low	Quote from article: "Randomization was performed for each stratum by selecting an intervention at random from an opaque envelope."
Allocation Concealment (Selection Bias)	Low	Comment: The allocation concealment was adequate on the basis of having a clinical coordinator open a randomly-selected opaque envelope
Blinding of Participants and Personnel (Performance Bias)	High	Comment: participants and personnel were not blinded to intervention
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Blinding of outcome assessment was not performed, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Quote from article: "Additional subjects were randomized to groups with high dropout rates, such as the ADF and exercise group, to ensure that the number of subjects would be the same in each group at the end of the trial. Dropouts were primarily due to scheduling conflicts." Comment: Dropout rates were different across experimental groups, however, given that this was primarily a result of scheduling and that baseline comparability of groups was adequate, this constitutes a threat to external but not internal validity. Furthermore, the measured characteristics of dropouts were not significantly different from those of successful study completers.
Selective Reporting	Unclear	Comment: No protocol or clinical trial registry entry

(Reporting Bias)		available.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias
Carter et al.[8]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Low	Quote from article: "Participants were divided into two groups, stratified by gender and BMI, and allocated 1:1 to treatment groups."
Allocation Concealment (Selection Bias)	Low	Comment: Study personnel utilized a computerized random number generator for allocation
Blinding of Participants and Personnel (Performance Bias)	High	Quote from article: "...and randomization was not blinded." Comment: neither participants nor personnel were blinded at any point in the study.
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Blinding of outcome assessment was not performed, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Comment: Drop out was low overall and was similar in both experimental groups
Selective Reporting (Reporting Bias)	Low	Quote: "This study has been registered with the Australia New Zealand Clinical Trial Registry (ANZCTR) www.anzctr.org.au and given the registration number ACTRN12615000383561." Comment: No differences found between publication and protocol/clinical trial register entry
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias

Harvie et al. Study 1[4]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Unclear	Comment: the protocol for random sequence generation is not described
Allocation Concealment (Selection Bias)	Unclear	Comment: the protocol for allocation concealment is not described
Blinding of Participants and Personnel (Performance Bias)	High	Comment: participants and study personnel were not blinded
Blinding of Outcome Assessment (Detection Bias)	Unclear	Quote from article: "Laboratory personnel were blinded to the sample identity." Comment: Serologic tests were not subject to detection bias, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Quote from article: "Eighteen women withdrew from the study before 6 months (IER=11, CER=7), representing 21% IER and 13% CER subjects (X^2=1.16, P=0.28). The main reasons for dropout were comparable between the groups: stress (IER=3, CER=2), pregnancy (IER=2, CER=1), change in employment (IER=2, CER=1), problems adhering to the diet (IER=3, CER=3) and personal illness (infected pacemaker, IER=1)"
Selective Reporting (Reporting Bias)	Unclear	Comment: No protocol or clinical trial registry entry available
Other Bias	Unclear	Comment: Tanita Europe provided Tanita TBF-300 equipment free of charge for use in study, though it is unclear if this represented introduction of bias. It is unclear if the study was at risk of any other bias
Harvie et al. Study 2[5]		

Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Unclear	Comment: the protocol for random sequence generation is not discussed
Allocation Concealment (Selection Bias)	Low	Quote from Article: "Group allocation was established by opaque, sealed envelopes that contained the assignment for each subject."
Blinding of Participants and Personnel (Performance Bias)	High	Comment: participants and study personnel were not blinded
Blinding of Outcome Assessment (Detection Bias)	Low	Quote from Article: "Personnel performing laboratory measurements, and inputting and analyzing trial data were blinded to group allocations. Anthropometric measures were performed by research dietitians who were not blinded to the treatment group" Comment: Blinding of outcome assessment was not performed for anthropometric data, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective.
Incomplete Outcome Data (Attrition Bias)	Low	Quote from article: "We considered it more appropriate to report a comparison of the three dietary groups (adjusting for multiple testing with Bonferroni correction) with an intention-to-treat analysis that includes all subjects in a last-observation-carried-forward (LOCF) analysis. Quote from article: "In total, twenty-seven women withdrew from the study (23%): IECR n=4 (11%), IECR+PF n=10 (26%) and DER n=13 (33%) (X^2=5.3, P=0.071). The reasons for the dropout were family/work issues (IECR n=3, IECR+PF n=4, DER n=5), unrelated personal illness (IECR n=1, IECR+PF n=1, DER n=1), problems adhering to the diet (IECR+PF n=2, DER n=3), and loss to follow up (IECR+PF n=3, DER n=4)."
Selective Reporting (Reporting Bias)	Unclear	Comment: No protocol or clinical trial registry entry available. Authors used Bonferroni correction to address

		multiple comparisons.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias
Hill et al.[9]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Unclear	Comment: the protocol for random sequence generation is not discussed
Allocation Concealment (Selection Bias)	Unclear	Comment: the protocol for allocation concealment is not discussed
Blinding of Participants and Personnel (Performance Bias)	High	Comment: neither participants nor study personnel were blinded to assignment to intervention or control groups
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Comment: Blinding of outcome assessment was not performed, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Unclear	Comment: The authors do not report comparability of dropout between groups. Intention-to-treat analyses were not used.
Selective Reporting (Reporting Bias)	Unclear	Comment: No protocol or clinical trial registry entry available.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias
Varady et al. Study 1[2]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement

Random Sequence Generation (Selection Bias)	Unclear	Comment: the protocol for random sequence generation is not discussed
Allocation Concealment (Selection Bias)	Unclear	Comment: the protocol for allocation concealment is not discussed
Blinding of Participants and Personnel (Performance Bias)	High	Comment: neither participants nor study personnel were blinded to assignment to intervention or control groups
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Comment: Blinding of outcome assessment was not performed, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Quote from article: "Sixty subjects commenced the study, with 49 completing the 12-week trial. The remaining subjects in each intervention group were as follows: ADF (n = 13), CR (n = 12), exercise (n = 12), and control (n = 12)."
Selective Reporting (Reporting Bias)	Unclear	Comment: Raw data for many outcomes not reported in tables or text but given in graphs or reported as either significant or non-significant. No protocol or clinical trial registry entry available.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias
Varady et al. Study 2[10]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Low	Quote from article: "Subjects were randomized by KAV by way of a stratified random sample. Subjects were first divided into strata based on sex (M/F), age (35–50 y/51-65 y), and BMI (20–24.9 kg/m2/ 25–29.9 kg/m2), and then subjects from each stratum were randomized 1:1 into either the ADF or control group"
Allocation	Unclear	Comment: the subjects were randomized based on

Concealment (Selection Bias)		predetermined strata, however, it is unclear if the experimenter who assigned subjects (KAV) was blinded in any way to the assignments generated
Blinding of Participants and Personnel (Performance Bias)	High	Comment: neither participants nor study personnel were blinded to assignment to intervention or control groups
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Comment: Blinding of outcome assessment was not performed, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Comment: Low overall dropout, with rate of dropout and characteristics of participants dropping out similar across experimental groups. One participant dropped out of fasting group due to difficult adhering to diet. One participant dropped out of the control group due to scheduling conflicts.
Selective Reporting (Reporting Bias)	Unclear	Comment: Weight change is only reported as "relative to control" but is also shown in Figure 2 to be negative overall. Absolute values for weight loss in the two groups are not presented. No protocol or clinical trial registry entry available.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias
Williams et al.[3]		
Bias	Author's Judgement of Risk of Bias	Support for Judgement
Random Sequence Generation (Selection Bias)	Unclear	Quote from article: "Eligible subjects were blocked by FPG after 2 weeks off diabetes medication (<7.8, 7.8-11.1, and >11.1 mmol/l) and then randomized, by blocks, to one of three treatment conditions. Comment: Randomization sequence generation is not explicitly discussed
Allocation	Unclear	Comment: it is not specified if block randomization was

Concealment (Selection Bias)		implemented in a manner that minimized allocation concealment.
Blinding of Participants and Personnel (Performance Bias)	High	Comment: neither participants nor study personnel were blinded to assignment to intervention or control groups
Blinding of Outcome Assessment (Detection Bias)	Unclear	Comment: Comment: Blinding of outcome assessment was not performed, however, it is unclear if unblinding of outcome assessment could have been a source of detection bias, as the measured outcomes were objective physical and serologic measurements.
Incomplete Outcome Data (Attrition Bias)	Low	Quote from article: "Dropout rate was similar across treatment conditions. Reported reasons for dropping out included illness in the family, a change in work schedule, or a move to another region of the country that precluded attendance at the weekly treatment meetings. Baseline characteristics of dropouts were not different from subjects who completed the study. Attendance rates at weekly treatment meetings did not differ between groups (P = 0.62)."
Selective Reporting (Reporting Bias)	Unclear	Comment: No protocol or clinical trial registry entry available.
Other Bias	Unclear	Comment: Study authors declared no conflicts of interest. Unclear if the study was at risk of any other bias

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