AHA SCIENTIFIC STATEMENT

Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention

A Scientific Statement From the American Heart Association

ABSTRACT: Eating patterns are increasingly varied. Typical breakfast, lunch, and dinner meals are difficult to distinguish because skipping meals and snacking have become more prevalent. Such eating styles can have various effects on cardiometabolic health markers, namely obesity, lipid profile, insulin resistance, and blood pressure. In this statement, we review the cardiometabolic health effects of specific eating patterns: skipping breakfast, intermittent fasting, meal frequency (number of daily eating occasions), and timing of eating occasions. Furthermore, we propose definitions for meals, snacks, and eating occasions for use in research. Finally, data suggest that irregular eating patterns appear less favorable for achieving a healthy cardiometabolic profile. Intentional eating with mindful attention to the timing and frequency of eating occasions could lead to healthier lifestyle and cardiometabolic risk factor management.

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The patterns of meal and snack eating behavior in American adults have changed over the past 40 years. Based on NHANES (National Health and Nutrition Examination Survey) data from 1971 to 1974 to 2009 to 2010 (n=62 298), women 20 to 74 years of age reported a decrease in 24-hour meal-derived total energy intake (TEI) from 82% in the 1970s to 77% in 2009 to 2010 and an increase in the proportion of TEI consumed from snacks from 18% to 23%.[1] Similar trends were reported among men. The proportion of men and women who reported consuming all 3 standard meals declined over this period (from 73% to 59% in men; from 75% to 63% in women),[1] reflecting changes in eating patterns rather than changes in eating frequency. Indeed, the traditional breakfast-lunch-dinner pattern was not observed in a population of healthy, non–shift-working adults.[2] In that study, the number of eating occasions, defined as consumption of any food or beverage providing at least 5 kcal, was ≈4.2 times a day in the lowest decile and 10.5 times a day for the top decile. There were only 5 hours during the 24-hour day when <1% of all eating occasions occurred: between 1 and 6 AM. This study clearly demonstrated that adults in the United States eat around the clock. Because feeding and fasting entrain clock genes, which regulate all aspects of metabolism, meal timing can have serious implications for the development of cardiovascular disease (CVD), type 2 diabetes mellitus, and obesity.[3,4]

The circadian rhythms of the body are controlled by the central clock located in the suprachiasmatic nucleus of the hypothalamus but also by clocks of peripheral organs. Although the master clock is strongly entrained by light, clocks of peripheral organs are additionally responsive to food supply, and temporal restriction of food can reset clock gene rhythms. In mice, food given in the normal sleeping period can uncouple peripheral clocks from the master clock.[5] In fact, time-restricted feeding

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in mice alters the robustness and coherence of rhythmic gene transcripts,[6] which may be relevant for cardiometabolic health. Indeed, the *CLOCK* and *BMAL1* genes are implicated in regulating genes involved in lipid metabolism.[7,8] Polymorphisms in the *CLOCK* gene correlated with the development of metabolic syndrome; those in *BMAL1*, with type 2 diabetes mellitus and hypertension. Therefore, time of eating and nutrient delivery may have cardiometabolic health implications via alterations in peripheral clocks, most notably that of the liver.

In this statement, we review epidemiological and clinical evidence linking various eating patterns with cardiometabolic health markers in adults. We focus on patterns of food consumption as they relate to meal times and number of eating occasions/eating frequency rather than dietary profiles such as nutrient intakes. However, some attention will be given to diet quality to the extent that food intake patterns influence overall diet macronutrient composition. A comprehensive literature search strategy was used to identify relevant articles for this review. We searched electronic databases (eg, MEDLINE, PubMed, PubMed Central) and reference lists from retrieved articles and consulted expert colleagues. For electronic searches, we crossed various key words related to cardiometabolic health markers: *lipid profile*, *fasting glucose*, *fasting insulin*, *homeostatic model assessment* (HOMA), *insulin resistance* (IR), *insulin sensitivity*, *blood pressure*, *body weight*, *overweight*, *obesity*, *fat mass*, *visceral fat*, *adiposity*, *lean body mass*, and *weight loss*. Key words relevant to eating patterns under review included *breakfast skipping*, *intermittent fasting*, *meal frequency*, and *meal timing*.

ADDITIONAL METHODS

A systematic search in MEDLINE PubMed was performed with the use of various combinations of the following search terms: *alternate day fasting*, *intermittent fasting*, *fasting*, *intermittent energy restriction*, *meal frequency*, *meal skipping*, *meal timing*, *late day eating*, *late day meals*, *evening eating*, *evening meals*, *obesity*, *body weight*, *weight loss*, *cardiovascular risk*, *coronary heart disease* (CHD), *cholesterol*, *plasma lipids*, *lipid profile*, *blood pressure*, *glucose*, *insulin*, and *insulin resistance*. Articles were excluded if they did not include original data; if they were editorials, letters, comments, or conferences proceedings; or if they did not meet the inclusion criteria described below. References of the retrieved articles were also screened for additional studies. Inclusion criteria were as follows: (1) randomized, controlled trials and nonrandomized trials; (2) cohort and observational studies; (3) sample size ≥7 subjects per study arm for intervention studies; (4) primary end points of body weight or ≥1 relevant cardiovascular risk parameters; (5) age between 18 and 75 years; (6) nonsmokers; and (7)

sedentary or moderately active individuals. Exclusion criteria included (1) trials that included dietary supplements, pharmacological substances, or exercise; (2) individuals with type 2 diabetes mellitus; and (3) very active individuals or athletes. This search was limited to clinical trials with human subjects reported in the English language.

BREAKFAST SKIPPING AND CARDIOMETABOLIC RISK: EPIDEMIOLOGICAL FINDINGS

It is commonly reported that "breakfast is the most important meal of the day."[9] However, ≈20% to 30% of US adults do not eat breakfast, and breakfast consumption has declined in recent decades.[10–14] Of all meals, the prevalences of breakfast and lunch consumption have seen the greatest decline over the past 40 years.[1] The decline in breakfast consumption has paralleled the increase in obesity prevalence, fostering studies of the association between breakfast consumption, cardiometabolic health risks, and chronic disease.[15–21] The definition of breakfast varies across studies.[9] However, 2 common definitions are the following: (1) the first meal of the day eaten before or at the start of daily activities within 2 hours of waking, typically no later than 10 AM, and consisting of a calorie level of 20% to 35% of total daily energy needs[18,20,22,23] and (2) the consumption of food or beverage (excluding water) between 5 and 9 AM.[12] Globally, adult population predictors of skipping breakfast have consistently included younger age, current tobacco use, late dinner, higher alcohol consumption, higher daily energy intake, and infrequent exercise.[13,20,24–34]

Breakfast Skipping and Diet Quality

There is an association between skipping breakfast and low nutritional adequacy of adult diets.[13,35] A cross-sectional survey of the Bogalusa Heart Study (n=504; 58% women; 70% white; mean age, 23 years [range, 19–28 years]) demonstrated that 74% of breakfast skippers did not meet two thirds of the Recommended Dietary Allowance for vitamins and minerals compared with 41% of those who consumed breakfast.[36] Using data from NHANES 1999 to 2002, investigators demonstrated that young adults (n=2615; age, 20–39 years) who reported skipping breakfast (defined as the absence of any food/beverage, excluding water) had greater TEI from added sugars, a lower mean adequacy ratio for nutrient intake, and a lower Healthy Eating Index.[37]

Breakfast Skipping and CVD Risk Factors: Obesity and Weight Gain

An abundance of data support an association between breakfast skipping and adiposity, which has led to rec-

ommendations to consume breakfast as a possible strategy to achieve a healthy body weight[38] and successful weight loss maintenance.[39] This association between breakfast skipping and higher body mass index (BMI) has been reported globally, primarily in cross-sectional studies.[33,40–51] For example, in NHANES 1999 to 2002, young adults (n=5316; age, 20–39 years) who reported consuming ready-to-eat cereal were 31% less likely to be overweight/obese and 39% less likely to have abdominal obesity compared with breakfast skippers.[52] Additionally, a meta-analysis of 19 studies in the Asian and Pacific regions (n=19 108 participants) demonstrated a pooled odds ratio (OR) of 1.75 (95% confidence interval [CI], 1.57–195) for prevalence of overweight or obesity among the lowest compared with the highest breakfast consumption frequency.[53]

The association between breakfast consumption and lower risk of obesity and weight gain is supported further by results from several large, long-term, prospective, observational studies. The prospective design minimizes the potential for reverse causation bias that hinders cross-sectional analyses. Among 6764 adults in the United Kingdom, a 1% increase in reported TEI at breakfast was associated with a relatively lower weight gain (–0.021 kg over an average of 3.7 years of follow-up). After adjustment for sociodemographic and dietary factors, the percentage of TEI consumed at breakfast was inversely associated with weight gain.[54] Among young adults (n=3598; baseline age, 18–30 years), daily breakfast eaters gained 1.91 kg less than infrequent breakfast consumers (<4 d/wk) over 18 years.[55] In men, breakfast consumers were less likely to gain ≥5 kg over 10 years, independently of lifestyle and BMI at baseline (hazard ratio [HR], 0.87; 95% CI, 0.82–0.93).[56] Interestingly, the inverse association between breakfast consumption and weight gain was greater in normal-weight men (adjusted HR, 0.78; 95% CI, 0.70–0.87) compared with overweight men (HR, 0.92; 95% CI, 0.85–1.00).[56]

Breakfast Skipping and Other CVD Risk Factors

In cross-sectional studies, daily breakfast eaters were less likely to have CVD risk factors, including elevated serum low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, and elevated blood pressure.[52,57] Conversely, among 415 healthy Korean adults, rare breakfast eaters (eating breakfast 1 of 3 days) were less likely to have elevated serum triglycerides (≥150 mg/dL).[35] Notably, in the Korean study, the percent of TEI from carbohydrates was lower and the percent from fat was higher in rare breakfast eaters, which may explain this observation.

Skipping breakfast has been associated with markers of impaired glucose metabolism, including elevated hemoglobin A_{1c},[44] higher fasting plasma glucose[58] and all-day postprandial hyperglycemia,[59,60] and a higher rate of impaired fasting glucose.[28] In contrast, HOMA-IR did not differ statistically between breakfast skippers and eaters.[57] Furthermore, breakfast skipping has been associated with a greater risk of clinically diagnosed diabetes mellitus, which is a cardiovascular risk equivalent, in 3 recent long-term, prospective studies. In a prospective study among men in the Health Professionals Follow-Up Study (n=29 205; age, 40–75 years at baseline), skipping breakfast (defined as not eating anything before lunch) was associated with a 21% higher risk of developing type 2 diabetes mellitus (relative risk, 1.21; 95% CI, 1.07–1.35) after adjustment for BMI, age, dietary quality, and other potential confounders.[61] Among women in the Nurses' Health Study (n=46 289; mean baseline age, 64.7 years), skipping breakfast even once per week was associated with a 28% higher risk of incident type 2 diabetes mellitus (HR, 1.28; 95% CI, 1.14–1.44) after adjustment for numerous confounders.[29] In a prospective analysis among 4631 middle-aged Japanese workers (age, 35–66 years at baseline), participants who skipped breakfast ≥2 d/wk had a 73% greater risk of diabetes mellitus (HR, 1.73; 95% CI, 1.24–2.42) compared with participants who consumed breakfast 6 or 7 d/wk over 8.9 years of follow-up after adjustment for confounders.[62] Finally, in a prospective analysis of young adults (n=3598; baseline age, 18–30 years), daily breakfast consumers had a multivariable-adjusted HR for diabetes mellitus of 0.66 (95% CI, 0.51–0.86) compared with infrequent breakfast eaters (0–3 d/wk) over 18 years of follow-up.[55] This association was mediated by BMI (HR, 0.81; 95% CI, 0.63–1.05). Furthermore, daily breakfast was not associated with a lower risk of diabetes mellitus among black women. The multivariable HR for diabetes mellitus comparing daily with infrequent breakfast consumption was 1.00 (95% CI, 0.66–1.50) in black women but 0.54 (95% CI, 0.39–0.75) in black men, white men, and white women. Additionally, in CARDIA (Coronary Artery Risk Development in Young Adults), daily breakfast eaters also had a lower risk of hypertension (HR, 0.74; 95% CI, 0.63–0.86) and metabolic syndrome (HR, 0.63; 95% CI, 0.54–0.75) compared with infrequent breakfast eaters (0–3 times a week), and these associations remained significant after adjustment for baseline measures of adiposity.[55] Thus, data from large, prospective studies, supported by data from cross-sectional studies, suggest that breakfast consumption may play an important role in the prevention of cardiometabolic outcomes.

Breakfast Skipping and CVD Risk

To the best of our knowledge, only 2 prospective studies have examined the association between breakfast skipping and risk of CVD.[62,63] Over 16 years of follow-up, men who reported usually skipping breakfast had a 27% (relative risk, 1.27; 95% CI, 1.06–1.53) higher risk of CHD (defined as a nonfatal myocardial infarction or fatal CHD)

compared with men who did not skip breakfast after adjustment for age, demographic factors, and dietary and lifestyle factors.[63] In the second study, conducted in Japan, infrequent breakfast consumption was associated with a greater risk of CVD, specifically greater risk of hemorrhagic stroke, after adjustment for age, sex, dietary and lifestyle factors, perceived mental stress, living alone, physical labor, and public health center area.[64] Individuals who consumed breakfast 0 to 2 times a week compared with those with daily breakfast eating had an HR of 1.14 (95% CI, 1.01–1.27) for total CVD, 1.18 (95% CI, 1.04–1.34) for total stroke, and 1.36 (95% CI, 1.10–1.70) for cerebral hemorrhage. In contrast, infrequent breakfast intake was not associated with greater risk of subarachnoid hemorrhage, cerebral infarction, or CHD in this population. Compared with the prevalence in Western countries, the prevalence of stroke, especially cerebral hemorrhage, is higher and the prevalence of CHD is lower in Japan, which may be attributable to differential CVD risk factor patterns between these countries.[65,66] The authors speculated that the low prevalence of CHD may explain the lack of association between breakfast skipping and CHD risk in Japan.[64]

Epidemiological studies provide strong evidence of a relation between breakfast skipping and cardiometabolic risk. These include greater risk of overweight and obesity, metabolic risk profile, diabetes mellitus, CVD, and hypertension. These risks seem to be independent of differences in diet quality between breakfast eaters and nonconsumers. Notably, it is possible that reverse causation is responsible in part for the findings in the cross-sectional analyses. Although findings from observational studies cannot establish causality, large, prospective studies with long-term follow-up and the assessment of clinical end points, including CVD and diabetes mellitus, can provide important insight into these associations. These are particularly meaningful when supported by evidence from experimental studies and clinical interventions.

BREAKFAST SKIPPING AND CARDIOMETABOLIC RISK: CLINICAL INTERVENTION FINDINGS

Few randomized, controlled trials have studied the impact of breakfast consumption on body weight. One of the pioneering studies in this field randomized breakfast eaters (≥4 times per week) and skippers to either maintaining their breakfast consumption patterns or switching to the alternative pattern while following a 1200-kcal/d diet for 12 weeks.[67] The breakfast skippers randomized to breakfast consumption lost 7.7 kg, whereas those maintained on a no-breakfast diet lost 6.0 kg. In comparison, breakfast consumers maintained on a breakfast-eating

weight loss diet lost 6.2 kg compared with 8.9 kg for those randomized to skip breakfast. It was therefore the change in breakfast eating habits, rather than breakfast consumption or skipping per se, that resulted in greater weight loss. However, behavioral data demonstrated that eating breakfast reduced overall dietary fat intake and minimized impulsive snacking, which are critical for successful weight reduction.[67] A subsequent clinical trial randomized >300 overweight and obese adults (age, 20–65 years) stratified by baseline breakfast habits to consume breakfast or to skip breakfast for 16 weeks.[68] No other dietary advice was provided. In contrast to the prior study, treatment assignment did not have a significant effect on weight. A 4-week trial randomized a total of 36 obese men and women to a higher-fiber breakfast (hot oat cereal), a nonfiber breakfast (frosted ready-to-eat cereal), or a no-breakfast arm.[69] The no-breakfast group had greater weight loss (−1.18 kg) compared with the breakfast groups; however, breakfast skippers had an increase in serum total cholesterol.[69] Another small, randomized, crossover trial of 10 normal-weight women also demonstrated that omitting breakfast for 2 weeks resulted in higher fasting total and LDL cholesterol.[70]

In an open-label trial, 93 overweight and obese women with metabolic syndrome (age, 30–57 years; BMI, 32.2±1.2 kg/m^2) were randomized to compare change in weight and metabolic outcomes on a high-calorie breakfast versus a high-calorie dinner.[71] Both groups consumed a 500-kcal lunch. However, the breakfast group consumed a 700-kcal breakfast and 200-kcal dinner. In contrast, the dinner group consumed a 200-kcal breakfast and 700-kcal dinner. After 12 weeks, although body weight, waist circumference, fasting glucose, and insulin were reduced in both groups, they were all significantly lower in the breakfast group. This suggests that a higher calorie intake during breakfast (earlier in the day) may influence weight and glucose metabolism. Additionally, despite weight loss in both groups, mean triglyceride levels decreased by 33% in the high-calorie breakfast group but increased by 14% in the dinner group, raising concerns about nocturnal postprandial lipid metabolism. However, despite the short trial duration, 17% of the breakfast group and 23% of the dinner group dropped out before completion.

Other studies suggest that the impact of breakfast skipping may differ by weight status. In obese participants randomized to consume at least 700 kcal before 11 AM (n=11) or to fast until noon (n=12), participants compensated for the lack of morning energy intake, and there was no impact of the intervention on body weight.[72] However, morning physical activity was reduced in the fasting group, and insulin sensitivity was reduced relative to the breakfast consumers. The lipid profile was unaffected by breakfast consumption patterns. This contrasts with an identical intervention study in which lean individuals did not compensate for the reduced morning caloric

intakes.[73] However, in that study also, body weight was unaffected by the intervention. Similar findings with respect to lipid profile and insulin sensitivity were reported. Despite the epidemiological association of breakfast skipping and higher BMI, the few clinical trial interventions have significant limitations and conflicting outcomes that prohibit evidence-based recommendations on daily breakfast consumption to promote weight loss solely.

In a small crossover study of individuals (n=26) with type 2 diabetes mellitus who regularly ate breakfast at baseline (age, 30–70 years; BMI, 22–35 kg/m^2; hemoglobin A_{1c}, 7%–9%), randomization to 2 days of consumption versus omitting breakfast suggested that skipping breakfast increases postprandial hyperglycemia after lunch and dinner in association with lower intact glucagon-like peptide-1 and impaired insulin response.[74] In clinical intervention studies, skipping breakfast has been associated with adverse metabolic and behavioral responses.[75,76] Adverse effects include higher blood glucose and serum insulin responses, higher plasma free fatty acids, and higher hunger and desire-to-eat ratings that likely result in a compensatory increase in energy intake later in the day.[75]

In summary, the limited evidence of breakfast consumption as an important factor in combined weight and cardiometabolic risk management is suggestive of a minimal impact. There is increasing evidence that advice related to breakfast consumption does not improve weight loss, likely because of compensatory behaviors during the day. On the other hand, breakfast consumption can contribute to a healthier eating pattern that leads to slight improvements in cardiometabolic risk profile. Additional, longer-term studies are needed in this field because most metabolic studies have been either single-day studies or of very short duration.

Summary

On the basis of the combined epidemiological and clinical intervention data, daily breakfast consumption among US adults may decrease the risk of adverse effects related to glucose and insulin metabolism. In addition, comprehensive dietary counseling that supports daily breakfast consumption may be helpful in promoting healthy dietary habits throughout the day.

INTERMITTENT FASTING, MEAL FREQUENCY, AND CARDIOMETABOLIC RISK: EPIDEMIOLOGICAL FINDINGS

Intermittent Fasting

Observational data on the long-term relationship between intermittent fasting and risk of cardiometabolic disease are limited. The Intermountain Heart Collaborative Study includes a large proportion of patients who identify themselves as having a Latter-Day Saint religious preference, in which routine fasting (1 time per month for 24 hours) is common.[77] A meta-analysis of 2 small studies within this cohort including patients from 2004 to 2006 (n=448) and from 2007 to 2008 (n=200) found that patients who fasted routinely had an OR of 0.65 (95% CI, 0.46–0.94) for coronary artery disease compared with individuals who did not fast routinely after adjustment for confounders. In the same study, the OR comparing routine fasting and nonfasting was 0.56 (95% CI, 0.36–0.88) for diabetes mellitus. However, these estimates were adjusted for age and sex only. Further studies are needed with larger sample sizes, adjustment for confounding by other lifestyle behaviors, and prospective data collection to determine the long-term relationship between routine fasting and disease outcomes. Furthermore, epidemiological studies involving participants with more frequent fasting days are needed.

Meal Frequency

Greater eating frequency has been associated with lower risk of obesity in several cross-sectional studies within free-living populations. In a cross-sectional analysis within the prospective SEASONS study (Seasonal Variation of Blood Cholesterol Study in Worcester County, Massachusetts; n=499; 50.3% men; mean age, 48 years), individuals who ate ≥4 times a day had a significantly lower risk of obesity (OR, 0.55; 95% CI, 0.33–0.91) compared with individuals who ate ≤3 times a day, after adjustment for age, sex, physical activity, and TEI.[48] In the Malmo Diet and Cancer study (n=1355 men, 1654 women; age, 47–68 years), meal frequency was associated with an increased risk of obesity in men but not women.[78] Compared with men who ate ≥6 times per day, men who ate ≤3 times a day were more likely to be obese (OR, 2.42; 95% CI, 1.02–5.73) and to have an increased waist circumference (≥102 cm; OR, 2.09; 95% CI, 1.03–4.27) after adjustment for TEI, lifestyle, and diet. However, the cross-sectional nature of these studies precludes us from establishing the causality or temporality of this association.

In a prospective analysis of adult men, increasing the number of eating occasions beyond 3 meals a day was associated with greater risk of gaining ≥5 kg over 10 years (HR, 1.15; 95% CI, 1.06–1.25 for ≥2 versus 0 additional eating occasions).[56] Additional prospective studies are needed to better understand the role of eating frequency on adiposity and long-term weight gain or loss.

In a large, cross-sectional study conducted within the Norfolk cohort of EPIC (European Prospective Investigation Into Cancer; n=14 666; age, 45–75 years), greater frequency of eating was associated with lower mean concentrations of total and LDL cholesterol.[79] Individuals who reported eating ≥6 times a day had mean

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total cholesterol levels that were ≈0.15 mmol/L lower than in individuals who ate 1 or 2 times a day, independently of TEI, age, BMI, smoking, physical activity, and nutrients. Eating frequency was not associated with HDL cholesterol.

Among men, infrequent meal frequency was associated with greater risk of type 2 diabetes mellitus over 16 years of follow-up.[61] Compared with men who ate 3 meals a day, men who ate 1 to 2 times a day had an HR for diabetes mellitus of 1.26 (95% CI, 1.09–1.46) after adjustment for age, lifestyle, diet, and other potential confounders. This risk was not altered after adjustment for BMI (HR, 1.25; 95% CI, 1.08–1.45). In contrast, more frequent eating (≥4 times a day) was not associated with risk of diabetes mellitus independently of BMI. In contrast, eating frequency was not associated with risk of diabetes mellitus among women in the Nurses' Health Study over 6 years of follow-up.[29] Compared with women who ate 3 times a day, the HRs for diabetes mellitus were 1.09 (95% CI, 0.84–1.41) for women who ate 1 to 2 times a day, 1.13 (95% CI, 1.00–1.27) for women who ate 4 to 5 times a day, and 0.99 (95% CI, 0.81–1.21) for women who ate ≥6 times a day.

To the best of our knowledge, there has been only 1 prospective, cohort study that quantified the association between eating frequency and risk of CHD.[63] Compared with men who ate 3 times a day, the HRs for CHD were 1.10 (95% CI, 0.92–1.32) for men who ate 1 to 2 times a day, 1.05 (95% CI, 0.94–1.18) for men who ate 4 to 5 times a day, and 1.26 (95% CI, 0.90–1.77) for men who ate ≥6 times a day after adjustment for TEI, diet quality, lifestyle, and other CVD risk factors.

Epidemiological studies of eating frequency lead to different conclusions, depending on the outcome of interest. The relation between eating frequency and obesity is mixed but seems to be more consistent with respect to CVD risk factors and diabetes mellitus. In those cases, greater eating frequency seems to be related to improved risk status.

INTERMITTENT FASTING, MEAL FREQUENCY, AND CARDIOMETABOLIC RISK: CLINICAL INTERVENTION FINDINGS

Intermittent Fasting

Intermittent-fasting diets have increased in popularity over the past decade, particularly with respect to clinical intervention studies. The 2 most common forms of intermittent fasting include alternate-day fasting and periodic fasting. Alternate-day fasting involves a "fast day," when individuals consume ≤25% of baseline energy needs during a 24-hour period, alternated with a "feast day," when ad libitum food consumption is permitted for 24 hours. Periodic fasting, on the other hand, requires participants

to fast only 1 or 2 d/wk and allows 5 to 6 days of ad libitum food consumption per week.

Changes in body weight by alternate-day fasting and periodic-fasting regimens are displayed in Table 1. Body weight decreased significantly in all studies by 3% to 8% after 3 to 24 weeks of treatment.[80–89] Studies that provided food on the fast day produced the greatest weight loss. For instance, overweight participants lost 8% of their body weight over an 8-week period when provided with a 320- to 380-kcal meal replacement shake on each fast day during an alternate-day fasting protocol.[82] Similar decreases in body weight (4%–7%) were demonstrated in the other 8-week alternate-day fasting studies that provided food on the fast day.[83–88] The frequency of weekly fast days also appears to affect the degree of weight loss. Not surprisingly, participants lost weight faster in the alternate-day fasting studies that required 3 to 4 days of fasting a week compared with periodic-fasting studies, which require participants to fast only 1 to 2 d/wk. On average, alternate-day fasting produces a 0.75-kg/wk reduction in body weight,[80–87] whereas periodic fasting produces a 0.25-kg/wk reduction in body weight.[88,89]

The impact of intermittent fasting on total and LDL cholesterol concentrations is variable (Table 1). Although some trials report reductions in total cholesterol ranging from 6% to 21% and LDL cholesterol ranging from 7% to 32%,[82–84,87–89] others report no effect.[81,85,86] The variation between studies cannot be clearly explained because the extent of weight loss is similar between studies.[81–89] On closer examination, however, it is possible that baseline cholesterol levels may play a role. Significant reductions in these lipid risk factors have been observed only in studies in which participants had mildly elevated cholesterol (ie, LDL cholesterol >110 mg/dL).[82–84,87–89] HDL cholesterol concentrations remained unchanged in most of the studies reviewed here (Table 1).

Triglyceride concentrations decreased in the majority of intermittent-fasting studies, with reductions ranging from 16% to 42% (Table 1). The greatest decreases in triglycerides were generally observed in studies with the greatest weight loss. For instance, in studies that achieved 1-kg/wk weight loss, triglycerides decreased by ≈30% to 40%,[82,83] whereas in the studies that achieved 0.25- to 0.5-kg/wk weight loss,[84,87–89] triglycerides decreased by ≈10% to 20%. Thus, both alternate-day fasting and periodic-fasting regimens appear to be effective in lowering triglyceride levels, but the effect is dependent on the amount of weight lost.

Systolic and diastolic blood pressures decreased only in the intermittent-fasting studies that achieved 6% to 7% weight loss.[81,83,87,89] In these trials, systolic blood pressure reductions ranged from 3% to 8% and diastolic blood pressure reductions ranged from 6% to 10% after 6 to 24 weeks of treatment.[81,83,87,89] Participants in these studies[81,83,87,89] all had borderline prehypertension,

Table 1. Intermittent Fasting: Effect on CHD Risk Parameters

Reference	Duration, wk	Subjects	Intervention	Weight, % Change	CHD Risk Parameters, % Change								
					TC	LDL	HDL	TG	SBP	DBP	Glucose	Insulin	HOMA-IR
Alternate-day fasting (fasting 3–4 d/wk)													
Heilbronn et al,[80] 2005	3	n=16, M and F; Age, 23–53 y; Overweight; Race/ethnicity: NR	Fast day: 0% intake; Feed day: ad libitum intake; Food not provided	↓3*	...	...	↑VNR in women only*	↓VNR*	...	...	↓1	↓57*	...
Eshghinia and Mohammadzadeh,[81] 2013	6	n=15, F; Age, 34±6 y; Obese; Race/ethnicity: NR	Fast day: 30% intake; Feed day: ad libitum intake; Food not provided	↓7*	↓6	↓12	↑19	↓11	↓8*	↓10*	↓6	...	...
Johnson et al,[82] 2007	8	n=10, M and F; Age: NR; Obese; Race/ethnicity: NR	Fast day: 20% intake; Feed day: ad libitum intake; Food provided on fast day	↓8*	↓9*	↓10	↑4	↓42*	...	...	↑6	↓37*	↓33*
Varady et al,[83] 2009	8	n=16, M and F; Age, 46±2 y; Obese; Prediabetic; Race/ethnicity: 6–H; 8–B; 2–W	Fast day: 25% intake; Feed day: ad libitum intake; Food provided on fast day	↓6*	↓21*	↓32*	↑9	↓35*	↓6*	↓6*	↓4*	↓20*	↓19*
Klempel et al,[84] 2012	8	n=32, F; Age, 42±2 y; Obese; Race/ethnicity: 8–H; 24–B; 0–W	Fast day: 25% intake, high fat; Feed day: ad libitum intake, high fat; Fast day: 25% intake, low fat; Feed day: ad libitum intake, low fat; Food provided all days in all groups	↓5*; ↓4*	↓13*; ↓16*	↓18*; ↓25*	↓1; ↑5	↓14*; ↓24*	↓2; ↓2	↓3; ↑3	↓2; ↓2	...;	...;

(Continued)

Table 1. Continued

Reference	Duration, wk	Subjects	Intervention	Weight, % Change	CHD Risk Parameters, % Change								
					TC	LDL	HDL	TG	SBP	DBP	Glucose	Insulin	HOMA-IR
Alternate-day fasting (fasting 3–4 d/wk) Continued													
Hoddy et al,[85] 2014	8	n=74, M and F Age, 45±3 y Obese Race/ethnicity: NR	Fast day: 25% intake as lunch	↓4*	↓1	↑1	↓4	↓6	↓2	↑1	↓2	0	↓10
			Feed day: ad libitum intake	↓4*	↓3	0	0	↓8	↓4	↓4	↑1	↓18	↓26
			Fast day: 25% intake as dinner	↓4*	0	0	↓2	↓1	↑5*	↑1	↑1	↓12	↓19
			Feed day: ad libitum intake										
			Fast day: 25% intake as small meals										
			Feed day: ad libitum intake										
			Food provided on fast day in all groups										
Bhutani et al,[86] 2013	12	n=32, M and F Age, 43±3 y Obese Race/ethnicity: 18–H 41–B 21–W 3–Other	Fast day: 25% intake	↓4*	↑7	↓1	0	↑3	↓3*	↓2	↓3	↓11†	↓9†
			Feed day: ad libitum intake	0	↑1	↑3	↑8	↑5	↓2	↓2	↑2	↑1	↑2
			Food provided on fast day										
			Control: ad libitum fed every day										
			Food not provided										
Varady et al,[87] 2013	12	n=32, M and F Age, 47±4 y Normal weight and overweight Prediabetic Race/ethnicity: 3–H 13–B 14–W	Fast day: 25% intake	↓7*	↓13*	↓16*	↓4	↓2*	↓6*	↓6*	↓8*	↓31†	↓28†
			Feed day: ad libitum intake	↓1	↓4	↓7	↑2	↑9	↑1	↑1	↑2	↑2	↑2
			Food provided on fast day										
			Control: ad libitum fed every day										
			Food not provided										

(Continued)

Table 1. Continued

Reference	Duration, wk	Subjects	Intervention	Weight, % Change	CHD Risk Parameters, % Change								
					TC	LDL	HDL	TG	SBP	DBP	Glucose	Insulin	HOMA-IR
Periodic fasting (fasting 1–2 d/wk)													
Klempel et al,[88] 2012	8	n=54, F Age, 48±2 y Obese Prediabetic Race/ethnicity‡: 9–H 34–B 6–W 5–A	1 d/wk: 0% intake 6 d/wk: 70% intake, liquid diet Food provided 1 d/wk: 0% intake 6 d/wk: 70% intake, food diet Food not provided	↓4* ↓3*	↓19* ↓8*	↓20* ↓7*	↓5 ↓2	↓17* ↓3	↓2 ↓5	↓5 0	↓3* ↓2	↓21* ↓13	↓23* ↓12
Harvie et al,[89] 2011	24	n=53, F Age, 30–45 y Overweight and obese Race/ethnicity: 2–B 103–W 2–Other	2 d/wk: 25% intake 5 d/wk: ad libitum intake Food not provided	↓7*	↓6*	↓10*	0	↓16*	↓3*	↓6*	↓2	↓29*	↓27*

A indicates Asian; B, black, African American, or Afro-Caribbean; CHD, coronary heart disease; DBP, diastolic blood pressure; F, female; H, Hispanic; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein cholesterol; M, male; NR, not reported; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; VNR, value not reported; and W, white.

*Posttreatment value significantly different from baseline value (P<0.05).

†Significantly different from control group (P<0.05).

‡Reflects 30 of 32 completing the study and included in the analyses.

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suggesting that these diets may prevent the progression of prehypertension to hypertension. Longer-term and larger-scale trials are needed to confirm this interesting preliminary finding.

Intermittent fasting appears to have no effect on fasting glucose concentrations in healthy individuals (Table 1). On the other hand, the diet seems to have a minor beneficial effect in those with prediabetes, with decreases in fasting glucose ranging from 3% to 6%.[83,87,88] The greatest decrease in fasting glucose was observed in individuals with prediabetes randomized to an alternate-day fasting group versus a no-intervention control group.[87] After 12 weeks, fasting glucose was reduced by 6% in the alternate-day fasting group relative to the control group.[87] Reductions in glucose (3%–4%) in patients with prediabetes were also demonstrated in 2 other 8-week studies of alternate-day fasting[83] and periodic fasting.[88]

In contrast to the variable findings for glucose, fasting insulin decreased in all but 1 study (Table 1). Decreases in fasting insulin ranged from 11% to 57% after 3 to 24 weeks of following the intermittent-fasting dietary pattern.[80,82,83,85–89] These reductions in insulin were not dependent on the prediabetes status of participants but rather appeared to be most strongly related to the degree of imposed energy restriction yet were somewhat independent of weight loss. Trials with the largest decrease in insulin had an average daily restriction of 40% to 50% of baseline energy needs.[80,82] For instance, in 1 study,[80] participants underwent 50% average daily restriction via complete fasting on fast days, alternating with ad libitum intake on the day of feeding. Although weight was reduced by only 3% from baseline, a 57% decrease in fasting insulin was observed.[80] Likewise, in a study in which participants underwent 40% average daily restriction,[82] a 37% reduction in fasting insulin levels was observed. In a comparison of periodic fasting and alternate-day fasting, it would appear that both dietary patterns produce sizeable reductions in insulin concentrations. Improvements in this CVD risk parameter may be observed with fasting 1 to 2 d/wk, as with periodic fasting, or fasting 3 to 4 d/wk, as with alternate-day fasting.

Intermittent-fasting protocols produce fairly consistent reductions in IR after 8 to 24 weeks of treatment (Table 1). In all studies, changes in IR were quantified by the HOMA-IR method.[82,83,86–89] The most pronounced decreases in IR occurred with the greatest weight loss. For example, in 1 alternate-day fasting study,[82] participants lost 8% of body weight, and this corresponded to the largest decline in HOMA-IR (33%). In another alternate-day fasting study in which the reduction in body weight was half as large (4%),[86] moderate reductions in HOMA-IR (9%) were observed. Notable reductions in IR were also demonstrated by periodic-fasting protocols. For example, HOMA-IR decreased by 23% after 8 weeks of fasting 1 d/wk.[88] Likewise, a 27% reduction in HOMA-IR

was demonstrated with 24 weeks of fasting on 2 d/wk.[89] Together, these studies show that intermittent-fasting protocols that produce at least 4% weight loss may be helpful in decreasing IR in obese patients. Whether these findings can be reproduced when more robust measures of insulin sensitivity, that is, the hyperinsulinemic-euglycemic clamp, are implemented warrants investigation.

Summary

There is evidence that both alternate-day fasting and periodic fasting may be effective for weight loss, although there are no data that indicate whether the weight loss can be sustained long term. In addition, both eating patterns may be useful for lowering triglyceride concentrations but have little or no effect on total, LDL, or HDL cholesterol concentrations. These protocols may also be beneficial for lowering blood pressure, but a minimum weight loss of 6% may be required to see an effect. Intermittent fasting may also be effective for decreasing fasting insulin and IR, but fasting glucose remains largely unchanged. Future work in this area should aim to examine whether these effects still persist in longer-term (>52 weeks) randomized, controlled trials.

Meal Frequency

To date, 9 trials[90–98] have been performed that examined the impact of meal frequency without calorie restriction on CHD risk. These trials implemented the following meal frequency regimens: 1, 3, 6, 9, 12, and 17 meals a day. The effects of these diets on key cardiometabolic risk factors are displayed in Table 2.

Because calorie restriction was not imposed in any of the trials reviewed,[90–98] body weight remained unchanged for all studies (Table 2). We intentionally chose not to include meal frequency studies that also applied calorie restriction because the effect of meal frequency on weight status would be difficult to isolate from that of weight loss. One study assessed the impact of meal frequency on energy expenditure in overweight women in a metabolic chamber.[99] Eight to 10 women participated in 3 separate studies testing consumption of 2 meals served at 11 AM and 7 PM or 6 meals served every 2 hours between 9 AM and 7 PM. In 1 study, additional foods could be consumed outside of those times, and in the third study, the 6-meal pattern was compared with 4 meals served at 1, 2, 5, and 7 PM. The third study also allowed additional food intake. No differences were observed between meal patterns in any of the 3 studies on total energy expenditure or energy balance. However, nighttime energy expenditure was higher in the first study when participants were given 2 meals compared with 6 meals. Nevertheless, these studies do not suggest a role of meal frequency on energy metabolism.

One study examined the effects of low versus high eating frequency on appetite (n=12 men and women;

Table 2.   Meal Frequency Regimens Without Calorie Restriction: Effect on CHD Risk Parameters

Reference	Duration, wk	Subjects	Intervention Baseline	Intervention Treatment	Weight, % Change	TC	LDL	HDL	TG	DBP	SBP	Glucose	Insulin	HOMA-IR
1 Meal per day														
Stote et al,[90] 2007	8	n=15, M and F Age, 45±1 y Normal weight Race/ethnicity: NR	Not stated	15% Pro 35% Fat 50% Carb Food provided	↓1	↑19*	↑25*	↑17*	↓4	↑1*	↑1*	...	...	...
3 Meals per day														
McGrath and Gibney,[91] 1994	Not stated	n=12, M Age: not stated Normal weight Race/ethnicity: NR	13% Pro 39% Fat 48% Carb	14% Pro 41% Fat 45% Carb Food not provided	0	↑1	↑3	0	↓19	...	...	...	...	...
Jenkins et al,[92] 1989	2	n=7, M Age, 31–51 y BMI: not stated Race/ethnicity: NR	Not stated	15% Pro 33% Fat 52% Carb Food provided	↓1	↓4	↑2	↓4	↓39	...	...	No Δ VNR	...	...
Murphy et al,[93] 1996	2	n=11, F Age, 22±1 y BMI: not stated Race/ethnicity: NR	Not stated	20% Pro 40% Fat 40% Carb Food not provided	0	↑3	0	↑7*	↓2	...	...	...	...	...
Arnold et al,[94] 1993	2	n=19, M and F Age, 32±2 y Normal weight Race/ethnicity: NR	15% Pro 28% Fat 57% Carb	15% Pro 28% Fat 57% Carb Food not provided	0	↓4	↓7	↑1	↑3	No Δ VNR	No Δ VNR	No Δ VNR	No Δ VNR	...
Arnold et al,[95] 1994	4	n=16, M and F Age, 50±2 y BMI: Not stated Race/ethnicity: NR	Not stated	17% Pro 35% Fat 48% Carb Food not provided	0	↓1	↑4*	↑1	↓23	No Δ VNR	No Δ VNR	No Δ VNR	No Δ VNR	...

(Continued)

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Table 2. Continued

Reference	Duration, wk	Subjects	Intervention Baseline	Intervention Treatment	Weight, % Change	TC	LDL	HDL	TG	DBP	SBP	Glucose	Insulin	HOMA-IR
3 Meals per day Continued														
Arciero et al,[96] 2013	4	n=10, M and F Age, 46±2 y Overweight Race/ethnicity: NR	Not stated	35% Pro 21% Fat 44% Carb Food not provided	↓1	...	...	...	...	...	...	No Δ VNR	No Δ VNR	No Δ VNR
Stote et al,[90] 2007	8	n=15, M and F Age, 45±1 y Normal weight Race/ethnicity: NR	Not stated	15% Pro 35% Fat 50% Carb Food provided	↑1	↑1*	↑4	↑6	↓4	↓3*	↓5*	...	...	...
6 Meals per day														
Farshchi et al,[97] 2004	2	n=9, F Age, 18–42 y Normal weight Race/ethnicity: NR	18% Pro 35% Fat 47% Carb	14% Pro 40% Fat 46% Carb Food not provided	↓1	↓1*	↓8*	↑8	↑5	—	—	↓6%	↓11%	↓11%
Farshchi et al,[98] 2005	2	n=10, F Age, 32–47 y Obese Race/ethnicity: NR	17% Pro 38% Fat 45% Carb	17% Pro 38% Fat 45% Carb Food not provided	0	↓3*	↓6*	↑1	↓4	...	...	No Δ VNR	No Δ VNR	...
Arciero et al,[96] 2013	4	n=10, M and F Age, 46±2 y Overweight Race/ethnicity: NR	Not stated	35% Pro 21% Fat 44% Carb Food not provided	↓1	...	...	...	...	...	...	No Δ VNR	No Δ VNR	No Δ VNR
McGrath and Gibney,[91] 1994	Not stated	n=11, M Age: not stated Normal weight Race/ethnicity: NR	13% Pro 39% Fat 48% Carb	14% Pro 41% Fat 45% Carb Food not provided	0	↓8*	↓12	↑1	↓15	...	...	...	...	...

CHD Risk Parameters, % Change

(Continued)

Table 2. Continued

Reference	Duration, wk	Subjects	Intervention Baseline	Intervention Treatment	Weight, % Change	TC	LDL	HDL	TG	DBP	SBP	Glucose	Insulin	HOMA-IR
9 Meals per day														
Arnold et al,[94] 1993	2	n=19, M and F Normal weight Race/ethnicity: NR	15% Pro 28% Fat 57% Carb	15% Pro 28% Fat 57% Carb Food not provided	0	↓10*	↓14*	↓3*	↑1	No Δ VNR	No Δ VNR	No Δ VNR	No Δ VNR	...
Arnold et al,[95] 1994	4	n=16, M and F BMI: not stated Race/ethnicity: NR	Not stated	17% Pro 35% Fat 48% Carb Food not provided	0	0	↑6	↓1	↓21	No Δ VNR	No Δ VNR	No Δ VNR	No Δ VNR	...
12 Meals per day														
Murphy et al,[93] 1996	2	n=11, F BMI: not stated Race/ethnicity: NR	Not stated	20% Pro 40% Fat 40% Carb Food provided	0	↓3	↓1	↓2	↑3	...	...	No Δ VNR	No Δ VNR	...
17 Meals per day														
Jenkins et al,[92] 1989	2	n=7, M 31–51 y BMI: not stated Race/ethnicity: NR	Not stated	15% Pro 33% Fat 52% Carb Food provided	↓1	↓16*	↓18*	↓2	↓26	...	...	No Δ VNR	...	...

BMI indicates body mass index; Carb, percent energy from carbohydrates; CHD, coronary heart disease; DBP, diastolic blood pressure; F, female; Fat, percent energy from fat; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein cholesterol; M, male; NR, not reported; Pro, percent energy from protein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; and VNR, value not reported.

*Posttreatment value significantly different from baseline value ($P<0.05$).

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age, 18–50 years; BMI ≥18 kg/m²).[100] Participants consumed 3 or 8 equally spaced meals daily for 21 days in a randomized, crossover design. Body weight and waist-to-hip ratio did not change during the study. After the 21-day period, appetite was assessed over a 4-hour window. In the low eating frequency condition, 1 meal was served, whereas in the high eating frequency condition, 2 meals were served. In each condition, participants consumed 33% of their energy requirements over the testing period. Mean hunger ratings were significantly lower in the low compared with the high eating frequency condition, but the area under the curve for the entire testing session did not differ between conditions. The mean and area under the curve over the entire session for desire-to-eat ratings were lower in the low eating frequency condition compared with the high eating frequency condition. The mean composite score for appetite and the area under the curve for the entire testing period were higher in the high eating frequency condition compared with the low eating frequency condition. This small study does not support the conclusion that increasing eating frequency reduces appetite.

The effects of various meal frequency strategies on total and LDL cholesterol are reported in Table 2. The greatest reductions in total cholesterol (16%) and LDL cholesterol (18%) concentrations were observed when normocholesterolemic men consumed 17 meals a day for 2 weeks.[92] Consuming 9 meals a day reduced total and LDL cholesterol by 10% and 14%,[94] respectively; consuming 6 meals a day lowered total cholesterol by 1% to 8% and LDL cholesterol by 6% to 8%[91,97,98]; and consuming 3 meals a day resulted in little or no change.[90–96] Interestingly, in a controlled feeding study,[90] participants who ate all of their daily energy needs in 1 sitting had increases in total and LDL cholesterol levels of 19% and 25%, respectively, after 8 weeks. Taken together, these findings indicate that increasing meal frequency may reduce cholesterol levels, whereas decreasing meal frequency may have unfavorable effects. However, it is important to note that macronutrient distribution did not change from baseline to after treatment in any of the studies reviewed here.[90–98] Average dietary fat intake ranged from 30% to 40% of daily energy needs, and in most studies, participants were consuming at least 35% of energy as fat and at least 10% of energy from saturated fat.[70,90,91,93,95,97,98] We also observed that diets providing >35% of energy as fat may negate the improvements observed as a result of increased meal frequency. For example, in a study providing 9 meals a day in the context of a low-fat diet (28% of energy as fat),[94] total and LDL cholesterol concentrations were reduced by 10% and 14%, respectively. In contrast, when the background diet provided 35% of energy as fat,[95] there was no effect of increasing meal frequency to 9 meals a day. Thus, the increased meal frequency pattern may be more effective at lowering total and LDL choles-

terol when combined with lower-fat diets (<30% energy as fat). The reason for this is not apparent.

The impact of meal frequency on HDL cholesterol concentrations has also been assessed (Table 2). In a randomized, crossover trial,[90] HDL cholesterol was augmented by 17% from baseline when participants ate all of their energy needs as 1 meal a day for 8 weeks but remained unchanged when 3 meals a day were consumed. These modulations in HDL cholesterol appear to be independent of dietary macronutrient composition because dietary cholesterol and fatty acid intakes were held constant. Increasing meal frequency to 6, 9, 12, or 17 meals a day did not affect HDL cholesterol concentrations.[91–98] These findings suggest that increasing meal frequency under isocaloric conditions has little effect on HDL cholesterol levels. The reason why increases in HDL cholesterol were observed with a reduction in meal frequency to 1 meal a day remains unclear.[90] Additional studies are needed to confirm this observation.

Studies suggest that altering meal frequency has no significant impact on triglyceride concentrations (Table 2).[90–98] Although several studies report large numeric reductions in triglyceride levels,[91,92,94,95] none of these reductions were significantly different when posttreatment values were compared with baseline values. This lack of a significant difference in triglyceride concentrations is most likely attributable to the large variability in subject responses reported in each trial.[91,92,94,95] Moreover, it is worth noting that these studies have not compared the effects of the intervention relative to the control but rather performed within-group comparison.

Only 1 study reported a significant impact of meal frequency on blood pressure (Table 2).[90] Results indicate that consuming 1 meal a day increases both systolic and diastolic blood pressures (1% increase from baseline) after 8 weeks of treatment. When these same individuals crossed over to a regimen of 3 meals a day, systolic and diastolic blood pressures decreased by 6% and 4%, respectively.[90] In other studies that examined the impact of 3 or 9 meals a day on blood pressure,[94,95] no change was noted after 2 to 4 weeks of treatment. Whether blood pressure would be affected with longer treatment duration remains uncertain.

Fasting glucose and insulin concentrations were examined in the majority of studies reviewed here (Table 2). Results from these small, uncontrolled, short-term trials indicate that consuming a few meals per day (ie, 1 or 3 meals a day)[90–96] or several meals per day (ie, 6, 9, 12, or 17 meals a day)[91–98] has no effect on either fasting glucose or insulin in the absence of weight loss.

Preliminary studies suggest that consuming 3 or 6 meals a day under isocaloric conditions for 2 to 4 weeks has no effect on IR.[96,97] These results are not surprising because glucose and insulin did not change during these trials.

These findings should be interpreted with caution, however, because each of these trials has several limitations. First, all of these trials lacked a control group, and very few studies implemented a controlled feeding protocol.[70,90–98] Second, sample sizes of the various study arms were quite small (n=7–19),[90,92] and the studies may have lacked power to detect significant differences within or between groups. In view of these limitations, larger-scale and longer-term controlled trials will be required before any definitive conclusions can be reached on the impact of meal frequency on these cardiometabolic risk parameters. Further insight into the effects of meal frequency on the long-term risk of clinical events such as CVD or diabetes mellitus may be gained through observational studies in free-living individuals. Moreover, the impact of meal frequency on TEI should be examined because increasing meal frequency may lead to undesirable increases in intakes that could lead to weight gain.

Summary

Altering meal frequency under isocaloric conditions may not be useful for decreasing body weight or improving traditional cardiometabolic risk factors.

MEAL TIMING AND CARDIOMETABOLIC RISK: OBSERVATIONAL FINDINGS

Late-night eating has been associated with a greater risk of poor cardiometabolic health in several cross-sectional studies. Late-night eating was associated with an OR for obesity of 1.62 (95% CI, 1.10–2.39) compared with no late-night eating among 3610 Swedish men and women.[50] In a small, cross-sectional study among 239 US adults, individuals who consumed ≥33% of their TEI in the evening had twice the risk of being obese (OR, 2.00; 95% CI, 1.03–3.89) compared with individuals who consumed <33% of their TEI at night.[101] Additionally, the combination of late-night eating and skipping breakfast was associated with a greater risk of having the metabolic syndrome among Japanese adults (n=60 800; age, 20–75 years).[102] Compared with individuals with healthy eating patterns, those who ate late at night, defined as eating dinner within 2 hours of bedtime, and skipped breakfast had an OR for the metabolic syndrome of 1.17 (95% CI, 1.08–1.28). The associations of eating frequency and timing with inflammation and IR biomarkers were assessed in female participants in NHANES 2009 to 2010 (n=2212; mean age, 46.8 years).[103] Independent variables included eating frequency (number of eating occasions per day), percent of TEI eaten between 5 PM and midnight, and nighttime fasting duration. Each 10% increase in the proportion of TEI consumed in the evening was associated with a 3% increase in C-reactive protein concentrations, whereas having 1 additional eating occasion per day was associated with an 8% decrease in C-reactive protein. There was no relation with nighttime fasting duration. None of the variables were associated with HOMA-IR. Interestingly, favorable effects of nighttime fasting on inflammation and IR were observed only in women who stopped eating before 6 PM, and lengthening nighttime fast duration by skipping breakfast did not have the same favorable effect. An important limitation to consider with these studies is that the definition of late-night eating differs among studies. Furthermore, the causality of these associations between eating patterns and CVD risk factors is unclear because of the cross-sectional nature of the studies.

To date, only 1 prospective, observational, epidemiological study has reported the association between late-night eating and risk of CHD.[63] In the Health Professional Follow-Up Study, men were asked to respond to the following question on a biennial questionnaire: "Please indicate the time of day that you usually eat (mark all that apply): before breakfast, breakfast, between breakfast and lunch, lunch, between lunch and dinner, dinner, between dinner and bedtime, after going to bed." Nighttime eating was defined as a positive response to eating after going to bed. Men with nighttime eating had a relative risk of CVD of 1.55 (95% CI, 1.05–2.29) compared with men who did not eat during the night after adjustment for demographic data, diet, lifestyle, and CHD risk factors. This association was mediated by BMI, hypercholesterolemia, hypertension, and diabetes mellitus. However, this eating behavior may be considered pathological and does not represent the more common late-night eating pattern of food consumption before bedtime. In this population, only 1% of the men reported late-night eating (n=29 cases).

MEAL TIMING AND CARDIOMETABOLIC RISK: CLINICAL INTERVENTION FINDINGS

Very few interventions have focused on meal timing and cardiometabolic risk, and most have been single-day studies with few participants. For example, 1 study tested the impact of a late dinner, given at 11 PM, relative to 6 PM dinner on glucose handling after breakfast the following day.[104] On the day before testing, standard meals were served at 7 AM, noon, and 6 or 11 PM. Breakfast on test day was served at 8:30 AM. Orocecal transit time was longer after breakfast consumption after a late dinner, and unabsorbed dietary carbohydrates were lower compared with the usual dinnertime. In addition, in these 12 young, healthy, normal-weight women, glucose was higher after breakfast in the late dinner condition compared with the usual dinner condition. The authors concluded that eating a late dinner could increase the risk of type 2 diabetes mellitus because high postprandial glucose is a risk factor for this disorder. Conversely, a high-energy breakfast was also tested in women with polycystic ovary syndrome over a 12-week period.[105]

Young, normal-weight women were randomized to consume an 1800-kcal diet with energy distribution among meals being either 54%, 35%, and 11% or 11%, 35%, and 54% TEI distribution at breakfast, lunch, and dinner, respectively. Women were instructed to consume breakfast between 6 and 9 AM, lunch between noon and 3 PM, and dinner between 6 and 9 PM. Compliance was assessed from biweekly 3-day diet records. There was no difference in change in BMI, waist circumference, and adiposity between groups. However, metabolic risk factors changed differently between groups. Women in the group who ate a large breakfast had reductions in fasting plasma glucose and insulin, along with a decrease in HOMA-IR and an increase in the insulin sensitivity index. There was no change in those parameters in women in the group who ate a large dinner. Oral glucose tolerance test glucose and insulin areas under the curve were also reduced in the breakfast group to a greater extent than in the dinner group. The authors concluded that the improvement in IR in the group consuming a large breakfast implies an eating schedule that is synchronized with the circadian pacemaker but that consuming a larger dinner does not worsen IR in these women.

This beneficial effect of a larger breakfast on the cardiometabolic risk profile is not universally observed, however. During Ramadan fasting, individuals eat breakfast 30 minutes before sunrise and eat dinner after sunset. Adult men with the metabolic syndrome were studied during this month, in which 58% of their TEI was consumed in the evening.[106] Self-reported TEI was reduced by ≈56 kcal/d, and body weight and waist circumference decreased by 2.4% during the month of Ramadan. Fasting plasma glucose and systolic and diastolic blood pressures decreased, and HDL cholesterol and insulin sensitivity increased, but fasting plasma insulin, triglycerides, and HOMA-IR did not change. The authors concluded that Ramadan fasting can improve some metabolic risk factors, but several limitations in this study are worth noting. There was no control group, and data were not adjusted for change in body weight or waist circumference. Moreover, discordant results were observed on 2 measures of IR. Therefore, a definitive conclusion cannot be drawn.

Other studies have focused on the amount and type of carbohydrates and cardiometabolic risk factors.[107,108] In a small study (n=6) of young, normal-weight adults, diets with low (34) versus high (84) glycemic index provided either mostly in the morning (60%, 20%, and 20% TEI at breakfast, lunch, and dinner, respectively) or in the evening (20%, 20%, and 60% TEI at breakfast, lunch, and dinner, respectively) were compared for their short-term effects on glycemia with a 2×2 factorial design.[107] Meals were served at 9:30 AM, 1:30 PM, and 8:30 PM, and blood samples were collected before and for 2 hours after each meal. Glucose and insulin areas under the curve were highest for the diet with a high glycemic index with the greater percent of energy provided in the evening. This was significant compared with all other diets for glucose and relative to the diets with low glycemic index for insulin. Triglycerides and nonesterified fatty acids were not affected by the glycemic index of the diets or the shift in caloric load between morning and evening. The authors suggested that eating patterns with the largest energy load in the evening may contribute to metabolic syndrome through deterioration of postprandial glucose and insulin and that avoiding large meals with a high glycemic index in the evening could improve glycemic profile.

One longer-term study tested whether changing both the carbohydrate content and the energy content of meals affected weight loss and weight loss maintenance in obese adult men and women.[108] Participants were instructed to follow a low-calorie diet with either a low- or high-carbohydrate (10% versus 20% of TEI, respectively) and –energy content breakfast for 16 weeks; follow-up continued after intervention for an additional 16 weeks. The low-carbohydrate, low-energy breakfast diet provided 300 kcal at breakfast and 600 to 700 kcal at dinner, whereas the high-carbohydrate, high-energy breakfast diet provided 600 kcal at breakfast and 300 to 400 kcal at dinner. The higher energy content of breakfast was achieved by including dessert for the high-carbohydrate group (chocolate, ice cream, cookies, cake, etc). During follow-up, participants were encouraged to continue their intervention dietary pattern. Weight loss was similar between groups during the intervention phase, but the high-carbohydrate group continued to lose weight during follow-up, whereas the low-carbohydrate group gained weight. This resulted in significantly different body weights between groups at the end of the follow-up period. Similar results were observed for glucose, insulin, and HOMA-IR. After the intervention, triglycerides were significantly lower and HDL cholesterol was significantly higher in the high-carbohydrate group. After follow-up, those differences remained, and total cholesterol and LDL cholesterol were also reduced in the high-carbohydrate compared with the low-carbohydrate group. In line with the greater weight loss observed in the high-carbohydrate group, craving scores were lower and the ghrelin nadir in response to a breakfast meal challenge decreased to a greater extent in the high-carbohydrate compared with the low-carbohydrate group at follow-up. This study had unusually high weight loss for an outpatient intervention study (≈21 kg), and the level of carbohydrate intake in both groups was extremely low (<100 g, on average).

Data from the above studies suggest that consuming a larger percentage of energy later in the day may lead to an adverse cardiometabolic risk profile, but these studies have major limitations. However, a separate study showed that providing 35 g of available starch from brown beans versus white wheat bread at dinner leads to a 23% lower glucose response and 16% lower insulin response after breakfast the following day.[109] Interleu-

kin-6 and interleukin-18 were also lower after breakfast consumed the day after the brown bean evening meal.

Another study tested whether late-night eating, without altering meal frequency, alters energy and glucose metabolism.[110] Eleven young, normal-weight women consumed a 200-kcal snack (45% carbohydrates, 50% fat) at 10 AM or 11 PM for 13 days in a randomized, crossover study. Body weight did not differ between phases. There were no differences in HDL cholesterol, triglycerides, nonesterified fatty acids, adiponectin, leptin, and oral glucose tolerance test glucose and insulin areas under the curve between snack patterns. Despite these results, the authors concluded that having late snacks could increase the risk of obesity and CVD. However, given the lack of significant difference between groups in metabolic risk factors, the data do not fully support this conclusion.

More extreme patterns of eating during nighttime hours were tested in a shift-work paradigm.[111,112] In 1 study, 11 female nurses were tested over 3 days of night-shift work.[111] Glycemic response to standard meals containing 440 kcal provided at 7:30 PM, 11:30 PM, and 3:30 AM was assessed over 4 hours. Basal glucose was similar before each meal, but postprandial concentrations were higher after the meal consumed at 11:30 PM. Basal insulin was highest before the 11:30 PM meal and lowest at 3:30 AM; postprandial values followed the same pattern. The authors concluded that glucose tolerance was lower around midnight, as the circadian oscillations would predict, and that the rise in CHD risk in night workers could be attributable to deregulated coupling of food intake to the circadian system. Furthermore, they posited that food quality and timing could play a role in metabolic responses to meals. The other study was performed in 8 young, lean men.[112] Participants were randomized to simulated day or night work for a single shift in a crossover design. The day shift occurred at noon to 8 PM with meals provided at 1 PM and 7 PM and a snack at 4 PM; the night shift was performed at midnight to 8 AM with meals at 1 and 7 AM and a snack given at 4 AM. Diets were identical in both phases. Glucose and triglyceride concentrations were higher during the night shift compared with the day shift. The authors reported relative lipid intolerance throughout the night shift with metabolic recovery of glucose tolerance toward the end of the night shift and suggested that restricting fat intake throughout the night would be beneficial. However, this was not directly tested in this study.

Even less extreme shifts in food intake could influence cardiometabolic risk status. A 2-week intervention study tested the effects of early (1 PM) or late (4:30 PM) lunch on glucose tolerance in young, normal-weight women (n=32; mean age, 24 years; BMI, 22.9 kg/m²).[113] Postprandial glucose area under the curve was increased by 46% relative to the early lunch condition. In addition, consumption of a late lunch blunted the daily cortisol profile. The authors concluded that delaying the timing of an identical meal for 1 week reduced glucose tolerance. However, because breakfast consumption occurred at a fixed time, 8 AM throughout the study, these results may be attributable to the longer intermeal interval in the late lunch condition relative to early lunch. It is unknown whether similar results would be observed if meals were consumed at similar intervals from one another, and the contributions of fasting duration and circadian cycle to these markers could not be distinguished.

Given the seemingly negative health effects of eating late during the day, studies have examined whether restricting food intake to earlier daytime hours would affect cardiometabolic health markers. In 1 study, men were asked not to eat between 7 PM and 6 AM daily for 2 weeks or to continue their regular eating pattern (n=27; mean age, 20.9 years; BMI, 24.4 kg/m²).[114] TEI was reduced when night eating was not permitted, resulting in a 0.4-kg weight loss compared with a 0.6-kg weight gain during the control period. Similarly, in a small pilot study (n=8) in which food intake was limited to a self-determined 10- to 12-hour window during the day, body weight decreased by 3.3 kg over 16 weeks.[2] This study did not include a control group. Nevertheless, both studies suggested that restricting the period of time during which food consumption occurs could be a promising method for weight management.[2,114]

Summary

The impact of meal timing, particularly related to the evening meal, deserves further study. Epidemiological findings suggest a potential detrimental effect of late meals on cardiometabolic health, but clinical intervention studies, which would address causality, have been limited in scope and too diverse to draw definitive conclusions and make recommendations. Moreover, the potential benefit of increased meal frequency should be evaluated in the context of timing and duration of the daily prandial period.

RESEARCH GAPS IN DEFINING MEALS AND EATING OCCASIONS

Studies have suggested that eating late in the day or skipping breakfast may be associated with weight gain and obesity, whereas intermittent fasting and high meal frequency may have beneficial cardiometabolic health effects.[48,55] However, research in this field has been impeded by the lack of consensus on the definition of a meal, snack, and meal timing. Two common definitions have been identified to distinguish between meals and snacks based on (1) participant identification of a meal, labeled as breakfast, brunch, lunch, dinner, and supper, and snack, labeled as snack, morning or afternoon tea, or beverage break, and (2) time-of-day reports, with a meal being the largest eating occasion within each time period:

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Table 3. Intentional Approach to Eating

Develop an intentional approach to eating that focuses on the timing and frequency of meals and snacks as the basis of a healthier lifestyle and improved risk factor management
Understand the patient's frame of reference in how he or she may define meals and snacks
Recommend distributing calories over a defined portion of the day
Recommend eating a greater share of the total calorie intake earlier in the day to have positive effects on risk factors for heart disease and diabetes mellitus
Promote consistent overnight fast periods
Link eating episodes to influence subsequent energy intake (eg, place snacks strategically before meals that might be associated with overeating)
Include intermittent fasting approaches as an option to help lower calorie intake and to reduce body weight
Use added eating episodes to introduce a wider variety of healthful food options and to displace less healthful foods
Use planned meals and snacks timed throughout the day to help manage hunger and to achieve portion control

One of the challenges of translating the findings reviewed here into clinical practice is the limited value of some of the definitions of meals and snacks. In Research Gaps in Defining Meals and Eating Occasions, we review and propose definitions for meals and snacks to be used for research purposes. However, from a practical perspective, people rarely think of meals or snacks as being defined by the amount of calories provided within the foods they consume. Studies show that cues such as time of day, portion size, food type, and preparation are more likely to be the bases for categorizing an eating episode as a meal or a snack.[122,123] Furthermore, most people do not consider energy-containing beverages, with the exception of meal replacements, as stand-alone snacks or meals, although they would meet our proposed definition of such because of their energy content.[124] Consequently, it may be best to frame discussions with patients by using language and references that the individual patient can identify with when counseling on the timing and frequency of eating episodes.

Another major challenge of addressing meal timing and frequency that is highlighted in the research reviewed here is the understanding that eating occasions are influenced by previous eating episodes, and thus, making adjustments in 1 period of the day or meal/snack timing has an influence on other opportunities for consumption. Meal timing and frequency may be as much about the amount of time between eating episodes as about the types and amounts of energy consumed at each eating episode. Many of the studies reviewed included controlled calorie conditions without opportunities for ad libitum intake. When calorie intake is not controlled, it is plausible to hypothesize that a longer interval

between eating episodes leads to greater consumption at the next available eating opportunity. However, it is clear from the data that longer periods of time between eating episodes during the day may have different implications from longer overnight fast periods.

Although most of the research reviewed in this document was not in the setting of weight reduction interventions, given that 1 in 3 adults in the United States is obese, understanding how meal frequency and timing influence energy balance may be helpful clinically.[125] Intermittent fasting approaches appear to be feasible to help patients lower calorie intake consistently. More data are needed on longer-term outcomes for weight reduction and risk factor modification. Additionally, the use of intermittent fasting for weight loss maintenance is a strategy that should be tested empirically. In the long run, approaches such as intermittent fasting may simply provide another way to help patients be more intentional about consuming energy within a given time period.

Focusing on meal timing and frequency as a starting point to address obesity and positive energy balance appears to be beneficial for several reasons on the basis of the data reviewed here. First, the data suggest that making changes that promote more regular intake of energy during the day, perhaps with a greater proportion of calories earlier in the day, has positive effects on risk factors for heart disease and diabetes mellitus. Several of the studies suggest that this may also have positive effects on body weight, but randomized, controlled trials are needed to test this hypothesis. Second, this approach may be a better way to focus on improving dietary quality because added eating episodes can be used to introduce a wider variety of healthful food options. Finally, if and when the individual is ready to reduce calories, having an intake structure on which to superimpose calorie restriction may improve the patient's ability to adhere to the weight loss plan. Given the fact that eating episodes are influenced by each other, portion control may be achieved more easily in the context of planned meals and snacks timed throughout the day to help manage hunger.

Eating frequency may also be influenced by eating speed, which was not evaluated in the present document. A meta-analysis on this topic has reported a small to medium effect of eating rate on energy intakes at a meal, with lower intakes when eating speed is slow.[126] The difference in energy intakes was proportional to the difference in eating speed. However, there was no effect of eating rate on hunger after the meal and no difference in hunger ratings between meals of fixed content eaten at different speeds. In a fixed-meal study, meal duration (30 versus 10 min) had no effect on appetite and hunger hormones or feelings of hunger or fullness after the meal.[127] Intakes throughout the rest of the day also were not different between eating speed conditions. Given that high heterogeneity between studies has been reported[126] and that no studies have assessed long-term

effects of eating speed on cardiometabolic risk factors, additional studies are needed in this area.

RECOMMENDATIONS FOR SPECIAL POPULATIONS

Although the research reviewed here generally supports an intentional eating approach with planned distribution of daily TEI for both weight management and cardiometabolic health, this body of work is limited in its investigation of vulnerable populations. There are established racial/ethnic disparities in the prevalence of obesity[128] and CVD.[129,130] With respect to obesity, black women, Mexican American women, Native Americans, and Pacific Islanders are disproportionately affected.[128] Similarly, death rates from heart disease are up to 3 times greater for blacks in the United States,[129,131] and hypertension among blacks is among the highest worldwide.[129] Despite the increased risk among these groups, the majority of studies available for review here did not include these populations or failed to report the racial/ethnic distribution of their samples. With known cultural variations in dietary intake, including TEI, meal frequency, and meal timing, adequate representation of racial/ethnic groups at higher risk is needed to increase confidence in generalizing findings from earlier studies. Furthermore, future research should include racially/ethnically diverse samples, a full description of the sample in publications, and subgroup analysis (as appropriate) and should specifically discuss limitations of findings relative to the level of diversity in their sample.[132]

There has also been limited published research investigating meal patterns and frequency among children and adolescents and body weight and other metabolic risk factors, although there has been tremendous focus on childhood obesity and early predictors of CVD risk.[133] Evidence from this scant body of literature primarily mirrors findings in adult populations. Namely, there is support for regular and more frequent main meals to lower obesity risk[134,135] among children and adolescents. Youths with less frequent eating are more likely to have greater body weight, even after adjustment for other confounders.[134] Likewise, skipping meals is associated with higher metabolic risk (eg, higher BMI, waist circumference, fasting serum insulin, and fasting plasma glucose; decreased fasting plasma HDL).[134,136] Again, more research with diverse samples of children and adolescents is needed to increase confidence in the findings of the aforementioned studies.

Finally, there is a critical need to better understand the implications of dietary patterns and frequency on CVD risk among older adults. In 2014, 46.2 million individuals ≥65 years of age were living in the United States (14.5% of the population). Over the next 25 years, it is expected that older Americans will grow to 22% of the US population. The nutritional needs of the elderly are complicated by the need to moderate caloric intake for weight management and CVD prevention while balancing the need to address nutritional deficiencies associated with diets of older adults.[137] For example, a recent research review explored the potential risks and benefits of calorie restriction among the elderly and urged caution as a result of mixed results from clinically based efficacy trials and a lack of effectiveness and community-based studies.[138] Most CVD prevention research has focused on younger adults; however, with the growing number of older adults and increases in the average life expectancy, more research on the nutrition behaviors of this group is warranted.

FOOTNOTES

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*Modest.

†Significant.

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Circulation

Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association
Marie-Pierre St-Onge, Jamy Ard, Monica L. Baskin, Stephanie E. Chiuve, Heather M. Johnson, Penny Kris-Etherton, Krista Varady and On behalf of the American Heart Association Obesity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council

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