Health effects of intermittent fasting: hormesis or harm? A systematic review[1]

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ABSTRACT

Background: Intermittent fasting, alternate-day fasting, and other forms of periodic caloric desistance are gaining popularity in the lay press and among animal research scientists. Whether clinical evidence exists for or is strong enough to support the use of such dietary regimens as health interventions is unclear.

Objective: This review sought to identify rigorous, clinically relevant research studies that provide high-quality evidence that therapeutic fasting regimens are clinically beneficial to humans.

Design: A systematic review of the published literature through January 2015 was performed by using sensitive search strategies to identify randomized controlled clinical trials that evaluated the effects of fasting on either clinically relevant surrogate outcomes (e.g., weight, cholesterol) or actual clinical event endpoints [e.g., diabetes, coronary artery disease (CAD)] and any other studies that evaluated the effects of fasting on clinical event outcomes.

Results: Three randomized controlled clinical trials of fasting in humans were identified, and the results were published in 5 articles, all of which evaluated the effects of fasting on surrogate outcomes. Improvements in weight and other risk-related outcomes were found in the 3 trials. Two observational clinical outcomes studies in humans were found in which fasting was associated with a lower prevalence of CAD or diabetes diagnosis. No randomized controlled trials of fasting for clinical outcomes were identified.

Conclusions: Clinical research studies of fasting with robust designs and high levels of clinical evidence are sparse in the literature. Whereas the few randomized controlled trials and observational clinical outcomes studies support the existence of a health benefit from fasting, substantial further research in humans is needed before the use of fasting as a health intervention can be recommended. *Am J Clin Nutr* 2015;102:464–70.

Keywords: intermittent fasting, alternate-day fasting, total caloric desistance, energy restriction, time-restricted feeding, caloric restriction, obesity, coronary artery disease, diabetes, cognitive performance

INTRODUCTION

Caloric restriction (CR)[5] and total caloric desistance [TCD; i.e., intermittent fasting, alternate-day fasting (ADF), routine periodic fasting, or intermittent energy restriction] are methods of energy deprivation (1–4). CR dramatically improves metabolic health and many other physiological and molecular markers of health and longevity (1), and TCD may also affect health. Animal models of CR and TCD have shown that limitations in energy intake extend longevity (5–7) and reduce the risk of atherosclerosis, metabolic dysregulation, and cognitive dysfunction (4, 5, 8–18). Whereas CR is better established for improving risk profiles (1), the basis for studying fasting approaches such as ADF—in part—is that compliance with the regimen may be greater. This is because of the periodic nature of fasting, which mitigates the constant hunger that practitioners of CR endure. Both CR and TCD require further research, but if the health benefits of TCD are at least as strong as those of CR, the less frequent but more intense energy deprivation of TCD may be preferred.

The case for a human health benefit is just beginning to be made. TCD may provide not just a greater dose of CR but powerful metabolic effects. Furthermore, TCD and CR may provide some of their health benefits through distinct pathways (4, 5, 8). Unfortunately, various fasting fad diets have appeared in the popular press, and the lines between these and valid research have become blurred (19). The vast majority of fasting research has been in animals, and evidence in humans of health improvements from fasting is preliminary.

Mechanistic explanations for the benefits from TCD include the following: *1*) the body uses fats for energy during TCD, reducing adipose mass and resulting in a small, long-term reduction in risk after each fasting episode (12, 20–23); and *2*) nutritional stress during TCD, at least in part, results in cellular-level repairs, functional optimization, and metabolic rejuvenation (4, 9–11) that may improve long-term health by reducing cardiovascular risk factors (4, 10, 18) and acting on the metabolism of glucose via Forkhead Box A genes (5, 8, 12, 24). In some animal models, TCD is at least as good as CR at improving markers of metabolic health (4, 10). TCD-associated cognitive performance has been extensively evaluated in animals

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[5] Abbreviations used: ADF, alternate-day fasting; CAD, coronary artery disease; CR, caloric restriction; FEELGOOD, Fasting and Enhanced Expression of Longevity Genes during Food Abstinence; HGH, human growth hormone; LDS, Latter-Day Saint; TCD, total caloric desistance.

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(4, 12–18), including its use to reduce circulating concentrations of brain-derived neurotrophic factor (16).

Various human TCD regimens—traditionally called fasting (which will be used in the remainder of the review)—such as ADF are being evaluated. In ADF, participants fast every other day and eat ad libitum on in-between days (25). In another regimen, fasting occurs twice per week on nonconsecutive days (26). Most human fasting interventional trials have been for the primary endpoint of weight loss and have not used control arms (some used multiple noncontrol energy-restriction regimens). Small studies of obese and nonobese individuals found that weight was lower by 2.5–8% after 3–8 wk of ADF (25, 27–29). In a larger 3-mo study, weight was 6.3% lower after the twice-weekly regimen (26). Fasting also may improve other endpoints such as cardiovascular and metabolic risk profiles (20, 25, 26, 28, 30–32), but many of those changes would not remain significant if corrected for multiple comparisons.

This review evaluated the clinical evidence in humans that fasting is beneficial, including from randomized controlled trials of the effects of fasting on clinically relevant surrogate outcomes (e.g., weight and cholesterol) or actual clinical event endpoints [e.g., diabetes and coronary artery disease (CAD)] and any other studies of clinical event outcomes.

METHODS

A systematic review of the literature was performed by searching computerized databases for published, peer-reviewed articles in English. Searches included the terms "intermittent fasting," "alternate-day fasting," "periodic fasting," and "intermittent energy restriction." In addition, the reference lists of articles identified to be related to fasting were examined for other trials or studies that were relevant.

The primary aims were to *1*) identify randomized clinical trials of fasting in which a standard diet or noninterventional control group was used and *2*) find all studies in which the research endpoint was the clinical outcome, such as diagnosis of diabetes, CAD, or cognitive impairment such as dementia (regardless of whether it was a clinical trial). Filters were also used for "humans" to eliminate animal studies and—for aim 1—"clinical trial" to eliminate clinical studies that did not have a control arm. Randomized trials with multiple interventional arms (e.g., an intermittent fasting arm and a CR arm) but no usual diet control arm were considered to be incomplete trials and were not counted as controlled trials of fasting. Because intermittent fasting and CR have not been conclusively proven to have beneficial effects in humans with acceptable safety profiles (1), they were not considered to be controls for trials that were identified. Studies whose endpoints were surrogate outcomes (e.g., weight loss, LDL cholesterol, and brain-derived neurotrophic factor) that themselves are predictors of clinical events were not considered to be clinical outcomes studies.

Searches for "intermittent fasting" identified 198 articles, including 83 studies in humans of which 8 were clinical trials. "Alternate-day fasting" searches identified 46 articles, of which 18 were in humans and 7 were labeled as clinical trials. For "periodic fasting," 19 articles were found: 9 in humans (including the only clinical outcomes studies that were found) and just 1 that was called a clinical trial. The term "intermittent energy restriction" retrieved only 12 articles: 8 in humans, of which only 2 were clinical trials.

From these searches, a total of only 3 randomized controlled clinical trials with standard diet or noninterventional controls were identified. The results of these 3 trials were published in 5 articles (1 trial's results were published in 3 articles). Furthermore, only 2 clinical outcomes studies were found, both of which were prospective observational studies.

RESULTS

Evidence of a fasting benefit for humans based on surrogate outcomes studies

The 5 reports from 3 randomized, controlled trials of fasting that had a control consisting of a noninterventional or standard diet are shown in **Table 1**. One of these trials was a 12-wk study

TABLE 1
Clinical studies of fasting that met this systematic review's inclusion criteria[1]

First author (ref)	Year	Sample size	Type of fasting regimen	Length of regimen	Primary endpoint
Randomized controlled clinical trials of fasting (all were for surrogate outcomes)					
Teng (33)	2011	25	2 d/wk + CR	12 wk	Multiple[2]
Hussin (34)	2013	32	2 d/wk + CR	12 wk	Multiple[2]
Teng (35)	2013	32	2 d/wk + CR	12 wk	Multiple[2]
Varady (36)	2013	32	Alternate-day fasting	12 wk	Weight loss
Horne (21)	2013	30	24 h water only	2 d	Multiple[3]
Clinical event outcomes studies of fasting (both were observational)					
Horne (37)	2008	445	Primarily religious, usually once per month[4]	Decades[5]	CAD diagnosis
Horne (38)	2012	200	Primarily religious, usually once per month[4]	Decades[5]	Diabetes diagnosis

[1]CAD, coronary artery disease; CR, caloric restriction; ref. reference.
[2]No primary endpoint was specified, and the results were not corrected for multiple hypothesis tests.
[3]Bonferroni-corrected statistical significance at $P \leq 0.00167$ (30 tests of hypothesis).
[4]Fasting was per a personally defined regimen, but the vast majority fasted approximately once per month for religious reasons (43).
[5]Specific length of regimen was not investigated, but the religious teaching is a life-long regimen after the age of 8 y.

of weight loss in 32 nonobese individuals, which confirmed the loss of 6.5% of body weight in the ADF intervention arm compared with the nonfasting control arm (36). The study also reported improvements in other cardiovascular and metabolic variables such as triglycerides, LDL-cholesterol particle size, and C-reactive protein, but it did not correct for multiple comparisons (a common scientific design problem of many fasting studies) (36). This study did not evaluate subject safety outcomes. Safety data for ADF regimens are lacking, but ADF has been shown to not cause an increase in caloric intake on nonfasting days, despite what some may expect from the effects of prolonged hunger (39, 40).

Some of the weight-loss studies, including the one trial just mentioned and some noted in the introduction, evaluated metabolic, cardiovascular, and cognitive benefits as secondary outcomes. The other 4 reports of randomized controlled trials of fasting provide information for primary outcomes other than weight.

The second randomized controlled trial of fasting was reported in 3 articles using the primary endpoints of "mood states and depression status" (34), "metabolic parameters and DNA damage" (35), and "mood and quality of life" (33). One of these articles was published before full enrollment in the trial (33), used similar outcomes as one of the other articles (34), and will not be discussed. Overall mood—including components from tension, anger, and confusion—was improved by fasting in a study of 32 subjects during 12 wk of the intervention phase. Unfortunately, correction for the 7 hypothesis tests of measures of mood was not done and would result in no finding being statistically significant (34). From the same 12-wk trial but in another article, blood pressure, total cholesterol, LDL cholesterol, weight, fat mass, and other factors—including DNA damage measures—were changed by fasting (35). As before, no primary hypothesis was specified, and no correction for multiple comparisons was made in what must be considered a subsequent analysis of the prior study (34). None of these reports evaluated safety outcomes for the trial (33–35).

The third randomized controlled clinical trial was the Fasting and Enhanced Expression of Longevity Genes during Food Abstinence (FEELGOOD) trial (21). It used a Latin-square crossover design to examine just one 24-h period of fasting and 1 day of ad libitum feeding. FEELGOOD is the only randomized controlled trial of fasting to correct for multiple comparisons (21). No primary endpoint was used, but $P \leq 0.00167$ was the threshold for significance for 30 tests of hypothesis. In FEELGOOD, fasting induced marked but temporary increases in human growth hormone (HGH), red blood cell count (and hemoglobin and hematocrit), and total cholesterol [resulting from increases in both LDL cholesterol and HDL cholesterol, despite substantially decreased triglycerides, as found in other fasting studies (41, 42)] (21). This trial evaluated only 1 day of fasting, and no safety outcomes were studied (21); thus, the findings are useful primarily in developing longer-term trials.

Fasting and major adverse clinical events

Two observational clinical events studies have examined fasting and major adverse clinical outcomes in humans. These epidemiologic studies of fasting began in 2001, based not on CR but on declining tobacco smoking. Smoking declined more from 1984 to 1996 in states such as California than in Utah, where the smoking rate was already low (43); however, mortality rankings were essentially unchanged over the same time period (44). An initial study was performed challenging the assumption that Utah's low CAD risk was only attributable to the proscription of smoking among members of the Church of Jesus Christ of Latter-Day Saints (LDSs), or Mormons (37). That study found that LDSs in Utah had a lower risk of CAD than did those of other religious preferences (adjusted OR: 0.81; 95% CI: 0.69, 0.95; $P = 0.009$), despite adjustment for smoking (37).

To better understand the low CAD risk among LDS individuals, fasting history was evaluated during 2004–2006 among 448 cardiac catheterization patients of unrestricted religious preference. Patients who reported routine fasting had a lower odds of CAD (adjusted OR: 0.46; 95% CI: 0.27, 0.81; $P = 0.007$) than did those who did not fast, despite extensive adjustment for potential confounders (37). Interestingly, those of religious preferences other than LDSs who reported routine fasting also benefited: for CAD (OR: 0.23; 95% CI: 0.06, 0.90; $P = 0.037$) (37). A secondary finding (NS after correction for multiple comparisons) was that fasting was associated with a lower odds of diabetes (37).

A second observational clinical outcomes study confirmed and expanded on the fasting associations with CAD and diabetes. Using the same fasting survey question (37), a study was conducted among 200 patients from 2007 to 2008 (38). This study evaluated a new set of cardiac patients for the primary outcome of diabetes, which was not significantly associated with fasting (after multiple-comparisons correction) in the first study (37) and, thus, required additional evaluation as the primary hypothesis test (38). The second study found that patients who fasted routinely had lower odds of diabetes (adjusted OR: 0.40; 95% CI: 0.16, 0.99; $P = 0.044$) and confirmed the first study's findings for CAD (adjusted OR: 0.37; 95% CI: 0.18, 0.88; $P = 0.019$) (**Figure 1**)

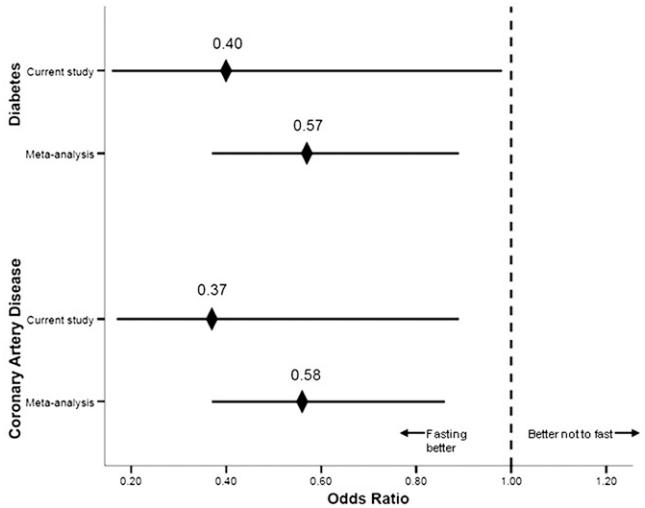

FIGURE 1 The association of routine periodic fasting with prevalent diabetes and coronary artery disease in the current study ($n = 200$) (38) and its association with outcomes in meta-analyses ($n = 648$) of this study's population and 448 previously studied angiographically examined patients (37). ORs (from logistic regression) for fasting were adjusted for age and sex for the diabetes endpoint; those for the coronary artery disease endpoint were adjusted for diabetes, age, sex, BMI, hypertension, hyperlipidemia, smoking, and family history of early coronary artery disease. Reproduced from reference 38 with permission.

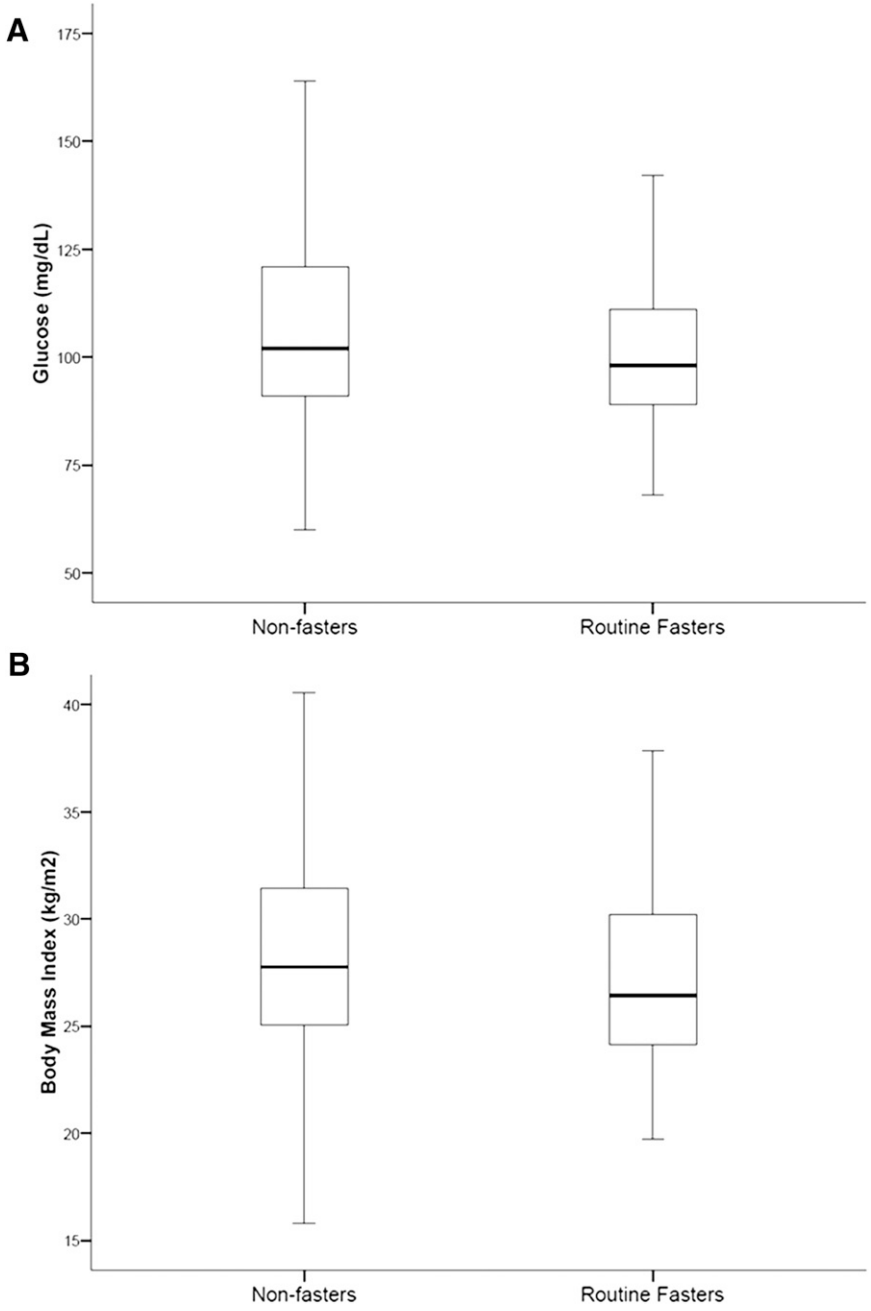

FIGURE 2 Meta-analysis box plots showing differences by fasting status in the distributions of serum glucose concentrations (A) ($P = 0.047$) and BMI (B) ($P = 0.044$) in the combined populations (meta-analysis, $n = 648$) of the current study ($n = 200$) (38) and a previous fasting study ($n = 448$) (37). Comparisons to determine differences were made by using ANOVA. Reproduced from reference 38 with permission.

(38). In addition, fasters had lower glucose concentrations and BMI (**Figure 2**) (38).

DISCUSSION

For fasting to be more than a weight-loss fad, greater scientific rigor is needed from interventional trials than is found in the literature. Whereas enthusiasm for fasting is increasing, clinical relevance remains low because of insufficient human data, including almost nonexistent controlled trials (21, 33–36), few clinical outcomes studies (37, 38), lack of correction for inflated type I error rates from multiple hypothesis tests, and limited safety data (39–41). The evidence suggests, however, that therapeutic fasting may provide substantial benefit for reducing clinical risk.

Important metabolic and cardiovascular benefits have been reported in humans that deserve further consideration in therapeutic fasting trials, such as decreases in fat mass, LDL-cholesterol particle size, LDL cholesterol, triglycerides, and C-reactive protein (35, 36). Interestingly, whereas in the FEELGOOD trial LDL cholesterol increased during fasting (21), another study reported both higher LDL cholesterol while fasting and lower LDL cholesterol after 6 wk of a fasting regimen (41, 42). Fasting also substantially increases HGH (21), facilitating

lipolysis and fatty acid release during fasting for use as energy (22, 23). The dramatic effect of fasting on HGH ended shortly after feeding resumed (21), but fasting may affect long-term health in part via periodic HGH-driven reductions in risk (23).

In addition to the various cardiovascular and metabolic findings, animal research strongly suggests that human fasting studies of cognitive performance should be conducted. Also, the frequency and duration of fasting requires further investigation, including with regard to whether frequent episodes (e.g., 1–4 times/wk) of therapeutic fasting should be done.

Of further note, despite the different designs, regimens, and study outcomes, the convergence of findings regarding fasting from the 2 epidemiologic clinical outcomes studies (that arose due to data regarding smoking and CAD outcomes, i.e., references 37 and 38) and the findings of interventional studies (most having arisen as extensions of CR research, i.e., references 20, 25–36, 39, 40) suggests that a prudent amount of fasting beneficially influences health outcomes. However, because the clinical outcomes studies involved observational epidemiologic research (37, 38), a randomized controlled clinical outcomes trial of fasting is needed to determine causality for clinical events.

On the point of observational compared with randomized trials, all of the previously mentioned interventional human studies of fasting (20–23, 25–36, 39–42) and most animal models of fasting have examined surrogate outcomes of cardiovascular, metabolic, and cognitive risk. A surrogate outcome, such as weight, glucose, or LDL cholesterol, is a factor that influences risk of a clinical event such as CAD but that is not equivalent because some individuals with the risk factor never experience the clinical event and some with the event do not have the risk factor. This is seen in data where the percentage of patients with and without CAD who have high cholesterol, high blood pressure, and other surrogate outcomes is not 100% and 0%, respectively (45, 46). The effect of a health intervention on surrogate measures of risk is of only academic, nonclinical interest if the treatment does not reduce subsequent major health events such as the onset of diabetes, dementia, and CAD. Unfortunately, some interventions that reduce surrogate endpoints may not affect the risk of disease or may even increase the risk of events. Examining major adverse clinical events is a crucial step in determining whether an intervention is actually beneficial.

Widely considered to be the best tests of clinical efficacy and safety, the randomized, placebo-, or standard-controlled clinical trial has a rigorous design that is engineered to balance both observed and unmeasured confounders between the intervention and control arms, which makes any resulting difference observed between the 2 trial arms a causal result of the intervention. Whereas this may be the optimal approach for studying the effects of fasting, no such randomized clinical trial has been performed. Furthermore, practical considerations make it unlikely that a fasting trial evaluating reductions in major adverse clinical events will be conducted in the near future. These considerations include study cost, the length of time and sample size required, and the difficulty in keeping the control arm free from crossover to the intervention (or fasting arm subjects from ceasing the intervention) during the many years of the trial. In contrast, observational clinical studies (e.g., references 37, 38) can provide the required information at a fraction of the cost and without the other concerns if statistical analyses appropriately adjust for important potential and known confounders. Historically, such considerations have made it unnecessary to conduct randomized trials of some interventions for evaluation of clinical event outcomes (47).

The observational studies are limited by a lack of a comprehensive dietary history; thus, residual confounding could remain (37, 38). Extensive adjustment was made in these studies for demographics, cardiac risk factors, physical activity, income, and education as well as factors that may differ between LDSs and other populations such as smoking, social support, frequency of church attendance, and use of alcohol, tea, and coffee. Furthermore, the fasting regimen of most participants was a 24-h fast once per month; thus, different regimens (e.g., ADF) may have different (i.e., perhaps stronger) effects on CAD and diabetes. Also, genetic evaluations previously showed the Utah LDS population to be an outbred, continental population genetically similar to the US Caucasian population (48, 49); thus, genetic differences are unlikely to explain the findings of the observational clinical events studies (50). It is also unclear whether fasting has an impact on CAD and diabetes in minority populations; thus, additional clinical events studies should be performed among minorities.

Beyond efficacy, safety data are critical for the therapeutic application of fasting but are sorely lacking. After many weeks of continuous fasting (~5–7 wk in healthy adults), fasting converts into starvation, wherein vital organs and muscles are consumed for energy. Starvation causes excessive weight loss, anemia, chronic diarrhea, delirium, and other adverse reactions and eventually death. Intermittent therapeutic fasting should not have these adverse effects, but it may still cause harm when practiced too frequently or for too many days consecutively. Commonly, fasting may result in mild adverse events such as headaches, fainting, weakness, dehydration, and hunger pangs. More importantly, excessive fasting could lead to malnutrition, eating disorders, susceptibility to infectious diseases, or moderate damage to organs. In a study of rats, ADF was found to result in increased left atrial diameter, myocardial fibrosis, and reduced cardiac reserve (51). Whereas left ventricular ejection fraction and ventricle size were not measurably affected by ADF, the observed changes suggest caution in the human application of regimens using frequent fasting (51). It may be that fasting multiple days or successive days per week is too frequent or intense for humans.

In conclusion, whether fasting actually causes improvements in metabolic health, cognitive performance, and cardiovascular outcomes over the long term; how much fasting is actually beneficial; and where the threshold of hormesis resides (i.e., a balance between long-term benefit from fasting compared with harm from insufficient caloric intake) remain open questions. Unfortunately, the vast majority of human studies of a fasting intervention were weight-loss studies using single-arm, nonrandomized approaches or multiple intervention arms with no control. Whereas further research of CR is needed [e.g., the ongoing CALERIE Trial (52, 53)], considerable additional clinical research of fasting is required before contemplating changes to dietary guidelines or practice. Dietary research has inherent challenges; thus, well-designed fasting trials of clinically relevant outcomes and populations are needed to avoid missteps [e.g., recent revision of 1980 guidelines on dietary fats and cholesterol (54–57)].

Future fasting research should determine whether and to what extent fasting regimens are safe. Further research is needed to determine whether fasting is effective for improving health in the general population, higher-risk people, and diseased individuals. Additional knowledge is also needed regarding the mechanisms of benefit and the optimal frequency and duration of fasting in apparently healthy and high-risk individuals. Finally, in deference to the current focus on lower-cost healthcare, fasting has no direct financial costs and represents a nominal savings on food expenses. In summary, intermittent fasting may improve health; however, substantial additional clinical research is needed before advocating its use for health purposes.

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