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REVIEW

Fasting for weight loss: an effective strategy or latest dieting trend?

A Johnstone

With the increasing obesity epidemic comes the search for effective dietary approaches for calorie restriction and weight loss. Here I examine whether fasting is the latest 'fad diet' as portrayed in popular media and discuss whether it is a safe and effective approach or whether it is an idiosyncratic diet trend that promotes short-term weight loss, with no concern for long-term weight maintenance. Fasting has long been used under historical and experimental conditions and has recently been popularised by 'intermittent fasting' or 'modified fasting' regimes, in which a very low-calorie allowance is allowed, on alternate days (ADF) or 2 days a week (5:2 diet), where 'normal' eating is resumed on non-diet days. It is a simple concept, which makes it easy to follow with no difficult calorie counting every other day. This approach does seem to promote weight loss, but is linked to hunger, which can be a limiting factor for maintaining food restriction. The potential health benefits of fasting can be related to both the acute food restriction and chronic influence of weight loss; the long-term effect of chronic food restriction in humans is not yet clear, but may be a potentially interesting future dietary strategy for longevity, particularly given the overweight epidemic. One approach does not fit all in the quest to achieve body weight control, but this could be a dietary strategy for consideration. With the obesity epidemic comes the search for dietary strategies to (i) prevent weight gain, (ii) promote weight loss and (iii) prevent weight regain. With over half of the population of the United Kingdom and other developed countries being collectively overweight or obese, there is considerable pressure to achieve these goals, from both a public health and a clinical perspective. Certainly not one dietary approach will solve these complex problems. Although there is some long-term success with gastric surgical options for morbid obesity, there is still a requirement for dietary approaches for weight management for the overweight and obese population, particularly as invasive interventions carry post-operative risk of death due to complications. Effective dietary interventions are required that promote long-term adherence and sustained beneficial effects on metabolic and disease markers. In general, such interventions need to be palatable and satiating, meet minimal nutritional requirements, promote loss of fat and preserve lean body mass, ensure long-term safety, be simple to administer and monitor and have widespread public health utility. Intermittent fasting or alternate day fasting may be an option for achieving weight loss and maintenance.

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There are multiple dietary approaches that vary in macronutrient composition and degree of energy restriction (for example, low-calorie diet and very low-calorie diet), which typically achieve long-term 5% weight loss (WL) in 30–35% of subjects, at least up to 3 years of follow-up; longer-term data are less promising on the ability of dietary approaches to control body weight. However, it is not yet possible to apply personalized nutrition to predict which diet will work best at an individual level. In shorter-term (3–4 month) studies, higher-protein diets providing 20–25% energy as protein consistently report greater satiety, preferential loss of fat and preservation of fat-free mass compared with lower-protein diets (15% energy as protein).[1,2] However, a recent large-scale, long-term (2-year) meta analysis reported that the short-term benefit of high protein persists only to a small degree in the longer term.[3,4] High-protein diets should be considered as a WL tool rather than a 'diet for life' as they can have a major impact on gut health due to breakdown of metabolites and fermentation products. This occurs very quickly in response to a diet composition, with our own data suggesting that maximal changes in faecal microbiota composition are reached within 2–4 days of switching to a different diet.[5]

Most weight-control programmes use daily energy restriction, but intermittent energy restriction has been suggested as a possible alternative approach: namely, intermittent fasting (IF) or alternate day fasting (ADF). ADF may be easier to follow and potentially has greater positive metabolic effects, as it includes repeated spells of more profound energy restriction than achieved with dietary control, albeit for shorter periods. In animal models, IF is superior or equivalent to dietary energy restriction with respect to longevity, reduction of breast, prostate and pancreatic cancers, and reduction of cardiovascular and cerebrovascular disease and dementia. However, what about data collected on humans? This is perhaps less convincing, as there are no well-controlled studies, particularly those examining long-term health/disease and longevity. The impact of a diet regime on mortality and morbidity risk should be considered. A short-term risk linked to the WL therapy *per se* may be outweighed by the longer-term health benefits of the WL, particularly when considered relative to the risk associated with invasive procedures. For example, bariatric surgery carries a 0.25% risk of death and 13% risk for serious post-operative complications, such as embolism, thrombosis or pulmonary

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complications, as indicated by the controlled Swedish Obese Subjects study.[6] Nonetheless, these short-term risks are outweighed by the long-term (10 year) benefits in reduction of cardiovascular risk factors.[7] Therefore, fasting should be considered in the modern day context of the range of therapies now available for WL. The risks of obesity and obesity-related conditions are now better documented, and thus treatments with known but low risks may need to be re-evaluated.

IF OR ADF

This paper will address the following three questions, which are pertinent to any WL therapy, and more so in assessing whether fasting is an effective and safe dieting approach.

How effective is the regime in achieving WL in terms of actual WL (kg) and the composition of the loss in terms of fat and lean mass? What impact does it have on psychology/behaviour? More specifically, how do people feel during and after restriction, because this is an important indicator as to whether they will be compliant on a regime and hence lose weight.
Does it work in the long term? Does it have an impact on physiology, exercise ability and weight re-gain and does it improve risk factors for disease and/or longevity?

HISTORICAL DATA—WHY DO PEOPLE FAST?

There are a lot of historical scientific data that we can refer to, and these vary from extreme food restriction to include published works on hunger strike, famine and experimental starvation to less extreme fasting study data from religious fasts and therapeutic starvation for obesity.

HUNGER STRIKERS

Elia[8] reports more recent data in which Republican prisoners in Northern Ireland in 1981 died of starvation after being on a hunger strike for 57–73 days (data compiled from newspaper reports).[8] This is in accordance with the view that death usually occurs in normal-weight mammals when there is loss of 40–50% of initial body weight. It follows that, as the obese have a much larger total energy store, primarily in the form of adipose tissue, they can survive a fast for much longer periods compared with lean subjects. Elia[8] suggested a survival time of 60–70 days for a lean subject and 200–300 days for an obese subject during fasting.[8]

FAMINE

Understandably, the type of data in this area tends to be anecdotal rather than reports from intervention studies, often containing accounts of energy and nutrient intakes under prisoner of war conditions. McCance and Widdowson[9] documented findings from Wuppertal in Germany, following WW II, with the remit to study the effects of civilian under-nutrition on the physical and moral well-being of a modern community.[9] From 1948 onwards, the Medical Research Council unit was mainly occupied by prisoners of war from Russia, and of particular interest in this unique report is Widdowson's documented response of the prisoners of war to unlimited food during re-habilitation. Nineteen men, aged 26–80 years, were given unlimited access to food for 8 weeks and recorded food intake of up to 3954 kcal (16.6 MJ) at one meal or 6000 kcal per day (25.2 MJ) over a period of weeks. These data on gorging have been used as a demonstration for the hypothesis that voluntary food restriction leading to substantial WL is casually related to binge eating.[10] This has been extrapolated to the notion that dieting *per se* leads to compulsive eating or binges, at least for some individuals.[11]

Hunger strike, famine and prisoner of war situations provide unique data on the consequences of starvation or semi-starvation in previously healthy, but usually non-obese, subjects. However, it should also be remembered that fear of death, illness and injury will all interact with nutritional status to determine survival time. For these reasons, these groups are far from ideal to study the influence of WL on body composition, physiology or psychology.

EXPERIMENTAL STUDIES

The most comprehensive data set on classical under-nutrition is that of Keys and his colleagues from their sensational 'Minnesota Experiment' on the consequences of WL in normal-weight men conducted in the 1940s.[12] Ancel Keys assembled a team of physiologists, biochemists, medical staff, psychologists and psychiatrists to assess the physiological and psychological effects of severe under-nutrition and rehabilitation, for military applications concerned with nutritional rehabilitation. This semi-starvation regime led to a loss of 24% of body weight (to a mean body mass of 17.5 kg m^{-2}).

Eating can occur when hunger ratings are low, and, conversely, it is also possible to be very hungry and not to eat, even to the point of death (such as in case of a hunger strike). Therefore, one can hypothesise that the response to this type of short-term, but extreme food restriction in previously obese subjects may be quite different, as their psychological disposition to maintain WL may over-ride the physiological drive to overeat.

FASTING FOR RELIGIOUS REASONS

One of the most cited religious events associated with fasting is the period of Ramadan. During the fasting month of Ramadan, Muslims abstain from food and drink from sunrise until sunset. Although Ramadan does not involve a continual fast, it provides a useful insight into short-term food restriction in otherwise healthy humans. There is a misconception that this religious fast results in decreased energy intake (EI), as investigators have found either increases in EI[13] or comparable levels of EI before, during and after Ramadan,[14] despite a decrease in meal frequency. Similarly, Finch *et al.*[15] reported no change in body weight during the period of Ramadan.[15] Thus, although the physiological effects of sleep deprivation and dehydration occurring during Ramadan may provide concern, there is no evidence for restricted EI during this religious fast. Thus, these data would suggest that adult humans are capable of making compensatory changes in food intake in response to a short-term fast in order to maintain body weight.

TREATMENT FOR 'GROSS REFRACTORY OBESITY'

These data provided the framework for therapeutic fasting as an accepted in-patient treatment modality for morbid obesity during the 1950s and 1960s. For example, Stuart and Flemming[16] published data from the longest fast found by a Medline literature search, conducted on an obese man in Dundee, for a total of 382 days, making the Guinness Book of Records as the longest total fast, in which the subject lost ~75% of his body weight.[16] The history of the study of therapeutic starvation starts with the classical experimental starvation studies of Benedict.[17] Further work has been carried out by Bloom,[18] Duncan *et al.*[19] Drenick *et al.*[20] and Cahill[21] who treated lean and obese subjects by total withdrawal of food for periods ranging from 10 to 117 days.[18–21] Starvation is not currently recommended as a clinical treatment option for obesity, and if it is carried out it should only be conducted under medical supervision. This is because starvation diets have been linked to various medical complications (ventricular fibrillation, lactic acidosis, vitamin and electrolyte deficiency) and sudden death syndrome either during fasting or during re-feeding.[22] The data on hunger are of interest here—is there a reduction or absence of hunger during starvation or is hunger perhaps maintained over time? Silverstone *et al.*[23] assessed feelings of hunger in obese individuals undertaking total starvation and noted that there was no decrease in mean hunger during the fast.[23] However, Bolinger *et al.*[24] and Lappalainen *et al.*[25] found that hunger returned to baseline levels as the study progressed, on average 4–5 days after initiation. As hunger is one of the main reasons why people break a diet, this is an important consideration.

FASTING—THE CURRENT DAY

Why do people fast in the current day? Some 40% of women and 20% of men are dieting at any given time. Dieting is usually initiated in the context of an attempt at self-improvement, in order to achieve enhanced health (reduced mortality and morbidity risk), body image/appearance and well-being (quality of life). A US Study on 1120 adults details self-reported dieting strategies used over 4 years; some 14% of the American population reported using short-term fasting to lose weight.[26] These reports of dieting were not predictive of weight change over time, suggesting poor compliance for WL efforts. The highly popularised book published in 2013 by UK author Michael Mosley details the 5:2 intermittent fasting plan [*http://thefastdiet.co.uk*], wherein you eat normally for five days a week (feast days) and diet for two days a week (fast days). In this plan, the 'fast' has been adapted to a modified fast (or very low-calorie diet), where you can cut your calorie intake to a one-fourth of the normal level to maintain energy balance, to approximately 500 kcal for females and 600 kcal for males.

SHORT-TERM IF OR ADF

Historical data suggest that lean subjects become hyperphagic upon restoration of *ad libitum* food intake and that humans are capable of consuming large amounts of energy to compensate for previous deficit. However, this may not be the case for obese subjects who are restraining intake for WL purposes. In our study[27] we hypothesised that *ad libitum* food intake would be markedly increased in response to a short-term fast (36 h). We studied 12 lean men and 12 lean women and the protocol was a within-subject randomised design with two experimental periods: (i) a 2-day control period (maintenance) where on day 1 subjects were fed to 1.6 × RMR and then on day 2 they were fed *ad libitum* from a supermarket-style diet with 45 choices; and (ii) a separate 3-day test period encompassing a 36-h total fast. For the latter, on the day prior to food restriction, food was provided at 1.6 × RMR to reduce any pre-fasting variability in food intake. Subjects were then fasted from 2000 hours on day 1 until 0800 hours on day 3. During this period, only water or non-caloric beverages were consumed. On day 3, they were given *ad libitum* access to the same 45 supermarket, ready-to-eat foods. All food intake was investigator-weighed prior to and after consumption. All subjects lost weight during the 36-hour fast (average − 1.33 kg (s.d. 0.55) in men and − 1.00 kg (s.d. 0.30) in women). There was slight evidence that men tended to lose more weight than women on account of their larger size. Post fast, subjects consumed much less energy than required to compensate for the energy deficit induced by the fast. EI only increased 20% above control values on the post-fast *ad libitum* day, increasing from 10.2 to 12.2 MJ/d ($P = 0.049$). On the control treatment, the *ad libitum* intakes remained at approximately 1.6 × RMR, adequate to maintain energy balance for this group.[27] Interestingly, in the post-fast response, the subjects preferentially selected a higher fat intake for the first meal-time at breakfast time (5.1 MJ d^{-1} of fat post fast vs 3.7 MJ d^{-1} of fat on control; $P < 0.01$), perhaps as a mechanism to increase EI by choosing the most energy-dense foods. This preferential selection of a high-fat intake at breakfast seemed to have returned motivation to eat and food intake to equilibrium. The effects of breakfast intake on satiety appear to have swamped any further increase in the urge to eat for the remainder of the day. Notably, both men and women appear similar in this respect. On average, subjective hunger, as measured by visual analogue scales, was affected by nutritional status with mean ratings of 35, 66 and 42 mm (sed 3.0) ($P < 0.001$), respectively, for all subjects. A closer inspection of the hourly data revealed that this effect was due to the higher pre-breakfast values. When these morning values were accounted for, there was no significant difference between days. Volunteers did not report any significant change in subjective thirst, energy, fatigue, tiredness, tenseness or contentment during the fast.[27]

We found the following answers to our questions on the consequences of short-term food restriction:

1. *How effective is the regime in achieving WL?* Subjects lost 1–2% body weight, which is most likely due to the mobilisation of glycogen stores and water, rather than metabolism of fat mass.
2. *What is the impact on psychology?* There were increased feelings of hunger during fasting that were quickly diminished by a high-fat breakfast meal. Subjects cannot, or are not inclined to, consume enough food to restore energy balance completely.
3. *What are the long-term effects?* Unfortunately, this was not monitored. This introduces a question on the role of IF in the control of body weight. What would happen if the experiment was repeated once a week over a three-month period? Would subjects quickly learn to compensate prior to and/or after fasting, or could they slowly reduce body weight, with no apparent negative impact on health and well-being? Furthermore, would obese subjects respond differently compared with lean subjects? Finally, would a longer fasting period provoke more efficient compensation and how would this compare to a more conventional calorie-restricted regime?

LONGER-TERM IF OR ADF

How effective is the regime in achieving WL? Does it work in the long term?

Similar to experiments performed in rodents, 2 weeks of ADF had no effect on body weight in normal-weight human subjects.[28] Nevertheless, when the intervention period was extended to 3 weeks for normal-weight subjects, a decrease in body weight (~2.5 %) was noted.[29] This decrease in body weight was likely to have resulted from an inability to consume an adequate amount of food on the re-feed day to sustain body weight. Only a handful of studies have been performed to test the effects of ADF on body weight and coronary heart disease (CHD) risk reduction, and almost all of these studies have been undertaken in obese populations (body mass index 30–39.9 kg m^{-2}).[30–32] Results from these initial trials indicate that ADF is effective for WL (5–6% reductions in body weight) and visceral fat mass loss (5–7 cm reductions in waist circumference) during 8–12 weeks of treatment in overweight subjects. These reports also suggest that ADF may aid in the retention of lean mass in obese individuals.[30–32] In addition to these favourable body composition changes, improvements in CHD risk have also been noted. For instance, decreases in low-density lipoprotein cholesterol (20–25%) and triacylglycerol concentrations (15–30%), and increases in low-density lipoprotein particle size, are often observed with short-term ADF (8–12 weeks).[30–32] Beneficial changes in blood pressure and adipokine profile (that is increases in adiponectin and decreases in leptin and resistin) have also been reported.[30–32] Taken together, this preliminary work suggests that ADF may be effective for WL and CHD risk reduction in *obese* adults.

It is interesting to note that these studies seem to suggest that hunger is maintained during ADF in normal-weight subjects, but is adaptive in obese subjects,[33] similar to suggestions in a previous fasting review.[34] This needs to be substantiated in controlled trials, where there could be a focus on also manipulating what is consumed on the fasting days to modify hunger by using high-protein diets.

An important question that remains unresolved is whether the favourable effects of ADF can also be observed in normal-weight and overweight populations. Only a few human studies have tested the effect of ADF on body weight and CHD risk in non-obese subjects. In a study by Heilbronn *et al.*,[29] normal-weight men and women (body mass index 23 $kg\,m^{-2}$) participated in an ADF regimen for 3 weeks.[29] Body weight decreased by 2% from baseline, but triacylglycerol concentrations decreased in men only. Contrary to these findings, Halberg *et al.*[28] demonstrated no change in body weight after 2 weeks of ADF in normal-weight men (body mass index 26 $kg\,m^{-2}$).[28] These trials are limited by their short durations (2–3 weeks) and lack of a control group. Varady *et al.*[33] conducted a 12-week study in normal-weight and overweight subjects (body mass index 20–30 $kg\,m^{-2}$), randomized to either an ADF group or a control group for 12 weeks.[33] They indicate that body weight decreased significantly by 5.2 ± 0.9 kg ($6.5 \pm 1.0\%$) in the ADF group, relative to the control group, by week 12. Fat mass was reduced by 3.6 ± 0.7 kg, and fat-free mass did not change, compared with controls. Triacylglycerol concentrations decreased ($20 \pm 8\%$) and low-density lipoprotein particle size increased in the ADF group relative to controls. C-reactive protein decreased ($13 \pm 17\%$) in the ADF group relative to controls at week 12. Plasma adiponectin increased ($6 \pm 10\%$), whereas leptin decreased ($40 \pm 7\%$), in the ADF group versus controls by the end of the study. Low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, homocysteine and resistin concentrations remained unchanged after 12 weeks of treatment. They conclude from these findings that ADF is effective for WL and cardio-protection in normal-weight and overweight adults, although further research implementing larger sample sizes is required before solid conclusion(s) can be reached.

Body composition change during ADF is an important consideration—both fat mass loss and potential [negative] impact on lean body mass. Adipose tissue mass or distribution is associated with the development of several disorders, including type 2 diabetes, cardiovascular disease and certain cancers.[35,36] One of the factors that may link body fat to disease risk are the hormonal mediators released by adipose tissue.[37,38] Calorie restriction (CR) regimens have received considerable attention, in part because of their ability to reduce the occurrence of chronic diseases and extend lifespan in experimental animals.[38,39] A reduction in daily EI by 20–40% of baseline requirements has consistently resulted in the prolongation of average and maximal lifespan in a variety of animal models,[38,39] as well as reduced cancer incidence, improved insulin sensitivity, reduced atherosclerotic lesion development, lowered inflammatory response and decreased the production of reactive oxygen species.[39,40] More recently, intermittent feeding regimens, typically consisting of ADF protocols, have been shown to reproduce many of the effects of CR on risk factors for disease.[41] True ADF regimens consist of a period (most often 24 h) of *ad libitum* feeding alternated with a period of fasting. Modified ADF regimens, which allow a small portion of calories to be consumed on the fast day, for example, 25–50% of baseline energy needs, have also been implemented and have been shown to reproduce several of the effects of true ADF.[42–43]

In summary, these preliminary findings suggest that ADF is a viable WL strategy for normal-weight and overweight individuals wishing to lose a moderate amount of weight (5–6 kg) within a relatively short period of time (12 weeks). This diet may also help lower CHD risk in non-obese individuals, although further investigation is warranted to confirm these effects.

WHAT IS THE IMPACT ON PSYCHOLOGY AND BEHAVIOUR?

Heilbronn *et al.*[29] have noted that alternate-day fasting is feasible in non-obese (normal weight) subjects, with a resultant increase in fat oxidation.[29] However, hunger on fasting days did not decrease, perhaps indicating the uncertainty associated with continuing this diet for extended periods of time. Adding one small meal on a fasting day may make this approach to dietary restriction more acceptable. Klempel *et al.*[44] studied sixteen obese subjects (12 women/4 men) completing a 10-week trial consisting of 3 phases: (1) a 2-week control phase; (2) a 4-week alternate day modified fast (ADMF) controlled feeding phase; and (3) a 4-week ADMF self-selected feeding phase.[44] Subjects consumed, on average, 95% of energy requirements on feed days—thus, there was no hyperphagic response. The physical activity level of subjects at each week of the trial was measured as steps per day. There were no changes in the number of steps per day taken over the course of the 10-week trial, on both fed and fasting day values and habitual physical activity. Similar results have also been reported in normal-weight individuals undergoing ADMF.[28] Changes in perceived hunger, satisfaction with diet, and fullness were also evaluated on each fast day throughout the trial. This study was the first to show that obese subjects become habituated with ADMF after approximately 2 weeks of diet (that is, feel very little hunger on the fast day). The data also demonstrate that subjects become more satisfied with ADMF after ~4 weeks of diet. Feelings of fullness, however, remained low across the course of the trial, suggesting that subjects never felt 'full' at any point while undergoing 8 weeks of ADMF. These findings may have important implications for long-term adherence to ADMF for obese men and women. It is important to note, however, that the subjects only completed the VAS scales before bedtime. Thus, the data only reflect their feelings immediately before going to bed and are not indicative of their feelings of hunger and satisfaction throughout the day. These findings indicate that obese subjects quickly adapt to ADMF, and that changes in energy/macronutrient intake, hunger and maintenance of physical activity have a role in influencing the rate of WL by ADMF.

ADF AND DISEASE RISK

It is important to understand whether the mechanisms by which ADF protects against chronic disease risk are similar to those of CR. Indirect evidence suggests that the two regimens may share mechanisms. For instance, the study by Descamps *et al.*[45] reported increases in spleen mitochondrial superoxide dismutase activity accompanied by decreases in mitochondrial generation of reactive oxygen species as a result of ADF, in rodent models.[45] Such findings suggest that ADF may act by increasing resistance to oxidative insult, which is a key feature of the stress resistance hypothesis.[46] In summary, the literature suggests that ADF may effectively modulate metabolic and functional risk factors, thereby preventing or delaying the future occurrence of common chronic diseases, at least in animal models. However, the effect of ADF on chronic disease risk in normal-weight human subjects remains unclear, as do the mechanisms of action. Much work remains to be done to understand this dietary strategy fully. A central element in the response to CR regimens is reduced body weight and adipose tissue mass.[31] In contrast, ADF regimens, particularly when modified to allow some EI on the restricted day, do not necessarily result in loss of body weight or adipose tissue mass in normal-weight subjects. Whether changes in adipose mass or physiology are required for the beneficial effects of CR or ADF regimens is an important question. Varady and Hellerstein[47] reviewed the effects of CR and ADF regimens on adipose tissue morphology, triglyceride metabolism and adipokine release, and attempted to link these changes to indicators of chronic disease risk.[47] In conclusion, CR regimens, which involve a reduction in daily EI of 20–40% of baseline needs, and ADF regimens, which involve intermittent reductions of EI, both beneficially alter several aspects of adipocyte biology, including morphology, lipid metabolism and adipokine release. Although these parameters may be related individually to decreased disease risk, they may also function together to protect against certain disorders. Varady and Hellerstein[47] identified three parameters that may be linked in the following manner: (1) CR- and ADF-induced increases in lipolysis may lead to net fat loss from the cell; (2) net fat loss would then result in decreased adipocyte size; and (3) smaller adipocytes may have reduced secretion of certain pro-inflammatory mediators such as leptin.[47] Modulations in adipocyte physiology of this type may play an important role in mediating the beneficial effects of CR and ADF on chronic disease.

Some discrepancies between human and animal ADF data are evident. With regard to the effect of ADF on the risk of type 2 diabetes mellitus, the results to date from human trials have been inconsistent, whereas animal evidence suggests favourable alterations. Similarly, although overall beneficial modulations in risk factors for vascular disease have been found with respect to blood pressure, the evidence from animal studies has shown a consistent decrease in both systolic and diastolic readings, whereas data from human trials have shown no effect on either variable. Varady and Hellerstein[47] suggest that longer-term interventions are required.[47]

In terms of diabetes risk, animal studies of ADF have found lower diabetes incidence and lower fasting glucose and insulin concentrations, effects that are comparable to those of CR. Human trials to date have reported greater insulin-mediated glucose uptake but no effect on fasting glucose or insulin concentrations. In terms of cardiovascular disease risk, animal ADF data show lower total cholesterol and triacylglycerol concentrations, a lower heart rate, improved cardiac response to myocardial infarction and lower blood pressure. The limited human evidence suggests higher high-density lipoprotein-cholesterol concentrations and lower triacylglycerol concentrations but no effect on blood pressure. In terms of cancer risk, there is no human evidence to date; yet, animal studies found decreases in lymphoma incidence, longer survival after tumor inoculation and lower rates of proliferation of several cell types. The findings in animals suggest that ADF may effectively modulate several risk factors, thereby preventing chronic disease, and that ADF may modulate disease risk to an extent similar to that of CR. More research is required to establish definitively the consequences of ADF. McCaffree[48] suggested, 'If the mechanism is intact, and if we can understand the mechanism, we should be able to activate it pharmacologically. This would be a much better way to go than actual caloric restriction.'[48] It is an interesting concept that 'popping a pill' in this context might prolong the lifespan and confer health benefits for the currently overweight and obese human population. If the pharma industry can identify mechanisms, it would be an amazing discovery for future generations.

IF AND LIFESPAN?

There is no long-term randomised controlled trial data on humans to refer to, and the likelihood of CR increasing longevity in humans is argued in the literature.[49] There are studies underway in the US, but no conclusions have been drawn. There are a number of interesting observations that are worthy of discussion. Is it a lower body mass or a lower EI that is linked to longevity? The two are linked, but have different implications for practical advice for 'living well longer'. CR diets typically lead to reduced body weight, and in some studies low body weight has been associated with increased mortality, particularly in late middle-aged or elderly subjects. CR is also known as CRON, for 'CR with optimal nutrition', which is defined as lowering calories while still keeping healthy levels of protein, vitamins and minerals—an important consideration for ageing populations. WL is not the primary goal of a CR diet, but it is apparent that if you eat fewer calories you will slim down and body weight will plateau as EI reaches energy expenditure. Research indicates that being overweight, or carrying excess body fat, is harmful to long-term health as risk factors increase for conditions ranging from diabetes to cancer to Alzheimer's, most likely due to the relationship between fat cells and chronic inflammation. Some part of the health benefits of CR are likely to stem from the accompanying loss of weight and body fat—although biochemical research indicates that there is clearly also adoption at a cellular level. One much-cited Spanish study published in 1956 seemingly investigated the effects of alternate-day CR for 3 years in an old-age home run by a religious order (discussed in full by ref. 50) In that study, the pensioners (all over 65 years of age) were allowed 1 l of milk and 2–3 pieces of fruit (about 900 kcal) on their energy-restricted day and 2300 kcal on the other day. The control group was fed the standard Institutional diet in the nursing home. The subjects randomly assigned to alternate-day CR spent less time in the infirmary and had a lower death rate compared with the control group (6 versus 13; NS).[50] However, the subjects did not lose weight, and the treatment subjects were either consuming 700 calories less (900) or 700 calories more (2300) than the daily requirement of 1600 calories on the two days. This study is therefore not a study of 'caloric restriction' but instead is a study of an oscillating pattern of consumption with no change in body weight. A study of long-term CR practitioners who had been consuming a CR diet (approximately 35% less calories than controls) for an average of 6.8 ± 5.2 years (mean age 52.7 ± 10.3 years) found that they had reduced bone mineral density at the level of the hip and spine, in accordance with a previous one-year weight-loss trial, but that after initial WL they had achieved a stable, normal level of bone turnover and the microarchitectural structure of their bones was healthy.[51] The authors of a 2007 review of the CR literature warned that '[i]t is possible that even moderate CR may be harmful in specific patient populations, such as lean persons who have minimal amounts of body fat.'[39]

In summary, data from animal studies suggest that it is not just CR that is important, but the degree and time of CR onset, the timing of food intake, and diet composition also play major roles in promoting health and longevity.[52] Data from human studies indicate that long-term CR with adequate intake of nutrients results in several metabolic adaptations that reduce the risk of developing type 2 diabetes, hypertension, cardiovascular disease and cancer. Moreover, CR opposes the expected age-associated alterations in myocardial stiffness, autonomic function and gene expression in the human skeletal muscle. However, it is possible that some of the beneficial effects on metabolic health are not entirely due to CR but also due to the high-quality diets consumed by the CR practitioners. More studies are needed to understand the interactions among single nutrient modifications (for example, protein/amino-acid dietary intake, fatty acid profile, vitamins and minerals, phytochemicals), the degree of CR, time of eating and the frequency of food consumption in modulating anti-ageing metabolic and molecular pathways and in the prevention of age-associated diseases.

CONCLUSIONS

How effective is the regime in achieving WL in terms of actual WL (kg) and composition of the loss (fat and lean mass)? We can conclude that fasting is a relative 'quick fix' to achieve a substantial WL over a period of a few weeks, and therefore may be a useful tool for WL.

What impact does it have on psychology/behaviour? Or more specifically how do people feel during and after restriction, because this is an important indicator as to whether they will be compliant on a regime (and hence lose weight). We do not have an approach to know which persons will adapt well to this eating regime. There is, however, the problem of elevated hunger during food restriction and this may provide too great a challenge to a 'faster' in not breaking compliance to the dieting regime and reaching for the biscuit barrel. The foods consumed (macronutrient profile) during the fasting days have not been considered in the published literature, and it could be speculated that a high-protein meal would help reduce hunger and promote satiety during energy deficit.[2] Further, protein should be recommended to maintain muscle mass during negative energy balance.

Does it work in the long term? Does it have an impact on physiology, exercise ability and weight re-gain and improve risk factors for disease and/or longevity? ADF regimens may be as efficacious as daily CR in improving certain indices of risk of type 2 diabetes and CVD, although the number of studies directly comparing the 2 regimens is small. Further analysis of the mechanisms responsible for beneficial effects of ADF are clearly warranted, particularly if these effects occur in the absence of negative energy balance. Novel mediators and therapeutic strategies may thereby be uncovered. Finally, it seems intuitively likely that persons will find it easier to fast or reduce intake on alternate days than to reduce their intake every day. For this reason, ADF regimens may allow better compliance than would CR regimens and may represent an attractive area for investigation. Post WL, it is unclear what mechanisms or behavioural traits promote weight stability, but in the longer term it seems likely that fasting can contribute to maintenance of WL in some phenotypes. IF remains an intriguing intervention that may provide a novel method of body weight control for certain individuals.

CONFLICT OF INTEREST

AMJ is a consultant for the food industry retail sector and conducted contract research for food industry partners.

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REFERENCES

1 Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr* 2013; **97**: 505–516.
2 Johnstone AM. Safety and efficacy of high-protein diets for weight loss. *Proc Nutr Soc* 2012; **71**: 339–349.
3 Santesso N, Akl EA, Bianchi M, Mente A, Mustafa R, Heels-Ansdell D *et al.* Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. *Eur J Clin Nutr* 2012; **66**: 780–788.
4 Clifton PM, Condo D, Keogh JB. Long term weight maintenance after advice to consume low carbohydrate, higher protein diets - a systematic review and meta analysis. *Nutr Metab Cardiovasc Dis* 2013; **24**: 224–235.
5 Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L *et al.* High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutr* 2011; **93**: 1062–1072.
6 Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; **273**: 219–234.
7 Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* 2012; **307**: 56–65.
8 Elia M. Effect of starvation and very low calorie diets on protein-energy interrelationships in lean and obese subjects. In: Scrimshaw N, Schurch B (eds) *Protein-Energy Interactions. International Dietary Energy Consultancy Group, Proceedings of an IDECG workshop*. Nestle Foundation: Lausanne, 1991; 249–284.
9 McCance RA, Widdowson EM. *Calorie Deficiencies and Protein Deficiencies*. Churchill: London, UK, 1951.
10 Polivy J, Zeitlin SB, Herman C, Peter B, Lynne C. Food restriction and binge eating: A study of former prisoners of war. *J Ab Psych* 1994; **103**: 409–411.
11 Polivy P. Psychological Consequences of Food Restriction. *J Am Diet Ass* 1996; **96**: 589–592.
12 Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The Biology of Human Starvation*. The University of Minnesota Press, North Central Publishing: Minneapolis, MN, USA, 1950.
13 Gharbi M, Akrout M, Zouari B. Food intake during and outside Ramadan. *East Mediterr Health J* 2003; **9**: 131–140.
14 Beltaifa L, Bouguerra R, Ben Slama C, Jabrane H, El-Khadhi A, Ben Rayana MC *et al.* Food intake, and anthropometrical and biological parameters in adult Tunisians during fasting at Ramadan. *East Mediterr Health J* 2002; **8**: 603–611.
15 Finch GM, Day JE, Razak, Welch DA, Rogers PJ. Appetite changes under free-living conditions during Ramadan fasting. *Appetite* 1998; **31**: 159–170.
16 Stuart WK, Flemming LW. Features of a successful therapeutic fast of 382 days duration. *Postgrad Med J* 1973; **49**: 203–209.
17 Benedict FG. Chemical and Physiological Studies of a Man Fasting Thirtyone Days. *Proc Natl Acad Sci USA* 1915; **1**: 228–231.
18 Bloom WL. Fasting as an introduction to the treatment of obesity. *Metabolism* 1959; **8**: 214–220.
19 Duncan GG, Jenson WK, Fraser RI, Cristofori FC. Correction and control of intractable obesity. Practicable application of intermittent periods of total fasting. *JAMA* 1962; **181**: 309–312.
20 Drenick EJ, Swendsoid BWH, Tuttle SG. Prolonged starvation as treatment for severe obesity. *JAMA* 1964; **187**: 140.
21 Cahill GF Jr.. Starvation in man. *N Engl J Med* 1970; **282**: 668–675.
22 Wadden TA, Stunkard AJ, Brownell KD. Very low calorie diets: their efficacy, safety, and future. *Ann Intern Med* 1983; **99**: 675–684.
23 Silverstone JT, Stark JE, Buckle RM. Hunger during total starvation. *Lancet* 1966; **1**: 1343–1344.
24 Bolinger RE, Lukert BP, Brown RW, Guevara L, Steinberg R. Metabolic balance of obese subjects during fasting. *Arch Intern Med* 1966; **118**: 3–8.
25 Lappalainen R, Sjödén PO, Hursti T, Vesa V. Hunger/craving responses and reactivity to food stimuli during fasting and dieting. *Int J Obes* 1990; **14**: 679–688.
26 French SA, Jeffery RW, Murray D. Is dieting good for you?: Prevalence, duration and associated weight and behaviour changes for specific weight loss strategies over four years in US adults. *Int J Obes Relat Metab Disord* 1999; **23**: 320–327.
27 Johnstone AM, Faber P, Gibney ER, Elia M, Horgan G, Golden BE *et al.* Effect of an acute fast on energy compensation and feeding behaviour in lean men and women. *Int J Obes Relat Metab Disord* 2002; **26**: 1623–1628.
28 Halberg N, Henriksen M, Söderhamn N, Stallknecht B, Ploug T, Schjerling P *et al.* Effect of intermittent fasting and refeeding on insulin action in healthy men. *J Appl Physiol (1985)* 2005; **99**: 2128–2136.
29 Heilbronn LK, Smith SR, Martin CK, Anton SD, Ravussin E. Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. *Am J Clin Nutr* 2005; **81**: 69–73.
30 Varady KA, Bhutani S, Church EC, Klempel MC. Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. *Am J Clin Nutr* 2009; **90**: 1138–1143.
31 Klempel MC, Kroeger CM, Varady KA. Alternate day fasting (ADF) with a high-fat diet produces similar weight loss and cardio-protection as ADF with a low-fat diet. *Metabolism* 2013; **62**: 137–143.
32 Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. *Obesity* 2013; **21**: 1370–1379.
33 Varady KA, Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Haus JM *et al.* Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. *Nutr J* 2013; **12**: 146.
34 Johnstone AM. Fasting - the ultimate diet? *Obes Rev* 2007; **8**: 211–222.
35 Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007; **132**: 2169–2180.
36 Hursting SD, Nunez NP, Varticovski L, Vinson C. The obesity-cancer link: lessons learned from a fatless mouse. *Cancer Res* 2007; **67**: 2391–2393.
37 Ahima RS. Adipose tissue as an endocrine organ. *Obesity* 2006; **14**: S242–S249.
38 Gredilla R, Barja G. Minireview: the role of oxidative stress in relation to caloric restriction and longevity. *Endocrinology* 2005; **146**: 3713–3717.
39 Rondinone CM. Adipocyte-derived hormones, cytokines, and mediators. *Endocrine* 2006; **29**: 81–90.
40 Fontana L, Klein S. Aging, adiposity, and calorie restriction. *JAMA* 2007; **297**: 986–994.
41 Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Annu Rev Med* 2003; **54**: 131–152.
42 Varady KA, Hellerstein MK. Alternate-day fasting and chronic disease prevention :a review of human and animal trials. *Am J Clin Nutr* 2007; **86**: 7–13.
43 Varady KA, Roohk DJ, Hellerstein MK. Dose effects of modified alternate-day fasting regimens on in vivo cell proliferation and plasma insulin-like growth factor-1 in mice. *J Appl Physiol* 2007; **103**: 547–551.

44 Varady KA, Roohk DJ, Loe YC, McEvoy-Hein BK, Hellerstein MK. Effects of modified alternate-day fasting regimens on adipocyte size, triglyceride metabolism and plasma adiponectin levels in mice. *J Lipid Res* 2007; **48**: 2212–2219.
45 Klempel MC, Bhutani S, Fitzgibbon M, Freels S, Varady KA. Dietary and physical activity adaptations to alternate day modified fasting: implications for optimal weight loss. *Nutr J* 2010; **9**: 35.
46 Descamps O, Riondel J, Ducros V, Roussel AM. Mitochondrial production of reactive oxygen species and incidence of age-associated lymphoma in OF1 mice: effect of alternate-day fasting. *Mech Ageing Dev* 2005; **126**: 1185–1191.
47 Kirkwood TL, Kapahi P, Shanley DP. Evolution, stress, and longevity. *J Anat* 2000; **197**: 587–590.
48 Varady KA, Hellerstein MK. Do calorie restriction or alternate-day fasting regimens modulate adipose tissue physiology in a way that reduces chronic disease risk? *Nutr Rev* 2008; **66**: 333–342.
49 McCaffree J. What you should know about calorie restriction. *J Am Dietet Assoc* 2004; **104**: 1524–1525.
50 Le Bourg E, Rattan SI. Can dietary restriction increase longevity in all species, particularly in human beings? Introduction to a debate among experts. *Biogerontol* 2006; **7**: 123–125.
51 Johnson JB, Laub DR, John S. The effect on health of alternate day calorie restriction; Eating less and more than needed on alternate days prolongs life. *Med Hypotheses* 2006; **67**: 209–211.
52 Villareal DT, Fontana L, Weiss EP, Racette SB, Steger-May K, Schechtman K *et al.* 'Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial". *Arch Int Med* 2006; **166**: 2502–2510.
53 Rizza W, Veronese N, Fontana L. What are the roles of calorie restriction and diet quality in promoting healthy longevity? *Ageing Res Rev* 2014; **13C**: 38–45.