The impact of intermittent dieting and the ketogenic diet on societal health

In relation to obese and overweight individuals, how effective are intermittent fasting and the ketogenic diet at improving general health?

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Introduction

Human beings' relationship with food has drastically changed since pre-industrial times. What used to be a seasonal resource has recently become an extremely abundant commodity that has both fueled relative prosperity but also a global health issue: obesity. The World Health Organization found that 39% of adults were overweight and 13% were obese in 2016 ("Obesity and overweight").

Repeated studies have related overweightness and obesity to higher risks of cardiovascular disease, diabetes, musculoskeletal diseases and some cancers (Aune et al. 11), even all-cause mortality (Prospective Studies Collaboration 1083). One large study conducted by the Global Disease Burden concluded that the overall prevalence of obesity by 2015 was 5% for children and 12% for adults world-wide (GBD Obesity Collaborators 16). Most of the 195 countries experienced increased obesity prevalence since 1980s; 73 of which showed doubled rates of prevalence (GBD Obesity Collaborators 19). Furthermore, even when accounting for relative wealth levels, these authors found a consistent increase in obesity prevalence, leading them to conclude that:

> "Increased availability, accessibility, and affordability of energy-dense foods, along with intense marketing of such foods, could explain excess energy intake and weight gain among different populations." (GBD Obesity Collaborators 22)

Other speculative causes of the obesity crisis could be the culture of refrigeration, a relatively sedentary modern lifestyle, increased dietary prevalence of saturated fat, added sugars and processed foods, elevated stress levels etc. Given this environment, individuals should try to control a factor which they can: their diet. The World Health Organization's emphasizes that "obesity can be prevented" ("Obesity and overweight"). By utilizing effective, palatable and sustainable diet strategies, there is hope to improve global societal health.

When trying to improve societal health, one needs to use objective and measureable results for comparison, which requires defining "healthy." Obesity most significantly affects cardiovascular health (CVH) and has significant overlap with general health as well. Therefore, parameters for measuring CVH will be used for this discussion. Also, it's important to note that obesity is not the only health issue in the world, and resolving it does not promise resolving all aspects of societal health.

In a collaborative effort to improve national cardiovascular health, the American Heart Association established a criterion that characterizes those with good cardiovascular health (See Table #1).

Trait	Specifics
Smoking	No record of smoking in the past 12 months
BMI	<25kg/m^2
Moderate physical activity	minimum 150 mins of moderate exercise per week, ~60 mins per day for children (e.g brisk walking)
Healthy diet	Low glycemic load, high fiber, high polyunsaturated fatty acids, low saturated fatty acids, low trans fat etc.
Cholesterol levels	<200mg/dL for adults; <170mg/dL for children
Blood pressure	<120/80 mmHg
Fasting Blood Glucose	<100mg/dL

Table #1: Ideal health traits for cardiovascular health derived from the American Heart Association (Lloyd-Jones et al., "Defining" 591)

In numerous studies, these factors have been shown to significantly improve cardiovascular health and limited related diseases. These traits of a healthy lifestyle have been shown to

decrease risks for coronary heart disease (Chuive et al., "Healthy Lifestyle" 160), stroke (Chuive et al., "Primary Prevention" 947), diabetes in women (Hu et al. 790), diabetes in the elderly (Mozaffarian et al. 2), life span for older adults (Knoops 1433), cardiovascular and non-cardiovascular death (Lloyd-Jones et al., "Lifetime Risks" 2), and overall subjective quality of life at old age (Daviglus 2460). These results illustrate the significance in a healthy lifestyle in maintaining or improving general health, and it's important to note that 5 of the 7 ideal traits suggested has a direct or indirect relationship to diet (BMI, diet, cholesterol, blood pressure, fasting blood glucose). It is also important to recognize that alcohol consumption is omitted in this criterion (See Table #1). Although moderate alcohol consumption has been included in many other criterions for optimum CVH, the authors believed that "the risks of alcohol abuse were significant and prevalent enough that the AHA should not recommend universal alcohol use as a means to achieve cardiovascular health" (Lloyd-Jones et al., "Defining" 608).

Combining scientific and statistical evidence, it is clear that there should be a stronger emphasis placed on improving societal diets, and this can start with investigating two recent and potentially beneficial diets, intermittent fasting and the ketogenic diet. This leads to the question: in relation to obese and overweight individuals, how effective are intermittent fasting and the ketogenic diet at improving general health?

Intermittent fasting (IF), also known as time-restricted feeding, is a diet mainly concerned with food timing rather than the food consumed. This diet, as the name suggests, recommends people to periodically fast, either as part-day fasts or full-day fasts. Another popular regimen is called alternate day fasting (ADF), which employs periodic 24-hour fasts a few times a week (Gunnars). Both of these diet regimens are under the broad category of intermittent energy restriction (IER), which involves *periodic* energy restriction rather than

the conventional diet of *daily* energy restriction (Gunnars). All forms of IER offer a level of freedom for the dieter to choose times of energy restriction that most suit their lifestyle, something that can significantly improve social compatibility, diet adherence, and thus long term health. In this discussion, however, the specific distinctions between different types of IER will not be explored as heavily, and some experimental results will be generalized and synthesized for all three diets. The intuitive benefits of IF are that by shrinking the feeding window, it becomes *more* difficult to consume one's daily caloric needs, and can often more *easily* lead to a caloric deficit despite eating "more" per meal. Metabolically, there has been some research on how restricting food in ways which are aligned with your cardiac rhythm can improve metabolic profiles (Patterson and Sears 386). The scientific research suggests that IER regimens have notable effects on weight loss, FFM retention, and blood lipid profiles, as well as having easier diet adherence than daily energy restriction or the ketogenic diet.

The ketogenic diet is one that only severely restricts carbohydrate intake (to usually less than 50 grams per day) (Paoli et al. 789), but no other macronutrient. Through limitation of glucose consumption, the diet aims to increases lipolysis (Paoli et al. 790) and gluconeogenesis (Veldhorst et al. 519) for energy. Therefore, ketogenesis occurs, a process where the body uses acetyl-coA in the liver to produce ketone bodies (Acetoacetate, ß-hydroxybutyric acid, and acetone), causing elevated levels of ketone bodies that are present in the blood circulation (Veech 309) – the most prominent feature of a ketogenic dieter. Ketone bodies can then be broken down for energy through the Krebs's Cycle using acetyl-coA (Westman et al. 477). But the dietary benefits of the ketogenic diet are limited to during ketogenesis (Paoli et al. 789). Practically, this means strictly limiting or removing starchy, grainy, and doughy foods, some common examples being rice, beans, pasta, cereal, bread etc. Decreased carbohydrate intake could then either reduce overall calorie intake or increase

proportional calories of protein and fat, both of which have certain implications for improved weight-loss. Overall, the ketogenic diet shows prominent benefits for weight loss and blood lipid profiles.

Impact of Intermitting Fasting (IF) and Ketogenic Diets (KD) on weight loss

One of the major risk factors for premature mortality is a high body mass index (BMI) (Aune et al. 1). BMI is calculated in kg/m^2 and measures the average distribution of mass throughout one's body. An "unhealthy" BMI, as determined by the AHA, is $>25kg/m^2$, with which individuals are classified as "overweight" (Lloyd-Jones et al., "Defining" 591). BMI is one of the most direct tools to measure the reduction of obesity and can be directly compared between diets. Also, assuming that subjects do not experience significant height growth during a study, reductions in bodyweight are just as important.

For intermittent energy restriction (IER) diets, studies show very positive results for lowering BMI and weight. In a 2015 systematic review, Horne et al concluded that "routine fasters" had a statistically significant lower BMI; however, this claim was undermined by its study count, containing only three randomized-controlled clinical trials and 2 observational studies (Horne et al. 467). Another systematic review covering 9 studies concluded that intermitting fasting (IF) is an "effective" alternative for weight loss in overweight and obese subjects (Antonelli et al. 34). A similar significant positive impact of IF regimens on weight control were also demonstrated in another review (Harris et al. 519). Furthermore, in a meta-analysis of studies lasting longer than 6 months, authors found that IER was successful at achieving weight loss as well (Headland et al. 9). Interestingly, all four studies note that the degree of success of IER in weight loss was indistinguishable from that of conventional diets. This highlights two potential conclusions: first, one could argue that IER offers no external benefit

to a conventional diet, making it more of a "fad"; but also that IER, a diet regimen that emphasizes leniency and flexibility, might offer the same benefits as the more restrictive alternative. Overall, IER interventions show a positive impact on obese and overweight populations' weight control.

Compared to IF, the ketogenic diet displays even more positive results for improving body mass index (BMI) and bodyweight. In a meta-analysis of 13 clinical trials of ketogenic diets, there was significant weight-loss at the 6-11, 12-23, and 24 months' check-in, and an average BMI decrease of 2.09 (Santos et al. 15). Similar results were shown in obese adolescents, who experienced rapid and consistent weight loss over a 12-week period, improving their BMI by 3.3 on average (Sondlike et al. 256). Led by one of the leading figures in ketogenic dieting, another review concluded that there was "no doubt" the ketogenic is effective at inducing beneficial weight loss (Paoli et al. 790). Professor Antonio Paoli's confidence is high, but it is important to note that clinical and interventional trials do not simulate every-day circumstances, and dietary success in research is not always completely transferable to real life. In contrast to intermittent fasting, studies on the ketogenic diet suggest that it may outperform other more conventional diets. In a 2-year study comparing the Mediterranean and ketogenic diet in obese subjects, the ketogenic diet had faster and ultimately more (though not statistically significantly) weight loss (Shai et al. 238). A similar superiority was found in a large review comparing the ketogenic diet to low-fat diets for weight loss (Bueno et al. 1181). However, no significant difference was found in a meta-analysis comparing a balanced and ketogenic diet (Naude et al. 14). Overall, the ketogenic diet shows promising results for weight loss in obese and overweight subjects, stronger than that of intermittent fasting.

Impact of IF and KD on the proportions of Fat Mass and Fat-free Mass loss

While successful weight loss is definitely important to any diet plan, the proportions of fat mass and fat-free mass lost should also be considered. Preserving more muscle mass not only maintains body functions, but can also limit the decreases of resting energy expenditure (REE) associated with loss of body mass. If not accounted for, a decreased REE can be a hidden cause of weight regain after dieting especially if compounded with unrealistic and drastic dietary changes.

Regarding fat-free mass (FFM) and fat-mass (FM) loss, intermittent energy restriction (IER) shows a predominantly null or positive effect, while normal diets show a consistent negative effect, giving IER a slight edge. One review concluded that low-fat alternate-day-fasting (ADF) diets showed promising results in decreasing FM and preserving FFM, but only three studies were included and lasted only 3, 8 and 12 weeks (Klempel et al. 7). In another review of ADF, mixed results for both FFM and FM were found (Hoddy et al. 8). Another meta-analysis of intermittent fasting (IF) on obese and overweight subjects had found a significant positive effect on FM but not FFM retention (Harris et al. 520). Similarly, a large review of IER diets concluded that most studies (20 out of 32) found positive effects on FM, while around half of the studies (9 out of 17) found negative effects on FFM and the other half found no effect (Seimon et al. 18). One other review concluded that the protein intake level of subjects was a more major determinant of FFM retention than the nature of the diet (Harvie et al. 10), which is supported by a large meta-regression study of protein intake and the preservation of FFM during diets (Krieger et al. 270). It should also be noted that regular diets have been shown to consistently decrease FFM with little evidence for otherwise (Harvie et al. 10). Overall, IER diets are potentially superior to regular diets in terms of FFM retention and FM loss due to the general conclusion of a non-negative effect on those

variables.

There exists of very few studies of ketogenic diets and its effects on the proportions fat mass (FM) and fat-free mass (FFM) loss, making their relationship very inconclusive. In a 1-year study with 377 obese subjects, authors found almost equal amounts of FM and FFM loss, both around 50% of total weight loss (Cicero et al. 391). Other pieces of research have been done through comparing the ketogenic diet to other diets. One study on obese women found that low-fat and low-carbohydrate diets show similar degrees of FM loss (Westman et al. 479). Similarly, another study compared a ketogenic diet with a low-fat diet for 12 weeks, and found no significant difference between them in terms of FM and FFM loss, both at about 2% (Noakes et al. 6). However, there is one study of 20 obese subjects on a ketogenic diet for 4 months that showed significant fat mass reduction, and a mild reduction in fat-free mass that was suspected to be actually body water (Gomez-Arbelaez et al. 494). As dietary carbohydrates are dramatically reduced in the ketogenic diet, intakes of fat and protein will most likely increase due to energy compensation, which means that individuals may retain FFM easier due to the muscle-conserving effect of high protein intakes (Krieger et al 270). However, the research shows mixed and limited results for the ketogenic diet on FFM.

Impact of IF and KD on Blood Serum Profiles

In many obese individuals, blood serum profiles are unhealthy. This may include (but is not limited to) high LDL and total cholesterol levels, blood glucose, triglycerides, C-reactive protein, lipoprotein (a), fibrinogen etc., most of which are risk factors for cardio-metabolic diseases (Ridker et al. 2481). The AHA review only mentions blood cholesterol and fasting blood glucose levels (Lloyd-Jones et al., “Defining” 591), suggesting some level of significance in these metrics, and thus will be the only ones discussed in this essay.

Impact of IF and KD on Blood Cholesterol levels

When considering cardiovascular health, LDL, HDL and total cholesterol levels are very important. After its consumption or natural production, cholesterol is transported by lipoproteins in the blood stream, generally labeled as low (LDL) and high density lipoproteins (HDL). An increased circulation of non-HDL cholesterol can penetrate the endothelium and clog blood vessels, leading to higher occurrences of atherosclerosis, which can contribute to numerous cardiovascular diseases ("Cholesterol"). On the contrary, HDL-cholesterol is known to transport fat out of artery walls, often referred to as the "good" cholesterol ("Cholesterol"). Globally, the World's Health Organisation reported that 39% of adults have elevated cholesterol levels ("Raised Cholesterol"), thereby making reducing LDL and total cholesterol levels and increasing HDL-cholesterol levels a noteworthy aspect of a successful diet.

Intermittent energy restriction (IER) diets show mixed but beneficial effects on blood cholesterol levels, ones that are comparable to regular diets. One large review of intermittent fasting (IF) interventions in obese and overweight subjects found no significant changes in low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol in two studies that reported this metric (Harris et al. 521). Contrarily, a different systematic review of IF showed that two 12-week studies, one of alternate day fasting (ADF) and one of IER, both showed improvements in LDL and total cholesterol levels in their subjects (Horne et al. 466). However, both mentioned reviews only contained two studies, making each study's conclusiveness slightly questionable. Positive effects on cholesterol profiles were also concluded in a review of 4 ADF studies (Hoddy et al. 9). Another review found a mixed but non-negative effect of low-fat ADF diets on all metrics of cholesterol (Klempel et al. 9). When one review compared IER diets to a regular diet for obese and overweight subjects, there were no significant differences between the two in improving cholesterol levels (Harris et al. 519), suggesting that perhaps IER diets offer no particular metabolic or cardiovascular

advantage over normal diets. Overall, many forms of IER diets have shown beneficial effects for cholesterol levels in the body, but this effect may not be different to that of regular diets.

Similarly, the ketogenic diet also shows positive effects on blood cholesterol, which may be counterintuitive due to the elevated cholesterol intake that often accompanies ketogenic dieting. In one review, authors reached an "unexpected finding" that a ketogenic diet can provide beneficial effects on low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol in the general public, but especially in obese individuals (Westman et al. 480). One long term study found persisting benefits of a ketogenic diet on LDL and HDL cholesterol even after 1 year (Cicero et al. 391). Similar positive results emerged from a 66-week study of obese men, in both high and normal cholesterol groups (Dashti et al. 4). Interestingly, the ketogenic diet seems to be metabolically different to other diets in this aspect. Some authors concluded that a low-fat diet is more beneficial for reducing LDL and total cholesterol, while a ketogenic diet only seems to improve HDL-cholesterol levels (Nordmann et al. 285), which is also supported by research by Volek et al (1340). A large systematic review comparing low-carbohydrate and balanced diets found inconsistent results in terms of cholesterol changes in the low-carbohydrate group, while these values consistently decreased in balanced diets (Naude et al. 16). Overall, the ketogenic diet shows beneficial effects on cholesterol levels, potentially through mechanisms that are different to a regular diet.

Impact of IF and KD on Fasting Blood Glucose levels

Fasting blood glucose is a measure of the concentration of circulating glucose in your blood, and is a primary indicator of a body's glucose control. High fasting blood glucose concentrations represent an inability of the liver to secrete insulin in an effective manner, which may have originated from some level of insulin resistance and may contribute to type 2

diabetes ("Symptoms and causes of diabetes"). Through weight management, fasting blood glucose levels should decline, but different diets may achieve different levels of such effect.

The limited evidence of intermittent energy restriction (IER) diets on fasting blood glucose (FBG) provides no significant conclusions for this metric. In one large review of the effect of intermittent fasting on cardiovascular disease (CVD) risk factors, authors found no consistent effect between any study and FBG levels (Antonelli et al. 23). Another large review of intermittent fasting (IF) research in obese and overweight subjects also found no significant changes in FBG, though there was a significant effect on blood insulin levels (Harris et al. 520). On that note, one large systematic review comparing IER to continuous restriction diets (CR) concluded that IER has potential benefits for glucose homeostasis (blood insulin and insulin sensitivity) but not significantly different to those of CR (Seimon et al. 27). Interestingly, a 10-week IF study of 54 obese women showed decreases in FBG and insulin only in the liquid-food group while not in the food-based group (Klempel et al. 1). However, the practicality of liquid-food for obesity interventions are questionable, as well as the limited sample size of 50 subjects. Overall, IER diets show no significant effect on FBG levels, and, if any, it is not significantly different from a traditional diet.

The ketogenic diet has demonstrated a positive impact on fasting blood glucose (FBG) levels, but they may be indistinguishable from other diets. One systematic review evaluated the ketogenic diet on cardiovascular disease (CVD) risk factors in overweight and obese subjects and found a "slight but significant" overall decrease in FBG levels (Santos et al. 8). Similarly, one middle-to-long term study of 337 obese subjects showed significant improvements in FBG at the end of a 4-week ketogenic diet intervention, and its effects persisted even at the 1 year follow up (Cicero et al. 391). A different review found that glucose levels "either improved or remained the same" across 5 ketogenic diet intervention

studies (Westman et al. 480). When compared with other diets, the ketogenic diet may not offer any relative benefits. In a large systematic review, authors compared the effects of ketogenic diets and low-fat diets on FBG and though results were in favour of the ketogenic diets, the difference was not significant (Bueno et al. 1182). A more recent large review compared ketogenic and balanced diets for cardiovascular outcomes, and found significant improvements of both diets for FBG at 3-6 months but none at 1-2 years, and with no significant difference between the diets (Naude et al. 18). Logically, the carbohydrate-restrictive nature of the ketogenic diet should allow it to demonstrate extreme effects on lowering FBG, yet the reality that it is nearly indistinguishable with other diets raises certain questions about the effectiveness of this diet. Overall, scientific research suggests that a ketogenic diet has a significant positive impact on fasting blood glucose, but may not differ in its ability to do so with other more conventional diets.

Impact of IF and KD on Blood Pressure

Hypertension is a very prevalent health concern, and is one of 7 risk factors related to cardiovascular diseases by the American Heart Association (Lloyd-Jones et al., "Defining" 591). This common disease is characterized by blood pressure measurements of 140/90 mmHg or higher ("High Blood Pressure | Hypertension"). Prevalence of hypertension in the US is around 32%, with increasing prevalence with age (Whelton, PK et al. 22), making it an important factor consider when selecting diets.

For forms of intermittent energy restriction (IER), studies that measured blood pressure are scarce, but existing studies show a non-negative effect on blood pressure. One large systematic review of 6 randomized trials concluded that IER had no significant effect in altering blood pressure metrics (Harris et al, 520). Another review of alternate day fasting (ADF) diets found an overall decrease in both systolic and diastolic blood pressure (Hoddy et

al. 11). One small pilot study with 25 obese subjects on a 16-8 intermittent fasting regimen (fast 16hrs, eat 8hrs) found significant effects for systolic but not diastolic blood pressure (Gabel et al. 351), however due to limited sample size this cannot be considered strong evidence. Furthermore, as another researcher also points out, blood pressure is also tightly related with weight loss (Klempel et al. 6), which means that it's difficult to isolate this metric between different dietary interventions. Therefore, only when comparing IER to a regular caloric restriction diet for outcomes of blood pressure can any meaningful conclusions be produced, however no such study exists. Overall, forms of IER show inconsistent results for blood pressure, however no significant negative effect has been documented.

Contrary to IER diets, the ketogenic diet shows a small net positive effect on blood pressure, but no particular advantage over other diets. One study showed that short term ketogenic dieting can produce and sustain long term improvements on numerous cardiovascular parameters, including both systolic and diastolic blood pressure (Cicero et al. 391). Similar positive results were also reported by a systematic review of ketogenic diets (Santos et al. 7). When placed in comparison with other diets, however, the ketogenic diet shows no clear distinction. In a systematic review comparing low-carbohydrate and low-fat diet studies that lasted longer than 12 months, authors reported no difference for systolic blood pressure but a significantly greater reduction of diastolic blood pressure in the low-carbohydrate diets (Bueno et al. 1182). Contrarily, one large meta-analysis comparing low-carbohydrate and balanced diets found no significant difference in changes in blood pressure between the two diets (Naude et al. 18). Another meta-analysis showed a short-term advantage of low-carbohydrate diets over low-fat diets for blood pressure, but the two diets' effects were indistinguishable at 12 months (Nordmann et al. 288). One two-year study in obese subjects showed no difference in reduction in blood pressure between a low-carbohydrate, low-fat and

Mediterranean diet (Shai et al. 235). Overall, the scientific literature suggests that the ketogenic diet can benefit blood pressure, but in no way specifically different to other diets.

Conclusion and Evaluation

Overall, intermittent energy restriction (IER) diets in obese and overweight populations show significant results in decreasing body weight (while also retaining fat-free mass (FFM)), improving blood serum profiles and blood pressure, and doing so in a relatively flexible manner. In comparison, the ketogenic diet is similar but out performs IER diets in terms of impact on weight loss and blood lipid profiles, yet has potential drawbacks in terms of adherence. Also, in many health metrics, the ketogenic diet is generally much more distinct from a conventional diet than an IER diet is. It should be noted that research on IER diets was more scarce and inconclusive (contrary to the ketogenic diet), indicating certain directions for future research. Despite being different to traditional diets in form or in premise, IER and ketogenic diets were not as distinguishable as one would expect, which begs the question of whether these diets are truly effective or even necessary. If these "special" diets (including but not limited to the Paleo diet, Whole30, carnivore etc.) do not produce dramatically better results to regular diets, perhaps the major lifestyle and dietary change – like with the ketogenic diet – may be pointless. However, due to limited research, there may be hidden benefits to certain diets that are channeling major health changes we have not discovered yet. For example, the extreme restriction of carbohydrates in the ketogenic diet may indirectly reduce intake of high-sugar foods or easily accessible fast food, both acting as an unintentional dietary change that will likely produce positive impacts on one's health. Further studies should try to compare health outcomes of different diets while normalizing for weight-loss, and investigate whether or not these diets are actually impactful. Ultimately, as George Thom and Mike Lean proposed in their literary review investigating the "optimal diet", the best diet is one which you can "stick to long enough to achieve the [goal] that you

desire" (Thom and Lean 20). As they describe it, this "obesogenic" (Thom and Lean 9) age will continue to overwhelm individuals (especially those who are obese or overweight) with health information that is very confusing and messy. This review aims to provide a very limited but clearer image of a small corner in the health industry, in effort to unveil the scientific reality piece by piece.

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