AMJ Australasian Medical Journal [AMJ 2018;11(8):426-433]

Intermittent fasting for cardiovascular disease risk factor reduction: A narrative review of current evidence

Callan Gavaghan[1], Rohan Jayasinghe[2]

1. Gold Coast University Hospital, Griffith University, Australia
2. Cardiology Department, Gold Coast University Hospital, Griffith University/ Bond University/ Macquarie University, Australia

REVIEW

Please cite this paper as: Gavaghan C, Jayasinghe R. Intermittent fasting for cardiovascular disease risk factor reduction: A narrative review of current evidence. AMJ 2018;11(8):426–433.
https://doi.org/10.21767/AMJ.2018.3485

Corresponding Author:
Callan Gavaghan
Gold Coast University Hospital,
Griffith University, Southport 4215, Australia
Email: callan.gavaghan@health.qld.gov.au

ABSTRACT

Background
The metabolic syndrome (MetSy), which is defined by the spectrum of obesity, insulin resistance and dyslipidaemia, is recognised as a major contributor to the overall risk of developing cardiovascular disease. Intermittent fasting (IF), which encompasses dieting plans with varying schedules of fasting, may be an effective method of reducing the burden of MetSy and the consequent cardiovascular events in the face of a worsening obesity epidemic in the contemporary society.

Aims
Despite the widespread public interest there is a serious lack of scientific understanding of the evidence base and the safe, optimal recommendations. This has created a level of public confusion that we endeavour to address by this narrative review of the published literature.

Methods
This narrative literature review summarises the current findings and suggests which regimens may be more effective and where future research in this area should be focused.

Results
Although the ideal regimen for IF remains unclear, there is promising evidence that alternate day fasting or modified fasting regimens, paired with or without continuous caloric restriction, may be more effective than continuous caloric restriction alone.

Conclusion
IF has been shown in the small number of human clinical trials discussed here to be an alternative to continuous caloric restriction in reducing the factors that contribute to the development of cardiovascular disease.

Long-term randomised, controlled trials comparing continual caloric restriction and IF are required to objectively assess energy intake, energy expenditure, adherence, disease outcomes and metabolic factors.

Key Words
Intermittent fasting, cardiovascular disease, dieting

What this review adds:

1. What is known about this subject?
Recent trials have revealed that certain IF regimens in combination with calorie-restriction may be more effective than caloric restriction alone in reducing cardiovascular disease risk.

2. What new information is offered in this review?
This review explores the effectiveness of the differing regimens of IF diets and provides a focus for future research.

3. What are the implications for research, policy, or practice?
Effective dieting minimises cardiovascular disease in the

community. The comparison of fasting methods described here provides guidance for practitioners.

Introduction

Excess energy consumption leading to weight gain and increased adiposity has been linked to increased rates of morbidity and mortality in western societies.[1,2] Obesity itself forms a component of MetSy, which includes the cluster of risk factors for cardiovascular disease[3] such as dyslipidaemia, increased insulin resistance and systemic hypertension.[4]

Numerous trials, both in animal and human models, have demonstrated that caloric restriction and intentional weight loss can significantly reduce the deleterious impact of MetSy.[5-7] Epidemiological studies suggest that even modest weight loss of only 5–10 per cent can significantly reduce MetSy, leading to reductions in blood pressure, cholesterol and insulin resistance.[8,9] Long-term, this could reduce the incidence of serious health effects including cardiovascular disease, diabetes, dementia and tumour burden.[10]

The health industry promotes a broad spectrum of weight loss treatments and quick-fixes of varying credibility. However, the obesity epidemic shows no signs of slowing. In 2016 the World Health Organisation estimates that there were more than 1.9 billion overweight adults worldwide, which represents 39 per cent of adults worldwide aged 18 years and over.[11]

Intermittent fasting (IF) is a weight loss strategy that involves subjecting participants to varying periods of fasting. An example of a more commonly used IF diet is alternate day fasting (ADF), which involves removing most, or all, oral intake every second day but eating as normal on alternate days. One of the perceived benefits of ADF over more traditional continual caloric restriction-type diets is that ADF only requires participants to focus on dieting every second day and therefore compliance may be improved long-term.[12]

IF has gained much interest in recent years after several small cohort clinical trials highlighted its potential to accelerate weight loss and reverse MetSy.[13-15] It has been theorised that IF diets encourage the body to use fats for energy and initiate cellular level repairs and metabolic rejuvenation. This process may reduce cardiovascular risk factors and therefore the health benefits of IF may exceed those of simple caloric restriction.[16]

This review will evaluate the clinical evidence that IF in humans is associated with a significant reduction in risk factors for cardiovascular disease and also identify subject areas where further clinical studies are needed.

Methods

Experimental studies and clinical trials on IF were collated from the PubMed and Medline databases. Studies available prior to the time of writing in March 2018 were assessed. Human studies were searched using the terms “fasting”, “intermittent fasting” or “alternate day fasting” alone or in combination with “cardiovascular disease”. Studies were included if they assessed 1) adult male or female patients and 2) if the end points of the study included measurement of risk factors for cardiovascular disease, such as cholesterol or body weight.

Population-based observational studies were excluded but for specific discussion where the presence of clinical trials was lacking. Studies assessing cultural fasting regimens, such as Ramadan were excluded. The outcomes of such studies have been extensively reviewed in the past.[17,18] These fasting patterns are not driven by health concerns and have generally been studied using population-based observational study designs. Following the literature search a total of 18 randomised, crossover or prospective cohort studies were identified and are discussed herein, categorised by the method of IF that was assessed.

Results

Alternate day fasting

As defined previously, ADF involves consuming heavily reduced or no calories on fasting days with ad libitum or modest calorie-controlled diet on alternate days. Currently, there are only a small number of human clinical trials that have assessed the effectiveness of ADF in reducing risk factors for cardiovascular disease in Table 1.

Haldberg et al.[19] enrolled 8 healthy, young men [mean age 25 years, mean BMI 25.7kg/m^2] to undergo ADF for a period of 15 days. Over this short period it was noted that insulin sensitivity, and therefore whole-body glucose uptake, significantly increased [6.3±0.6 to 7.3±0.3mg/kg/min, p=0.03]. A similar study by Soeters et al.[20] also took eight healthy, young men and performed a comparison between simple calorie restriction and ADF using a two week cross-over method. However this study failed to show any significant difference between the two dieting methods in terms of whole-body glucose, lipid or protein metabolism.

It is worth noting that both studies above had significant limitations in that subject sizes were small, participants

were not overweight and the study durations were short.

A more recent study by Varady et al.[15] took 32 participants with a normal to overweight BMI (20–29kg/m^2) and randomised them to either an ADF diet or no dieting over a 12 week period. On reduced intake days participants were allowed to consume up to 25 per cent of recommended daily requirements. Compared to the control group, those on the ADF diet had significantly reduced CRP [p<0.01], increased adiponectin [p<0.01], reduced leptin [p=0.03] and reduced triglyceride levels [p=0.01]. LDL particle size was increased, but LDL and HDL levels were not significantly different between the two groups. Weight loss was also greater in the ADF group, with an average weight loss of 5.2±0.9 kg (6.5±1.0 per cent) relative to the control group. Although the sample size is small, this study suggested that ADF was an effective method of weight loss and was also potentially cardio protective.

Four further small studies[13,14,21,22] enrolled overweight participants and placed them on an ADF diet over an 8–12 week period. These studies demonstrated that body weight, total cholesterol, LDL-C and triglycerides were significantly decreased compared to baseline. These findings support those of Varady et al.[15]

Although they did not directly assess the effect of ADF on reducing risk of CVD, Klempel et al.[23] noted the important finding that on the feeding days of an ADF diet participants appetite and calorie consumption did not increase compared to baseline. On the feed day, subjects consumed on average only 95 per cent ± 6 per cent of their calculated daily energy requirements. Hunger on the fasting days also decreased during the 10 week period [p<0.05]. The possibility of hyperphagia on feed days and high levels of hunger on fasting days has been a criticism of ADF diets previously.[24]

Unfortunately most published studies on ADF, such as those mentioned previously, do not directly compare outcomes to a calorie-restricted control group. At least one study[25] has acknowledged this limitation by randomising subjects to either an ADF diet or a calorie restricted diet for eight weeks. Volunteers in the ADF group consumed zero calories on fasting days but could eat ad libitum on alternate days, while the calorie restricted group was limited to approximately 20 per cent of usual daily energy requirements. At the conclusion of this study there was no significant difference in weight loss, lipid profile and insulin sensitivity between the two groups. Importantly, there was no increased risk of rebound weight gain in the ADF group at twenty four weeks follow-up after completing the intervention. Although the sample size in the study was small [n=26], the findings suggest that ADF dieting may at least be as effective as simple daily caloric restriction.

The small number of quality human trials on ADF dieting generally favour ADF as an effective method for not only weight loss but also as a means of reducing risk factors for MetSy. Decreasing cholesterol, body weight and insulin resistance should also decrease individual risk for cardiovascular disease, but this has not yet been directly observed.

Time-restricted feeding

IF diets that utilise time-restricted feeding (TRF) usually involve participants forgoing nutrition during a specific portion of the day, or missing one or two of their three main daily meals[26] in Table 2.

Two human studies[27,28] assessed the impact of TRF by taking normal weight volunteers and restricting oral intake to one evening meal over eight weeks. Subjects then completed an 11 week wash-out period and resumed three meals/day. The researchers found that glucose tolerance, as measured by an oral glucose tolerance test, was significantly impaired [p<0.05] while consuming one meal per day, as compared to three meals per day. Whilst fat mass was decreased [mean 2.1kg], blood pressure, total cholesterol and LDL-c were all significantly increased. Subjects consuming one meal per day demonstrated a total cholesterol, LDL-C, and HDL-C 11.7 per cent, 16.8 per cent, and 8.4 per cent higher on average, respectively, compared to when eating three meals per day.

These two studies suggested that restricting subjects to one meal per day worsened risk factors for CVD. It was noted, however, that the single meal that was provided consisted of the same number of calories as the 3 meal per day eating plan. It was proposed that reducing the calories within the one meal may have led to more favourable health outcomes.

Hunger in those following the 1 meal per day plan was rated as high in the two previous studies, indicating that compliance long-term may be poor.[27,28] An alternative to this strict diet is a two meal/day TRF diet. However, one study[29] demonstrated that, similar to omitting breakfast and lunch, omitting breakfast alone was also associated with increased LDL-C in healthy volunteers, when followed over a two week period [mean change -0.08mmol/L in full diet, +0.20mmol/L in TRF, p=0.001].

The question remained regarding whether the same effects would be seen in overweight individuals. Chowdhury et al.[30] took 23 overweight individuals and randomised them to either three meals per day or two meals per day with breakfast excluded. Calorie restriction was not enforced. After 6 weeks there was no significant difference in any of the measured risk factors for cardiovascular disease, including body weight, total cholesterol, LDL-C, HDL-C and triglycerides. The only significant finding in this regard was that, insulin sensitivity, as measured by an oral glucose tolerance test, was decreased in the two meal per day cohort [p=0.05].

Of particular interest is a similar study[31] that compared no breakfast to either oats or cereal in 36 overweight volunteers [mean BMI 32.8kg/m^2] over four weeks. Researchers noted that although body weight decreased [mean weight loss -1.18kg], total cholesterol increased in those who omitted breakfast [mean change +0.4±0.1mmol/L *vs.* 0.1±0.2mmol/L in control, p=0.014]. This suggested that overall risk for CVD may be increased in this group.

Conversely, in patients with T2DM, a short two week trial where volunteers omitted their morning meal led to significant weight loss [mean 1.4kg, p=0.009], as well as a favourable reduction in fasting glucose levels [mean change -6.10%].32 However, volunteers in the two meal/day plan also consumed approximately 15 per cent fewer calories compared to when eating regular meals so this may account for both of these findings.

There is a sparsity of randomised human trials assessing the metabolic effects of omitting breakfast. However, the studies discussed here and the observational studies currently published,[33-38] indicate that it is unlikely to be beneficial and furthermore may worsen risk factors for CVD, such as hypercholesterolemia.

Modified fasting regimens

Modified fasting regimens (MFR), or periodic very low calorie diets, are IF diets where 1–5 days per week are allocated as days with strictly reduced, or absent, calorie consumption Table 3. An early human trial[39] found that in overweight, type 2 diabetics, severely restricting intake either one or five days day per week, with modest calorie restriction for the remainder of the week, was superior to modest calorie restriction alone. After 15 weeks, those on the one day per week MFR lost a mean of 9.6kg, Five day per week MFR lost 10.4kg and those on calorie restriction alone lost significantly less weight at 5.4kg [p=0.04]. HbA1C was also significantly reduced in both MFR groups after 15 weeks [p=0.04].

Harvie and colleagues[40] demonstrated a lesser response in their comparison of 25% energy restriction 2 days per week against continuous calorie restriction. This study was conducted over a six month period in 107 overweight females. Weight change and lipid profile was similar whilst reduction in insulin resistance was higher in the MFR group [mean change -29 per cent *vs.* -19 per cent, p=0.04]. Interestingly, only 58% of volunteers in the MFR group indicated that they would continue the regimen beyond the six month period compared with 85 per cent in the calorie restriction group, indicating potential difficulties with long-term adherence.

Two further studies[41,42] that randomised a total of 115 overweight volunteers to either very low calorie diet for 2–4 days per week, or a simple calorie controlled diet, over 12 weeks, showed no significant difference in weight loss or markers for MetSy between the two groups. Of note, neither of these studies limited calorie intake on non-fasting days which may explain the absence of significant weight loss when compared to a continuous calorie controlled diet.

Once again, there are only a limited number of large cohort human trials that have assessed the efficacy of MFR diets in reducing risk factors for CVD. Based on the current evidence, MFR is most likely to be beneficial when paired with a calorie restricted diet. The ability of MFR to improve insulin resistance in patients with T2DM is promising but requires further research.

Conclusion

The development of cardiovascular disease is a leading cause of death worldwide. IF has been shown in the small number of human clinical trials discussed here to be an alternative to continuous caloric restriction in reducing the factors that contribute to the development of cardiovascular disease. Although the ideal regimen for IF remains unclear, there is promising evidence that ADF or MFR, paired with or without continuous caloric restriction, may be more effective than continuous caloric restriction alone in achieving this target. Unfortunately there is limited data linking IF directly with disease outcomes, such as cardiovascular disease, diabetes or cancer. Large population, long-term, randomised studies will be required to effectively assess these outcomes.

The patient adherence and long-term safety data for IF requires further human studies. Few trials have analysed

these important factors beyond six months of follow-up. A diet that is too difficult to adhere to and reduces a patients' perceived quality of life is unlikely to be a worthy alternative long-term. Long-term randomised, controlled trials comparing continual caloric restriction and IF are required to objectively assess energy intake, energy expenditure, adherence, disease outcomes and metabolic factors.

References

1. Prospective Studies C, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083–1096.
2. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1345–1422.
3. Noto D, Barbagallo CM, Cefalu AB, et al. The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a mediterranean population. Atherosclerosis. 2008;197:147–53.
4. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23:469–80.
5. Diabetes prevention program research group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study. Lancet. 2009;374:1677–1686.
6. Kritchevsky SB, Beavers KM, Miller ME, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. PLoS One. 2015;10:e0121993.
7. Wong SK, Chin KY, Suhaimi FH, et al. Animal models of metabolic syndrome: a review. Nutr Metab (Lond). 2016;13:65.
8. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. Prog Cardiovasc Dis. 2014;56:448–56.
9. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365:1415–1428.
10. Chung KW, Kim DH, Park MH, et al. Recent advances in calorie restriction research on aging. Exp Gerontol. 2013;48:1049–1053.
11. Obesity and overweight". World Healh Organisation, 2018. (Accessed 24/03/2018, 2018, at http://www.whoint/mediacentre/factsheets/fs311/en/
12. Wegman MP, Guo MH, Bennion DM, et al. Practicality of intermittent fasting in humans and its effect on oxidative stress and genes related to aging and metabolism. Rejuvenation Res. 2015;18:162–172.
13. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med. 2007;42:665–674.
14. Bhutani S, Klempel MC, Kroeger CM, et al. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. Obesity (Silver Spring). 2013;21:1370–1379.
15. Varady KA, Bhutani S, Klempel MC, et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. Nutr J. 2013;12:146.
16. Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. Am J Clin Nutr. 2015;102:464–470.
17. Mazidi M, Rezaie P, Chaudhri O, et al. The effect of Ramadan fasting on cardiometabolic risk factors and anthropometrics parameters: A systematic review. Pak K Med Sci. 2015;31:1250–1255.
18. Rouhani MH, Azadbakht L. Is Ramadan fasting related to health outcomes? A review on the related evidence. J Res Med Sci. 2014;19:987–992.
19. Halberg N, Henriksen M, Soderhamn N, et al. Effect of intermittent fasting and refeeding on insulin action in healthy men. J Appl Physiol. 2005;99:2128–36.
20. Soeters MR, Lammers NM, Dubbelhuis PF, et al. Intermittent fasting does not affect whole-body glucose, lipid, or protein metabolism. Am J Clin Nutr. 2009;90:1244–1251.
21. Bhutani S, Klempel MC, Berger RA, et al. Improvements in coronary heart disease risk indicators by alternate-day fasting involve adipose tissue modulations. Obesity (Silver Spring). 2010;18:2152–2159.
22. Varady KA, Bhutani S, Church EC, et al. 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.
23. Klempel MC, Bhutani S, Fitzgibbon M, et al. Dietary and physical activity adaptations to alternate day modified fasting: implications for optimal weight loss. Nutr J. 2010;9:35.
24. Heilbronn LK, Smith SR, Martin CK, et al. Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. Am J Clin Nutr. 2005;81:69–73.
25. Catenacci VA, Pan Z, Ostendorf D, et al. A randomized pilot study comparing zero-calorie alternate-day fasting

to daily caloric restriction in adults with obesity. Obesity (Silver Spring). 2016;24:1874–1883.
26. Patterson RE, Sears DD. Metabolic effects of intermittent fasting. Annu Rev Nutr. 2017;37:371–393.
27. Carlson O, Martin B, Stote KS, et al. Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women. Metabolism. 2007;56:1729–1734.
28. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. Am J Clin Nutr. 2007;85:981–988.
29. Farshchi HR, Taylor MA, Macdonald IA. Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women. Am J Clin Nutr. 2005;81:388–96.
30. Chowdhury EA, Richardson JD, Holman GD, et al. The causal role of breakfast in energy balance and health: a randomized controlled trial in obese adults. Am J Clin Nutr. 2016;103:747–756.
31. Geliebter A, Astbury NM, Aviram-Friedman R, et al. Skipping breakfast leads to weight loss but also elevated cholesterol compared with consuming daily breakfasts of oat porridge or frosted cornflakes in overweight individuals: a randomised controlled trial. J Nutr Sci. 2014;3:e56.
32. Arnason TG, Bowen MW, Mansell KD. Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study. World J Diabetes. 2017;8:154–164.
33. Sharma K, Shah K, Brahmbhatt P, et al. Skipping breakfast and the risk of coronary artery disease. QJM. 2018. doi: 10.1093/qjmed/hcy162.
34. Maugeri A, Kunzova S, Medina-Inojosa JR, et al. Association between eating time interval and frequency with ideal cardiovascular health: Results from a random sample Czech urban population. Nutr Metab Cardiovascular Dis. 2018; doi: 10.1016/j.numecd.2018.04.002.
35. Batista-Jorge GC, Barcala-Jorge AS, Oliveira Dias AF, et al. Nutritional status associated to skipping breakfast in brazilian health service patients. Ann Nutr Metab. 2016;69:31–40.
36. Uzhova I, Fuster V, Fernandez-Ortix A, et al. The importance of breakfast in atherosclerosis disease: insights from the pesa study. J Am Coll Cardiol. 2017;70:1833–1842.
37. Safiee G, Kelishadj R, Qorbani M, et al. Association of breakfast intake with cardiometabolic risk factors. J Pediatr (Rio J). 2013;89:575–582.
38. Sakata K, Matamura Y, Yoshimura N, et al. Relationship between skipping breakfast and cardiovascular disease risk factors in the national nutrition survey data. Nihon Koshu Eisei Zasshi. 2001;48:837–841.
39. Williams KV, Mullen ML, Kelley DE, et al. The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. Diabetes Care. 1998;21:2–8.
40. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes (Lond). 2011;35:714–27.
41. Carter S, Clifton PM, Keogh JB. The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. Diabetes Res Clin Pract. 2016;122:106–112.
42. Ash S, Reeves MM, Yeo S, et al. Effect of intensive dietetic interventions on weight and glycaemic control in overweight men with type II diabetes: a randomised trial. Int J Obes Relat Metab Disord. 2003;27:797–802.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

Table 1: Summary of studies on alternate day fasting

Reference	Fasting Regimen	Study Type and Duration	Study Population	Results
Haldberg et al.[19]	ADF.	Prospective, 15 day follow-up.	8 men, mean age 25 years, mean BMI 25.7kg/m^2	Improved insulin sensitivity
Soeters et al.[20]	ADF *vs*. simple calorie restriction.	Crossover, 14 day follow-up	8 men, average BMI	Nil significant differences
Varady et al.[15]	ADF diet (25% of regular intake on feeding days) *vs.* regular diet.	Randomised, 12 week follow-up.	32 men and women, BMI 20-29kg/m^2	In ADF: Reduced CRP Increased Adiponectin Reduced leptin Reduced triglyceride levels LDL particle size increases Greater weight loss
Johnson et al. [13]	ADF – 20% of regular intake on feeding days.	Prospective, 8 week follow-up	10 men and women - >30 BMI	Decreased total cholesterol Reduced triglycerides Reduction in markers of oxidative stress
Bhutani et al. [14]	ADF *vs*. ADF + exercise *vs*. exercise *vs*. control.	Randomised, 12 week follow-up.	64 obese men and women	Body weight reduced most in ADF + exercise group LDL decreased in ADF + exercise group only
Bhutani et al. [21]	ADF.	Prospective, 8 week follow-up.	16 obese men and women	Reduced body weight Reduced LDL-C and triglycerides Reduced leptin
Varady et al. [22]	ADF.	Prospective, 8 week follow-up.	16 obese men and women	Reduced body weight Reduced total cholesterol, LDL-C and triglycerides Reduced systolic BP
Catenacci et al. [25]	ADF *vs.* moderate daily caloric restriction.	Randomised, 8 week follow-up.	26 obese men and women (BMI >30)	Nil significant differences

Table 2: Summary of studies on time restricted fasting

Reference	Fasting Regimen & Study Type	Study Type and Duration	Study Population	Results
Carlson et al. [27]	3 meals/day *vs*. 1 meal/day.	Crossover, 8 weeks follow-up.	15 men and women, BMI 18-25kg/m^2	In TRF – higher fasting glucose, delayed insulin response.
Stote et al. [28]	3 meals/day *vs.* 1 meal/day.	Crossover, 8 weeks follow-up.	15 men and women, normal weight	In TRF - reduced fat mass, increased total cholesterol and LCL-C
Farshchi et al. [29]	TRF – breakfast omitted.	Crossover, 2 weeks follow-up.	10 women, normal weight	In TRF – higher fasting total and LCL-C, impaired insulin sensitivity.
Chowdhury et al. [30]	TRF- breakfast omitted *vs*. normal diet.	Randomised, 6 week follow-up.	23 men and women, obese	Insulin sensitivity increased with breakfast compared to fasting
Geliebter et al. [31]	TRF – breakfast omitted *vs.* normal diet.	Randomised, 4 week follow-up.	36 overweight men and women	In TRF - reduced body, increased total cholesterol

Arnason et al. [32]	TRF – breakfast omitted *vs.* normal diet.	Crossover, 2 week follow-up.	10 obese men and women, T2DM	In TRF – reduced body weight fasting glucose.
Sharma et al. [33]	TRF – breakfast omitted *vs.* normal diet.	Population-based observational study.	1607 men and women	In TRF – strong risk factor for CVD and hypertension
Maugeri et al. [34]	TRF – breakfast omitted *vs.* normal diet.	Population-based observational study.	2030 men and women	In TRF – reduced cardiovascular health composite score
Batista-Jorge et al. [35]	TRF - breakfast omitted *vs.* normal diet.	Population-based observational study.	400 men and women	In TRF – higher risk of obesity
Uzhova et al. [36]	TRF - breakfast omitted *vs.* normal diet.	Population-based observational study.	4052 men and women	In TRF – higher incidence of noncoronary and generalised atherosclerosis
Shafiee et al. [37]	TRF – breakfast omitted *vs.* normal diet.	Population-based observational study.	5625 male and females aged 10-18 years	In TRF – higher LDL-C, higher BMI, higher triglycerides
Sakata et al. [38]	TRF – breakfast omitted *vs.* normal diet.	Population-based observational study.	11778 men and women aged 20-59	In TRF - higher total cholesterol, higher BP

Table 3: Summary of studies on modified fasting regimens

Reference	**Fasting Regimen & Study Type**	**Study Type and Duration**	**Study Population**	**Results**
Williams et al. [39]	MFR – 1 day/week or 5 days/week very low calorie intake compared to control.	Randomised, 15 week follow-up.	54 men and women, overweight, with T2DM	In MFR – reduced body weight, reduced HbA1c.
Harvie et al. [40]	MFR – 25% energy restriction 2 days/week *vs.* continuous low calorie diet.	Randomised, 6 month follow-up.	107 overweight or obese women	In MFR – greater reduction in insulin resistance
Carter et al. [41]	MFR – 2 days/week severe energy restriction *vs.* moderate continuous low calorie diet.	Randomised, 12 week follow-up.	63 overweight or obese men and women	Nil significant differences
Ash et al. [42]	MFR – 4 days/week very low calorie diet *vs.* continuous low calorie diet.	Randomised, 12 week follow-up.	51 overweight men with T2DM	Nil significant differences