Clinical application of intermittent fasting for weight loss: progress and future directions

Krista A. Varady ✉, *Sofia Cienfuegos, Mark Ezpeleta and Kelsey Gabel*

Abstract | Intermittent fasting diets have become very popular in the past few years, as they can produce clinically significant weight loss. These diets can be defined, in the simplest of terms, as periods of fasting alternating with periods of eating. The most studied forms of intermittent fasting include: alternate day fasting (0–500 kcal per 'fast day' alternating with ad libitum intake on 'feast days'); the 5:2 diet (two fast days and five feast days per week) and time-restricted eating (only eating within a prescribed window of time each day). Despite the recent surge in the popularity of fasting, only a few studies have examined the health benefits of these diets in humans. The goal of this Review is to summarize these preliminary findings and give insights into the effects of intermittent fasting on body weight and risk factors for cardiometabolic diseases in humans. This Review also assesses the safety of these regimens, and offers some practical advice for how to incorporate intermittent fasting diets into everyday life. Recommendations for future research are also presented.

Intermittent fasting diets have grown in popularity in the past few years as they can produce clinically significant weight loss (>5% loss from baseline[1]) in many people and are often considered to be less complicated than traditional forms of dieting such as calorie restriction[2–9]. Intermittent fasting requires fasting for a period of time, typically a minimum of 12 h, followed by a period of ad libitum eating. One of the reasons for the sudden rise in popularity of intermittent fasting is its simplicity. Previous popular diets have generally required individuals to vigilantly monitor energy intake or meticulously count carbohydrates. Intermittent fasting can often be a refreshing alternative for many individuals, in that it does not require people to track calories every day, nor does it forbid individuals from eating certain food groups. Moreover, some intermittent fasting regimens permit individuals to eat freely during certain periods of the day, which is another attractive feature of this diet. Simply stated, as long as they can accurately determine the date and time of day, most people can do intermittent fasting.

Although intermittent fasting is growing in popularity, there are currently few studies that have investigated the benefits and risks of these diets in humans. This Review discusses the currently available research on the efficacy of intermittent fasting as an intervention to reduce body weight and decrease the risk of cardiometabolic disease. The article also evaluates the safety of these regimens, and provides advice to clinicians and patients on how to undertake intermittent fasting in a safe and effective manner. Recommendations for studies to address current knowledge gaps are also discussed.

Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL, USA.

✉*e-mail: varady@uic.edu*

https://doi.org/10.1038/s41574-022-00638-x

Types of intermittent fasting

Three types of intermittent fasting have received the most research attention: alternate day fasting (ADF), the 5:2 diet and time-restricted eating (TRE)[4,10–12] (FIG. 1).

ADF involves a 'fast day' alternating with a 'feast day'. On fast days, individuals can choose to consume only water, which is termed 'zero-calorie alternate day fasting'[13,14], or, alternatively, individuals can consume 25% of their energy needs (approximately 500 kcal per day), which is called 'modified alternate day fasting'[15–17]. The fast day meal can be consumed all at once or spread throughout the day, without affecting the degree of weight loss achieved[18]. The timing of the fast day meal is optional. However, participants generally prefer to consume the meal at dinner time so they can engage in their habitual social eating patterns, such as eating dinner with their family or friends[19]. On feast days, individuals can eat freely, with no restrictions on types or quantities of foods consumed. The 5:2 diet is a modified version of ADF, which involves two fast days (500–1,000 kcal per day), and five feast days per week[20–22]. The fast days can occur on consecutive or non-consecutive days in the week.

TRE differs from ADF and the 5:2 diet in that it necessitates individuals to fast for a certain period of

Key points

- The three main forms of intermittent fasting (alternate day fasting, the 5:2 diet and time-restricted eating) produce mild to moderate weight loss (3–8% loss from baseline) over short durations (8–12 weeks).
- The degree of weight loss achieved with intermittent fasting is on a par with that achieved with traditional dieting approaches (daily calorie restriction).
- The ability of these intermittent fasting protocols to help to manage weight long-term is still poorly understood, as the majority of studies to date have run for short durations.
- Some studies demonstrate that intermittent fasting improves cardiometabolic risk factors such as blood pressure, levels of LDL cholesterol and triglycerides, insulin resistance and HbA_{1c}, while others show no benefit on these parameters.
- Intermittent fasting is generally safe and produces few gastrointestinal, neurological, hormonal or metabolic adverse effects.

time every day. TRE involves confining the eating window to a specified number of hours per day (typically 4 to 8 h), and fasting with water or zero-calorie beverages for the remainder of the day[23–27]. TRE is a unique form of intermittent fasting in that it does not require individuals to monitor their energy intake or count calories during the eating window.

The effects of intermittent fasting

The effects of intermittent fasting on body weight. The effects of the three main forms of intermittent fasting on clinical outcome measures are reported in TABLE 1 (ADF and the 5:2 diet), TABLE 2 (TRE) and FIG. 2. Studies were included in the assessments in TABLES 1 and 2 if they were randomized trials, conducted in adults, had a trial duration of 5 weeks or longer and implemented either a control group (no change in diet or physical activity throughout the study) or a daily calorie restriction group as a comparator in their design. Findings to date reveal that ADF[14,16,28–31] and the 5:2 diet[32,33] produce similar degrees of weight loss (4–8% loss from baseline) over short intervention periods (8–12 weeks) in men and women with obesity. Longer-term studies have found that ADF[17] and the 5:2 diet[20–22,34,35] (24–52 weeks) do not result in greater body weight reductions than found in short-term studies, suggesting that the weight loss efficacy of these diets might peak at 12 weeks. The degree of weight loss achieved with TRE seems to be less pronounced (3–4% loss from baseline) over 8–12 weeks[23,26,36] than with ADF and the 5:2 diet. Of note, no study to date has demonstrated clinically significant weight loss (>5% loss from baseline[1]) with TRE. The TRE literature is limited, however, in that no study longer than 12 weeks has been performed. It is possible that clinically significant weight loss would occur with longer durations of TRE. Moreover, no trial to date has directly compared the different forms of intermittent fasting with each other. Thus, it is difficult to draw meaningful conclusions regarding the superiority of one regimen over another.

Several different population groups were evaluated in these studies (TABLES 1 and 2). ADF, the 5:2 diet and TRE were effective for weight loss in individuals with obesity[14,17,21–23,26,28,29,32,34–36] and overweight[16,17,20,33], and produced approximately 0.2–0.5 kg of weight loss per week, although findings were variable and only ADF and the 5:2 diet were able to produce clinically significant weight loss. Intermittent fasting also facilitated minor reductions in weight in individuals of normal weight (BMI 18.5–24.9 kg/m^2), inducing approximately 0.2 kg of weight loss per week[31]. The efficacy of intermittent fasting in reducing weight does not seem to vary according to an individual's sex or menopausal status[37]. Individuals with insulin resistance or prediabetes also benefit from intermittent fasting interventions, and seem to lose similar amounts of weight as those who do not have these conditions[38]. Only two trials have examined if fasting is effective for weight loss in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)[22,35]. After 52 weeks of the 5:2 diet, patients with T1DM and obesity lost 7% of their body weight from baseline[35]. Complementary to these findings, patients with T2DM and obesity showed 7% weight loss after 52 weeks of fasting 2 days per week[22]. Taken together, these findings suggest that intermittent fasting might benefit several different populations, including those with obesity, overweight, insulin resistance, prediabetes, T1DM and T2DM. Whether these improvements are also noted in patient groups with other metabolic disorders, such as those with polycystic ovary syndrome or thyroid disorders, is not yet known.

The efficacy of intermittent fasting in maintaining weight has only been tested in four trials in humans. The results of these trials revealed that both ADF[14,17] and the 5:2 diet[22,34] are effective in preventing weight regain during 12–24 weeks of follow-up. The weight maintenance versions of these diets differ slightly from the original regimens. For instance, the ADF and the 5:2 maintenance diets permit greater energy intake on fast days (1,000–1,200 kcal per day instead of approximately 500 kcal per day). These modifications could help to improve the long-term tolerability of these regimens by giving people the freedom to eat slightly more on fast days. As for TRE, no study to date has examined whether this form of fasting can facilitate weight maintenance. Evidently, much more data is required before any solid conclusions can be reached regarding the efficacy of these regimens in helping people to manage their weight long-term.

The effects of intermittent fasting compared with traditional dieting (daily calorie restriction) on body weight have been investigated in several trials[14,17,20–22,28,32–35] and meta-analyses[39–41]. In a 2017 study[17], ADF and calorie restriction (25% daily calorie restriction, approximately 1,500 kcal per day) produced similar degrees of weight loss (5–6% loss from baseline) over 52 weeks in adults with overweight or obesity. Short-term studies (less than 12 weeks duration) of ADF have also shown similar body weight reductions to calorie restriction[14,28]. As for the 5:2 diet, similar degrees of weight loss have been reported when this diet is compared with calorie restriction in short-term[32] and long-term trials[20–22,33–35]. In patients with T1DM or T2DM, the 5:2 diet and calorie restriction produced nearly equivalent degrees of weight loss (4–7% loss from baseline in both groups) over 52 weeks[22,35]. Whether TRE also results in similar weight reductions versus calorie restriction remains unknown, as no study to date has directly compared these two interventions. Although the data are limited, these preliminary findings

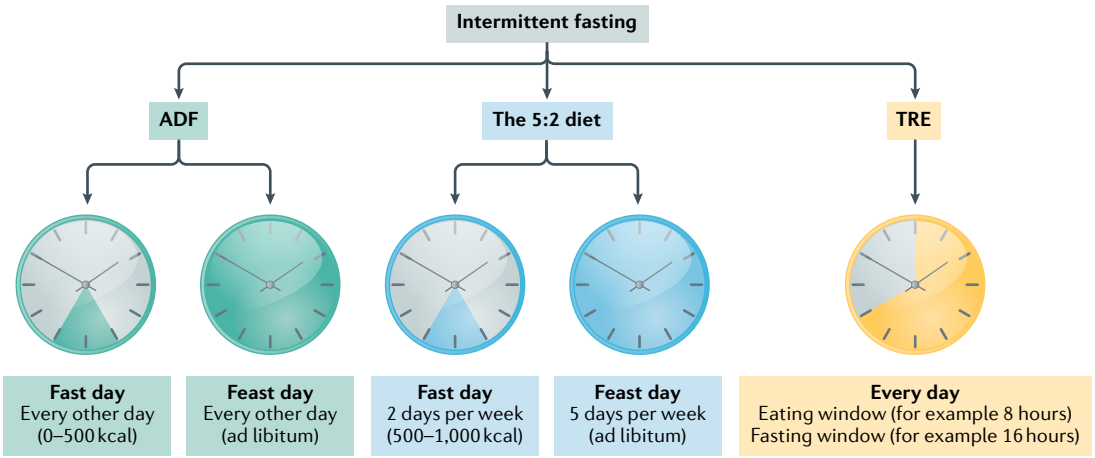

Fig. 1 | **Types of intermittent fasting.** Timing of food intake during alternate day fasting (ADF), the 5:2 diet and time-restricted eating (TRE). Periods of food intake are depicted by the shaded portions of the clock icon. For TRE, in the majority of trials the suggested eating window is 8 h. For ADF and the 5:2 diet, the suggested food intake window is 17:00 h to 19:00 h. However, the fast day meal can be consumed all at once or spread throughout the day, based on individual preference.

indicate that intermittent fasting and traditional dieting produce similar reductions in body weight in individuals with overweight, obesity, T1DM and T2DM.

The effects of intermittent fasting on body composition. When body weight is reduced as a result of consuming a calorie-restricted diet, approximately 75% of the weight lost is fat mass, and 25% is lean mass[42–45]. Based on the evidence reviewed here, the majority of studies evaluating ADF, the 5:2 diet and TRE found a similar ratio of fat mass to lean mass loss (75% to 25%) as calorie restriction. Thus, it is probable that intermittent fasting does not help individuals with obesity to lose more fat mass or retain more lean mass during weight loss than traditional dieting. The effects of intermittent fasting combined with exercise on body composition have also been evaluated. When endurance training was combined with ADF, changes in lean mass did not differ from that of ADF alone[29]. However, when TRE was combined with resistance training, some studies in lean individuals who exercised regularly (resistance training several times per week) before the start of the study found muscle mass maintenance or accretion, accompanied by statistically significant subcutaneous fat mass loss[25,46]. Whether resistance training can help individuals with obesity to preserve lean mass during periods of fasting is of interest but has yet to be tested.

Changes in visceral fat mass have also been examined. In the majority of trials evaluating ADF and the 5:2 diet that found clinically significant weight loss, visceral fat mass decreased statistically significantly in those receiving the dietary interventions compared with no-intervention controls (no change in diet or physical activity during the study)[14,17,20–22,28,34]. By contrast, reductions in visceral fat mass were not generally observed with TRE, but this could have been due to the limited amount of weight loss (3–4% loss from baseline) achieved with this intervention in these short-term trials (less than 12 weeks duration). When changes in visceral fat mass were directly compared between calorie restriction and ADF or the 5:2 diet, no statistically significant differences were observed[14,17,20–22,28,34]. This finding would suggest that both daily energy restriction and intermittent fasting produce similar reductions in visceral fat mass when equivalent weight loss is achieved.

Energy intake and diet quality

Effects of intermittent fasting on energy intake. The main reason why individuals lose weight with intermittent fasting is because these interventions help people to reduce energy intake[17,31,47]. Findings from trials in humans indicate that ADF, the 5:2 diet and TRE reduce overall energy intake by approximately 10–30% relative to baseline[17,31,47]. Clinicians are often worried that patients on ADF or the 5:2 diet will overeat on feast days. However, accumulating evidence suggests that this does not occur. Participants typically only consume an extra 10–15% of their energy needs (approximately 200–300 kcal) on feast days relative to their calculated energy needs[17,31,47]. Indeed, one study found reduced energy intake on feast days in individuals on the 5:2 diet compared with energy intake before the start of the study[48]. As participants do not fully compensate for lack of food consumed on the fast day by eating more on the feast day, a net energy deficit is created, resulting in mild to moderate weight loss.

Clinicians have also expressed concern over patients overeating during the eating window of TRE. Contrary to what might be expected, most individuals are not able to consume the amount of food they previously ate within the prescribed 4-h to 8-h eating window. As such, TRE results in an unplanned reduction in daily energy intake, in the range of 10–30%[23,24,36]. TRE also has the added benefit of not requiring individuals to count calories in order to lose weight. One of the main reasons why people drop out of ADF and calorie restriction trials is because they grow tired of having to vigilantly monitor their food intake on a regular basis[17,49,50]. TRE diets are able to avoid this requirement by allowing participants to simply 'watch the clock' instead of monitoring

Table 1 | **Trials of ADF and the 5:2 diet in humans**

Participants	Trial weeks	Intervention groups	Body weight	Blood pressure		Plasma lipids			Glucoregulatory factors				Ref.
				SBP	DBP	LDL	HDL	Triglycerides	Fasting glucose	Fasting insulin	Insulin resistance	HbA_{1c}	
ADF													
n = 26, men and women with obesity and without T1DM or T2DM	8	ADF (0-kcal fast day)	↓8%[a]	NA	NA	↓22%[a]	↓11%[a]	↓17%[a]	↑7%[a]	NSD	NA	NA	14
		Calorie restriction (1,500 kcal per day)	↓6%[a]	NA	NA	↓16%[a]	↓10%[a]	NSD	NSD	NSD	NA	NA	
n = 31, men and women with overweight and without T1DM or T2DM	8	ADF (500-kcal fast day)	↓5%[b]	NA	NA	NSD	NSD	NSD	NSD	NSD	NSD	NA	16
		Exercise (endurance)	NSD	NA	NA	NSD	NSD	NSD	↓41%[b]	NSD	NSD	NA	
		ADF with exercise	↓5%[b]	NA	NA	NSD	NSD	NSD	NSD	NSD	NSD	NA	
		Control (ad libitum intake, no exercise)	NSD	NA	NA	NSD	NSD	NSD	NSD	NSD	NSD	NA	
n = 69, men and women with obesity and without T1DM or T2DM	8	ADF (500-kcal fast day)	↓5%[a]	↓11%[b]	↓10%[a]	NSD	NSD	↓26%[a]	↓6%[b]	↓15%[a]	↓22%[a]	NA	28
		Calorie restriction (1,500 kcal per day)	↓3%[a]	NSD	NSD	NSD	NSD	↓18%[a]	NSD	NSD	↓12%[a]	NA	
n = 83, men and women with obesity and without T1DM or T2DM	12	ADF with exercise	↓7%[b]	NSD	NSD	NSD	↑18%[b]	NSD	NSD	NSD	NSD	NSD	29
		ADF	↓4%[b]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	
		Exercise only (endurance)	↓1%[b]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	
		Control (ad libitum, no exercise)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	
n = 32, men and women of normal weight and without T1DM or T2DM	12	ADF (500-kcal fast day)	↓7%[b]	NSD	NSD	NSD	NSD	NSD	NA	NA	NA	NA	31
		Control (ad libitum)	NSD	NSD	NSD	NSD	NSD	NSD	NA	NA	NA	NA	
n = 100, men and women with overweight and without T1DM or T2DM	52	ADF (500-kcal fast day)	↓6%[b]	NSD	NSD	NSD	NSD	↓24%[b]	NSD	↓38%[b]	NSD	NSD	17
		Calorie restriction (1,500 kcal per day)	↓5%[b]	NSD	NSD	↓9%[b]	NSD	NSD	↓10%[b]	NSD	NSD	NSD	
		Control (ad libitum)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	
The 5:2 diet													
n = 36, men and women with obesity and without T1DM or T2DM	8	5:2 (500-kcal fast day)	↓4%[b]	NA	NA	NSD	NSD	NSD	NSD	NA	NA	NA	32
		Calorie restriction (1,600 kcal per day)	↓4%[b]	NA	NA	NSD	NSD	NSD	NSD	NA	NA	NA	
		Control (ad libitum)	NSD	NA	NA	NSD	NSD	NSD	NSD	NA	NA	NA	
n = 115, women only, with overweight and without T1DM or T2DM	12	5:2: fast day (600 kcal)	↓6%[a]	NSD	NSD	NSD	NSD	NSD	NSD	↓18%[a]	↓25%[b]	NA	33
		5:2: low carbohydrate	↓6%[a]	NSD	NSD	NSD	NSD	NSD	NSD	↓14%[a]	↓16%[b]	NA	
		Calorie restriction (1,500 kcal per day)[c]	↓4%[a]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	

Table 1 (cont.) | **Trials of ADF and the 5:2 diet in humans**

Participants	Trial weeks	Intervention groups	Body weight	Blood pressure		Plasma lipids			Glucoregulatory factors				Ref.
				SBP	DBP	LDL	HDL	Triglycerides	Fasting glucose	Fasting insulin	Insulin resistance	HbA_{1c}	
The 5:2 diet (cont.)													
n = 89, women only, with overweight and without T1DM or T2DM	24	5:2: fast day (500 kcal)	↓7%[a]	↓4%[a]	↓7%[a]	↓10%[a]	NSD	↓16%[a]	↓2%[a]	↓29%[a]	↓27%[b]	NA	20
		Calorie restriction (1,500 kcal per day)[c]	↓5%[a]	↓6%[a]	↓7%[a]	↓10%[a]	↓6%[a]	↓23%[a]	NSD	↓15%[a]	↓18%[a]	NA	
n = 150, men and women with obesity and without T1DM or T2DM	24	5:2: fast day (500 kcal)	↓7%[b]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	21
		Calorie restriction (1,600 kcal per day)	↓5%[b]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	
		Control (ad libitum)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	
n = 112, men and women with obesity and without T1DM or T2DM	48	5:2: fast day (500 kcal)	↓7%[a]	↓3%[a]	↓3%[a]	NSD	↓10%[a]	↓16%[a]	NSD	NA	NA	↓0.3[a]	34
		Calorie restriction (1,500 kcal per day)	↓7%[a]	↓3%[a]	↓3%[a]	NSD	↓11%[a]	↓6%[a]	NSD	NA	NA	↓0.2[a]	
n = 10, men and women with obesity and with T1DM	52	5:2: fast day (500 kcal)	↓7%[a]	NSD	NSD	NSD	NSD	NSD	NA	NA	NA	NSD	35
		Calorie restriction (1,500 kcal per day)	↓4%[a]	NSD	NSD	NSD	NSD	NSD	NA	NA	NA	NSD	
n = 97, men and women with obesity and T2DM	52	5:2: fast day (500 kcal)	↓7%[a]	NA	NA	↓ND[a]	↓ND[a]	↓ND[a]	↓ND[a]	↓ND[a]	NA	↓0.5[a]	22
		Calorie restriction (1,500 kcal per day)	↓5%[a]	NA	NA	↓ND[a]	↓ND[a]	↓ND[a]	↓ND[a]	↓ND[a]	NA	↓0.3[a]	

ADF, alternate day fasting; DBP, diastolic blood pressure; NA, not applicable (parameter not measured); ND, data not disclosed; NSD, non-significant difference ($P > 0.05$); SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; ↓, decrease in the indicated parameter; ↑, increase in the indicated parameter. [a]$P < 0.05$, significantly different from baseline (within-group effect). [b]$P < 0.05$, significantly different from the control or calorie-restricted group (between-group effect). [c]Isocaloric: overall energy consumed by the intermittent fasting group was matched to this control group.

food intake, while still producing mild weight loss. Unfortunately, no study to date has shown clinically significant weight loss with TRE. It will be interesting to see if the observed reductions in energy intake during TRE persist during longer intervention periods (>24 weeks) and if these reductions in energy intake translate into clinically significant weight loss.

Effects of intermittent fasting on diet quality. As intermittent fasting permits ad libitum food intake on certain days of the week, or during certain time windows in the day, dieticians and physicians have expressed concerns regarding the effects of these eating patterns on diet quality. These concerns include worries that individuals would lower their fruit and vegetable intake and eat more energy-dense and high-fat foods while on intermittent fasting diets. Changes in macronutrient and beverage intake have been assessed in eight trials[17,20,23,25,29,31,36,46]. In these trials, the proportions of dietary fat, carbohydrates and protein intake did not change over the course of the trials in participants on ADF, the 5:2 diet and TRE compared with baseline levels[17,20,23,25,29,31,36,46]. Moreover, levels of sugar, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol and sodium intake did not differ statistically significantly in participants on these regimens compared from baseline intake[17,20,23,25,29,31,36,46]. Most trials found low levels of fibre intake (approximately 10–15 g per day) at the beginning of the study[17,20,23]. Fibre consumption generally does not change over the course of the study in people on intermittent fasting or calorie-restriction diets, even when dietary counselling to increase fruit, vegetable and whole grain intake is provided[17,18,20,23,51]. Intake of beverages, such as coffee, tea, diet sodas, energy drinks and alcohol, also remains unchanged during intermittent fasting[23,52]. The effect of intermittent fasting diets on vitamin and mineral intake is not yet known, as no study has directly evaluated changes in micronutrient consumption during fasting. However, as it is currently unclear whether long-term fasting could result in lower intakes of key micronutrients, such as vitamin D, vitamin B_{12} and electrolytes, amongst others, circulating levels of these vitamins and minerals should be routinely assessed to monitor for deficiencies.

Table 2 | **Trials of TRE in humans**

Participants	Trial weeks	Intervention groups	Body weight	Blood pressure		Plasma lipids			Glucoregulatory factors				Ref.
				SBP	DBP	LDL	HDL	Triglycerides	Fasting glucose	Fasting insulin	Insulin resistance	HbA_{1c}	
4-h TRE													
n = 15, men and women of normal weight without T1DM or T2DM	8	4-h TRE (16:00–20:00 h)	NSD	NA	NA	NA	NA	NA	↑ND[a]	NSD	NSD	NA	103
		Control (no meal timing restrictions)	NSD	NA	NA	NA	NA	NA	NSD	NSD	NSD	NA	
n = 18, men and women of normal weight without T1DM or T2DM	8	4-h TRE (16:00–20:00 h) with resistance training	NSD	NA	NA	NA	NA	NA	NA	NA	NA	NA	24
		Control (no meal timing restrictions) with resistance training	NSD	NA	NA	NA	NA	NA	NA	NA	NA	NA	
6-h TRE													
n = 8, men only with obesity and prediabetes	5	6-h TRE (~08:00 to 14:00 h)	NSD	↓8%[a]	↓13%[a]	NSD	NSD	↑47%[a]	NSD	↓14%[a]	↓ND[a]	NA	53
		Control (12-h eating window)[b]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	
n = 58, men and women with obesity and without T1DM or T2DM	8	6-h TRE (13:00–19:00 h)	↓3%[a]	NSD	NSD	NSD	NSD	NSD	NSD	↓11%[a]	↓12%[a]	NSD	23
		Control (no meal timing restrictions)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	
8-h TRE													
n = 34, men only of normal weight without T1DM or T2DM	8	8-h TRE (12:00–20:00 h) with resistance training	NSD	NA	NA	NSD	NSD	↓36%[a]	NSD	NSD	NA	NA	46
		Control (no meal timing restrictions) with resistance training[b]	NSD	NA	NA	NSD	NSD	NSD	NSD	NSD	NA	NA	
n = 40, women only of normal weight without T1DM or T2DM	8	8-h TRE (12:00–20:00 h) with resistance training	↑2%[a]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	NA	25
		Control (no meal timing restrictions) with resistance training[b]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	NA	
n = 46, men and women with obesity and without T1DM or T2DM	12	8-h TRE (10:00–18:00 h)	↓3%[a]	↓6%[a]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	36
		Control (no meal timing restrictions)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NA	
n = 20, men and women with obesity and without T1DM or T2DM	12	8-h TRE (self-selected)	↓4%[a]	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	26
		Control (no meal timing restrictions)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	
n = 116, men and women with obesity and without T1DM or T2DM	12	8-h TRE (12:00–20:00 h)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	54
		Control (no meal timing restrictions)	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	

DBP, diastolic blood pressure; NA, not applicable (parameter not measured); ND, data not disclosed; SBP, systolic blood pressure; TRE, time-restricted eating (prescribed eating window shown in parentheses); ↓, decrease in the indicated parameter; ↑, increase in the indicated parameter. [a]$P < 0.05$, significantly different from the control or calorie restriction group (between group effect). [b]Isocaloric: overall energy consumed by the intermittent fasting group was matched to this control group.

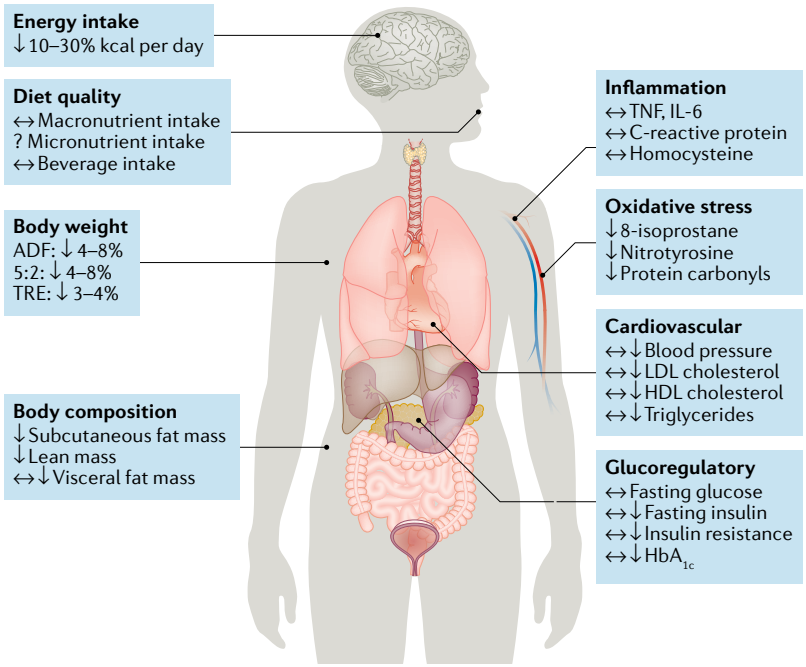

Fig. 2 | **Effects of intermittent fasting on cardiometabolic risk factors.** Alternate day fasting (ADF), the 5:2 diet (5:2) and time-restricted eating (TRE) produce mild to moderate weight loss (3–8% loss from baseline) and reductions in energy intake in the range of 10–30% of total kilocalories consumed per day. The majority of weight is lost through reductions in subcutaneous fat mass, with minor reductions in lean mass and visceral fat mass. Diet quality and beverage intake generally remain unchanged with intermittent fasting. The effect of intermittent fasting protocols on cardiometabolic risk parameters is still unclear. Although some trials have demonstrated improvements in blood pressure, LDL cholesterol, triglycerides, fasting insulin, insulin resistance, HbA_{1c} and markers of oxidative stress, others have shown no benefit. These conflicting findings highlight the need for more rigorous long-term studies in this area. Downwards arrows indicate parameters that decrease over the trial duration, sideways arrows indicate parameters that remain unchanged and question marks indicate that no studies have examined this parameter.

Taking these findings together, fasting does not seem to have any beneficial or detrimental effects on diet quality. However, it should be noted that many of these studies advised participants to be mindful of their eating habits during periods of ad libitum intake, which might have confounded the dietary intake data.

Metabolic disease risk factors

Effects of intermittent fasting on blood pressure. The effects of ADF, the 5:2 diet and TRE on blood pressure are highly variable. While several studies have demonstrated reductions in systolic blood pressure (3–11% decrease from baseline) and diastolic blood pressure (3–13% decrease from baseline)[20,28,34,36,53], several others have shown no effect[17,21,23–25,29,31,33,35,53,54]. However, it would seem that many of the trials that showed improvements involved participants with elevated blood pressure at baseline[28,34,36]. Thus, it is possible that intermittent fasting might only help to lower blood pressure in people with hypertension or borderline hypertension at the start of treatment. Based on findings to date, the three forms of intermittent fasting seem to produce similar reductions in blood pressure, with no apparent deviations between diets.

Greater degrees of weight loss did not seem to produce more pronounced reductions in blood pressure than lower levels of weight loss for all three forms of intermittent fasting. It was also noted that with early TRE (eating all food before 15:00 h), blood pressure was reduced in the absence of body weight reductions[53]. These findings suggest that the improvements in blood pressure could be partially due to the fasting itself (that is, due to long periods of food intake abstention), and not just due to the weight loss. The physiological explanation as to why fasting might improve blood pressure in the absence of weight loss is still unclear, but might involve mild increases in efferent sympathetic nerve activity and venous plasma levels of noradrenaline[55]. It is also possible that early TRE might promote natriuresis (that is, salt excretion in the urine) by shifting salt intake to earlier in the day, when sodium excretion is upregulated by the circadian system[56].

Effects of intermittent fasting on plasma levels of lipids. Changes in plasma concentrations of lipids are routinely assessed in trials evaluating intermittent fasting. Levels of LDL cholesterol decreased by 10–22% from baseline in three trials of intermittent fasting[14,20,22], but showed no change in the majority of studies. Triglyceride concentrations also decreased by 16–36%[14,17,20,22,28,34,46] from baseline, but this decrease was not consistent between studies. When direct comparisons were made between intermittent fasting and calorie restriction, similar decreases in levels of LDL cholesterol and triglycerides were noted, suggesting that these two interventions have equivalent effects on these lipid parameters[20,22,34]. Due to the limited number of studies to date, it is difficult to determine whether the degree of lipid reduction varies by the patient's BMI category, the intervention duration, the patient's baseline lipid levels or the amount of weight loss the patient achieves. It is also difficult to ascertain whether one form of intermittent fasting produces greater reductions in LDL cholesterol or triglyceride levels compared with another. A study that directly compares the effects of ADF, the 5:2 diet and TRE on metabolic variables would be instrumental in helping to clarify whether one diet is superior to another in altering these risk factors.

Levels of HDL cholesterol, by contrast, generally remain unchanged or slightly decrease with intermittent fasting[14,22,34]. This finding is somewhat surprising as levels of HDL cholesterol typically reduce during periods of acute weight loss due to reductions in lecithin cholesterol ester transfer protein[57]. Consequently, during periods of weight maintenance, HDL cholesterol tends to rebound to baseline levels[57]. The reason why this pattern was not noted in trials evaluating intermittent fasting is unclear, but could be related to the low amount of weight loss achieved during the acute weight loss phase in these trials. The only study that demonstrated distinct increases in HDL cholesterol was a 2013 study[29] that combined ADF with endurance exercise. As endurance training has been shown to augment levels of HDL cholesterol[58,59], this effect was most probably due to the exercise component, rather than the fasting intervention.

A major limitation to the evidence discussed in this Review is the lack of clarity regarding the timing of the blood samples taken throughout the intermittent fasting studies. In the majority of studies, whether the blood draws were performed on fast days or feast days was not specified. The duration of fasting before blood was taken for testing would have considerable effects on plasma levels of lipids. For instance, longer acute fasting durations (>18 h) can lead to elevated circulating concentrations of triglycerides and free fatty acids through augmented lipolysis[19,60–62], as noted in one study of early TRE[53]. It will therefore be important for future research to clarify how changes in the levels of lipids and other metabolic risk factors vary according to these two distinct phases of the diet, namely, fasting versus feasting.

Effects of intermittent fasting on glucoregulatory factors. The ability of intermittent fasting to modulate glycaemic parameters is also routinely assessed in studies of intermittent fasting. Fasting concentrations of glucose generally remain unchanged during ADF[16,17,29], the 5:2 diet[21,32–34] and TRE[23,25,26,36,46,53,54]. However, the majority of these studies involved individuals who did not have T1DM or T2DM at baseline. Fasting levels of glucose are typically well controlled in participants who do not have diabetes mellitus[63], so this finding is not surprising. Fasting levels of insulin, on the other hand, were reduced by 11–38% from baseline in several trials[17,20,22,23,28,33,53]. Furthermore, this effect was observed more frequently in individuals with elevated levels of insulin at baseline (>13 μIU/ml) compared with individuals with baseline levels of insulin in the normal range[17,22,23,28]. The effects of intermittent fasting diets on insulin resistance and insulin sensitivity are highly variable, with some studies showing improvements[20,23,28,53], but most showing no effect. Regarding HbA_{1c}, the majority of studies show no change in this parameter in individuals who do not have either T1DM or T2DM[17,23,26,29,54].

Very few studies have examined how fasting affects glycaemic control in individuals with diabetes mellitus. In patients with T2DM, the 5:2 diet produced notable reductions in body weight (7%) and HbA_{1c} (0.5%) after 52 weeks of treatment[22]. These beneficial changes were similar to those of calorie restriction, which produced 5% weight loss and a 0.3% reduction in HbA_{1c}[22]. The use of oral hypoglycaemic agents and insulin decreased significantly over time in both the 5:2 diet group and the calorie restriction group, and was correlated with weight change[22]. By contrast, in patients with T1DM and obesity, the 5:2 diet resulted in a 7% weight loss, but had no effect on HbA_{1c} levels after 52 weeks[35]. Both of these trials demonstrated that fasting 2 days per week is safe in patients with T1DM and T2DM and is associated with few hypoglycaemic events[22,35]. Nonetheless, much more research in people with diabetes mellitus is needed to clarify the safety and efficacy of these diets in this population group.

Effects of intermittent fasting on inflammation and oxidative stress. Inflammation and oxidative stress have an integral role in the development and progression of cardiovascular disease and T2DM[64–69]. The effects of fasting on key markers of inflammation, such as TNF, IL-6, homocysteine and C-reactive protein, have been examined in seven trials in humans. The results of these studies indicate that ADF[17,29], the 5:2 diet[21] and TRE[23,36,46,53] generally have no effect on these circulating inflammatory markers. By contrast, intermittent fasting has been routinely demonstrated to reduce markers of oxidative stress. For instance, levels of 8-isoprostane (a marker of oxidative degradation of lipids), fast-acting advanced oxidation protein products, nitrotyrosine and protein carbonyls have been shown to decrease fairly consistently after 8–24 weeks of following an intermittent fasting diet[15,20,23,53]. It is possible that these decreases in markers of oxidative stress are associated with improvements in insulin sensitivity due to fasting[70,71]. Insulin signalling is impaired under oxidative conditions, which leads to cellular insulin resistance[70,71]. Moreover, insulin sensitivity is improved in individuals with overweight following administration of antioxidants, such as vitamin E, compared with insulin sensitivity in those receiving placebo[72,73]. Therefore, one of the mechanisms by which intermittent fasting might improve insulin sensitivity is by decreasing oxidative stress.

Safety implications

Evidence from clinical trials suggests that ADF and TRE do not result in an increased frequency of constipation, diarrhoea, nausea, dry mouth, halitosis, irritability, fatigue or dizziness[23,74,75]. Headaches are occasionally reported during the first 2 weeks of fasting[23,74] due to dehydration, but these can be corrected with sufficient water intake[76,77].

It has been speculated that intermittent fasting could increase the risk of developing an eating disorder. Data from a 2015 trial evaluating ADF and a 2019 trial evaluating TRE show that fasting does not increase the rates of binge eating, purgative behaviour, depression or fear of becoming overweight[74,75]. However, participants with a history of an eating disorder were excluded from these trials[74,75]. Thus, it remains unknown whether fasting is safe in those with a diagnosed eating disorder. Moreover, whether these regimens are safe in individuals at risk of developing an eating disorder, such as those with low self-esteem, poor body image, negative affect (a personality variable that involves the experience of negative emotions and poor self-concept), disordered eating behaviours or internalized weight bias is still uncertain. In view of the lack of safety data in this area, clinicians should exercise caution when recommending fasting approaches to individuals who might be at risk of developing an eating disorder.

Changes in reproductive hormone levels during fasting have only been assessed in two trials to date[20,46]. In premenopausal women, circulating concentrations of androstenedione, testosterone, dehydroepiandrosterone sulfate, sex hormone-binding globulin and prolactin remained unchanged after 24 weeks on the 5:2 diet[20]. In young, lean men, 8 weeks of TRE decreased free and total testosterone concentrations, but these reductions were not related to deleterious changes in lean mass or muscle strength[46]. The effects of fasting on fertility remains unknown, as no trial has been performed to date. As for thyroid hormone levels, circulating

levels of free tetraiodothyronine, triiodothyronine and thyroid-stimulating hormone remain unchanged in healthy individuals[46] and in those with subclinical hypothyroidism[78].

It has also been postulated that intermittent fasting could have deleterious effects on resting metabolic rate. Despite this widely held belief amongst the general public, evidence shows that fasting either has no effect on resting metabolic rate when weight is maintained[25,46,79], or results in minor reductions (100–200 kcal per day) when weight is reduced by 5–7% from baseline[17,34]. Moreover, these decreases in resting metabolic rate caused by intermittent fasting during weight loss are similar to those caused by daily calorie restriction[17,34].

Taken together, these preliminary findings suggest that intermittent fasting produces few gastrointestinal, neurological, hormonal or metabolic adverse outcomes. However, as adverse events are seldom assessed in trials in humans of fasting, definitive conclusions regarding the safety of these diets are difficult to draw at present.

Practical considerations

Indications and contraindications. Intermittent fasting should not be prescribed to children under the age of 12 years, or women who are pregnant or lactating, as no study to date has evaluated the safety of these diets in these population groups (BOX 1). Fasting is not recommended in people with a history of an eating disorder or a BMI of less than 18.5 kg/m^2. Elderly individuals over the age of 70 years should also be cautioned against the use of these diets, as the effects of fasting on ageing-induced sarcopenia remains uncertain. Moreover, patients who need to take medications with meals at certain times of the day might find it difficult to follow certain TRE regimens. These patients should work with their clinicians to find a fasting protocol that works best with their medication regimen. Healthy adults with overweight or obesity, who do not have T1DM, T2DM or other comorbidities, can safely undertake these diets without medical supervision.

Findings from the past few years suggest that fasting might be effective for weight control in adolescents with obesity[80–82]. However, fasting in this group should only be recommended when weight loss is clinically indicated and should only be undertaken under medical supervision. Opinions of clinicians and researchers vary regarding the safety of fasting in adolescents with obesity. Some feel that fasting might be too extreme in this population, as adolescence is the peak life stage for eating disorder development[83–85]. By contrast, others point to evidence suggesting that medically supervised weight loss diets do not increase the risk of an eating disorder in adolescents with obesity[86]. More research is undoubtedly needed to further elucidate the safety of these diets in this group.

Advice when starting, following and stopping intermittent fasting. Contrary to what would be expected, intermittent fasting is generally not difficult to incorporate into day-to-day life[4,11,14,26,29,87–89]. Clinicians should be aware, however, that there is an adjustment period of 1 to 2 weeks with any of these diets (BOX 2). Headaches are commonly reported during this initial period[23], but these tend to subside when water intake is increased to 1.5 l per day[76,77]. Once patients have adapted to their fasting protocol, they can engage in their normal exercise routine, even during periods of fasting. Trials from the past few years show that participants are able to do moderate-intensity to high-intensity endurance or resistance exercise during 12-h to 36-h periods of food abstention without any adverse effects[16,24,25,29,46].

As for the types of foods consumed during intermittent fasting, patients should be encouraged to consume plenty of fruits, vegetables and whole grains to boost their fibre and micronutrient intake. It is also advisable to consume at least 50 g of lean protein on the fast day of ADF and the 5:2 diet to help to control hunger[90–92] and prevent excessive lean mass loss[93,94]. Alcohol is permitted, but it is not recommended on the fast day of ADF or the 5:2 diet, as energy intake is already limited on these days to approximately 500 kcal. Caffeinated beverages (such as energy drinks or coffee and tea without sugar, milk or cream) and diet sodas are allowed during the fasting window. However, diet soda intake should be limited to two servings per day as these beverages can increase sugar craving[95].

Behavioural change strategies should be encouraged as an adjunct therapy to fasting to help promote weight management. Structured behavioural change programmes help patients achieve their weight loss goals by teaching them how to regularly self-monitor their food intake, activity levels and body weight[96–98]. Behavioural therapy can be provided by a trained interventionist in a group or one-on-one setting. Alternatively, behavioural change programmes are also available online and as mobile health apps[99].

Considerations for diabetes mellitus

Although the evidence is still very limited, preliminary findings suggest that intermittent fasting might be safe in patients with T1DM and T2DM[22,35]. However, patients with diabetes mellitus need to be monitored closely by their physician during periods of intermittent fasting. Studies show that occurrences of hypoglycaemia and hyperglycaemia are rare in these patients when appropriate medical management is in place[22,35].

Box 1 | **Indications and contraindications**

Who should not do intermittent fasting?

- Children under the age of 12 years
- Adolescents who are normal weight
- Women who are pregnant or lactating
- Individuals with a history of an eating disorder
- Individuals with a BMI below 18.5 kg/m^2
- Individuals over the age of 70 years

Who can do intermittent fasting?

- Adolescents with severe obesity (>95th BMI percentile)
- Adults with normal weight, overweight or obesity
- Adults with hypertension and/or dyslipidaemia
- Patients with insulin resistance or prediabetes
- Patients with type 1 diabetes mellitus or type 2 diabetes mellitus

Blood glucose monitoring. It is recommended that patients with T1DM or T2DM test and record their fasting blood levels of glucose regularly throughout the day during intermittent fasting (for example, immediately before and 2 h after each meal, and before sleeping). Patients should be in weekly contact with their physician during the active weight loss period (typically the first 3 months of the diet) to monitor adverse effects and adjust medications. If their blood levels of glucose are less than 70 mg/dl on two consecutive occasions, patients should contact their physician for medication changes[22,100]. If blood levels of glucose are higher than 180 mg/dl, dietary compliance with the fasting protocol should be checked and changes to medications should be made if necessary[22,100].

Medication management in patients with T1DM. Based on the available literature[35,101], patients with T1DM who are on ADF or the 5:2 diet might be advised to reduce their basal insulin dose by 50% on fast days and by 10% on non-fast days. Insulin doses should be adjusted weekly during active weight loss, based on the lowest pre-meal blood level of glucose measured in the preceding 7 days. A medication management protocol during TRE is still unknown, as no study has been performed in patients with T1DM.

Medication management in patients with T2DM. Based on the available literature, patients with T2DM with an HbA_{1c} level of <7% might be advised to discontinue sulfonylureas and insulin during ADF and the 5:2 diet[22,100,101]. However, if the patient's HbA_{1c} level is between 7% and 10% at the start of the diet, sulfonylureas and insulin could be discontinued on the fast day only, and long-acting insulin could be discontinued the night before a fast day[22,100]. If the HbA_{1c} level is >10% when starting ADF or 5:2, sulfonylurea medications could remain unchanged, but long-acting insulin could be decreased by approximately 10 units on fast days only[22,100]. An endocrinologist should work with each patient individually to ensure the best care; note that patients should be advised not to adjust their medication without medical advice. A medication protocol during TRE in patients with T2DM has yet to be clarified as no data are available. Moreover, there is currently no clear protocol for managing newer agents, such as SGLT2 inhibitors and GLP1 receptor agonists, as there are no published safety or efficacy data available for these medications during fasting at present.

Box 2 | **Advice when starting, following and stopping intermittent fasting**

Starting intermittent fasting

- Adjustment period: Typically 1–2 weeks of adjustment to intermittent fasting is needed. Headaches are common but usually subside when water intake is increased.
- Exercise: Fasting will typically not alter daily exercise routines.
- Fibre: Fruits, vegetables and whole grains can boost fibre and micronutrient intake.
- Protein: At least 50 g of lean protein on the fast day of alternate day fasting (ADF) and the 5:2 diet can control hunger and prevent excessive lean mass loss.
- Beverages: Alcohol in moderation is permitted on feast days of ADF and the 5:2 diet, and during the eating window of time-restricted eating (TRE). Caffeinated beverages and calorie-free drinks are allowed during the fasting window in moderation.

What should be monitored during intermittent fasting?

- Adverse effects: Clinicians should regularly assess the frequency of adverse effects during the first 3 months.
- Nutrient deficiencies: Clinicians should monitor for deficiencies in circulating levels of vitamins and minerals (such as vitamin D, vitamin B_{12} and electrolytes).
- Medications: Medications to control blood pressure and circulating levels of lipids and glucose should be monitored and might need to be reduced if the patient loses weight.
- Therapy: Patients should participate in structured behavioural change programmes, either in person or online, to help them achieve long-term weight management.

Stopping intermittent fasting

- It is important that patients who wish to stop intermittent fasting upon reaching their weight loss goal transition to a weight maintenance regimen involving regular calorie intake monitoring, daily self-weighing and increased physical activity.
- Alternatively, patients can continue following a modified version of the fasting regimen, for example, by increasing energy intake on the fast day to 1,000–1,200 kcal per day of ADF and the 5:2 diet, or widening the eating window to 12 h for TRE.

Future directions

As of 2010, only four single-arm trials[15,79,102,103] had been performed to evaluate the effects of intermittent fasting on health-related outcomes in human participants. Over the past 10 years, interest in these diets has grown tremendously, and more data on the effects of intermittent fasting diets are beginning to emerge every month. Despite the influx of data in the past few years, much more needs to be done to increase our understanding of the field (BOX 3). Specifically, long-term (>1 year) clinical trials are critically needed. To date, the vast majority of studies in this field have been very short (between 4 and 12 weeks), with only three studies testing long-term effects (52 weeks)[17,22,35]. Randomized controlled trials and qualitative studies running for multiple years will offer important insights into the safety, feasibility and long-term weight and cardiometabolic benefits of these protocols. Future studies should also prioritize testing the health benefits of these diets in patients with T1DM and T2DM, polycystic ovary syndrome and thyroid disorders. Trials in humans that directly compare the effects of ADF, the 5:2 diet and TRE are also needed to help to ascertain whether one regimen is superior to the others. Moreover, studies that aim to tease apart the effects of weight loss versus fasting on metabolic parameters are also warranted. Findings generated from such studies could help elucidate the mechanisms that underlie the metabolic improvements observed with fasting.

Limitations to the current evidence

While these studies offer promise for the use of intermittent fasting in improving metabolic health, the quality of available evidence to date is limited. For instance, the majority of these trials had small sample sizes, including 10–150 participants. This limitation puts into question whether these studies were adequately powered to detect statistically significant differences in primary and secondary outcome measures. Moreover, the majority of studies were conducted in one geographical region, namely the USA. Additional research in other areas of the world is needed to tailor recommendations for fasting to other populations and food cultures.

Box 3 | **Directions for future research**

- Long-term (>1 year) randomized controlled clinical trials (RCTs) and qualitative studies that test the feasibility and long-term efficacy of alternate day fasting (ADF), the 5:2 diet and time-restricted eating (TRE).
- RCTs and qualitative studies that examine the effects of these diets in different population groups, such as individuals with type 1 diabetes mellitus and type 2 diabetes mellitus, polycystic ovary syndrome and thyroid disorders.
- RCTs and qualitative studies that directly compare the effects of ADF, the 5:2 diet and TRE will help to ascertain whether one regimen is superior to the others.
- RCTs that tease apart the effects of fasting from the effects of weight loss will help to further elucidate the mechanisms that underlie the metabolic improvements observed with fasting.

We also performed a risk of bias assessment using the Cochrane Collaboration tool[104]. Random sequence generation, allocation concealment, blinding and incomplete outcome data were graded as having a high, low or unclear risk of bias (Supplementary Fig. 1). We found that 15 of the 22 trials we assessed were at high risk of bias, mostly as a result of missing participant outcome data. Moreover, none of the studies blinded study personnel or participants as this was not possible owing to the nature of the dietary interventions. These findings highlight the need for more well-powered, high-quality, randomized controlled trials that clearly and accurately report outcome data.

Conclusions

The health benefits of intermittent fasting are slowly being clarified as new evidence continues to emerge. Findings to date suggest that ADF, the 5:2 diet and TRE produce mild to moderate weight loss (3–8% loss from baseline) over 8–12 weeks. This degree of weight loss is on a par with that achieved with traditional dieting approaches (daily calorie restriction). The ability of these intermittent fasting protocols to help to manage weight long-term is still poorly understood, as the majority of studies to date have run for short durations. The impact of intermittent fasting on cardiometabolic risk parameters is still uncertain. While some studies have demonstrated improvements in blood pressure, LDL cholesterol, triglycerides, insulin resistance and HbA_{1c}, others have shown no benefit on these parameters. Regarding safety, preliminary data indicate that fasting produces few gastrointestinal, neurological, hormonal or metabolic adverse effects. However, as adverse outcomes are not regularly assessed in human trials of fasting, definitive conclusions regarding the safety of these diets are difficult to draw at present. Taken together, these initial findings suggest that fasting might be effective for weight loss, but the effects of these diets in the prevention and management of metabolic disorders needs further clarification. Although some progress has been made in this field over the past 10 years, data from well-powered, long-term randomized controlled trials is needed to further elucidate the safety and efficacy of these popular diets in various population groups.

Published online: 22 February 2022

1. Williamson, D. A., Bray, G. A. & Ryan, D. H. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity* **23**, 2319–2320 (2015).
2. Brody, J. E. The benefits of intermittent fasting. *The New York Times* (23 Feb 2020).
3. Kohik, S. Why is intermittent fasting so popular? *BBC News* (3 Jun 2019).
4. de Cabo, R. & Mattson, M. P. Effects of intermittent fasting on health, aging, and disease. *N. Engl. J. Med.* **381**, 2541–2551 (2019).
5. Brandhorst, S. & Longo, V. D. Dietary restrictions and nutrition in the prevention and treatment of cardiovascular disease. *Circ. Res.* **124**, 952–965 (2019).
6. Longo, V. D. & Panda, S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metab.* **23**, 1048–1059 (2016).
7. Mattson, M. P., Longo, V. D. & Harvie, M. Impact of intermittent fasting on health and disease processes. *Ageing Res. Rev.* **39**, 46–58 (2017).
8. Paoli, A., Tinsley, G., Bianco, A. & Moro, T. The influence of meal frequency and timing on health in humans: the role of fasting. *Nutrients* **11**, 719 (2019).
9. St-Onge, M. P. et al. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. *Circulation* **135**, e96–e121 (2017).
10. Harvie, M. & Howell, A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight and normal weight subjects–a narrative review of human and animal evidence. *Behav. Sci.* **7**, 4 (2017).
11. Patterson, R. E. & Sears, D. D. Metabolic effects of intermittent fasting. *Annu. Rev. Nutr.* **37**, 371–393 (2017).
12. Tinsley, G. M. & La Bounty, P. M. Effects of intermittent fasting on body composition and clinical health markers in humans. *Nutr. Rev.* **73**, 661–674 (2015).
13. Stekovic, S. et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. *Cell Metab.* **31**, 878–881 (2020).
14. Catenacci, V. A. et al. A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity. *Obesity* **24**, 1874–1883 (2016).
15. Johnson, J. B. 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.* **42**, 665–674 (2007).
16. Cho, A. R. et al. Effects of alternate day fasting and exercise on cholesterol metabolism in overweight or obese adults: a pilot randomized controlled trial. *Metabolism* **93**, 52–60 (2019).
17. Trepanowski, J. F. et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern. Med.* **177**, 930–938 (2017).
18. Hoddy, K. K. et al. Meal timing during alternate day fasting: impact on body weight and cardiovascular disease risk in obese adults. *Obesity* **22**, 2524–2531 (2014).
19. Antoni, R., Johnston, K. L., Collins, A. L. & Robertson, M. D. Investigation into the acute effects of total and partial energy restriction on postprandial metabolism among overweight/obese participants. *Br. J. Nutr.* **115**, 951–959 (2016).
20. Harvie, M. N. 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.* **35**, 714–727 (2011).
21. Schubel, R. et al. Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: a randomized controlled trial. *Am. J. Clin. Nutr.* **108**, 933–945 (2018).
22. Carter, S., Clifton, P. M. & Keogh, J. B. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. *JAMA Netw. Open* **1**, e180756 (2018).
23. Cienfuegos, S. et al. Effects of 4- and 6-h time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity. *Cell Metab.* **32**, 366–378 (2020).
24. Tinsley, G. M. et al. Time-restricted feeding in young men performing resistance training: a randomized controlled trial. *Eur. J. Sport. Sci.* **17**, 200–207 (2017).
25. Tinsley, G. M. et al. Time-restricted feeding plus resistance training in active females: a randomized trial. *Am. J. Clin. Nutr.* **110**, 628–640 (2019).
26. Chow, L. S. et al. Time-restricted eating effects on body composition and metabolic measures in humans who are overweight: a feasibility study. *Obesity* **28**, 860–869 (2020).
27. Wilkinson, M. J. et al. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. *Cell Metab.* **31**, 92–104.e5 (2020).
28. Parvaresh, A. et al. Modified alternate-day fasting vs. calorie restriction in the treatment of patients with metabolic syndrome: a randomized clinical trial. *Complement. Ther. Med.* **47**, 102187 (2019).
29. Bhutani, S., Klempel, M. C., Kroeger, C. M., Trepanowski, J. F. & Varady, K. A. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. *Obesity* **21**, 1370–1379 (2013).
30. Bhutani, S. et al. Effect of exercising while fasting on eating behaviors and food intake. *J. Int. Soc. Sports Nutr.* **10**, 50 (2013).
31. Varady, K. A. et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. *Nutr. J.* **12**, 146 (2013).
32. Fitzgerald, K. C. et al. Effect of intermittent vs. daily calorie restriction on changes in weight and patient-reported outcomes in people with multiple sclerosis. *Mult. Scler. Relat. Disord.* **23**, 33–39 (2018).
33. Harvie, M. et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction

on weight loss and metabolic disease risk markers in overweight women. *Br. J. Nutr.* **110**, 1534–1547 (2013).
34. Sundfor, T. M., Svendsen, M. & Tonstad, S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: a randomized 1-year trial. *Nutr. Metab. Cardiovasc. Dis.* **28**, 698–706 (2018).
35. Overland, J. et al. The safety and efficacy of weight loss via intermittent fasting or standard daily energy restriction in adults with type 1 diabetes and overweight or obesity: a pilot study. *Obes. Med.* **12**, 13–17 (2018).
36. Gabel, K. et al. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study. *Nutr. Healthy Aging* **4**, 345–353 (2018).
37. Lin, S. et al. Does the weight loss efficacy of alternate day fasting differ according to sex and menopausal status? *Nutr. Metab. Cardiovasc. Dis.* **31**, 641–649 (2020).
38. Gabel, K. et al. Differential effects of alternate-day fasting versus daily calorie restriction on insulin resistance. *Obesity* **27**, 1443–1450 (2019).
39. Cioffi, I. et al. Intermittent versus continuous energy restriction on weight loss and cardiometabolic outcomes: a systematic review and meta-analysis of randomized controlled trials. *J. Transl. Med.* **16**, 371 (2018).
40. Harris, L., McGarty, A., Hutchison, L., Ells, L. & Hankey, C. Short-term intermittent energy restriction interventions for weight management: a systematic review and meta-analysis. *Obes. Rev.* **19**, 1–13 (2018).
41. Headland, M., Clifton, P. M., Carter, S. & Keogh, J. B. Weight-loss outcomes: a systematic review and meta-analysis of intermittent energy restriction trials lasting a minimum of 6 months. *Nutrients* **8**, 354 (2016).
42. Willoughby, D., Hewlings, S. & Kalman, D. Body composition changes in weight loss: strategies and supplementation for maintaining lean body mass, a brief review. *Nutrients* **10**, 1876 (2018).
43. Heymsfield, S. B., Gonzalez, M. C., Shen, W., Redman, L. & Thomas, D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. *Obes. Rev.* **15**, 310–321 (2014).
44. Pownall, H. J. et al. Changes in body composition over 8 years in a randomized trial of a lifestyle intervention: the look AHEAD study. *Obesity* **23**, 565–572 (2015).
45. Ravussin, E. et al. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. *J. Gerontol. A Biol. Sci. Med. Sci.* **70**, 1097–1104 (2015).
46. Moro, T. et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *J. Transl. Med.* **14**, 290 (2016).
47. Klempel, M. C., Bhutani, S., Fitzgibbon, M., Freels, S. & Varady, K. A. Dietary and physical activity adaptations to alternate day modified fasting: implications for optimal weight loss. *Nutr. J.* **9**, 35 (2010).
48. Harvey, J., Howell, A., Morris, J. & Harvie, M. Intermittent energy restriction for weight loss: spontaneous reduction of energy intake on unrestricted days. *Food Sci. Nutr.* **6**, 674–680 (2018).
49. Dansinger, M. L., Gleason, J. A., Griffith, J. L., Selker, H. P. & Schaefer, E. J. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* **293**, 43–53 (2005).
50. Das, S. K. et al. Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. *Am. J. Clin. Nutr.* **85**, 1023–1030 (2007).
51. Jospe, M. R. et al. Intermittent fasting, Paleolithic, or Mediterranean diets in the real world: exploratory secondary analyses of a weight-loss trial that included choice of diet and exercise. *Am. J. Clin. Nutr.* **111**, 503–514 (2020).
52. Kalam, F. et al. Beverage intake during alternate-day fasting: relationship to energy intake and body weight. *Nutr. Health* **25**, 167–171 (2019).
53. Sutton, E. F. et al. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab.* **27**, 1212–1221.e3 (2018).
54. Lowe, D. A. et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: the TREAT randomized clinical trial. *JAMA Intern. Med.* **180**, 1491–1499 (2020).
55. Andersson, B., Wallin, G., Hedner, T., Ahlberg, A. C. & Andersson, O. K. Acute effects of short-term fasting on blood pressure, circulating noradrenaline and efferent sympathetic nerve activity. *Acta Med. Scand.* **223**, 485–490 (1988).
56. Johnston, J. G., Speed, J. S., Jin, C. & Pollock, D. M. Loss of endothelin B receptor function impairs sodium excretion in a time- and sex-dependent manner. *Am. J. Physiol. Ren. Physiol.* **311**, F991–F998 (2016).
57. Rolland, C. & Broom, I. The effects of very-low-calorie diets on HDL: a review. *Cholesterol* **2011**, 306278 (2011).
58. Kodama, S. et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch. Intern. Med.* **167**, 999–1008 (2007).
59. Leon, A. S. & Sanchez, O. A. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med. Sci. Sports Exerc.* **33**, S502–S515 (2001).
60. Browning, J. D., Baxter, J., Satapati, S. & Burgess, S. C. The effect of short-term fasting on liver and skeletal muscle lipid, glucose, and energy metabolism in healthy women and men. *J. Lipid Res.* **53**, 577–586 (2012).
61. Halberg, N. et al. Effect of intermittent fasting and refeeding on insulin action in healthy men. *J. Appl. Physiol.* **99**, 2128–2136 (2005).
62. Salgin, B. et al. Effects of prolonged fasting and sustained lipolysis on insulin secretion and insulin sensitivity in normal subjects. *Am. J. Physiol. Endocrinol. Metab.* **296**, E454–E461 (2009).
63. Freckmann, G. et al. Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. *J. Diabetes Sci. Technol.* **1**, 695–703 (2007).
64. Cervantes Gracia, K., Llanas-Cornejo, D. & Husi, H. CVD and oxidative stress. *J. Clin. Med.* **6**, 22 (2017).
65. Donath, M. Y. & Shoelson, S. E. Type 2 diabetes as an inflammatory disease. *Nat. Rev. Immunol.* **11**, 98–107 (2011).
66. Maritim, A. C., Sanders, R. A. & Watkins, J. B. 3rd Diabetes, oxidative stress, and antioxidants: a review. *J. Biochem. Mol. Toxicol.* **17**, 24–38 (2003).
67. Siti, H. N., Kamisah, Y. & Kamsiah, J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vasc. Pharmacol.* **71**, 40–56 (2015).
68. Tsalamandris, S. et al. The role of inflammation in diabetes: current concepts and future perspectives. *Eur. Cardiol.* **14**, 50–59 (2019).
69. Wellen, K. E. & Hotamisligil, G. S. Inflammation, stress, and diabetes. *J. Clin. Invest.* **115**, 1111–1119 (2005).
70. Houstis, N., Rosen, E. D. & Lander, E. S. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* **440**, 944–948 (2006).
71. Rains, J. L. & Jain, S. K. Oxidative stress, insulin signaling, and diabetes. *Free Radic. Biol. Med.* **50**, 567–575 (2011).
72. Zaulkffali, A. S. et al. Vitamins D and E stimulate the PI3K-AKT signalling pathway in insulin-resistant SK-N-SH neuronal cells. *Nutrients* **11**, 2525 (2019).
73. Manning, P. J. et al. Effect of high-dose vitamin E on insulin resistance and associated parameters in overweight subjects. *Diabetes Care* **27**, 2166–2171 (2004).
74. Gabel, K., Hoddy, K. K. & Varady, K. A. Safety of 8-h time restricted feeding in adults with obesity. *Appl. Physiol. Nutr. Metab.* **44**, 107–109 (2019).
75. Hoddy, K. K. et al. Safety of alternate day fasting and effect on disordered eating behaviors. *Nutr. J.* **14**, 44 (2015).
76. Blau, J. N., Kell, C. A. & Sperling, J. M. Water-deprivation headache: a new headache with two variants. *Headache* **44**, 79–83 (2004).
77. Spigt, M. G. et al. Increasing the daily water intake for the prophylactic treatment of headache: a pilot trial. *Eur. J. Neurol.* **12**, 715–718 (2005).
78. Akasheh, R. T. et al. Weight loss efficacy of alternate day fasting versus daily calorie restriction in subjects with subclinical hypothyroidism: a secondary analysis. *Appl. Physiol. Nutr. Metab.* **45**, 340–343 (2020).
79. Heilbronn, L. K., Smith, S. R., Martin, C. K., Anton, S. D. & Ravussin, E. Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. *Am. J. Clin. Nutr.* **81**, 69–73 (2005).
80. Jebeile, H. et al. Intermittent energy restriction is a feasible, effective, and acceptable intervention to treat adolescents with obesity. *J. Nutr.* **149**, 1189–1197 (2019).
81. Lister, N. B. et al. Fast track to health – intermittent energy restriction in adolescents with obesity. A randomised controlled trial study protocol. *Obes. Res. Clin. Pract.* **14**, 80–90 (2020).
82. Vidmar, A. P., Goran, M. I. & Raymond, J. K. Time-limited eating in pediatric patients with obesity: a case series. *J. Food Sci. Nutr. Res.* **2**, 236–244 (2019).
83. Culbert, K. M., Racine, S. E. & Klump, K. L. The influence of gender and puberty on the heritability of disordered eating symptoms. *Curr. Top. Behav. Neurosci.* **6**, 177–185 (2011).
84. Klump, K. L. Puberty as a critical risk period for eating disorders: a review of human and animal studies. *Horm. Behav.* **64**, 399–410 (2013).
85. Klump, K. L., Culbert, K. M., O'Connor, S., Fowler, N. & Burt, S. A. The significant effects of puberty on the genetic diathesis of binge eating in girls. *Int. J. Eat. Disord.* **50**, 984–989 (2017).
86. Jebeile, H. et al. Treatment of obesity, with a dietary component, and eating disorder risk in children and adolescents: a systematic review with meta-analysis. *Obes. Rev.* **20**, 1287–1298 (2019).
87. Antoni, R., Johnston, K. L., Collins, A. L. & Robertson, M. D. Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants. *Br. J. Nutr.* **119**, 507–516 (2018).
88. Chaix, A., Manoogian, E. N. C., Melkani, G. C. & Panda, S. Time-restricted eating to prevent and manage chronic metabolic diseases. *Annu. Rev. Nutr.* **39**, 291–315 (2019).
89. Wegman, M. P. et al. Practicality of intermittent fasting in humans and its effect on oxidative stress and genes related to aging and metabolism. *Rejuvenation Res.* **18**, 162–172 (2015).
90. Apolzan, J. W., Carnell, N. S., Mattes, R. D. & Campbell, W. W. Inadequate dietary protein increases hunger and desire to eat in younger and older men. *J. Nutr.* **137**, 1478–1482 (2007).
91. Leidy, H. J., Tang, M., Armstrong, C. L., Martin, C. B. & Campbell, W. W. The effects of consuming frequent, higher protein meals on appetite and satiety during weight loss in overweight/obese men. *Obesity* **19**, 818–824 (2011).
92. Weigle, D. S. et al. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. *Am. J. Clin. Nutr.* **82**, 41–48 (2005).
93. Cava, E., Yeat, N. C. & Mittendorfer, B. Preserving healthy muscle during weight loss. *Adv. Nutr.* **8**, 511–519 (2017).
94. Mettler, S., Mitchell, N. & Tipton, K. D. Increased protein intake reduces lean body mass loss during weight loss in athletes. *Med. Sci. Sports Exerc.* **42**, 326–337 (2010).
95. Swithers, S. E. Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. *Trends Endocrinol. Metab.* **24**, 431–441 (2013).
96. Hartmann-Boyce, J. et al. Cognitive and behavioural strategies for weight management in overweight adults: results from the Oxford Food and Activity Behaviours (OxFAB) cohort study. *PLoS ONE* **13**, e0202072 (2018).
97. Kelley, C. P., Sbrocco, G. & Sbrocco, T. Behavioral modification for the management of obesity. *Prim. Care* **43**, 159–175 (2016).
98. Teixeira, P. J. et al. Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. *BMC Med.* **13**, 84 (2015).
99. Ghelani, D. P., Moran, L. J., Johnson, C., Mousa, A. & Naderpoor, N. Mobile apps for weight management: a review of the latest evidence to inform practice. *Front. Endocrinol.* **11**, 412 (2020).
100. Carter, S., Clifton, P. M. & Keogh, J. B. Intermittent energy restriction in type 2 diabetes: a short discussion of medication management. *World J. Diabetes* **7**, 627–630 (2016).
101. Grajower, M. M. & Horne, B. D. Clinical management of intermittent fasting in patients with diabetes mellitus. *Nutrients* **11**, 873 (2019).
102. Varady, K. A., Bhutani, S., Church, E. C. & Klempel, M. C. Short-term modified alternate-day fasting: a novel

dietary strategy for weight loss and cardioprotection in obese adults. *Am. J. Clin. Nutr.* **90**, 1138–1143 (2009).
103. Carlson, O. et al. Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women. *Metabolism* **56**, 1729–1734 (2007).
104. Higgins, J. P. et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928 (2011).

Acknowledgements
The authors thank the participants in the trials discussed in this Review for their time and effort. The authors acknowledge support from the National Institute of Diabetes and Digestive and Kidney Diseases (grant no. R01DK119783). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contributions
K.A.V., S.C., M.E. and K.G. contributed to all aspects of the preparation and writing of this Review.

Competing interests
K.A.V. received author fees from Hachette Book Group for the book, *The Every Other Day Diet*. The other authors declare no competing interests.

Peer review information
Nature Reviews Endocrinology thanks M. Harvie, K. Petersen and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41574-022-00638-x.