The effect of intermittent energy restriction on weight loss and diabetes risk markers in women with a history of gestational diabetes: a 12-month randomized control trial

Kristy L Gray,[1,2] *Peter M Clifton,*[1,2] *and Jennifer B Keogh*[1,2]

[1]University of South Australia, Clinical and Health Sciences, Adelaide, Australia; and [2]Alliance for Research in Exercise, Nutrition and Activity (ARENA), University of South Australia, Adelaide, Australia

ABSTRACT

Background: Weight loss after gestational diabetes (GDM) can prevent or delay the onset of type 2 diabetes. Intermittent energy restriction (IER) may offer an alternative to continuous energy restriction (CER) for weight loss.

Objectives: We compared the effects of IER (2 days per week) to daily CER over 12 mo on weight loss and diabetes risk markers in overweight women with previous GDM.

Methods: Overweight females ($n = 121$) ≥18 y were randomized 1:1 to either IER [2-d 500 kcal (2100 kJ); $n = 61$] or CER [1500 kcal (6000 kJ); $n = 60$] in this 12-mo noninferiority trial.

Results: The trial was completed by 62 participants with a median age of 39.6 y [Quartile (Q) 1 to Quartile 3, 34.9 to 43.9 y] with a median BMI of 32.6 kg/m^2 (Q1 to Q3, 28.5 to 37.9 kg/m^2) at a median of 2.9 y after GDM (Q1 to Q3, 2.1 to 6.4 y; 49% attrition; IER $n = 29$; CER $n = 30$; $P = 0.8$). The mean ± SD weight loss was significant over time ($P < 0.001$) but not by diet group (IER −4.8 ± 5.0 kg; CER −3.2 ± 5.0; $P = 0.2$). The mean between-group difference was −1.6 kg (95% CI: −4.2 to 1.0 kg; $P = 0.2$). There were no significant between-group differences in change in HbA1c, fasting plasma glucose, fasting serum insulin, HOMA-IR or 2-h oral glucose tolerance at 12 mo ($p>0.05$). The trial was registered at https://www.anzctr.org.au/ (ACTRN12617001476325).

Conclusions: IER produces comparable weight loss to CER over 12 mo in overweight women with previous GDM. The high dropout rate in this study is a limitation in the interpretation of these results. Larger studies are needed to confirm noninferiority of IER compared to CER. *Am J Clin Nutr* 2021;114:794–803.

Keywords: intermittent energy restriction, intermittent fasting, diabetes prevention, gestational diabetes, weight loss, women, overweight

Introduction

In 2016–17, 15% of pregnancies resulting in a live birth in Australia were affected by gestational diabetes (GDM) (1). A diagnosis of GDM in Australia is based on the Australian Diabetes in Pregnancy Society's criteria of a fasting plasma glucose level 5.1–6.9 mmol/L or a 2-h 75 g oral glucose tolerance of 8.5–11.0 mmol/L during pregnancy (2). Globally, around 1 in 5 pregnancies are affected by GDM (3), with 18.4 million births from GDM pregnancies in 2017 (4). Women with GDM have a nearly 10-fold risk of developing type 2 diabetes mellitus (T2DM) compared to women who do not develop GDM (5), and up to half of these women develop T2DM later in life (6). T2DM has lifelong consequences that can lead to the development of other chronic diseases, including heart disease and cancer early in life (7, 8), making diabetes a major health concern in Australia and globally (4) and raising the importance of diabetes prevention.

GDM is more prominent in women who are overweight or obese, who have double the risk of T2DM compared to those in a healthy weight range (6). Weight loss interventions are effective in reducing the risk of T2DM (9); however, engagement is low in this population (10). Weight loss of 5 kg reduces the risk of developing T2DM by half in women with impaired glucose tolerance and prior GDM (11); however, factors such as fatigue, a lack of family support, diet not fitting into family meals, family responsibilities, and further pregnancies make weight loss difficult for women with children (12–14).

Continuous energy restriction (CER) remains the most common strategy for weight loss and diabetes prevention (15), and requires individuals to restrict their energy intake by 25–30%,

This research has been funded by University of South Australia. Some of the participants in this study were recruited as registrants of the National Diabetes Services Scheme, an initiative of the Australian Government administered by Diabetes Australia.

Address correspondence to JK (e-mail: jennifer.keogh@unisa.edu.au).

Abbreviations used: AAS, Active Australia Survey; CER, continuous energy restriction; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; IER, intermittent energy restriction; OGTT, oral-glucose-tolerance test; PSQI, Pittsburgh sleep quality index; Q, quartile; T2DM, type 2 diabetes mellitus.

Received July 3, 2020. Accepted for publication February 16, 2021.

First published online April 8, 2021; doi: https://doi.org/10.1093/ajcn/nqab058.

or 500–600 kcal (2100–2500 kJ), daily (16, 17). This diet is difficult to adhere to in the long term (18). Alternative weight loss regimes, such as intermittent energy restriction (IER), have gained attention recently. IER involves periods of severe energy restriction followed by periods of habitual eating, and may provide more flexibility with less disruption to daily life than CER. IER has been found to produce weight loss and metabolic benefits comparable to those of CER (15, 19–21); however, to our knowledge an IER diet has not been tested in overweight women with a history of GDM. The purpose of this study was to investigate the effects of a 2-d 500 kcal (2100 kJ) IER regime to CER over 12 mo on weight loss and diabetes risk markers in overweight women with previous GDM. The hypothesis was that weight loss resulting from an IER diet would not be inferior to that from a CER diet at 12 mo.

Methods

Participants

Recruitment occurred between March 2018 and March 2019. Recruitment was achieved through a mail-out by the National Diabetes Services Scheme to women registered on the Australian Gestational Diabetes Register, interviews on television and local radio, advertisements on social media, posts on online parenting websites, and flyers displayed on community and university notice boards. Participants were females aged ≥18 y with a previous diagnosis of GDM during pregnancy and a current BMI ≥ 25 kg/m^2. The following exclusion criteria applied: diagnosis of type 1 or type 2 diabetes; taking any diabetes or other medications that could affect glucose levels; pregnant or less than 12 wk postpartum; previous bariatric surgery; participating in any other clinical study involving medical or lifestyle interventions; had been following an intermittent diet in the last 3 mo; non-English speaking; or diagnosis of an eating disorder or any significant illness or disease. Due to low levels of recruitment, the eligibility criteria were changed from a diagnosis of GDM in the previous 5 y to include women with a diagnosis of GDM at any time. This change occurred after the recruitment of 19 participants. The eligibility criteria were also modified to allow women who reported having a history of an eating disorder to be considered if it was completely treated and a letter was sent to their medical practitioner (n = 1). Participants were randomized 1:1 at their baseline visit to either an intermittent or continuous diet. Randomization was undertaken using an online random number generator (www.randomization.com) and was stratified by the number of years since GDM (≤5 y and >5 y) and BMI (<30 kg/m^2 and ≥30 kg/m^2). Participants received $50 upon completion of the 12-mo trial.

Dietary intervention

Participants in the IER diet were advised to follow a very low–energy diet of 500 kcal (2100 kJ) per day (40% protein, 35% carbohydrates, and 25% fat with 7.5% saturated fat) for 2 nonconsecutive days each week. They were encouraged to follow their habitual eating pattern for the remainder of the week, but no specific guidance on energy restrictions was given. Participants in the CER group were advised to follow a diet of 1500 kcal (6000 kJ) per day (30% protein, 45% carbohydrates, and 25% fat with 7.5% saturated fat) for 7 days a week. Both diets provided approximately 25% energy restriction per week. Participants were seen by a qualified dietitian at each visit (0, 1, 2, 3, 6, 9, and 12 mo). All participants received a detailed diet plan, education on how to adhere to their diet, information on the energy content of foods, and sample meal plans. No food was provided. Participants were encouraged to engage in at least 30 min of physical activity on most days of the week. They were asked to keep diet records for 2 days each week to help with compliance and were asked to return the completed records at each subsequent visit. Diet records for 1 wk prior to visits at 3 and 12 mo were analyzed (IER n = 23; CER n = 20) using an Australian dietary analysis program (FoodWorks Version: 10.0.4266 Xyris Software Brisbane Australia Pty Ltd). Women who were breastfeeding (n = 12) were advised on a modified diet that provided up to an extra 500 kcal (2100 kJ) per day, depending on the age of the infant and whether supplemental formula or solids had been introduced. Breastfeeding mothers were provided with a set of bathroom scales and were required to weigh themselves weekly at home to ensure weight loss did not exceed 0.5 kg per week. These women received fortnightly contact with the study dietitian for the first 3 mo and a minimum of monthly follow-ups after.

Clinical measurements

Participants attended the University of South Australia's Health Research Clinical Trials Facility 7 times over 12 mo; they visited monthly for the first 3 mo and then every 3 mo to the 12-month time point (**Figure 1**). Participants were also offered a noncompulsory visit with the dietitian between the 3 monthly visits. The primary outcome was weight loss and secondary outcomes were BMI, glycated hemoglobin (HbA1c) level, fasting glucose and insulin levels, HOMA-IR score, and 2-h oral-glucose-tolerance test (OGTT) results. Height was measured at the baseline visit without shoes using a wall-mounted stadiometer (SECA) and was recorded to the nearest 0.1 cm. Body weight was measured at each visit in light clothing without shoes using calibrated electronic digital scales (SECA) and was recorded to the nearest 0.1 kg. BMI was calculated as weight(kg)/height(m^2). Participants fasted overnight for their weight measurements at baseline, 3 mo, and 12 mo. HbA1c was measured by finger-prick analysis using disposable lancets and a Diabetes Care Analyzer Vantage Analyser (Siemens Healthcare Diagnostics) at baseline, 3 mo, and 12 mo. The machine was calibrated monthly. A 2-h 300-ml 75-g OGTT (Carbotest, ThermoFisher Scientific Australia) was administered at baseline and 12 mo following an overnight fast. Blood was taken by finger-prick at 0, 60, and 120 min using disposable lancets and a glucometer (Freestyle Optium H, Abbott Australia). The 2-h OGTT was changed from a venous blood draw to the finger-prick method after 8 participants had been recruited to allow volunteers to receive their results immediately (n = 2 of these participants declined the 2-h OGTT). None of the participants who had their 2-h OGTT taken via a venous blood draw completed the study. A venous blood sample to measure fasting glucose and fasting insulin and to calculate HOMA-IR was also taken at 0, 3, and 12 mo. Participants in the IER group were told to consume their usual diet and not to fast on the day before an appointment, to avoid potential acute effects on glucose and insulin levels

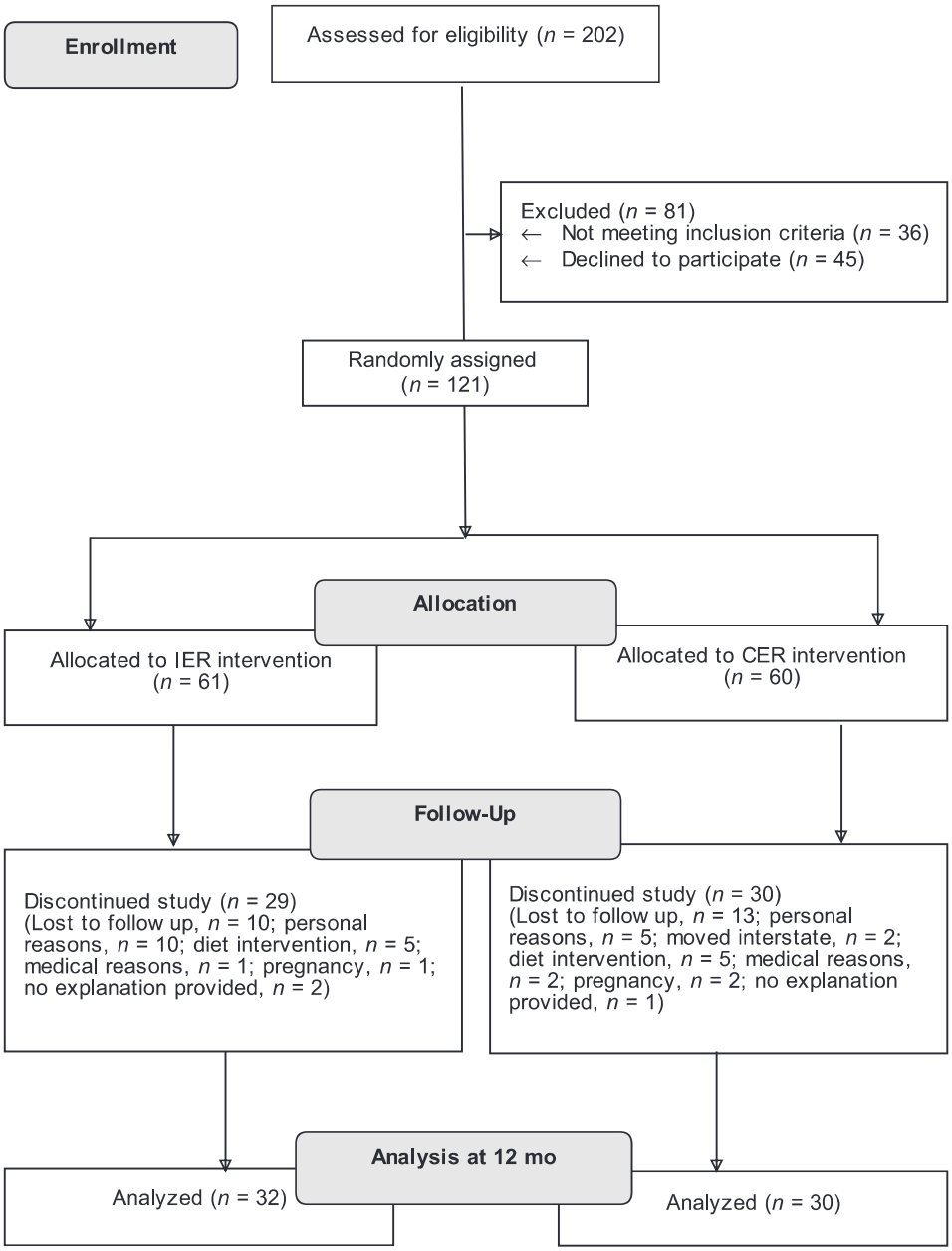

FIGURE 1 Experimental design and measurements at each visit. Abbreviations: CER, continuous energy restriction; IER, intermittent energy restriction.

from fasting. They were also asked to attend the clinic for blood samples in the same condition at each visit, so that individuals had the same number of days after a fasting day for each blood sample. Blood samples for plasma glucose were collected into a tube with sodium fluoride EDTA and were placed on ice immediately until processing. Blood samples for serum insulin were collected into a tube with no additives and remained upright at room temperature for 30 min to clot before being placed on ice until processing. Blood samples were separated via centrifuge (Universal 32R; Hettich Zentrifugen) at 4000 × *g* at 4°C for 10 min and were stored at −80°C until study completion. Plasma glucose was measured using an automated spectrophotometric analyzer (KoneLab 20XTi, ThermoFisher Scientific). Serum insulin was measured using commercial ELISA kits (Mercodia Insulin ELISA, lot# 29,991, Mercodia AB). HOMA-IR was calculated from the plasma glucose and serum insulin analysis using the equation (fasting insulin mU/L × fasting glucose mmol/L)/22.5. Physical activity and sleep quality were assessed at each visit using the Active Australia Survey (AAS) and Pittsburgh Sleep Quality Index (PSQI).

Statistics

This was a randomized noninferiority trial. A completion sample size of 70 participants ($n = 35$ each for IER and CER) was needed to demonstrate noninferiority of IER using 80% power, a P value < 0.05, and a 95% CI noninferiority limit of +3.3 kg with an SD of 6.0 kg, which was based

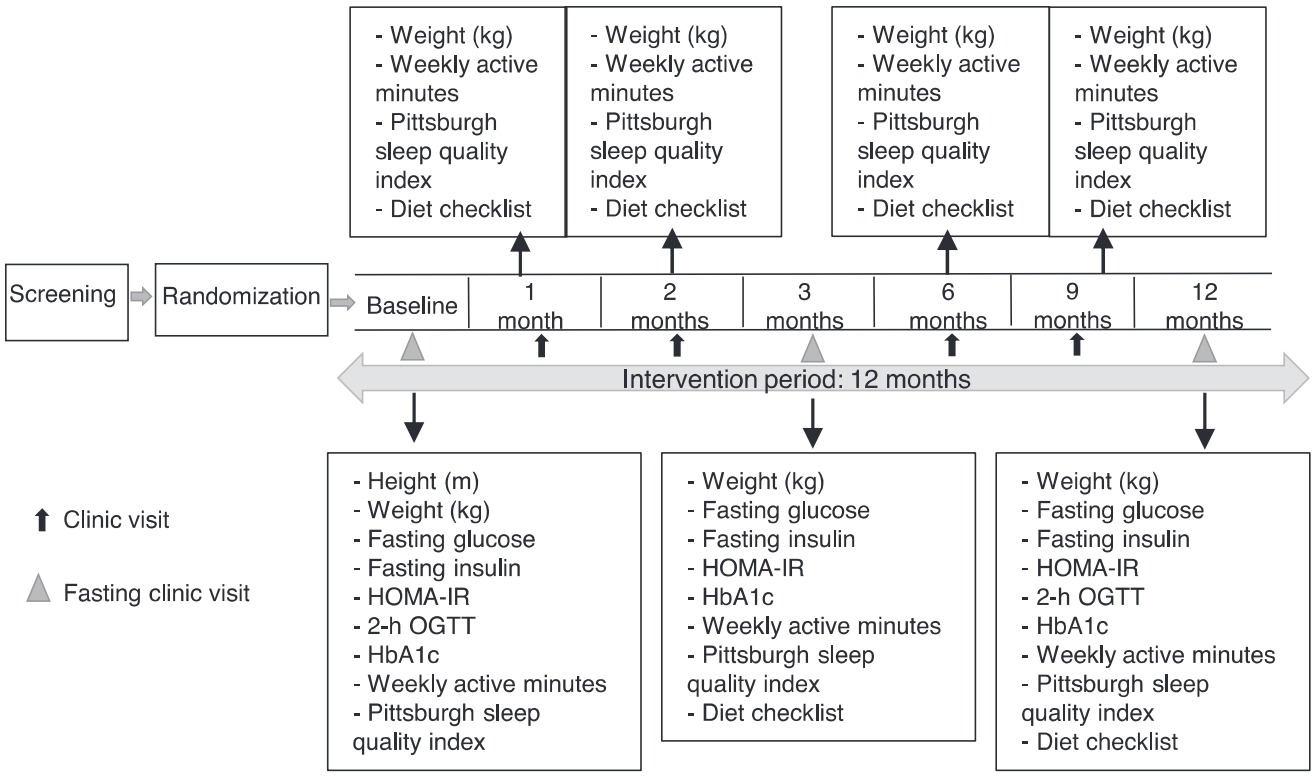

FIGURE 2 Participant flow diagram. Abbreviations: HbA1c, glycated hemoglobin; OGTT, oral-glucose-tolerance test.

on results from a 12-month controlled weight loss study in a comparable population (22). We hypothesized that a 3.3-kg weight difference between diets (66% of a desirable 5-kg weight loss) would be clinically meaningful and have an impact on the future diabetes risk. A noninferiority limit was set for the primary outcome only; superiority tests were performed for all other outcome measures. Data were analyzed using IBM SPSS Statistical Software version 26 for Windows. Significance was set at a P value < 0.05. Data were tested for normality using Q-Q plots, histograms, and Shapiro-Wilk tests. Variables that were not normally distributed were log transformed. Variables that remained skewed after log transformation were analyzed using nonparametric tests. Independent-sample t-tests and Pearson χ^2 tests were used to compare differences at baseline between diet groups and between completers and noncompleters. A general linear model of repeated measures was used to assess change over time and time × treatment interactions. Both completer and intention-to-treat analyses were performed. The intention-to-treat analysis was performed using the last measure carried forward on the primary outcome only. A descriptive analysis of dietary intake, physical activity, and sleep quality was performed, and within-group differences were assessed with a paired-sample t-test for normally distributed variables and a Wilcoxon signed rank test for nonnormally distributed variables. Data for normally distributed variables are presented as means ± SDs and data for nonnormally distributed data are presented as medians (IQRs).

Ethics

The research study was approved by The University of South Australia's Human Research Ethics Committee (protocol number 200,165) and was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001476325). All participants gave written informed consent.

Results

Of the 202 women assessed for eligibility, 166 satisfied the inclusion criteria and 121 women were randomly assigned. There were 61 participants randomly assigned to the IER group and 60 participants randomly assigned to the CER group. In total, 62 participants completed the trial to 12 mo (49% attrition). The withdrawal rates were similar between diet groups [IER, 48% (n = 29); CER, 50% (n = 30); P = 0.8]. **Figure 2** shows the recruitment and withdrawal of participants. Baseline characteristics were similar between the IER and CER group and between completers and noncompleters (**Table 1**). There were 6 volunteers whose baseline 2-h OGTT measurements were taken by plasma glucose, and there was no significant difference in glucose levels at fasting (n = 105; P = 1.0) or after 1 h (n = 105; P = 1.0) or 2 h (n = 105; P = 0.7) when these participants were excluded from the analysis. Participants were predominately in the obese weight category, with a median BMI of 32.6 kg/m^2 (IQR, 9.4 kg/m^2), had a median age of 40 y (IQR, 9 y) and were 3 y (IQR, 4 y) postpartum (IQR = Quartile 3 − Quartile 1) at baseline. There were 26 participants (22%) with a baseline HbA1c level of ≥5.7% (IER n = 17; CER n = 9), and 43 (36%) with a fasting plasma glucose level >5.5 mmol/L (IER n = 22; CER n = 21). At commencement of the trial, 12 mothers were breastfeeding (IER n = 8; CER n = 4), and 9 of these participants completed the trial to 12 mo (IER n = 6; CER n = 3).

TABLE 1 Baseline characteristics of participants

Characteristic	All Participants $n = 121$	IER $n = 61$	CER $n = 60$	P value	Completers $n = 62$	Noncompleters $n = 59$	P value
Age, y	39.6 (9.0)	39.3 (8.9)	40.2 (9.2)	0.75	41.2 (11.2)	38.3 (7.7)	0.21
Years postpartum, y	2.9 (4.2)	2.4 (5.4)	3.1 (4.0)	0.81	3.2 (5.2)	2.3 (3.0)	
Times had GDM, n	1.0 (1)	1.0 (1)	1.0 (0)	0.77	1.0 (1)	1.0 (0)	0.27
GDM managed, *n* (%)				0.96			0.06
Diet	65 (54.2)	33 (53.2)	32 (55.2)		40 (64.5)	25 (43.1)	
Metformin	12 (10)	6 (9.7)	6 (10.3)		4 (6.5)	8 (13.8)	
Insulin	43 (35.8)	23 (37.1)	20 (34.5)		18 (29)	25 (43.1)	
Children, *n*	2.0 (0)	2 (0)	2.0 (1.0)	0.43	2.0 (0)	2.0 (0)	0.98
Weight, kg	89.9 (27.1)	90.3 (26.7)	87.0 (21.9)	0.12	89.3 (20.6)	90.4 (28.8)	0.65
BMI, kg/m^2	32.6 (9.4)	34.8 (9.6)	32.6 (8.4)	0.19	32.4 (9.6)	34.3 (9.5)	0.47
HbA1c, %	5.4 ± 0.6	5.4 ± 0.4	5.3 ± 0.4	0.24	5.3 ± 0.4	5.4 ± 0.4	0.73
Fasting glucose, plasma, mmol/L	5.5 ± 0.5	5.5 ± 0.6	5.5 ± 0.5	0.74	5.4 (0.7)	5.5 (0.8)	0.99
Fasting insulin, mU/L	10.0 (8.1)	10.0 (5.9)	10.2 (9.6)	0.24	9.1 (4.8)	10.3 (10.2)	0.08
HOMA-IR	2.3 (2.2)	2.3 (1.3)	2.4 (2.8)	0.25	2.2 (1.5)	2.5 (2.5)	0.08
Fasting glucose, finger-prick, mmol/L	5.4 ± 0.5	5.4 ± 0.6	5.3 ± 0.5	0.29	5.4 ± 0.7	5.4 ± 0.8	0.48
1-h OGTT, finger-prick, mmol/L	10.4 ± 2.3	10.4 ± 2.5	10.4 ± 2.1	0.98	10.5 ± 2.3	10.4 ± 2.3	0.73
2-h OGTT, finger-prick, mmol/L	8.2 (2.4)	7.9 (2.2)	8.3 (2.0)	0.99	7.9 (2.8)	8.3 (2.2)	0.64
Weekly physical activity, min	180 (315)	240 (430)	170 (290)	0.11	203 (337)	170 (313)	0.21
PSQI	7 (6)	7 (5)	7 (6)	0.42	7 (6)	6.5 (4)	0.42

Data are available for IER ($n = 61$), CER ($n = 60$), completers ($n = 62$), and noncompleters ($n = 59$) for all variables except HbA1c and fasting finger-prick glucose (IER, $n = 61$; CER, $n = 59$; completers, $n = 62$; noncompleters, $n = 58$); 1-h glucose and 2-h glucose (IER, $n = 57$; CER, $n = 53$; completers, $n = 58$; noncompleters, $n = 52$); and fasting plasma glucose, fasting insulin, and fasting HOMA-IR (IER, $n = 51$; CER, $n = 54$; completers, $n = 54$; noncompleters, $n = 50$). Results are displayed as medians [IQRs (IQR = Quartile 3 − Quartile 1)] for variables that were not normally distributed: age, years postpartum, number of times had GDM, number of children, weight, BMI, 2-h glucose, fasting insulin, fasting plasma glucose (completers and noncompleters only), HOMA-IR, weekly physical activity minutes, and PSQI. HbA1c, fasting finger-prick glucose, 1-h finger-prick glucose, and fasting plasma glucose (all participants and IER and CER) were normally distributed and are displayed as means ± SDs. The categorical variable "GDM managed" is displayed as a count (percentage). *P* values were obtained from independent-sample t-tests. Variables that were not normally distributed were log transformed. A Mann-Whitney U test was used for variables that remained skewed after log transformation [number of times had GDM, number of children, BMI, fasting glucose finger-prick (completers and noncompleters only), and PSQI]. The *P* value for "GDM managed" was obtained from Pearson's chi-square test.

Abbreviations: CER, continuous energy restriction; GDM, gestational diabetes; HbA1c, glycated hemoglobin; IER, intermittent energy restriction; OGTT, oral-glucose-tolerance test; PSQI, Pittsburgh sleep quality index.

Weight loss

Weight and BMI data were not normally distributed. Results were obtained from a repeated-measures ANOVA using log transformation for weight. The *P* values for weight loss were obtained from the Kruskal-Wallis test for the between-group delta (diet × time) and the Friedman's test for the change over time, as these variables remained skewed after log transformation. Weight loss between baseline and 3 mo was not normally distributed; however, weight loss between baseline and 12 mo was normally distributed.

Weight loss was statistically significant over time ($P < 0.001$) but not time by diet group at 12 mo (IER, −4.8 ± 5.0 kg; CER, −3.2 ± 5.0 kg; $P = 0.2$; $n = 62$; **Table 2**). Results from an intention-to-treat model did not differ [IER median, −4.2 kg (IQR, 7.4 kg); CER median, −2.9 kg (IQR, 7.6 kg); $P = 0.06$; $n = 121$]. The mean between-group difference for weight loss for the IER compared to CER group at 12 mo was −1.6 kg (95% CI: −4.2 to 1.0 kg; $P = 0.2$; $n = 62$), which fell within the noninferiority margin of +3.3 kg.

At 12 mo, participants had lost an average (mean ± SD) of 4.3 ± 5.5% of their starting weight (IER, 5.0 ± 5.4%; CER, 3.5 ± 5.6%; $P = 0.3$) and 37% ($n = 23$) of participants had lost ≥5 kg (IER $n = 13$; CER $n = 10$; $P = 0.6$). At 3 mo, 29% (IER $n = 7$; CER $n = 11$; $P = 0.3$) had lost ≥5 kg of their starting weight. At 12 mo, 21% (IER $n = 5$; CER $n = 8$; $P = 0.6$) of participants had no overall weight loss and 14.5% (IER $n = 5$; CER $n = 4$; $P = 1.0$) lost >10% of their starting body weight.

In a stepwise linear regression, there were no significant associations between weight loss and age, years postpartum, years past GDM, months breastfeeding, change in sleep quality, or change in the weekly number of active minutes. Results did not differ in an intention-to-treat model.

Dietary compliance

Completion of the food records was variable; 35 participants provided records at 3, 6, and 12 mo and 43 provided records at 3 and 12 mo (IER $n = 23$; CER $n = 20$). Diet recalls were taken when participants failed to return their records ($n = 17$). An analysis of the records at 3 and 12 mo showed no changes in energy intake in the IER group [59 ± 787 kJ (95% CI: −281 to 399; $P = 0.7$) and 14 ± 188 kcal (95% CI: −67 to 95; $P = 0.7$), respectively] on fasting days or in the CER group [−86 ± 1021 kJ (95% CI: −564 to 392; $P = 0.7$) and −21 ± 244 kcal (95% CI: −135 to 94; $P = 0.7$), respectively]. There were no statistically significant between-group differences from 3 to 12 mo between the IER and CER groups in either the changes in energy intakes [145 ± 276 kJ (95% CI: −413 to 702; $P = 0.60$) and 35 ± 66 kcal

TABLE 2 Changes in primary and secondary outcomes for individuals who completed the study

		Baseline	3 mo	12 mo	*P* value, time	*P* value, diet × time
Primary outcome						
Weight, kg	IER	90.0 (20.5)	85.8 (20.0)	85.3 (17.8)	<0.001	0.22
	CER	87.6 (20.9)	83.8 (22.9)	81.3 (22.7)		
Weight loss, kg	IER	—	−3.5 (2.0)	−4.8 ± 5.0		0.17
	CER	—	−4.3 (4.5)	−3.2 ± 5.0		
Secondary outcomes						
BMI, kg/m^2	IER	32.4 (10.3)	31.6 (9.3)	32.2 (7.6)	<0.001	0.17
	CER	32.4 (8.8)	31.0 (9.1)	31.0 (7.6)		
HbA1c, %	IER	5.3 ± 0.4, [5.2–5.4]	5.2 ± 0.3, [5.1–5.3]	5.2 ± 0.3, [5.1–5.3]	<0.001	0.34
	CER	5.4 ± 0.4, [5.2–5.5]	5.1 ± 0.2, [5.0–5.2]	5.2 ± 0.3, [5.1–5.3]		
Fasting plasma glucose, mmol/L	IER	5.5 ± 0.5, [5.3–5.7]	5.4 ± 0.6, [5.2–5.6]	5.8 ± 0.5, [5.6–6.0]	<0.001	0.17
	CER	5.5 ± 0.4, [5.3–5.6]	5.2 ± 0.5, [5.0–5.4]	5.5 ± 0.5, [5.3–5.7]		
Fasting serum insulin, mU/L	IER	8.8 (4.5)	6.1 (4.9)	6.7 (4.2)	<0.001	0.25
	CER	9.1 (8.7)	7.5 (5.0)	9.3 (6.9)		
Fasting HOMA-IR, index	IER	2.2 (1.2)	1.5 (1.4)	1.7 (1.2)	<0.001	0.68
	CER	2.2 (2.4)	1.8 (1.0)	2.3 (1.9)		
Fasting finger-prick glucose, mmol/L	IER	5.4 (0.7)	5.4 (1.0)	5.7 (1.3)	0.65	0.29
	CER	5.3 (0.7)	5.2 (0.3)	5.3 (0.6)		
1-h OGTT finger-prick, mmol/L	IER	10.0 ± 2.4, [9.2–10.8]	—	10.4 ± 3.1, [9.4–11.3]	0.72	0.29
	CER	11.1 ± 2.0, [10.2–11.9]	—	10.9 ± 1.9, [9.9–11.9]		
2-h OGTT finger-prick, mmol/L	IER	7.5 (2.6)	—	7.8 (1.6)	0.87	0.59
	CER	8.4 (2.8)	—	8.3 (3.8)		

Data are available for IER ($n = 32$) and CER ($n = 30$) for weight, BMI, and HbA1c; fasting finger-prick glucose IER ($n = 31$) and CER ($n = 30$); 1-h and 2-h OGTT finger-prick IER ($n = 31$) and CER ($n = 27$); fasting plasma glucose, fasting serum insulin, and fasting HOMA-IR IER ($n = 24$) and CER ($n = 27$). Results are displayed as medians (IQRs) (IQR = Quartile 3 − Quartile 1) for variables that were not normally distributed (weight, weight loss at 3 mo, BMI, fasting serum insulin, fasting HOMA-IR, fasting finger-prick glucose, and 2-h finger-prick glucose). Weight loss at 12 mo, HbA1c, fasting plasma glucose, and 1-h OGTT finger-prick data were normally distributed and are displayed as means ± SDs [95% CIs]. Results were obtained from a repeated-measures ANOVA using log transformation for weight, fasting finger-prick glucose, fasting serum insulin, fasting HOMA-IR, and 2-h OGTT finger-prick. *P* values for weight loss and BMI were obtained from the Kruskal-Wallis test for the between-group delta (diet × time) and from Friedman's test for the change over time, as these variables remained skewed after log transformation. *P* values for HbA1c, fasting plasma glucose, and 1-h OGTT finger-prick were obtained from a repeated-measures ANOVA using the raw data, as these variables were normally distributed. Abbreviations: CER, continuous energy restriction; HbA1c, glycated hemoglobin; IER, intermittent energy restriction; OGTT, oral glucose tolerance test.

(95% CI: −99 to 168; $P = 0.60$), respectively] or the changes in intakes of fat, saturated fat, mono- or poly-unsaturated fat, cholesterol, carbohydrate, fiber, total sugar, protein, caffeine, or alcohol ($P > 0.05$; **Table 3**). There were no statistically significant within-group differences in the changes in total energy intake or in fat, saturated fat, mono- or poly-unsaturated fat, cholesterol, carbohydrate, fiber, total sugar, protein, caffeine, or alcohol intakes between 3 and 12 mo (Table 3).

Secondary outcomes

Results were obtained from a repeated-measures ANOVA using log transformation for fasting finger-prick glucose, fasting serum insulin, fasting HOMA-IR, and 2-h OGTT finger-prick data, as these variables were not normally distributed. The *P* values for HbA1c, fasting plasma glucose, and 1-h OGTT finger-prick data were obtained from a repeated-measures ANOVA using the raw data, as these variables were normally distributed.

At 12 mo, HbA1c levels ($n = 62$), fasting plasma glucose levels ($n = 51$), fasting serum insulin levels ($n = 51$), and HOMA-IR scores ($n = 51$) showed significant changes over time ($P < 0.001$), with no significant between-group differences (Table 2). There were no significant changes in finger-prick fasting glucose levels ($n = 61$), 1-h OGTT results ($n = 58$), or 2-h OGTT results ($n = 58$) over time, with no time × diet interactions at 12 mo. Changes in fasting plasma glucose levels, serum insulin levels, and HOMA-IR scores followed a similar pattern over time, with reductions seen in the first 3 mo and levels increasing between 3 and 12 mo (Table 2).

In stepwise linear regression, baseline weight was positively correlated with a reduction in HbA1c (adjusted $r^2 = 0.06$; $P = 0.03$). A change in HbA1c levels was correlated with weight loss ($P = 0.03$). Weight loss was positively correlated with a reduction in fasting insulin levels, accounting for 9% of the variance in the change of fasting insulin levels (adjusted $r^2 = 0.07$; $P = 0.03$). Weight loss also accounted for 9% of the variance in the change in HOMA-IR scores (adjusted $r^2 = 0.08$; $P = 0.03$).

Physical activity and sleep quality

Between baseline and 12 mo, the weekly number of active minutes (AAS) decreased by a mean of −11 ± 191 min for the IER group ($n = 31$) and −2 ± 269 min for the CER group ($n = 27$; $P = 0.9$). The weekly number of active minutes

TABLE 3 Dietary intake and physical activity for IER and CER groups at 3 and 12 mo, assessed by 2-d/wk diet checklists

	IER				CER				
	3 mo $n = 23$	12 mo $n = 23$	Difference $n = 23$	P value	3 mo $n = 20$	12 mo $n = 20$	Difference $n = 20$	P value	Between-group difference P value
Energy, kJ	2594 ± 770	2653 ± 652	59 ± 787 [−281 to 399]	0.72	6407 ± 1152	6321 ± 1454	−86 ± 1021 [−564 to 392]	0.71	0.60
Energy, kcal	620 ± 184	634 ± 156	14 ± 188 [−67 to 95]	0.72	1531 ± 275	1511 ± 348	−21 ± 244 [−135 to 94]	0.71	0.60
Protein, g	50 ± 15	55 ± 13	6 ± 18 [−2 to 13]	0.16	91 ± 19	89 ± 19	−2 ± 22 [−12 to 9]	0.74	0.25
Protein, % of energy	33 ± 4	36 ± 8	3 ± 10 [−2 to 7]	0.21	25 ± 6	25 ± 7	0 ± 6 [−2 to 3]	0.76	0.39
Total fat, g	23 ± 12	19 ± 7	−4 ± 111 [−9 to 1]	0.14	57 ± 18	50 ± 18	−7 ± 20 [−17 to 3]	0.14	0.49
Total fat, % of energy	31 ± 8	26 ± 8	−5 ± 12 [−10 to 1]	0.08	33 ± 6	29 ± 6	−3 ± 8 [−7 to 1]	0.83	0.71
Saturated fat, g	7 ± 4	6 ± 3	−1 ± 4 [−3 to 1]	0.19	21 ± 6	19 ± 8	−3 ± 8 [−7 to 1]	0.18	0.46
Saturated fat, % of energy	10 ± 3	8 ± 4	−2 ± 4 [−4 to 0]	0.11	12 ± 3	11 ± 3	−1 ± 4 [−3 to 1]	0.16	0.92
Cholesterol, mg	260 ± 161	242 ± 161	−18 ± 162 [−88 to 52]	0.61	336 ± 172	296 ± 108	−39 ± 187 [−127 to 48]	0.36	0.69
Polyunsaturated fat, g	3 ± 2	3 ± 2	0 ± 2 [−1 to 1]	0.60	9 ± 5	7 ± 3	−2 ± 4 [1 to −4]	0.05	0.11
Monounsaturated fat, g	10 ± 5	8 ± 3	−2 ± 5 [−4 to 0]	0.09	22 ± 7	20 ± 8	−2 ± 10 [−7 to 3]	0.38	0.99
Carbohydrate, g	47 ± 15	52 ± 25	5 ± 24 [−5 to 15]	0.32	145 ± 32	152 ± 49	6 ± 36 [−10 to 23]	0.43	0.88
Carbohydrate, % of energy	30 ± 7	31 ± 8	2 ± 9 [−2 to 5]	0.36	37 ± 5	39 ± 8	2 ± 10 [−3 to 6]	0.46	0.99
Total sugar, g	37 ± 10	37 ± 9	0 ± 12 [−4 to 6]	0.76	73 ± 17	69 ± 25	−3 ± 21 [−13 to 6]	0.49	0.43
Fiber, g	14 ± 4	15 ± 5	1 ± 5 [−2 to 3]	0.52	23 ± 8	24 ± 6	2 ± 8 [−3 to 6]	0.38	0.69
Fiber, % of energy	5 ± 1	5 ± 2	0 ± 1 [−1 to 1]	0.84	3 ± 1	3 ± 1	0 ± 1 [0–1]	0.15	0.54
Caffeine, mg	0 (112)	4 (71)		0.95	60 (184)	126 (309)		0.06	0.13
Alcohol, g	1 ± 2	0 ± 2	0 ± 2 [−1 to 0]	0.33	4 ± 7	6 ± 11	−2 ± 12 [−8 to 3]	0.39	0.15
Physical activity, mins	337 ± 259	292 ± 228	−46 ± 254 [−139 to 47]	0.32	324 ± 298	264 ± 240	−60 ± 239 [−153 to 33]	0.19	0.79

Data are available for IER ($n = 31$) and CER ($n = 28$) participants for minutes of physical activity. All other variables have data available for IER ($n = 23$) and CER ($n = 20$) participants. Data are presented as means ± SDs [95% CIs] with P values obtained from paired-sample t-tests for the within-group time trend for all variables except caffeine. Caffeine was not normally distributed and data are displayed as medians (IQRs), (IQR = Quartile 3 − Quartile 1) with a P value obtained from a Wilcoxon signed-rank test. P values for differences between groups from the within-group changes in dietary intake between 3 and 12 mo were calculated using independent-sample t-tests for all variables except caffeine, which was obtained from a Mann-Whitney U test. Abbreviations: CER; continuous energy restriction; IER; intermittent energy restriction.

increased between baseline and 3 mo by a median of 20 min (IQR 275 min) for the IER group ($n = 46$) and 20 min (IQR 158 min) for the CER group ($n = 38$; $P = 0.7$). Between 3 and 12 mo, the weekly number of active minutes decreased by a mean of -46 ± 254 min (95% CI: -139 to 47; $P = 0.3$) in the IER group ($n = 31$) and by -60 ± 239 min (95% CI: -153 to 33; $P = 0.2$) in the CER group ($n = 28$; Table 3).

There was an overall improvement in the sleep quality score (PSQI) in both the IER and CER groups, with a mean difference from baseline to 12 mo of -2 ± 3 index points for the IER group ($n = 31$) and -2 ± 3 index points ($n = 27$) for the CER group ($P = 0.96$). The sleep quality scores improved by medians of -1 index point (IQR, 4 index points) for the IER group and -1 index point (IQR, 4 index points) for the CER group between 0 and 3 mo ($P = 0.2$). Between 3 and 12 mo, sleep quality showed a median change of 0 index points (IQR, 3 index points) in the IER group and an improvement of 0.5 index points (IQR, 4 index points) in the CER group ($P = 0.4$).

Discussion

This randomized controlled trial was designed to determine whether an intermittent 2-d very low–calorie diet was noninferior to moderate daily caloric restriction over 12 mo in overweight women with previous GDM. IER has previously been investigated in overweight women; however, to our best knowledge, this is the first study that investigated the effects of IER compared to CER in women with previous GDM. The results demonstrated that a 2-d 500 kcal (2100 kJ) IER diet can result in comparable weight loss to a daily 1500 kcal (6000 kJ) CER diet in this population. This outcome may be confounded by the high attrition rate, which resulted in fewer completers than planned in the study. Although the analysis indicated that the difference between the groups remained within the predetermined noninferiority margin, we cannot confirm noninferiority with any degree of confidence due to the high number of dropouts.

The present study adds to the growing body of research showing that IER can produce comparable weight loss to CER in overweight or obese men and women. A recent systematic review comparing IER to CER in overweight and obese adults included 12 studies ranging from 8 wk to 1 y in duration, and found that weight loss ranged from 4.6% to 13% of the starting body weight, with no significant between-group differences (19). Weight loss in the present study was slightly lower at 12 mo ($4.3 \pm 5.5\%$); however, only 2 studies in the review lasted for 12 mo or longer, and these studies reported weight loss of 5.6% and 6.8% (23, 24). Our study focused on a population of women with previous gestational diabetes, who often achieve lower levels of weight loss (25), which may explain why weight loss was slightly less in our study than in other 12-mo IER studies. In the present study, most of the weight loss was seen in the first 3 mo of the trial, with some weight gain seen in the CER group from 3 to 12 mo and a small amount of weight loss seen from 3 to 12 mo in the IER group; however, there was no significant between-group effect. Other IER studies lasting 12 mo or longer have shown similar weight loss patterns, with weight decreasing for 3 to 6 mo and plateauing or rising thereafter (21, 23), reinforcing the complexities around long-term lifestyle changes and weight management with both IER and CER.

Weight loss of 5 kg resulting from lifestyle changes has been shown to reduce the risk of diabetes by 53% in women with previous GDM (11). In the present study, mean weight loss was less than this at 3 mo (IER -3.5 ± 2.0 kg; CER -4.3 ± 4.5 kg) and 12 mo (IER -4.8 ± 5.0 kg; CER -3.2 ± 5.0 kg); however, improvements in HbA1c levels, fasting plasma glucose levels, fasting serum insulin levels, and fasting HOMA-IR scores were still seen at 3 mo. There were no significant between-group differences in diabetes risk factors at 3 or 12 mo, which is consistent with other recent research comparing IER to CER (26). The improvements in fasting glucose levels, insulin levels, HOMA-IR scores, and glucose tolerance observed at 3 mo were attenuated at 12 mo, suggesting participants were in a hypercaloric state for the final blood draw. An analysis of the dietary checklists suggests that both IER and CER participants were consuming close to their allocated energy allowance; however, to minimize the participant burden, these checklists were only completed for 2 days a week (fasting days for IER and any "usual day" for CER). It is likely that some participants were either overeating on their nonrecording days or underreporting their food intake, which is a common problem in dietary interventions (27). Many participants lost weight throughout the 12 mo, which suggests they were complying with the diet. Despite weight loss maintenance, the 2-h glucose values from the OGTT remained just above the desirable levels at 12 mo, suggesting the group had continuing glucose intolerance. Overall, the participants remained in the obese category. HbA1c levels, which are a measure of longer-term average plasma glucose levels, are less sensitive to sudden dietary changes and remained slightly improved at 12 mo in both the IER and CER groups. The higher weight loss for the IER group, although not statistically superior to that of the CER group, might explain the improvements in insulin levels and HOMA-IR scores observed at 12 mo in the IER group but not in the CER group. It is also possible these results are confounded by the high attrition rate, by wide variation in the ages of the participants, or by starting weights.

There were some limitations to our study. The high withdrawal rate, which resulted in a smaller completion sample than required, is a serious limitation. Low levels of engagement in long-term weight loss interventions in this population are well documented (10), and our study showed that adherence to either an IER or CER regime is challenging for women with previous GDM. In order to minimize the participant burden, we did not measure body composition or satiety, which is another limitation to the study. Furthermore, as we only assessed dietary compliance for 2 days a week, we are unable to compare total weekly energy intakes between the 2 groups. We also altered our method to test 2-h glucose tolerance using a finger-prick test with capillary whole blood instead of venous plasma, to reduce the participant burden. The finger-prick method allowed participants to receive their results immediately. Women who have had GDM are recommended to have a 2-h glucose tolerance test every 1–2 y in Australia; by withholding results until study completion, the women would have been required to have another test with their physician. Capillary blood glucose has previously been shown to be suitable for use in health-care settings for a GDM diagnosis where a laboratory analysis is

not available (28), and is accepted as a screening tool in large epidemiological studies in developing countries (29). In addition to the smaller-than-planned sample size at the end of the study, other confounders may include previous episodes of weight gain or the number of attempts to lose weight since a diagnosis of GDM.

Our study shows that IER produces comparable weight loss to CER, with similar improvements in diabetes risk markers, suggesting that IER is as effective as CER for weight loss in overweight women with previous GDM. However, the high dropout rate is a limitation in our interpretation of the results, as well as a potential limitation in the sustainability/implementation of both interventions. Larger long-term studies with better adherence investigating the effects of IER on weight loss and diabetes risk markers in women with previous GDM would be beneficial.

We thank Louise Massie, coordinator of The University of South Australia Health Research Clinical Trials Facility; and Emma Tregoweth for her help with the laboratory analysis.

The authors' responsibilities were as follows—JBK: designed the research (project conception, development of overall research plan and study oversight); KLG: contributed to the study design and conducted the research (submitted the ethics application, hands-on conduct of the experiments and data collection), performed the laboratory analysis and initial statistical analysis, and drafted the manuscript; PMC: contributed to the study design, provided medical oversight for the project, and supervised the statistical analyses. JBK, PMC: contributed to the interpretation of the data and critically reviewed the manuscript; and all authors: read and approved the manuscript.

Author disclosures: KLG was supported by a Research Training Program (RTP) Stipend Scholarship with the University of South Australia. PMC and JBK, no conflicts of interest.

Data Availability

Deidentified data will be made available upon request pending approval from the University of South Australia's Human Research Ethics Committee.

References

1. Australian Institute of Health and Welfare. Incidence of gestational diabetes in Australia. Report No.: [Cat. no. CVD 85]. Canberra, Australia: Australian Institute of Health and Welfare; 2019.
2. Australian Diabetes in Pregnancy Society. ADIPS Consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand. Sydney, Australia: Australian Diabetes in Pregnancy Society; 2014.
3. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJ, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care 2012;35(3):526–8.
4. International Diabetes Federation. IDF diabetes atlas. 9th edition. Brussels, Belgium: International Diabetes Federation; 2019.
5. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: Systematic review and meta-analysis. BMJ 2020;369:m1361.
6. Rayanagoudar G, Hashi AA, Zamora J, Khan KS, Hitman GA, Thangaratinam S. Quantification of the type 2 diabetes risk in women with gestational diabetes: A systematic review and meta-analysis of 95,750 women. Diabetologia 2016;59(7):1403–11.
7. Collins KK. The diabetes-cancer link. Diabetes Spectr 2014;27(4):276–80.
8. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol 2018;17(1):83.
9. Sumamo Schellenberg E, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med. 2013;159(8):543–51.
10. Dasgupta K, Terkildsen Maindal H, Kragelund Nielsen K, O'Reilly S. Achieving penetration and participation in diabetes after pregnancy prevention interventions following gestational diabetes: A health promotion challenge. Diabetes Res Clin Pract 2018;145:200–13.
11. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE. Prevention of diabetes in women with a history of gestational diabetes: Effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93(12):4774–9.
12. Bennett WL, Ennen CS, Carrese JA, Hill-Briggs F, Levine DM, Nicholson WK, Clark JM. Barriers to and facilitators of postpartum follow-up care in women with recent gestational diabetes mellitus: A qualitative study. J Womens Health 2011;20(2):239–45.
13. Dennison RA, Ward RJ, Griffin SJ, Usher-Smith JA. Women's views on lifestyle changes to reduce the risk of developing type 2 diabetes after gestational diabetes: A systematic review, qualitative synthesis and recommendations for practice. Diabet Med 2019;36(6):702–17.
14. Gray KL, McKellar L, O'Reilly SL, Clifton PM, Keogh JB. Women's barriers to weight loss, perception of future diabetes risk and opinions of diet strategies following gestational diabetes: An online survey. Int J Environ Res Public Health 2020;17(24):9180.
15. Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL. Effectiveness of intermittent fasting and time-restricted feeding compared to continuous energy restriction for weight loss. Nutrients 2019;11(10):10.
16. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129(25 Suppl 2):S102–38.
17. National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Canberra, Australia: National Health and Medical Research Council; 2013.
18. Middleton KR, Anton SD, Perri MG. Long-term adherence to health behavior change. Am J Lifestyle Med 2013;7(6):395–404.
19. Welton S, Minty R, O'Driscoll T, Willms H, Poirier D, Madden S, Kelly L. Intermittent fasting and weight loss: Systematic review. Can Fam Physician 2020;66(2):117–25.
20. Harris L, Hamilton S, Azevedo LB, Olajide J, De Brun C, Waller G, Whittaker V, Sharp T, Lean M, Hankey C, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: A systematic review and meta-analysis. JBI Database Systematic Rev Implement Rep 2018;16(2):507–47.
21. Headland M, Clifton PM, Carter S, Keogh JB. Weight-loss outcomes: A systematic review and meta-analysis of intermittent energy restriction trials lasting a minimum of 6 months. Nutrients 2016;8(6:):354.
22. Nicklas JM, Zera CA, Rosner BA, Levkoff SE, Seely EW. A web-based lifestyle intervention to decrease postpartum weight retention in women with recent gestational diabetes mellitus: The balance after baby pilot RCT. Obstet Gynecol 2014;124(3):563–70.
23. Headland M, Clifton P, Keogh J. Intermittent compared to continuous energy restriction on weight loss and weight maintenance: Effects after 12 months. Obes Res Clin Pract 2019;13(3):268–9.
24. Carter S, Clifton PM, Keogh JB. 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 2018;1(3):e180756.
25. Goveia P, Canon-Montanez W, De P, Santos D, Lopes GW, Ma RCW, Duncan BB, Ziegelman PK, Schmidt MI. Lifestyle intervention for the prevention of diabetes in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2018;9:583.

26. Cioffi I, Evangelista A, Ponzo V, Ciccone G, Soldati L, Santarpia L, Contaldo F, Pasanisi F, Ghigo E, Bo S. Intermittent versus continuous energy restriction on weight loss and cardiometabolic outcomes: A systematic review and meta-analysis of randomized controlled trials. J Transl Med 2018;16(1):371.
27. Wehling H, Lusher J. People with a body mass index ≥30 under-report their dietary intake: A systematic review. J Health Psychol 2019;24(14):2042–59.
28. Balaji V, Madhuri BS, Paneerselvam A, Arthi T, Seshiah V. Comparison of venous plasma glucose and capillary whole blood glucose in the diagnosis of gestational diabetes mellitus: A community-based study. Diabetes Technol Ther 2012;14(2):131–4.
29. Bhavadharini B, Mahalakshmi MM, Maheswari K, Kalaiyarasi G, Anjana RM, Deepa M, Ranjani H, Priya M, Uma R, Usha S, et al. Use of capillary blood glucose for screening for gestational diabetes mellitus in resource-constrained settings. Acta Diabetol 2016;53:91–7.