Metabolic impact of intermittent fasting in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of interventional studies

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Abstract

Context: Intermittent fasting (IF) has been proposed as a weight-loss strategy with additional cardio-metabolic benefits in individuals with obesity. Despite its growing popularity, the effect of IF in patients with type 2 diabetes (T2DM) remains unclear.

Objective: We conducted a systematic review and meta-analysis to evaluate the metabolic impact of IF as compared to standard diet in patients with T2DM.

Data sources: Embase, PubMed, and clinicaltrials.gov between 1950 and August-12-2020.

Study selection: Randomized, diet-controlled studies evaluating any IF intervention in adults with T2DM.

Data extraction: We examined the impact of IF on weight loss and glucose-lowering by calculating pooled estimates of the absolute differences in bodyweight and glycated hemoglobin (HbA1c) as compared to control group using random-effects model.

Data Synthesis: Seven studies (n=338 participants; mean BMI 35.65kg/m^2, mean baseline HbA1c of 8.8%) met our inclusion criteria. IF induced greater decrease in bodyweight by -1.89kg (95%CI -2.91 to -0.86 kg) as compared to regular diet, with no significant between-study heterogeneity ($I^2$21.0%, P=0.28). The additional weight loss induced by IF was greater in studies with heavier population (BMI >36kg/m^2) [-3.24kg (95%CI -5.72 to -1.15 kg)] and in studies of shorter duration (≤ 4 months) [-3.73kg (95%CI -7.11 to -0.36kg)]. IF was not associated with further reduction in HbA1c as compared to standard diet [HbA1c -0.11% (95%CI -0.38 to 0.17%)].

Conclusions: Current evidence suggests that IF is associated with greater weight loss in patients with T2DM as compared with standard diet, with similar impact on glycemic control.

Keywords: intermittent fasting, type 2 diabetes, glycated hemoglobin, bodyweight

INTRODUCTION

Obesity plays a role in 61% to 79% of type 2 diabetes mellitus (T2DM)[1] and confers additional morbidity as increased body mass index (BMI) has been linked to poorer cardiovascular risk profile and increased mortality in this patient population [2-5]. Although lifestyle interventions represent an important pillar of diabetes management, maintaining weight loss and obtaining sustained glycemic control with non-pharmacological approaches is a difficult goal to achieve [6].

Intermittent fasting (IF), where energy consumption is repeatedly and intentionally interrupted or markedly reduced for a period of time, has been a focus of recent research and proposed as a weight-loss strategy with additional cardio-metabolic benefits in individuals with overweight and obesity. These additional benefits include reduction in total cholesterol and blood pressure, and improved insulin sensitivity [7-12]. While IF interventions have not been standardized, common regimens include time-restricted feeding (TRF), in which feeding is allowed for only a window of 4-8 hours/day with 16-20 hours of fasting [13-16], and intermittent or short-term energy restriction through very-low calorie diets (VLCD), in which caloric consumption remains between 300-600 kcal/day [17].

Despite the growing popularity of IF in lay media, limited research has been done in patients with T2DM [18]. Previous reports in individuals with T2DM have suggested that IF interventions can induce similar weight loss and reduction in glycated hemoglobin (HbA1c) as standard dietary recommendations [19-23]. However, the small sample sizes preclude definitive conclusions based on these individual studies, indicating the need for a robust and systematic evaluation of the effect of IF in T2DM. Thus, the purpose of this systematic review and meta-analysis is to evaluate the metabolic impact of IF interventions in patients with T2DM.

MATERIAL AND METHODS

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered with the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/prospero/; CRD42020159009)[24].

Data Sources and Searches

We selected relevant studies published between 1950 and August 12, 2020. We searched PubMed, Embase, and clinicaltrials.gov using the following combined text and Medical Subject Heading (MeSH) terms: “type 2 diabetes”, “intermittent fasting”, “time restricted feeding”, “very low calorie diet”. The complete PubMed search was as follows: ((((intermittent fasting [Text Word] OR time restricted feeding [Text Word] OR very low calorie diet [Text Word]) OR))) AND ("diabetes mellitus, type 2" [MeSH Terms] OR type 2 diabetes mellitus [Text Word]). All potentially eligible studies were considered for review, regardless of the primary outcome or language. We also conducted a manual search using references of key articles published in English.

Study Selection

Studies were eligible for inclusion if they were: (1) interventional studies, which could be either randomized parallel-arm trial or cross-over trial conducted in adults with T2DM, (2) compared any IF intervention to a standard diet consisting of either healthy pattern dietary recommendation with caloric deficit or normal caloric intake (control group), and (3) reported changes in body weight or HbA1c. Exclusion criteria were as follows: studies that did not report a control group, retrospective studies or observational studies. If a study was reported in more than one publication, we included the data reporting the primary outcome.

Intervention Investigated and Outcome Measurements

We evaluated any IF intervention, which includes (i) 24-h complete fasting, (ii) intermittent restricted energy intake (25% total caloric intake), and (iii) time-restricted feeding (feeding allowed for only a window of 4-8 hours daily with 16-20 hours of fasting). The IF intervention could be applied on alternate days, twice weekly or during a continuous period of time and were compared to a standard dietary recommendation consisting of regular eating hours. The primary outcomes were mean differences in the changes in (i) body weight and (ii) HbA1c, between baseline and end of intervention. The following secondary outcomes were assessed: changes in fasting glucose, total

cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and waist circumference.

Data Extraction and Quality Assessment

Two independent investigators (EB, CK) reviewed study titles and abstracts. Studies that satisfied the inclusion criteria were retrieved for full-text assessment. Studies selected for review by both investigators had an agreement value (k) of 98.3%; disagreements were resolved by a third investigator (JM).

The following data was extracted from each study: age, percent of males participants, total number of participants, duration of intervention, baseline body mass index (BMI), baseline HbA1c, mean changes in body weight (mean [SD]), mean changes in HbA1c (mean [SD]), and mean changes in other metabolic parameters (secondary outcomes listed above). The risk of bias was evaluated according to the PRISMA recommendations[24].

Data Synthesis and Analysis

We examined the impact of IF on two primary outcomes: (1) weight reduction, as assessed by mean change in body weight (kg), and (2) glucose-lowering effect, as assessed by mean change in HbA1c (%). We calculated pooled estimates of the absolute differences between arithmetic means before and after interventions as compared to control group using a random-effects model (DerSimonian-Laird method). The I^2 value was used to evaluate the magnitude of heterogeneity between studies, with values greater than 50% indicating moderate-to-high heterogeneity[25]. Recognizing that the duration of intervention and baseline characteristics of the study population could affect the impact of IF on the outcomes, we performed stratified analyses by the mean values for each of the following variables: (i) study duration (less than or equal to 4 months and longer than 4 months), (ii) baseline BMI (less than or equal to 36 kg/m^2 and higher than 36 kg/m^2), and (iii) baseline HbA1c (less than or equal to 9.0% and higher than 9.0%). To further evaluate the impact of IF on metabolic profile of patients with T2DM, sensitivity analyses were performed: (i) using random effects models, and (ii) after excluding Kahleova et al.[26], because this study was the only randomized

crossover trial included in our analyses with the remaining consisting of randomized parallel arm trials. In addition, Kahleova et al.[26] was the only study that evaluated a time-restricted feeding protocol.

The possibility of publication bias was evaluated using a funnel plot of effect size against the standard error for each trial. Funnel plot asymmetry was evaluated by Begg's and Egger's tests, with significant publication bias defined as a *P* value <0.1[27]. The trim-and-fill computation was used to estimate the effect of publication bias [28].

All analyses were performed using Stata 14.0 (Stata Corp, College Station, Texas).

RESULTS

Study Characteristics

We identified 210 studies, of which 194 were excluded on the basis of title and abstract. Sixteen studies were retrieved for detailed assessment, nine of which excluded (four due to lack of control group and five were considered duplicates as there were additional publications from included trials). Seven studies [21-23,26,29-31] (with data from 338 participants) met our inclusion criteria; 6 were randomized parallel-arm trials [21-23,29-31] and one was a randomized crossover trial [26]. Included studies were published between 1991 and 2018, with median study duration of 24 weeks (ranging from 19 to 260 weeks). Patients had a mean age of 56.3 years old (ranging from 51.2 to 65 years), 24.2-54% were male, baseline BMI of 35.65 kg/m^2 (ranging from 32.4 to 37.9 kg/m^2), mean baseline HbA1c of 8.8% (ranging from 7.2 to 10.4%), representing a population largely obese with poor glycemic control (Table 1). Two studies reported duration of diabetes (mean duration of diabetes of 8.0 years). Five studies [21,23,26,29,30] reported data on background diabetic treatment with the majority of participants taking oral anti-diabetic medications or on diet-only (75-100%) [21,23,29,30] while 20-25% were also taking insulin [21,23,29,30].

The IF intervention adopted in these studies varied, with one study evaluating TRF [26], two studies evaluating intermittent energy restriction [21,22], and four studies assessing short-term energy

restriction through VLCD [23,29-31]. Table 1 gives a detailed overview of the IF interventions followed in each study. The included studies did not evaluate macronutrient content. Regarding physical activity, three studies[22,23,30] recommended participants to increase physical activity level without further assessment of adherence to this recommendation. Kahleova et al[26] evaluated physical activity using a pedometer, but did not find any differences between the intervention arms.

A risk of bias assessment is shown in Table 2. All 7 studies reported adequate randomization and none were stopped early. Two trials reported intention-to-treat analyses [21,26] while the remaining 5 reported results per protocol [22,23,29-31]. The dropout rates varied from 8.3% to 44% with no differences between intervention and control arms (Table 2).

Impact of Intermittent Fasting on Weight Loss

Six studies assessed the change in body weight between IF and standard diet [21-23,26,29,31]. Pooling the data from these studies showed a significant decrease in body weight by 1.89 kg (95%CI -2.91 to -0.86 kg) in the IF arm compared to control, with no significant between-study heterogeneity (I^2 21.0%, P = 0.28) (Figure 1A). In this analysis, there was evidence of publication bias on the Egger test (P = 0.034); however, the trim-and-fill test showed that effect estimates were not significantly impacted as no trimming was necessary to adjust the overall estimate.

Sensitivity analyses were performed stratifying by baseline BMI (≤36 vs >36 kg/m^2) and study duration (≤4 vs >4 months) (Figure 2). As compared to standard diet, the additional weight loss induced by IF was greater in studies with heavier population (BMI >36 kg/m^2) [-3.24 kg (95%CI -5.72 to -1.15 kg)] than in those with BMI ≤36 kg/m^2 [-1.42 kg (95%CI -1.90 to -0.95 kg)] (Figure 2A). In addition, IF interventions led to more pronounced weight loss as compared to standard diet in both short-term [-3.73 kg (95%CI -7.11 to -0.36 kg)] and long-term study duration [-1.44 kg (95%CI -1.91 to -0.97 kg)] (Figure 2B). In these analyses, there was no significant between-study heterogeneity.

We repeated the analyses excluding Kahleova *et al*[26] given that this study was the only cross-over trial evaluating a time-restricted feeding intervention while the other studies consisted of parallel design evaluating very restricted energy intake. In this analysis, there was a decrease in body weight by 2.6 kg (95%CI -4.18 to -1.02 kg) in the IF arm compared to control arm.

Impact of Intermittent Fasting on Glycemic Control

The pooled analysis of the 6 trials [21-23,26,29,31] that assessed the change in HbA1c showed a non-significant decrease of -0.11% (95%CI -0.38 to 0.17%) in the IF arm compared to control, with no significant between-study heterogeneity (Figure 1B). There was no publication bias in this analysis as assessed by Egger's test (P = 0.30).

Recognizing that IF interventions may differentially impact those with higher baseline HbA1c, and that changes in HbA1c are more evident over a period of several months, we repeated this analysis stratifying by baseline HbA1c (Figure 3A) and study duration (Figure 3B). Similarly to the results observed in the pooled analysis, there were no significant differences in HBA1c reduction conferred by IF interventions as compared to standard diet detected amongst subgroups, and no significant between-study heterogeneity (Figure 3).

Furthermore, we repeated the analyses excluding Kahleova *et al*[26] and demonstrated no significant reduction in HbA1c comparing IF with control arm [-0.26% (95%CI -0.73 to 0.22%)].

Impact of Intermittent Fasting on Additional Metabolic Parameters

To further evaluate the metabolic impact of IF interventions as compared to standard diet, we pooled the data of studies that assessed changes in fasting glucose, lipid profile, blood pressure, and waist circumference. IF was not associated with additional positive effects on any of these parameters as compared to standard diet (Table 3).

DISCUSSION

Our results suggest that, compared to standard diet, IF induces additional weight loss (~1.9 kg) while having similar effect on HbA1c, lipid profile and blood pressure in adults with T2DM representing a population largely obese with poor glycemic control. The positive impact of IF on weight reduction was more pronounced in heavier patient populations and in studies with shorter duration.

Although weight loss plays a central role in the treatment of T2DM associated with obesity [32], poor adherence to physical activity recommendations and sustained healthy diet has limited the effectiveness of non-pharmacological strategies in adults with T2DM [33]. Our results demonstrated that IF may represent a therapeutic alternative, as this intervention significantly decreased body weight when compared to standard diet, an effect observed irrespective of baseline BMI or study duration. Reinforcing the results of our analyses, in the longest trial evaluating IF in T2DM (12 months duration), Carter et al (21) observed a -6.8 kg weight loss in the IF arm as compared to -5.0 kg in the control group, with HbA1c reduction of -0.5% vs. -0.2%, respectively. Despite the steeper impact on weight loss achieved, Carter et al (21) demonstrated similar reduction in fat-free mass in the IF arm as compared to the control group. Notably, the additional reduction in body weight induced by IF was modest in the context of the baseline BMI of our study population (35.6 kg/m^2), however, this additional weight loss may facilitate the overall goal of 5% reduction in total body weight in obese individuals with T2DM [32,34-41].

Despite the greater weight loss induced by IF interventions, our results demonstrate a neutral impact in HbA1c reduction. A previous meta-analysis evaluating the impact of IF in the general population (n=545 participants)[42] demonstrated a modest reduction in fasting glucose of -4.16 mg/dL in addition to a significant reduction in BMI . It should be noted, however, that despite the lack of statistical superiority of IF as compared to standard diet on glycemic control in individuals with T2DM, there may still be important clinical implications. Williams *et al.* [22] found no difference in HbA1c values between the IF and standard diet arms after a 20-week intervention, however more

subjects in the IF group achieved the target HbA1c than in the control group [22]. Another aspect to consider is the concomitant use of anti-diabetic medications. Wing *et al.* found that, despite similar reduction in HbA1c among study arms, there was a significant difference in the number of participants taking glucose-lowering medications 1 year post-intervention,(45% of participants in the IF arm and 69% of participants in the control arm) [23], suggesting that IF may represent another lifestyle option to optimize diabetes care, reducing the requirement of anti-diabetic medications.

Other potential positive effects of IF beyond weight loss and glycemic control have been described in the literature, possibly due to its potential to shift the preferential utilization of glucose from glycogenolysis to fatty-acids and fatty acid-derived ketones. Specifically, during the period of prolonged fasting when glycogen stores in hepatocytes are depleted, an accelerated lipolysis produces fatty acids and glycerol in a metabolic pathway independent of pancreatic insulin secretion [43]. By inducing this change, IF could promote positive metabolic changes independent of weight loss. This concept was demonstrated in a crossover trial evaluating the effect of IF in pre-diabetic men while maintaining weight. In that study, IF improved insulin sensitivity, beta-cell responsiveness, blood pressure, and oxidative stress levels, independently of weight loss [44].

A limitation of our meta-analyses is the heterogeneity amongst the IF protocols. Currently, dietary regimens consisting of very restrictive caloric intake such as 400-500 kcal/daily as well as complete fasting have been described in the literature as IF protocols[18,45]. There is a lack of standardization of IF interventions as fasting interventions have differed in the number of calories allowed per day, the timing and duration of the fasting window, the number of fasting days per week, and the length of the intervention. However, this is not expected to impact our results as both fasting and severely restricted diets induce a ketogenetic state characterized by an increase in free fatty acids and ketone bodies acetoacetate and β-hydroxybutyrate, which is the likely mechanism through which the benefits of this intervention are obtained [45]. Another limitation is that the long-term adherence to IF is uncertain as the majority of included trials lasted between 1 and 24 weeks. In addition, detailed information on how caloric deficit was achieved in these studies are lacking. Finally, in our analyses, it was not possible to evaluate the safety of IF in T2DM which is particularly relevant for patients

taking insulin. In this context, data from a previous report, demonstrated that the rates of hypoglycemia in individuals with T2DM undergoing both 2 consecutive and non-consecutive days of IF are acceptable and decreased with proper education and titration of anti-diabetic medications [20].

In conclusion, given the historical challenges of non-pharmacological approaches in T2DM, our results support IF as a non-inferior alternative strategy for weight loss. Our analyses demonstrate the therapeutic potential of IF as a weight reduction strategy in T2DM and highlight the need for further research in this field. Specifically, there is a need for trials comparing the different IF protocols with longer duration of follow-up and with deeper phenotyping of the clinical and metabolic effects of this intervention in patients with T2DM.

Contributions: CKK conceived the systematic review and analysis plan. EB, CKK, and JM selected studies for inclusion and abstracted data. EB performed the statistical analyses, interpreted the data, and wrote the first draft. EB, CKK, and JM critically revised the manuscript for important intellectual content and approved the final draft.

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Declarations of Interests: Dr. Kramer reports grants from Boehringer Ingelheim, outside the submitted work.

Data availability: Datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Meta-analysis of the mean difference in body weight (kg) **(Panel A)** and HbA1c (%) **(Panel B)** between intermittent fasting interventions and standard diet. CI = confidence interval. Weight (%) representing weighted average of the effect sizes.

Figure 2. Meta-analysis of the mean difference in bodyweight (kg) between intermittent fasting interventions and standard diet in analyses stratified by baseline body mass index (BMI) **(Panel A)**, and study duration **(Panel B)**. CI = confidence interval. Weight (%) representing weighted average of the effect sizes.

Figure 3. Meta-analysis of the mean difference in HbA1c (%) between intermittent fasting interventions and standard diet in analyses stratified by baseline HbA1c **(Panel A)** and study duration **(Panel B)**. CI = confidence interval. Weight (%) representing weighted average of the effect sizes.

Table 1. Characteristics of included studies

Author	Year of publication	Sample size	Study design	Study intervention	IF duration (days)	Total study duration (weeks)	Mean age (years)	Percentage of males (%)	Baseline mean BMI (kg/m^2)	Baseline HbA1c (%)
Wing *et al.*[29]	1991	36	Randomized parallel-arm	**Intervention arm:** VLCD (400 kcal/day) weeks 5-12 (run-in period 0-5), remainder of weeks behavior therapy + l,000-1,500 kcal/day **Control arm:** behavior therapy + 1,000-1,500 kcal/day for 20 weeks	56	20 *outcomes also available after 1yr	51.2	24.2	37.7	10.4
Wing *et al.*[23]	1994	93	Randomized parallel-arm	**Intervention arm**: VLCD (400-500kcal/day) weeks 0-12 and 12-24, LCD (1,000-1,200kcal/day) remainder of weeks **Control arm**: LCD (1,000-1,200kcal/day) throughout	168	50	51.8	35.5	37.9	10.4
Williams *et al.*[22]	1997	54	Randomized parallel-arm	**Intervention arm 1**: VLCD (400-600kcal) 5 consecutive days on week 2, then VLCD 1x/week and regular	20	20	52.2	38.9	35.9	8.1

				diet (1,500-1,800kcal) 6x/week for remaining 15 weeks **Intervention arm 2**: VLCD (400-600kcal) 5 consecutive days during weeks 2, 7, 12, and 17, and regular diet (1,500-1,800kcal) remaining weeks **Control arm**: regular diet (1,500-1,800 kcal) 7x/week for duration of study						
Paisey *et al.*[30]	2002	45	Randomized parallel-arm	**Intervention arm:** VLCD (450 kcal/day for women, 650 kcal/day for men) for 6 weeks, followed by slow reintroduction of standard eating **Control arm:** intensive conventional diet and exercise (diet/exercise sessions 2x/week for 6 months)	42	260	53.9	36.7	36.8	Not reported
Kahleova *et al.*[26]	2014	54	Randomized crossover	**Intervention arm**: 12-weeks of two meals/day (breakfast between 6-10am and lunch between 12-4pm)	84	24	59.4	54.0	32.6	7.2

				Control arm: 12-weeks of six meals/day (breakfast/lunch/dinner + 3 snacks)						
Li *et al.*[31]	2017	46	Randomized parallel-arm	**Intervention arm:** 2 days pre-fasting (1,200 cal) followed by 7 days VLCD (300 cal/day), followed by slow re-introduction of food in Mediterranean diet **Control arm:** Mediterranean diet, normal calorie intake	7	16	65.0	NA	32.4	7.7
Carter *et al.*[21]	2018	137	Randomized parallel-arm	**Intervention arm**: intermittent restricted diet (500-600 kcal/day) 2x/week, regular diet remaining 5x/week **Control arm**: continuous restricted diet (1,200-1,500 kcal/day) 7x/week	104	52	61.0	43.8	36	7.3

IF = intermittent fasting; VLCD: very low calorie diet; LCD: low calorie diet; BMI = body mass index; HbA(1c) = glycated hemoglobin; NA: not available

Table 2. Risk of bias

Author	Intention to treat analysis	Intermittent fasting efficacy evaluated	Stopped early	Dropout rate (%)			Outcome assessment accurate
				Overall	Intervention arm	Control arm	
Wing et al. (1991)	No	Yes	No	8.3	0	15.8	Yes
Wing et al. (1994)	No	Yes	No	15.0	15.6	14.6	Yes
Williams et al.	No	Yes	No	16.7	16.7	16.7	Yes
Paisey et al.	No	Yes	No	16.7	13.3	20.0	Yes
Kahleova et al.	Yes	Yes	No	6.7	5.8	7.5	Yes

Li et al.	No	Yes	No	30.4	30.4	30.4	Yes
Carter et al.	Yes	Yes	No	29.2	27.1	31.3	Yes

N/A = not applicable

Table 3. Meta-analysis comparing metabolic parameters (mean difference) between intermittent fasting interventions and standard diet in patients with type 2 diabetes.

Clinical Characteristic	No of Studies	Absolute mean difference	95% Confidence interval	I^2
Fasting glucose (mmol/l)	4	-0.75	-2.24 to 0.75	85.7
Total Cholesterol (mmol/l)	6	0.070	-0.13 to 0.26	36.5
LDL cholesterol (mmol/l)	5	0.040	-0.04 to 0.12	0
HDL cholesterol (mmol/l)	6	-0.05	-0.17 to 0.08	88.1
Triglycerides (mmol/l)	6	0.090	-0.03 to 0.21	0
Systolic blood pressure (mmHg)	3	-0.68	-14.85 to 13.49	89.1
Diastolic blood pressure (mmHg)	3	-1.80	-15.02 to 11.41	93.2
Waist circumference (cm)	2	-2.44	-7.94 to 3.06	0

LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Figure 1

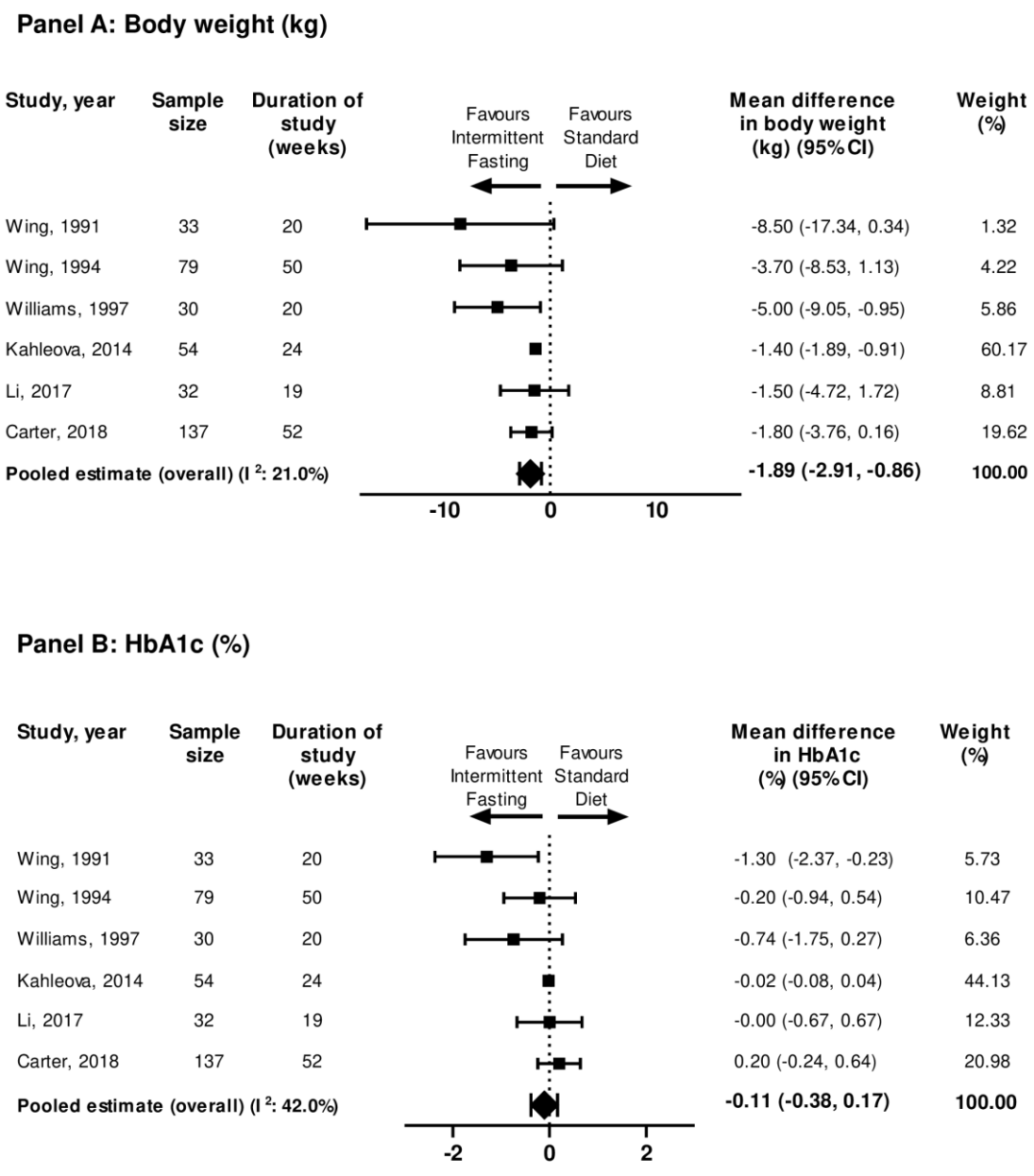

Figure 2

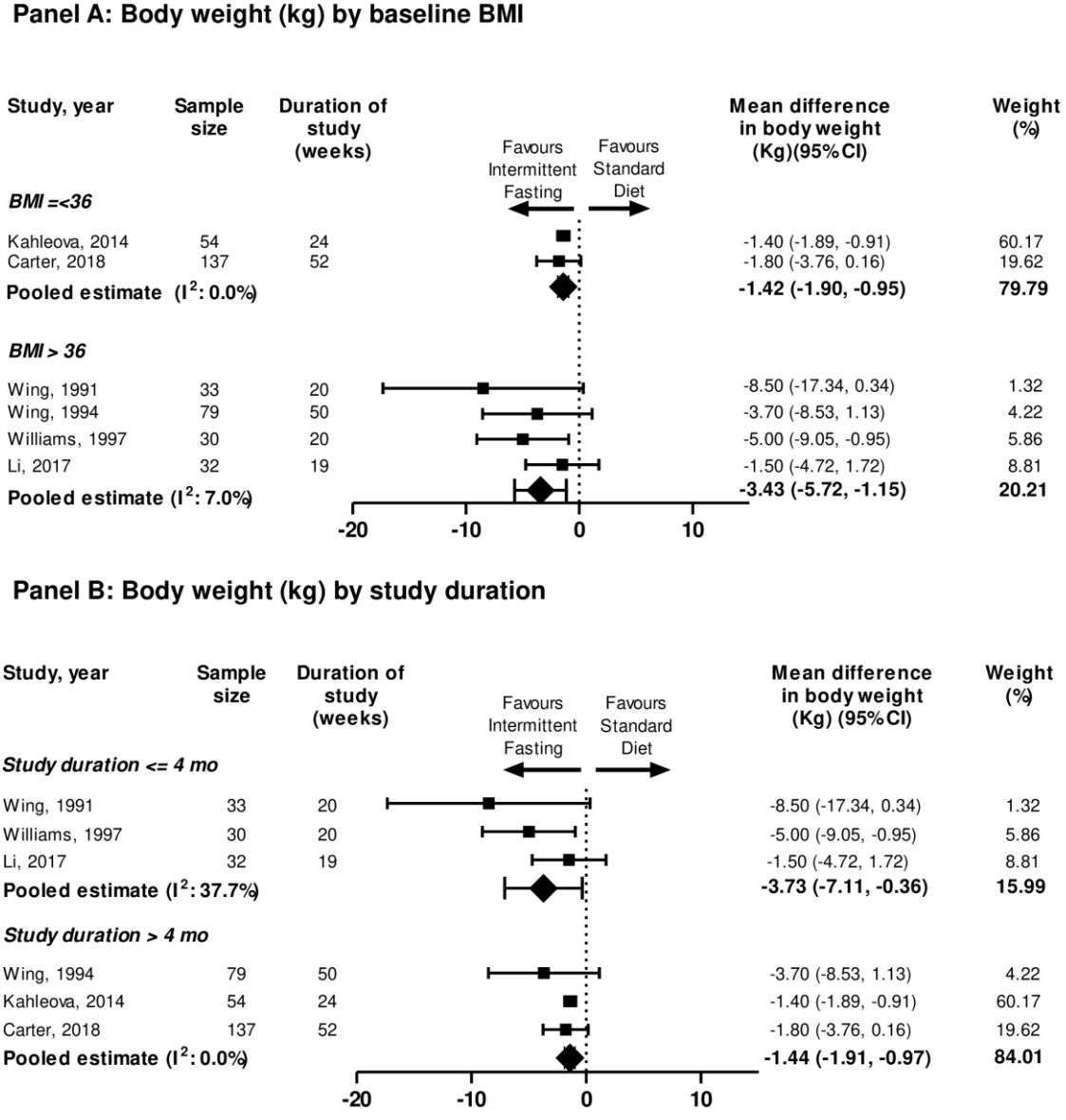

Figure 3