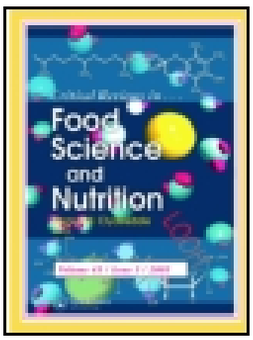

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REVIEW

The effect of fasting and energy restricting diets on markers of glucose and insulin controls: a systematic review and meta-analysis of randomized controlled trials

Somaye Fatahi[a,b], Ali Nazary-Vannani[c], Mohammad Hassan Sohouli[a,b], Zeinab Mokhtari[d,e], Hamed Kord-Varkaneh[d], Vihan Moodi[f,g], Shing Cheng Tan[h], Teck Yew Low[h], Fernando Zanghelini[i]*, and Farzad Shidfar[b]

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ABSTRACT

Inconsistencies exist with regard to influence of fasting and energy-restricting diets on markers of glucose and insulin controls. To address these controversial, this study was conducted to determine the impact of fasting diets on fasting blood sugars (FBSs), insulin, homeostatic model assessment insulin resistance (HOMA-IR) and hemoglobin A1c (HbA1c) levels. A comprehensive systematic search was carried out in electronic databases, i.e., Scopus, PubMed, and Web of Science through June 2019 for RCTs that investigated the impact of fasting and energy-restricting diets on circulating FBS, insulin, HOMA-IR and HbA1c levels from. Weighted mean difference (WMD) with the 95% CI were used for estimating combined effect size. The subgroup analysis was applied to specify the source of heterogeneity among articles. Pooled results from 30 eligible articles with 35 arms demonstrated a significant decrease in FBS (WMD): −3.376 mg/dl, 95% CI: −5.159, −1.594, $p < 0.001$), insulin (WMD: −1.288 μU/ml, 95% CI: −2.385, −0.191, $p = 0.021$), HOMA-IR (WMD: −0.41 mg/dl, 95% CI: −0.71, −0.10, $p = 0.01$) levels following fasting or energy-restricting diets. Nevertheless, no significant changes were observed in serum HbA1c levels. The subgroup analyses showed that overweight or obese people with energy restricting diets and treatment duration >8 weeks had a greater reduction in FBS, insulin and HOMA-IR level compared with other subgroups. The evidence from available studies suggests that the fasting or energy-restricting diets leads to significant reductions in FBS, insulin and HOMA-IR level and has modest, but, non-significant effects on HbA1c levels.

KEYWORDS

Energy restricting; fasting diets; glucose markers; insulin; insulin resistance

Introduction

Obesity and diabetes are two major non-communicable diseases that contribute heavily to public health burden. According to the latest statistics released by WHO, ∼13% of adults worldwide are categorized as being obese while another ∼39% being overweight; whereas >450 million people are diabetics (WHO 2019; Cho et al. 2018). These worrying figures are expected to grow steadily in the next decades (Cho et al. 2018; Agha and Agha 2017).

Pathophysiologically, obesity and diabetes are characterized by high levels of glucose and insulin in the blood, which can lead to undesirable consequences such as oxidative stress, that disrupts the normal functioning of biological pathways and causes complications (Buysschaert and Sadikot 2013). An example of the complications is retinopathy, which occurs when excess glucose generates byproducts that can lead to the thickening of the retinal vasculature, causing inadequate blood flow, and results in necrosis of the retina cells and the nerves (Jung et al. 2016). Since these two conditions are often associated with poor outcomes and complications such as increased risks of infection, benign prostatic hyperplasia and hypertension (Goyal et al. 2014; Kopp 2018), the levels of circulating glucose and insulin must be tightly controlled.

As the prevalence of overweight and obesity increases, so does the prevalence of certain obesity-related disorders,

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including coronary heart disease and type 2 diabetes (Cho et al. 2018). Losing weight by means of dietary restriction has been shown to improve indicators of disease risk losing weight, is asserted to play an important role in modulating indicators of cardiovascular risks, insulin resistance and levels of circulating glucose (Varady 2011). A commonly applied approach to weight loss is energy restriction (Fontana 2009). The major form of dietary restriction currently implemented is daily calorie restriction (CR). CR diet, decreasing energy intake by 15%–60% of daily needs, is a common dietary manipulation for weight loss, and frequently uses for clinical practices (Del Corral et al. 2009). Although the positive result of CR diet has been documented among several diseases in which obesity/overweight is known as a risk factor for cardiovascular disease, the compliance of the diet by subjects over long periods is usually low (Del Corral et al. 2009). Another dietary strategy that may be more feasible than CR diet in practice is a Fasting regimen. Fasting refers to the deliberate abstinence from food and drink for a defined and recurring period of time (Wei et al. 2017). Apart from weight loss, fasting or energy restriction can also deplete liver glycogen, decreased level of insulin and hydrolysis of triglycerides (TGs) to free fatty acids (FFAs) in adipocytes in healthy individuals (Browning et al. 2012).

The purported health benefits of fasting and energy restriction include weight loss, reduction of fat mass, improvements in both cardiovascular risk factors and insulin resistance (Redman et al. 2008; Redman and Ravussin 2011). Since fasting and energy restriction both reduce caloric intake, they potentially decrease blood glucose, insulin and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) levels (Cho, Hong, et al. 2019; Shojasaadat et al. 2019). To date, many studies have investigated the influence of fasting and energy-restricting diets on markers of glucose and insulin controls but the results from these investigations remain inconclusive. Among some of these contradicting findings, fasting and energy restriction were found to: (1) significantly associated with increased glucose and insulin levels (Cherif et al. 2017); (2) significantly associated with decreased glucose, insulin HOMA-IR levels (Shojasaadat et al. 2019; Skrha et al. 2005; Horne et al. 2013) or (3) not associated with any significant effects on the levels of glucose, insulin (Bowen et al. 2018), HOMA-IR (Lambert et al. 2017) and HbA1c (Astbury et al. 2018) between the fasting and non-fasting groups. We reason that these discrepancies can be attributed to sample size, types of intervention (fasting vs. energy-restricting diet) or duration of fasting. Therefore, in this work, we attempted to address these inconsistencies by performing a systematic review and meta-analysis of randomized controlled trials to better evaluate the effects of fasting and energy-restricting diets on fasting glucose, insulin, HOMA-IR and HbA1c levels.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) was used to guide the performance and reporting of the study (McInnes et al. 2018; Guyatt et al. 2008).

Search strategy

We searched three electronic databases, i.e., Scopus, PubMed, and Web of Science through June 2019. A secondary search was implemented where reference lists of all relevant reviews and trials were reviewed for additional studies. The search strategy was described in detail in Supplementary Table 1.

Eligibility criteria

Controlled trials that compared fasting and energy restricting diets with controls were first selected. To be eligible, trials needed to meet the following criteria: (1) Population: adult subjects $\geq$18 years. (2) Intervention: different types of fasting and energy restricting diets (Low-energy diet, very low energy diet, intermittent energy restriction, alternate day fasting, fasting mimicking diet, Ramadan model of intermittent fasting). (3) Comparison: control group. (4) Primary outcomes: articles that report sufficient information on baseline and final study of fasting blood sugar (FBS), insulin, HOMA-IR and HbA1c in both fasting and energy restricting diets and control groups. The studies performed on children, pregnant women or animals, were not controlled trials, did not reported enough data for the results in fasting or energy restricting diets and control groups, investigated the effects of fasting and energy restricting diets along with other components were excluded. Experimental study, unpublished trials, comments, reviews, letters, animal study and trials published only in abstract format were excluded. Also, only studies published in English were considered. Moreover, the most recent information was used for duplicates.

Data extraction

Two independent reviewers extracted information from each study with the use of a standard excel sheet and a predesigned, standardized data-extraction form. The information sought included: (1) study characteristics (publication year, inclusion and exclusion criteria, dates of enrollment, total number of participants in intervention and control groups, country where study performed); (2) baseline patient characteristics (age, gender, obesity); (3) intervention characteristics (type of intervention, duration of treatment); and (4) clinical results, as previously defined. When necessary, we emailed the corresponding authors to acquire study details.

Quality assessment

All studies were evaluated for methodological quality with the use of the Cochrane Risk of Bias tool (Higgins et al. 2011). If more than one of the domains was rated as high, the study was considered at high risk of bias. If all domains were refereed as low, the study was considered at low risk of bias. Else, the study was reflected as having an unclear risk

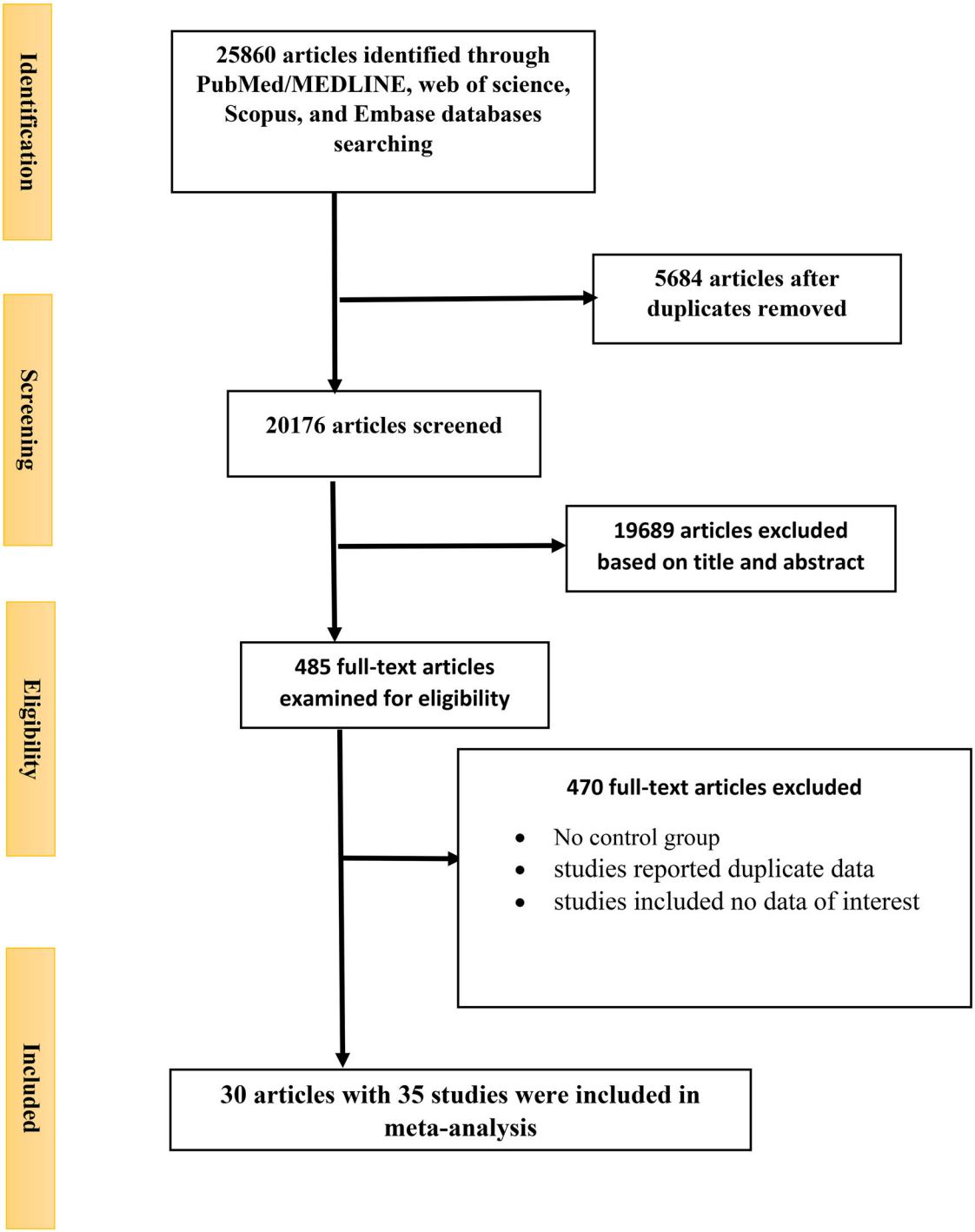

Figure 1. Flow chart for study examined and included into the meta-analysis.

of bias. Also, the Jadad scale (Clark et al. 1999) were used to declare the quality of trials.

Statistical methods

Data were combined, if there were ≥3 trials within a single grouping using the generic inverse variance approach with random effects model and reported as weighted mean differences (WMDs). We applied Stata software (Stata Corp., College Station, TX) for primary, sensitivity analyses, and publication bias. If data was expressed in a different format, standard calculations were executed to obtain the mean and SD (Higgins and Green 2011; Hozo, Djulbegovic, and Hozo 2005). For instance, if the SD of the change was not stated in the trials, we derived it using the following formula: SD changes = square root $[(SD_{baseline}{}^2+SD_{final}{}^2) - (2 \times R \times SD_{baseline} \times SD_{final})]$. Heterogeneity was examined through the use of forest plots and the I^2 statistic. Sources of heterogeneity were explored by sensitivity analyses in which each study was excluded independently and the pooled effect size re-estimated. Publication bias was measured through the use of visual calculation of funnel plots

Table 1. Characteristics of included studies.

Author	Country	year	Study Design	Study population	Gender	Age (year)	outcome	Sample Size case/control	Intervention diet (details)	Control diet (details)	JADAD score
Shojasaadat et al.	Iran	2019	Parallel randomized controlled trial	Nonalcoholic fatty liver disease	Both	41	FBS, insulin, HOMA-IR	35/34	Low-energy diet (350–700 Kcal energy deficit (30% of energy as fat, 52% as carbohydrate, and 18% as protein)	Habitual diet	3
Hirsh et al.	USA	2019	Parallel randomized controlled trial	Healthy overweight adults	Both	43	FBS, insulin, HOMA-IR	10/12	Intermittent energy restriction (2 fasting days and followed by 5 d of habitual diet) (730 kcal/d by consuming a commercially shake 170 kcal/d)	Habitual diet without any restriction	3
Cho et al. (a)	Republic of Korea	2019	Parallel randomized controlled trial	Overweight or obese adults	Both	33.5	FBS, insulin, HOMA-IR	8/5	Alternate day fasting (ADF) (3 fasting day per week and 4 d/wk consumed food ad libitum) (consumed approximately 500 kcal/d or 25% of their daily energy intake on each fast day)	Regular eating and exercise habits	3
Cho et al. (b)	Republic of Korea	2019	Parallel randomized controlled trial	Overweight or obese adults	Both	34.5	FBS, insulin, HOMA-IR	9/9	ADF + resistance training and aerobic exercise (500 kcal/d or 25% + Resistance training for 40 min and aerobic exercise for 20 min)	Resistance training and aerobic exercise	3
Solianik et al.	Lithuania	2018	Cross-over randomized controlled trial	Overweight women	Female	20	FBS	11/11	2-day fasting state (2-day zero-calorie diet with water provided ad libitum)	2-day usual diet (feding state)	2
Papageorgiou et al.	UK	2018	Randomized crossover design	Without any diseasea	Female	24	Insulin	10/10	Low energy availability (LEA) through dietary energy restriction (D-RES) (15 kcal·kgLBM/d (D-RES) (50% carbohydrates, 20% protein and 30% fat))	Controlled energy availability (CON: 45 kcal/kgLean Body Mass/d)	3
Kessler et al.	Germany	2018	Parallel nonrandomized controlled clinical trial	Healthy volunteers	Both	42.45	FBS, insulin, HOMA-IR	20/13	Intermittent fasting (IF) one fixed fasting day per week (24 h/wk) (maximum intake of 300 kcal/d resulting from defined fasting beverages: standard fruit and/or vegetable juices)	A regular healthy diet over the 8-wk study period	1
Izadi et al.	Iran	2018	Parallel randomized controlled clinical trial	Adults men and women	Both	43.3	FBS	30/30	Low-energy-dense diet (LD) (certain amount of calories based on the body weight of participants (60% carbohydrates, 15% protein, 25% fat) withlow-energy-dense foods (broth, soup))	Usual diet (50% carbohydrate, 35% fat, 15% protein)	3
Clayton et al.	UK	2018	Experimental trials in a randomized, counterbalanced order	Without any disease	Male	25	FBS, insulin	7/5	Severely energy-restricted diet (ER) (consume 25% (2622 kJ) of estimated energy requirements)	Energy balance (EB) providing 100% (10 441 kJ) of estimated energy requirements	2
Headland et al.	Australia	2018	Randomized single-blinded crossover study	Adults men and women	Both	46	FBS	33/33	Very low energy diet on 2 consecutive days per week and 5 days of habitual eating (consume 500/600 kcal/d (women/men) on 2 consecutive day (47% protein, 15% fat, 32% carbohydrate, 6% fibre)	Habitual eating	3
Bowen et al.	Australia	2018	Parallel, single-center, randomized, controlled trial	Adults with overweight/obesity	Both	40	FBS, insulin	67/68	Daily continuous energy restriction (DER) + modified, ADF (DER + ADF) (DER 5000 kJ/d (Tuesday, Thursday, and Sunday), ADF 2400 kJ/d (Monday, Wednesday, and Friday) and 1 d/wk to eat ad libitum 10,000 kJ/d (Saturday)	DER, Monday-Sunday, 5000 kJ/d	3
Astbury et al.	UK	2018	Randomized, two arm, open label, parallel design	Obese adults	Both	48.2	FBS, insulin, HOMA-IR, HbA1c	89/76	Low Energy total diet replacement Treatment (TDR) (energy intake comprised 810 kcal/d (3389 kJ/d), participants replaced all food with four formula food products daily (soups, shakes, and bars)	Usual diet	3
Trepanowski et al. (ADF)	USA	2017	A single-center randomized clinical trial /parallel	Overweight and obese adults	Both	46.2	FBS, HOMA-IR	25/25	ADF (consuming 25% of energy needs on Fast day and 125% on Feast day) a diet of 500 kcal/d on fast days and 2500 kcal/d on feast days (25%–26% fat, 59%–60% carbohydrate, 16%–14% protein)	Usual diet (consuming 100% of needs every day)	3
Trepanowski et al. (CR)	USA	2017	A single-center randomized clinical trial /parallel	Overweight and obese adults	Both	44	FBS, HOMA-IR	29/25	Daily calorie restriction (CR) (consuming 75% of energy needs every day) a diet of 1500 kcal/d on every day (25% fat, 61% carbohydrate, 14% protein)	Usual diet (consuming 100% of needs every day)	3
Wei et al.	USA	2017	Randomized trial in 2-arm, cross-over	Generally healthy participants	Both	43.3	FBS	30/37	Fasting-mimicking diet (FMD) for 5 consecutive days per month for 3 months Day 1 of the FMD supplies ∼4600 kJ (11% protein, 46% fat, and 43% cho)whereas days 2 to 5 provide∼3000 kJ (9% protein, 44% fat, and 47% cho)per day	Unrestricted or normal diet	2
Li et al.	Germany	2017	Randomized controlled clinical pilot study	Patients with type-2 diabetes mellitus and metabolic syndrome	Both	64.7	FBS, insulin, HOMA-IR, HbA1c	16/16	One-week fasting period (During the 7 days fasting participants received total daily energy intake of 1255 kJ/d (300 kcal/d))	Usual care (follow the principles of a Mediterranean diet)	3

Lambert et al. (a)	Australia	2017	Parallel randomized controlled trial	Male subjects with overweight	Both	24	FBS, insulin, HOMA-IR	10/6	Prescribed a hypocaloric diet (a caloric deficit of 600 kcal/d (the diet consisted of 30% fat, 48% carbohydrate, and 22% protein))	Usual dietary and exercise habits	3
Lambert et al. (b)	Australia	2017	Parallel randomized controlled trial	Male subjects with overweight	Both	25	FBS, insulin, HOMA-IR	11/10	Prescribed a hypocaloric diet + Moxonidine treatment (a caloric deficit of 600 kcal/d (The diet consisted of 30% fat, 48% cho, and 22% protein)+Moxonidine treatment (0.2 mg/d for 2 weeks and then 0.4 mg/d for 24 weeks))	Moxonidine treatment (0.2 mg/d for 2 weeks and then 0.4 mg/d for 24 weeks)	3
Harder-Lauridsen et al.	Denmark	2017	Nonrandomized crossover intervention study	Healthy lean men	Male	25.2	FBS, insulin, HOMA-IR, HbA1c	10/10	Ramadan model of intermittent fasting (RIF) (fasting for 14 consecutive houres for 28 consecutive days)	Usual eating and exercise habits	3
Cherif et al.	Qatar	2017	Randomized counter-balance experimental trials	Healthy male Muslim adults	Male	29.8	FBS, insulin	21/21	IF (fasting session (FS) FS): conducted on the third consecutive day of IF (no food or drink from dawn (∼4:00 am) to sunset (∼4:45 pm))	Normal fed state	1
Lee et al.	UK	2016	Parallel randomized controlled trial	Without any disease	Both	55.2	FBS	30/30	Energy restriction (ER) (∼20% reduced intake of energy from food)	Energy balance	1
Koehler et al. (a)	Germany	2016	Repeated-measures cross-over randomized experimental design	Exercising men	Male	18–30	FBS, insulin	6/6	LEA (15 kcal per kg FFM per day)	Normal energy availability (control condition): 40 kcal per kg FFM per day	2
Koehler et al. (b)	Germany	2016	Repeated-measures cross-over randomized experimental design	Exercising men	Male	18–30	FBS, insulin	6/6	LEA + exercise (15 kcal per kg FFM per day) + exercise	Normal energy availability (control condition) + exercise	2
Karimi et al.	Iran	2016	Randomized controlled clinical trial study in a parallel design	Subjects with the history of weight reduction	Both	55.2	FBS	30/30	Low energy density diet (LED) (LED group contained, 30% fat, 15% protein and 55% carbohydrate)	Usual diet (35% fat, 15% protein, and 50% carbohydrate)	3
Fernandes et al.	Brazil	2015	Open-label, randomized, clinical trial, parallel	Obese patients with obstructive sleep apnea	Both	39.09	FBS, insulin, HOMA-IR	11/10	Energy restriction (ER) (energy intake in the ERG was 3347·2 kJ/d (800 kcal/d) reduction in baseline total daily energy expenditure (±15%–20% proteins, ±25%–30% % fat, ±50%–60% carbohydrates))	Control group (CG) were advised not to change their food intake	3
Karatoprak et al.	Turkey	2013	Randomized, retrospective, observational study	Type 2 diabetes mellitus	Both	57	FBS, HbA1c	76/781	Fasted during Ramada (details were no reported)	Non-fasting group	2
Teng et al.	Malaysia	2013	Parallel randomized controlled study	Healthy older adult men	Male	59.6	FBS	28/28	Fasting calorie restriction (FCR) (FCR diet consisted of 2 days of Muslim Sunnah fasting combined with a reduction of 300–500 kcal/d from the habitual energy intake)	Maintain their present lifestyle	2
Home et al.	USA	2013	Randomized cross-over trial	Healthy individuals	Both	43.3	FBS, insulin, HOMA-IR	30/30	Fasting period (water-only fasting)	Fed period	2
Bhutani et al. (a)	USA	2013	Randomized, controlled, parallel-arm feeding trial	Obese humans	Both	42	FBS, insulin, HOMA-IR	16/16	ADF (participants consumed 25% of their baseline energy needs on the "fast day"and consumed food ad libitum on each "feed day" (25% fat, 20% protein, 55% carbohydrate))	Control group (maintained their regular eating habits)	3
Bhutani et al. (b)	USA	2013	Randomized, controlled, parallel-arm feeding trial	Obese humans	Both	45	FBS, insulin, HOMA-IR	16/16	Combination (ADF + endurance exercise) (ADF (fast and feed day) + exercise (3 times/wk))	Exercise group (3 times/wk)	3
Tapsell et al. (a)	Australia	2010	Randomize dcontrolled trial parallel	Overweight men and women	Both	46.1	FBS, insulin	21/26	Low fat-low calorie diet (LC) (low fat diet with a 2 MJ/d energy restriction)	Isocaloric low fat diet (LF)	2
Tapsell et al. (b)	Australia	2010	Randomize dcontrolled trial parallel	Overweight men and women	Both	42.8	FBS, insulin	27/21	Low calorie with 10% PUFA (LF-PUFA-LC) (low fat diet inclusive of 10% polyunsaturated fatty acid with a 2 MJ energy restriction)	Isocaloric with10% poly unsaturated fatty acids (LF-PUFA)	2
Khoo et al.	Australia	2010	Nonrandomized controlled trial parallel	Obese men	Male	44.5	FBS, insulin	25/24	Low-calorie diet (LCD) (total energy intake of approximately 850–900 kcal per day)	Normal diet	1
Ong et al.	UK	2009	Parallel conteolled trial	Overweight or obese at moderately increased risk of breast cancer: BMI 28 and 40	Female	40	FBS, insulin	10/9	Dietary energy restriction: 864 kcal/d (pro: 26%, CHO: 62%, 12%: fat, 7%: saturated fat)	Normal eating patterns	2

(*continued*)

Table 1. Continued.

Author	Country	year	Study Design	Study population	Gender	Age (year)	outcome	Sample Size case/control	Intervention diet (details)	Control diet (details)	JADAD score
Cox et al. (a)	Australia	2004	Randomize dcontrolled trial parallel	Overweight, sedentary subjects	male	41	FBS, insulin	15/11	Restrict their energy: 1000–1500 kcal/d + light exercise group (pro: 15%, fat: 30%, carbohydrates: 55%)	Normal energy + light exercise group	2
Cox et al. (b)	Australia	2004	Randomize dcontrolled trial parallel	Overweight, sedentary subjects	male	41	FBS, insulin	14/12	Restrict their energy: 1000–1500 kcal/d + vigorous-intensity exercise group for three 0.5-h sessions/wk (pro: 15%, fat: 30%, carbohydrates: 55%)	Normal energy + vigorous-intensity exercise group for three 0.5-h sessions/wk	2
Skrha et al.	Czech Republic	2006	Parallel conteolled clinical trial	Obese type 2 diabetic patients	Both	41	FBS	12/13	VLCD: 600 kcal/d	No treatment	1

and Egger's regression tests (Egger et al. 1997). If any publication bias was revealed, it was investigated via the 'trim and fill' method (Palmer et al. 2008). Statistical significance was evaluated at an α level of 0.05.

Results

Study selection

The initial database search found 25,860 articles; after duplicates were eliminated, 20,176 articles remained. After reviewing across the titles and abstracts, 20,159 articles were outputted for full-text examination. Finally, 30 articles were included in this systematic review and meta-analysis (Shojasaadat et al. 2019; Cherif et al. 2017; Skrha et al. 2005; Horne et al. 2013; Bowen et al. 2018; Lambert et al. 2017; Astbury et al. 2018; Hirsh et al. 2019; Cho, Moon, et al. 2019; Trepanowski et al. 2018; Solianik and Sujeta 2018; Papageorgiou et al. 2018; Kessler et al. 2018; Izadi et al. 2018; Headland, Clifton, and Keogh 2018; Clayton et al. 2018; Wei et al. 2017; Li et al. 2017; Harder-Lauridsen et al. 2017; Lee et al. 2016; Koehler et al. 2016; Karimi et al. 2016; Fernandes et al. 2015; Teng et al. 2013; Karatoprak et al. 2013; Bhutani et al. 2013; Tapsell et al. 2010; Khoo et al. 2010; Ong et al. 2009; Cox et al. 2004). Of 30 eligible articles, 35 arms reported the influences of fasting and energy restricting diets on FBS, 28 trails on insulin, 16 arms on HOMA-IR and 4 trials HbA1c (Figure 1).

Characteristics of the eligible studies

The characteristics of the eligible trials are summarized in Table 1. Studies were performed in a wide range of countries, including USA, UK, Australia, Iran, Republic of Korea, Lithuania, Germany, Denmark, Qatar, Brazil, Turkey, Malaysia, and Czech Republic. Included articles were published between 2004 and 2019. Mean age of participants ranged from 18 to 64.7 years in eligible studies. Eligible publications involved investigations conducted on both genders, nine arms on men (Cherif et al. 2017; Clayton et al. 2018; Harder-Lauridsen et al. 2017; Koehler et al. 2016; Teng et al. 2013; Khoo et al. 2010; Cox et al. 2004), and three arms on women (Solianik and Sujeta 2018; Papageorgiou et al. 2018; Ong et al. 2009). The sample size in the included arms ranged from 12 to 165. Participants in eligible studies were: obese type 2 diabetic patients (Skrha et al. 2005; Li et al. 2017; Karatoprak et al. 2013); nonalcoholic fatty liver disease patients (Shojasaadat et al. 2019); obese patients with obstructive sleep apnea (Fernandes et al. 2015), and healthy individuals. The results of the quality assessment of eligible articles are presented in Supplementary Figure 1 and Table 1. The risk of bias was attributed to incomplete outcome data of included studies. The Jadad score for 6 (Cherif et al. 2017; Skrha et al. 2005; Kessler et al. 2018; Lee et al. 2016; Khoo et al. 2010) and 10 trials (Wei et al. 2017; Horne et al. 2013; Solianik and Sujeta 2018; Clayton et al. 2018; Koehler et al. 2016; Teng et al. 2013; Karatoprak et al. 2013; Tapsell et al. 2010; Ong et al. 2009; Cox et al. 2004) were 1 and 2 of 5

points respectively. Other studies scored 3 out of 5 points. Since, blinding is not easily possible for studies involving diet, all studies lost 2 points. Therefore, the interpretation of these results should be done with caution because these scores do not necessarily mean the low quality of the articles.

Meta-analysis results

Effect of fasting and energy restricting diets on FBS

Thirty-five studies including a total of 1581 participants (case = 811, and control = 770) reported FBS as an outcome measure. Combined results from the random-effects model indicated that FBS did change significantly following fasting and energy restricting diets intervention (WMD: −3.376 mg/dl, 95% CI: −5.159, −1.594, $p < 0.001$) with significant heterogeneity among the studies ($I^2 = 68.5\%$, $p < 0.001$) (Figure 2). We subsequently stratified studies based on intervention type and treatment duration. These analyses showed that studies with both gender (WMD: −3.006 mg/dl, 95% CI: −5.043, −0.968, $I^2 = 56.7\%$), only energy restricting diets (WMD: −4.046 mg/dl, 95% CI: −6.147, −1.945, $I^2 = 59.2\%$ %) and treatment duration >8 weeks (WMD: −2.99 mg/dl, 95% CI: −4.82, −1.17, $I^2 = 59.2\%$) significantly reduced FBS. Also subjects with overweight or obese showed a greater reduction in FBS levels compared to other groups (WMD: −4.06 mg/dl, 95% CI: −6.53, −1.59, $I^2 = 68.2\%$) (Supplementary Figures 2–5).

Effect of fasting and energy restricting diets on insulin levels

Twenty-eight studies including a total of 1090 participants (case = 562, and control = 528) reported IN as an outcome measure. Overall results from the random-effects model indicated that fasting and energy restricting diets did result in significant change in insulin (WMD: −1.288 μU/ml, 95% CI: −2.385, −0.191, $p = 0.021$) (Figure 3). There was significant heterogeneity among studies ($I^2 = 70.0\%$, $p = 0.000$). Results of the subgroup analyses showed that studies with both gender (WMD: −2.072 mg/dl, 95% CI: −3.544, −0.600, $I^2 = 53.6\%$), overweight or obese subjects (WMD: −2.07 μU/ml, 95% CI: −3.49, −0.65, $I^2 = 68.2\%$), energy restricting diets (WMD: −1.685 μU/ml, 95% CI: −2.767, −0.603, $I^2 = 60.4\%$) and treatment duration >8 weeks (WMD: −2.995 μU/ml, 95% CI: −4.819, −1.170, $I^2 = 48.7\%$) had a significantly reduction in IN (Supplementary Figures 2–5).

Effect of fasting and energy restricting diets on HOMA-IR

Sixteen studies including a total of 649 participants (case = 342, and control = 307) reported HOMA-IR as an outcome

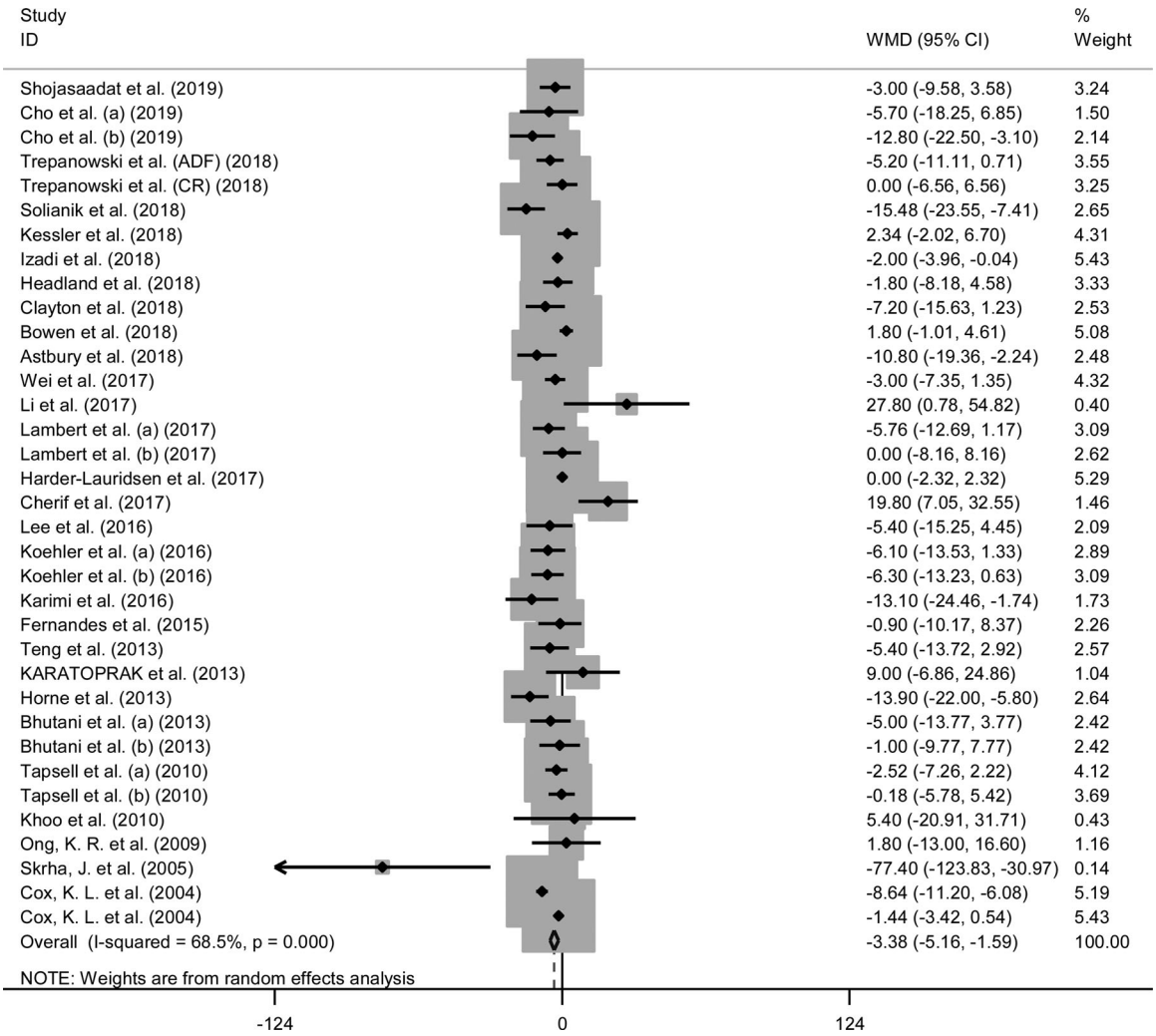

Figure 2. Forest plot of randomized controlled trials investigating the effects of fasting and energy restricting diets on FBS.

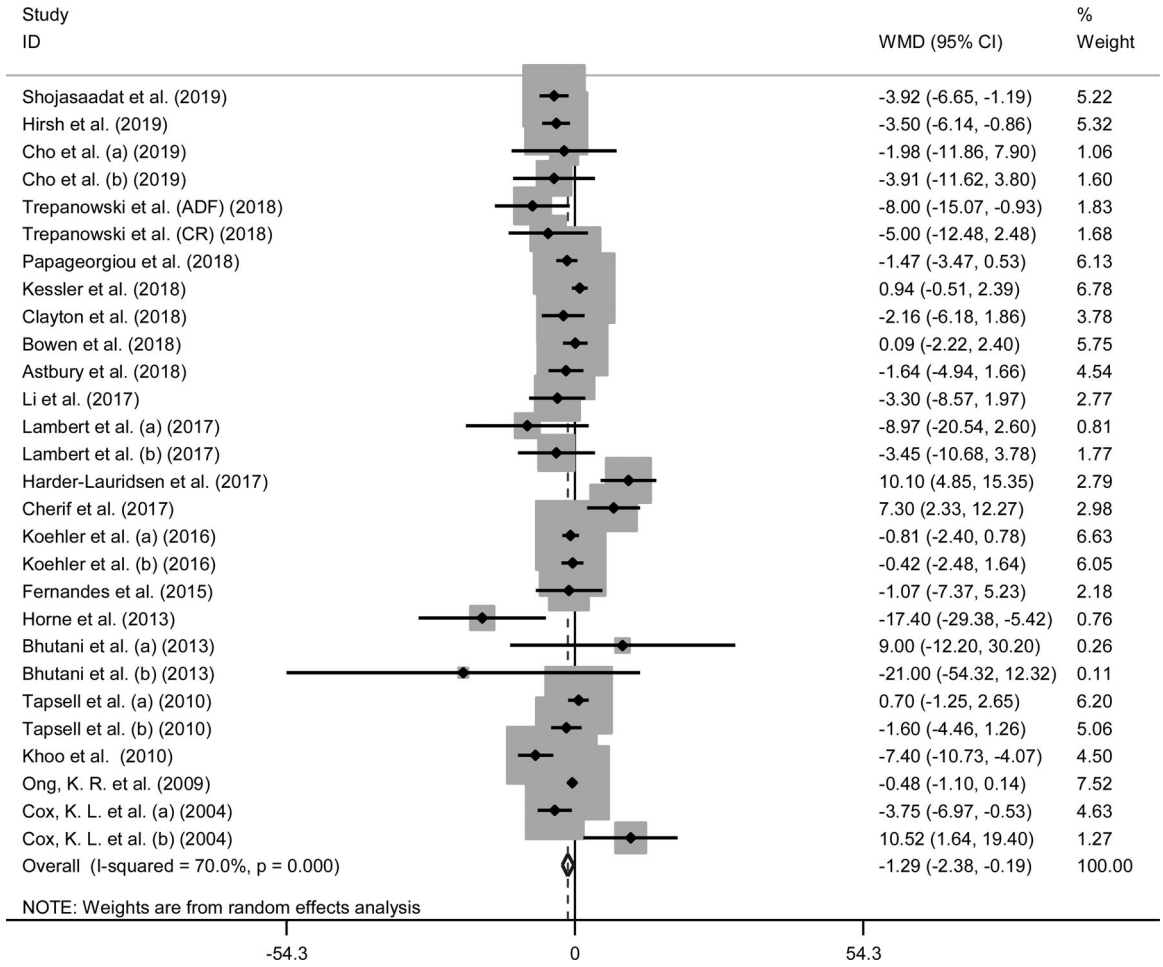

Figure 3. Forest plot of randomized controlled trials investigating the effects of fasting and energy restricting diets administration on insulin.

measure. Combined results from the random-effects model showed a significant reduction in HOMA-IR following fasting and energy restricting diets (WMD: −0.41 mg/dl, 95% CI: −0.71, −0.10, $p = 0.01$) with significant heterogeneity among the studies (I^2 = 70.9%, $p = 0.001$) (Figure 4). After subgroup analyses, results showed that overweight or obese individuals (WMD: −0.58, 95% CI: −.83, −0.32, I^2 = 0.0%) with energy restricting diets (WMD: −2.99, 95% CI: −4.82, −1.17, I^2 = 59.2%) and treatment duration >8 weeks (WMD: −0.67, 95% CI: −0.99, −0.35, I^2 = 0.0%) significantly reduced HOMA-IR (Supplementary Figure 2–4).

Effect of fasting and energy restricting diets on HbA1c

Four studies including a total of 363 participants (case = 192, and control = 171) reported HbA1c as an outcome measure. Our finding revealed that no significant decreasing in HbA1c level following intervention (WMD: −0.01 mg/dl, 95% CI: −0.65, 0.63, $p = 0.9$) without significant heterogeneity among the studies (I^2 = 22.6%, $p = 0.2$) (Figure 5).

Sensitivity analysis

To discover the impact of each single study on the combined effect size, we removed each trial from the analysis step by step. We observed no significant effect of any individual study on the combine effect sizes of FBS, insulin, HOMA-IR and HbA1c levels (Supplementary Figure 6).

Publication bias

Evolution of publication bias by visual inspection of funnel plot demonstrated no evidence of publication bias in the meta-analysis of Fasting and energy restricting diets on FBS, and insulin levels (Supplementary Figure 7). Egger's linear regression test also revealed the same result (FBS: $p = 0.273$, and IN: $p = 0.224$). Whereas publication bias for HOMA-IR had a significant result. The "trim and fill" method did not find any study.

Discussion

In this meta-analysis of 35 randomized controlled trials, participants who received fasting or energy restriction diets had significantly lower FBS, insulin, and HOMA-IR levels compared to controls. We also observed modest improvements in insulin resistance following interventions, which, however, did not reach statistical significance.

Scientific studies have demonstrated that reduction in calorie intake improves health, slows down ageing and extends longevity (Golbidi et al. 2017). These benefits are associated with the abilities of reduced calorie intake in not only

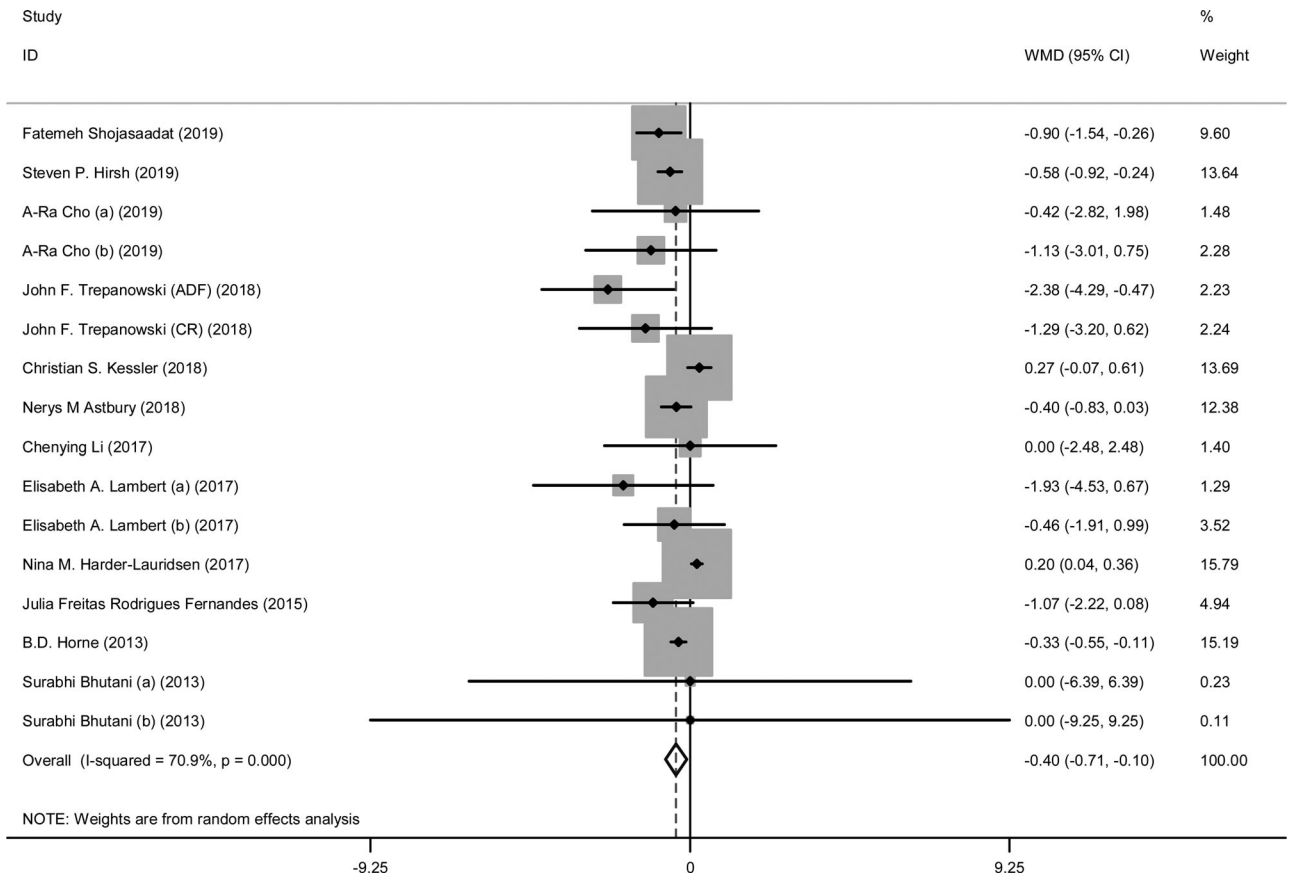

Figure 4. Forest plot of randomized controlled trials investigating the effects of fasting and energy restricting diets administration on HOMA-IR.

reducing oxidative stress, but also in activating a number of adaptive molecular mechanisms that are evolutionarily conserved to counteract deficiency in energy sources, leading to reduced inflammation, optimized energy metabolism, enhanced cellular protection and improved fitness (Longo and Mattson 2014). Collectively, these adaptive responses ensure that organisms respond to low-energy challenge by minimizing anabolic processes, while prioritizing maintenance such as improving stress resistance, tissue repair, and recycling of damaged molecules (de Cabo and Mattson 2019).

Experimentally, it is well-established that whereas the fed state is characterized by the elevated level of circulating insulin, preferential utilization of glucose as an energy source and the net flow of FFAs from liver to adipose tissues, states of fasting or energy restriction is followed by depletion of liver glycogen, decreased level of insulin and hydrolysis of TGs to FFAs in adipocytes (Browning et al. 2012). Circulating FFAs are subsequently transported into hepatocytes, whereby they stimulate the production of ketone bodies acetoacetate and β-hydroxybutyrate (β-HB). Hence, fasting and energy restriction are accompanied by increased levels of circulating ketones, while at the same time circulating fatty acids, amino acids, glucose, and insulin are maintained at low concentrations.

In reality, the effectiveness of fasting and energy restriction on the levels of blood sugar, insulin level and insulin resistance on human subjects remains inconsistent. This can be illustrated by the studies capitalizing on intermittent fasting diet (IFD), whereby in some studies, no significant association was found between IFD and blood sugar (St-Onge et al. 2017). On the other hand, when performed in different sub-categories of individuals, IFD was found to result in a 3%–6% decline in FBS in the prediabetics (Varady et al. 2013; Klempel et al. 2012) but not in healthy participants (Eshghinia and Mohammadzadeh 2013). Cho et al., in a previous systematic review, included participants with or without prediabetes in his meta-analysis (Cho, Moon, et al. 2019). As a result, they reported an improvement in FBS and HOMA-IR in the general population with the inclusion of some obese with prediabetes population groups. Nevertheless, this study was also limited by sample size and the exclusion of patients with chronic metabolic diseases such as diabetes mellitus. In our work, we included participants of more diverse health status and backgrounds in order to better clarify the association of fasting and energy restricting diets with FBS, insulin levels and insulin resistance. Our findings regarding the long-term impact of the fasting and energy restricting diets on blood markers indicated that this diet can reduce HbA1c levels, but this was not significant. Therefore, it is not possible to comment definitively and further studies are needed.

Likewise, there are several limitations in our study which are important to consider. First, this study considered both men and women in the same meta-analysis, despite the fact that energy metabolism such as that of lipid and glucose, does manifest sexual dimorphism (Lebeck 2016). Similarly, studies that are included here encompass different ethnicities and our study disregarded genetic variations that may

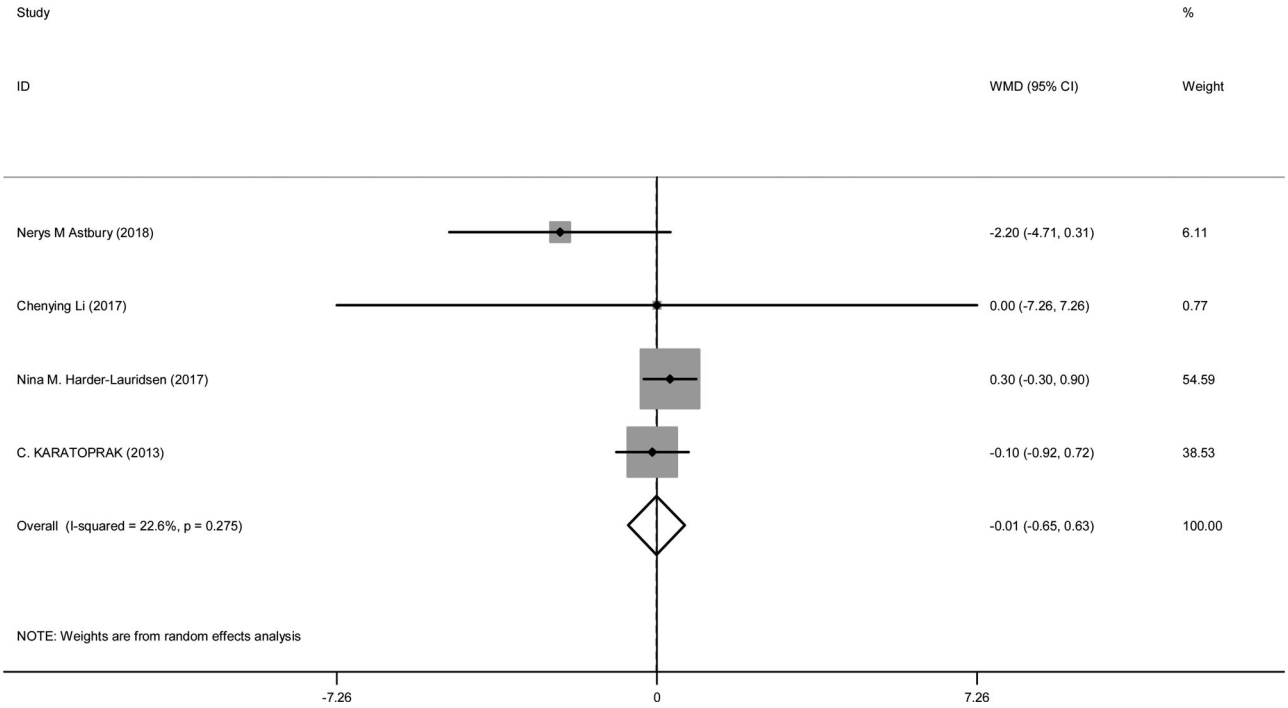

Figure 5. Forest plot of randomized controlled trials investigating the effects of fasting and energy restricting diets administration on HbA1c.

underlie the levels of FBS, insulin, HOMA-IR and HbA1c levels. In addition, this study roughly divided eligible publications into only two feeding regimens, i.e., (1) fasting and (2) energy restricting diets, whilst there existed a substantial degree of heterogeneity in experimental designs, with a wide range of intervention durations and dietary intervention protocols. In addition, it was not possible to subgroup HbA1c because of limited studies in each group. Despite these heterogeneities, the random-effects model methodology applied to the current study represents a significant design strength in further controlling for such factors.

There are also a few major strengths of the present systematic review and meta-analysis. First, we provided the first and most comprehensive quantitative evidence that fasting and energy restricting diets may decrease FBS, insulin and HOMA-IR levels. We successfully pooled the results of 30 published articles to yield a highly powered estimate of the influence of fasting and energy restricting diets on FBS, insulin and HOMA-IR levels. Besides, we included only RCTs, which represent the highest level in the hierarchy of scientific evidence, thus making our results highly relevant. We also included studies whose participants comprised a range of subject types, including obese, sedentary overweight and healthy-weight adults, as well as those suffering from type-2 diabetes and nonalcoholic liver disease, and considered alterations from baseline rather than the absolute levels of FBS, insulin, HOMA-IR and HbA1 so as to assess the true impact of fasting and energy restricting diets on these parameters regardless of the health status of the participants.

Conclusion

In conclusion, we have successfully demonstrated that fasting and energy restricting diets may decrease FBS, insulin and HOMA-IR levels. Whereas, this results was not significant for HbA1c level. Subgroup analysis revealed that the relationship was only significant in overweight or obese people who were prescribed energy restricting regimens and those who were given the intervention for >8 weeks. This information is important for giving recommendation to people with obesity and diabetes, as it may help to decrease their levels of glucose, insulin and insulin resistance, which contribute to a number of adverse health consequences. Further studies are required to clarify the exact molecular mechanisms by which fasting and energy restricting diets cause a reduction in the level of HbA1c.

Authors' contributions

S.F., H.K.-V., S.C.T., and T.Y.L. contributed in conception, design, and statistical analysis. F.Z., S.F., A.N.-V., M.H.S., and Z.M. contributed in data collection and manuscript drafting. F.S. supervised the study. All authors approved the final version of the manuscript.

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Disclosure statement

None of the authors had any personal or financial conflicts of interest.

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