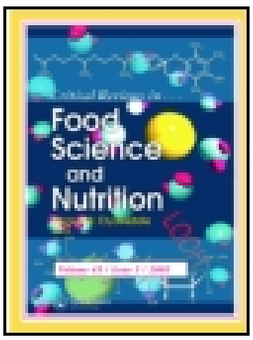

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Damoon Ashtary-Larky, Reza Bagheri, Omid Asbaghi, Grant M. Tinsley, Wesam Kooti, Amir Abbasnezhad, Reza Afrisham & Alexei Wong (2021): Effects of resistance training combined with a ketogenic diet on body composition: a systematic review and meta-analysis, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1890689

To link to this article: https://doi.org/10.1080/10408398.2021.1890689

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1890689

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REVIEW

Effects of resistance training combined with a ketogenic diet on body composition: a systematic review and meta-analysis

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ABSTRACT

We evaluated the effects of ketogenic diets (KDs) on body mass (BM), fat mass (FM), fat-free mass (FFM), body mass index (BMI), and body fat percentage (BFP) compared to non-KDs in individuals performing resistance training (RT). Online electronic databases including PubMed, the Cochrane Library, Web of Science, Embase, SCOPUS, and Ovid were searched to identify initial studies until February 2021. Data were pooled using both fixed and random-effects methods and were expressed as weighted mean difference (WMD) and 95% confidence intervals (CI). Out of 1372 studies, 13 randomized controlled trials (RCTs) that enrolled 244 volunteers were included. The pooled results demonstrated that KDs significantly decreased BM [(WMD = −3.67 kg; 95% CI: −4.44, −2.90, $p < 0.001$)], FM [(WMD = −2.21 kg; 95% CI: −3.09, −1.34, $p < 0.001$)], FFM [(WMD = −1.26 kg; 95% CI: −1.82, −0.70, $p < 0.001$)], BMI [(WMD = −1.37 kg.m^{-2}; 95% CI: −2.14, −0.59, $p = 0.022$)], and BFP [(WMD = −2.27%; 95% CI: −3.63, −0.90, $p = 0.001$)] compared to non-KDs. We observed beneficial effects of KDs compared to non-KDs on BM and body fat (both FM and BFP) in individuals performing RT. However, adherence to KDs may have a negative effect on FFM, which is not ameliorated by the addition of RT.

KEYWORDS

Ketogenic diet; weight loss; resistance training; fat-free mass; fat mass; body composition; meta-analysis

Introduction

The combination of resistance training (RT) with dietary approaches is acknowledged as an effective strategy to improve body composition (Bagheri, Hooshmand Moghadam, et al. 2021; Haghighat et al. 2020b; Lasevicius et al. 2018). Indeed, numerous studies have demonstrated the influence of diverse macronutrient ratios on body composition in resistance-trained populations (Antonio et al. 2015; Antonio et al. 2016; Aragon et al. 2017; Wycherley et al. 2010). Existing sports nutrition guidelines propose carbohydrate-based or periodized carbohydrate-based diets to augment athletic performance and muscular adaptations to RT (Burke et al. 2011; Jeukendrup 2017; Kerksick et al. 2018; Thomas, Erdman, and Burke 2016). However, in the last decades, there has been a surge in the popularity of low-carbohydrate and high-fat approaches such as the ketogenic diet (KD), largely due to purported benefits for body composition (Paoli, Bianco, and Grimaldi 2015; Tinsley and Willoughby 2016). KD is commonly characterized by decreasing carbohydrate intake to a maximum of approximately 50 g/d, or 5% of daily energy intake, while protein consumption is moderate or high (e.g. ≈1.2 to 1.5 g/kg/d). The remaining energy intake is predominantly from fats (≈60–80%), with relative fat intake depending on the degree of displacement of carbohydrates and proteins (Aragon et al. 2017). This macronutrient distribution leads to an increase in the production of ketone bodies (KB), such as acetoacetate, β-hydroxybutyrate, and acetone, and consequently to the state of physiological ketosis (i.e., elevated KB concentrations in the plasma as compared to a mixed diet) (Hall et al. 2016; Paoli and Health 2014). Some investigations have highlighted the efficacy of low-carbohydrate diets, including KD, in reducing body mass (BM) and fat mass (FM) as compared to other calorie-restricted diets (Krieger et al. 2006; Volek et al. 2004). A previous meta-analysis indicated that individuals assigned to a KD experienced greater BM loss than those assigned to a low-fat diet (LFD) for up to one year (Bueno et al. 2013). In addition to the investigation as a dietary intervention to combat overweight and obesity, ketogenic diets (KDs) have received increasing attention among normal-weight adults and those with esthetic goals, including resistance-trained individuals (Kang et al. 2020).

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Supplemental data for this article can be accessed at https://doi.org/10.1080/10408398.2021.1890689.

It is recognized that RT is partially dependent upon muscle glycogen stores as a form of energy supply (Cholewa, Newmire, and Zanchi 2019; Haff et al. 2003). Carbohydrate intake and consequent intramuscular glycogen concentrations play a critical role in the energy status and intracellular signaling pathways, namely by influencing the activity of AMP-activated protein kinase (AMPK) (Aschenbach, Sakamoto, and Goodyear 2004; Escobar, VanDusseldorp, and Kerksick 2016; Hawley et al. 2011; Hawley, Tipton, and Millard-Stafford 2006; McBride et al. 2009), which is a key factor that limits muscle size and capacity for hypertrophy and promotes muscle atrophy (Thomson 2018). Moreover, it has been demonstrated that KDs (Paoli, Bianco, and Grimaldi 2015) and low-glycogen concentrations (Aschenbach, Sakamoto, and Goodyear 2004; Hawley et al. 2011; Wojtaszewski et al. 2003) may result in up-regulated AMPK activity, which in turn attenuates the Tuberous Sclerosis 1 (TSC1) while increases Tuberous Sclerosis 2 (TSC2) activity (Laplante and Sabatini 2009). Ultimately, these changes would lead to the downregulation of the mechanistic target of rapamycin complex 1 (mTORC1) activity, thereby decreasing muscle protein synthesis (MPS) rates (Dreyer et al. 2006; Wilkinson et al. 2008; Xu, Ji, and Yan 2012). Furthermore, KDs can be considered rapid BM loss diets in some instances, (Harvey, Holcomb, and Kolwicz 2019; Masood, Annamaraju, and Uppaluri 2020; Muscogiuri et al. 2019; Oh and Uppaluri 2020) and there is a limited amount of evidence indicating that fat-free mass (FFM) loss may be a consequence of rapid loss of BM (Ashtary-Larky, et al. 2018; Ashtary-Larky, et al. 2017; Bagheri, Ashtary-Larky, et al. 2021). However, it is also acknowledged that the early, more rapid BM loss with a KD is related to loss of glycogen stores and associated water weight (Tinsley and Willoughby 2016). On the other hand, a KD can contain moderate to high protein content (approximately 30–35% of daily calorie intake), (Masood, Annamaraju, and Uppaluri 2020) which is an important factor for RT-based muscular hypertrophic adaptations (Bagheri, Hooshmand Moghadam, et al. 2021; Bagheri et al. 2020). Moreover, it has been recently shown that a high protein diet could preserve muscle mass during BM and/or fat loss phase (Haghighat et al. 2020; Johnston et al. 2017; Kim et al. 2016; Luger et al. 2013; Mettler, Mitchell, and Tipton 2010). The conceivable FFM-preserving mechanism of high protein diets can be related to dietary protein-induced alterations in protein turnover, particularly MPS, inhibiting AMPK phosphorylation, and activating mTORC1 signaling (Cuthbertson et al. 2005; Fujita et al. 2007; Krieger et al. 2006; Pasiakos et al. 2013). Accordingly, the question as to whether and how KD could affect FFM in those performing RT remains unclear.

It has been hypothesized that KDs lead to greater BM and FM loss while maintaining FFM (Manninen and Metabolism 2006), and therefore these diets may effectively improve body composition in individuals who participate in RT. However, the general impact of KD on body composition changes in resistance-trained individuals is unsettled and has varied in prior investigations, demonstrating a need for a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) on this topic. Therefore, we aimed to conduct a systematic review and meta-analysis of the pooled data from RCTs to compare the efficacy of KDs in individuals performing RT on body composition variables, including BM, body mass index (BMI), FM, FFM, and body fat percentage (BFP).

Materials and methods

Search strategy

Our meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2010). The participants (age $>$ 16 yr), intervention (KD), comparison (non-KD control group), outcome (body composition) (PICOS) model was used and included BM, BMI, FFM, BFP, and FM measures collected from RCTs. Briefly, included studies were RCTs with a pre-post design that reported outcomes of a KD intervention greater than two weeks in duration, as compared to a non-KD, in individuals $>$ 16 yr. The following scientific databases were searched up to 3 February 2021 with no limitation on time and language in six databases, including PubMed, the Cochrane Library, Web of Science, Embase, SCOPUS, and Ovid. Our search strategy consisted of the following keywords: "ketogenic diet", "very low-carbohydrate diet, keto-adaptation", "VLCD", "KD", "ketosis", "high fat diet", "low carbohydrate diet", "carbohydrate-restricted diet", "resistance training", "strength training", "weight training", "Pilates", "CrossFit", "exercise, athletes", "body composition", "anthropometric indices", "weight loss", "fat loss", "fat-free mass", "muscle mass", "muscle adaptation", and "performance". In addition, to minimize the risk of missing any relevant trials, all reference lists of the included studies and previous review articles were searched.

Study selection and eligibility criteria

The title and abstract of all articles found in the initial search were evaluated independently by two authors (WK and RA). Articles were included in the present meta-analysis if they met the following inclusion criteria: (1) parallel and crossover trials; (2) investigated the impact of KD ($<$ 50 g/d, or $<$ 5% of daily energy intake) on body composition measures including BM, BMI, FFM, BFP, and FM; (3) presented outcome data of interest as mean and standard deviation (SD) in both intervention and control groups; and (4) had a trial duration of more than 2 weeks. RCTs that did not meet the eligibility criteria were excluded via screening title, abstract, and full-text review. Exclusion criteria were: (1) All studies that supplemented another compound combined with KD in the intervention group; (2) animal, review, and experimental studies; (3) studies without a control group; 4) studies performed on children ($<$16 yr) (Clark, Tobias, and Ness 2006) and pregnant or lactating women.

Data extraction

Two authors (DAL and AB) extracted data from eligible RCTs: (1) the first author's last name, and year of publication; (2) trial design as crossover or parallel randomized controlled trial (RCT); (3) age, BMI, and the number of participants; (4) trial duration, (5) training intervention. In addition, the mean and SD of anthropometric measures before and after intervention were extracted. Any reported standard error of the mean (SEM) was converted to standard deviations (SDs) through the following formula by $SD = SEM \times \sqrt{n}$ (n is the number of participants in each group).

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria (Higgins et al. 2011). The quality of all included RCTs was evaluated by two authors (DAL and RB) for the following items: selection bias (adequacy of sequence generation and allocation concealment), flawed outcome data (dropouts), detection (blinding), reporting bias (selective outcome reporting), and other possible causes of bias. Based on The Cochrane Handbook recommendation, studies were ranked as low (L), or high risk of bias (H) or unclear (U) regarding each field of bias (Moher et al. 2010).

Statistical analysis

Mean change and SD for BM, BMI, FFM, BFP, and FM measures in the intervention and placebo groups were used to calculate the effect size. For studies with no reported SD of the mean difference, the following formula was used (Borenstein et al. 2011):

$$SD_{Change} = \sqrt{((SD_{Baseline})^2 + (SD_{Final})^2) - (2 \times 0.8 \times SD_{Baseline} \times SD_{Final})}$$

The pooled effect size was estimated using the DerSimonian-Laird method. The estimates of effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). The heterogeneity across studies was evaluated by using Cochrane's Q and I^2 tests (DerSimonian and Kacker 2007). A significance level of I^2>50% was considered clinically important heterogeneity (Ashtary-Larky et al. 2020). To find the possible sources of between-study heterogeneity, pre-planned subgroup analysis was performed based on participant's health condition, baseline BMI and waist circumference (WC), intervention type, and carbohydrate content of the diet. Moreover, since it has been indicated that several weeks to several months may be necessary for adaptation, for the symptoms of fatigue to subside, and for adjustments in glycogen homeostasis (Harvey, Holcomb, and Kolwicz 2019; Volek et al. 2016), we performed a subgroup analysis based on trial duration (≤8 and >8 weeks). Publication bias was evaluated by means of Begg's test, Egger's regression test, and visual inspection of funnel plots (Egger et al. 1997). All statistical analysis and data synthesis were performed using STATA MP V.14.0. (StataCorp, College Station, Texas, USA).

Results

Study selection

The initial search yielded 1372 articles, 593 of which were removed due to duplication. Another 751 articles were excluded due to the following reasons: unrelated title and abstract ($n = 606$), animal studies ($n = 91$), and review studies ($n = 54$). Consequently, 28 relevant studies remained for full-text review. Among these, 15 articles were excluded because of a lack of reporting of anthropometric indices. Finally, 13 studies were included in the present meta-analysis (Greene et al. 2018; Gregory et al. 2017; Hadizadeh et al. 2020; Jabekk et al. 2010; Kephart et al. 2018; LaFountain et al. 2019; Paoli et al. 2021; Paoli et al. 2012; Rhyu and Cho 2014; Vargas-Molina et al. 2020; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012). The flow diagram of the search process is depicted in Figure 1.

Study characteristics

The characteristics of the RCTs included are outlined in Table 1. In total, 244 volunteers were included (case = 130, control = 134), and the dates of publications were between 2010 and 2021. Eleven studies (Gregory et al. 2017; Hadizadeh et al. 2020; Jabekk et al. 2010; Kephart et al. 2018; LaFountain et al. 2019; Paoli et al. 2021; Rhyu and Cho 2014; Vargas-Molina et al. 2020; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012) were designed as parallel RCT and two studies (Greene et al. 2018; Paoli et al. 2012) were designed as a crossover. The study duration ranged between three and 12 weeks, and the sample size ranged from eight to 29 participants. Participant's ages ranged from 16.4 to 58.8 yr, while baseline BMI varied between 21.2 and 34.5 $kg.m^{-2}$. Six studies enrolled only males (Paoli et al. 2021; Paoli et al. 2012; Rhyu and Cho 2014; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012), two contained only female participants(Jabekk et al. 2010; Vargas-Molina et al. 2020), four studies included both sexes (Greene et al. 2018; Gregory et al. 2017; Kephart et al. 2018; LaFountain et al. 2019), and one study did not report the sex of participants (Hadizadeh et al. 2020). The carbohydrate content of the KD in these studies ranged from 5-50 g/d. These studies were performed in overweight females (Jabekk et al. 2010), elite artistic gymnasts (Paoli et al. 2012), males with metabolic syndrome (Wood et al. 2012), Taekwondo athletes (Rhyu and Cho 2014), CrossFitters (Gregory et al. 2017; Kephart et al. 2018), resistance-trained males (Paoli et al. 2021; Vargas et al. 2018; Wilson et al. 2017) and females (Vargas-Molina et al. 2020), intermediate to elite competitive lifting athletes (Greene et al. 2018), healthy adults from various military branches (LaFountain et al. 2019), and untrained adults (Hadizadeh et al. 2020).

Results from quality assessments

For random sequence generation, most of the studies had an unclear risk of bias (Greene et al. 2018; Gregory et al. 2017; Hadizadeh et al. 2020; Jabekk et al. 2010; LaFountain et al.

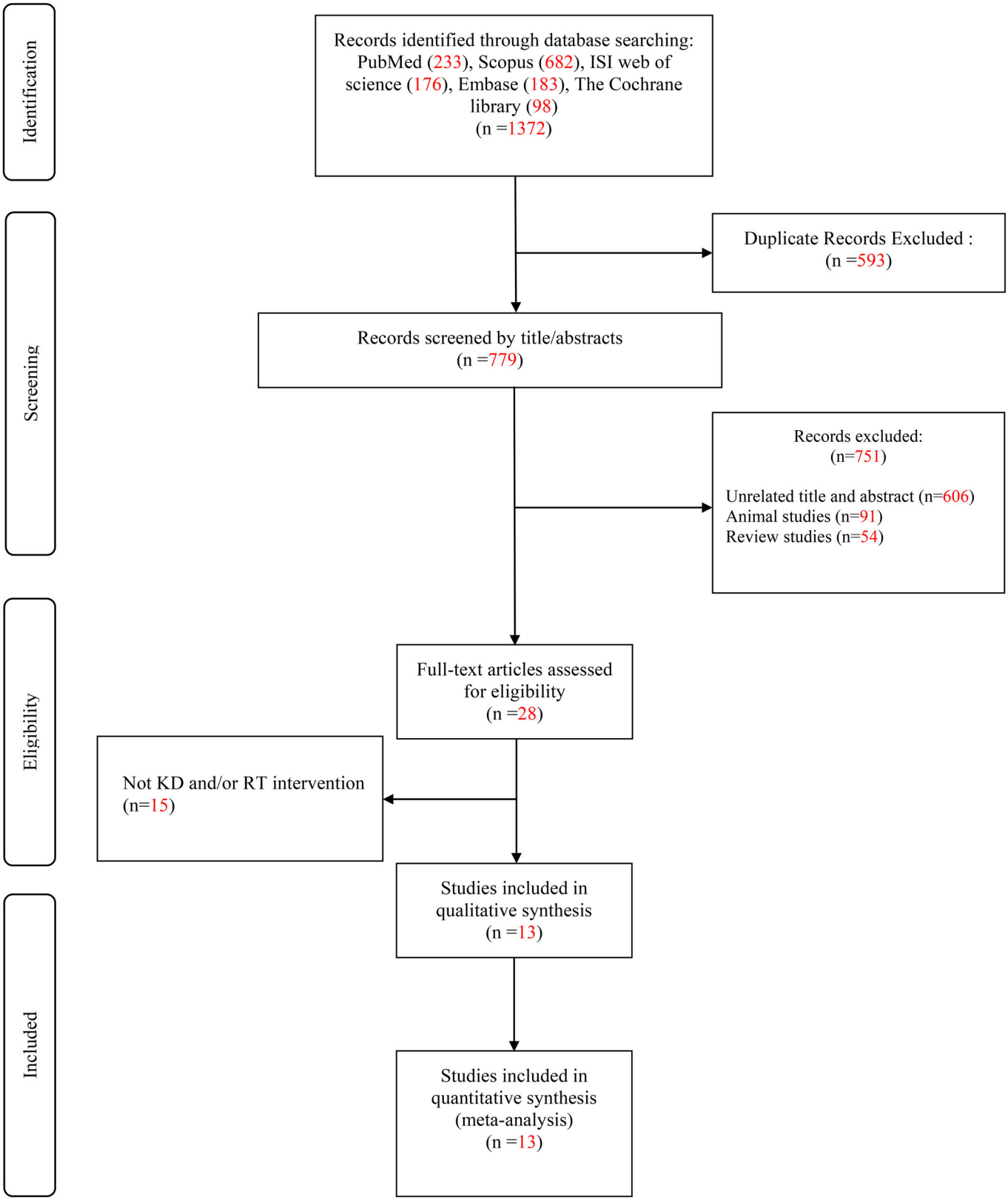

Figure 1. Flow diagram of the search process.

2019; Rhyu and Cho 2014; Vargas-Molina et al. 2020; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012) except two studies that had a high risk of bias (Kephart et al. 2018; Paoli et al. 2012), and one study had low risk of bias (Paoli et al. 2021). Allocation concealment was described clearly in four studies (Gregory et al. 2017; Paoli et al. 2021; Vargas-Molina et al. 2020; Vargas et al. 2018) and not clearly in seven studies (Greene et al. 2018; Hadizadeh et al. 2020; Jabekk et al. 2010; LaFountain et al. 2019; Rhyu and Cho 2014; Wilson et al. 2017; Wood et al. 2012). Regarding blinding (participants, personnel, and outcome assessment), all studies had a high risk of bias (Greene

Table 1. The characteristics of the included trials. Abbreviations: RT, resistance training; BMI, body mass index; BFP, body fat percentage; 1-RM, 1-repetition maximum; KDs, ketogenic diets; CHO, carbohydrate, Prt, protein; kcal, kilocalorie; kg, kilogram; d, day; ND, non-defined; FFM, fat free mass; LBM, lean body mass; DXA, Dual-energy X-ray absorptiometry; BIA, Bioelectrical impedance analysis.

Study	Subjects	N (% female)	Obesity classification (BMI/BFP)	RT intervention	Duration	Parallel or crossover	Body analyzer method	Macronutrient ratio in KDs	Macronutrient ratio in non-KDs	Ad libitum (Yes / No)	Effects of KD on weight and/or BMI (compared to non-KD)	Effects of KD on FM and/or PBF (compared to non-KD)	Effects of KD on FFM and/or LBM (compared to non-KD)
Jabekk et al. (2010)	Overweight and obese females	16 (100%)	32.3 / 47.6%	60–100 min of progressive RT (8–12 of 1-RM) twice weekly	10 weeks	Parallel	DXA	CHO: 23 g Prt: 95 g Fat: 131 g Energy: 1756 kcal	CHO: 196 g Prt: 79 g Fat: 76 g Energy: 1974 kcal	Yes	↓	↓	↔
Wood et al. (2012)	Metabolic syndrome patients	16 (0%)	34.2 / 32.9%	3 sessions/wk of progressive RT	12 weeks	Parallel	BIA	CHO: 52 g Prt: 120 g Fat: 98 g Energy: 1573 kcal	CHO: 235 g Prt: 78 g Fat: 40 g Energy: 1590 kcal	No (in KD group only)	↔	↔	↔
Paoli et al. (2012)	elite artistic gymnasts	8 (0%)	ND / 7.8%	Their normal training schedule and explosive strength training	30 days	Crossover	Skinfold measurement	CHO: 22 g Prt: 201 g Fat: 120 g Energy: 1973 kcal	CHO: 266 g Prt: 83 g Fat: 97 g Energy: 2275 kcal	Yes	↓	↓	↔
Rhyu and Cho (2014)	Taekwondo athletes	20 (0%)	21.2 / 11.9	1 h of low intensity dawn exercise; 2 h of morning RT; and 2 h of afternoon Taekwondo skills training	3 weeks	Parallel	BIA	CHO: 4.3% (≈22 g) Prt: 40.7% Fat: 55% Energy: 75% of daily mean calories	CHO: 40% Prt: 30% Fat: 30% Energy: 75% of daily mean calories	No	↔	↔	↔
Wilson et al. (2017)	Resistance-trained men	25 (0%)	ND / 17.1%	3 sessions/wk of progressive RT ranged from 65 to 95% of 1-RM	10 weeks	Parallel	DXA	CHO: 31 g Prt: 136 g Fat: 218 g Energy: 2631 kcal	CHO: 316 g Prt: 131 g Fat: 84 g Energy: 2539 kcal	No	↔	↔	↔
Gregory et al. (2017)	non-elite CrossFitter	27 (81%)	25.9 / 32.1%	CrossFit training	6 weeks	Parallel	DXA	CHO: 44 g Prt: 91 g Fat: 114 g Energy: 1580 kcal	CHO: 187 g Prt: 73 g Fat: 80 g Energy: 1746 kcal	Yes	↓	↓	↔
Greene et al. (2018)	intermediate to elite competitive lifting athletes	12 (42%)	ND / 17.5%	Subject's normal strength training	3 months	Crossover	DXA	CHO: 42 g Prt: 118 g Fat: 159 g Energy: 2072 kcal	CHO: 230 g Prt: 113 g Fat: 76 g Energy: 2058 kcal	Yes	↓	↔	↓
Kephart et al. (2018)	CrossFitter	12 (25%)	27.6 / 22.9%	Subject's normal CrossFit training	12 weeks	Parallel	DXA	CHO: 15 g Prt: 89 g Fat: 170 g Energy: 1948 kcal	ND	Yes	↓	↓	↔
Vargas et al. (2018)	Strength-trained men	19 (0%)	24.1 / 15.1%	4 sessions/wk (divided into a 2-	8 weeks	Parallel	DXA	CHO: <10% (≈42g) Prt: 20%	CHO: 55% Prt: 20% Fat: 25%	No	↔	↔	↓

(*continued*)

Table 1. Continued.

Study	Subjects	N (% female)	Obesity classification (BMI/BFP)	RT intervention	Duration	Parallel or crossover	Body analyzer method	Macronutrient ratio in KDs	Macronutrient ratio in non-KDs	Ad libitum (Yes / No)	Effects of KD on weight and/or BMI (compared to non-KD)	Effects of KD on FM and/or PBF (compared to non-KD)	Effects of KD on FFM and/or LBM (compared to non-KD)
				days upper- and 2-days lower-limb)				Fat: 70% Energy: ≈39 kcal/kg/d	Energy: ≈39 kcal/kg/d				
LaFountain et al. (2019)	Military personnel	29 (14%)	26.4 / 22.8%	2 sessions/wk and 60 min/session with the intensity of 60 to 95%	12 weeks	Parallel	DXA	CHO: <50 g Prt: 0.6-1.0 g/kg of LBM Fat: ND Energy: ND	CHO: ≈40% Prt: ND Fat: ND Energy: ND	Yes	↓	↓	↓
Vargas-Molina et al. (2020)	Strength-trained women	21 (100%)	23.7 / 29.5%	4 sessions/wk (divided into 2 4-week cycles)	8 weeks	Parallel	DXA	CHO: 39 g Prt: 115 g Fat: 122 g Energy: 1710 kcal	CHO: 282 g Prt: 97 g Fat: 51 g Energy: 1980 kcal	Yes	↓	↓	↓
Hadizadeh et al. (2020)	Untrained individuals	20 (ND)	23.8 / ND	3 sessions/wk and 60-90 min/session with the intensity of 8RM	8 weeks	Parallel	BIA	CHO: 5% Prt: 25% (2 g/kg) Fat: 70% Energy: 39 kcal/kg/day	CHO: 55% Prt: 25% (2 g/kg) Fat: 20% Energy: 39 kcal/kg/day	ND*	↓	↓	↔
Paoli et al. (2021)	Competitive natural body builders	19 (0%)	26.8 / ND	3-4 sessions/wk, volume and the intensity of the workouts were decided by each individual	2 months	Parallel	BIA (participants kept their own training routine)	CHO: <5% (<50 g) Prt: 2.5 g/kg Fat: 68% Energy: 45 kcal/kg/day	CHO: 55% Prt: 2.5 g/kg Fat: 20% Energy: 45 kcal/kg/day	No	↔	↔	↓

*macronutrient intake and dietary compliance was not reported in Hadizadeh et al. study.

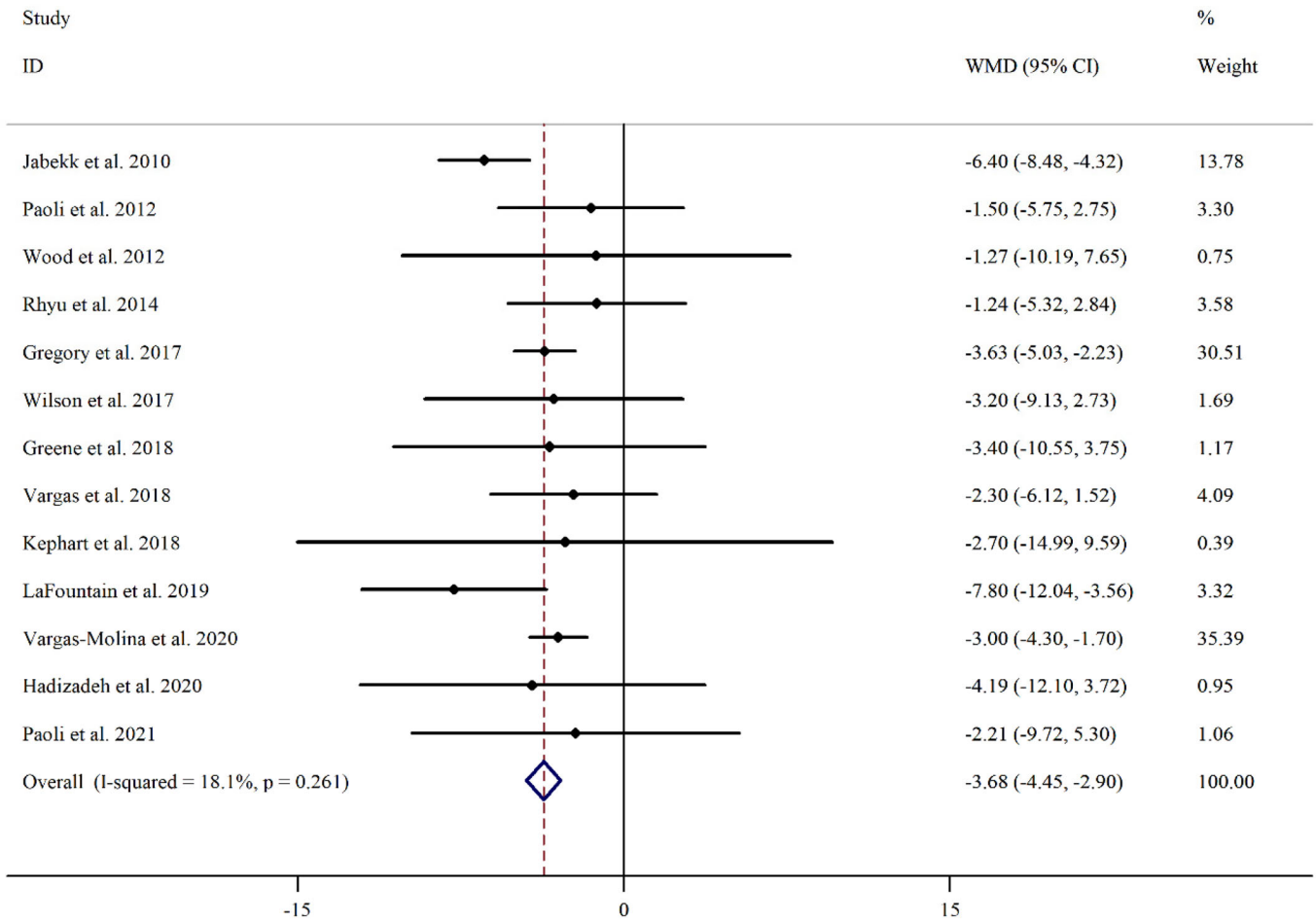

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ketogenic diet (KD) on body mass (BM).

et al. 2018; Gregory et al. 2017; Hadizadeh et al. 2020; Jabekk et al. 2010; Kephart et al. 2018; LaFountain et al. 2019; Paoli et al. 2021; Paoli et al. 2012; Rhyu and Cho 2014; Vargas-Molina et al. 2020; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012). Most of the included studies had a low risk of bias for incomplete outcome data (Greene et al. 2018; Gregory et al. 2017; Jabekk et al. 2010; Kephart et al. 2018; LaFountain et al. 2019; Paoli et al. 2012; Rhyu and Cho 2014; Vargas-Molina et al. 2020; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012), except for two studies (Hadizadeh et al. 2020; Paoli et al. 2021). All of the included studies had a high risk of bias for selective outcome reporting (Greene et al. 2018; Gregory et al. 2017; Hadizadeh et al. 2020; Jabekk et al. 2010; Kephart et al. 2018; LaFountain et al. 2019; Paoli et al. 2021; Paoli et al. 2012; Rhyu and Cho 2014; Vargas-Molina et al. 2020; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012). Details of the risk of bias assessment are described in supplementary file 1.

Meta-analysis

The results of analysis demonstrated that compared to controls (non-KD), KD had a significant effect on BM [(WMD = −3.67 kg; 95% CI: −4.44, −2.90, $p < 0.001$), (Figure 2)], FM [(WMD = −2.21 kg; 95% CI: −3.09, −1.34, $p < 0.001$)], (Figure 3)], FFM [(WMD = −1.26 kg; 95% CI: −1.82, −0.70, $p < 0.001$), (Figure 4)], BMI [(WMD = $-1.37\ kg.m^{-2}$; 95% CI: −2.14, −0.59, $p = 0.022$), (Figure 5)], and BFP [(WMD = −2.27%; 95% CI: −3.63, −0.90, $p = 0.001$), (Figure 6)]. Although between-study heterogeneity was significant for FM ($p = 0.002$, $I^2 = 62.4\%$), BMI ($p = 0.022$, $I^2 = 68.9\%$), and BFP ($p = 0.001$, $I^2 = 79.8\%$), no significant heterogeneity was detected for BM ($p = 0.261$, $I^2 = 18.1\%$) and FFM ($p = 0.214$, $I^2 = 22.7\%$). To find the probable source of heterogeneity, subgroup analysis was conducted based on baseline BMI (25–29.9 vs. $30\ kg.m^{-2} \leq$), trial duration (≤8 vs. >8 weeks) and carbohydrate content of the KD (≥30 vs. <30 g). Subgroup analysis showed that KD intervention had significant effect on BM, BMI, FFM, BFP, and FM in all of the subgroups. However, it was found that KD had no significant effect on FFM in overweight participants (Table 2).

Publication bias

Based on Egger's regression test, there was no evidence of publication bias for studies examining the effect of KDs on BM ($p = 0.798$), BMI ($p = 0.916$), FM ($p = 0.575$), BFP ($p = 0.702$) and FFM ($p = 0.215$). The visually inspected funnel plot test also confirmed this point (Supplementary material 2).

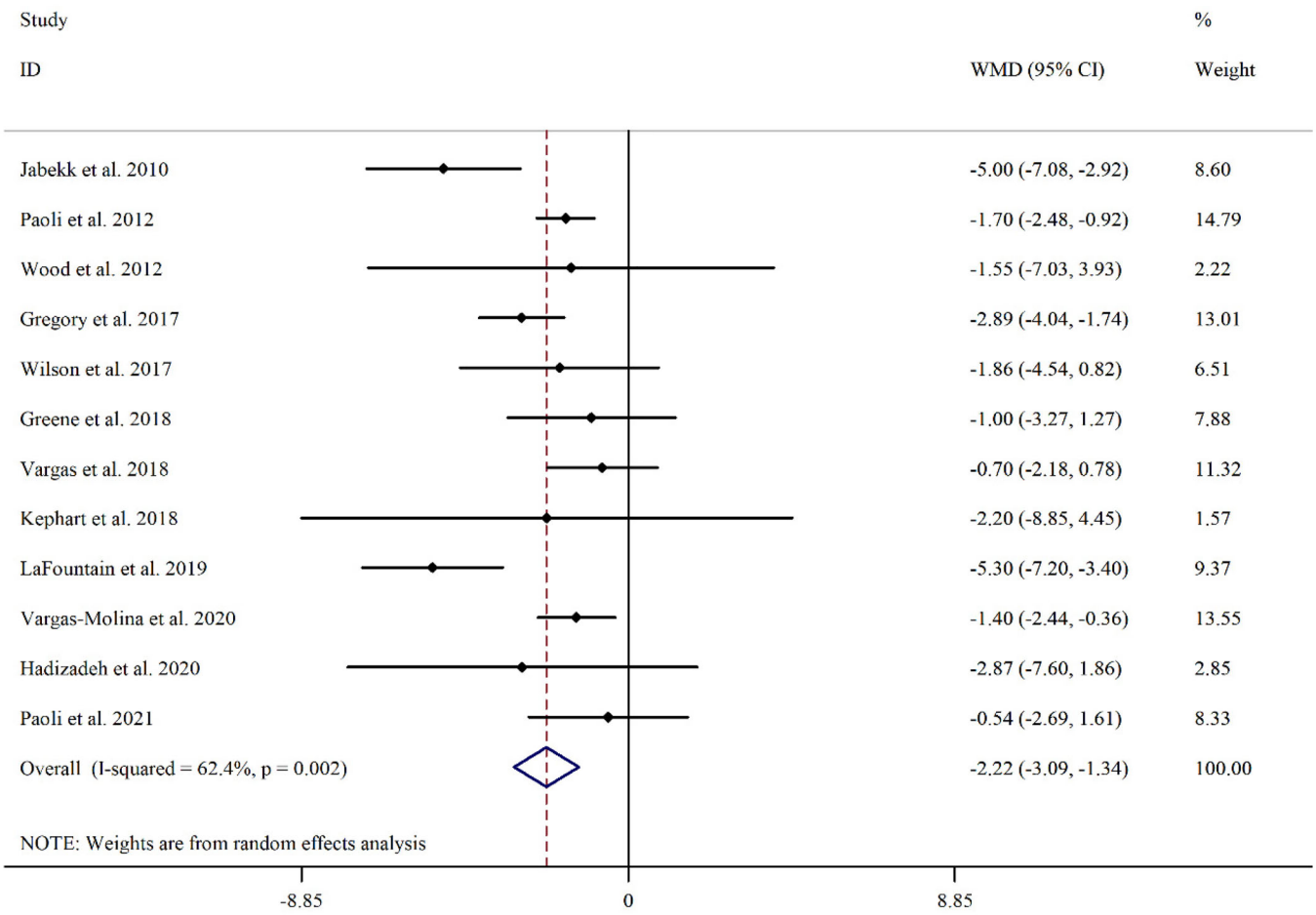

Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ketogenic diet (KD) on fat mass (FM).

Sensitivity analysis

There were no significant effects of any individual effect size on the overall effect sizes of all parameters.

Discussion

In this meta-analysis, we evaluated the effects of KDs on body composition in individuals participating in RT. According to the results derived from this study, a combination of RT with KD was associated with declines in all body composition parameters including BM, BMI, FM, BFP, and FFM. Meanwhile, subgroup analyses based on the duration of interventions ($\leq$8 and $>$ 8 weeks), the carbohydrate content of the KD ($\geq$30 and $<$30 g/d), and baseline BMI (18.5–24.9, 25–29.9, and $>$30 kg.m^{-2}) demonstrated that KDs showed statistically similar results across these subgroups. However, BM, FM, and FFM tended to decrease more following longer interventions ($>$ 8 weeks) and in participants with obesity (BMI $>$30 kg.m^{-2}) (Table 2).

Our results of reduced BM and BMI are similar to the findings of the previous meta-analytic and meta-regressive work on non-exercising populations (Bueno et al. 2013; Krieger et al. 2006). One meta-analysis indicated that KD produces slightly greater BM loss as compared to non-KD (WMD: 0.91 kg; 95% CI: 0.17–1.65 kg) over durations of 12–24 months (Bueno et al. 2013). Several putative explanations for greater BM loss with KD have previously been discussed. Importantly, differences in stored glycogen and the associated water content could influence BM results, along with other body composition outcomes, when comparing KD and non-KD regimens (Tinsley and Willoughby 2016). Nonetheless, it has been hypothesized that the beneficial effect of a KD on BM may be due to the preservation of resting energy expenditure (Bueno et al. 2013). For instance, Ebbeling et al. found that a KD had more beneficial effects on energy expenditure compared to an LFD (Ebbeling et al. 2012). However, other data have indicated that any increases in energy expenditure with KD are small and likely inconsequential (Hall et al. 2016; Hall 2019). Alternatively, Westman et al. (Westman et al. 2007) hypothesized that a KD reduces insulin concentrations, which would explain the satietogenic effects of this type of diet and potentially lead to reduced ad libitum energy intake. Consistent with contemporary energy balance concepts (Hall et al. 2016), our results illustrated that although KD resulted in more BM and FM loss, significant changes occurred only in ad libitum studies (Greene et al. 2018; Gregory et al. 2017; Jabekk et al. 2010; Kephart et al. 2018; LaFountain et al. 2019; Paoli et al. 2012; Vargas-Molina et al. 2020) but not in isocaloric studies (Paoli et al. 2021; Rhyu and Cho 2014; Vargas et al. 2018; Wilson et al. 2017; Wood et al. 2012) (Table 1). In ad libitum settings, physiological ketosis elicited by KDs may result in suppressing appetite (Gibson et al. 2015) and a resultant

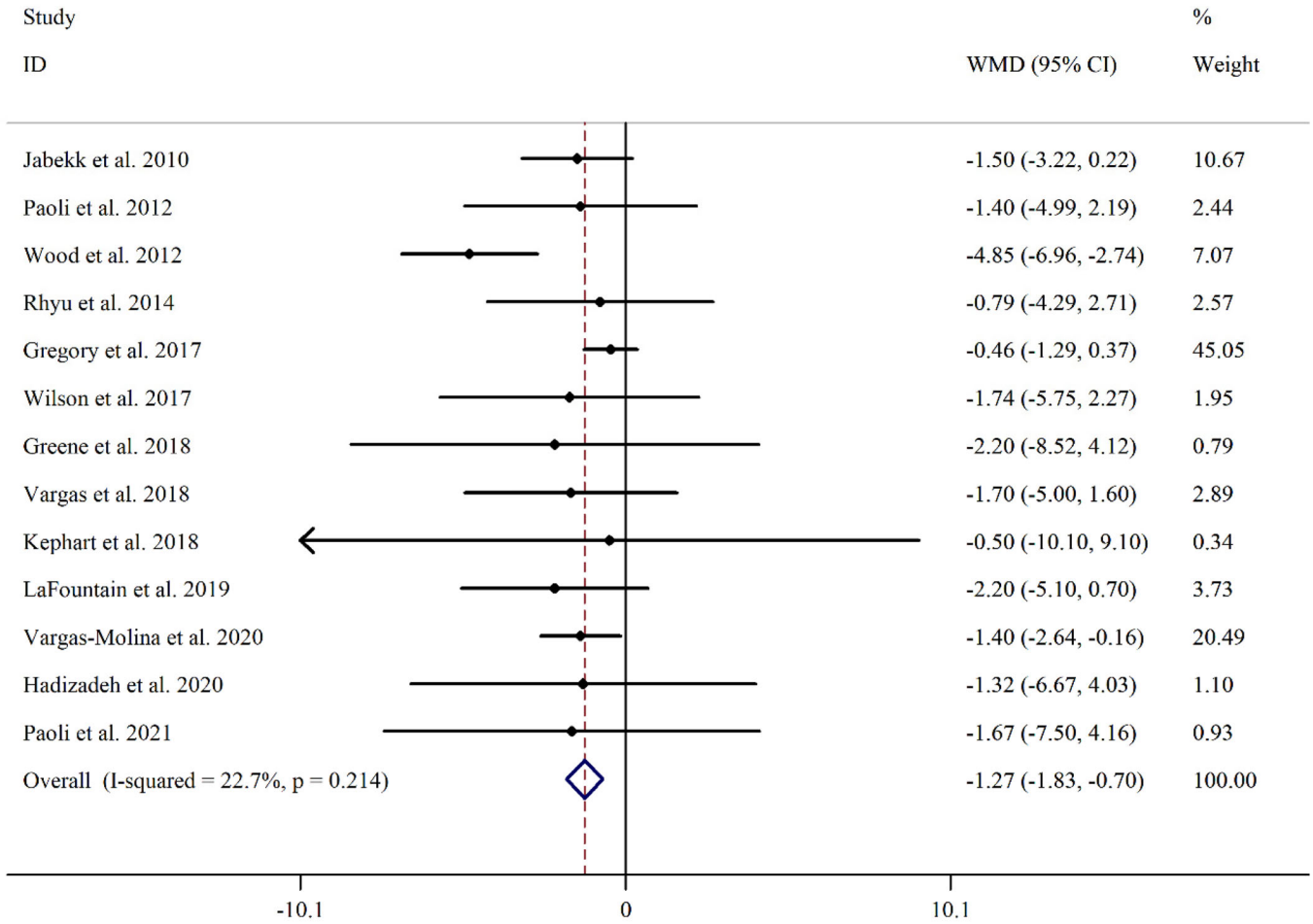

Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ketogenic diet (KD) on fat-free mass (FFM).

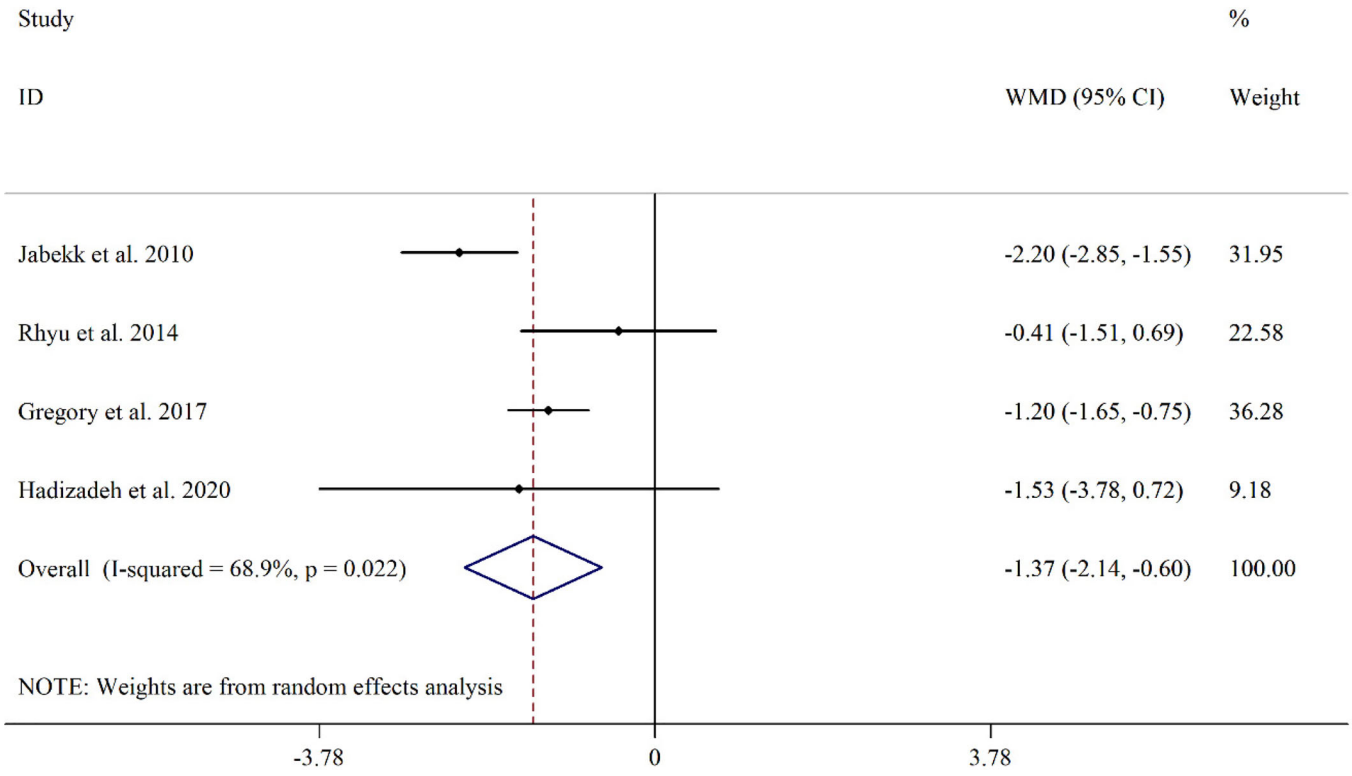

Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ketogenic diet (KD) on body mass index (BMI).

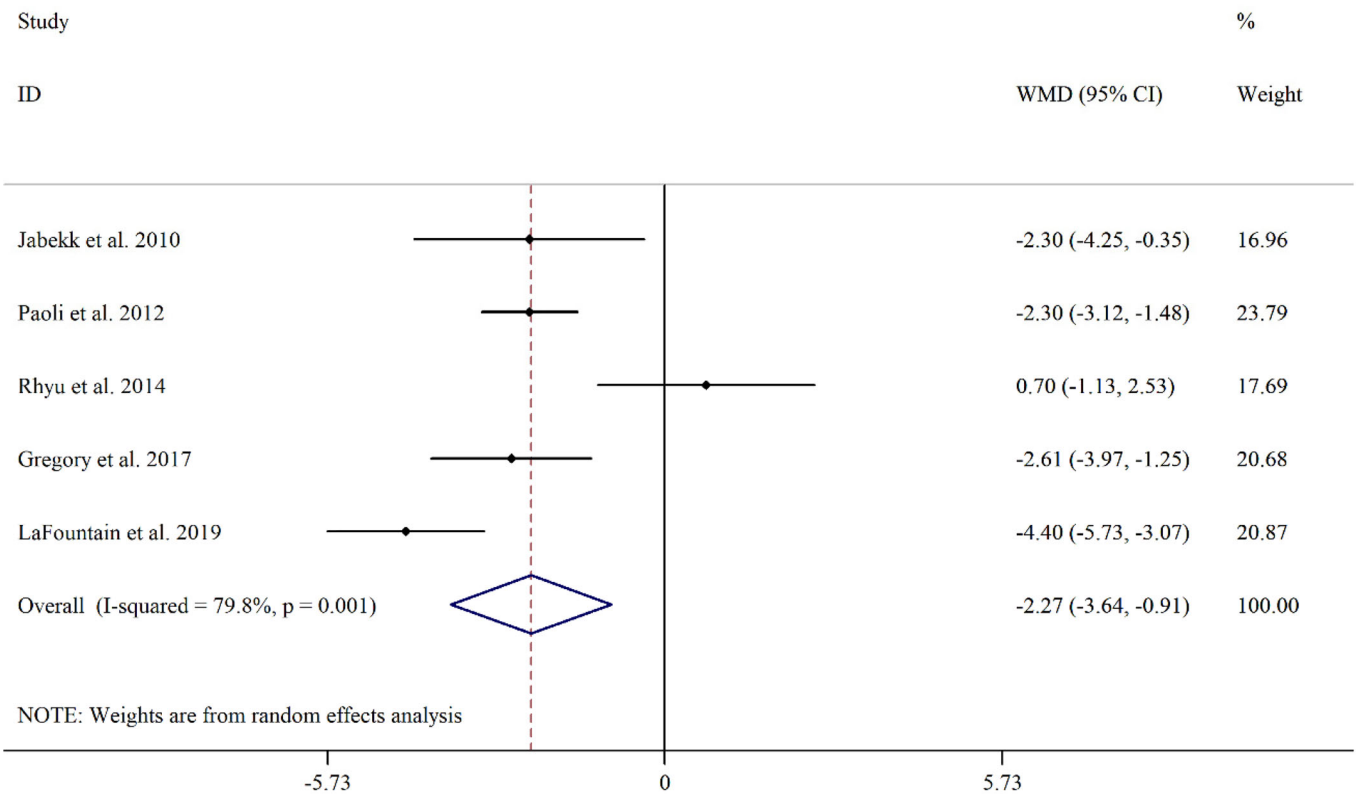

Figure 6. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of ketogenic diet (KD) on body fat percentage (BFP).

decrease in daily calorie intake. It has been previously demonstrated that both KDs and non-KDs have similar effects on BM and FM loss when calorie intake decreased the same amount (Dansinger et al. 2005; Hall et al. 2016). Consequently, greater BM loss observed following KDs in the present analysis could likely be due to lower calorie intake. Therefore, the metabolic advantage and hyperinsulinaemic effects of the KD (i.e., the carbohydrate-insulin model of obesity) that claims diets rich in carbohydrates are particularly fattening due to their propensity to elevate insulin secretion, which was not evidenced in these included studies. Nonetheless, for those able to adhere to this regimen, the results of the present analysis indicate that the KD is a viable option for enhancing BM and FM loss in ad libitum settings.

Some additional possible mechanisms are underlying the apparent advantageous effects of KDs compared to non-KD on BM loss. Initial BM loss in participants adhering to a KD may be due to metabolic alterations and body fluid shifts. For example, it appears that initial BM loss can be partially attributed to diuresis due to ketone body excretion (ketonuria), which increases renal sodium and hence urinary water loss (McPherson and McEneny 2012). In addition, glycogenolysis, which is a prominent feature of the early stage of a KD, is associated with concomitant water release as ~3 g of water are stored for every 1 g of glycogen (Denke 2001; Fernández-Elías et al. 2015; Tinsley and Willoughby 2016). However, subsequent BM loss is more likely attributable to FM loss due to restrictive food choices, increased satiety-derived-effects of dietary protein intake (Westerterp-Plantenga et al. 2009), and an increase in the concentrations of b-hydroxybutyrate, (i.e. a ketogenic state), which may contribute to the increased appetite suppression (Veldhorst et al. 2010). Previous studies have suggested that calorie-for-calorie, protein is more satiating than either carbohydrates or fats (Barkeling, Rössner, and Björvell 1990; Stubbs, Johnstone, and Harbron 1996), and it could be suggested that the higher protein intake in the KD played a role in limiting food intake. Therefore, it can be tentatively concluded that KDs may have a corresponding effect of inducing a negative energy balance in ad libitum settings (Gibson et al. 2015). A well-designed randomized crossover study demonstrated that high-protein, low-carbohydrate KDs reduce hunger and lower food intake significantly more than high-protein, medium-carbohydrate non-KDs (Johnstone et al. 2008), suggesting that reduced carbohydrate content between the two high-protein diets resulted in an energy intake decrease of 0.7 MJ/d (294 kcal/d). These findings support the “calories in, calories out" hypothesis, which states BM loss is not primarily determined by varying proportions of carbohydrate and fat in the diet per se, but instead by the number of calories ingested, while also providing evidence that manipulating the macronutrient content of the diet can influence ad libitum energy intake (Howell and Kones 2017). Other data have indicated more beneficial effects of prescribed KD regimens for fat loss over six months, as compared to an LFD (Brehm et al. 2003).

In contrast to reports of longer-term implementation of KD in the general population, there is no scientific evidence on the effects of long-term KD on body composition changes in resistance-trained populations. Indeed, all studies included in our analysis were short-term (three weeks to

Table 2. Subgroup analysis of ketogenic diet on anthropometric measures. Abbreviations: CI, confidence interval; KD, ketogenic diet; WMD, weighted mean differences; BM, body mass; FM, fat mass; FFM, fat free mass; BMI, body mass index; BFP, body fat percentage.

	NO	WMD (95%CI)	P within group	P heterogeneity	I^2
Subgroup analyses of KD on BM					
Overall effect	13	−3.67 (−4.44, −2.90)	**<0.001**	0.261	18.1%
Baseline BMI (kg/m^2)					
18.5–24.9	4	−2.81 (−3.98, −1.65)	**<0.001**	0.841	0.0%
25–29.9	3	−3.98 (−5.29, −2.67)	**<0.001**	0.167	44.0%
>30	2	−6.13 (−8.16, −4.11)	**<0.001**	0.272	17.0%
Trial duration (week)					
≤8	7	−3.06 (−3.93, −2.19)	**<0.001**	0.899	0.0%
>8	6	−5.94 (−7.62, −4.26)	**<0.001**	0.616	0.0%
Carbohydrate count (gram)					
≥30	6	−3.41 (−4.30, −2.52)	**<0.001**	0.399	2.8%
<30	7	−4.45 (−6.10, −2.90)	**<0.001**	0.224	26.9%
Subgroup analyses of KD on FM					
Overall effect	12	−2.21 (−3.09, −1.34)	**<0.001**	0.002	62.4%
Baseline BMI (kg/m^2)					
18.5–24.9	3	−1.22 (−2.06, −0.38)	**0.004**	0.591	0.0%
25–29.9	3	−2.95 (−5.23, −0.67)	**0.011**	0.005	81.3%
>30	2	−4.24 (−7.04, −1.44)	**0.003**	0.249	24.9%
Trial duration (week)					
≤8	6	−1.65 (−2.33, −0.98)	**<0.001**	0.185	33.5%
>8	6	−3.18 (−5.00, −2.36)	**0.001**	0.0331	58.9%
Carbohydrate count (gram)					
≥30	6	−2.19 (−3.53, −0.85)	**0.001**	0.002	52.0%
<30	6	−2.26 (−3.65, −0.88)	**0.001**	0.064	73.4%
Subgroup analyses of KD on FFM					
Overall effect	13	−1.26 (−1.82, −0.70)	**<0.001**	0.214	22.7%
Baseline BMI (kg/m^2)					
18.5–24.9	4	−1.37 (−2.44, −0.29)	**0.014**	0.986	0.0%
25–29.9	3	−0.61 (−1.40, 0.18)	0.131	0.495	0.0%
>30	2	−2.83 (−4.16, −1.50)	**<0.001**	0.016	82.9%
Trial duration (week)					
≤8	7	−0.83 (−1.47, −0.18)	**0.012**	0.915	0.0%
>8	6	−2.59 (−3.73, −1.46)	**<0.001**	0.269	21.9%
Carbohydrate count (gram)					
≥30	6	−1.23 (−1.85, −0.60)	**<0.001**	0.009	67.2%
<30	7	−1.40 (−2.65, −0.14)	**0.028**	1.000	0.0%
Subgroup analyses of KD on BMI					
Overall effect	4	−1.37 (−2.14, −0.59)	**0.001**	0.022	68.9%
Subgroup analyses of KD on BFP					
Overall effect	5	−2.27 (−3.63, −0.90)	**0.001**	0.001	79.8%

three months). Similar to BM loss, a significant difference in FM was observed only in libitum studies. Therefore, it seems that even in short-term interventions, the fat loss benefit of KDs is related to calorie intake reduction. These findings suggest that in resistance-trained athletes, when calorie intake is equal, KDs do not have more beneficial effects on fat loss.

One concern of KDs is the potential loss of FFM. It seems that in an untrained population, the amount of FFM loss is slightly higher following KDs compared to non-KD (Brehm et al. 2005; Noakes et al. 2006; Tinsley and Willoughby 2016). In our analysis of resistance-trained populations, FFM decreased significantly in individuals assigned to a KD as compared to non-KD. This catabolic or anti-anabolic effect of KDs might be attributable to the mechanistic target of rapamycin (mTOR) signaling pathway inhibition (McDaniel et al. 2011). Animal and human studies have also shown that AMPK is altered following KD interventions. In rodents, a KD has increased AMPK activity in skeletal muscle and AMPK phosphorylation in the liver. Additionally, a low-carbohydrate diet supplemented with ketone esters increased AMPK content in brown adipose (Kennedy et al. 2007; McDaniel et al. 2011; Srivastava et al. 2012). In humans, a non-ketogenic, low-carbohydrate diet (comprised of 50% fat, 30% carbohydrates, and 20% protein) increased AMPK phosphorylation in skeletal muscle (Draznin et al. 2012). Increased AMPK activation inhibits mTOR signaling, which is an important factor involved in regulating muscle mass gains (Sandri et al. 2013).

Positive effects of carbohydrate intake on net muscle protein balance could be another possible mechanism of higher FFM loss in KDs. Although it is reported that carbohydrates may not significantly affect MPS (Churchward-Venne, Burd, and Phillips 2012), some previous studies have shown that carbohydrate consumption can improve net muscle protein balance by reducing muscle protein breakdown (MPB) (Børsheim et al. 2004; Roy et al. 1997); an effect that may be mediated by insulin (Biolo et al. 1999; Gelfand and Barrett 1987; Greenhaff et al. 2008). However, it seems that the anti-catabolic of carbohydrate is small compared to protein or protein plus carbohydrate intake (Børsheim et al. 2002; Miller et al. 2003; Rasmussen et al. 2000; Roy et al. 1997; Tipton et al. 1999; Tipton et al. 2001).

It is well established that increasing dietary protein intake alongside an exercise intervention, especially RT, attenuates the BM loss-induced reduction in muscle mass (Mettler, Mitchell, and Tipton 2010; Verreijen et al. 2015; Weiss et al. 2007). In most studies included in our analysis, participants

adhering to a KD consumed significantly higher dietary protein than those adhering to non-KD. Nonetheless, based on our findings, KDs produced greater FFM loss in resistance-trained individuals compared to a non-KD, indicating that the higher protein intake of the KD was insufficient to preserve FFM despite concurrent RT. While it is important to note that FFM and skeletal muscle are distinct but overlapping entities, KDs may result in a significant loss of muscle mass as the body recruits amino acids (through de-amination or transamination) from skeletal muscle protein to maintain blood glucose via gluconeogenesis. Carbohydrate restriction leads to decreases in blood glucose, and it is possible that increased gluconeogenic activity could promote MPB to provide an amino acid substrate. Therefore, the primary source for a substrate for gluconeogenesis is the amino acid pools with some help from glycerol from adipose tissue triglycerides (Fromentin et al. 2013). Using amino acids through gluconeogenesis can be the reason for the increase in amino acids released from muscle tissue, resulting in skeletal muscle mass decrements (Pozefsky et al. 1976). Regarding the importance of carbohydrate intake for muscle mass preservation in individuals participating in an RT program, it has been shown that non-ketogenic hypocaloric diets (1250 calories= 55–60% carbs, 20–25% protein) combined with RT have led to FFM preservation (Figueroa et al. 2013a; Figueroa et al. 2013b), which might be related to a lesser degree of amino acid used for gluconeogenesis, because of higher carbohydrate intake. While high protein diets may generally be beneficial for FFM preservation (Haghighat et al. 2020) and participants adhering to KDs typically consumed more protein, this was ultimately insufficient for attenuating FFM loss, likely resulting from amino acid used for gluconeogenesis. Further long-term intervention studies with a higher amount of daily protein intake and optimally designed RT programs may be needed to allow for additional evaluation of changes in FFM following KDs compared to non-KDs. Additionally, more direct estimates of skeletal muscle size should be employed alongside whole-body FFM estimation.

Our results should be interpreted in the context of the following limitations. First, since all RCTs lasted less than three months, our analysis is unable to show the long-term differences in KDs and non-KDs on body composition in resistance-trained athletes. Moreover, included studies utilized varying body composition assessment methods, and some provide different estimates of nonfat tissue (i.e. lean body mass and FFM terms), which are often used interchangeably despite theoretical differences (Prado, Heymsfield, and Nutrition 2014). There are additional limitations of the studies included in the present analysis, including difficulty in establishing isocaloric diets in free-living conditions and lack of RT supervision or standardization in several investigations. Furthermore, significant heterogeneity was encountered, perhaps due to various populations enrolled. The included studies were performed in various types of participants, such as elite and amateur athletes in different sports and untrained individuals. This is a notable limitation and should be considered as it may significantly undermine the validity of results. Finally, it should be mentioned that a higher BM loss could result in great FFM decrements (Saris 2001), which could potentially explain the higher FFM loss after KDs in our analysis.

In conclusion, KDs lead to a loss of BM, BMI, FM, FFM, and BFP in RT cohorts. Additional longer-term and high-quality RCTs are needed to further evaluate and confirm these findings. As higher protein intake can exert favorable effects on FFM (Haghighat et al. 2020), further research employing KDs with higher protein intakes than observed in the present analysis may help determine whether FFM can be adequately preserved or increased in resistance-trained individuals. Moreover, future investigations should focus on optimizing external RT variables, such as load and rest periods, to create a greater hypertrophic stimulus and, therefore, potentially reduce the loss of FFM during KDs in resistance-trained individuals. Future research should also employ more direct estimates of skeletal muscle size to further clarify the effects of KDs on this important body component.

Disclosure statement

The authors declare no conflict of interest.

Funding

This work received no specific external funding.

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