

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Cao, Jingguo; Lei, Siman; Wang, Xiuqiang; Cheng, Sulin

Title: The Effect of a Ketogenic Low-Carbohydrate, High-Fat Diet on Aerobic Capacity and Exercise Performance in Endurance Athletes : A Systematic Review and Meta-Analysis

Year: 2021

Version: Published version

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland.

Rights: CC BY 4.0



Rights url: <https://creativecommons.org/licenses/by/4.0/>

Please cite the original version:

Cao, J., Lei, S., Wang, X., & Cheng, S. (2021). The Effect of a Ketogenic Low-Carbohydrate, High-Fat Diet on Aerobic Capacity and Exercise Performance in Endurance Athletes : A Systematic Review and Meta-Analysis. *Nutrients*, 13(8), Article 2896. <https://doi.org/10.3390/nu13082896>

Review

The Effect of a Ketogenic Low-Carbohydrate, High-Fat Diet on Aerobic Capacity and Exercise Performance in Endurance Athletes: A Systematic Review and Meta-Analysis

Jingguo Cao ¹, Siman Lei ^{1,2}, Xiuqiang Wang ^{1,3,*} and Sulin Cheng ^{1,3,4}

¹ Exercise, Health and Technology Centre, Department of Physical Education, Shanghai Jiao Tong University, Shanghai 200240, China; 370321199703212716@sjtu.edu.cn (J.C.); alicelei@um.edu.mo (S.L.); sulin.cheng@jyu.fi (S.C.)

² Faculty of Education, University of Macau, Macau SAR, China

³ Exercise Translational Medicine Centre, Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai 200240, China

⁴ Faculty of Sport and Health Science, University of Jyväskylä, 40014 Jyväskylä, Finland

* Correspondence: wangxiuqiang@sjtu.edu.cn

Abstract: A low-carbohydrate, high-fat (LCHF) diet has been proposed to enhance the fat utilization of muscle and the aerobic capacity of endurance athletes, thereby improving their exercise performance. However, it remains uncertain how the macronutrient intake shift from carbohydrate to fat affects endurance exercise training and performance. This study performed a systematic review and meta-analysis to explore the effects of a ketogenic low-carbohydrate, high-fat (K-LCHF) diet on aerobic capacity and exercise performance among endurance athletes. Searches were carried out in five electronic databases, and we followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The search included studies using an LCHF diet as an intervention protocol and compared data on factors such as maximum oxygen uptake ($VO_2\max$) and rating of perceived exertion (RPE) from the graded exercise test. In this case, 10 studies met the criteria and were included in the meta-analysis. We did not find a significant effect of K-LCHF diet interventions on $VO_2\max$, time to exhaustion, HRmax or RPE. However, a significant overall effect in the substrate oxidation response to respiratory exchange rate was observed. The meta-analysis showed that K-LCHF diets did not affect aerobic capacity and exercise performance. Therefore, high-quality interventions of a K-LCHF diet are needed to illustrate its effect on various endurance training programs.

Keywords: ketogenic low-carbohydrate; high-fat diet; aerobic capacity; endurance athletes



check for updates

Citation: Cao, J.; Lei, S.; Wang, X.; Cheng, S. The Effect of a Ketogenic Low-Carbohydrate, High-Fat Diet on Aerobic Capacity and Exercise Performance in Endurance Athletes: A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 2896. <https://doi.org/10.3390/nu13082896>

Academic Editor: Jill Parnell

Received: 17 May 2021

Accepted: 19 August 2021

Published: 23 August 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The low-carbohydrate, high-fat (LCHF) diet has become popular as a treatment for excess weight, epilepsy and type 2 diabetes in recent decades [1–3]. The first LCHF diet study to optimize fat oxidation in endurance athletes was conducted in 1983 by Phinney et al. [4]. He spotlighted various mechanisms to boost endurance performance by promoting a shift in substrate utilization to enhance physiological training benefits by adopting the LCHF diet. However, the concept of improving athletic performance by adapting to a high-fat diet was reconsidered after a series of studies failed to prove significant benefits [5]. As a result, the pace of research in this area has slowed significantly. However, with the resurgence in popularity of “Paleolithic” and “ketogenic” diets, there has been renewed interest in the LCHF diet [6].

Limiting carbohydrate (CHO) consumption can reduce the muscle glycogen concentration, resulting in greater fat oxidation [7,8]. After adapting to the LCHF diet, the body uses more fat for energy, and fat stores are far more abundant than CHO, thus theoretically providing energy for a longer period [9]. A ketogenic LCHF (K-LCHF) diet may

influence the adaptation of the body through the molecular mechanism of regulating cell signal transduction [10–13]. In addition, this signaling pathway's activation may lead to increased physical and motor ability through, for example, mitochondrial biogenesis, capillary thinning and regeneration processes, especially the efficient utilization of fat energy substrates [14–16]. Of note, in the study on adopting ketogenic diets in mice, they found that long-term ketogenic diet might decreased mitochondrial biogenesis, impaired cellular respiration and increased myocardial apoptosis and myocardial fibrosis [17]. The energy obtained from fat under aerobic conditions produces acetoacetic acid, β -hydroxybutyric acid (β -HB) and acetone, of which β -HB accounts for about 70% of the ketone body, which serves as a stable energy source for the body and brain [17,18].

The review by Hawley et al. was the first to summarize the effect of the LCHF diet on exercise performance and metabolism. He found that long-term (>7-day) use of the LCHF diet extended endurance for a fixed, sub-maximum workload in well-trained athletes [19]. One study from Burke examined the LCHF diet's acute effect and found that it took just five days for muscles to adapt [20]. The metabolic adaptations needed for the full benefit produced from adaptation to LCHF diets are suggested by the long time it takes to lower the rate of carbohydrate oxidation and glycogen utilization [21]. However, LCHF diets have been shown to have mixed results [22], with some studies reporting positive effects [23,24], while other studies finding that prolonged adaptation might not change performance [25,26]. A relatively long period on the LCHF diet did not affect performance in endurance exercise and resistance training [27,28]. In addition, individuals might have different adaptation processes to the LCHF diet [29]. Studies have suggested that, beyond diet duration, other variables may influence the effect of the LCHF diet on exercise performance (e.g., training status, performance test type, intensity and sex differences [30]).

The ketogenic diet is a special case of an LCHF diet. Some studies have suggested that LCHF diets with CHOs accounting for less than 5% [31] or between 5% and 10% [32] of total energy intake belong to the ketogenic diet. Furthermore, it is proposed that diets with less than 10% CHOs can induce ketosis [33]. As there is overlap in the definitions of the LCHF and ketogenic diets, most studies use the term "LCHF", some use the term "keto" and some use "K-LCHF", even though the content of these diets are similar. In this study, we use K-LCHF [30] to indicate the diet intervention.

Recent studies on the K-LCHF diet have not systematically analyzed the effects of the K-LCHF diet on endurance performance and related indicators. The effects of the K-LCHF diet on athletes during endurance exercise are controversial. Hence, the objective of this systematic review and meta-analysis was to aggregate the results from experimental data to investigate the overall effects of the K-LCHF diet on aerobic capacity and exercise performance in endurance athletes.

2. Materials and Methods

2.1. Literature Search

By following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines, we systematically searched online databases for studies published until April 2021. The study protocol was registered in the international database of prospectively registered systematic reviews in health and social care (PROSPERO: 226008). The literature search identified full-text articles published in peer-reviewed scientific journals in English from five online databases: Ovid Web of Science, PubMed, Science Direct, ProQuest and Cochrane library. The search strategy (Table S2) was conducted independently by two authors (J.C. and S.L.). When conflicting opinions arose, the eligibility of the studies was discussed with the other authors (S.C and X.W.) until an agreement was reached. The search strategy and keywords/terms included "low-carbohydrate high-fat diet" or "ketogenic diet" and "aerobic capacity" or "athlete" or "VO₂max" or "exercise" or "training". Additional studies were retrieved by examining the reference lists of the relevant articles.

Reference lists from previous relevant reviews and included studies were further examined as complementary sources.

2.2. Inclusion and Exclusion Criteria

The screening process was divided into two phases: a preliminary selection by title and abstract only, and a second phase of screening the full text of the remaining articles. Articles that met the following criteria were included: (1) randomized controlled intervention trial or controlled intervention trial or crossover trial in endurance athletes (including professional athletes and individuals who participated in endurance exercise as their hobby); (2) a LCHF diet with less than 10% CHOs is considered a K-LCHF diet [31,32]; (3) comparison of the effects of the K-LCHF diet with those of the non-LCHF diet; (4) performed graded exercise test (GXT); (5) reported daily nutrition intake based on food diaries or recalls; (5) endurance training was defined as long-duration continuous sustain moderate or submaximal intensity exercise of 5 min to 4 h [34,35].

The exclusion criteria included (1) systematic reviews or meta-analyses, (2) observational studies, (3) no appropriate control group and (4) non-endurance athletes.

2.3. Data Extraction

Data extracted from the studies included number of subjects, age, gender, study design, intervention duration, dietary components, energy intake, type of exercise, maximal oxygen uptake ($VO_2\max$), time to exhaustion (TTE), maximal heart rate during exercise (HRmax), respiratory exchange rate (RER) and rating of perceived exertion (RPE). The authors, publication year, study design, outcome variables, testing protocol for outcomes, participant characteristics and exercise protocol were extracted and are summarized in Table 1. Baseline and post-intervention outcome variables were taken from all intervention and control groups as the mean and standard deviation (SD), as recommended by the *Cochrane Collaboration Handbook* [36]. If the mean or SD was reported in the original article, the established methods were used [36,37]; otherwise, the original data were obtained by contacting the study authors directly.

$VO_2\max$ indicates the aerobic capacity, the $VO_2\max$ test [38] refers to the aerobic capacity measurement, and TTE represents the endurance exercise performance [39] in a laboratory environment.

2.4. Risk of Bias and Quality Assessment

Two of the authors (J.C. and S.L.) assessed the risk of bias using Review Manager software (RevMan, version 5.4, Cochrane Collaboration, Oxford, UK), which is summarized as a risk of bias in Figure 1. The validity of the studies was assessed using the Cochrane Collaboration risk-of-bias tool. This tool includes the following items: "Random sequence generation (selection bias)", "Concealment of the allocation sequence (selection bias)", "Blinding of participants and personnel (performance bias)", "Blinding of outcome assessment (detection bias)", "Incomplete outcome data (attrition bias)", "Selective outcome reporting (reporting bias)" and "Other biases", which were assigned as "low risk of bias", "unclear risk of bias" or "high risk of bias".

The quality of the included articles was evaluated using the Assessment of Multiple Systematic Review (AMSTAR) measurement tool [40] and is presented in Table S1. This tool has 11 items (i.e., "A priori design", "Duplicate selection and data extraction", "Comprehensive search", "Gray literature search", "List of included and excluded studies", "Characteristics of studies", "Scientific quality assessed", "Scientific quality in conclusions", "Methods to combine studies", "Publication bias assessment" and "Conflict of interest") with four subscales (i.e., "yes", "no", "can't answer" or "not applicable").

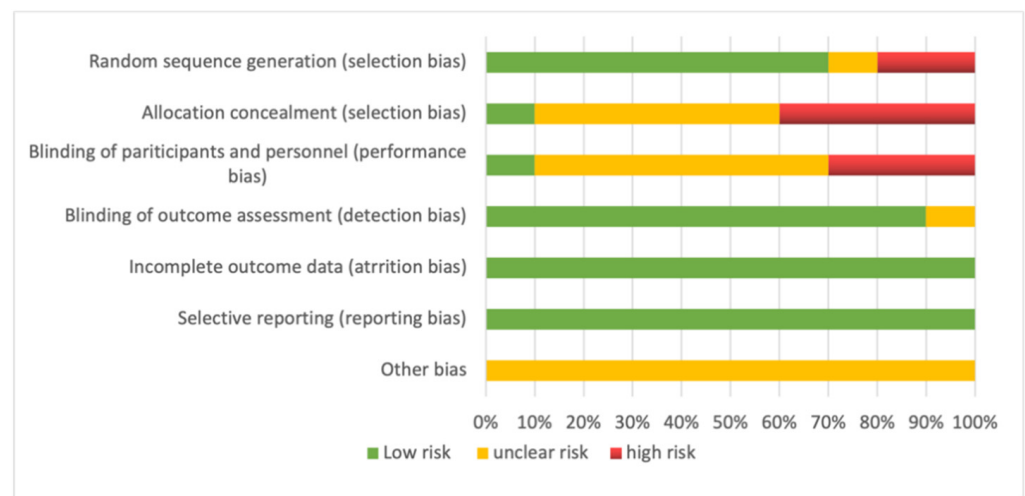


Figure 1. Risk of bias included studies in meta-analysis.

2.5. Statistical Analysis

The outcome data were extracted from the GXT and expressed as mean \pm SD. The meta-analysis was conducted using Review Manager software (RevMan, version 5.4). For each study, the standardized mean difference (SMD) with 95% confidence intervals (95% CI) was calculated to quantify changes in the performance variables, in which the mean or mean difference and corresponding SD were extracted from the pre- and post-intervention exercise tests and converted to the same unit. The effect of the K-LCHF diet on aerobic capacity and exercise performance was tested by inverse variance and a random effects model. The mean differences and 95% CI between studies were obtained through productive forest plots. SMD is the difference between the mean of the experiment group and the mean of the control group divided by the mean standard deviation, eliminating the effect of the “unit” so that the mean differences of different dimensions can be combined. SMD = 0 represents no difference, SMD > 0 represents more occurrence in the experimental group and SMD < 0 represents less occurrence in the experimental group. I^2 statistics evaluated heterogeneity, with I^2 values of 25%, 50% and 75% indicating low, medium and high heterogeneity, respectively. $I^2 > 50\%$ indicated high heterogeneity between studies.

3. Results

3.1. Synopsis of Included Studies

Of a total of 3946 non-duplicate studies, 3789 records were excluded by title and abstract inspection. The remaining 157 studies were assessed with full text, and 25 studies that met the inclusion criteria were selected. A further exclusion assessment was performed to remove the studies with no measurement of VO_{2max} ($n = 8$), case-study design ($n = 1$), an inconsistent unit of VO_{2max} ($n = 4$), use of a ketone ester supplement ($n = 1$) and having only an intervention arm ($n = 1$) (Figure 2). Finally, 10 articles were eligible for this report, including four crossover and six control studies.

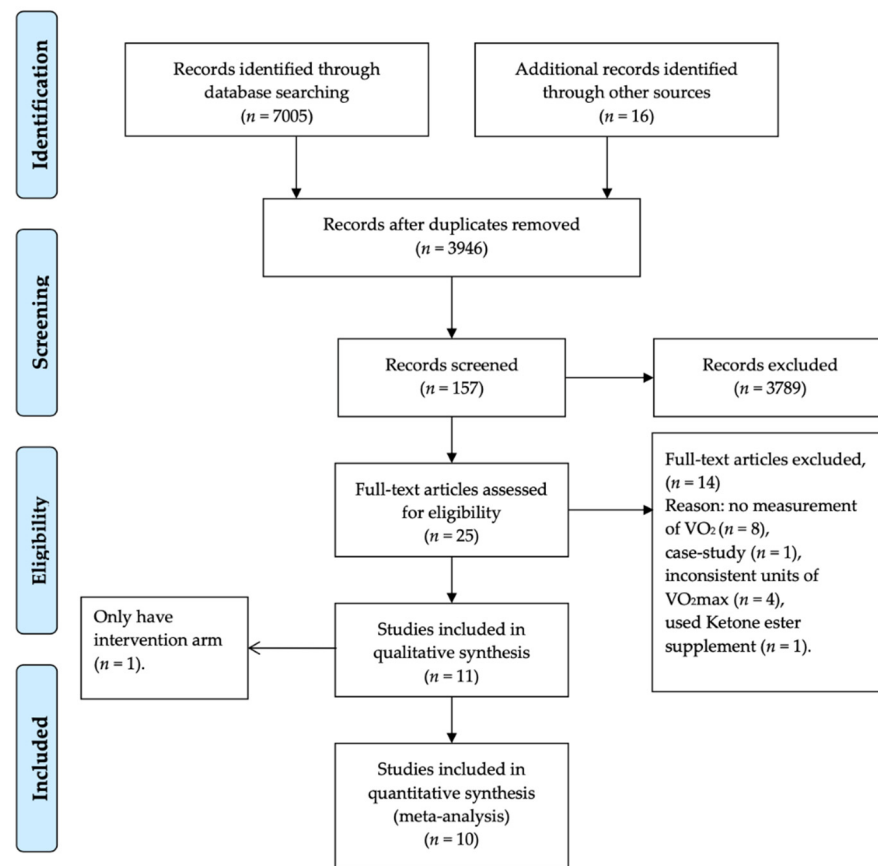


Figure 2. Flowchart for studies in the meta-analysis.

3.2. Characteristics of Subjects

A total of 139 participants (5–24 healthy and/or trained adults in each study) in 10 studies [18,41–49] were included in this review. Except for the study of Burke et al. [18], all participants were male athletes. The four crossover studies had a small sample size (5–8 males) with older athletes (aged 30–50 years) compared with the other control trials. Six other control trials had a larger sample size (13–24 individuals) and young adults (aged 20–30 years, see Table 1).

Table 1. Characteristics of included studies.

Citation, Year	Subjects	Age (Years)	Body Mass Change	Study Design	Dietary Components	Energy Intake	Intervention Duration	VO ₂ max Test Type	Other Exercise Test	Exercise Session during the Intervention
Burke et al. 2017 [42]	19 highly competitive male race walkers K-LCHF: <i>n</i> = 10 HC: <i>n</i> = 9	K-LCHF: 28.3 ± 3.5 HC: 25.4 ± 4.0	K-LCHF: significant reduction HC: no significant change	Control study	K-LCHF: 3.5% CHO 17% protein 78% fat HC: 60% CHO 16% protein 20% fat	K-LCHF: 3560 kcal/d HC: 3519 kcal/d	3 weeks	Graded economy test: Treadmill	10-km race; 20-km race	Race walking, resistance training and cross-training (running, cycling or swimming)
Burke et al. 2020 (a) [41]	13 male race walkers K-LCHF: <i>n</i> = 6 HC: <i>n</i> = 7	K-LCHF: 28.3 ± 2.7 HC: 32.7 ± 4.8	K-LCHF: significant reduction HC: no significant change	Parallel control study	K-LCHF: 4% CHO 16% protein 80% fat HC: 65% CHO 15% protein 20% fat	K-LCHF: 3766 ± 477 kcal/d HC: 3957 ± 726 kcal/d	5 days	Incremental testing: Treadmill	10-km race 25-km race	25–40 km walk, interval training session (8–12 × 1 km on a 6-min cycle), tempo hill session (14 km with ~450 m elevation gain). Low-intensity walking sessions (6–12 km each), and a strength training session
Burke et al. 2020 (b) [18]	18 highly competitive race walkers K-LCHF (M: 8; F: 2) HC (M: 5; F: 3)	K-LCHF: 29.9 ± 2.1 HC: 25.5 ± 3.6	K-LCHF: significant reduction HC: no significant change	Parallel control study	K-LCHF: 4% CHO 16% protein 78% fat HC: 65% CHO 15% protein 18% fat	K-LCHF: 3679 ± 382 kcal/d HC: 3345 ± 529 kcal/d	25 days	Graded exercise test (GXT): Treadmill	10-km race; 20-km race	Race walking, resistance training and cross-training (e.g., running, cycling or swimming)
Cipryan et al. 2018 [43]	17 moderately trained males K-LCHF: <i>n</i> = 9 HD: <i>n</i> = 8	K-LCHF: 23.8 ± 2.4 HD: 23.8 ± 1.8	K-LCHF: significant reduction HD: no significant change	Control study	K-LCHF: 8% CHO 29% protein 63% fat HD: 48% CHO 17% protein 35% fat	No report	4 weeks	Graded exercise test (GXT): Treadmill	No report	HIIT: 10-min warmup at 60% VO ₂ max, followed by 5 high-intensity exercises consisting of 3 min at 100% VO ₂ max (work to rest ratio, 2:1) Endurance-based running sessions or exercise (3–5 times a week)

Table 1. Cont.

Citation, Year	Subjects	Age (Years)	Body Mass Change	Study Design	Dietary Components	Energy Intake	Intervention Duration	VO ₂ max Test Type	Other Exercise Test	Exercise Session during the Intervention
Dostal et al. 2019 [44]	24 recreational trained runners K-LCHF: <i>n</i> = 12 HD: <i>n</i> = 12	K-LCHF: 25.3 ± 2.0 HD: 23.9 ± 3.8	K-LCHF: significant reduction HD: no significant change	Parallel control study	K-LCHF: 8% CHO 23% protein 69% fat HD: 45% CHO 18% protein 37% fat	K-LCHF: 1960 ± 316 kcal/d HC: 1782 ± 412 kcal/d	12 weeks	Graded exercise test (GXT): Treadmill	No report	HIIT (sessions lasted approximately 40 min in total and consisted of a 4-min warmup followed by 5 × 6-min sets, separated by 2-min recovery), endurance exercise (e.g., running, cycling, sport games)
Fleming et al. 2003 [45]	20 non-highly trained men K-LCHF: <i>n</i> = 12 HC: <i>n</i> = 8	K-LCHF: 35 ± 13 HC: 36 ± 12	No report	Control study	K-LCHF: 8% CHO 30% protein 61% fat HC: 59% CHO 15% protein 25% fat	K-LCHF: 2235 ± 375 kcal/d HC: 1815 ± 195 kcal/d	6 weeks	Graded exercise test: Cycle ergometer	Wingate Sprint, Time ride	Walking, running, cycling and cross-training
Heatherly et al. 2018 [46]	8 trained runners	39.5 ± 9.9	K-LCHF: significant reduction HC: no significant change	Crossover study	K-LCHF: 7 ± 4% CHO 29 ± 9% protein 64 ± 9% fat HC: 43 ± 11% CHO 17 ± 8% protein 38 ± 7% fat	K-LCHF: 1886 ± 520 kcal/d HC: 2820 ± 955 kcal/d	3 weeks	Graded exercise test: Treadmill	50-min run in heat, 5-km time trial	No report
Lambert et al. 1994 [47]	5 endurance trained male cyclists	22.0 ± 1.80	No report	Crossover study	K-LCHF: 7% CHO 23% protein 70% fat HC: 74% CHO 14% protein 12% fat	No report	2 weeks	Progressive exercise test: Cycle ergometer	30-s Wingate test	No report

Table 1. Cont.

Citation, Year	Subjects	Age (Years)	Body Mass Change	Study Design	Dietary Components	Energy Intake	Intervention Duration	VO ₂ max Test Type	Other Exercise Test	Exercise Session during the Intervention
Prins et al. 2019 [48]	7 competitive recreational distance male runners	35.6 ± 8.4	No report	Randomized counterbalance crossover study	K-LCHF: 6.0 ± 1.3% CHO 25.1 ± 1.5% protein 69 ± 2% fat HC: 56.4 ± 2.6% CHO 15.3 ± 1.1% protein 28 ± 2% fat	K-LCHF: 2837 ± 251 kcal/d HC: 2947 ± 284 kcal/d	6 weeks	Graded exercise test: Treadmill	5-km time trial	Maintain usual training
Shaw et al. 2019 [49]	8 trained male endurance athletes	29.6 ± 5.1	K-LCHF: significant reduction HD: no significant change	Randomized crossover study	K-LCHF: 4.1 ± 0.8% CHO 18.2 ± 3.5% protein 78 ± 4% fat HD: 42.9 ± 7.8% CHO 18.6 ± 1.4% protein 39 ± 7% fat	K-LCHF: 3122 kcal/d HD: 3280 kcal/d	31 days	Graded metabolic test: Treadmill	Run to exhaustion trial	Running and cycling

Note: K-LCHF: ketogenic low-carbohydrate, high-fat diet group; HD: habitual diet group; HC: high-carbohydrate diet; CHO: carbohydrate; HIIT: high-intensity interval training.

3.3. Study Protocol

Ten studies investigated the effects of the K-LCHF diet on $VO_2\max$ [18,41–49]. Among them, three studies investigated the effects of the K-LCHF diet on TTE [43,44,49]; eight studies investigated the effects of the K-LCHF diet on HRmax [18,39–44,46,47]; eight studies investigated the effects of the K-LCHF diet on RER [18,41,44–49]; and six studies investigated the effects of the K-LCHF diet on RPE [18,41,43–45,49]. The intervention protocol of the studies included in the review differed by dietary components, intervention duration, $VO_2\max$ test type, other exercise tests and exercise session during intervention (Table 1). Most of the studies were conducted by using a treadmill test [18,41–43,46,48,49], while two studies were performed on a cycle ergometer [45,47]. All studies adopted the GXT to measure $VO_2\max$.

3.4. Intervention Implementation

In all studies, the intervention group received the K-LCHF diet, and the control group received a high-carbohydrate or habitual diet. The K-LCHF diet consisted of $\leq 10\%$ CHO and $\geq 60\%$ fat; all non-LCHF diets consisted of $\geq 40\%$ CHO and $\leq 40\%$ fat. Eight studies reported the daily energy intake (Table 1). Among those studies, the energy intake from the K-LCHF groups was in the range of 2000–4000 kcal/d; five studies reported a range of 3000–4000 kcal/d [18,41,42,48,49], while three studies reported a range of 2000–3000 kcal/d [44–46].

The durations of most interventions were two to six weeks [18,42,43,47–49]. One study had a short intervention of five days [41], while another had a relatively long intervention of 12 weeks [44].

3.5. Effect of K-LCHF Diet on $VO_2\max$ during a GXT

No significant overall difference in $VO_2\max$ was found between the K-LCHF and HF/HD diets (SMD: -0.06 , CI: $-0.36, 0.25$, $p = 0.72$). There was low heterogeneity in this analysis ($I^2 = 0\%$) (Figure 3). Only one study [42] reported a significantly increased $VO_2\max$ within the group after the K-LCHF diet intervention.

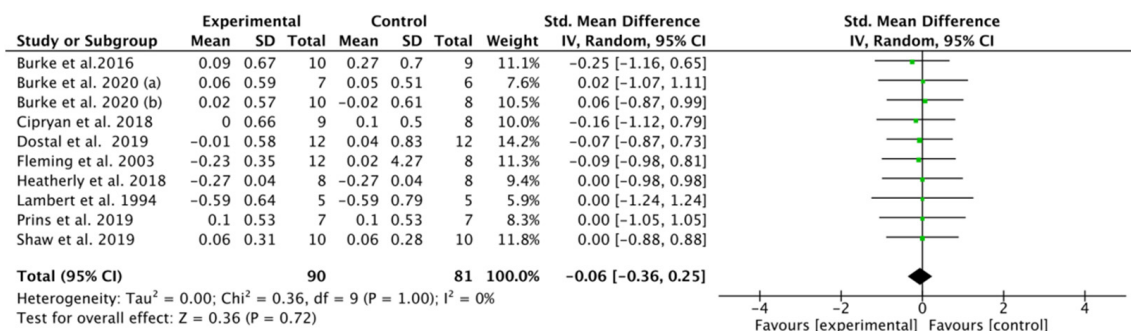


Figure 3. Effect of the ketogenic low-carbohydrate, high-fat (K-LCHF) diet on $VO_2\max$ during graded exercise test (GXT); CI: confidence interval; SMD: standardized mean difference.

3.6. Effect of K-LCHF Diet on TTE during a GXT

TTE (minutes) was reported in three studies [43,44,48] involving 48 trained endurance athletes. No significant overall difference in TTE was found between the K-LCHF and HC/HD diet (SMD: -0.13 , CI: $-0.66, 0.40$, $p = 0.64$), with an overall effect size of $Z = 0.47$ (Figure 4). There was low heterogeneity in this analysis ($I^2 = 0\%$).

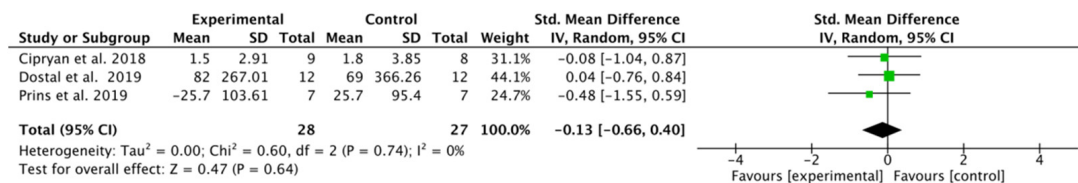


Figure 4. Effect of the ketogenic low-carbohydrate, high-fat (K-LCHF) diet on total time to exhaustion (TTE) during graded exercise test (GXT); CI: confidence interval; SMD: standardized mean difference.

3.7. Effect of K-LCHF Diet on Maximal Heart Rate (HRmax) during GXT

HRmax was recorded in eight studies [18,41–46,48,49] involving 126 trained endurance athletes. No significant overall difference in HRmax was found between the K-LCHF and HC/HD diet (SMD: 0.14, CI: -0.35, 0.63, $p = 0.58$), with an overall effect size of $Z = 0.55$ (Figure 5). There was high heterogeneity in this analysis ($I^2 = 52\%$). Only one study [49] reported a significant increase in HRmax.

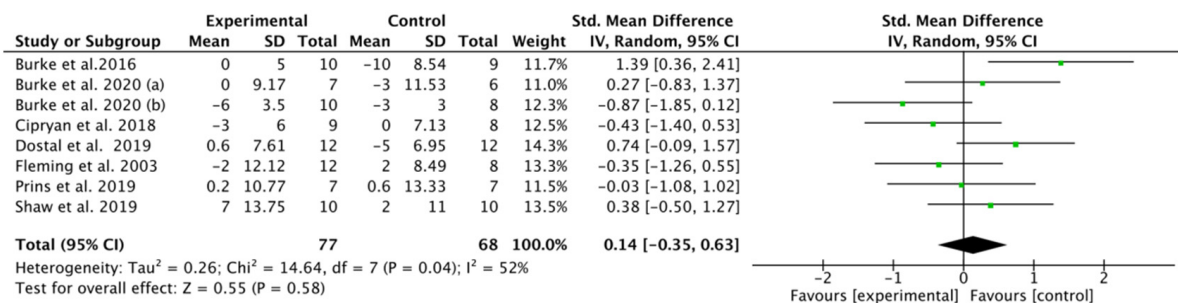


Figure 5. Effect of the ketogenic low-carbohydrate, high-fat (K-LCHF) diet on maximal heart rate (HRmax) during graded exercise test (GXT); CI: confidence interval; SMD: standardized mean difference.

3.8. Effect of K-LCHF Diet on Maximal Respiratory Exchange Ratio (RER) during GXT

RER was presented in eight studies [18,41,44–49] involving 103 trained endurance athletes. A significant overall difference in RER was found between the K-LCHF and HC/HD diets (SMD: -1.81, CI: -2.49, -1.13, $p < 0.00001$), with an overall effect size of $Z = 5.22$ (Figure 6). There was high heterogeneity in this analysis ($I^2 = 58\%$). Those studies all showed a significant decrease in RER after the intervention.

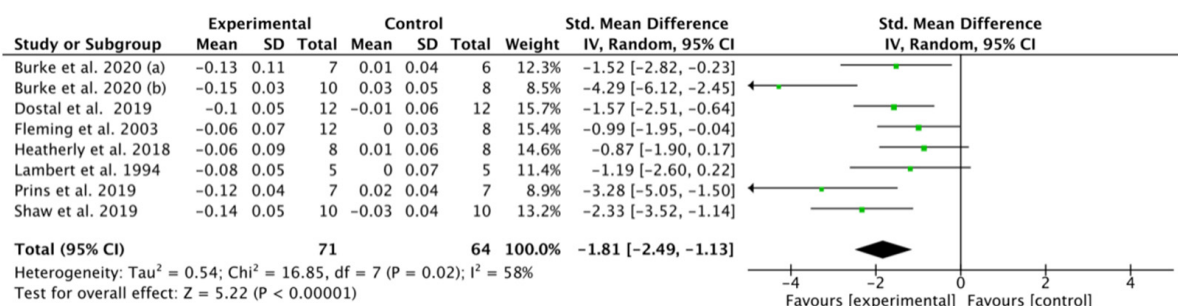


Figure 6. Effect of the ketogenic low-carbohydrate, high-fat (K-LCHF) diet on respiratory exchange ratio (RER) during graded exercise test (GXT); CI: confidence interval; SMD: standardized mean difference.

3.9. Effect of K-LCHF Diet on RPE during GXT

RPE was presented in six studies [18,41,43–45,49] involving 102 trained endurance athletes. No significant overall difference in RPE was found between the K-LCHF and HC/HD diets (SMD: 0.14, CI: -0.58, 0.86, $p = 0.71$), with an overall effect size of $Z = 0.38$ (Figure 7). There was high heterogeneity in this analysis ($I^2 = 70\%$). Only one study [45] showed a significant increase in RPE after the intervention.

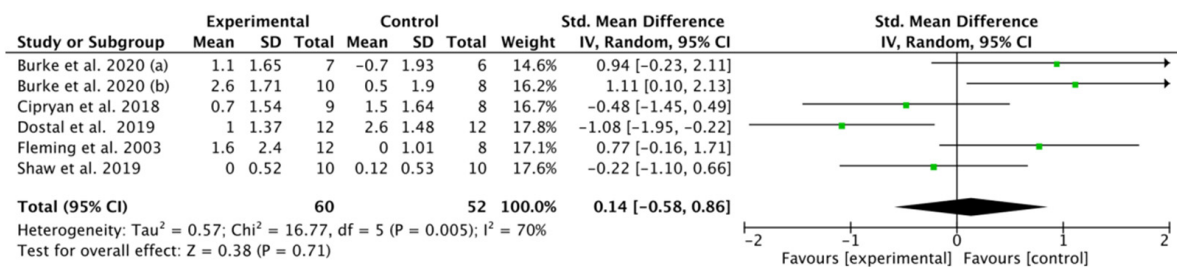


Figure 7. Effect of the ketogenic low-carbohydrate, high-fat (K-LCHF) diet on rating of perceived exertion (RPE) during graded exercise test (GXT); CI: confidence interval; SMD: standardize mean difference.

4. Discussion

After reviewing the limited literature on the K-LCHF diet in endurance athletes, 10 eligible studies were included in the meta-analysis. Based on the outcomes of aerobic capacity, exercise performance and substrate oxidation in endurance athletes, we only found a significant effect of K-LCHF on RER, but not on VO₂max, HRmax, TTE and RPE. This finding aligns with those of previous studies [18,41,43–49] that found that the K-LCHF diet had little effect on maximal aerobic capacity.

Under normal circumstances, glycogen stores in the liver and muscle cells need to break down to generate energy, and endogenous carbohydrates are stored mainly in the liver and muscle as a primary energy source in distance races [50–55]. In a previous study, Heatherly et al. [46] found that adaptation to a high-fat diet had a negative effect on VO₂max owing to body mass reduction in middle-aged male runners. However, Helge et al. [56] found an increased VO₂max after a fat-rich diet in untrained healthy males, and Phinney et al. found no change in endurance-trained athletes [4]. The K-LCHF diet might alter the maximal aerobic capacity through weight loss [45], but might not change VO₂max as weight loss was not the primary objective in those studies, and is not the objective for endurance athletes generally. In another study, the K-LCHF diet was effective in extending some older athletes' professional life by controlling or losing weight [9]. Another study analyzed gender differences after adopting the K-LCHF diet for four weeks and found a reduction in VO₂max in women after the intervention, which was not observed in men [31]. We found that body mass was significantly decreased after the K-LCHF diet intervention in seven studies, but no significant changes in VO₂max were observed. Of note, most studies have only reported on absolute VO₂max. Absolute values indicate the total quantity of oxygen being used during exercise, while relative values indicate how aerobically fit someone is compared with their peers. In this report, two studies reported both absolute and relative VO₂max, but neither showed a significant change after intervention [45,48]. Therefore, the interpretation of a K-LCHF diet strategy should be cautiously considered for athletic prowess in endurance sports if VO₂max has not changed but body weight has decreased.

Moreover, no significant effect of K-LCHF diet was found on TTE. However, caution should be paid as only three studies with limited available data were used to examine the impact of the K-LCHF diet on the TTE. A reasonable explanation is that, during adaptation to the K-LCHF diet, individuals still had sufficient muscle glucose stores to sustain high-intensity exercise [57]. A high-fat diet significantly enhanced subsequent prolonged exercise at approximately 60% of VO₂max, but, at the beginning of the workout, they only had 50% muscle glycogen content stored compared with the high-CHO-diet group [51]. In contrast, high-level athletes showed higher rates of fat oxidation, and their bodies utilized fat to replace part of the muscle glycogen for energy at a higher intensity [4]. This study also showed that after the body adapted to the K-LCHF diet, glycogen declined dramatically in muscle [4]. It remains to be studied whether long-term K-LCHF adaptation can restore the muscle glycogen to a comparable level [30]. Even though the ability to utilize fat was theoretically increased after the K-LCHF diet, no positive training effect was found on TTE, which may be related to the combination of diet and training.

Furthermore, no overall effect of the K-LCHF diet on HRmax was found. The potential neurological effect of a high-fat diet is that ketone adaptation increases the metabolic stress response during submaximal exercise. HR could be 7–9 bpm higher, potentially because of increased sympathetic nervous system activity [58]. A previous study suggested that the HR increases associated with obesity are caused by cardiac vagus nerve tension reduction [49]. Helge et al. [59] reported that subjects consuming a high-fat diet had significantly higher catecholamine and HR during submaximal exercise. Those changes may be related to changes in the autonomic nervous system activity at rest and in response to exercise after a short-term reduction in CHO intake (increased sympathetic and possibly decreased parasympathetic response) [59,60]. However, in our analysis, we did not find a significant effect of the K-LCHF diet on HRmax, which implies there is no evidence of a significant performance advantage after the K-LCHF diet (ketogenic or not). The ability to exercise at high intensity may be impaired by the K-LCHF diet.

The RER can indirectly indicate the ability of muscle to obtain energy [61]. A high RER indicates that carbohydrates are mainly used, while a low RER indicates that more fat is oxidized [61]. In our study, we found that the RER was significantly reduced after the adoption of the K-LCHF diet, indicating that more fat is involved in energy supply (Figure 6). In a study that simulated mountaineering after 4 h of cycling, eight out of nine participants improved their exercise ability during the climb after switching to a K-LCHF diet [62]. Throughout the study, five of the nine subjects enhanced their exercise ability by switching to the K-LCHF diet. Interestingly, comparing the high-CHO diet with the LCHF diet, RER improved. Exercise performance increased by an average of 375 s when climbing the mountain [62], indicating that a K-LCHF diet may be more advantageous to RER improvement in athletes. In addition, a study by Durkaleck-Michalski et al. [63] found males were more prone to switch macronutrient use from carbohydrate to more fat after the K-LCHF diet, reaching significance at the lower VO_2 max levels. Conversely, females did not significantly decrease carbohydrate oxidation at any volume of VO_2 max. Our finding agrees with that of a previous report [62] suggesting that decreased RER after the K-LCHF diet may involve an energy supply drawing more from fat in endurance athletes.

RPE may decrease after a K-LCHF diet. Some studies have shown that ketones provide most of the fuel for the brain when CHO availability is insufficient and circulating β -HB concentrations are in the 1–5 mmol/L range (ketosis) [9,64,65]. However, not all K-LCHF diets may lead to ketosis [66]. Moreover, to a large extent, even minor dietary abnormalities can lead to an increase in the concentration of ketones in the body even though the diet is still LCHO [67]. After K-LCHF adaption, exercise may improve the brain center's fatigue and cognitive function. This may be caused by the oxidation of β -HB, which provides a continued stable energy supply for the brain, delays the time of fatigue in the central nervous system and improves exercise performance [68–70]. However, no significant changes were found in RPE in this meta-analysis.

There was a large variation in the duration of the diet interventions among the included studies. However, when excluding the study by Burke et al. [41], with a five-day intervention, the results remained the same. Of note, the process of metabolic remodeling may initially take two weeks, with further adaptation in the following months to years [30]. In our report, most of the studies used interventions that were longer than two weeks. Even though we do not know the long-term adaptations, the results derived from these moderate lengths of interventions hint at the direction of the effect of K-LCHF on the aerobic capacity and exercise performance in endurance athletes.

4.1. Future Research

Different training strategies and study designs may explain the different impacts of the outcomes. Future studies should focus on developing an appropriate diet for endurance exercise and proposing guidelines for the intervention duration and intensity of training sessions for various groups of athletes. Furthermore, high-quality trials are required to prove the precise influence of different nutritional strategies.

4.2. Limitations

This study had some limitations. First, most of the studies only reported absolute VO₂max, and TTE in the increment GXT was chosen as the primary outcome of exercise performance rather than the race time of real competitions. Second, only articles published in English were included, and gray literature and articles in other languages were not included. Third, we did not have CHO/fat oxidation data, so future study on analyses of CHO/fat oxidation would be useful. Finally, the subjects selected were all endurance athletes and almost all male, which is not representative of the general population. Moreover, there was no analysis of gender differences.

5. Conclusions

In summary, we found no significant overall effect of a ketogenic low-carbohydrate, high-fat diet on VO₂max, HRmax, TTE and RPE, but a significant overall effect on RER. The K-LCHF diet did not lead to a positive change in aerobic capacity, possibly because the expected improvement was not achieved during the training period. Therefore, a K-LCHF diet is unlikely to change the aerobic capacity and exercise performance of endurance athletes, and there is a need to conduct high-quality intervention studies to assess the impact of different diet treatments for enhancing exercise performance in endurance athletes.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/nu13082896/s1>, Table S1: AMSTAR checklist items for each systematic review, Table S2: Search strategy used in each database.

Author Contributions: J.C. initiated and designed the study, selected studies, extracted data, assessed the quality of included studies, performed the data analysis and drafted the manuscript. S.L. selected studies, extracted data, assessed the quality of included studies, contributed to the interpretation of the results, edited the manuscript and contacted authors for original data. S.C. initiated and designed the study, contributed to the interpretation of the results and edited the manuscript. X.W. contributed to the interpretation of the results and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the start-up plan for new young teachers grant (Grant AF4150043) and by the 111 Project (B17029) at Shanghai Jiao Tong University.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We thank Xiao Tan for insightful comments on a previous version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Paoli, A.; Rubini, A.; Volek, J.S.; Grimaldi, K.A. Beyond weight loss: A review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur. J. Clin. Nutr.* **2013**, *67*, 789–796. [[CrossRef](#)] [[PubMed](#)]
2. Devrim-Lanpir, A.; Hill, L.; Knechtle, B. Efficacy of Popular Diets Applied by Endurance Athletes on Sports Performance: Beneficial or Detrimental? A Narrative Review. *Nutrients* **2021**, *13*, 491. [[CrossRef](#)] [[PubMed](#)]
3. Valsdottir, T.D.; Øvrebø, B.; Falck, T.M.; Litleskare, S.; Johansen, E.I.; Henriksen, C.; Jensen, J. Low-Carbohydrate High-Fat Diet and Exercise: Effect of a 10-Week Intervention on Body Composition and CVD Risk Factors in Overweight and Obese Women—A Randomized Controlled Trial. *Nutrients* **2020**, *13*, 110. [[CrossRef](#)]
4. Phinney, S.; Bistrian, B.; Evans, W.; Gervino, E.; Blackburn, G. The human metabolic response to chronic ketosis without caloric restriction: Preservation of submaximal exercise capability with reduced carbohydrate oxidation. *Metabolism* **1983**, *32*, 769–776. [[CrossRef](#)]
5. Burke, L.M.; Kiens, B. “Fat adaptation” for athletic performance: The nail in the coffin? *J. Appl. Physiol.* **2006**, *100*, 7–8. [[CrossRef](#)]
6. Kaspar, M.B.; Austin, K.; Huecker, M.; Sarav, M. Ketogenic Diet: From the Historical Records to Use in Elite Athletes. *Curr. Nutr. Rep.* **2019**, *8*, 340–346. [[CrossRef](#)]

7. Starling, R.D.; Trappe, T.A.; Parcell, A.C.; Kerr, C.G.; Fink, W.J.; Costill, D.L. Effects of diet on muscle triglyceride and endurance performance. *J. Appl. Physiol.* **1997**, *82*, 1185–1189. [[CrossRef](#)]
8. Pitsiladis, Y.P.; Maughan, R.J. The effects of exercise and diet manipulation on the capacity to perform prolonged exercise in the heat and in the cold in trained humans. *J. Physiol.* **1999**, *517*, 919–930. [[CrossRef](#)]
9. Volek, J.S.; Noakes, T.D.; Phinney, S. Rethinking fat as a fuel for endurance exercise. *Eur. J. Sport Sci.* **2015**, *15*, 13–20. [[CrossRef](#)]
10. Evans, M.; Cogan, K.E.; Egan, B. Metabolism of ketone bodies during exercise and training: Physiological basis for exogenous supplementation. *J. Physiol.* **2017**, *595*, 2857–2871. [[CrossRef](#)]
11. Sumithran, P.; Prendergast, L.A.; Delbridge, E.; Purcell, K.; Shulkes, A.; Kriketos, A.D.; Proietto, J. Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur. J. Clin. Nutr.* **2013**, *67*, 759–764. [[CrossRef](#)] [[PubMed](#)]
12. Vidali, S.; Aminzadeh, S.; Lambert, B.; Rutherford, T.; Sperl, W.; Kofler, B.; Feichtinger, R.G. Mitochondria: The ketogenic diet—A metabolism-based therapy. *Int. J. Biochem. Cell Biol.* **2015**, *63*, 55–59. [[CrossRef](#)] [[PubMed](#)]
13. Puchalska, P.; Crawford, P.A. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell Metab.* **2017**, *25*, 262–284. [[CrossRef](#)]
14. Grabacka, M.; Pierzchalska, M.; Reiss, K. Peroxisome proliferator activated receptor α ligands as anticancer drugs targeting mitochondrial metabolism. *Curr. Pharm. Biotechnol.* **2013**, *14*, 342–356. [[CrossRef](#)]
15. Draznin, B.; Wang, C.; Adochio, R.; Leitner, J.W.; Cornier, M.-A. Effect of Dietary Macronutrient Composition on AMPK and SIRT1 Expression and Activity in Human Skeletal Muscle. *Horm. Metab. Res.* **2012**, *44*, 650–655. [[CrossRef](#)]
16. McCarty, M.F.; DiNicolantonio, J.J.; O’Keefe, J.H. Ketosis may promote brain macroautophagy by activating Sirt1 and hypoxia-inducible factor-1. *Med. Hypotheses* **2015**, *85*, 631–639. [[CrossRef](#)]
17. Xu, S.; Tao, H.; Cao, W.; Cao, L.; Lin, Y.; Zhao, S.-M.; Xu, W.; Cao, J.; Zhao, J.-Y. Ketogenic diets inhibit mitochondrial biogenesis and induce cardiac fibrosis. *Signal Transduct. Target. Ther.* **2021**, *6*, 1–13. [[CrossRef](#)]
18. Burke, L.M.; Sharma, A.P.; Heikura, I.A.; Forbes, S.F.; Holloway, M.; McKay, A.K.A.; Bone, J.L.; Leckey, J.J.; Welvaert, M.; Ross, M.L. Crisis of confidence averted: Impairment of exercise economy and performance in elite race walkers by ketogenic low carbohydrate, high fat (LCHF) diet is reproducible. *PLoS ONE* **2020**, *15*, 31.
19. Hawley, J.; Brouns, F.; Jeukendrup, A. Strategies to Enhance Fat Utilisation During Exercise. *Sports Med.* **1998**, *25*, 241–257. [[CrossRef](#)]
20. Burke, L.M. Re-Examining High-Fat Diets for Sports Performance: Did We Call the ‘Nail in the Coffin’ Too Soon? *Sports Med.* **2015**, *45*, 33–49. [[CrossRef](#)]
21. Chang, C.-K.; Borer, K.; Lin, P.-J. Low-Carbohydrate-High-Fat Diet: Can it Help Exercise Performance? *J. Hum. Kinet.* **2017**, *56*, 81–92. [[CrossRef](#)]
22. Cermak, N.M.; van Loon, L.J. The use of carbohydrates during exercise as an ergogenic aid. *Sports Med.* **2013**, *43*, 1139–1155. [[CrossRef](#)] [[PubMed](#)]
23. Bartlett, J.D.; Hawley, J.; Morton, J.P. Carbohydrate availability and exercise training adaptation: Too much of a good thing? *Eur. J. Sport Sci.* **2015**, *15*, 3–12. [[CrossRef](#)] [[PubMed](#)]
24. Wycherley, T.; Buckley, J.D.; Noakes, M.; Clifton, P.M.; Brinkworth, G.D. Long-Term Effects of a Very Low-Carbohydrate Weight Loss Diet on Exercise Capacity and Tolerance in Overweight and Obese Adults. *J. Am. Coll. Nutr.* **2014**, *33*, 267–273. [[CrossRef](#)] [[PubMed](#)]
25. Jeukendrup, A.E.; Craig, N.P.; Hawley, J. The bioenergetics of world class cycling. *J. Sci. Med. Sport* **2000**, *3*, 414–433. [[CrossRef](#)]
26. Spriet, L.L. Regulation of Substrate Use During the Marathon. *Sports Med.* **2007**, *37*, 332–336. [[CrossRef](#)]
27. Paoli, A.; Grimaldi, K.; D’Agostino, D.; Cenci, L.; Moro, T.; Bianco, A.; Palma, A. Ketogenic diet does not affect strength performance in elite artistic gymnasts. *J. Int. Soc. Sports Nutr.* **2012**, *9*, 34. [[CrossRef](#)]
28. Zajac, A.; Poprzecki, S.; Maszczyk, A.; Czuba, M.; Michalczyk, M.; Zydek, G. The Effects of a Ketogenic Diet on Exercise Metabolism and Physical Performance in Off-Road Cyclists. *Nutrients* **2014**, *6*, 2493–2508. [[CrossRef](#)]
29. Murphy, N.E.; Carrigan, C.T.; Margolis, L.M. High-Fat Ketogenic Diets and Physical Performance: A Systematic Review. *Adv. Nutr.* **2021**, *12*, 223–233. [[CrossRef](#)]
30. Burke, L.M. Ketogenic low-CHO, high-fat diet: The future of elite endurance sport? *J. Physiol.* **2021**, *599*, 819–843. [[CrossRef](#)]
31. Durkalec-Michalski, K.; Nowaczyk, P.M.; Głównka, N.; Ziobrowska, A.; Podgórski, T. Is a Four-Week Ketogenic Diet an Effective Nutritional Strategy in CrossFit-Trained Female and Male Athletes? *Nutrients* **2021**, *13*, 864. [[CrossRef](#)]
32. Masood, W.; Annamaraju, P.; Uppaluri, K.R. Ketogenic Diet. In *StatPearls, StatPearls Publishing Copyright © 2021; StatPearls Publishing LLC.: Treasure Island, FL, USA, 2021.*
33. Greene, D.A.; Varley, B.J.; Hartwig, T.; Chapman, P.; Rigney, M. A Low-Carbohydrate Ketogenic Diet Reduces Body Mass Without Compromising Performance in Powerlifting and Olympic Weightlifting Athletes. *J. Strength Cond. Res.* **2018**, *32*, 3373–3382. [[CrossRef](#)] [[PubMed](#)]
34. Jones, A.M.; Carter, H. The Effect of Endurance Training on Parameters of Aerobic Fitness. *Sports Med.* **2000**, *29*, 373–386. [[CrossRef](#)]
35. Bazylar, C.D.; Abbott, H.A.; Bellon, C.R.; Taber, C.B.; Stone, M.H. Strength Training for Endurance Athletes: Theory to Practice. *Strength Cond. J.* **2015**, *37*, 1–12. [[CrossRef](#)]
36. Green, S.; Higgins, J.; Alderson, P. *Cochrane Handbook for Systematic Reviews of Interventions*; Version 5.10 ed.; The Cochrane Collaboration: London, UK, 2008.

37. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res. Methodol.* **2014**, *14*, 1–13. [[CrossRef](#)] [[PubMed](#)]
38. Tran, D. Cardiopulmonary Exercise Testing. *Methods Mol. Biol.* **2018**, *1735*, 285–295. [[CrossRef](#)]
39. Gross, I.; Hirsch, H.J.; Constantini, N.; Nice, S.; Pollak, Y.; Genstil, L.; Eldar-Geva, T.; Tsur, V.G. Physical activity and maximal oxygen uptake in adults with Prader–Willi syndrome. *Eat. Weight. Disord. Stud. Anorex. Bulim. Obes.* **2017**, *23*, 615–620. [[CrossRef](#)]
40. Shea, B.J.; Grimshaw, J.M.; Wells, G.A.; Boers, M.; Andersson, N.; Hamel, C.; Porter, A.C.; Tugwell, P.; Moher, D.; Bouter, L.M. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res. Methodol.* **2007**, *7*, 10. [[CrossRef](#)]
41. Burke, L.M.; Whitfield, J.; Heikura, I.A.; Ross, M.L.R.; Tee, N.; Forbes, S.F.; Hall, R.; McKay, A.K.A.; Wallett, A.M.; Sharma, A.P. Adaptation to a low carbohydrate high fat diet is rapid but impairs endurance exercise metabolism and performance despite enhanced glycogen availability. *J. Physiol.* **2021**, *599*, 771–790. [[CrossRef](#)]
42. Burke, L.M.; Ross, M.L.; Garvican-Lewis, L.A.; Welvaert, M.; Heikura, I.A.; Forbes, S.G.; Mirtschin, J.G.; Cato, L.E.; Strobel, N.; Sharma, A.P.; et al. Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. *J. Physiol.* **2017**, *595*, 2785–2807. [[CrossRef](#)] [[PubMed](#)]
43. Cipryan, L.; Plews, D.J.; Ferretti, A.; Maffetone, P.B.; Laursen, P.B. Effects of a 4-Week Very Low-Carbohydrate Diet on High-Intensity Interval Training Responses. *J. Sports Sci. Med.* **2018**, *17*, 259–268. [[PubMed](#)]
44. Dostal, T.; Plews, D.J.; Hofmann, P.; Laursen, P.B.; Cipryan, L. Effects of a 12-Week Very-Low Carbohydrate High-Fat Diet on Maximal Aerobic Capacity, High-Intensity Intermittent Exercise, and Cardiac Autonomic Regulation: Non-randomized Parallel-Group Study. *Front. Physiol.* **2019**, *10*, 912. [[CrossRef](#)] [[PubMed](#)]
45. Fleming, J.; Sharman, M.J.; Avery, N.G.; Love, D.M.; Gómez, A.L.; Scheett, T.P.; Kraemer, W.J.; Volek, J.S. Endurance capacity and high-intensity exercise performance responses to a high fat diet. *Int. J. Sport Nutr. Exerc. Metab.* **2003**, *13*, 466–478. [[CrossRef](#)] [[PubMed](#)]
46. Heatherly, A.J.; Killen, L.G.; Smith, A.F.; Waldman, H.S.; Seltsman, C.L.; Hollingsworth, A.; O’Neal, E.K. Effects of Ad libitum Low-Carbohydrate High-Fat Dieting in Middle-Age Male Runners. *Med. Sci. Sports Exerc.* **2018**, *50*, 570–579. [[CrossRef](#)] [[PubMed](#)]
47. Lambert, E.; Speechly, D.P.; Dennis, S.C.; Noakes, T.D. Enhanced endurance in trained cyclists during moderate intensity exercise following 2 weeks adaptation to a high fat diet. *Graefes Arch. Clin. Exp. Ophthalmol.* **1994**, *69*, 287–293. [[CrossRef](#)] [[PubMed](#)]
48. Prins, P.J.; Noakes, T.D.; Welton, G.L.; Haley, S.J.; Esbenschade, N.J.; Atwell, A.D.; Scott, K.E.; Abraham, J.; Raabe, A.S.; Buxton, J.D.; et al. High Rates of Fat Oxidation Induced by a Low-Carbohydrate, High-Fat Diet, Do Not Impair 5-km Running Performance in Competitive Recreational Athletes. *J. Sports Sci. Med.* **2019**, *18*, 738–750.
49. Shaw, D.M.; Merien, F.; Braakhuis, A.; Maunder, E.; Dulson, D.K. Effect of a Ketogenic Diet on Submaximal Exercise Capacity and Efficiency in Runners. *Med. Sci. Sports Exerc.* **2019**, *51*, 2135–2146. [[CrossRef](#)] [[PubMed](#)]
50. Lambert, E.; Goedecke, J.H.; Zyle, C.; Murphy, K.; Hawley, J.A.; Dennis, S.C.; Noakes, T.D.; Van Zyl, C. High-Fat Diet versus Habitual Diet Prior to Carbohydrate Loading: Effects on Exercise Metabolism and Cycling Performance. *Int. J. Sport Nutr. Exerc. Metab.* **2001**, *11*, 209–225. [[CrossRef](#)]
51. Beelen, M.; Burke, L.M.; Gibala, M.J.; van Loon, L.J. Nutritional Strategies to Promote Postexercise Recovery. *Int. J. Sport Nutr. Exerc. Metab.* **2010**, *20*, 515–532. [[CrossRef](#)]
52. Jentjens, R.; Jeukendrup, A.E. Determinants of Post-Exercise Glycogen Synthesis During Short-Term Recovery. *Sports Med.* **2003**, *33*, 117–144. [[CrossRef](#)]
53. Thomas, D.T.; Erdman, K.A.; Burke, L.M. American College of Sports Medicine Joint Position Statement. Nutrition and Athletic Performance. *Med. Sci. Sports Exerc.* **2016**, *48*, 543–568.
54. Romijn, J.A.; Coyle, E.F.; Sidossis, L.S.; Gastaldelli, A.; Horowitz, J.F.; Endert, E.; Wolfe, R.R. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am. J. Physiol. Metab.* **1993**, *265*, E380–E391. [[CrossRef](#)]
55. Van Loon, L.J.C.; Greenhaff, P.; Constantin-Teodosiu, D.; Saris, W.H.M.; Wagenmakers, A. The effects of increasing exercise intensity on muscle fuel utilisation in humans. *J. Physiol.* **2001**, *536*, 295–304. [[CrossRef](#)]
56. Helge, J.; Richter, E.A.; Kiens, B. Interaction of training and diet on metabolism and endurance during exercise in man. *J. Physiol.* **1996**, *492*, 293–306. [[CrossRef](#)]
57. Soeters, M.; Soeters, P.B.; Schooneman, M.G.; Houten, S.; Romijn, J.A. Adaptive reciprocity of lipid and glucose metabolism in human short-term starvation. *Am. J. Physiol. Metab.* **2012**, *303*, E1397–E1407. [[CrossRef](#)] [[PubMed](#)]
58. Havemann, L.; West, S.; Goedecke, J.; Macdonald, I.; Gibson, A.S.C.; Noakes, T.D.; Lambert, E. Fat adaptation followed by carbohydrate loading compromises high-intensity sprint performance. *J. Appl. Physiol.* **2006**, *100*, 194–202. [[CrossRef](#)] [[PubMed](#)]
59. Helge, J.W. Long-term fat diet adaptation effects on performance, training capacity, and fat utilization. *Med. Sci. Sports Exerc.* **2002**, *34*, 1499–1504. [[CrossRef](#)]
60. Pellizzer, A.M.; Straznicky, N.E.; Lim, S.; Kamen, P.W.; Krum, H. Reduced dietary fat intake increases parasympathetic activity in healthy premenopausal women. *Clin. Exp. Pharmacol. Physiol.* **1999**, *26*, 656–660. [[CrossRef](#)] [[PubMed](#)]
61. Pendergast, D.R.; Leddy, J.J.; Venkatraman, J.T. A perspective on fat intake in athletes. *J. Am. Coll. Nutr.* **2000**, *19*, 345–350. [[CrossRef](#)]
62. Havemann, L. The effect of Fat-Adaptation Followed by Carbohydrate-Loading on Simulated Ultra-Endurance Race Performance. Ph.D. Thesis, University of Cape Town, Cape Town, South Africa, 2008.

63. Durkalec-Michalski, K.; Nowaczyk, P.M.; Siedzik, K. Effect of a four-week ketogenic diet on exercise metabolism in CrossFit-trained athletes. *J. Int. Soc. Sports Nutr.* **2019**, *16*, 16. [[CrossRef](#)] [[PubMed](#)]
64. Cahill, G.F. Alternate fuel utilization by brain. In *Cerebral Metabolism and Neural Function*; Passonneau, J.V., Hawkins, R.A., Lust, W.D., Welsh, F.A., Eds.; Williams & Wilkins: Baltimore, MD, USA, 1980.
65. Owen, O.E.; Morgan, A.P.; Kemp, H.G.; Sullivan, J.M.; Herrera, M.G.; Cahill, G.F. Brain Metabolism during Fasting*. *J. Clin. Investig.* **1967**, *46*, 1589–1595. [[CrossRef](#)]
66. Wentz, A.; D'Avignon, D.A.; Weber, M.L.; Cotter, D.G.; Doherty, J.M.; Kerns, R.; Nagarajan, R.; Reddy, N.; Sambandam, N.; Crawford, P.A. Adaptation of Myocardial Substrate Metabolism to a Ketogenic Nutrient Environment. *J. Biol. Chem.* **2010**, *285*, 24447–24456. [[CrossRef](#)] [[PubMed](#)]
67. Owen, O.E. Ketone bodies as a fuel for the brain during starvation. *Biochem. Mol. Biol. Educ.* **2005**, *33*, 246–251. [[CrossRef](#)]
68. Han, Y.-M.; Ramprasath, T.; Zou, M.-H. β -hydroxybutyrate and its metabolic effects on age-associated pathology. *Exp. Mol. Med.* **2020**, *52*, 548–555. [[CrossRef](#)]
69. Achanta, L.B.; Rae, C.D. β -Hydroxybutyrate in the Brain: One Molecule, Multiple Mechanisms. *Neurochem. Res.* **2017**, *42*, 35–49. [[CrossRef](#)]
70. Newman, J.C.; Verdin, E. β -Hydroxybutyrate: A Signaling Metabolite. *Annu. Rev. Nutr.* **2017**, *37*, 51–76. [[CrossRef](#)] [[PubMed](#)]