Caloric restriction benefits on cardiorespiratory fitness and muscle strength with and without exercise training in humans: a systematic review and meta-analysis

Benefícios da restrição calórica na aptidão cardiorrespiratória e força muscular com e sem treino de exercício em humanos: uma revisão sistemática e meta-análise

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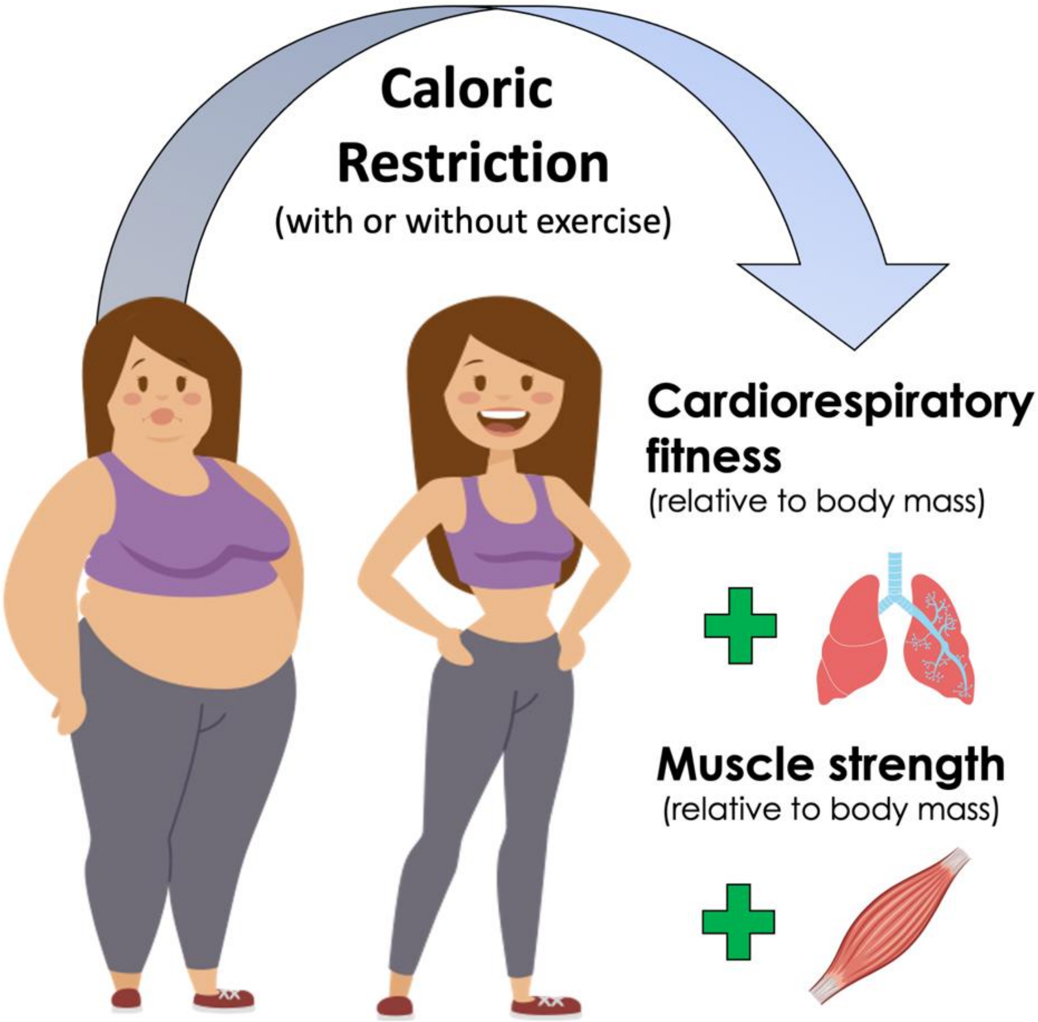
RESUMO
Objetivo: Identificar os verdadeiros efeitos da restrição calórica (RC) sobre o consumo máximo de oxigênio (VO_2máx) relativo e absoluto e força muscular. Métodos: Uma revisão sistemática foi conduzida em 5 bancos de dados, até novembro de 2019. Vinte e oito ensaios controlados foram incluídos nas meta-análises comparando RC sozinho vs. Dieta padrão (RC vs. controle) ou comparando RC mais treinamento físico vs. treinamento de exercício sozinho (RC + EX vs. EX) sobre o VO_2máx e a força muscular. Resultados: RC + EX teve um efeito positivo para o VO_2máx relativo (1,13 [0,49; 1,78]ml/kg/min, p <0,001), mas não teve nenhum efeito sobre a força muscular relativa (0,41 [-0,28; 1,09], p = 0,25) quando comparados ao EX. RC aumentou significativamente o VO_2máx relativo (2,08 [0,90; 3,27]ml/kg/min, p <0,001) e a força relativa (0,47 [0,35; 0,59)], p <0,001), em comparação com dieta padrão. A análise complementar confirmou reduções significativas na massa corporal total, massa gorda e massa muscular entre todos os subgrupos, como esperado. O VO_2máx absoluto e a força não foram melhorados por RC + EX ou RC quando comparados a EX e controle, respectivamente. Conclusão: A RC sozinha melhora significativamente o VO_2máx relativo e a força muscular em indivíduos fisicamente não ativos.

Palavras-Chave: Dieta de Baixa Caloria, Teste de Esforço, Saúde, Desempenho, Aptidão física.

ABSTRACT
Aim: To identify the true Caloric restriction (CR) effects on relative and absolute maximum oxygen uptake (VO_2max) and muscular strength. Methods: A systematic review was conducted in 5 databases, up to November 2019. Twenty-eight controlled trials were included in the meta-analyses comparing CR alone vs. standard diet (CR vs. control) or comparing CR plus exercise training vs. exercise training alone (CR+EX vs. EX) on VO_2max and muscle strength. Results: CR+EX had a positive effect on relative VO_2max (1.13 [0.49; 1.78]ml/kg/min, p<0.001), but had no additional effect on relative muscle strength (0.41 [-0.28; 1.09], p=0.25) when compared to EX. CR significantly increased relative VO_2max (2.08 [0.90; 3.27]ml/kg/min, p<0.001) and relative strength (0.47 [0.35; 0.59)], p<0.001), compared with standard diet. Complementary analysis confirmed significant reductions in total body mass, fat mass and muscle mass among all subgroups, as expected. Absolute VO_2max and strength were not improved by CR+EX or CR when compared to EX and control, respectively. Conclusion: CR alone significantly improve relative VO_2max and muscle strength in non-physically active individuals.

Keywords: Low-Calorie Diet, Exercise Test, Health, Performance, Physical Fitness.

Abstract Figure.



1 INTRODUCTION

Caloric restriction (CR), defined as a reduction in energy intake without nutrient deficiency, has been shown to increase lifespans and attenuate the harmful effects of aging across the evolutionary spectrum [1,2]. In humans, CR has improved numerous metabolic and hormonal factors that regulates the pathogenesis of type 2 diabetes, cardiovascular diseases, cancer, being associated with increased health span [3–5]. The exact mechanism underlying the benefits of CR remains unknown, but it involves changes in nutrient-sensing pathways, metabolic homeostasis, and body composition [1,6].

Regarding physical fitness, CR effects has been shown to delay the aging changes such as muscle weakness, poor endurance, slowness, low physical activity, and frailty in primates[7]. However, in humans while a few studies show improvements of cardiorespiratory fitness (VO_2max) [8,9] and muscle strength [10] with CR, other studies have shown negative or null effects[11,12].

Many factors might influence those different results such as different characteristics of the individuals, interventions, and methods of physical fitness assessments. For example, considering that CR leads to important reduction in body mass, the increase in physical fitness absolute values may be considerably lower than the increase in relative to body mass values[13]. Thus, both unit measurements (absolute and relative) need to be analyzed separately. Another confounding factor is the common use of adjuvant interventions such as exercise training. Exercise training per se is the most powerful stimuli to increase VO_2max and muscle strength and when combined with CR should be carefully interpreted [14].

The aim of this study was to identify the effects of CR on relative/absolute values of VO_2 max in a range of physically inactive individuals. This meta-analysis included published human-controlled trials with and without exercise.

2 METHODS

This review was reported according to PRISMA (Preferred Reporting Items for systematic Reviews and Meta-Analyses) Guidelines [15].

2.1 LITERATURE SEARCH

The search was conducted on studies published before November 16, 2019 on PubMed, Web of Science, Embase, Scopus and Cochrane databases, combining CR, physical fitness, and clinical trial terms. The PubMed search terms included were ("intermittent fasting"[tiab] OR "fasting"[mh] OR "caloric restriction"[mh] OR "diet, reducing"[mh] OR "Low-Calorie Diet" [tiab] OR "time restricted feeding"[tiab]) AND (("athletic performance" [mh] OR "Sports Performance" [tiab] OR "muscle strength" [mh] OR "exercise test" [mh] OR "Fitness Testing" [tiab] OR "Cardiopulmonary Exercise Test" [tiab] OR "Treadmill Test" [tiab] OR "Bicycle Ergometry Test" [tiab]) AND (("Clinical Trial" [Publication Type]) OR ("Clinical Trials as Topic"[mh])). Equivalent search terms were properly applied in each of the other databases.

2.2 ELIGIBILITY CRITERIA

We selected controlled trials (CTs) testing CR interventions (at least 8 weeks) with or without exercise training on cardiorespiratory fitness and muscle strength. To assess the isolated effects of CR on physical fitness outcomes (VO_2max and muscle strength), the comparison groups were: CR alone vs. control keeping usual dietary intake

(CR vs. control), or testing CR in exercise interventions, CR plus exercise training vs. Exercise training alone (CR+EX vs. EX). It is noteworthy that although we searched for any type of CR (e.g., intermittent fasting and time restricted feeding), interventions without confirm reduction on caloric restriction were not considered CR. No restriction was applied for date of publication, characteristics of the population (i.e., age, sex or body mass index), or language of the studies; and thus, the only study writing not English (in French) was translated by a specialized translator [16]. Regarding the outcomes, we just included studies assessing absolute or relative to the body mass maximum oxygen consumption, or absolute or relative to the body mass strength assessed by lb, Kg, or Nm. We only searched for original controlled trials. Reviews, conference papers, letters, and commentaries were excluded. Inadequate controlled studies such as 1) studies comparing CR versus exercise training interventions; 2) studies comparing different types of exercise training interventions combined to CR without an only exercise training intervention; 3) studies comparing exercise training with exercise training associated to increased calories (instead of CR) were also excluded. The acute CR effects were excluded and only interventions equal or longer than 8 weeks were included considering the aim was to investigate the CR chronic effects. In this way, we could not include the three studies carried out in highly trained individuals [18–20] (they tested only 7, 10- and 12-days intervention), and unfortunately our analysis ended-up restricted to non-physically active individuals. We did not exclude studies by age or body mass index (BMI), however, regarding BMI most studies included overweight (BMI between 25kg/m^2 and 30 kg/m^2) and obese individuals (BMI $\geq$ 31 kg/m^2) due to the main purpose of CR (lose weight).

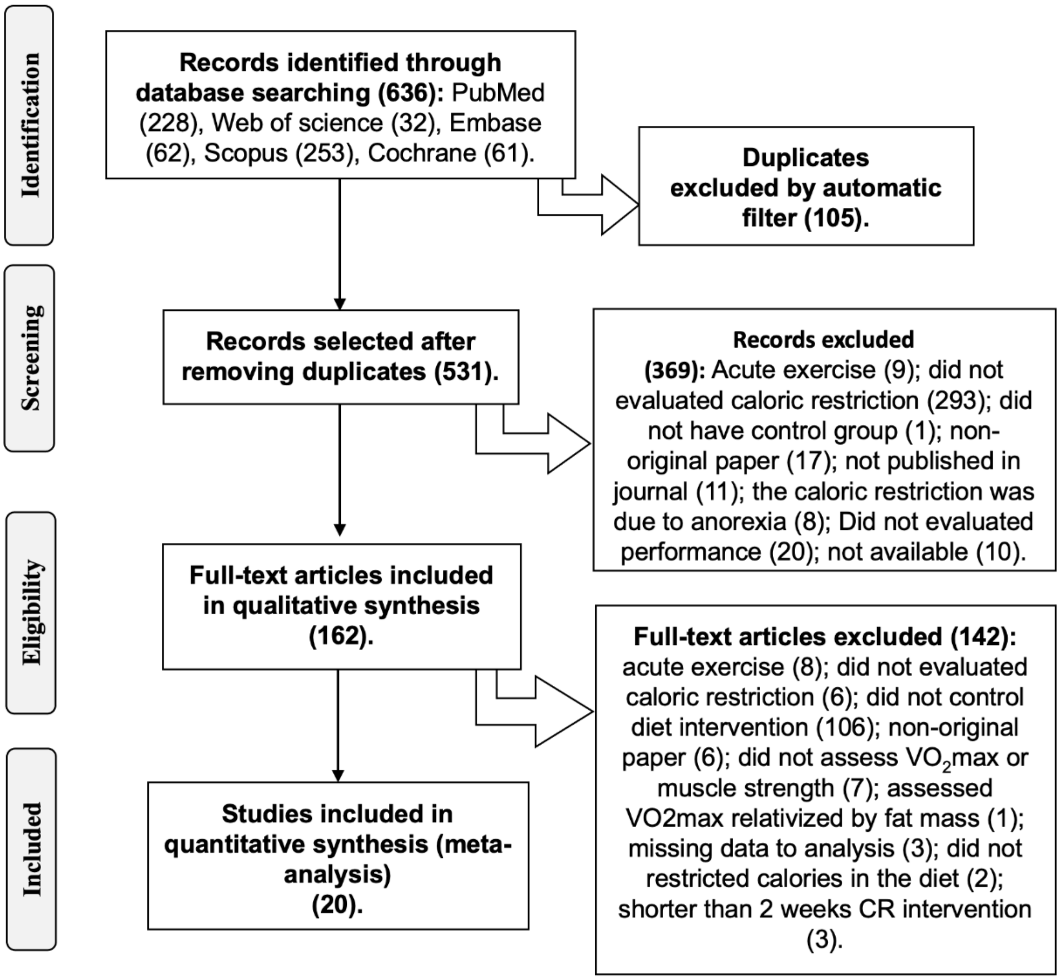
Physical activity level was not used as an exclusion criterion since included studies may have not reported it or stated that participants were not physically active. [9,16]. The physical inactivity was reported in different ways such as sedentary lifestyle, not engaged in a sport or fitness program, not engaged in vigorous physical activity for ≥30 min five or more times per week, or more than 4h of activity per week, or more than twice per week of physical activity. Previous engagement in physical activity was assessed as past 6 and 12 months or it was not reported.

2.3 STUDY SELECTION

Articles retrieved through the systematic search were exported into Mendeley, a reference management software program, where the duplicates were removed. Two reviewers independently screened all titles and abstracts for eligibility using a

Spreadsheet. Any disagreements about inclusion of studies were resolved by discussion and details of this process can be seen in Figure 1. Among the 20 studies, there was 28 different groups of interventions, and each one was treated as a separate study for analysis.

Figure 1. Flowchart of the studies selection.



2.4 DATA EXTRACTION

The necessary data for meta-analyzing the CR effects on body composition and physical fitness were extracted from the eligible papers by two independent researchers. Data were extracted from each study for the main variables, absolute/relative VO_2max, and muscle strength. Additional data were collected for secondary variables such as body mass, lean mass, and fat mass. We did not convert absolute to relative values or viceversa; we only used these two options when studies originally presented it. Furthermore, the relative values were included only when they were relativized by body mass and not lean body mass. We searched for average, standard deviation (SD), and sample size of all these variables before and after CR and control interventions. Studies presenting mean and 95% CI values were converted to SD using the equation: $(\sqrt{(n)} \times (UL - LL)/(2 \times T.INV\,(0.05; n-1))$, where n is the sample size, UL is the upper limit, LL is the lower limit and T.INV is the function that calculates the left-tailed inverse of the Student`s T distribution. Studies presenting their variance as standard error (SE) were converted according to the equation $SD = SE \times \sqrt{n}$.

Data about studies population (e.g., number of participants, age, sex and BMI), interventions (e.g., CR doses, duration, combination with exercise interventions, type of exercise added), and other outcomes such as changes in body mass, body fat and lean mass were also collected to further subgroup analysis.

The authors of studies with missing data were contacted via e-mail and unfortunately due to the lack of response, these studies were not included in this meta-analysis[21–23].

2.5 RISK-OF-BIAS ASSESSMENT

The quality of studies was assessed using the PEDro scale [24] removing questions 5 and 6, since it is not possible to the participant and the researcher offering the treatment to be blinded during CR, and the scores ranged from zero to nine.

2.6 STATISTICAL ANALYSIS

Considering the hypothesis that the divergence in the literature was firstly explained by relative and absolute measurements and secondly by the adjuvant exercise interventions added to CR, these factors were isolated within 8 meta-analyses: four outcomes (relative and absolute VO_2max and relative and absolute muscle strength) with two comparisons each (CR vs. Control and CR + EX vs. EX).

We calculated raw mean difference (RMD) for relative cardiorespiratory fitness (ml/kg/min) and absolute cardiorespiratory fitness (L/min), based on the difference in changes of CR and CR+EX against Control and EX, respectively. Nevertheless, muscle strength was assessed in different ways, by different unit measures and therefore standardized mean difference (SMD) was applied for its relative and absolute meta-analyses. Fixed effects models were used for almost all the 8 meta-analyses because they were significantly homogeneous (Q-test); and random effects models were applied for the two heterogeneous meta-analyses (CR vs. Control on relative VO_2max and CR+EX vs. EX on relative muscle strength).

The other confounding factors selected for subgroup analysis were sex, age, BMI, level of physical activity, CR protocols, type of exercise intervention, duration of intervention and characteristics of VO_2max and strength tests. Nevertheless, considering the meta-analyses were homogeneous and did not presented considerable inconsistency (I^2 = 75% to 100%) these tests were not done. Only the meta-analysis of CR+EX vs. EX on relative muscle strength were considerably inconsistent (I^2 = 84.19%), but since it had only 3 studies no subgroup analysis was performed.

The inclusion of different muscle groups strength assessments in the same studies lead to sample overlapping and thus we run further exploratory sensitivity analyses to re-isolate these effects even though the meta-analysis comparing CR and Control on absolute muscle strength had very low inconsistency (I^2 = 17.63%).

To confirm the CR effectiveness between the studies included in the review, we ran three complementary meta-analyses for total body mass (kilograms), fat mass (SMD) and lean mass (SMD), including all the CTs presenting this information.

All analyses were performed using the comprehensive meta-analysis software version 3.3.070, assuming 95% confidence. At last, the risk of publication bias was assessed by Egger's test for each of the 8 meta-analyses.

3 RESULTS

3.1 RISK OF BIAS

The controlled trials ranged from 3 to 8 on the PEDro scale, suggesting a diversity of quality levels. The p-value for Egger's test above 0.1 for the four main meta-analyses suggests no risk of publication bias (relative VO_2max = 0.17, absolute VO_2max = 0.76, relative strength = 0.70 and absolute strength = 0.47).

Table 1. Quality of the studies included (PEDro scale)

first author, year	**1**	**2**	**3**	**4**	**7**	**8**	**9**	**10**	**11**	**Sum**
Amati, 2008 [36]	1	1	0	1	0	1	1	1	1	6
Armamento-Villareal, 2014 [37]	1	1	0	1	1	1	1	1	1	7

Bouchard, 2009 [38]	1	1	0	1	0	1	0	1	1	5
Cox, 2003 [39]	1	1	0	1	0	1	0	1	1	5
Davis, 2009 [40]	1	1	0	1	1	1	0	1	1	6
Dengel, 1996 [41]	1	1	0	1	1	1	0	1	1	6
Elloumi, 2011 [42]	1	1	0	1	0	1	0	1	1	5
Figueroa, 2013 [43]	1	1	0	1	0	1	0	1	1	5
García-Hermoso, 2018 [44]	1	0	0	1	0	1	0	1	1	4
Ghroubi, 2008 [16]	1	1	0	1	0	0	0	0	1	3
Larson-Meyer, 2010 [9]	1	1	1	1	1	1	1	1	1	8
Melanson, 2004 [45]	1	1	1	1	1	1	0	1	1	7
Nicklas, 2015 [10]	1	1	1	1	0	1	0	1	1	6
Nicklas, 2019 [8]	1	1	1	1	0	1	0	1	1	6
Nordby, 2012 [46]	1	1	1	1	0	1	0	1	1	6
Racette, 2017 [13]	1	1	0	1	0	1	1	1	1	6
Rosenkilde, 2018 [47]	1	1	1	1	0	1	0	1	1	6
Ross, 2004[49]	1	1	1	1	0	1	0	1	1	6
Villareal, 2011 [48]	1	1	0	1	0	1	1	1	1	6
Wierik, 1994 [11]	1	1	0	1	0	1	1	1	1	6

Legend: 1: yes; 0: no; N/A: not applicable. Questions:1) Eligibility criteria specified; 2) Random allocation; 3) Concealed allocation; 4) Groups similar at baseline; 5) Subject blinding; 6) Therapist blinding; 7) Assessor blinding; 8) Less than 15% dropouts; 9) Intention-to-treat analysis;10) Between-group statistical comparisons;11) Point measures and variability data. Sum excluding question 1 (0-10).

3.2 PARTICIPANTS

From 531 studies found in the highly sensitive search, 20 met the inclusion criteria comprising a total of 1270 participants. Within these 20 studies, 28 controlled trials were treated as separate studies for analyses. Despite we expected the diverse of the individual's characteristics in the studies included would influence the results, there was significant homogeneity in our findings including in the same analysis men, women, from 10 to 70 years, normal weight, overweight and/or obese subjects, non-physically active (Table 2).

It is necessary to highlight those studies with four intervention groups (CR+EX, EX, CR and Control), for example, Ghroubi et al. [16], were analyzed in the CR+EX vs. EX and in the CR vs. Control meta-analysis. Detailed characteristics about the studies included are described in Table 2.

Table 2. Characteristics of the studies included.

First Author, Year	Subgroups (n#)	Age (Years Mean ± SD)	Sex	BMI (kg/m²)	CR or BM Reduction	Duration (Weeks)	Type of training	ΔBM kg (SMD: Δ FM/ Δ ΔLM)
Amati, 2008 [36]	CR+EX (17)	66.2±0.9	both	32.2±0.8	-500 to 1000 kcal/day	16	AT	**-7.3kg (-2.066/ - 0,696)**
	EX (36)	67±0.6		29.7±0.6				
Armamento-Villareal, 2014 [37]	CR+EX (28)	70±4	both	37.2±5.4	-500 to 750 kcal/day	52	CT	**-6.8kg** (NR/ - 1.174)
	EX (26)	70±4		36.9±5.4				
Armamento-Villareal, 2014 [37]	CR (26)	70±4	both	37.2±4.5	-500 to 750 kcal/day	52	-	**-8.8kg** (NR/ - **1.274)**
	Control (27)	69±4		37.3±4.7				
Bouchard, 2009 [38]	CR+EX (12)	64.4±4.5	F	31.7±2.6	0.5 to 1 kg/week	12	RT	-1.9kg (-0.607/ - 0.138)
	EX (12)	62.8±3.7		30.8±2.2				
Bouchard, 2009 [38]	CR (12)	60.7±4.6	F	31.9±2.7	0.5 to 1 kg/week	12	-	-4kg (-0.488/ - 0.092)
	Control (12)	62.5±3.1		32.3±2.4				
Cox, 2003 (light exercise) [39]	CR+EX (14)	42.4±5	M	30.9±4.3	-4,186 to 6,279 kJ/day	16	AT	**-10.296kg (-2.088/ - 1.798)**
	EX (17)			29.7±3.4				
Cox, 2003 (vigorous exercise) [39]	CR+EX (15)	42.4±5	M	33.3±3.6	-4,186 to 6,279 kJ/day	16	AT	**-10.068kg** (-1.754/ - 0.586)
	EX (13)			30.5±3.9				
Davis, 2009 [40]	CR (10)	15.3±1.1	F	33.8±5.7	-10% of total daily calorie intake	16	-	0.6kg (-0.274/ - 0.07)
	Control (7)	15.1±1.1		34.6±7.4				
Dengel, 1996 [41]	CR+EX (14)	57.6±1.6	M	NR	-300 to 500 kcal/day	40	AT	-8.4kg (**-1.152**/ - 0.094)
	EX (10)	60.3±2.4						
Dengel, 1996 [41]	CR (14)	59.6±2.4	M	NR	-300 to 500 kcal/day	40	-	-8.3kg (**-0.899**/ - 0.3)
	Control (9)	62.8±2.5						
Elloumi, 2011 [42]	CR+EX (7)	13.1±1	M	30.3±4.5	-500 kcal/day	8	AT	-4.3kg (-0.695/ 0.095)
	EX (7)	13.1±1		30.3±4.6				
	CR (6)	13.3±0.6	M	30.3±2.9		8	-	-6.1kg

Elloumi, 2011 [42]	Control (8)	13.2±0.2		30.2±2.2	-500 kcal/day			(-0.879/ 0.016)
Figueroa, 2013 [43]	CR+EX (14)	54±6	F	33.8±0.5	1250 kcal/day	12	RT	-3.3kg (-0.295/ -0.149)
	EX (14)							
García-Hermoso, 2018 [44]	CR+EX (10)	10.7±0.9	M	27.9±3.9	1500 kcal/day	144	AT	0.44kg (-0.709/ NR)
	EX (8)			27.7±2.95				
Ghroubi, 2008 [16]	CR+EX (15)	41.41±3.9	NR	37.45±3.68	-25 to 30% of total daily calorie intake	8	CT	-3.83kg (-0.621/ 0.562)
	EX (13)	39.77±13.1		37.14±5.7				
Ghroubi, 2008 [16]	CR (14)	41.5±11.7	NR	38.74±6.15	-25 to 30% of total daily calorie intake	8	-	-2.42kg (-0.361/ 0.022)
	Control (14)	42.36±9.8		39.2±3.7				
Larson-Meyer, 2010 [9]	CR (12)	39±5	both	27.8±0.3	-25% CR from baseline energy requirements	24	-	**-7.594kg** (0.373/ NR)
	Control (12)	38±8						
Melanson, 2004 [45]	CR+EX (22)	42.6±6	both	31.5±2.8	-500 kcal/day	24	AT	-7.1kg (-0.025/ 0.023)
	EX (19)							
Nicklas, 2015 [10]	CR+EX (55)	69.5±3.7	both	30.6±2.3	-600 kcal/day	20	RT	**-4.8kg (-1.339/ -0.961)**
	EX (56)							
Nicklas, 2019 (moderate CR) [8]	CR+EX (58)	69.2±3.5	both	34.7±3.7	−250 kcal/day	20	AT	**-6.5kg** (**-0.667**/ -0.199)
	EX (44)			34.6±3.1				
Nicklas, 2019 (intense CR) [8]	CR+EX (53)	69.2±3.5	both	34.4±3.7	−600 kcal/day	20	AT	**-7.5kg** (**-0.803**/ -0.233)
	EX (44)			34.6±3.1				
Nordby, 2012 [46]	CR (12)	32±2	M	28±0.4	-600 kcal/day	12	-	-5.2kg (**-1.996**/ 0.311)
	Control (12)	31±2		28±0.4				
Racette, 2017 [13]	CR (120)	37.9±0.5	F	NR	-25% CR relative to daily energy expenditure	96	-	**-7.9kg** (NR/ **-1.09)**
	Control (71)							
Rosenkilde, 2018 [47]	CR (12)	NR	M	NR	-600 kcal/day	12	-	**-5.1kg** (NR/ -0.782)
	Control (12)							
Ross, 2004[49]	CR (15)	43.9±4.9	F	31.3±2	-500 kcal/day	14	-	-7kg (-0.73/ -0.189)
	Control (10)	43.7±6.4						
Villareal, 2011 [48]	CR+EX (28)	70±4	both	37.2±5.4	-500 to 750 kcal/day	52	CT	**-8.1kg**

	EX (26)	70±4		36.9±5.4				**(-1.868/ -1.876)**
Villareal, 2011 [48]	CR (26)	70±4	both	37.2±4.5	-500 to 750 kcal/day	52	-	**-9.6kg (-1.824/ -1.058)**
	Control (27)	69±4		37.3±4.7				
Wierik, 1994 [11]	CR (16)	43±4	M	NR	-20% of total daily calorie intake	10	-	**-4.7kg (-2.329/** - 0.322)
	Control (8)	43±5						

Legend: #: n = participants that completed the entire study; AT: aerobic training; BM: body mass; CR+EX: CR plus exercise training group; CR: caloric restriction group without exercise training; CT: combined training (AT plus RT, and in some cases balance and flexibility exercises too); CR+EX vs. EX: CR controlled trial comparisons with exercise in both groups; EX: only exercise training group; F: female; FM: fat mass; LM: lean mass; M: male; CR vs. Control: CR controlled trial comparisons without exercise in any group; CONTROL: no diet group; NR: not reported; RT: resistance training; Δ: (change); SMD: standardized mean difference; *SMD of body composition changes were described for each study (and subgroup), taking to account differences between CR and C, and the significant reductions ($p<0.05$) were highlighted in bold.

3.3 INTERVENTIONS

The lack of inconsistency also suggested no influence of the different intervention protocols in the results. In general, the CR varied from ~250 kcal/day to more than 1000 kcal/day, however some studies just reported the caloric consumption without show the previous habits and thus, limiting the comparison between protocols. CR interventions last from 8 weeks to 3 years, combining or not exercise protocols (e.g., aerobic, combined or resistance training). The aerobic training (AT) incorporated walking, cycling, jogging, multi-sports games, stair climbing and rowing that varied between intensity (moderate to high) and duration. The resistance training (RT) was based in large muscles groups like leg and chest. The intensity in RT was predominantly moderate. The combined training (CT) was a combination of AT and RT with flexibility and balance exercises, in this type of training, the intensity was of moderate to high. The CR interventions were based in the reduction of total daily calorie intake or body mass weekly reduction in a safe design.

3.4 STUDY OUTCOMES

Significant reduction of body mass, fat mass and lean mass were confirmed following CR compared to non-CR groups (i.e., Control and EX) among the studies included (Table 4), and the body composition effects of each study were reported in table 2.

The addition of CR+EX increased significantly relative VO_2max compared to EX; However, CR+EX did not increase relative strength significantly, compared to EX.

Without EX, CR alone significantly increased both relative VO_2 max and strength (Figure 2). On the other hand, no significant effects were found for any absolute values (Figure 3).

Exploratory sensitivity analyses (data not shown) comparing CR vs. Control on absolute strength for each muscle group showed non-significant improvements for neither knee extension (p=0.16), knee flexion (p=0.08), leg press (p=0.10), other quadriceps exercises (p=0.99), handgrip (p=0.05), bench press (p= 0.05), and total strength (p=0.88). Relative muscle strength was not tested, due to the low number of studies.

Table 3. CR effects on physical fitness.

Outcomes	**k**	**Studies**	**ES (LL; UL)**	**p-value**	**p-diff**
Absolute VO_2max (L/min)					
CR+EX vs. EX (R)	8	[8,39,41,42,45]	0.05 (-0.04; 0.14)	0.25	0.21
CR vs. Control (F)	7	[9,11,13,41,42,47,49]	-0.02 (-0.08; -0.05)	0.60	
Overall (F)	15	[8,9,11,13,39,41,42,45,47,49]	0.01 (-0.05; 0.06)	0.82	
Relative VO_2max (ml/kg/min)					
CR+EX vs. EX (F)	7	[8,36,42,45,48]	1.13 (0.49; 1.78)	**p<0.001**	0.17
CR vs. Control (R)	6	[9,11,13,42,47,48]	2.08 (0.90; 3.27)	**p<0.001**	
Overall (R)	13	[8,9,11,13,36,42,45,47,48]	1.58 (0.83; 2.35)	**p<0.001**	
Absolute Strength (SMD)					
CR+EX vs. EX (F)	10	[10,16,37,38,43,44,48]	-0.05 (-0.23; 0.12)	0.56	0.79
CR vs. Control (F)	16	[9,13,16,37,38,40,48]	-0.08 (-0.19; 0.03)	0.14	
Overall (F)	26	[9,10,13,16,37,38,40,43,44,48]	-0.07 (-0.16; 0.02)	0.12	
Relative Strength (SMD)					
CR+EX vs. EX (R)	3	[10,43]	0.41 (-0.28; 1.09)	0.25	0.86
CR vs. Control (F)	6	[13]	0.47 (0.35; 0.59)	**p<0.001**	
Overall (F)	9	[10,13,43]	0.47 (0.36; 0.58)	**p<0.001**	

Legend: ES: effect size; CR+EX vs. EX: CR controlled trial comparisons with exercise in both groups; k: number of controlled groups; LL: Lower limit; CR vs. control: CR controlled trial comparisons without exercise in any group; p: p-value of hypothesis test for differences between CR and control groups; F: fixed effects; R: random effects; SMD: standardized mean difference; UL: Upper limit. *Significant p-values were highlighted in bold (p<0.05).

Table 4. CR effects on body composition.

Outcomes	k	ref	ES (LL; UL)	p-value	p-diff
Body mass (kg)					
CR+EX vs. EX (R)	16	8,10,16,36–39,41–45,48	-6.59 (-8.03; -5.15)	**p<0.001**	0.63
CR vs. Control (R)	13	9,11,13,16,37,38,40–42,46–49	-5.95 (-8.15; -3.74)	**p<0.001**	
Overall (R)	29	8–11,13,16,36–49	-6.23 (-7.51; -4.94)	**p<0.001**	
Fat mass (SMD)					
CR+EX vs. EX (R)	15	8,10,16,36,38,39,41,42,44,45,48	-1 (-1.32; -0.69)	**p<0.001**	0.79
CR vs. Control (R)	10	9,11,16,38,40–42,46,48,49	-0.92 (-1.45; -0.39)	**p<0.001**	
Overall (R)	25	8–11,16,36,38–46,48,49	-0.97 (-1.24; -0.70)	**p<0.001**	
Lean mass (SMD)					
CR+EX vs. EX (R)	15	8,10,16,36–39,41–43,45,48	-0.50 (-0.82; -0.18)	**p<0.001**	0.92
CR vs. Control (R)	12	11,13,16,37,38,40–42,46–49	-0.48 (-0.81; -0.14)	**p<0.001**	
Overall (R)	27	8,10,11,13,16,36–43,45–49	-0.49 (-0.72; -0.26)	**p<0.001**	

Legend: ES: effect size; CR+EX vs. EX: CR controlled trial comparisons with exercise in both groups; k: number of controlled groups; LL: Lower limit; CR vs. Control: CR controlled trial comparisons without exercise in any group; ref: reference; p: p-value of hypothesis test for differences between CR and control groups; R: random effects; SMD: standardized mean difference; UL: Upper limit. *Significant p-values were highlighted in bold (p<0.05).

Figure 2. Forest plots of CR effects on Relative Physical fitness. Positive values favor CR+EX or CR, while negative values favor EX or Control.

First author, year (Subgroup)	MD	LL	UL	p-Value	Weight
Amati, 2008	-6.100	-13.477	1.277	0.105	0.76
Elloumi, 2011	0.600	-0.499	1.699	0.285	34.08
Melanson, 2004 (Home based)	0.300	-3.876	4.476	0.888	2.36
Melanson, 2004 (Instruction)	1.100	-2.619	4.819	0.562	2.98
Nicklas, 2019 (Intense CR)	1.400	-0.676	3.476	0.186	9.55
Nicklas, 2019 (Moderate CR)	1.100	-1.075	3.275	0.322	8.70
Villareal, 2011	1.700	0.705	2.695	0.001	41.59
Summarized effects	**1.134**	**0.493**	**1.776**	**0.001**	**100**

Overall: p=0.00; I²=1.04%

First author, year	MD	LL	UL	p-Value	Weight
Elloumi, 2011	1.400	0.212	2.588	0.021	21.54
Larson-Meyer, 2010	3.800	2.008	5.592	0.000	16.39
Nordby, 2012	1.600	-3.586	6.786	0.545	3.96
Racette, 2017	3.000	1.325	4.675	0.000	17.32
Rosenkilde, 2018	1.700	-0.821	4.221	0.186	11.56
Villareal, 2011	2.600	1.558	3.642	0.000	22.84
Wierik, 1994	-3.360	-7.233	0.513	0.089	6.39
Summarized effects	**2.083**	**0.972**	**3.194**	**0.000**	**100**

Overall: p<0.001; I²=65%

First author, year (Subgroup)	SMD	LL	UL	p-Value	Weight
Figueroa, 2013	0.097	-0.644	0.838	0.798	27.65
Nicklas, 2015 (Handgrip)	1.000	0.605	1.395	0.000	35.94
Nicklas, 2015 (KE)	0.055	-0.317	0.428	0.771	36.42
Summarized effects	**0.406**	**-0.280**	**1.093**	**0.246**	**100**

Overall: p=0.25; I²=84.19%

First author, year (Subgroup)	SMD	LL	UL	p-Value	Weight
Racette, 2017 (Isometric KE 45)	0.395	0.097	0.692	0.009	16.80
Racette, 2017 (Isometric KF 45)	0.563	0.263	0.864	0.000	16.49
Racette, 2017 (KE 180)	0.520	0.221	0.820	0.001	16.58
Racette, 2017 (KE 60)	0.516	0.217	0.816	0.001	16.59
Racette, 2017 (KF 180)	0.373	0.076	0.670	0.014	16.83
Racette, 2017 (KF 60)	0.451	0.152	0.749	0.003	16.71
Summarized effects	**0.469**	**0.347**	**0.591**	**0.000**	**100**

Overall: p<0.001; I²=0%

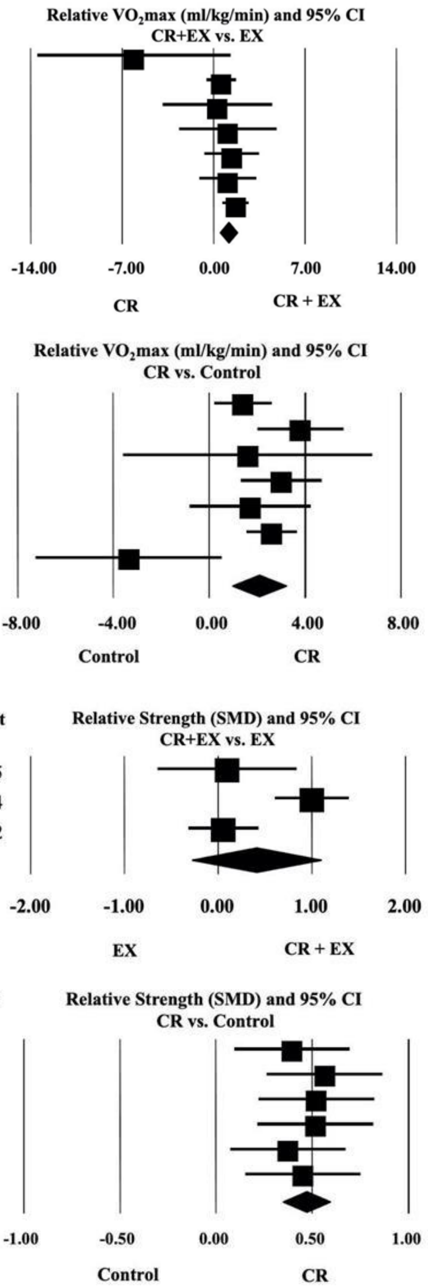
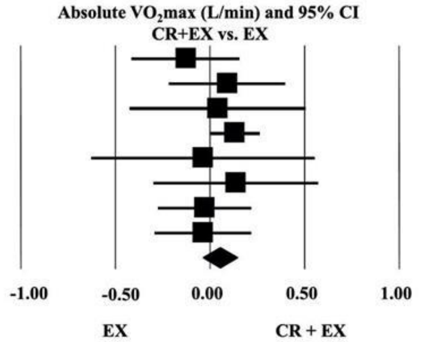


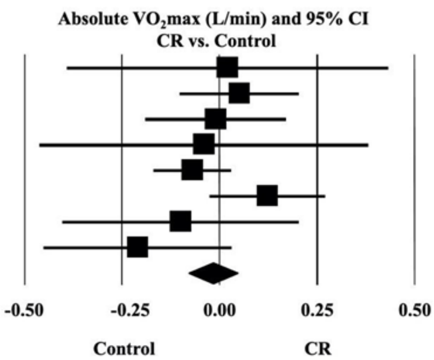
Figure 3. Forest plots of CR effects on Absolute Physical fitness. Positive values favor CR+EX or CR, while negative values favor EX or Control.

First author, year (subgroup)	MD	LL	UL	p-Value	Weight
Cox, 2003 (Light)	-0.130	-0.414	0.154	0.370	9.84
Cox, 2003 (Vigorous)	0.090	-0.218	0.398	0.566	8.40
Dengel, 1996	0.040	-0.426	0.506	0.866	3.67
Elloumi, 2011	0.130	-0.001	0.261	0.052	46.13
Melanson, 2004 (Home based)	-0.039	-0.629	0.551	0.897	2.28
Melanson, 2004 (Instruction)	0.136	-0.299	0.571	0.540	4.19
Nicklas, 2019 (Intense CR)	-0.030	-0.276	0.216	0.811	13.15
Nicklas, 2019 (Moderate CR)	-0.039	-0.293	0.215	0.763	12.33
Summarized effects	**0.052**	**-0.037**	**0.141**	**0.251**	**100**



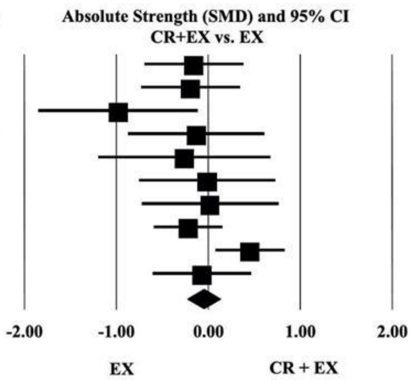
Overall: p=0.25; I^2=0%

First author, year	MD	LL	UL	p-Value	Weight
Dengel, 1996	0.020	-0.391	0.431	0.924	2.25
Elloumi, 2011	0.050	-0.102	0.202	0.518	16.56
Larson-Meyer, 2010	-0.010	-0.190	0.170	0.913	11.73
Nordby, 2012	-0.040	-0.461	0.381	0.852	2.15
Racette, 2017	-0.070	-0.169	0.029	0.165	39.00
Rosenkilde, 2018	0.122	-0.025	0.269	0.105	17.53
Ross, 2004	-0.100	-0.403	0.203	0.517	4.16
Wierik, 1994	-0.210	-0.450	0.030	0.087	6.61
Summarized effects	**-0.017**	**-0.079**	**0.044**	**0.584**	**100**



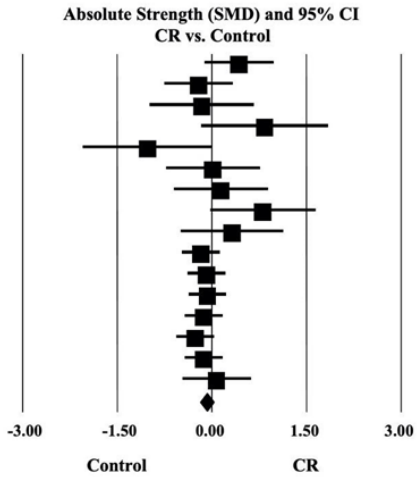
Overall: p=0.60; I^2=25.66%

First author, year (Subgroup)	SMD	LL	UL	p-Value	Weight
Armamento-Villareal, 2014 (KE)	-0.157	-0.692	0.377	0.564	10.72
Armamento-Villareal, 2014 (KF)	-0.193	-0.728	0.342	0.480	10.70
Bouchard, 2009	-0.983	-1.849	-0.117	0.026	4.08
Figueroa, 2013 b	-0.132	-0.873	0.610	0.728	5.57
García-Hermoso, 2019	-0.261	-1.194	0.673	0.584	3.51
Ghroubi, 2008 (Quadriceps)	-0.013	-0.756	0.729	0.972	5.55
Ghroubi, 2008 (KF)	0.017	-0.726	0.760	0.964	5.55
Nicklas, 2015b (KE)	-0.219	-0.592	0.154	0.250	21.99
Nicklas, 2015b (Handgrip)	0.452	0.076	0.829	0.019	21.57
Villareal, 2011	-0.069	-0.603	0.465	0.801	10.74
Summarized effects	**-0.052**	**-0.227**	**0.123**	**0.561**	**100**



Overall: p=0.56; I^2=29.64%

First author, year (Subgroup)	SMD	LL	UL	p-Value	Weight
Armamento-Villareal, 2014 (KE)	0.429	-0.116	0.974	0.123	3.78
Armamento-Villareal, 2014 (KF)	-0.212	-0.752	0.328	0.442	3.85
Bouchard, 2009	-0.159	-0.979	0.660	0.703	1.67
Davis, 2009 (Leg press)	0.838	-0.168	1.844	0.103	1.11
Davis, 2009 (Bench press)	-1.018	-2.043	0.006	0.051	1.07
Ghroubi, 2008 (Quadriceps)	0.019	-0.722	0.759	0.961	2.04
Ghroubi, 2008 (KF)	0.143	-0.599	0.885	0.706	2.04
Larson-Meyer, 2010 (KE)	0.811	-0.021	1.643	0.056	1.62
Larson-Meyer, 2010 (KF)	0.322	-0.484	1.127	0.434	1.73
Racette, 2017 (Isometric KE 45)	-0.171	-0.467	0.124	0.256	12.86
Racette, 2017 (Isometric KF 45)	-0.082	-0.377	0.213	0.587	12.90
Racette, 2017 (KE 180)	-0.067	-0.362	0.228	0.654	12.90
Racette, 2017 (KE 60)	-0.129	-0.424	0.167	0.393	12.88
Racette, 2017 (KF 180)	-0.265	-0.561	0.031	0.079	12.80
Racette, 2017 (KF 60)	-0.128	-0.423	0.168	0.397	12.88
Villareal, 2011	0.075	-0.464	0.614	0.785	3.87
Summarized effects	**-0.079**	**-0.185**	**0.026**	**0.141**	**100**



Overall: p=0.14; I^2=17.63%

4 DISCUSSION

The main results of these meta-analyses demonstrated that CR alone improved relative VO_2max and relative strength compared to control. These findings suggest that CR may reduce all-cause mortality risks and contributes to the maintenance of daily life activities in older individuals. Previous studies demonstrated that improvements in VO_2max are associated with reduced risk of mortality [26]. An increase in VO_2max of ~2.5-2.8 mL/kg/min may benefit high-risk populations (VO_2max < 18.4 mL/kg/min) by reductions in fatigue and disability [8].

In the same way, a decrease in strength affects the daily life activities function and mortality in old adults [12]. During aging there is a progressive muscle atrophy and a decline in muscle contractile function, negatively influencing quality of life and predisposing elderly individuals to increased risk of falls, morbidity, and mortality [27,28]. CR by itself has proved to delay the sarcopenia onset in Rhesus monkeys besides the attenuation of other age-declines[29]. CR might improve muscle cell function by reduction in oxidative stress and inflammation, which occurs during aging or with increased body fat. Additionally, CR may benefit cell function by repairing other mechanisms such as autophagy [30–32].

Oxidative stress is thought to play an important role in skeletal muscle dysfunction and atrophy seen in aging, disuse, and many skeletal muscle pathologies [33]. Considering that exercise training is associated with reduced oxidative stress and higher muscle strength, it makes sense that CR had no additional benefits on muscle strength compared to exercise intervention (CR+EX vs. EX), but was effective in non-exercise interventions (CR vs. Control). Furthermore, we expected exercise training intervention to prevent muscle loss at some extent, that could also blunt the CR effects in the exercise trials. Contradictorily, in the present study, CR led to the same lean mass reduction in the exercise (CR+EX vs. EX: -0.48 [-0.81; -0.14], $p<0.001$) and non-exercise trials (CR vs. Control: -0.50 [-0.82; -0.18], $p<0.001$). Likely it could be explained by the diverse type of exercise training in these trials. Only three studies prescribed RT alone, which could be the safest option to prevent muscle loss. The other three studies prescribed CT and one of them AT, and these types of training could further exacerbate caloric expenditure without prevent muscle loss.

Regarding the endurance capacity, CR also led to additional benefits in exercise trials (CR+EX vs. EX), suggesting CR effects on VO_2max could be complementary to exercise effects concomitantly with muscle loss. The improvement in mitochondrial function, efficient mitophagy, and other metabolic pathways could also favor VO_2max to a higher extent than just exercise training would do [1,34].

This study revealed substantial weight loss after CR intervention (-6.23[-7.51; -4.94]kg, p<0.001), large fat reduction (SMD: -0.97 [-1.24; -0.70], p<0.001), and moderate muscle mass reduction (SMD: -0.49 [-0.72; -0.26], p<0.001) within the studies included. Although CR improved relative VO_2max, there was no statistically significant changes in absolute values. This result suggests that changes in VO_2max were dependent on weight loss, which may reduce the workload caused on the cardiorespiratory system and causes improvements in oxygen delivery to the muscles. The effects of CR on relative VO_2max raises a new question: How long the physical fitness benefits can be maintained in the new "lighter" body weight? Future studies following up individuals after the end of interventions would clarify this issue.

Although muscle mass loss could be considered a negative side effect of CR, previous studies in animals support an increase in muscle quality with CR [7]. In fact, the increase in relative VO_2max and strength with CR vs. Control also indicates that the moderate muscle mass reduction did not impair the physical fitness. Since we know the muscle mass maintenance has its own benefits on health, it is noteworthy that adding RT intervention to CR completely prevent CR-induced muscle loss [35].

It is necessary to highlight that although we did not exclude studies by age, BMI or baseline level of physical activity most studies included overweight, obese and non-physically active individuals. Therefore, this meta-analysis included only non-physically active individuals and the outcomes cannot be extended to athletes and healthy physically active individuals. The few previous studies analyzing the effects of CR on athletes or highly physically active individuals are controversial, presenting null, beneficial and malefic effects on performance [18–20]. Moreover, there are some confounding factors influencing the performance of these highly physically active individuals such as the type of nutrition intake [50] or the intervention duration. Thus, based on the benefits we found, we strongly recommend other researchers to investigate the potential benefits of CR in highly training individuals, especially the benefits on endurance.

Some limitations should be considered. Firstly, such findings refer to a non-physically active, overweight or obese population, as it was the population included in most studies. Thus, it is not possible to extrapolate our findings to athletes and healthy physically active individuals for example. Secondly, muscle strength results should be interpreted carefully since the meta-analysis of relative muscle strength included only 3 studies, while absolute strength included 10 studies with considerable overlapping of the same samples.

5 CONCLUSION

In addition to improvements in many health aspects, this meta-analysis confirms that CR also improves cardiorespiratory fitness (VO_2max) and muscle strength in non-physically active individuals, even when compared to exercise training alone. Additionally, increases in VO_2max are dependent on weight loss magnitude.

The practical application of this study suggests that non-active or obese individuals may benefit their overall health and relative physical fitness by reducing energy intake without nutrient deficiency.

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REFERENCES

1. Fontana L, Partridge L. Promoting health and longevity through diet: From model organisms to humans. Cell. 2015; 161(1):106–18. doi:10.1016/j.cell.2015.02.020.

2. Mitchell SJ, Madrigal-Matute J, Scheibye-Knudsen M, Fang E, Aon M, González-Reyes JA, et al. Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice. Cell Metab. 2016; 23(6):1093–112. doi:10.1016/j.cmet.2016.05.027.

3. Balasubramanian P, Howell PR, Anderson RM. Aging and Caloric Restriction Research: A Biological Perspective With Translational Potential. EBioMedicine. 2017; 21: 37–44. doi:10.1016/j.ebiom.2017.06.015.

4. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: An update. Ageing Research Reviews. 2017; 39: 36–45. doi:10.1016/j.arr.2016.08.005.

5. Ott B, Skurk T, Hastreiter L, Lagkouvardos I, Fischer S, Büttner J, et al. Effect of caloric restriction on gut permeability, inflammation markers, and fecal microbiota in obese women. Sci Rep. 2017; **7**(1): 1-10. doi:10.1038/s41598-017-12109-9.

6. Brestoff JR, Artis D. Immune regulation of metabolic homeostasis in health and disease. Cell. 2015; 161(1): 146–60. doi:10.1016/j.cell.2015.02.022.

7. Yamada Y, Kemnitz JW, Weindruch R, Anderson RM, Schoeller DA, Colman RJ. Caloric Restriction and Healthy Life Span: Frail Phenotype of Nonhuman Primates in the Wisconsin National Primate Research Center Caloric Restriction Study. J Gerontol A. 2018; **7**3(3): 273–8. doi:10.1093/gerona/glx059.

8. Nicklas BJ, Brinkley TE, Houston DK, Lyles MF, Hugenschmidt CE, Beavers KM, et al. Effects of Caloric Restriction on Cardiorespiratory Fitness, Fatigue, and Disability Responses to Aerobic Exercise in Older Adults with Obesity: A Randomized Controlled Trial. Journals Gerontol A. 2019; 74(7): 1084–90. doi:10.1093/gerona/gly159.

9. Larson-Meyer DE, Redman L, Heilbronn LK, Martin CK, Ravussin E. Caloric restriction with or without exercise: the fitness versus fatness debate. Med Sci Sports Exerc. 2010; 42(1): 152–9. doi:10.1249/MSS.0b013e3181ad7f17.

10. Nicklas BJ, Chmelo E, Delbono O, Carr JJ, Lyles MF, Marsh AP. Effects of resistance training with and without caloric restriction on physical function and mobility in overweight and obese older adults: a randomized controlled trial. Am J Clin Nutr. 2015; 101(5): 991–9. doi:10.3945/ajcn.114.105270.

11. Velthuis-te Wierik EJ, Hoogzaad L V, van den Berg H, Schaafsma G. Effects of moderate energy restriction on physical performance and substrate utilization in non-obese men. Int J Sports Med. 1994; 15(8): 478–84. doi:10.1055/s-2007-1021091.

12. Naharudin MN Bin, Yusof A. The effect of 10 days of intermittent fasting on Wingate anaerobic power and prolonged high-intensity time-to-exhaustion cycling performance. Eur J Sport Sci. 2018; 18(5): 667–76. doi:10.1080/17461391.2018.1438520.

13. Racette SB, Rochon J, Uhrich ML, Villareal DT, DAS SK, Fontana L, et al. Effects of Two Years of Calorie Restriction on Aerobic Capacity and Muscle Strength. Med Sci Sports Exerc. 2017; 49(11): 2240–9. doi:10.1249/MSS.0000000000001353.

14. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011; 43:1334–59. doi:10.1249/MSS.0b013e318213fefb.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine. 2009; 339: b2535. doi:10.1371/journal.pmed.1000097.

16. Ghroubi S, Elleuch H, Kaffel N, Echikh T, Abid M, Elleuch MH. [Contribution of exercise and diet in the management of knee osteoarthritis in the obese]. Ann Readapt Med Phys. 2008; 51: 663–70. doi:10.1016/j.annrmp.2008.07.035.

17. Dhahbi JM, Kim HJ, Mote PL, Beaver RJ, Spindler SR. Temporal linkage between the phenotypic and genomic responses to caloric restriction. Proc Natl Acad Sci U S A. 2004; 101: 5524–9. doi:10.1073/pnas.0305300101.

18. Artioli GG, Iglesias RT, Franchini E, Gualano B, Kashiwagura DB, Solis MY, et al. Rapid weight loss followed by recovery time does not affect judo-related performance. J Sports Sci. 2010; 28(1): 21–32. doi:10.1080/02640410903428574.

19. Naharudin MN Bin, Yusof A. The effect of 10 days of intermittent fasting on Wingate anaerobic power and prolonged high-intensity time-to-exhaustion cycling performance. Eur J Sport Sci. 2018; 18(5): 667–76. doi:10.1080/17461391.2018.1438520.

20. Booth CK, Coad RA, Forbes-Ewan CH, Thomson GF, Niro PJ. The Physiological and Psychological Effects of Combat Ration Feeding during a 12-Day Training Exercise in the Tropics. Mil Med. 2003; 168(1): 63–70. doi:10.1093/milmed/168.1.63.

21. Imayama I, Alfano CM, Kong A, Foster-Schubert KE, Bain CE, Xiao L, et al. Dietary weight loss and exercise interventions effects on quality of life in overweight/obese postmenopausal women: a randomized controlled trial. Int J Behav Nutr Phys Act. 2011; 8(1): 1-12. doi:10.1186/1479-5868-8-118.

22. Vissers D, Verrijken A, Mertens I, Van Gils C, Van de Sompel A, Truijen S, et al. Effect of long-term whole body vibration training on visceral adipose tissue: a preliminary report. Obes Facts. 2010; 3: 93–100. doi:10.1159/000301785.

23. Mihalko SL, Cox P, Beavers DP, Miller GD, Nicklas BJ, Lyles M, et al. Effect of intensive diet and exercise on self-efficacy in overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. Transl Behav Med. 2019; 9(2): 227–35. doi:10.1093/tbm/iby037.

24. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003; 83(8): 713–21. doi.org/10.1093/ptj/83.8.713.

25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650): 924-6. doi:10.1136/bmj.39489.470347.AD.

26. Jiménez-Pavón D, Lavie CJ, Blair SN. The role of cardiorespiratory fitness on the risk of sudden cardiac death at the population level: A systematic review and meta-analysis of the available evidence. Prog Cardiovasc Dis. 2019; 62(3): 279–87. doi:10.1016/j.pcad.2019.05.003.

27. Anagnostou M-E, Hepple RT. Mitochondrial Mechanisms of Neuromuscular Junction Degeneration with Aging. Cells. 2020; 9(1): 197. doi:10.3390/cells9010197.

28. Angulo J, El Assar M, Rodríguez-Mañas L. Frailty and sarcopenia as the basis for the phenotypic manifestation of chronic diseases in older adults. Molecular Aspects of Medicine. 2016; 50: 1–32. doi:10.1016/j.mam.2016.06.001.

29. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun. 2014; 5(1): 1–5. doi:10.1038/ncomms4557.

30. Il'yasova D, Fontana L, Bhapkar M, Pieper CF, Spasojevic I, Redman LM, et al. Effects of 2 years of caloric restriction on oxidative status assessed by urinary F2-isoprostanes: The CALERIE 2 randomized clinical trial. Aging Cell. 2018; 17. doi:10.1111/acel.12719.

31. Meydani SN, Das SK, Pieper CF, Lewis MR, Klein S, Dixit VD, et al. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: A randomized controlled trial in non-obese humans. Aging (Albany NY). 2016; 8(7): 1416–31. doi:10.18632/aging.100994.

32. Yang L, Licastro D, Cava E, Veronese N, Spelta F, Rizza W, et al. Long-Term Calorie Restriction Enhances Cellular Quality-Control Processes in Human Skeletal Muscle. Cell Rep. 2016; 14(3): 422–8. doi:10.1016/j.celrep.2015.12.042.

33. Powers SK, Smuder AJ, Judge AR. Oxidative stress and disuse muscle atrophy: Cause or consequence?. Curr Opin Clin Nutr Metab Care. 2012; 15(3) 240–5. doi:10.1097/MCO.0b013e328352b4c2.

34. Brown-Borg HM, Rakoczy S. Metabolic adaptations to short-term every-other-day feeding in long-living Ames dwarf mice. Exp Gerontol. 2013; 48(9): 905–19. doi:10.1016/j.exger.2013.06.009.

35. Sardeli A V, Komatsu TR, Mori MA, Gáspari AF, Chacon-Mikahil MPT. Resistance Training Prevents Muscle Loss Induced by Caloric Restriction in Obese Elderly Individuals: A Systematic Review and Meta-Analysis. Nutrients. 2018; 10(4): 423. doi:10.3390/nu10040423.

36. Amati F, Dubé JJ, Shay C, Goodpaster BH. Separate and combined effects of exercise training and weight loss on exercise efficiency and substrate oxidation. J Appl Physiol. 2008; 105:825–31. doi:10.1152/japplphysiol.90384.2008.

37. Armamento-Villareal R, Aguirre L, Napoli N, Shah K, Hilton T, Sinacore DR, et al. Changes in thigh muscle volume predict bone mineral density response to lifestyle therapy in frail, obese older adults. Osteoporos Int. 2014; 25(2): 551–8. doi:10.1007/s00198-013-2450-2.

38. Bouchard DR, Soucy L, Senechal M, Dionne IJ, Brochu M. Impact of resistance training with or without caloric restriction on physical capacity in obese older women. Menopause. 2009; 16(1): 66–72. doi:10.1097/gme.0b013e31817dacf7.

39. Cox KL, Burke V, Morton AR, Beilin LJ, Puddey IB. The independent and combined effects of 16 weeks of vigorous exercise and energy restriction on body mass and composition in free-living overweight men--a randomized controlled trial. Metabolism. 2003; 52(1): 107–15. doi:10.1053/meta.2003.50017.

40. Davis JN, Tung A, Chak SS, Ventura EE, Byrd-Williams CE, Alexander KE, et al. Aerobic and strength training reduces adiposity in overweight latina adolescents. Med Sci Sports Exerc. 2009; 41(7): 1494–503. doi:10.1249/MSS.0b013e31819b6aea.

41. Dengel DR, Pratley RE, Hagberg JM, Rogus EM, Goldberg AP. Distinct effects of aerobic exercise training and weight loss on glucose homeostasis in obese sedentary men. J Appl Physiol. 1996; 81: 318–25. doi:10.1152/jappl.1996.81.1.318.

42. Elloumi M, Makni E, Ounis O Ben, Moalla W, Zbidi A, Zaoueli M, et al. Six-minute walking test and the assessment of cardiorespiratory responses during weight-loss programmes in obese children. Physiother Res Int. 2011; 16(1): 32–42. doi:10.1002/pri.470.

43. Figueroa A, Vicil F, Sanchez-Gonzalez MA, Wong A, Ormsbee MJ, Hooshmand S, et al. Effects of diet and/or low-intensity resistance exercise training on arterial stiffness, adiposity, and lean mass in obese postmenopausal women. Am J Hypertens. 2013; 26(3): 416–23. doi:10.1093/ajh/hps050.

44. García-Hermoso A, Saavedra JM, Escalante Y, Domínguez AM, Castro-Piñero J. Effects of an exercise program with or without a diet on physical fitness in obese boys: A three-year follow-up. Prog Nutr. 2018; 20(1): 94–103. doi:10.23751/pn.v20i1.5836.

45. Melanson KJ, Dell'Olio J, Carpenter MR, Angelopoulos TJ. Changes in multiple health outcomes at 12 and 24 weeks resulting from 12 weeks of exercise counseling with or without dietary counseling in obese adults. Nutrition. 2004; 20(10): 849–56. doi:10.1016/j.nut.2004.06.004.

46. Nordby P, Auerbach PL, Rosenkilde M, Kristiansen L, Thomasen JR, Rygaard L, et al. Endurance training per se increases metabolic health in young, moderately overweight men. Obesity. 2012; 20(11): 2202–12. doi:10.1038/oby.2012.70.

47. Rosenkilde M, Rygaard L, Nordby P, Nielsen LB, Stallknecht B. Exercise and weight loss effects on cardiovascular risk factors in overweight men. J Appl Physiol. 2018; 125(3): 901–8. doi:10.1152/japplphysiol.01092.2017.

48. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011; 364(13): 1218–29. doi:10.1056/NEJMoa1008234.

49. Ross R, Janssen I, Dawson J, Kungl A-M, Kuk JL, Wong SL, et al. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obes Res. 2004; 12(5): 789–98. doi:10.1038/oby.2004.95.

50. Ribeiro JLC, Silva AF, Mendes GS, Aguiar LL, Oribe LA. Intermittent fasting is better than simple caloric restriction? A review. Braz. J. Hea. Rev. 2020; 3 (4): 9340-9343. doi: :10.34119/bjhrv3n4-171.