Published in final edited form as:

Curr Nutr Rep. 2015 June ; 4(2): 143–155. doi:10.1007/s13668-015-0123-9.

Caloric restriction for treatment of geriatric obesity: Do the benefits outweigh the risks?

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Abstract

Most evidence for the health benefits of prescribing caloric restriction (CR) for weight loss is derived from randomized, controlled trials (RCTs) in young/middle-aged adults; there are very few RCTs in older adults in which the isolated effects of CR can be deciphered. The purpose of this review is to summarize the RCT evidence of the benefits (and potential risks) of CR for the treatment of obesity in older adults. We identified only 19 published papers from 10 RCTs ranging from 3 to 18 months that met the criteria of independent effects of a CR component and were conducted in adults with a mean age 65 yrs. Overall, the results show a beneficial treatment effect for improving some metabolic, functional and body composition outcomes with few documented risks. However, all outcomes were assessed immediately after treatment cessation. Thus, until additional scientifically rigorous evidence with long-term follow-up is available, the risk-to-benefit ratio of CR for the treatment of obesity in older adults remains unclear.

Keywords

Overweight; Obesity; Weight loss; Caloric restriction; Older adults; Randomized Clinical trial; Physical Function; Body Composition

Introduction

Obesity is a chronic disease that affects individuals of all ages. Treatment of obesity, through modifications in diet and physical activity behavior that cause reductions in body weight, markedly improves individual cardiometabolic risk and reduces collective incidence of metabolic syndrome and type 2 diabetes [1–3]. However, the vast majority of evidence for the health benefits of weight loss is derived from randomized, controlled trials (RCTs)

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Eve Normandin, Denise K. Houston, and Barbara J. Nicklas declare that they have no conflict of interest.

conducted in young to middle-aged adults (e.g., <65 years). Thus, treating obesity in young-old (e.g., 65–74 years), and especially in old (those greater than 75 years), adults is controversial given the dearth of RCTs conducted in this population, the lack of consensus regarding the health risks associated with obesity in this age group, the uncertain long-term benefits of intentional weight loss, and the potentially harmful effects of weight loss on muscle mass and bone mineral density [4–8]. Hence, the purpose of this review is to summarize the RCT evidence of the health benefits and risks resulting from reducing caloric intake to treat obesity in older adults. We focused solely on trials designed to elicit weight loss via caloric restriction (CR) since the health benefits of exercise are evident in this age group [9].

The aging, obese population

In the 4th century BC, Plato divided the human lifespan into six phases, the last two constituting “Old Age” (62–79 years) and “Advanced Age (80+ years)”. The last phase, he noted, “is one that, fortunately, few attain” [10]. This statement is less true in the 21st century, as both the proportion of older people and maximal lifespan are increasing [11]. According to the United States Census Bureau, about 27 million people are young-old (65–74 years) and 20 million are old-old (75+ years), and these numbers are expected to nearly double by 2030 [12]. Moreover, people are living longer (life expectancy for women is 81.2 years, and for men is 76.4 years [13, 14]) and can expect to live nearly 20 years in Plato’s defined “old age” phase of life. Fortunately, most individuals in their 60s and 70s are healthy, and still functional and able to care for themselves. In fact, disability trends are decreasing even as life expectancy is increasing [15, 16].

Whereas the major health threats of earlier generations were infectious and parasitic disease, currently, chronic diseases, such as heart disease and cancer (the current leading causes of death), are more common and impose the greatest burden on global health [11, 14]. Unfortunately, the trends for increased life expectancy with decreased disability may not continue or could be reversed in future generations, in part because of the rising prevalence of obesity among all ages. Obesity, operationalized as a body mass index (BMI) ≥ 30 kg/m², leads to a higher risk of numerous chronic illnesses and premature death in young and middle-aged adults [17, 18]. Thus, the increase in obesity over the past half-century [19] may potentially limit growth in life expectancy [20]. Data from the 2007–2010 U.S. National Health and Nutrition Examination Survey showed that 34.6% of adults 65+ years, and 27.8% of those 75+ years, were obese [21]. Alarming, this is a nearly 10% increase since 1999–2003, illuminating the effects of the shifting age demographics on the prevalence of obesity among the geriatric population. Since obesity is a major risk factor for disability [22], the growing prevalence of obesity in this age group could lead to a reversal of improved disability trends.

Defining obesity in older adults

The condition and diagnoses of obesity should be applied to individuals with excess accumulation of adipose tissue to the extent that health is impaired. The current World Health Organization classification of obesity is based on BMI cut-points that are associated

with increased mortality and risk for type 2 diabetes and CVD [23]. However, this definition of obesity may not be as applicable in older adults for at least two reasons: 1) BMI is a crude measure of adiposity, especially in older people in whom stature and body composition are changing, nor does it account for the wide variation in location of body fat which poses even stronger health risks than total adiposity [24, 25]; and 2) the adverse consequences of excess adipose tissue may extend beyond chronic disease and early mortality in this age group. Thus, there is potential misclassification of the health risks related to obesity in older adults using the current standards.

Aging is characterized by considerable changes in body composition. Most notably a loss of skeletal muscle mass (sarcopenia) [26, 27], and gain and redistribution of fat to less desirable locations (i.e. within the abdominal cavity and muscle) [28]. The combination of sarcopenia and fat mass accumulation in an aging population, known as sarcopenic obesity [29], may be a stronger risk factor than BMI in this population, as it is associated with higher morbidity, mortality, and disability [30–32]. In addition, waist circumference may be as good as, or even better, than BMI as a measure of excess adiposity in older adults [33–36]. However, more data are needed to accurately determine appropriate cut-points of sarcopenic obesity and/or waist circumference that are more closely associated with impaired health than BMI. These data are critical for identifying those older adults for whom the benefits of weight loss would outweigh potential treatment risks.

Caloric restriction for the treatment of obesity in older adults: What is the evidence?

The recently updated treatment guidelines for managing obesity in adults recommends an intensive lifestyle intervention involving behavioral counseling, caloric restriction (CR), and regular exercise to achieve weight loss for adults of all ages [3]. However, this report also acknowledges that available literature does not address whether age modifies the benefits of weight loss and that *“there is a need for further research to understand the most appropriate strategies and prescriptions for weight loss for some key populations, including older adults”* [3]. Furthermore, although a position statement by the American Society for Nutrition and The Obesity Society from a decade ago stated that *“...current data show that weight-loss therapy improves physical function, quality of life, and the medical complications associated with obesity in older persons”*, the authors acknowledged that most of the studies they reviewed were conducted primarily in middle-aged persons (ages 40–65 years at baseline) [37]. Thus, the risk-to-benefit ratio of obesity treatment (e.g., CR for weight loss) remains controversial in older adults. Here we summarize the entirety of the published scientific evidence from RCTs comparing a CR treatment to a control group (to allow for isolation of the independent effects of the CR/diet component) that were conducted in adults with a mean age 65 yrs. We identified 19 published papers from 10 RCTs (Table 1) with a combined sample size of 1981 (range of n=22 to n=585) [38–56]. The treatments ranged from CR alone (achieved through behavioral counseling, meal replacements, or controlled feeding interventions) to CR plus exercise training that were compared to a control group that consisted of usual care (e.g., no intervention) or to an identical exercise training intervention without CR. For this review, we only summarize the main effects of the

CR/diet treatment. Treatment duration ranged from three to 18 months and the degree of weight loss achieved in the treatment arms varied from very little in several trials (–3.5 kg) to up to –10.6 kg in the IDEA study [51]. Most of the reported health outcomes either involved physical function, body composition, or cardiometabolic variables, which are relevant geriatric outcomes, but no trial reported a comprehensive assessment of health risks and benefits in a single population.

Benefits of obesity treatment in older adults

Effects of treatment on body composition and regional fat distribution

The published trials show that adherence to CR is capable of inducing a 5–10% loss of body weight in older adults, which, in younger and middle-aged adults, is a clinically significant decrease that improves health [57]—though what constitutes a clinically significant weight loss in older adults is not known. This reduced body weight can be maintained for 12–18 months with a continued weight maintenance program in several of the longer-term trials (see Table 1) [38, 40, 46, 48, 51]. Some of the trials examined changes in body composition and, as expected, the CR treatment resulted in greater loss of both fat and lean (muscle) mass compared to control or exercise without CR [42, 45, 47, 48, 51, 53, 56].

Abdominal fat—The accumulation of abdominal fat, especially within the abdominal cavity (visceral) [58], is more strongly associated with insulin resistance [59], hyperlipidemia [59, 60], hypertension and low-grade inflammation [61] than total adiposity. Therefore, decreasing abdominal fat in older adults may have important beneficial effects on risk factors for diabetes and CVD [62]. Four trials show an independent effect of CR on some index of abdominal fat [43, 47, 54, 55], but results do not show a preferential loss of visceral adipose tissue.

Thigh fat content—A decrease in intermuscular fat may also be clinically relevant in older adults since excess fat within leg muscles is the strongest body composition predictor of impaired physical function in older individuals [63, 64]. Six trials examined the effect of CR on total thigh fat [47, 48, 55, 56], subcutaneous and intermuscular fat, [47, 55, 56] and/or intramyocellular lipid content of thigh muscle [42, 45] in older adults. The addition of CR to exercise decreased total and/or subcutaneous thigh fat in four studies [47, 48, 55, 56]; however, interestingly, no significant independent effect of CR on the magnitude of intermuscular fat was observed in any trial [47, 56]. As for intramyocellular lipid content, one small study found that, despite a greater loss of body mass in the CR with exercise group, intramyocellular lipid decreased as much in the exercise only group [42]. However, another small study showed separate effects of CR and exercise on intramyocellular lipid [45]; they observed that an 8% decrease in body mass with CR corresponded to a 16% decrease in intramyocellular lipid, whereas a 2% decrease in body mass with exercise corresponded to a 40% increase in intramyocellular lipid. Obviously, more data are needed before any definitive conclusions can be made regarding the effects of diet-induced weight loss on fat accumulation between and within skeletal muscle in this age group.

Effects of treatment on physical function

Obesity strongly predisposes individuals to the onset of mobility disability, which is one of the most costly complications of obesity in this age group [65, 66]. Studies consistently show that elevated BMI in older women and men is strongly associated with the presence of poor function and future decline in physical performance or the development of disability [67, 68]. Obesity-associated inflammatory milieu, sarcopenia, and impairment of muscle function are important contributing factors through which obesity poses a threat to earlier onset of disability with aging [31, 32, 69].

Although obesity is an important risk factor for disability in older adults, to date, only a handful of RCTs have quantified the effectiveness of CR on physical function in older individuals [40, 46–48, 51, 56]. The results of these trials are difficult to compare due to the variable direct and indirect approaches used to measure physical function and differences in the initial health of participants. Four trials examined the effects of a CR intervention on self-reported functional ability [40, 48, 51, 56] and all demonstrate an independent main effect of CR, though all of these interventions also included an exercise component. Notably, two of these trials showed no difference in self-reported function between CR alone and exercise alone [48, 51], indicating that the exercise component may be just as effective, at least for subjective measures of function. Several trials also examined the effects of CR on objective measures of function [40, 46–48, 51, 56]. Two of these did not observe an additive effect of adding CR to exercise compared to exercise alone for overall function assessed by a battery of tests [47, 56], whereas one trial did observe an additive improvement in overall function with CR and exercise compared to exercise alone [48]. None of the trials point to an independent main effect of CR on muscle strength or gait speed [48, 56]. However, adding CR to exercise (either aerobic or resistance) improves mobility as assessed by long-distance walk tests [46, 51, 56]; yet, two trials showed that CR alone does not improve mobility more than exercise alone [40, 51], or compared to a control group [40]. Hence, adding CR to an exercise intervention seems to improve mobility/endurance and self-reported functional ability, but there is less evidence for a beneficial independent effect of CR on other measures of physical function.

Effects of treatment on inflammation and cardiometabolic health

Numerous studies show that obesity, especially excess abdominal fat, leads to dyslipidemia and insulin resistance, along with other metabolic disturbances, including chronic inflammation, even in old age [34, 70, 71]. Four RCTs examined the effects of CR on inflammation in older adults [41, 50, 51, 55]. Results are consistent in showing a reduction in IL-6 concentrations with CR, and there is likely a dose-response relationship with the magnitude of weight lost [50, 51]. However, IL-6 is one of many cytokines and results were less uniform for changes in other inflammatory markers.

There is no doubt that CR interventions resulting in weight loss cause improvements in insulin sensitivity in younger individuals [72]. However, results from the few intervention trials that examined this outcome in older adults are inconsistent. There were three trials with small samples ($N < 25$) that assessed insulin sensitivity directly with a euglycemic clamp and the results do not show a difference of adding CR to an exercise intervention

compared to exercise alone in this age group [42, 43, 45]. However, two trials show an independent effect of CR for improving fasting measures of glucose control [54, 45]. While both the Diabetes Prevention Program and the Look AHEAD trial showed a beneficial effect of lifestyle intervention for reducing diabetes risk and related risk factors in older adults (60+ years), these interventions were a combination of CR and physical activity and the independent effects of the CR component cannot be isolated [73, 74]. Thus, the four trials identified here are the only ones, to date, that examined whether there is an independent effect of adding CR to a lifestyle intervention for improving insulin sensitivity or glucose control.

Experimental studies that evaluated the efficacy of CR on blood pressure and lipid risk factors in older adults are even more scarce. The Trial of Non-Pharmacological Interventions in the Elderly (TONE) [38] provides convincing evidence for a beneficial effect of CR on blood pressure and decreased need for antihypertensive medication use in older patients with hypertension. A different trial found a beneficial effect of CR for systolic blood pressure only, but not all participants in this trial were hypertensive [54]. Finally, a smaller study did not show a reduction in blood pressure from CR plus exercise compared to exercise alone [43]. Notably, only two trials examined independent effects of CR on blood lipids in older adults and both showed no effect of CR on total cholesterol, LDL-cholesterol, HDL-cholesterol or triglycerides [43, 54]. Obviously, very few well-powered trials have been conducted to clearly answer how diet-induced weight loss affects cardiometabolic risk factors in older adults, and there is a critical need for future larger, well-designed RCTs.

Effects of treatment on longevity

Data from observational studies show that weight loss is associated with increased risk of mortality in older adults [75–77]; however, these studies cannot definitively resolve whether the weight loss was intentional or not. A follow-up of two of the larger RCTs (TONE and ADAPT) conducted by Shea et al. specifically examined the effects of randomization to CR for weight loss on mortality [44, 49]. In the first study, after 8 years of follow-up, the total mortality rate was 50% lower in those assigned to CR compared to control [44]. In the second study, there was no difference in all-cause mortality between adults assigned to CR and those who were not [49]. Hence, these data indicate that intentional weight loss via CR is not associated with an increased mortality risk; however, additional RCTs are necessary to validate these results.

Risks of obesity treatment in older adults

Despite evidence that obesity contributes to functional decline and disability, there are potential benefits associated with being overweight or obese in old age. Observational data show that unintentional weight loss is associated with increased disability [78, 79]. In addition, overweight and mild obesity are associated with protection against osteoporosis and fractures [80], with better prognostic recovery from certain illness and injuries [81], and with reduced mortality risk [81] in older adults. A position statement from The Obesity Society states that “*appropriate treatment for obesity in older persons is controversial because of the reduction in relative health risks associated with increasing BMI and the concern that weight loss could have potential harmful effects*” [37]. Moreover, based on

clinical judgment, many geriatricians strongly advocate that recommending CR for weight loss in their older patients will be harmful in the long run [82, 83]. Thus, it is important to clarify the extent to which diet-induced weight loss affects these proposed health benefits of overweight/obesity in older adults.

Yet, there is essentially no long-term health outcome data from RCTs of diet-induced weight loss in older adults. All of the reported benefits of CR listed in Table 1 were examined immediately after completion of the intervention, and there are no controlled data on the long-term effects of treatment on intermediate endpoints (body composition/fat distribution, physical function, or cardiometabolic risk) or disease incidence or prognosis. Therefore, presently, there is a lack of definitive evidence of any long-term risks of prescribing CR for weight loss in adults ≥ 65 years; however, we summarize below the available data on the effects of CR on loss of muscle and bone density, which are important risk factors for aging-related sarcopenia, frailty, and fractures.

Effects of treatment on lean (muscle) mass and sarcopenia

There is a prevailing concern that weight loss may worsen age-related loss of muscle that leads to sarcopenia [84]. Data from the RCTs in Table 1 consistently show that a reduction in body weight, achieved through CR either with or without exercise, results in greater loss of lean mass (by DXA) and thigh muscle volume (by CT) compared to control or exercise without CR [45, 48, 51, 53, 54, 56]. Even though absolute lean mass loss can be substantial (up to 4.7 kg in IDEA [51]), in all trials, the majority of total mass lost was fat. Thus, relative sarcopenia (muscle mass to body weight) is reduced despite this absolute loss of muscle, indicative of overall favorable changes in body composition with CR in older adults. Other trials show that there are strategies (such as performing resistance exercise, increasing protein intake, or losing weight at a slower pace) that reduce the amount of lean mass lost during CR [85]. However, these strategies do not totally prevent loss of muscle with weight loss—thus it is important to identify the long-term ramifications of this loss of muscle.

Since aging is associated with loss of muscle and gain in fat, a cycle of weight loss and subsequent regain may exacerbate sarcopenia over time if lean mass is not recovered. Some early data are beginning to show a preferential accumulation of fat over lean mass during weight regain following intentional weight loss [86]. In fact, in three studies, weight regain following weight loss was comprised entirely of fat in middle-aged to older adults [87–89]. Observational data also show proportionally more lean mass is lost during periods of weight loss than is gained during periods of weight gain or regain [90, 91], and that weight cycling increases the risk for physical disability [92]. Thus, since maintenance of lost weight is extremely difficult due, in part, to the biological adaptations that occur for the evolutionary purpose of defending existing energy stores [93, 94], an obesity treatment involving CR that leads to short-term weight loss followed by weight gain could accelerate sarcopenia over time in older adults. However, presently, there are no RCT data to support or refute this hypothesis.

Effects of treatment on bone mineral density, osteopenia/osteoporosis, and fracture risk

A potential beneficial effect of obesity in late life is protection from osteoporosis-related fractures [95]. Obesity, which increases weight-bearing stress on the skeleton, is associated with greater bone mineral density (BMD) [96] and fat around the trochanter can protect against hip fracture during a fall [95]. Thus, a concern is that weight loss may have deleterious effects in older adults by causing bone loss on top of age-related bone loss [97].

Four of the trials analyzed the independent effects of CR on BMD [39, 47, 48, 52]. Two of them found that CR decreased BMD in the hip, but not the spine region, and that the decrease in hip BMD correlated with the magnitude of weight lost [48, 52]. The other two trials either did not observe a significant decline in BMD [47], or did not observe a significantly different decline in BMD between the CR and control groups [39]. As indicated by Beavers et al. [52], even though the CR intervention decreased hip BMD, the clinical classification of osteoporosis and osteopenia remained unchanged. Thus, whether the magnitude of BMD loss observed in these trials translates into osteopenia, osteoporosis, and increased fracture risk remains to be determined.

Conclusion

Presently, there are no evidence-based treatment guidelines to inform clinicians on the proper management of geriatric obesity. Guidelines geared towards younger populations should not automatically apply to older adults in view of the unique health concerns of this population. Given the unarguable benefits of exercise on both physical function and metabolic health, even in older adults with obesity, the real question of interest is whether obesity treatment via a dietary intervention that encourages or enforces CR is effective and whether its benefits outweigh any risks. The evidence summarized here is from the most rigorously designed and scientifically valid research to date that will inform age-specific treatment guidelines—that is randomization of older adults (65+ years) to either: 1) an intervention that included a diet component targeting reduced caloric intake, or 2) a control intervention that did not receive the diet component (to allow for isolation of the effects of CR versus exercise).

Overall, the results show a treatment effect of CR for improving some metabolic and functional outcomes with few documented risks. However, there are confounding factors that must be noted which make it difficult to interpret the results and definitively recommend CR as an effective obesity treatment in older adults. First, several of the trials were likely underpowered as only five of them randomized more than 50 individuals per group (TONE, ADAPT, CLIP, IDEA, I'M FIT). Second, it is impossible to discern whether some of the observed treatment effects of the CR group were due to weight loss *per se*, since in several trials the control (non-CR) group lost weight also, even losing as much as 50% of the weight loss seen in the treatment group. Third, the CR interventions used across trials were highly variable and many altered dietary composition or nutrient intake in addition to caloric intake. Next, although we limited this review to RCTs that used a sample with a mean age 65 years, all were within a very small mean age range of 65–70 years. Clearly, more research is needed that either reports the independent effects of CR in subgroups that are older or are *de novo* trials that recruit individuals in their 7th and 8th decades of life.

Finally, all of the available RCTs only provide data on health outcomes assessed immediately after treatment cessation. There is a critical need for additional research in this area that focuses on the long-term health benefits and risks of prescribing CR to induce weight loss for the treatment of geriatric obesity.

Acknowledgments

Denise K. Houston has received financial support through a grant from the National Institutes of Health (NIH) National Institute on Aging (NIA).

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Table 1

Description of published randomized controlled trials examining effects of a caloric restriction (CR) intervention for weight loss compared to a control intervention (no-CR) in older (mean age 65 years) adults

Author (Year)	Sample size and mean age	Study population	Interventions	Health Outcomes	Isolated effects of caloric restriction
Whelton et al. (1998) [38] Trial of non-pharmacologic intervention in the elderly (TONE)	N=585 66.5 yrs	53% women BMI: 31 ± 2 kg/m ² Health: Hypertensive	1 Sodium reduction (no-CR) (Wt= -0.9 kg) 2 CR (dietary counseling, 4.5 kg WL goal) (Wt= -3.9 kg) 3 Sodium reduction+CR (Wt= -4.0 kg) 4 Usual care (control) (Wt= -0.9 kg) Duration: 15–36 mos (median, 29 mos)	Blood pressure Withdrawal of antihypertensive medication	Systolic and diastolic BP: Main effect of CR for reducing systolic and diastolic BP Other: 39% (95% CI, 32%–46%) among those in CR interventions compared to 26% (95% CI, 19%–34%) of those in No-CR interventions remained free of trial endpoints (high BP, antihypertensive medication, CVD events) at 30 months
Chao et al. (2000) [39] TONE	N=67 65.9 yrs	100% women BMI: 31 ± 3 kg/m ² Health: Hypertensive	1 CR (Wt= -7.7 kg) 2 No-CR (Wt= -1.9 kg) Duration: 12 months	BMD Biomarkers of bone formation and resorption	No effect of CR compared to No-CR on BMD or bone biomarkers Decreases in total body BMD and increases in osteocalcin correlated with magnitude of CR
Messier et al. (2004) [40] Arthritis, Diet, and Activity Promotion Trial (ADAPT)	N=316 69 yrs	72% women BMI: 34 ± 0.6 kg/m ² Health: Knee osteoarthritis, self-reported disability and sedentary	1 EX (aerobic+resistance) (Wt= -3.5 kg) 2 CR (group-based counseling and education, 5% WL goal) (Wt= -4.6 kg) 3 CR+EX (Wt= -5.2 kg) 4 Usual care (control) (Wt= -1.1 kg) Duration: 18 months	Self-report physical function and pain Mobility	Physical function and pain: No difference between CR+EX and EX, between CR and Control, or between CR and EX Mobility: No difference in 6 min walk time between CR+EX and EX, between CR and Control, or between CR and EX
Nicklas et al. (2004) [41] ADAPT	N=272 68.5 yrs	72% women BMI: 34 ± 0.4 kg/m ² Health: Knee osteoarthritis, self-reported disability and sedentary	1 EX (aerobic+resistance) (Wt= -4.1 kg) 2 CR (group-based counseling and education, 5% WL goal) (Wt= -12.8 kg) 3 CR+EX (Wt= -8.2 kg) 4 Usual care (control) (Wt= -2.3 kg)	Inflammation	Main effect of CR for reducing CRP, IL-6, sTNFRI and sTNFR2; No effect of CR on IL-6sR or TNF- α Decreases in sTNFRI correlated with decreases in body weight

Author (Year)	Sample size and mean age	Study population	Interventions	Health Outcomes	Isolated effects of caloric restriction
			Duration: 18 months		
Solomon et al. (2008) [42]	N=23 66 yrs	Gender % not specified BMI: $33 \pm 1 \text{ kg/m}^2$ Health: Impaired glucose tolerance	1 EX (aerobic) (Wt= -3.3 kg) 2 CR+EX (500 kcal/d reduction) (Wt= -7.9 kg) Duration: 12 weeks	IMCL Insulin sensitivity Body composition	IMCL: Decreased by 34% in CR+EX (26% in EX); No between group difference Insulin sensitivity: Increased by 65% in CR+EX (55% in EX); No between group difference Other: CR+EX had greater decrease in body and fat mass than EX; No effect of adding CR on LM or aerobic fitness
Yassine et al. (2009) [43]	N=24 65.5 yrs	63% women BMI: $35 \pm 5 \text{ kg/m}^2$ Health: Metabolic syndrome	1 EX (aerobic) (Wt= -3.7 kg) 2 CR+EX (500 kcal/d reduction) (Wt= -6.8 kg) Duration: 12 weeks	Insulin sensitivity Body composition & abdominal fat Cardiometabolic risks factors	Insulin sensitivity: Increased 30% in CR+EX (31% in EX); No between group difference Body composition: No between group difference for FM, LM, waist girth or VAT; CR+EX reduced SAT area more than EX Other: No difference between groups for BP reduction or decreases in total and LDL cholesterol
Shea et al. (2010) [44] ADAPT	N=316 69 yrs	72% women BMI: $34 \pm 0.6 \text{ kg/m}^2$ Health: Knee osteoarthritis, self-reported disability and sedentary	1 EX (aerobic+resistance) and usual care/control (No-CR) (Wt= -1.4 kg) 2 CR (group-based counseling and education, 5% WL goal) and CR+EX (Wt= -4.8 kg) Duration: 18 months	Mortality over 8.2 yrs (CR groups) and 7.8 yrs (No-CR groups) follow-up	15 deaths in CR groups and 30 deaths in No-CR groups; CR groups had lower mortality rate compared to No-CR groups (HR [95% CI] = 0.5 [0.3-0.9], p = 0.01)
Dubé et al. (2011) [45]	N=22 67.2 yrs	56.2% women BMI: $31 \pm 0.8 \text{ kg/m}^2$ Health: Sedentary	1 EX (aerobic) (Wt= -1.7 kg) 2 CR (10% WL goal) (Wt= -7.4 kg) Duration: 16 wks	IMCL Insulin sensitivity Body composition	IMCL: Decreased 16% in CR group (+41% in EX); Significant difference between groups Insulin sensitivity: Increased 21% in CR group (19% in EX); No between group difference; Fasting insulin decreased more in CR than EX Other: FM and LM decreased more in CR than EX
Rejeski et al. (2011) [46] Cooperative Lifestyle Intervention Program (CLIP)	N= 288 67 yrs	67% women BMI: $33 \pm 4 \text{ kg/m}^2$ Health: CVD or cardiometabolic dysfunction	1 EX (home-based, aerobic) (Wt= -0.8 kg) 2 CR+EX (group-based counseling and education, 7-10% WL goal) (Wt= -7.1 kg) 3 Control (Wt= -0.9 kg) Duration: 18 months	Mobility Physical activity	Mobility: CR+EX improved 400-m walk time compared to EX Physical activity: No difference in minutes of moderate-vigorous physical activity between CR +EX and EX
Santanasto et al. (2011) [47]	N=36 70.3 yrs	83.3% women BMI: $33 \pm 3 \text{ kg/m}^2$ Health: Sedentary	1 EX+Successful Aging Education (aerobic, strength, balance) (Wt= -1.0 kg)	Body composition Thigh and abdominal fat BMD	Body composition: % fat and FM decreased more in EX+CR compared to EX+SA; No between group difference in LM

Author (Year)	Sample size and mean age	Study population	Interventions	Health Outcomes	Isolated effects of caloric restriction
			2 EX+CR (Diabetes Prevention Program, 7% WL goal) (Wt=-4.9 kg) Duration: 6 months	Physical function and strength	Thigh fat: Total muscle CSA decreased more in EX+CR compared to EX+SA; No between group difference in total thigh fat or IMAT Abdominal fat: Total fat and VAT areas decreased more in CR+EX compared to EX+SA; No between group difference in SAT or waist Total body and hip BMD: No change in either group Physical function: No between group difference in knee strength or SPPB changes
Villareal et al. (2011) [48]	N=107 70 yrs	62% women BMI: 37 ± 5 kg/m ² Health: Sedentary, mild-to-moderate frailty	1 EX (aerobic+strength +balance) (Wt=-1.8 kg) 2 CR (500–750 kcal/d reduction) (Wt=-9.7 kg) 3 CR+EX (Wt=-8.6 kg) 4 Control (Wt=-0.9 kg) Duration: 12 months	Physical function and strength Whole body and thigh composition BMD	PPT: Improved 12% in CR, 15% in EX, and 21% in CR+EX; Significant effect of CR compared to Control and CR+EX compared to EX Gait speed and 1-RM knee strength: No effect of CR or CR+EX VO₂peak: Increased 10% in CR, 8% in EX, and 17% in CR+EX; Significant effect of CR compared to Control and CR+EX compared to EX Functional Status Questionnaire: Significant effect of CR compared to Control Body comp: FM, LM, thigh muscle and fat volume decreased more in CR compared to Control and CR+EX compared to EX BMD: No change in whole body or spine BMD; Hip BMD decreased 2.6% in CR (+1.5% in EX, -1.1% in CR+EX); Significant effect of CR compared to Control and CR+EX compared to EX
Shea et al. (2011) [49] TONE	N=585 65 yrs	53% women BMI: 31 ± 2 kg/m ² Health: Hypertensive	1 CR (dietary counseling, 4.5 kg WL goal) (Wt=-3.9 kg) 2 No-CR (Wt=-0.9 kg) Duration: 15–36 mos (median, 29 mos)	Mortality over mean follow-up of 12.7 yrs	49 deaths in CR groups and 52 deaths in No-CR groups Mortality rate in the CR and No-CR groups did not differ
Beavers et al. (2013) [50] CLIP	N=288 67 yrs	67% women BMI: 33 ± 4 kg/m ² Health: CVD or cardiometabolic dysfunction and mobility limitation	1 EX (home-based, aerobic) (Wt=-0.8 kg) 2 CR+EX (7–10% WL goal) (Wt=-7.1 kg) 3 Control (Wt=-0.9 kg) Duration: 18 months	Inflammation	CR+EX decreased leptin and IL-6 more than EX; No effect of CR+EX compared to EX on sTNFR1, adiponectin, IL6sR or IL-8
Messier et al. (2013) [51] Intensive Diet and Exercise for Arthritis (IDEA)	N=454 66 yrs	72% women BMI: 33 ± 4 kg/m ² Health: Sedentary, osteoarthritis of one or both knees	1 EX (aerobic+resistance) (Wt=-1.8 kg) 2 CR (800–1000 kcal/d reduction; 10% WL goal) (Wt=-8.9 kg)	Self-report function and pain Mobility Inflammation (IL-6) Body composition	Function and pain: CR+EX improved function and decreased pain more than EX; No difference between CR and EX Mobility: CR+EX improved 6-min walk time more than EX, while EX improved more than CR IL-6: Decreased more in CR+EX than EX

Author (Year)	Sample size and mean age	Study population	Interventions	Health Outcomes	Isolated effects of caloric restriction
			3 CR+EX (Wt= -10.6 kg) Duration: 18 months		Body composition: FM and LM decreased more in CR and CR+EX compared to EX
Beavers et al. (2014) [52] IDEA	N=284 66 yrs	74% women BMI: 33 ± 4 kg/m ² Health: Sedentary, osteoarthritis of one or both knees	1 EX (aerobic+resistance) (Wt= -1.3 kg) 2 CR (800–1000 kcal/d reduction; 10% WL goal) (Wt= -9.1 kg) 3 CR+EX (Wt= -10.4 kg) Duration: 18 months	BMD Osteoporosis/osteopenia	BMD: Hip and femoral neck BMD decreased more in CR and CR+EX vs EX; No group differences in spine BMD Osteoporosis/Osteopenia: Progressed from normal BMD to osteopenia (N=2 EX, 3 CR, 6 CR+EX); Progressed from osteopenia to osteoporosis (N=1 in CR)
Beavers et al. (2014) [53] CLIP	N=288 67 yrs	67% women BMI: 33 ± 4 kg/m ² Health: CYD or cardiometabolic dysfunction and mobility limitation	1 EX (home-based, aerobic) (Wt= -0.8 kg) 2 CR+EX (7–10% WL goal) (Wt= -7.1 kg) 3 Control (Wt= -0.9 kg) Duration: 18 months	Body composition	Body composition: FM and LM decreased more in CR+EX compared to EX; % LM increased more in CR+EX than EX
Bouchonville et al. (2014) [54]	N=107 70 yrs	62% women BMI: 37 ± 5 kg/m ² Health: Sedentary, mild-to-moderate frailty	1 EX (aerobic+strength +balance) (Wt= -0.5 kg) 2 CR (500–750 kcal/d reduction) (Wt= -9.7 kg) 3 CR+EX (Wt= -8.6 kg) 4 Control (Wt= -0.1 kg) Duration: 12 months	Insulin sensitivity Oral glucose tolerance Body composition and abdominal fat Inflammation Cardiometabolic risk factors	Insulin sensitivity index: Greater increase in CR compared to Control and CR+EX compared to EX OGTT variables: Greater decrease in insulin and glucose AUC, fasting insulin and HOMA-IR in CR +EX compared to EX Body composition and abdominal fat: Greater decrease in trunk fat, VAT, SAT and LM in CR compared to Control and CR+EX compared to EX Inflammation: Greater decrease in CRP and greater increase in adiponectin, in CR compared to Control; No difference between CR+EX and EX; greater decrease in sTNFR1 in CR compared to Control and in CR+EX compared to EX; Cardiometabolic risk factors: No between group difference for fasting glucose, HDL-cholesterol, TG, and diastolic BP; greater decrease in systolic BP in CR +EX compared to EX
Beavers et al. (2015) [55] IDEA	N=454 66 yrs	72% women BMI: 33 ± 4 kg/m ² Health: Sedentary, osteoarthritis of one or both knees	1 EX (aerobic+resistance) (Wt= -1.8 kg) 2 CR (800–1000 kcal/d reduction; 10% WL goal) (Wt= -8.9 kg) 3 CR+EX (Wt= -10.6 kg)	Abdominal and thigh fat Inflammation	Abdominal fat: Greater decrease in total fat, VAT, SAT, IMAT in CR+EX compared to EX Thigh fat: Greater decrease in total fat, IMAT and SAT in CR+EX compared to EX Inflammation: IL-6 and CRP decreased more in CR +EX than EX

Author (Year)	Sample size and mean age	Study population	Interventions	Health Outcomes	Isolated effects of caloric restriction
Nicklas et al. (2015) [56] Improving Muscle for Functional Independence Trial (UMFIT)	N=126 70 yrs	56% women BMI: 31 ± 2 kg/m ² Health: Sedentary	Duration: 18 months 1 EX (resistance) (Wt= -0.1 kg) 2 CR+EX (600kcal/d reduction) (Wt= -4.9 kg) Duration: 5 months	Body and thigh composition Physical function, strength and mobility	Body composition: Greater decrease in FM, LM and % fat in CR+EX compared to EX Thigh composition: Greater decrease in total thigh fat, SAT, thigh muscle volume in CR+EX compared to EX; No between group difference in IMAT decrease Physical function: No between group difference for knee strength, muscle quality, gait speed, chair rise or SPPB score; Grip strength, 400m walk time and self-reported disability improved more in CR+EX compared to EX

AUC= area under the curve; BP= Blood pressure; BMD= Bone mineral density; Chol=Cholesterol; CR= Caloric restriction; CVD= Cardiovascular disease; EX= Exercise; FM= fat mass; HDL-chole= High density lipoproteins; HOMA-IR= Homeostasis model assessment of insulin resistance; CRP= C-reactive protein; IL-6= Interleukin-6; PPT= Physical Performance; IL-6sR= IL-6 soluble receptor; IMAT= Inter-muscular adipose tissue; IMCL= Intramyocellular lipids; LM= Lean mass; LDL= Low density lipoproteins; Mos= months; OGTT= Oral glucose tolerance test; SPPB= Short physical performance battery; sTNFR1= soluble TNF- α receptor 1; sTNFR2= soluble TNF- α receptor 2; SAT; Subcutaneous adipose tissue; TG= Triglycerides; TNF- α = Tumor necrosis factor alpha; VAT= Visceral adipose tissue; wks=weeks; WL= Weight loss; 1-RM= One-repetition maximum