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Calorie Restriction in Overweight Older Adults: Do Benefits Exceed Potential Risks?

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Abstract

The evidence regarding recommendations of calorie restriction as part of a comprehensive lifestyle intervention to promote weight loss in obese older adults has remained equivocal for more than a decade. The older adult population is the fastest growing segment of the US population and a greater proportion of them are entering old age obese. These older adults require treatments based on solid evidence. Therefore the purpose of this review is three-fold: 1) to provide a more current status of the knowledge regarding recommendations of calorie restriction as part of a comprehensive lifestyle intervention to promote weight loss in obese older adults 2) to determine what benefits and/or risks calorie restriction adds to exercise interventions in obese older adults and 3) to consider not only outcomes related to changes in body composition, bone health, cardiometabolic disease risk, markers of inflammation, and physical function, but, also patient-centered outcomes that evaluate changes in cognitive status, quality of life, out-of-pocket costs, and mortality. Seven randomized controlled trials were identified that examined calorie restriction while controlling for exercise intervention effects. Overall, the studies found that calorie restriction combined with exercise is effective for weight loss. Evidence was mixed regarding other outcomes. The risk-benefit ratio regarding calorie restriction in older adults remains uncertain. Greater long-term follow-up is necessary, and complementary effectiveness studies are needed to identify strategies currently used by obese older adults in community settings.

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INTRODUCTION

In 2005, the American Society for Nutrition (ASN) and the North American Association for the Study of Obesity (NAASO) (currently known as The Obesity Society (TOS)) issued a Position Statement on Obesity in Older Adults (Villareal et al., 2005). The statement concluded that: "[A]ppropriate clinical approaches to obesity in older persons is controversial because of: the reduction in relative health risks associated with increasing body mass index (BMI) in older adults, the uncertain effectiveness of obesity treatment in this group, and the potential harmful effects of weight loss on muscle and bone mass." In 2013, TOS, the American Heart Association (AHA), and the American College of Cardiology (ACC) issued Guidelines for the Management of Overweight and Obesity in Older Adults (M. D. Jensen et al., 2014). Similar to the previously published Position Statement, these experts concluded that:

> "The overall safety of weight loss interventions for patients aged 65 and older remains controversial. Although older participants tend to respond well to comprehensive behavioral weight loss treatments, and they experience the same improvements in CVD risk factors as do middle-age participants, the effect of weight loss treatment on risk of CVD, longevity, and osteoporosis has not been extensively studied. More studies on the health consequences of weight loss treatment with this age group are needed."

In nearly a decade between the publications of the first and second consensus statements, conclusions regarding recommendations of calorie restriction in overweight seniors remain the same. The purpose of this narrative review is to provide a current status of the knowledge regarding calorie restriction as an adjunct to exercise on weight loss in overweight seniors.

Demographic and Health Status Overview of Older Adults

This review is especially necessary and timely given current demographic trends. In 2010, there were an estimated 40 million adults over the age of 65 representing 13% of the United States (USA) population. By 2030, older adults are expected to comprise 20 percent of the population (Federal Interagency Forum on Aging-Related Statistics, 2012). American men and women at age 65 have a life expectancy that exceeds an additional 15 years (Federal Interagency Forum on Aging-Related Statistics, 2012). Most of these remaining years will be spent in relative good health. Despite increased longevity, many older adults experience comorbidities and functional limitations that are associated with obesity. For example, commonly reported chronic health conditions typically associated with obesity reported by people aged 65 and older include hypertension (men: 54%/women: 57%), arthritis (men: 45%/women: 56%), heart disease (men: 37%/women: 26%), cancer (men 28%/women: 21%), and type 2 diabetes (men: 24%/women: 18%); and 19% of men and 30% of women report being unable to perform some physical function (Federal Interagency Forum on Aging-Related Statistics, 2012).

Prevalence of Obesity among Adults Aged 65 and Older

More than a third of adults in the USA aged 65 and older are obese (men: 34.4%/women: 34.7%) (Fakhouri, Ogden, Carroll, Kit, & Flegal, 2012). Being obese is defined as having a BMI of greater than or equal to 30 (World Health Organization, 2015). Obesity cuts across all racial/ethnic groups, but is highest among African American women, reaching 53.9% for those between the ages of 65–74 (Fakhouri et al., 2012). Trends in the prevalence of obesity over time reflect those of the general population and have increased. A reasonable response to obesity in older adults on the part of both patients and health care providers is to consider weight loss strategies, and among these, lifestyle interventions that involve both exercise and restriction of calories are the first approaches frequently considered.

Changes in Body Weight and Body Composition with Aging

The process of aging favors an increase in adiposity and basic measures like body mass index (BMI) may not fully capture these changes. Persons gain weight as they age, but they gain a greater proportion of weight as fat compared to lean muscle mass (Newman et al., 2005). Older adults also experience a greater relative increase in intra-abdominal fat compared to subcutaneous or total body fat, as well as a greater relative decrease in peripheral than in central fat free mass because of the loss of skeletal muscle (Kuk et al., 2009). It is also the case that some older adults experience loss of height with aging that is associated with compression of vertebral bodies and kyphosis (Sorkin, Muller, & Andres, 1999). Reliance upon BMI as an indicator of obesity or fatness, as is commonly done, is problematic, especially in older adults because of changes in body composition that underestimate fatness and loss of height that overestimate fatness.

Benefits and Risks of Obesity in Old Age

Older persons who are overweight have a lower risk of mortality than normal weight older adults and the increased survival among obese older adults has been demonstrated in numerous epidemiological studies (Childers & Allison, 2010; Flegal, Kit, Orpana, & Graubard, 2013). These findings, though, are not without scientific and political controversy (Hughes, 2013). Several reasons have been suggested for the so-called obesity paradox that occurs in older adults, including: extra weight may be protective during illness, individuals with obesity may have died at earlier ages, there is a balance of risks across the life course, and methodology and confounding may play a role (Childers & Allison, 2010). The association between obesity and multiple diseases linked with mortality has been well-established. However, most studies have not been conducted in older populations. One recent paper appearing in the Journal of Gerontology: Medical Sciences concludes that the evidence for obesity being associated with risks in older adults is either mixed, weak, or non-existent for many diseases (Canning, Brown, Jamnik, & Kuk, 2014). It is speculated that while comorbid conditions increase with age, the harmful effects of obesity may have occurred earlier.

With respect to functional status, most studies show that obesity is associated with increased bone mineral density and decreased risks of osteoporosis and hip fracture (Shapses & Sukumar, 2012). On the other hand, obesity is associated with declines in mobility, increased risk of frailty (especially as it relates to exhaustion, fatigue, and vitality), and increased risk of need for long term care (associated with increased sarcopenic obesity). Obesity may impact quality of life in older adults if it leads to a restriction of activities. Finally, it is the case that when older adults lose weight (whether intentionally or unintentionally), they disproportionately lose a greater share of that weight as muscle mass (Newman et al., 2005). This may lead to sarcopenic obesity and loss of physical function. Therefore, the ASN and NAASO position statement observed that:

> "Preventing and treating the medical complications of obesity may be the most important goal of therapy in young and middle-aged adults, whereas improving physical function and quality of life may be the most important goals of therapy in older adults…. In addition, the therapeutic approach may differ between younger and older adults, because of the increased importance of preventing loss of muscle and bone mass that occurs with weight loss in older persons". (Villareal et al., 2005)

Three recent reviews have been published that reported on outcomes associated with obesity interventions in older adults with a focus on body composition, cardio-metabolic biomarkers, and physical function (G. L. Jensen & Hsiao, 2010; Porter Starr, McDonald, & Bales, 2014; Waters, Ward, & Villareal, 2013). These reviews highlighted various types of interventions, including those that comprised exercise-only interventions or single-arm studies. The controversy, though, lies in ascertaining whether the addition of calorie restriction to an exercise intervention improves outcomes without causing harm. Therefore the purpose of this review is three-fold 1) to provide a more current status of the knowledge regarding recommendations of calorie restriction as part of a comprehensive lifestyle intervention to promote weight loss in obese older adults 2) to determine what benefits and/or risks calorie restriction adds to exercise interventions in obese older adults and 3) to consider not only outcomes related to changes in body composition, bone health, cardiometabolic disease risk, markers of inflammation, and physical function, but, also patient-centered outcomes that evaluate changes in cognitive status, quality of life, out-of-pocket costs, and mortality.

CURRENT STATUS OF KNOWLEDGE

Studies were identified with *a priori* criteria that included: 1) randomized controlled trials (RCT); 2) a lifestyle intervention as a basis for evidence compared with an exercise alone intervention; and 3) adults with a mean age of 65+. Lifestyle interventions were defined as comprising components of diet (calorie restriction), exercise, and at least one other element (e.g., behavior modification, stress management counseling, behavioral weight loss support, risk factor modification, etc.). When interventions had multiple arms (i.e., exercise, diet, diet/exercise, and control), only the exercise alone and diet + exercise groups were described. Because of the paucity of the trials that have been conducted to date, we used a looser definition for age (i.e., mean age 65+ versus 65+). This narrative review conducted an electronic database search (PubMed) using a Boolean search strategy which included words related to: 1) exercise 2) caloric restriction 3) behavioral therapy and 4) RCT. There was no restriction placed upon date. Authors screened the title, abstract, and full text of potentially relevant articles to determine eligibility.

Seven studies matched our inclusion criteria (Messier et al., 2004; Messier et al., 2013; Nicklas et al., 2015; Rejeski et al., 2011; Santanasto et al., 2011; Solomon et al., 2008; Villareal et al., 2011), as well as subsequent reports of secondary outcomes reported from these studies are included (Armamento-Villareal et al., 2012; D. P. Beavers et al., 2014; K. M. Beavers, Ambrosius, Nicklas, & Rejeski, 2013; K. M. Beavers et al., 2014; K. M. Beavers et al., 2015; Bouchonville et al., 2014; Chua et al., 2008; Napoli et al., 2014; Nicklas et al., 2004; Sevick, Miller, Loeser, Williamson, & Messier, 2009; Shah et al., 2011; Shea et al., 2010; Solomon, Haus, Marchetti, Stanley, & Kirwan, 2009; Yassine et al., 2009). Descriptive information for each study is summarized in reverse chronological order and summarized in Table 1. Findings for each study are summarized in Table 2.

In the most recent study, Nicklas et al. 2015 (Nicklas et al., 2015) conducted a RCT (Muscle for Functional Independence Trial [I'M FIT]) in 126 older (69.5±3.7 yr) overweight or obese (30.6±2.3 kg/m^2) adults, 86.5% who were white and 56.3% who were women. Participants were randomized to a progressive resistance training (RT) performed at moderate intensity (70% one-repetition max [1RM]) 3 days per week for 5 months with or without a calorie restriction (CR) weight loss intervention. Two exercise interventionist supervised the training session to ensure compliance to training sessions. Calorie prescription was derived by subtracting 600 kcal per day from each participant's daily energy needs for weight maintenance. Participants in the RT+CR group lost more body mass than did those in the RT group (−5.67% compared with −0.15% loss of initial mass, respectively). Decreases in total body fat mass, lean mass, and percentage of fat were all greater in the RT+CR group than in the RT group. Within each group knee strength, power, and gait speed increased in both groups, however no differences were observed between the groups. The RT+CR group also significantly improved grip strength, 400-m walk time, and self-reported disability; whereas these outcomes did not change in the RT group. The findings suggest that calorie restriction induced weight loss plus RT leads to a greater range of improvements in physical function than RT alone. The author's findings also support the incorporation of RT into obesity treatments for this population regardless of whether CR is part of the treatment.

Messier et al. 2013 (Messier et al., 2013) conducted a RCT (Intensive Diet and Exercise for Arthritis [IDEA] study) in 454 older (66.0±6.2 years) overweight or obese (33.6±3.7 kg/m^2) adults with knee osteoarthritis, of whom 81% were white and 72% were women. Participants were randomized to one of three groups: exercise alone (E), diet alone (D), and combination diet and exercise (D + E). The exercise intervention was performed 3 days per week and consisted of aerobic walking (15 minutes), strength training (20 minutes), a second aerobic phase (15 minutes) and cool down (10 minutes). During the first 6 months exercise was center based, after 6 months participants could opt for home based exercise or a combination of facility and home based. Initial adherence was 70% and 66% for D+E and E groups respectively. As participants incorporated home based exercise, adherence decreased to 58% and 54% for D+E and E groups respectively. The initial diet plan provided an energy deficit of 800 to 1000 kcal per day as predicted by individual energy expenditure. The intervention lasted 18 months. Both diet groups lost more weight, fat mass ([D] 13%, [D +EX] 18%), lean mass ([D] 8%, [D+EX] 9%), and regional fat mass (except for all thigh fat measures); experienced decreases in bone mineral density in the hip and femoral neck regions. Compared with E alone participants, knee compressive forces were lower in the D alone participants and IL-6 levels and CRP were lower in the D alone and D+EX groups. The D + E experienced greater combined improvements in functional outcomes and quality of life compared with either group alone. The authors concluded after 18 months participants in the D + E group and D alone group loss more weight and saw greater reductions in IL-6 than E alone.

Rejeski et al. 2011 (Rejeski et al., 2011) conducted a RCT (ancillary study to Cooperative Lifestyle Intervention Program [CLIP]) in 288 older (67.1±4.8 yr) overweight and obese (32.8±3.8 kg/m^2) adults at risk for cardiovascular disease, of whom 81.9% were white and 67.0% were women. Participants were randomized to one of three groups: progressive physical activity (PA) at moderate intensity (including walking and later aerobics/walking) for 30 minutes a session, 150 min per week for 18 months with or without dietary weight loss (WL) and a successful aging (SA) health education active control group. Weekly trackers (written self-monitoring logs that documented walking that took place each week) were used to document walking behavior. The WL goal was to reduce caloric intake to produce a WL of approximately 0.3 kg per week for the first 6 months for a total loss in mass of 7–10%. Changes in body composition (Rejeski et al., 2011; D. P. Beavers et al., 2014), reduction in systemic markers of inflammation (K. M. Beavers et al., 2013), and improvements in physical function (Rejeski et al., 2011) were evaluated. While markers of cardiometabolic disease risk were collected in this study, differences between groups were not reported; only associations between fat mass loss and these risk factors were reported. Fat mass and lean mass were both reduced in the PA + WL group compared to both other groups. The PA + WL group lost three times the lean mass as the other groups. Adipokines and biomarkers of inflammation, including adiponectin, leptin, hsIL-6, IL-6sR, IL-8, and sTNFR1, were measured; only leptin and hsIL-6 were observed to be significantly lower in the PA + WL group compared to the other two groups. The PA + WL group improved their 400 meter walk test time (a measure of mobility and physical function) compared with PA and SA. No other differences between groups were observed. The authors concluded that compared with the SA group, both the PA and PA+WL groups experienced statistically significant increases in PA; whereas the PA+WL group lost considerably more weight at 18 months compared with either the SA or PA groups.

Villareal et al. 2011 (Villareal et al., 2011) conducted a RCT in 107 older (69.7±4.0 yr) obese (37.2±5.0 kg/m^2) adults with mild to moderate frailty, of whom 84.8% were white and 62.7% were women. Participants were randomized to one of four groups: a control group, a weight-management (diet) group, an exercise group, or a weight-management-plus-exercise (diet-exercise) group. Exercise sessions were approximately 90 minutes in duration and consisted of aerobic (65% HR_{peak}) and resistance exercises (65% 1RM). The exercise sessions were led by a physical therapist. Participants in the diet group were prescribed a balanced diet that provided an energy deficit of 500 to 750 kcal per day from their daily energy requirement. The intervention lasted for twelve months. Outcomes measured included: body composition, bone metabolism, cardiometabolic disease, systemic markers of inflammation, physical function, cognitive status and quality of life. There was a substantial decrease in body weight in the diet-exercise group (9.7±5.4kg), diet alone (8.3±3.8kg), but not in the exercise (1.8±2.7kg) or control (0.9±1.5kg) from baseline. Both the exercise and diet- exercise groups experienced improvements in physical performance test, VO_{2peak}, functional status, strength, balance, and gait, obstacle course time, one-leg stance, and gait speed. The diet-exercise group experienced decreased weight, loss of lean body mass, loss of fat mass, loss of thigh muscle and fat, and decreased bone mineral density at total hip. The exercise group experienced increased lean body mass, increased thigh muscle, decreased thigh fat, and decreased bone mineral density at total hip. Villareal and his colleagues are unique with respect to inclusion of multiple outcomes, including quality of life (Villareal et al., 2011) and measures of cognition (Napoli et al., 2014). For both of these outcomes, improvements were observed for the diet-exercise group and for quality of life for the diet group, however neither were significantly different from the exercise only group. The authors suggest that weight loss alone or exercise alone improves multiple outcomes in obese older adults; however a combination of both interventions provides the greatest improvement in physical function and frailty.

Santanasto et al. 2011 (Santanasto et al., 2011) conducted a RCT in 36 sedentary older adults (70.3±5.9 yr) overweight to moderately obese (33.0±3.2 kg/m^2), of whom 83.3% were white and 83.4% were women. Participants were randomized to one of two groups: physical activity that combined aerobic, strength, balance, and flexibility exercises plus dietary weight loss (PA + WL) or physical activity plus successful aging health education (PA + SA). The PA program focused on treadmill walking of at least 150 minutes per week with average sessions of 60 minutes duration. The intervention was divided into three phases: adoption, transition, and maintenance. During the adoption phase participants attended three center based exercise sessions, during the transition phased two center based sessions, and one home based session and during the maintenance phase participants could attend optional exercise sessions at the center once a week. The goal of the PA + WL intervention was a 7% reduction in body weight. The intervention lasted for six months. Changes in body composition and physical function were measured. The PA + WL groups experienced beneficial changes in every measure except total body and hip bone mineral density and lean muscle mass in the right quadriceps; while the PA + SA group experienced changes in only three measures (thigh muscle density, lean muscle mass and quadriceps muscle density). The PA + WL group compared with the PA + SA experienced greater reduced waist circumference, body weight, BMI, percent body fat, total fat mass, abdominal fat mass, abdominal visceral fat, and thigh muscle mass. No differences were observed for physical function. Changes in body composition (both reduced fat and increased muscle) were associated with strength and physical function and attributed to a more optimal lean mass to fat mass ratio. The authors concluded a PA + WL intervention significantly improved function and decreased both fat and muscle CSA, compared to PA plus successful aging. PA + WL also conferred a 6 fold decrease in thigh fat mass compared with PA and successful aging.

Solomon et al. 2008 (Solomon et al., 2008) conducted a RCT in 23 older obese men and women (66.0±1.0 yrs, 34.3±5.2 kg/m^2) with impaired glucose tolerance. The principal investigator of the randomized clinical trial was Dr. John Kirwan. Participants were divided into two matched groups: aerobic exercise training with either normal caloric intake or reduced-calorie diet. Both groups participated in 60 minutes of moderate intensity aerobic exercise at 75% VO_2max for twelve weeks. All exercise sessions were supervised by trained clinical staff. The hypocaloric group was instructed to reduce their daily energy intake by

500 kcal. Changes in body composition and improvements in cardiometabolic disease risk and physical function were assessed. Both groups experienced weight loss, improvements in BMI, reductions in body fat mass and waist circumference, improved insulin sensitivity, decreased leptin concentration, decreased intramuscular lipids, decreased RQ, and increased in VO_2max. The reduced-calorie diet group experienced greater changes in weight, BMI, fat mass, leptin concentrations, and basal fat oxidation. Changes in body composition were associated with changes in insulin sensitivity via a euglycemic clamp, leptin, and basal fat oxidation for the entire sample. The authors concluded moderate intensity aerobic exercise is the driving force behind improvements in insulin sensitivity, when older adults participate in diet and exercise interventions.

Yassine et al. 2009 (Yassine et al., 2009) used a subset of the participants enrolled in Kirwan's clinical trial and included 24 older obese men and women (65.5±5.0 yr, 34.3±5.2 yr kg/m^2). Changes in body composition and improvements in cardiometabolic disease risk and physical function were assessed. Both groups experienced significant weight loss with 3.8% and 7.4% in the EX and EX+CR group respectively. Both groups also experienced reduced waist circumference, total abdominal, subcutaneous, and visceral fat; improvements in insulin sensitivity, systolic and diastolic blood pressure, glucose, triglycerides, and total and low-density lipoprotein cholesterol; and improved aerobic capacity. However, only weight loss and subcutaneous fat differed between the groups, with the reduced calorie group experiencing greater improvements. The authors concluded the addition of CR to an EX intervention was successful in generating greater weight loss, but surprisingly this did not translate into greater improvements in clinical measures related to metabolic syndrome.

Solomon et al. 2009 (Solomon et al., 2009) used another subset of the Kirwan trial and included 16 older (66.0±1.0 yr) overweight to obese (32.8±1.8 kg/m^2) men and women. Both groups demonstrated improvements in body weight (EX group, −3.3±0.7%; and EX −CR, −7.7±0.5%); and fat mass (EX group, −4.6±2.4%; EX−CR, −14.9±4.1%). Insulin stimulated glucose disposal rates were improved in both groups. The authors conclude that although weight loss via reduced caloric intake and PA may alleviate elevation in circulating lipids by reducing free fatty acid turnover, this does not determine the magnitude of the gain in function with respect to peripheral tissue insulin sensitivity.

Messier et al. 2004 (Messier et al., 2004) conducted the earliest RCT identified. The Arthritis, Diet, and Activity Promotion Trial (ADAPT) randomized 316 older (68.7±0.8 yr) overweight and obese (34.2±0.6 yr kg/m^2) white (75.9%) females (72%) with knee osteoarthritis to one of four groups: healthy lifestyles (control), diet only, exercise only (including aerobic and resistance exercise), and diet plus exercise. The exercise was completed 3 days a week, an aerobic phase (15 minutes), resistance training (15 minutes), a second aerobic phase (15 minutes), and a cool down phase. The first 4 months of the 18 month intervention was facility based. At any time after the first 4 months participants who wished to exercise at home underwent a transition program, alternating between home and facility exercise. The goal of the dietary intervention was to produce and maintain an average weight loss of 5% during the 18-month intervention period. Both diet groups lost more weight ([D] 4.9%, [D+EX] 5.7% and [E] 3.7% of body weight) than exercise alone. Changes in body composition and improvements in cardiometabolic risk, bone mineral metabolism, systemic markers of inflammation, and physical function were evaluated. Unfortunately, for the primary analyses, weight loss and changes in lateral and medial joint space were measured, but differences between groups were not reported. The same was true for self-reported physical function using the WOMAC, 6-minute walk distance, the stair-climb test, and changes in self-reported pain. The authors concluded that diet plus exercise provides the best overall improvements in function, pain and performance mobility compared with other groups. Without the addition of exercise, however, dietary weight loss alone does not result in significant improvements in mobility or function and pain..

Additionally, long term follow-up to this study assessed mortality and cost-effectiveness. In a long-term, post-hoc analysis, participants who were randomized to either diet group (i.e., the weight loss group) were compared to those randomized to exercise only and control (i.e., the non-weight loss group) (Shea et al., 2010). The mortality rate for those randomized to the weight loss group was lower than those not randomized to a weight loss group. In a cost analyses from the payer perspective, cost effectiveness varied by outcome (Sevic et al., 2009). The diet intervention was most cost-effective for reducing weight; the exercise intervention was most cost-effective for improving mobility for both 6-minute walking distance and time stair climbing task; and the exercise and diet intervention was most cost-effective for improving self-reported function and symptoms of arthritis.

CONCLUSIONS

Each study reviewed demonstrated modest effects of calorie restriction on weight loss, with all trials demonstrating between a 5–10% loss of weight. Compared with exercise alone, calorie restriction typically resulted in loss of both fat and lean mass.

The earlier referenced Position Statement maintained that in addition to reducing the medical complications associated with disease, weight loss therapy in older adults ought to focus on improving physical function and quality of life (Villareal et al., 2005). All studies included measures of various aspects of physical function, however what was measured varied tremendously with one study (reported in three manuscripts) measuring only VO_2max performance, an indicator of aerobic fitness primarily (Solomon et al., 2008; Solomon et al., 2009; Yassine et al., 2009). Other studies measured VO_2 as well as both self-reported and performance-based measures. In some of these studies, physical function improved with calorie restriction, but a similar number of studies found that exercise without calorie restriction may be as beneficial in improving function. For example, Nicklas et al. (2015) found that there were no differences between the RT groups with and without calorie restriction across multiple functional measures (including knee strength) except for the 400-m walk time and self-reported disability.

Of note, only two studies reported on quality of life (Messier et al., 2013; Villareal et al., 2011). While both studies observed benefits of caloric restriction on quality of life in older adults, only one study (Messier et al., 2013) found that caloric restriction had additional benefits beyond exercise alone. Additionally, only one study examined the effect of CR on cognitive status; while cognition improved in the CR combined with exercise group, it was no better than exercise alone (Napoli et al., 2014).

Similar to the functional measures, there were mixed findings with respect to the effect of CR on cardiometabolic disease risk and inflammation. Only two of the studies reported on differences between exercise with and without calorie restriction with respect to cardiometabolic outcomes and these results were mixed (Solomon et al., 2008; Solomon et al., 2009; Villareal et al., 2011; Yassine et al., 2009). In fact, only one of the studies found a positive association between calorie restriction and insulin sensitivity (Villareal et al., 2011). Four studies included measures of inflammation; and again the findings were mixed (Messier et al., 2004; Messier et al., 2013; Rejeski et al., 2011; Villareal et al., 2011). Two studies did report that improvements in IL-6 were associated with calorie restriction (Messier et al., 2004; Messier et al., 2013).

All studies that assessed the effect of calorie restriction on lean mass and bone mineral density found that greater losses of muscle and bone mineral density were associated with calorie restriction. With respect to loss of muscle mass, it was also the case, that when study participants lost weight that they also lost a greater proportion of that weight as fat mass. Whether this relative greater loss of fat vis a vis muscle has risky effects long-term is not known. Recent evidence finds that if older adults regain weight (i.e., weight cycling) after intentional weight loss, they disproportionately regain fat, and this weight cycling is associated with increased physical disability (Arnold, Newman, Cushman, Ding, & Kritchevsky, 2010; Lee et al., 2010; Newman et al., 2005). Whether this is an inevitable consequence of weight regain requires further investigation. Three studies also reported on the association between calorie restriction and bone mineral density (Beavers et al., 2014; Santanasto et al., 2011; Villareal et al., 2011), with two of the three studies showing decreased bone mineral density associated with calorie restriction. Whether this loss increases risks in the longer term for osteoporosis and fracture is not known.

In a recently published European guideline (Mathus-Vliegen & Obesity Management Task Force of the European Association for the Study of Obesity, 2012) that addressed adding diet to physical exercise for obese older adults, the authors conclude that calorie restriction is desirable if individuals experience greater weight loss and fat loss along with better maintenance of weight loss and physical performance—the latter two are unknown. In this series of studies, there was evidence of limited short-term benefit of calorie restriction as an adjunct to exercise for improving physical function; however, it is unclear if this benefit is maintained over time, especially if those who lose weight and lean mass never recover the lean mass subsequently. Progressive effects of aging that lead to further loss of lean mass may reverse short-term improvements in physical function associated with calorie restriction because the total lean mass is lower following calorie restriction (i.e., there is less reserve). None of the studies in this systematic review were able to address this issue. Only one study assessed long-term outcomes of calorie restriction on mortality (Shea et al., 2010). The study found that calorie restriction was associated with decreased mortality. This study also assessed cost from payers' perspective and found mixed results. No study assessed the costs to patients for either exercise or changes in diet. This is an additional element that requires attention as costs may be great to participate in lifestyle interventions.

In sum, calorie restriction provides some benefit, especially with respect to loss of weight and fat mass. Weight loss, in and of itself, is not the most important primary outcome. Some studies examined the association between weight loss and improved health outcomes (especially, cardiometabolic disease risk and functional status) and found that there was a beneficial association (in spite of loss of lean mass and bone mineral density). This may be due to relative improvements in the ratio of higher quality muscle, decreased systemic inflammation, and decreased mechanical burden of excess adiposity. Calorie restriction may be beneficial in the short-term, especially for obese older adults with risk of cardio-metabolic disease or physical impairment. The evidence remains uncertain regarding long-term benefit-risk profile. Additionally, whether changes in diet composition without caloric restriction may accomplish the same positive outcomes remains to be studied in older adults.

Strengths and Weaknesses of the Literature

It is important to distinguish between limitation of the literature and our review. Limitations of the literature include: 1) a paucity of literature investigating the additive effects of calorie restriction coupled with aerobic and resistance exercise, 2) a paucity of data focusing on samples (>65 yrs) thus the rationale for including studies with a mean age of 65 years (only three studies included participants who were at least 65 years old), 3) the majority of interventions focused exclusively on women, 4) a paucity of the literature regarding patient-centered outcomes (e.g., cognition, quality of life) and costs, 5) a lack of understanding of whether reductions in body fatness and inflammation due to calorie restriction preserve or improve bone quality (as suggested in younger adults) and thus may protect against fractures, 6) a lack of understanding of whether improvements in physical function in response to calorie restriction decrease the risks of falls and outweigh potential risk of fractures, and 7) lack of long-term follow-up that may answer some unresolved concerns.

Limitations of this review include studies varied along several important methodological domains that could affect outcomes. These include, most notably: 1) components of both the exercise/physical activity arm and the dietary/calorie restriction arm were different, 2) the length of the interventions varied from twelve weeks to eighteen months, 3) the outcomes used to measure different domains varied, 4) some samples included overweight and obese (only two studies included participants with a BMI of 30 or greater), 5) the disease burden of the samples varied (e.g., osteoarthritis, cardiometabolic disease, frailty), and 6) the drop-out rates varied from 0% to 24%(mean adherence: 89.3%). Thus, it is difficult to make overarching conclusions.

Strengths of this review include: 1) providing a current status of the knowledge regarding calorie restriction in older adults, 2) including articles with information regarding both resistance and aerobic exercise training, and 3) using a quasi-experimental search strategy to locate articles. Future directions include studies with long term follow-up periods with a comprehensive assessment of patient-centered outcomes and costs are needed to determine how to best achieve sustained lifestyle change. These studies are needed to determine if there is long term benefit despite the risks associated with weight regain and loss of bone mineral density, or if functional improvements and changes in cardiometabolic risk return to levels consistent with the non-calorie restricted groups. In fact, the assumptions around weight regain and associated risk levels may need to be evaluated in older adult populations. There is evidence to suggest that older adults engage in behavioral lifestyle interventions in different ways, have different levels of adoption of new lifestyle behaviors, and some of these effects combined with changes in body composition associated with natural aging may modify risk probabilities typically expected in younger populations of adults who have lost weight (Diabetes Prevention Program Research Group, 2006). Additional studies are also need to address specific exercise and training modalities and dietary composition prescriptions. Larger trials with sufficient sample sizes with adequate controls are needed as well.

All findings included in this review were based on efficacy studies that involved a high amount of intervention time and expertise, including supervised exercise time, intensive behavioral counseling, and provision of food/meals. For most older adults who seek to engage in lifestyle changes to address obesity or a consequence of obesity, they will not have access to these levels of intervention outside of participation in a randomized controlled trial. While these type of efficacy studies are critical to establishing the cause and effect relationships and identifying potential impact, we are still in need of complementary effectiveness studies to determine how effectively seniors can implement reduced calorie diets and how safely they can do these interventions using resources and settings that are community-based.

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Abbreviations

The following abbreviations are used in this paper:

ASN	American Society for Nutrition
NAASO	the North American Association for the Study of Obesity
TOS	The Obesity Society
BMI	body mass index
AHA	American Heart Association
ACC	the American College of Cardiology
CVD	cardiovascular disease
USA	United States
RCT	randomized controlled trials
I'M FIT	Muscle for Functional Independence Trial
RT	resistance training
CR	calorie restriction

IDEA	Intensive Diet and Exercise for Arthritis
E	exercise
D	diet
IL-6	Interleukin 6
CRP	c-Reactive Protein
CLIP	Cooperative Lifestyle Intervention Program
WL	weight loss
PA	physical activity
SA	successful aging
hsIL-6	high-sensitivity interleukin-6
IL-6sR	interleukin-6 soluble receptor
IL-8	Interleukin 8
sTNFR1	soluble tumor necrosis factor receptors 1
sTNFR2	soluble tumor necrosis factor receptors 2
VO2peak, VO2max	maximal oxygen consumption
RQ	respiratory quotient
ADAPT	Arthritis, Diet, and Activity Promotion Trial
WOMAC	Western Ontario and McMaster Universities Arthritis Index
SF-36	Short-form 36 Health Survey
TGF-β1	Transforming growth factor beta 1
BMD	bone mineral density
IWQOL	Impact of Weight on Quality of Life
SPPB	Short Physical Performance Battery
LDL-C	low density lipoprotein cholesterol
HDL-C	high density lipoprotein cholesterol

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Table 1

Descriptive Characteristics of the Subjects and Interventions

Reference	Health Outcomes (primary/secondary)	Study Design & Intervention	Sample	Summary of Findings
1. Nicklas et al. 2015	Body composition Physical function	RCT: 5 months 2 groups: resistance training (RT); RT plus caloric restriction (RT+CR)	n=126 women & men Age: 69.5± 3.7 yr (65–79) BMI: 30.6±2.3 kg/m^2 (27–35)	RT+CR had greater improvements in: total body fat mass, percentage of fat, grip strength, 400-m walk time, and self-reported disability
2. Messier et al. 2013	Body composition Inflammation Physical function Quality of life	RCT: 18 months 3 groups: exercise alone (E), diet alone (D), and combination diet and exercise (D + E)	n=454 women with knee osteoarthritis Age: 66.0±6.2 yr (55+) BMI: 33.6±3.7 kg/m^2 (27–41)	Both diet groups had greater decreases in: weight, fat mass, lean mass, regional fat mass, bone mineral density, knee compressive force, IL-6 and CRP. The D + E had improvements in functional outcomes and quality of life
3. Rejeski et al. 2011	Body composition Inflammation Physical function	RCT: 18 months 3 groups: : physical activity (PA) with or without dietary weight loss (WL) and a successful aging (SA) control group	n=288 women with cardiovascular disease risk factors Age: 67.1±4.8 yr (60–79) BMI: 32.8±3.8 kg/m^2 (28–39.9)	Fat mass, lean mass, leptin and hsIL-6 were reduced in the PA + WL group. The WL group lost three times the lean mass as the other groups. The WL + PA group improved their 400 meter walk test time compared with PA and SA
4. Villareal et al. 2011	Body composition Cardiometabolic disease Bone Metabolism Inflammation Physical function Cognitive status Quality of life	RCT: 12 months 4 groups: control group, a weight-management (diet) group, an exercise group, or a weight-management-plus-exercise (diet-exercise) group.	n=107 women w/ mild to moderate frailty Age: 69.7±4.0 yr BMI: 37.2±5.0 kg/m^2	Both the exercise and diet-exercise group had improvements in physical performance tests and functional status questionnaire. The diet-exercise group had decreased weight, lean mass, fat mass, thigh muscle and fat, bone mineral density, The exercise group had increased lean mass and thigh muscle, and decreased thigh fat, bone mineral density at total hip
5. Santanasto et al. 2011	Body Composition Physical Function	RCT: 6 months 2 groups: physical activity plus dietary weight loss (PA + WL) or physical activity plus successful aging health education (PA + SA)	n=36 women Age: 70.3±5.9 yr (60+) BMI: 33.0±3.2 kg/m^2 (28–39.9)	The PA + SA group had increased thigh muscle density and lean muscle mass and quadriceps muscle density. The PA + WL group compared with the PA + SA had greater decrease in waist circumference, weight, BMI, percent fat, total fat mass, abdominal fat mass, visceral fat, and thigh muscle mass. No differences were observed for physical function.
6a. Solomon et al., 2008	Body composition Cardiometabolic disease Physical function	RCT: 12 weeks 2 groups: Aerobic exercise (EX) or exercise plus caloric restriction (EX+CR)	n=23 women & men with impaired glucose tolerance Age: 66.0±1.0 yr (66+/−1 yr) BMI: 34.3±5.2 kg/m^2	Both groups had reductions in weigh, total fat mass and waist circumference, leptin, intramuscular lipids, andRQ. Insulin sensitivity and VO2max increased in both groups. The Ex+CR group had greater changes in weight, fat mass, leptin concentrations, and basal fat oxidation than the EX group
6b. Solomon et al. 2009	Body composition Cardiometabolic disease	RCT: 12 weeks 2 groups: Exercise (EX) or exercise plus caloric restriction (EX−HYPO)	n=16 women & men Age: 66.0±1.0 yr (66+/−1 yr) BMI: 33.2±1.4kg/m^2 (BMI 33.2+/−1.4)	Both groups had decreases in weight, total fat mass, and increases in insulin sensitivity.

Reference	Health Outcomes (primary/secondary)	Study Design & Intervention	Sample	Summary of Findings
6c. Yassine et al. 2009	Body composition Cardiometabolic disease Physical function	RCT: 12 weeks 2 groups: Exercise (EX) or exercise plus caloric restriction (EX+CR)	n=24 women & men with metabolic syndrome Age: 65.5±5.0 yr (65.5 +/−5 yrs) BMI: 34.3±5.2 kg/m^2 (30–40)	Both groups had significantly decreased weight, waist circumference, total abdominal, subcutaneous, and visceral fat; improvements in insulin sensitivity, systolic and diastolic blood pressure, glucose, triglycerides, and total and low-density lipoprotein cholesterol; and improved aerobic capacity. Ex+CR group had greater decrease in weight and and subcutaneous fat than Ex group.
7. Messier et al. 2004	Physical function Bone Metabolism	RCT: 18 months 4 groups: healthy lifestyles (control), diet only, exercise only, and diet plus exercise	n=316 women with knee osteoarthritis Age: 68.7±0.8 yr BMI: 34.2±0.6 kg/m^2	The diet plus exercise group had significant improvements in self-reported physical function, 6-minute walk distance, stair-climb time, and knee pain compared to the healthy lifestyle group. The diet-only group did not differ from the healthy lifestyle group for any of the functional or mobility measures. Both weight-loss groups had significantly greater decreases in weight than did the healthy lifestyle group. CR had no significant effect on markers of bone metabolism

[*] Note 6a, 6b, and 6c emanate from the same study. However, because they report on different subsets of the sample with varying sample sizes and characteristics, we report the descriptions of the papers separately in this table.

Table 2

Study Outcomes

Reference	Body Composition	Bone Metabolism	Cardio-metabolic Disease	Systemic Markers of Inflammation and Adipokines	Physical Function	Cognitive Status	Quality of Life
1. Nicklas et al. 2015	Weight + Lean mass − Fat mass ±	NA	NA	NA	Knee Strength ± Knee Power ± Knee Quality ± Gait Speed ± 400 Meet Walk +	NA	NA
2. Messier et al. 2013	Weight + Fat mass + % Fat mass + Lean mass − % Lean mass − Abdominal fat + Abdominal visceral fat + Abdominal subcutaneous fat + Abdominal intermuscular fat + Total thigh fat ± Thigh intermuscular fat ± Thigh subcutaneous fat ± Hip BMD − Neck BMD − Spine BMD ± Osteoporosis ±	Kertain Sulfate ± TGF-β1 ±	NA	IL-6 + CRP +	Knee Compressive Force + WOMAC Pain Score + WOMAC Function Score + Gait Speed + 6-Minute Walk ±	NA	SF-36 Physical + SF-36 Mental ±
3. Rejeski et al. 2011	Weight +	NA	*1*	hsIL-6 + IL-6sR ± IL-8 ± sTNFR1 ± Adiponectin ± Leptin +	400 meter walk test +	NA	NA
4. Villareal et al. 2011	Weight + Bone mineral density hip − Trunk fat + Visceral fat + Subcutaneous fat + Waist circumference ± Fat mass + Thigh muscle − Thigh fat + Bone mineral	Sclerostin − C-terminal telopeptide of type 1 collagen − Osteocalcin – Intact N- type I Terminal propeptide of collagen −	Insulin sensitivity Index + Insulin area under curve + Glucose area under curve ± Fasting insulin + HOMA-IR + Fasting	Hs-CRP ± sTNF R1 + Adiponectin ±	Physical Performance Test + VO2peak + Functional Status Questionnaire ± Strength ± Balance ± Gait ± Obstacle	Modified Mini-Mental State Exam ± Word Fluency Test ± Trail Making Test Part A ± Trail Making Test Part B ±	IWQOL ± Geriatric Depression Scale ±

Reference	Body Composition	Bone Metabolism	Cardio-metabolic Disease	Systemic Markers of Inflammation and Adipokines	Physical Function	Cognitive Status	Quality of Life
	density hip − Trunk fat + Visceral fat + Subcutaneous fat + Waist circumference ±		Glucose ± HDL Cholesterol ± Triglyceride ± Systolic blood Pressure + Diastolic blood pressure ±		Course ± One-leg Stance + Gait speed ±		
5. Santanasto et al. 2011	Waist circumference ± Weight + BMI + % Body fat + Fat mass + Lean mass ± Appendicular lean mass ± Total body BMD ± Hip BMD ± Total abdominal fat + Visceral abdominal fat + Subcutaneous abdominal fat ± Total thigh fat ± Subcutaneous Thigh fat ± Thigh muscle mass − Thigh muscle density ± Thigh lean muscle mass ± Quadriceps muscle mass ± Quadriceps muscle density ± Quadriceps lean muscle mass ±	NA	NA	NA	Quadriceps specific torque ± Knee extensor peak torque ± Knee extensor average torque ± SPPB score ±	NA	NA
6. Solomon et al. 2008 (Solomon et al., 2009 and Yassine et al. 2009)	Solomon et al., 2008 Weight + BMI + Fat mass ± Fat free mass ± Waist circumference ± Waist-to-hip Ratio ± Visceral fat ±	NA	Leptin ± Adiponectin ± Insulin Sensitivity ± Instramuscular lipids ± Basal substrate metabolism ±	NA	Solomon et al., 2008 $V0_2$max ± Solomon et al., 2009 $V0_2$max + Yassine et al., 2009 VO_2max ±	NA	NA

Reference	Body Composition	Bone Metabolism	Cardio-metabolic Disease	Systemic Markers of Inflammation and Adipokines	Physical Function	Cognitive Status	Quality of Life
	Subcutaneous Fat + Solomon et al., 2009 Weight + BMI + Fat mass ± Fat-free mass ± Yassine et al., 2009 Weight + BMI + Fat mass ± Fat-free mass ± Waist circumference ± Waist-to-hip Ratio ± Visceral fat ± Subcutaneous Fat +		Energy expenditure ± Carbohydrate oxidation ± Fat oxidation ± Protein oxidation ± Solomon et al., 2009 Fasting Plasma Glucose ± Fasting Plasma Insulin+ Leptin + Fasting TG + Total Cholesterol + Yassine et al. 2009 Systolic blood pressure ± Diastolic blood pressure ± Fasting Glucose ± Fasting insulin ± Glucose Disposal rate ± Glucose Infusion rate ± Oral glucose Tolerance test ± Triglycerides ± Cholesterol ± HDL ± LDL ±				
7. Messier et al. 2004	*2*	Cartilage oligomeric protein hyaluronan ± Antgenic Keratin sulfate ± TGF-β1	NA	C-reactive protein + Interleukin 6 + Soluble interleukin 6 Receptor ± TNF alpha ± sTNFR1 + sTNFR2 ±	*3*	NA	NA

+ Beneficial Change, − Harmful Change, ± Neither Beneficial nor Harmful, NA = Not Evaluated

[1]Glucose, serum insulin, total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) were all measured, but differences between groups were not reported.

[2]Weight loss and changes in lateral and medial joint space were measured, but differences between groups were not reported.

[3]Self-reported physical function using the WOMAC, 6-minute walk distance, the stair-climb test, and changes in self-reported pain were measured, but differences between groups were not reported.