PREDICTORS OF CLINICALLY MEANINGFUL GAIT SPEED RESPONSE TO CALORIC RESTRICTION AMONG ODLER ADULTS PARTICIPATING IN WEIGHT LOSS INTERVENTIONS

BY

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ADLs	Activities of daily living
BMI	Body mass index
CR	Caloric restriction
CRP	C-reactive protein
CVD	Cardiovascular disease
IADLs	Instrumental activities of daily living
IL-6	Interleukin 6
NoCR	No Caloric Restriction
PAT-D	Pepper Assessment Tool for Disability
RCTs	Randomized controlled trials
SPPB	Short physical performance battery
TNF- α	Tumor necrosis factor alpha
VO_{2max}	Maximal oxygen consumption

ABSTRACT

The purpose of this study was to examine whether select baseline characteristics influence the likelihood of an older adult experiencing a clinically meaningful gait speed response (±0.05 m/s) to caloric restriction. Individual level data from 1188 older adults participating in eight, five/six-month, dietary-based weight loss interventions were pooled, with treatment arms collapsed into caloric restriction (CR; n=667) or no caloric restriction (NoCR; n=521) categories. Poisson risk ratios (95% CI) were used to examine whether CR assignment interacted with select baseline characteristic subgroups (age, sex, race, BMI, comorbidity status, baseline gait speed, or inflammatory burden) to influence achievement of ±0.05 m/s fast gait speed change. Main effects were also examined. The study sample (69.5% female, 80.1% white) was 67.6±5.3 years old with a BMI of 33.8±4.4 kg/m^2. Interaction effects were non-significant across all subgroups. However, those with low baseline gait speed were more likely to experience a clinically meaningful gait speed improvement; and, females and those with hypertension or CVD were more likely to experience a gait speed decrement, regardless of CR assignment (all $p \leq 0.04$). Compared with NoCR, CR does not result in a clinically meaningful change in gait speed among older adults. This finding is robust across several baseline subgroupings.

INTRODUCTION

Obesity among Older Adults is Common, Costly, and Serious

Adults over the age of 65 currently comprise about 9% of the global population (1). This is the fastest growing age group worldwide, with numbers expected to reach 16% of the global population — or 1.5 billion people — by 2050 (2). Likewise, this share of total U.S. population will increase from 16% to 23% over the same period (1); and, within this, the prevalence of obesity is also on the rise. Commonly defined as a body mass index (BMI) equal or greater than 30 kg/m^2, the number of older adults living with obesity has steadily increased from 35% to 42.8% over the past decade (3). By 2030, nearly 1 in 2 adults nationwide is projected to be obese — underscoring that obesity is a prevalent and growing condition for older Americans (4).

Obesity — particularly among older adults — contributes to healthcare burden. For example, data from the Medical Expenditure Panel Survey indicate that medical costs for adults with obesity increased 14.3% between 2005 and 2010 (5). During the same period, the total cost of obesity in U.S. adults rose from $212.4 billion to $315 billion — a 48.7% increase in just five years — and is attributed to the increase in medical spending among older adults (6). Data from the Milken Institute suggests obesity and its chronic diseases accounted for $480.7 billion in direct U.S health care costs in 2016, with additional $1.24 trillion in indirect costs due to lost economic productivity (7).

Obesity is directly or indirectly associated with numerous chronic diseases and medical complications. The excess lipids with weight gain are distributed to many body locations, where they are known to directly affect metabolic pathways and physiological characteristics (8). For instance, intramuscular lipid accumulation contributes to insulin

and glucagon resistance (8). Likewise, accumulation of fatty acids within the pancreas, leads to blunted insulin secretion and significantly increases the risk of type II diabetes (8). Other common conditions that are directly associated with obesity include osteoarthritis, obstructive sleep apnea, and gastroesophageal reflux disease, caused (at least in part) by increased mechanical stress on joints, soft tissues, and intraabdominal pressure, respectively.

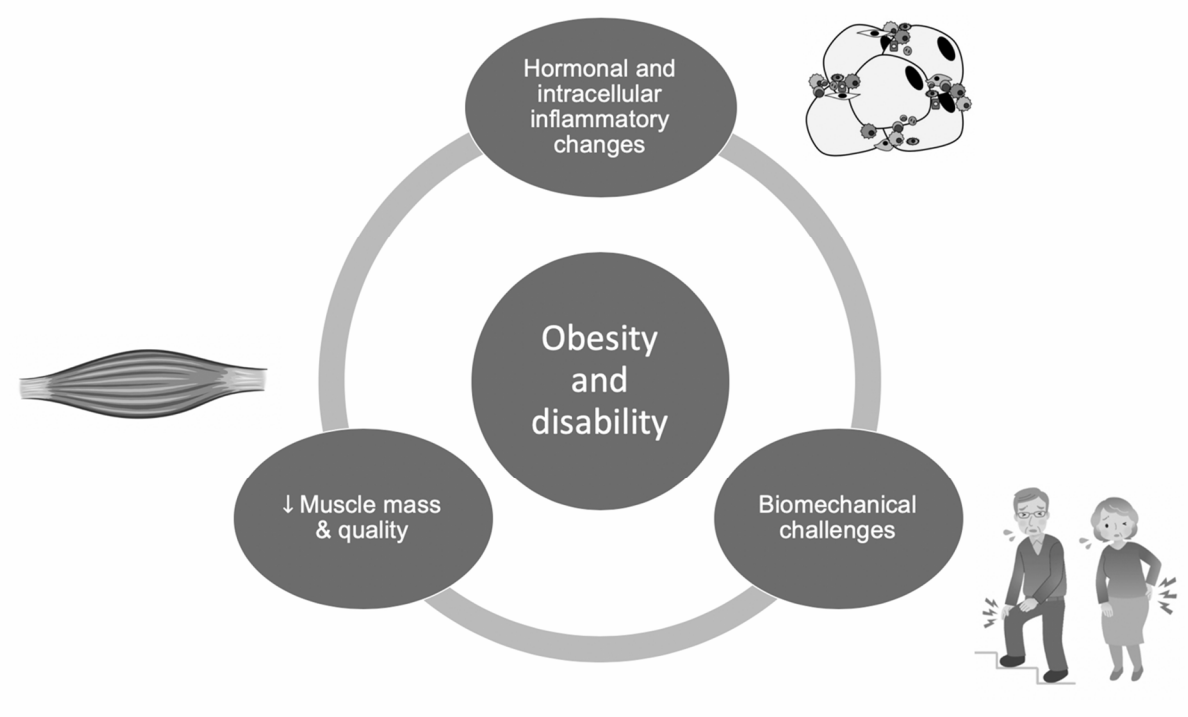
Indirectly, obesity-related inflammation plays a key role in the pathophysiology of major chronic diseases, and even increases overall mortality risk (9). For example, obese individuals overexpress tumor necrosis factor alpha (TNF-α) (9); and, elevated levels of TNF-α are associated with insulin resistance and tumorigenesis, which in turn contribute to increased risk of type II diabetes and various types of cancer (10). Lipid accumulation also increases the production of interleukin-6 (IL-6), with evidence associating an IL-6 concentration beyond 2.5 pg/mL with increased risk of mobility disability among older adults (11). Elevated level of IL-6 also increases the expression of the acute phase reactant, C-reactive protein (CRP). CRP is a sensitive marker of vascular inflammation and predictor of atherosclerosis (12), with evidence associating a CRP concentration above 3 mg/L with a two to three fold increase in risk of cardiovascular diseases (CVD), such as peripheral arterial disease, stroke and sudden cardiac death (13).

Impact of Obesity of Physical Function among Older Adults

In addition to the strong association with chronic disease, obesity also significantly contributes to functional limitation and disability among older adults. Indeed, compared to older adults with a BMI within healthy range, those with BMI $\geq$30 are twice as likely to experience functional limitation, with stronger relationship shown in

women (14). Unsurprisingly then, the additional average obesity cost of people with disability is almost three times that of people without disability (15). While the mechanisms underlying this association are likely varied and not fully understood, prominent theories include: 1) hormonal and intracellular inflammatory changes; 2) reductions in muscle mass and innervation, as well as fat infiltration into skeletal muscle; and 3) global biomechanical challenges, and osteoarthritis in particular (see **Figure 1)** (16).

Figure 1. Prominent obesity-related disability theories.



Excessive adipose tissue accumulation is associated with a pro-inflammatory state, with elevations in the cytokines TNF-α and IL-6 specifically linked to impaired physical function (17,18). Mechanistically, this occurs via muscle catabolism and progression of articular cartilage destruction, which begins when TNF-α binds to muscle receptors and triggers cellular apoptosis (17). Elevated levels of IL-6 are also thought to

accelerate muscle catabolism (18), with observational data linking high levels of IL-6 with lower muscular strength (19), reduced walking ability (18), and higher risk of developing mobility disability (18) among older women. In addition to increased inflammatory burden, obesity-related hormonal changes such as increased insulin resistance and reduced oxidative capacity (20) can also significantly impact physical function.

Muscle mass and strength also decrease with aging due to deterioration in motor neurons innervating the muscle fiber (21). Indeed, during the period of 20-70 years of age, up to 40% of fat free mass decreases (22). Satellite cells normally maintain muscle function by forming new muscle fibers or melding with mature muscle cells to assist existing myonuclei. However, due to age-related changes in oestrogen and testosterone, satellite cell activity and regenerative capacity decrease (21). This age-associated muscle degeneration is known as sarcopenia (23), and the coexistence of obesity with sarcopenia significantly worsens the adverse effects of obesity on physical function in older adults. For instance, individuals with sarcopenic obesity are two to three times more likely to develop instrumental activities of daily living (IADLs) disability than lean sarcopenic or nonsarcopenic obese individuals (24). Obesity upregulates the inflammatory response, promoting muscle catabolism among individuals with sarcopenia (25). With the satellite cell function impairment and regeneration caused by infiltration of fat into muscle in advancing age, physical function is severely impacted.

Finally, obesity-related biomechanical issues — particularly related to osteoarthritis — are a common cause of reduced physical function among older adults. Major symptoms of osteoarthritis include joint pain, swelling and stiffness, which are

mostly caused by inflammation (26). In addition, the excess weight in older adults with obesity dramatically impact the weight bearing joints through skeletal misalignment and mechanical compression. Commonly affected areas are the hip, knee, and ankle (16). Individuals with obesity often have reduced trunk. This biomechanical shift minimizes torque and suppresses pain temporarily, but worsens aberrant loading (16). The musculoskeletal pain and impairment in the lower extremity significantly disrupts their normal gait to stand or walk. Chronic lower back pain is also a common condition among older adults with obesity due to excess weight burden on spine, which often leads to structural compromise and damages (27). Combined with the effects of osteoarthritis on lower extremity, the ability to perform activities of daily living (ADLs) is significantly diminished.

Older adults with obesity are also more likely to have low self-compassion and rumination on pain (16). The fear of exacerbating pain with movement often leads to physical inactivity. These psychosocial issues can intensify disability among these individuals tremendously.

Physical Function as a Predictor of Disability

Different physical performance tests have been established to predict disability and mortality (28), and are often used as surrogate endpoints in clinical trials enrolling older adults. One of the most common ways to assess physical function in older adults is by measuring gait speed. Gait speed is a strong predictor of disability and survival, as walking requires movement control, energy, and places demand on heart, lung, circulatory, nervous, and musculoskeletal systems (29). In research settings, fast endurance gait speed is often derived as the time it takes to walk 400 meters or as the

distance walked over six-minutes. During the 400-meter walk test, participants are asked to walk 10 laps of a 40-meter course (20 meters out and 20 meters back) and given a maximum of 15 minutes to complete the test. Similarly, during the six-minute walk test, participants are asked to walk as far as they can around a circular track in six minutes. In both cases a script is used to standardize instructions and participants are told that they may rest during the test at any point, if necessary. In practice, 400 meters is about two to three city blocks; thus, the ability to walk 400 meters is considered vital to the independence and functional capacity of older adults living in the community. Indeed, in an observational cohort study, individuals who were unable to walk 400 meters had significantly higher mobility limitation [HR: 1.86 (95% CI: 1.58-2.18)] and mobility disability [HR: 1.95 (95% CI: 1.56-2.44)] compared to those without walking difficulty (30). Among those who completed 400 meters, each additional minute of performance time was associated with 29% higher rate of mortality and 52% higher rates of mobility limitation and disability (30). Importantly, increments of 0.1 m/s in gait speed are predictive of increased survival in older adults (29), and 0.05 m/s is considered a clinically meaningful change (31).

Another common test of physical — and in particular, lower extremity — function in older adults is the Short Physical Performance Battery (SPPB). Consisting of timed five chair stands test, balance test with three positions (side by side, semi-tandem, tandem), and a four-meter walk test to assess usual gait speed, the total SPPB score ranges from 0 (worst performance) to 12 points (best performance), with a 0.3-0.8 point change considered clinically significant (32). A recent systematic review showed an SPPB score lower than 10 at baseline is predictive of all-cause mortality in all

individuals, including both inpatients and outpatients across different geographical areas, age groups and durations of follow up (33). In addition, older individuals who have been hospitalized with poor SPPB score (0-4) had a steeper increase in ADLs difficulty and higher risk of rehospitalization or death in one year follow up, compared to those with better SPPB scores (8-12) (34). A more recent study showed older adults aged 75 years and older who scored <7 in SPPB test has significantly lower survival in ten years compared to those who scored ≥7, after adjusting age, gender, number of drugs prescribed, cognitive status, BMI and visual sharpness (35). A limitation of the traditional SPPB is the inability to discriminate between high-functioning older adults. As such, an expanded SPPB — which adds a narrow four-meter walk test of balance and replaces the standing balance task with a 30 seconds single leg stand — is often used in research settings to minimize ceiling effects of the traditional SPPB.

Grip strength is another simple way to screen for overall strength and is often used in large scale research studies as the reliability and validity of this measurement has been tested in different age groups, ethnicities, and clinical populations (36). Grip strength is defined as the maximum amount of static force the hand can squeeze around a dynamometer, and a change of greater than six kg is not considered clinically meaningful (37). Grip strength declines linearly with age (38), and consistently predicts future disability, morbidity and mortality (39). For example, one prospective cohort study examined association between grip strength and ADLs disability among 2,493 older adults over seven years. Participants in the lowest hand grip strength quartile (<22 kg in men, <14 kg in women) were twice as likely to report an ADLs limitation over time, compared to those in the highest hand grip strength quartile (≥35 kg in men, ≥22 kg in

women). Each one kg increase in hand grip strength was associated with 3% (in men) and 5% (in women) decrease risk of any ADLs limitation (40). Another prospective cohort study examined relationship between grip strength and mortality rate among 502,293 middle to older aged adults (41) and showed that all-cause mortality was associated with a hazard ratio of 1.20 (95% CI: 1.17-1.23) per five kg lower grip strength. In addition, grip strength was inversely associated with cause specific mortality from CVD, respiratory disease, and cancer.

Finally, a more idiosyncratic physical function assessment tool that utilized within the Older Americans Independence Centers is the Pepper Assessment Tool for Disability (PAT-D) (42). This self-administered questionnaire consists of 19 items that are broadly used to assess mobility, ADLs, and IADLs. For each item, participants are asked to provide a rating from 1 ("usually did with no difficulty") to 5 ("unable to do"), or they can check the box of "usually did not do for other reasons". Response of 1 on PAT-D questionnaire item is commonly defined as no difficulty, and response of 2-5 is defined as having difficulty. PAT-D total mean scale score is calculated by summarizing across and then diving by total amount of items, and subscale mean scores in mobility, ADLs, and IADLs are calculated with the same method. One prospective study used PAT-D to examine transitional states of disability in 480 older adults with knee pain, and demonstrated that difficulty to perform stair climbing and lifting heavy objects predicted the disability onset for the next 30 months (43). Severity of disability is lowest among those who only have difficulty to perform mobility-related tasks, and highest among those who have difficulty to perform IADLs (43). Internal consistency and test-retest reliability is >0.70 for each domain (42). Importantly, PAT-D score tracks with objective

measures of physical function, such as gait speed. For instance, fast walkers self-reported better function on the PAT-D questionnaire compared to slow walkers (42). PAT-D scores are also associated with increased BMI and body fat percentage (44), lower percent of appendicular lean mass (44), and CVD (42).

Controversy of Weight Loss in Older Adults with Obesity

Lifestyle based interventions are effective at promoting weight loss and fat mass loss in older adults with obesity. Weight loss can reduce chronic inflammation among older adults with obesity, likely due to overall reductions in adipose tissue (45). Inflammation in older adults with obesity can have serious health consequences; thus, reduction in inflammatory burden lowers the risk of chronic diseases (46), mobility disability (47) and mortality (48). However, weight loss interventions can be risky, particularly among older adults. Changes in body composition caused by weight loss intervention usually consist of two-thirds fat mass and one-third lean mass (49). This has led some to suggest weight loss associated loss of lean mass may exacerbate functional decline in this population (50,51). Indeed, observational studies indicate that low lean mass is associated with impaired gait speed ($\leq$0.8m/s) (52), and low SPPB score (<7 — classified as severe mobility impairment) (53); and loss in muscle mass is associated with physical disability and hospitalization (54). Weight loss also contributes to increased fracture risk (55) via loss of bone mineral density (56). Taken together, although there are health benefits associated with loss of excess fat mass, weight loss associated reductions in fat-free mass have the potential to increase the risk of disability, institutionalization, and mortality among older adults (50,57).

Moreover, evidence shows only 20% of people who voluntarily lost weight are successful at long term weight maintenance (58); and for older adults, sobering data suggest that this weight regain is associated with a shift in body composition toward a higher percentage of total body fat. In one of the first studies to examine weight regain associated change in body composition in older adults, Beavers et al. followed 78 postmenopausal women for a year after a successful five months hypocaloric diet intervention ended (59) — classifying women as weight re-gainers (n=54; regained $\geq$2 kg body weight during the 12 months follow up) or weight loss maintainers (n=24) — and described the ensuing change in body composition for both groups. Among women classified as weight re-gainers, every one kg of fat mass lost during intervention was associated with 0.26 kg lean tissue was lost; yet, for every one kg fat regained during follow up, only 0.12 kg lean mass was regained. The decreasing trend in lean-to-fat ratio led authors to speculate that older women who regain weight following a successful weight loss intervention may actually be more susceptible to develop mobility disability later in life than had they not undergone intentional weight loss.

Using data from the Look AHEAD study, authors examined the impact of body weight change following intentional weight loss on a battery of physical function measures (60). In this study, 450 middle aged adults with type 2 diabetes who lost weight after one year of being in a lifestyle weight loss intervention were followed for the next seven years and classified as weight cyclers, weight re-gainers (based on ± 5% annual change in weight). Women who were classified as weight cyclers were shown to have worsened expanded SPPB scores (1.46±0.07) and slower 20-m walking speed (1.10±0.04 m/s) compared to women who continued to lose weight or maintained their weight loss

(1.63±0.07 and 1.17±0.04 m/s, respectively). Interestingly, men who identified as weight cyclers had weaker grip strength compared to re-gainers or continued losers/maintainers (30.12±2.21 vs. 34.46±2.04 and 37.39±2.26 kg).

Thus, for the reasons stated above, weight loss among older adult remains a controversial topic. While, the current national guidelines do recommend weight loss therapy that minimizes muscle and bone losses for older adults who are obese and who have functional impairments or medical complications that can benefit from weight loss (57), ultimately this decision is one that needs to be carefully and individually considered.

Effect of Weight Loss on Physical Function among Older Adults: Evidence from RCTs

Although some observational evidence supports the premise that weight loss in old age can exacerbate functional decline; consideration of data from randomized controlled trials (RCTs) are necessary, as they provide the highest level of evidence. In the section below, we specifically focus on lifestyle based weight loss trials which report on change in gait speed, as it is valid, reliable, and sensitive measure of functional status and overall health (61).

Pubmed was searched exhaustively through 07/13/2020 using the search string (Gait Speed & Weight Loss) and identified 12 studies conducted over the past 16 years that examined the independent effects of weight loss (either alone (n=329), or in combination with exercise (n=688)) to non-weight loss control condition (either exercise alone (n=538) or attention control (n=310)) on change in gait speed (47,62–72). Relevant study design details are presented in **Table I**. Briefly, study duration ranges from five to

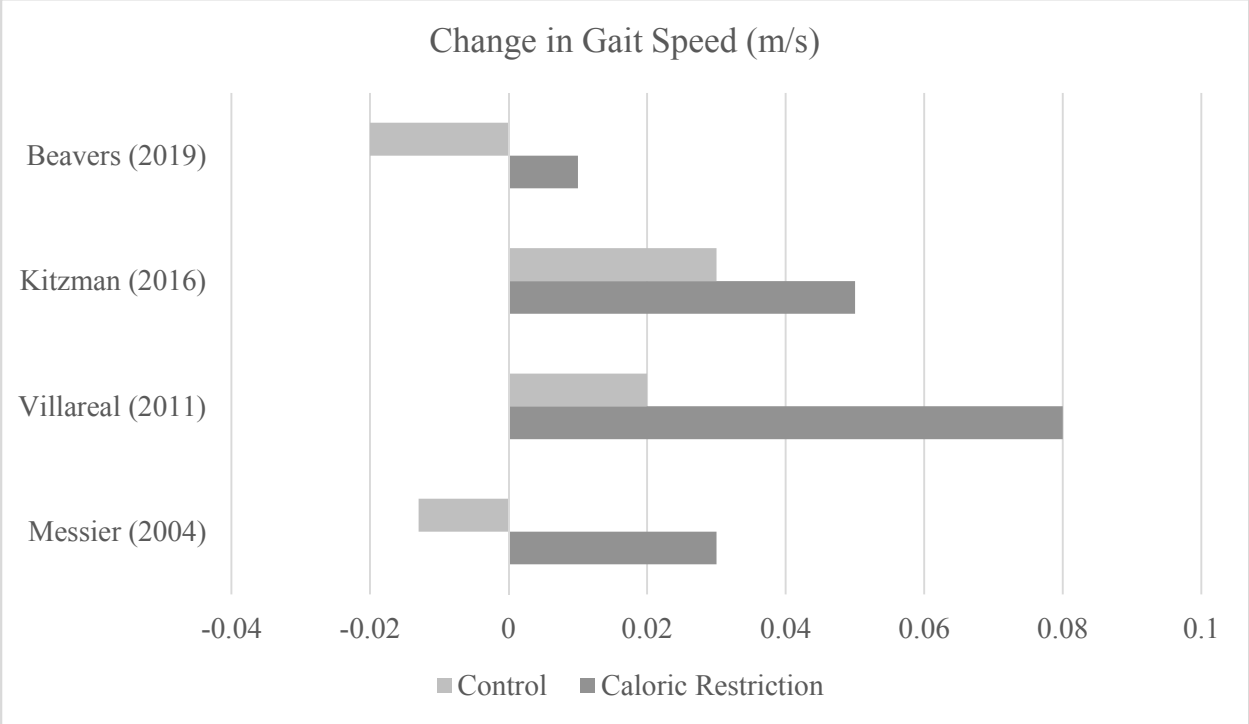
18 months, sample consist of 56 to 100% of female and 47 to 98% of white. Four studies showed a modest improvement in gait speed with weight loss, with four studies specifically allowing the comparison of CR and control condition (**Figure 2**). Overall, these studies showed gait speed change ranges from 0.01 m/s to 0.08 m/s in CR groups, and -0.013 m/s to 0.03 m/s in control groups (63,66,69,71), with two of the four showing clinically meaningful gait speed improvement of $\geq$ 0.05 m/s attributed to CR induced weight loss (63,69). Specially, Villareal et al (69) examined the effect of a 12 months exercise and CR intervention on physical function in 93 overweight or obese older adults (72% female, 98% white; n=26 in CR, n=27 in control) and found 0.08 m/s gait speed improvement in CR group compared to 0.02 m/s in control group. Kiztman et al (63) examined effect of a five month CR or aerobic training intervention on exercise capacity and quality of life in 100 overweight or obese older adults with heart failure with preserved ejection fraction (81% Female, 55% White; n=24 in CR, n=25 in control) and found 0.05 m/s gait speed improvement in CR group compared to 0.03 m/s in control group. Messier et al (71) examined the effect of a 18 months exercise and CR intervention on pain, mobility and physical function in 309 overweight or obese older adults with knee osteoarthritis (72% Female, 78% White; n=80 in CR, n=76 in control) and found 0.03 m/s gait speed improvement in CR group compared to -0.013 m/s in control group. Finally, Beavers et al (66) examined the effect of a 6 months CR intervention on body composition and mobility in 96 obese older adults (74% Female, 73% White; n=47 in CR, n=49 in control) and found 0.01 m/s gait speed improvement in caloric

Table I. RCT reporting on gait speed change after lifestyle-based weight loss interventions.

Author (year)	N (% F; %W)	Age (years)	Duration (months)	Intervention (n)	Δ Gait Speed (m/s)
Messier (2004) (71)	309 (72%; 78%)	69	18	CR (n=80)	0.03
				AE (n=79)	0.13†
				CR+AE (n=74)	0.17†
				Control (n=76)	-0.013
Villareal (2006) (68)	27 (67%; 85%)	71	6	CR+EX (n=17)	0.08*
				Control (n=10)	0.02
Villareal (2011) (69)	93 (72%; 98%)	70	12	CR (n=26)	0.08
				EX (n=26)	0.14*
				CR+EX (n=28)	0.28*
				Control (n=27)	0.02
Rejeski (2011) (72)	288 (67%; 83%)	67	18	CR+AE (n=98)	0.1†
				AE (n=97)	0.05
				Control (n=93)	0.04
Anton (2011) (65)	34 (100%; 47%)	63	6	CR+EX (n=17)	0.16†
				Control (n=17)	0.02
Messier (2013) (70)	454 (72%; 83%)	66	18	CR (n=152)	0.09
				AE (n=150)	0.07
				CR+AE (n=152)	0.12†
Manini (2014) (67)	34 (100%; 86%)	63	6	CR+EX (n=14)	0.15
				Control (n=13)	0.00
Nicklas (2015) (64)	126 (56%; 87%)	70	5	CR+RT (n=63)	0.09*
				RT (n=63)	0.08
Haywood (2017) (62)	117 (NA; NA)	70	3	CR (low)+AE (n=41)	0.23*
				CR (high)+AE (n=40)	0.18*
				AE (n=36)	0.14*
Kitzman (2016) (63)	100 (81%; 55%)	67	5	CR (n=24)	0.05
				AE (n=26)	0.05
				CR+AE (n=25)	0.18
				Control (n=25)	0.03
Nicklas (2019) (47)	180 (76%; 83%)	69	5	CR (low)+AE (n=60)	0.13
				CR (high)+AE (n=59)	0.13
				AE (n=61)	0.11
Beavers (2019) (66)	96 (74%; 73%)	70	6	CR (n=47)	0.01
				Control (n=49)	-0.02

Abbreviations: N= sample size; F= female; W= white; m/s= meters per second; CVD/METS= cardiovascular disease or metabolic syndrome; HFPEF= heart failure with preserved ejection fraction; CR= caloric restriction; AE= aerobic exercise; RT= resistance training; EX= combined aerobic exercise and resistance training; OA= osteoarthritis; *= significant change from baseline. †= significant difference between groups.

Figure 2. Comparison of gait speed change in caloric restriction and control group in four RCTs.



restriction group compared to -0.02 m/s in control group. Although the CR groups in two of these studies (66,71) did not achieve clinically meaningful improvement in gait speed, gait speed was increased in caloric restriction groups, and notably, control groups experienced slow gait speed over the course of the intervention. While modest improvements in gait speed can be attributed to caloric restriction, it is apparent that significant variability about the magnitude of this change exists. Indeed, across trials included in **Table I**, gait speed change ranges from 0.01 m/s to 0.28 m/s among individuals randomized to some type of weight loss groups. In further support of this point, when examining change in gait speed among IDEA study (70) participants who were randomized to weight loss and experienced a 5% weight loss during the first six months of intervention, we previously reported that although average gait speed increased

by 0.05±0.10 m/s, individual changes varied from -0.27 to 0.29 m/s, with nearly one-quarter (24%) showing no improvement (i.e. $\Delta \leq 0.00$ m/s) (73). Thus, we conclude that despite overall benefit, substantial variation in the magnitude of improvement exists, with a subset of participants likely to experience a null, or even negative functional response to weight loss.

Although often ignored, consideration of inter-individual differences in functional response to weight loss holds tremendous clinical significance as it has the potential to inform personalized geriatric obesity management strategies and provide important insight into underlying adaptive mechanisms. To date, no studies have examined the heterogeneity in functional response to weight loss in older adults; however, we draw parallels from the larger literature to understand how to conduct and interpret treatment response variability studies.

Heterogeneity in Treatment Response

Heterogeneity is commonly defined as the quality or state of being diverse in character or content. In clinical disciplines, heterogeneity of treatment effect is the magnitude of the variation of individual treatment effect across a population (74). The inter-individual response variation can be driven by different factors, such as genotype, phenotype, and the environment. Although no studies have examined the heterogeneity in functional response to weight loss in older adults, heterogeneity in treatment response has been examined in other disciplines and provides a useful framework upon which to build this thesis.

The exercise literature, for example, is fraught with studies aimed at understanding response variability. In one of the seminal studies to examine

heterogeneity in cardiorespiratory fitness response to exercise training, the HERITAGE study (75) noted that among over 600 adults who engaged in a standardized 20-week cycle ergometer training program, although maximal oxygen consumption (VO_{2max}) significantly increased in all participants, individual responses varied widely. Specifically, lower percentage change in VO_{2max} (ml/kg/min) was observed in women compared to men (15.9±8.5 vs. 19.5±10.6). Lower absolute change in VO_{2max} (ml/kg/min) was observed in black compared to white (4.9±2.3 vs. 5.5±3.0), and older (50-65 years) compared to younger (30-49 years and 17-29 years) individuals (4.5±2.3 vs. 5.3±2.6 and 5.7±3.1). The observed variability in physical response to exercise training has been replicated in several studies (76), with findings extended to include heterogeneity in body composition and cardiometabolic outcomes — even after controlling for protocol adherence (77–80). For older adults, wide variations in the magnitude of improvement were seen in the SPPB after five months of aerobic or resistance training, with 13% and 30% of participants showing no improvements in peak oxygen consumption and strength respectively, despite sufficient levels of adherence (81). Similar examples of response variability have been observed in response to pharmacotherapy (82), radiation therapy (83) and nutrition (84), in general provides the basis for the field of precision medicine (85).

Quantitative outcomes from clinical trials are frequently commonly analyzed with the goal of determining whether the randomly assigned active treatment effect mean differs on average from the average control mean, frequently assuming similar variances between groups under typical assumptions used in methods such as analysis of variance. Similar assumptions are used for discrete outcomes, with the caveat that variances for

discrete data are often functions of the distribution under the null hypothesis. However, such methods often ignore the potential heterogeneity of a treatment effect, in which an individual responds differently to a treatment based on his or her demographic characteristics, comorbidities, risk factors, functional status, etc. Treatment response heterogeneity frequently manifests as differences in both means and variances among subgroups; however formal tests for heterogeneous treatment effects frequently crudely focus on subgroup analyses to detect differences in treatment means. Even when performed properly, individual trials often lack statistical power to detect significant effects, particularly within small subgroups.

One useful approach is to pool individual participant data from multiple similar studies (86). Differences in eligibility criteria and outcome ascertainment can impose challenges to such analyses, but when possible the larger sample size and additional sample diversity can potentially uncover differential treatment effects ultimately leading to greater precision in identifying which participants may experience benefit or harm from a treatment. This has been performed commonly in the exercise literature but less so for weight loss interventions, particularly among older adults for whom comorbidity burden is higher and risks for harm are more deleterious. Uncovering the determinants of heterogeneity in functional response to a weight loss treatment effect can ultimately identify the characteristics of older adults who stand to benefit from a weight loss intervention and open new possibilities for treatment for those less likely to benefit.

Thesis Purpose

The purpose of this thesis is to using individual-level data housed within the Wake Forest University Pepper Center (P30 AG021332) repository to produce estimates

of the overall probability of achieving clinically meaningful functional response to weight loss and to identify predictors of achieving "responder" status. Specifically, we will examine whether the observed associations between intentional weight loss and functional response vary by age, sex, race, BMI, comorbidities, inflammation, and body composition, as these well-known risk factors were consistently collected across studies. Collectively, this work aims to identify predictors of weight loss-associated functional improvement so that geriatric obesity treatment recommendations can be tailored to a patient's probability of success.

METHODS

Study Participants

This analysis includes middle-aged and older (≥50 years) adults who were overweight or obese and enrolled in eight separate dietary-based weight loss trials at Wake Forest University and Wake Forest School of Medicine between 1997 and 2017 (47,63,64,70–72,87,88). All studies assessed common measures of physical function (including fast-paced gait speed) before and five/six month after assignment to a CR intervention or to a NoCR control condition, with or without exercise. Brief descriptions of each study, including sample size, baseline characteristics, intervention strategy, and average change in gait speed are previously published (89). The Wake Forest Health Sciences institutional review board approved all secondary analyses pertaining to the pooled project (IRB# 54086).

Of the 1590 baseline visits conducted across all included studies, 1382 participants had a five/six-month follow-up visit, and 1359 had non-missing five/six-month weight change. Of these participants, 42 subjects were excluded from the primary

analysis due to missing at least one baseline covariate [race: n=17, education: n=8, diabetes: n=14, hypertension: n=15, CVD: n=6], and 61 subjects were excluded due to missing inflammatory biomarkers [CRP: n=49; IL-6: n=54], yielding a sample of 1256. An additional 68 participants did not have gait speed at baseline; therefore, final analyses were based on dataset of 1188 participants with complete exposure, outcome, and covariate information.

Exposure Measure: Randomization to Caloric Restriction or Non-Caloric Restriction

Arms within each study were collapsed into CR (n=667) and NoCR (n=521) categories based on whether weight loss via CR was specified in the original study protocol. Among 13 study-specific arms collapsed into the CR arm, six included participants randomized to CR only (n=249), and seven included participants randomized to CR combined with exercise (n=418). Among 10 study-specific arms collapsed into the NoCR arm, four included participants randomized to attention control (n=181), and six included participants randomized to exercise only (n=340).

Outcome Measure: Objectively Measured Fast Gait Speed

Fast gait speed change was assessed by trained, blinded assessors using standardized protocols at baseline and five/six month follow-up. Time recorded from the six-minute walk [612 (51.5%)] of the study sample or fast-paced 400-m walk [576 (48.5%)] was used to derive fast-paced gait speed. During the six-minute walk test, participants were asked to walk as far as they could around a circular track in six minutes. During the 400-m walk test, participants were asked to walk 10 laps of a 40-m course and

were given a maximum of 15 minutes to complete the test. A clinically meaningful increase in gait speed of ≥0.05 m/s from baseline was used to separate participants into improvement [n=698 (58.8%)] and no improvement [n=490 (41.3%)] categories. Participants with clinically meaningful decrement in gait speed were similarly grouped according to gait speed ≥0.05 m/s decrease from baseline into decrement [n=183 (15.4%)] or no decrement [n=1005 (84.6%)] categories.

Covariate Measures

All studies captured self-reported demographic characteristics (age, sex, race) and presence of select comorbidities (diabetes, hypertension, or CVD) at baseline. Standing height was measured using a clinical stadiometer and body mass was measured at baseline and five/six month follow up with a standard scale (with shoes and outer garments removed). BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Lastly, high-sensitivity CRP and IL-6 were measured on all available blood samples using standard methodology, as previously described (90).

Covariate subgroups were defined based on clinically meaningful cut points when appropriate. Specifically: age (≥65 versus <65), sex (female versus male), race (black versus white), and class II obesity (BMI; ≥35 kg/m^2 versus <35 kg/m^2), diabetes (yes versus no), hypertension (yes versus no), CVD (yes versus no), low baseline gait speed (<1.0 m/s versus ≥1.0 m/s) (29), having high CRP (≥3.0 mg/L versus <3.0 mg/L) (13), and high IL-6 (≥2.5 pg/mL versus <2.5 pg/mL) (11).

Statistical Analysis

Baseline data were analyzed using descriptive statistics, with means and standard deviations computed for continuous variables and counts and proportions for discrete

variables. Six-month pooled tests of treatment differences within subgroups on improvement or decrement in gait speed were estimated using Poisson regression models and presented as unadjusted results or fully adjusted for age, sex, race, study and baseline gait speed (except for models including the covariate). Tests of heterogeneity of change between CR and subgroups were tested using a two-way interaction term. If the two-way interaction was non-significant, the main effect of subgroup was examined as risk ratios and 95% confidence intervals of change in gait speed. Sensitivity analysis examining the potential influence of exercise was performed by only including individuals not randomized to exercise (n=430) and comparing the main effect of CR only versus control only on the likelihood of achieving a clinically meaningful gait speed improvement and decrement. All analyses use 2-sided hypothesis tests and assuming a Type 1 error rate of 0.05 for all comparisons. $p<0.05$ indicated significance.

RESULTS

Participant Characteristics

Table II presents relevant baseline characteristics for the pooled study sample overall and by CR assignment. Briefly, participants were 67.6±5.3 years of age and presented with class I obesity (BMI: 33.8±4.4 kg/m^2), with the majority of the study sample represented by white (80.1%) women (69.5%). Over half of the sample presented with hypertension at baseline (57.7%) and one third with CVD (32.8%), while diabetes was much less prevalent (14.1%). Average fast-paced gait speed was 1.2 m/s, reflective of a moderate to high-functioning group. Conversely, baseline CRP and IL-6 values of 6.9±9.1 mg/L and of 3.7±7.4 pg/mL, respectively, indicate prevalent sub-chronic

inflammatory burden. No differences in baseline characteristics were observed by treatment group.

Table II. Baseline characteristics presented overall and by caloric restriction group assignment.

	Overall (n=1188)	**Caloric Restriction (n=667)**	**No Caloric Restriction (n=521)**
Age (years)	67.6±5.3	67.6±5.3	67.5±5.3
Female, n (%)	826 (69.5)	471 (70.6)	355 (68.1)
Race, n (%)			
White	952 (80.1)	527 (79.0)	425 (81.6)
Black	236 (19.9)	140 (21.0)	96 (18.4)
BMI (kg/m²)	33.8±4.4	33.9±4.2	33.8±4.6
Presence of select comorbidities, n (%)			
Diabetes	167 (14.1)	89 (13.3)	78 (15.0)
Hypertension	685 (57.7)	388 (58.2)	297 (57.0)
CVD	390 (32.8)	216 (32.4)	174 (33.4)
Fast-paced gait speed (m/s)	1.2±0.2	1.3±0.2	1.2±0.2
CRP (mg/L)	6.9±9.1	7.2±9.0	6.6±9.3
IL-6 (pg/mL)	3.7±7.4	4.0±9.6	3.4±2.5

Note.: n=sample size; BMI: body mass index; CVD= cardiovascular disease; CRP=C-reactive protein; IL-6=interleukin 6.

Overall Treatment Effects on Weight and Gait Speed

In pooled analyses, average six-month weight loss achieved among those randomized to CR was (Mean±SE) -7.8±0.3%, while individuals randomized to NoCR were weight stable (-0.9±0.3%); $p<0.01$. Mean gait speed change was +0.10±0.01 m/s versus +0.07±0.01 m/s in the CR and NoCR groups, respectively, with 411 (61.6%) of CR and 287 (55.1%) of NoCR participants achieving a ≥0.05 m/s gait speed improvement; and 88 (13.2%) of CR and 95 (18.2%) of NoCR participants experiencing a ≥0.05 m/s gait speed decrement. No main effect of CR was observed on the likelihood of achieving a clinically meaningful gait speed improvement [RR: 1.09 (95% CI: 0.93,1.27)] or gait speed decrement [RR: 0.77 (95% CI: 0.57,1.04)].

Likelihood of Experiencing a Clinically Meaningful Gait Speed Change by Baseline Subgrouping

No significant interaction effects were observed between CR assignment and membership in any baseline subgrouping and the likelihood of experiencing clinically meaningful improvement or decrement in gait speed (**Figures 3a and 3b)**. However, several subgroups displayed an increased likelihood of experiencing a clinically meaningful change in gait speed (independent of CR assignment), as shown in **Table III**.

Figures 3a&b. Adjusted Poisson risk ratios (95% CI) of achieving a ±0.05 m/s change in gait speed by baseline characteristics according to caloric restriction assignment. Models adjusted for study, age, sex, race, and baseline gait speed (except for the subgroup test including the covariate) and subgroup by caloric restriction interaction.

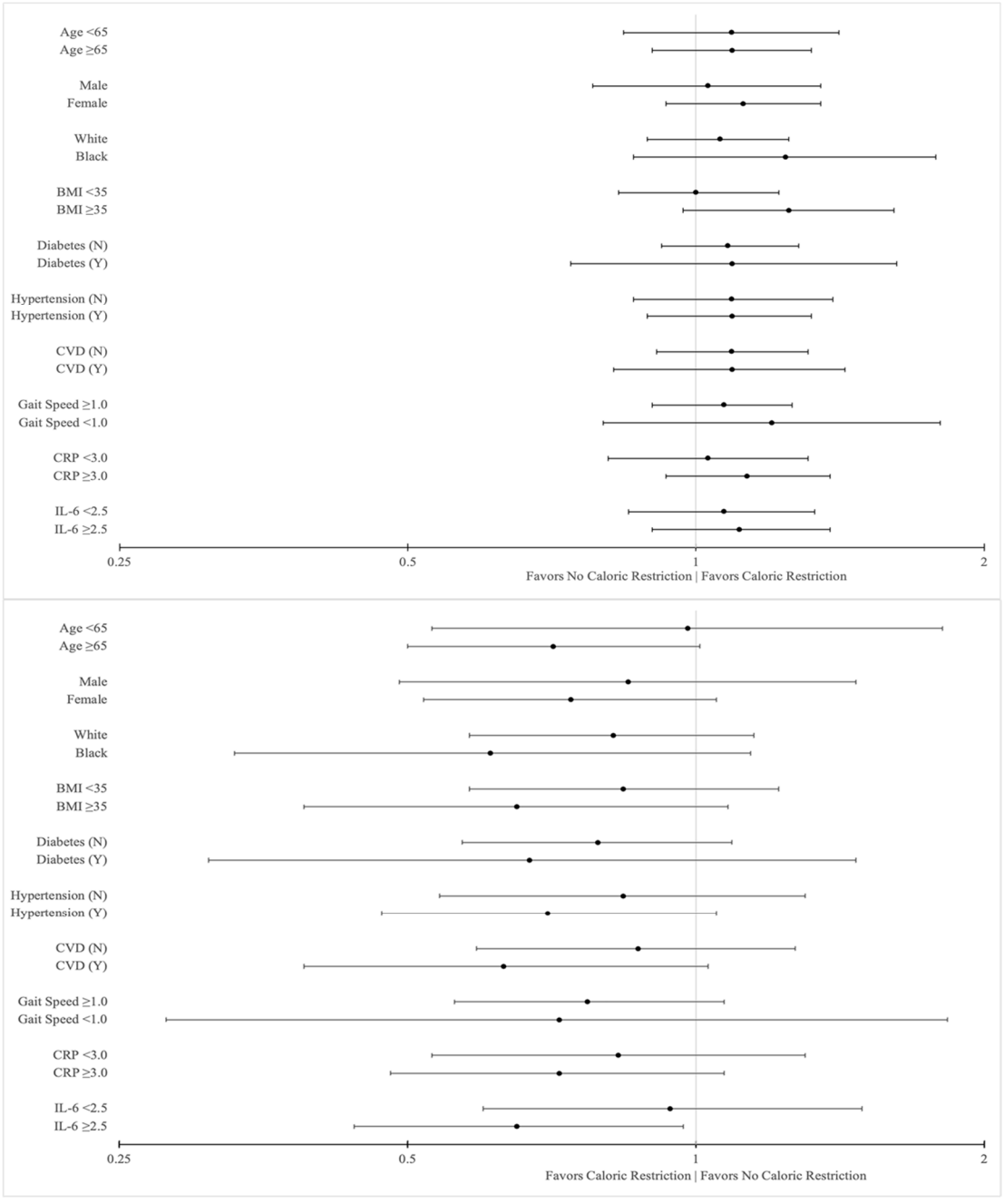


Table III. Adjusted Poisson risk ratios and 95% CI for the likelihood of achieving a 0.05 m/s increase or decrease in gait speed from baseline, according to subgroup membership (n=1188).

Subgroup Category	Likelihood of +0.05 m/s		Likelihood of -0.05 m/s	
	RR (95% CI)*	*p*-value	RR (95% CI)*	*p*-value
Age (≥ vs < 65 years)	0.87 (0.73,1.04)	0.13	1.37 (0.92,2.05)	0.12
Sex (female vs male)	0.86 (0.72,1.02)	0.08	1.49 (1.04,2.12)	0.03
Race (black vs white)	0.84 (0.68,1.03)	0.09	1.32 (0.92,1.90)	0.14
BMI (≥ vs <35 kg/m^2)	0.91 (0.77,1.07)	0.26	1.26 (0.89,1.79)	0.19
Diabetes (yes vs no)	0.95 (0.76,1.18)	0.63	1.46 (0.93,2.27)	0.11
Hypertension (yes vs no)	0.95 (0.80,1.12)	0.51	1.54 (1.09,2.20)	0.01
CVD (yes vs no)	0.86 (0.73,1.01)	0.07	1.45 (1.05,1.98)	0.02
Gait Speed (< vs ≥1.0 m/s)	1.37 (1.09,1.73)	0.01	0.67 (0.40,1.12)	0.11
CRP (≥ vs <3 mg/L)	0.91 (0.77,1.07)	0.24	1.08 (0.79,1.47)	0.63
IL-6 (≥ vs <2.5 pg/mL)	0.91 (0.78,1.07)	0.27	1.11 (0.81,1.51)	0.52

Notes. BMI= body mass index; CVD= cardiovascular disease; CRP= C-reactive protein; IL-6= interleukin 6; m/s=meters per second; RR= risk ratio; CI=confidence interval.
*Models adjusted for study, age, sex, race, baseline gait speed (except for the subgroup test including the covariate), and interaction between CR and subgroup.

Specifically, participants with baseline gait speed <1.0 m/s were more likely to experience a meaningful improvement [RR: 1.37 (95% CI: 1.09,1.73)]. Conversely, females were more likely to experience a meaningful decrement [RR: 1.49 (95% CI: 1.04,2.12)], as were those with hypertension [RR: 1.54 (95% CI: 1.09,2.20)] and CVD [RR: 1.45 (95% CI: 1.05,1.98)]. Sensitivity analysis revealed no potential influence of exercise when comparing the likelihood of achieving a clinically meaningful gait speed improvement within the 430 participants in the CR only (n=249) and control only (n=181) conditions, with the exception of the effect of hypertension on experiencing a meaningful gait speed decrement being attenuated after removing participants assigned to exercise from the analytic sample (data not shown).

DISCUSSION

The purpose of this study was to produce estimates of the overall probability of achieving clinically meaningful gait speed response (±0.05 m/s) to CR, and to identify predictors of achieving "responder" status. Contrary to our hypothesis, there was no main effect of CR on the likelihood of experiencing clinically meaningful gait speed change; and, this finding was robust across all subgroupings. However, participants with low baseline gait speed were more likely to experience a 0.05 m/s gait speed improvement whereas women and those with either hypertension or CVD were more likely to experience a 0.05 m/s gait speed decrement, regardless of CR assignment. Despite the well documented cardiometabolic benefits of CR, consistency in the observed lack of functional decrement with CR confers clinical utility since the potential exacerbation of functional decline continues to temper enthusiasm for global weight loss recommendation in this population. Additionally, observed main effects identifying subgroups likely to

experience a clinically meaningful change in gait speed (regardless of CR) suggests the importance of considering additional lifestyle-based intervention components influencing functional change.

An overarching goal of this pooled analysis was to explore potential heterogeneity in treatment response. Although we did not observe a significant interaction between CR and baseline subgroupings regarding clinically meaningful improvement or decrement in gait speed; results do provide a framework for additional work in this area. Specific future directions include examination of change in gait speed as a continuous (versus categorical) outcome, consideration of additional measures of physical function, and application of this modeling approach to other datasets of sufficient size and diversity in baseline subgrouping. Moreover, it is worth noting that across a wide array public health disciplines (91), consideration of inter-individual differences in treatment responses is regarded as holding tremendous promise for tailoring intervention delivery to an individual's probability of success.

Robustness of null main effect findings, while not supportive of an independent effect of CR to yield clinically meaningful gait speed improvement, should temper concerns regarding CR-induced functional decline. Indeed, mean absolute change in gait speed for CR *and* NoCR conditions exceeded +0.05 m/s. Additionally, identification of main effects for low baseline gait speed (and improvement) and gender and comorbidities (for decrement) aligns with prior work (92–94) and points toward consideration of additional intervention components as harbingers of functional change. Specifically, baseline level of an outcome measure is often a strong predictor of change. For gait speed in particular, baseline values of ≥1.0 m/s lend itself to a ceiling effect; thus, individuals

presenting with a gait speed <1.0 m/s have greater improvement potential. Main effects observed in women and in CVD and hypertension subgroups are also consistent with observational data suggesting slower gait speed in women versus men (92) and in those with CVD and hypertension versus those without (93,94). Mechanistically, these discrepancies may be due to differences in body composition and hormonal changes after menopause (in the case of the gender difference), as well as the influence of arterial stiffness on walking ability (in the case of CVD and hypertension, as this aspect of underlying etiology is similar). Finally, it is worth noting that some intervention elements were delivered consistently across CR/NoCR strata, which could be influencing main effects. A conspicuous example is exercise, as it is an important determinant of functional status in older adults (95) and was included in intervention delivery across most treatment groups, regardless of CR assignment.

Strengths of this study include the unique ability to generate a large sample by pooling individual level data from RCTs with similar major design elements and standardized protocols collecting gait speed data. Our analyses featured empirically derived cut points, for both outcome and exposure variables, to aid in clinical interpretability. That said, varying cut points could be used (96), and, in general, treating continuous variables dichotomously limits power and ignores smaller (although potentially statistically significant) changes. Finally, variation in exercise and diet prescriptions designed to elicit CR were not considered in this analysis.

In sum, data presented in this brief report do not suggest that CR independently influences the likelihood of experiencing a clinically meaningful improvement or decrement in gait speed; and, this finding is robust across several subgroupings. Future

work aims to explore clinically meaningful threshold of other physical function indices, consideration of potential moderating effects of exercise and amount of achieved weight loss on functional change, and application of statistical methodology to other large datasets.

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Ka Ki Tse

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Education

Wake Forest University, Winston-Salem, NC 05/2021
M.S. Health and Exercise Science
Advisor: Kristen M. Beavers, Ph.D.
Thesis Title: Predictors of clinically meaningful gait speed response to caloric restriction among older adults participating in weight loss interventions

University of Rhode Island, Kingston, RI 05/2019
Bachelor's of Science: Kinesiology
Bachelor's of Art: Psychology

Teaching Experience

Graduate Teaching Assistant 08/2019 – present
Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC
HES101: Exercise for Health

- Prepare and deliver lectures to undergraduate students; facilitate lab activities; grading assignments and tests

Undergraduate Teaching Assistant 09/2017 – 05/2019
Department of Kinesiology, University of Rhode Island, Kingston, RI
KIN 375G: Exercise Is Medicine (Spring 2018 & Spring 2019)

- Provide the professor with classroom assistance during laboratory activities; provide grading assistance when needed

KIN 300: Physiology of Exercise (Fall 2017 & Fall 2018)

- Hold office hours and review sessions to enhance student learning

Research Experience

Research Interventionist 03/2020 – present
Incorporating Nutrition, Vests, Education, and Strength Training in Bone Health (INVEST)
Wake Forest University, Winston-Salem, NC

- Supervise and monitor resistance training program; facilitate 1RM strength test
- Deliver virtual group sessions on various topics related to physical activity
- Assist with intervention orientation and monthly in person visits
- Instruct participants on weighted vest wearing and safety

Undergraduate Research Assistant 09/2018 – 05/2019
Department of Kinesiology (Dr. Jacob Earp)
University of Rhode Island, Kingston, RI

- Analyze ultrasound images using Dartfish software

- Provide investigators assistance with study session set up, testing procedures, and data collection; contact and follow up with participants through email
- Assist graduate students with survey administration; contact and follow up with participants through email

Research Assistant Intern 10/2016 – 05/2017
Weight Control & Diabetes Research Center
Brown University, Providence, RI

- Participate in fitness assessment administration (vital signs at rest and during exercise, body composition measurement)
- Assist with weekly exercise visits; provide guidance for participants when completing treadmill and elliptical training; assessing resting and exercise heart rate, blood pressure, and rating of perceived exertion
- Conduct participant phone screenings and in person interviews
- Responsible for completing data entry in a timely and accurate fashion

Work Experience

Evening Program Coordinator & Exercise Specialist 08/2019 – present
Healthy Exercise & Lifestyle Program, Wake Forest University, Winston-Salem, NC
Evening Program Coordinator

- Facilitate flow and coordinate geriatric participants of the program
- Train incoming graduate students on vital assessment and exercise prescription

Exercise Specialist

- Perform clinical assessments (blood test, physical function test, anthropometric measurements)
- Assess heart rhythm and blood pressure before, during and after exercise
- Assist with stress test and exercise prescription for chronic disease prevention
- Lead Silver Sneakers, strength training and flexibility classes
- Give instructions on weight machine usage and guide participants through free weight exercises

Personal Trainer 01/2019 – 05/2019
Fitness Together Providence, Providence, RI

- Create individualized exercise programs for clients to improve fitness level and prevent injuries
- Lead one-on-one, small group and circuit training sessions; guide clients through warm up and cool down routines
- Perform fitness assessments on clients to evaluate progress and discuss about their fitness goals
- Provide general guidance on nutrition and cardio recommendations

Wellness Center Staff & Fitness Center Attendant 05/2016 – 05/2019
Campus Recreation, University of Rhode Island, Kingston, RI
Wellness Center Staff

- Primary instructor for the "Ladies Lift" class; provide assistance for special events and programs

Fitness Center Attendant

- Provide excellent customer service for all center members; responsible for monitoring patrons for safe use of the fitness center; complete required safety checks for equipment and maintenance when necessary

Strength Coach 01/2018 – 05/2018

Primal Athlete Training Center, Cranston, RI

- Coach athletes through warm up routine, strength movements, conditioning circuits and accessory exercises
- Assist with development of training programs for both youth and adult athletes; provide individualized exercise prescriptions for each athlete based on fitness level and specific sport demands

Conferences/Memberships/Certifications

Attendee, Southeast ACSM Conference	2020 & 2021
Attendee, New England ACSM Conference	2017 & 2018
Attendee, ACSM International Health & Fitness Summit	2018
Student Member, American College of Sports Medicine	2018-present
Certified, Silver Sneaker Yoga Instructor	2020-present
Certified, Silver Sneaker Instructor (Classic and Foundation)	2019-presnet
Certified, American Council on Exercise Certified Personal Trainer	2018-present
Certified, American Heart Association Basic Life Support	2021-present

Honors and Awards

Wake Forest University Teaching Assistantship	2019-2021
Picerne Family Foundation Scholarship	2015-2021
Summa Cum Laude	2019
University of Rhode Island Outstanding Contribution to Psychology	2019
Franscis H. Horn Scholarship	2017-2019
Rhode Island Academic Promise Scholarship	2016-2019
Centreville Bank Charitable Foundation Scholarship	2016-2019
Dean's list	2015-2019
Rhode Island State Scholarship	2015-2016

Presentations

Tse KK, Pasniewski A, Ward-Ritacco C. Effects of Educating URI General Education Students on Physical Activity Behavior and Chronic Disease Risk Factor Knowledge. The Third Annual Academic Health Collaborative Research Event, Kingston, Rhode Island, May 2019.

Tse KK, Neiberg RH, Beavers DP, Kritchevsky SB, Nicklas BJ, Kitzman DW, Rejeski WJ, Messier SP, Beavers KM. Predictors of Clinically Meaningful Gait Speed Response among Older Adults Participating in Weight Loss Interventions. Southeast ACSM 2021 Virtual Annual Meeting, Feb 2021.