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Research Report

Predictors of Clinically Meaningful Gait Speed Response to Caloric Restriction Among Older Adults Participating in Weight Loss Interventions

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Abstract

Background: The purpose of this study was to examine whether select baseline characteristics influenced the likelihood of an overweight/obese, older adult experiencing a clinically meaningful gait speed response (±0.05 m/s) to caloric restriction (CR).

Methods: Individual level data from 1 188 older adults participating in 8, 5/6-month, weight loss interventions were pooled, with treatment arms collapsed into CR (n = 667) or no CR (NoCR; n = 521) categories. Exercise assignment was equally distributed across groups (CR: 65.3% vs NoCR: 65.4%) and did not interact with CR (p = .88). Poisson risk ratios (95% confidence interval [CI]) were used to examine whether CR assignment interacted with select baseline characteristic subgroups: age (≥65 years), sex (female/male), race (Black/White), body mass index (BMI; ≥35 kg/m^2), comorbidity (diabetes, hypertension, cardiovascular disease) status (yes/no), gait speed (<1.0 m/s), or inflammatory burden (C-reactive protein ≥3 mg/L, interleukin-6 ≥2.5 pg/mL) to influence achievement of ±0.05 m/s fast-paced gait speed change. Main effects were also examined.

Results: 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. Average weight loss achieved in the CR versus NoCR group was −8.3 ± 5.9% versus −1.1 ± 3.8%; p < .01. No main effect of CR was observed on the likelihood of achieving a clinically meaningful gait speed improvement (risk ratio [RR]: 1.09 [95% CI: 0.93, 1.27]) or gait speed decrement (RR: 0.77 [95% CI: 0.57, 1.04]). Interaction effects were nonsignificant across all subgroups.

Conclusion: The proportion of individuals experiencing a clinically meaningful gait speed change was similar for CR and NoCR conditions. This finding is consistent across several baseline subgroupings.

Keywords: Clinical trials, Obesity, Physical function

By 2030, over 20% of the U.S. population will be over the age of 65 years. The prevalence of obesity within this subgroup continues to rise (1), where it significantly contributes to functional limitation and disability risk (2). Left unabated, medical complications associated with the older, obese phenotype are poised to overwhelm the current health care system.

Clinical trials designed to intervene upon disability risk in older adults often use objective physical performance tests as surrogate endpoints. Gait speed is commonly assessed as it provides a quick, global summary of functional status (3), and has demonstrated efficacy in predicting disability. Indeed, data from the Health ABC study show that individuals unable to walk 400 m have significantly higher

risk of incident mobility limitation and mobility disability in the next 5 years (as compared to those without walking difficulty). Among those who are able to complete the 400-m walk test, each additional minute of performance time is associated with 52% increased risk of incident mobility limitation and disability, respectively (4). Importantly, increments of 0.1 m/s in gait speed are predictive of increased survival in older adults (3), and 0.05 m/s is considered a clinically meaningful change (5).

Caloric restriction (CR) induced weight loss improves many of the medical complications associated with excess adiposity in older persons (6); however, clinical recommendation remains controversial due to concomitant loss of lean mass, which can contribute to increased risk of functional decline (7). Randomized controlled trials designed to examine the independent effect of CR (either alone or in combination with exercise vs control or exercise alone) on gait speed change are few (8–11), but do suggest a modest benefit (mean increase ranging from 0.01 to 0.08 m/s). However, it is currently unknown whether participant characteristics can influence the likelihood of achieving a clinically meaningful improvement. Better understanding of the interindividual variability in functional response to CR has the potential to inform personalized geriatric obesity management strategies and provide important insight into underlying adaptive mechanisms. Moreover, as CR is not without risk, better understanding of the characteristics associated with the likelihood of experiencing a clinically meaningful decrement in gait speed also confers clinically useful information.

Using individual-level data housed within the Wake Forest Older Americans Independence Center (P30 AG21332) data repository (https://pepperwfu.phs.wakehealth.edu/public/dspISADR.cfm), the purpose of this brief report is 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. Specifically, we examine whether associations between CR and gait speed response vary by age, sex, race, body mass index (BMI), comorbidity status, baseline gait speed, and inflammatory burden, as these well-known risk factors were consistently collected across studies. We hypothesize that heterogeneity will exist in treatment response and select baseline characteristics will impact main effects.

Method

Study Participants

This analysis includes middle-aged and older (≥50 years) adults who were obese, or overweight with an indication for weight loss, and enrolled in eight separate dietary-based weight loss trials at Wake Forest University and Wake Forest School of Medicine between 1997 and 2017 (NCT00979043, NCT02239939, NCT00119795, NCT01049698, NCT00381290, NCT01048736, NCT02730988, and NCT00959660). Main outcome papers for each study are previously published (8,11–17). All studies assessed common measures of physical function (including fast-paced gait speed) before and 5/6 months after assignment to a CR intervention or to a non-CR (NoCR) control condition, with or without exercise. The Wake Forest Health Sciences institutional review board approved all secondary analyses pertaining to the pooled project (IRB# 54086).

Of the 1 590 baseline visits conducted across all included studies, 1 382 participants had a 5/6-month follow-up visit, and 1 359 had non-missing 5/6-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, cardiovascular disease [CVD]: n = 6), and 61 subjects were excluded due to missing inflammatory biomarkers (C-reactive protein [CRP]: n = 49; interleukin-6 [IL-6]: n = 54), yielding a sample of 1 256. An additional 68 participants did not have gait speed at baseline; therefore, final analyses were based on dataset of 1 188 participants with complete exposure, outcome, and covariate information. Compared to those included in our study sample (n = 1 188), those who were excluded due to missing follow-up data (n = 402) were more likely to be female, Black, and presented with slower gait speed at baseline (all $p < .05$).

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, 6 included participants randomized to CR only (n = 249), and 7 included participants randomized to CR combined with exercise (n = 418). Among 10 study-specific arms collapsed into the NoCR arm, 4 included participants randomized to attention control (n = 181), and 6 included participants randomized to exercise only (n = 340). Importantly, exercise assignment was equally distributed across groups (CR: 65.3% vs NoCR: 65.4%), and exercise did not interact with CR to influence gait speed response (p = .88).

Outcome Measure: Objectively Measured Fast Gait Speed

Data from both the 6-minute walk (n = 612 [51.5%]) and 400-m walk (576 [48.5%]) tests were used to calculate fast-paced gait speed (by dividing distance walked by 360 seconds in the 6-minute walk test, and by dividing 400 m by time in seconds in the 400-m walk test) among completers at baseline and 5/6 months. In both cases, tests were administered by trained and blinded assessors using standardized protocols. During the 6-minute walk test, participants were asked to walk as far as they could around a circular track in 6 minutes. During the 400-m walk test, participants were asked to walk 10 laps of a 40-m course "as quickly as possible, at a pace you can maintain" and were given a maximum of 15 minutes to complete the test. Unpublished data from our institution collected on individuals (n = 54) who longitudinally performed both the 6-minute walk and 400-m walk tests suggest that change in fast paced gait speed from both tests are highly correlated (r = .84). 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, and 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 5/6-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 (18).

Covariate subgroups were defined based on clinically meaningful cut points when appropriate. Specifically: age (≥65 vs <65), sex (female vs male), race (Black vs White), and class II obesity (BMI; ≥35 kg/m² vs <35 kg/m²), diabetes (yes vs no), hypertension (yes vs no), CVD (yes vs no), low baseline gait speed (<1.0 m/s vs ≥1.0 m/s) (3), having high CRP (≥3.0 mg/L vs <3.0 mg/L) (19), and high IL-6 (≥2.5 pg/mL vs <2.5 pg/mL) (20).

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 2-way interaction term. If the 2-way interaction was nonsignificant, the main effect of subgroup was examined as risk ratios and 95% confidence intervals of change in gait speed. Sensitivity analyses examined: (i) continuous weight loss (instead of CR assignment), and (ii) the subgroup of individuals not randomized to exercise (n = 430), in both cases using the same modeling strategy described above. All analyses use 2-sided hypothesis tests and assuming a Type 1 error rate of 0.05 for all comparisons. $p < .05$ indicated significance.

Results

Participant Characteristics

Table 1 presents relevant baseline characteristics for the pooled study sample overall and by CR assignment. Briefly, participants were 67.6 ± 5.3 years of age, 80.1% were White, and 69.5% were women. Average BMI was 33.8 ± 4.4 kg/m², with the majority (80.4%) presenting with a BMI ≥30 kg/m². 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. Supplementary Table 1 presents relevant baseline characteristics among individual who were not randomized to exercise (CR: n = 249; NoCR: n = 181). No between-group differences were observed among baseline characteristics in this subset, except for fast-paced gait speed (CR: 1.3 ± 0.2 m/s vs NoCR: 1.2 ± 0.2 m/s); $p < .01$.

Overall Treatment Effects on Weight and Gait Speed

In pooled analyses, 6-month weight loss achieved among those randomized to CR was mean ± SD: −8.3 ± 5.9% (range: −25.1% to 11.7%) and among those randomized to NoCR was −1.1% ± 3.8% (−17.8% to 12.1%); $p < .01$. Gait speed change was +0.10 ± 0.15 m/s versus +0.07 ± 0.15 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 (effect size [Cohen's w]: 0.08); and 88 (13.2%) of CR and 95 (18.2%) of NoCR participants experiencing a ≥0.05 m/s gait speed decrement (effect size [Cohen's w]: 0.14). No main effect of CR was observed on the likelihood of achieving a clinically meaningful gait speed improvement (risk ratio [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. However, several subgroups displayed an increased likelihood of experiencing a clinically meaningful change in gait speed (independent of CR assignment) as given in Table 2. 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 using continuous weight change instead of CR assignment yielded similar

Table 1. Baseline Characteristics Presented Overall and by Caloric Restriction Group Assignment

	Overall (n = 1 188)	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
≥30 kg/m², n (%)	956 (80.4)	546 (81.9)	410 (78.7)
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, mean ± SD (m/s)	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2
Fast-paced gait speed, median (IQR) (m/s)	1.24 (1.11, 1.38)	1.25 (1.12, 1.38)	1.23 (1.09, 1.37)
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
Exercise assignment, n (%)	776 (65.3)	436 (65.4)	340 (65.3)

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

results (data not shown). Further sensitivity analysis limited to individuals without exercise in CR (n = 249) and NoCR (n = 181) arms revealed similar findings as the main model, with the exception an attenuated effect of hypertension on gait speed decrement (Table 3).

Discussion

The purpose of this brief report was to examine whether select baseline characteristics influenced the likelihood of an older adult living with obesity (or overweight and an indication for weight loss) experiencing a clinically meaningful gait speed response (±0.05 m/s) to CR. Contrary to our hypothesis, we did not observe an independent main effect of CR on the likelihood of experiencing clinically meaningful gait speed change; and, this finding was robust across all examined subgroupings. That said, 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. Primary clinical implications of our findings are 2-fold. First, average gait speed change observed in our sample *regardless of CR* (CR: +0.10 ± 0.15 m/s; NoCR: +0.07 ± 0.15 m/s), indicates that alternate intervention components (ie, exercise and/or social facilitation) should be considered as drivers of clinically meaningful gait speed improvement. Second, our observed lack of clinically meaningful gait speed decrement with CR (and perhaps trending toward protection; RR: 0.77 [95% CI: 0.57, 1.04]) should help temper concerns regarding the potential exacerbation of functional decline attributed to weight loss recommendation in this population.

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 (vs 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 of public health disciplines (21), consideration

Table 2. 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 = 1 188)

	Likelihood of +0.05 m/s		Likelihood of -0.05 m/s	
Subgroup Category	RR (95% CI)*	p-value	RR (95% CI)*	p-value
Age (≥ vs < 65 years)	0.87 (0.73,1.04)	.13	1.37 (0.92,2.05)	.12
Sex (female vs male)	0.86 (0.72,1.02)	.08	1.49 (1.04,2.12)	.03
Race (Black vs White)	0.84 (0.68,1.03)	.09	1.32 (0.92,1.90)	.14
BMI (≥ vs <35 kg/m^2)	0.91 (0.77,1.07)	.26	1.26 (0.89,1.79)	.19
Diabetes (yes vs no)	0.95 (0.76,1.18)	.63	1.46 (0.93,2.27)	.11
Hypertension (yes vs no)	0.95 (0.80,1.12)	.51	1.54 (1.09,2.20)	.01
CVD (yes vs no)	0.86 (0.73,1.01)	.07	1.45 (1.05,1.98)	.02
Gait speed (< vs ≥1.0 m/s)	1.37 (1.09,1.73)	.01	0.67 (0.40,1.12)	.11
CRP (≥ vs <3 mg/L)	0.91 (0.77,1.07)	.24	1.08 (0.79,1.47)	.63
IL-6 (≥ vs <2.5 pg/mL)	0.91 (0.78,1.07)	.27	1.11 (0.81,1.51)	.52

Notes: BMI = body mass index; CVD = cardiovascular disease; CI = confidence interval; CRP = C-reactive protein; IL-6 = interleukin 6; m/s = meters per second; RR = risk ratio.

*Models adjusted for study, age, sex, race, baseline gait speed (except for the subgroup test including the covariate), and interaction between CR and subgroup.

Table 3. 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, Among Participants Who Were Not Randomized to Exercise and According to Subgroup Membership (n = 430)

	Likelihood of +0.05 m/s		Likelihood of –0.05 m/s	
Subgroup Category	RR (95% CI)*	p-value	RR (95% CI)*	p-value
Age (≥ vs < 65 years)	0.82 (0.58, 1.17)	.28	1.26 (0.72, 2.21)	.41
Sex (female vs male)	0.82 (0.58, 1.18)	.29	2.02 (1.18, 3.45)	.01
Race (Black vs White)	0.81 (0.53, 1.23)	.31	1.21 (0.75, 1.96)	.45
BMI (≥ vs <35 kg/m^2)	0.88 (0.62, 1.24)	.46	1.14 (0.72, 1.81)	.57
Diabetes (yes vs no)	0.96 (0.61, 1.53)	.88	1.10 (0.50, 2.42)	.82
Hypertension (yes vs no)	0.79 (0.55, 1.15)	.23	1.52 (0.88, 2.64)	.13
CVD (yes vs no)	0.82 (0.58, 1.16)	.25	1.91 (1.22, 2.99)	.01
Gait speed (< vs ≥1.0 m/s)	1.69 (1.11, 2.58)	.02	0.63 (0.32, 1.25)	.17
CRP (≥ vs <3 mg/L)	0.81 (0.58, 1.13)	.22	0.95 (0.62, 1.45)	.82
IL-6 (≥ vs <2.5 pg/mL)	0.76 (0.54, 1.07)	.12	1.23 (0.99, 1.54)	.07

Notes: BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; IL-6 = interleukin 6; m/s = meters per second; RR = risk ratio.

*Models adjusted for study, age, sex, race, baseline gait speed (except for the subgroup test including the covariate), and interaction between CR and subgroup.

of interindividual 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 sex and comorbidities (for decrement) aligns with prior work (22–24) and points toward consideration of additional subgroup by intervention component interactions 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 (22) and in those with CVD and hypertension versus those without (23,24). Mechanistically, these discrepancies may be due to differences in body composition and hormonal changes after menopause (in the case of the sex 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 (25) 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 (26), and, in general, treating continuous variables dichotomously limits power and ignores smaller (although potentially statistically significant) changes. Finally, variations 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 other intervention component (including exercise and/or dietary components), and application of statistical methodology to other large datasets.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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