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The Fountain Of Youth?: Calorie Restriction And Its Relationship With Hand Grip Strength As A Marker Of Longevity And Aging

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ABSTRACT

Background and Purpose: Evidence supports a beneficial effect of calorie restriction on longevity within numerous animal models, while data for humans is limited to intermediate biomarkers of aging. The purpose of this study was to determine the association between calorie restriction in humans with respect to hand grip strength, a biomarker of aging and longevity, that has been understudied in relation to caloric restriction.

Methods: We analyzed hand grip strength among 184 individuals enrolled in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE), a 2-year randomized trial of 25% calorie restriction vs. control. Peak hand grip strength was assessed by hand dynamometer as an average of 3 measurements at each time point; a higher value equates to greater strength and a marker of lower aging. Differences in percent change peak force grip strength from baseline to 24 months between the study groups was assessed via t-tests and ANCOVA. We used linear regression with backward stepwise selection to determine characteristics associated with baseline grip strength. We then evaluated potential effect modification by any factors associated with baseline grip strength in both hands as well as handedness and physical activity level.

Results: There was no statistically significant difference between the percent change in peak force from baseline to month 24 by study arm for either the left or (Intervention: -3.53%, Control: -5.08%, p=0.633); right hand (Intervention: -1.58%, Control: -2.77%, p=0.710). Only male sex was positively associated with baseline grip strength is both hands (left & right; $p < 0.001$). There was no evidence effect modification of the intervention effect on grip strength by sex, handedness, or physical activity levels.

Conclusions: Though we did not see evidence for an improvement in hand grip strength as a biomarker of aging in this caloric restriction study in humans, this was not a primary outcome of CALERIE and so we were not powered to detect small changes. Further research in larger trials with better adherence to caloric restriction are needed in order to understand if grip strength could be impacted by calorie intake. Better understanding of the effects of calorie restriction can lead to the development of low cost, non-invasive, therapeutic treatments for age-related disease and specific dietary plans can be used to potentially combat disease etiology and delay prognosis.

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I would also like to thank the research team involved with the CALERIE study for allowing me to use their data for secondary data analysis to add to the sparse literature surrounding calorie restriction and human health.

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INTRODUCTION

Hand grip strength measured via hand dynamometer has been assessed as a metric of aging in humans in several settings. One large study published in 1998 measured grip strength changes over 27 years in 8,006 Japanese-American men and found that overtime, grip strength decreased by an average of 1.0% each year [1], suggesting this could be an easy to assess marker of aging. In addition, the quality and thickness of muscle in the anterior forearm has been related to hand grip strength and it is well established that muscle quality declines as individuals age [2]. Grip strength has also been associated with numerous health indicators and conditions, including "overall strength, upper limb function, bone mineral density, fractures, falls, malnutrition, cognitive impairment, depression, sleep problems, diabetes, multimorbidity, and quality of life" [3]. Based on these parameters, grip strength is considered a biomarker of aging [1-4].

Beginning in 1935, McCay et al. studied the effects of a calorie restricted diet, rich in vitamins and minerals, in rat models. He found that male rats who were calorie restricted lived 75% longer than the comparison group and had a maximum lifespan of 1 year longer (35% greater) than controls [4-5]. Weindruch et al. (1986) performed similar experiments in mice, with greater calorie restriction (ranging from 10-70%) resulting in a positive correlation with greater lifespan and increased calorie restriction level [6]. Weindruch et al. also found that calorie restricted mice had lower body temperature, lower short term metabolic rate, maintained youthful activity longer, maintained immune function longer, and had less oxidative damage, lower mean blood glucose levels, better working memory, and were more resistant to carcinogens [7].

The longevity findings in rodents were supported by one primate calorie restriction study [8]. However, a second similar study in primates [9] observed lower body weight, lower fat and lean mass, lower fasting glucose, lower short-term metabolic rate, lower body temperature, and lower triglycerides in calorie restricted animals compared to controls but did not observe a significant improvement in longevity [9].

At present, human studies are more nuanced and require further longitudinal evidence, but some small studies provide an opportunity to look at effects of calorie restriction on various measures of aging. Heilbronn et al. (2006) conducted a randomized controlled trial (RCT) in 48 men and women, which found that a 25% calorie restriction improved two biological markers of longevity – decreased fasting insulin level and body temperature [10]. The Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) study was a two-year RCT among 220 normal and overweight individuals. The intervention group achieved an average of 11.7% calorie restriction, but there was no significant difference for the primary outcome of resting metabolic rate between the calorie restricted and ad libitum groups [11]. CALERIE also assessed measures of muscle and aerobic capacity. While absolute VO_2 max decreased at month 12 and month 24, VO_2 max expressed relative to body weight increased at both month 12 and 24. Similarly for muscle strength, absolute flexor and extensor leg strength decreased, but increased relative to body weight. These findings provided support that calorie restriction did not compromise aerobic capacity and muscle strength in healthy non-obese adults [12].

This thesis utilized data on hand grip strength from the CALERIE study to assess the impact of a calorie restriction intervention on this biomarker of aging. We hypothesized that there would be favorable changes in hand grip strength in the intervention group compared to the control group as calorie restriction has been beneficial for several other biomarkers of aging. To our knowledge, there are no published RCTs of the effects of calorie restriction in relation to hand grip strength. This thesis will add to the sparse data on calorie restriction in relation to objective measures of aging in humans.

MATERIALS & METHODS

Study Population & Recruitment

CALERIE enrolled men aged 21-50 and women aged 21-47[11]. To be included in the study, participants had to have a body mass index (BMI) of 22-27.9 kg/m^2 with an absence of significant health problems (cancer, AIDS, diabetes, etc.), absence of medication use except oral contraceptives, no recent substantial weight loss, and no history of eating disorders or psychiatric problems. Participants were recruited from three clinical sites: Pennington Biomedical Research Center (PBRC), Baton Rouge, LA; Tufts University Boston, MA; and Washington University School of Medicine. This study was organized by the Duke Clinical Research Institute in Durham, NC.

Enrollment was largely balanced between the three clinical sites (PBRC n=80, Tufts n=72, and Washington n=68). These 238 potential participants underwent baseline procedures and 18 were deemed ineligible/dropouts. The remaining 220 completed baseline testing and were randomized. Two individuals did not start the intervention. There was complete follow-up at month 24 for 191 (87%) participants (incomplete follow-up for 25 individuals from the intervention group and 4 from control group).

Calorie Restriction Intervention

Individualized 25% calorie restriction prescriptions from baseline ad libitum diets were determined by doubly-labeled water analysis (DLW) [13]. Group adherence to this diet prescription was assessed at month 6, 12, 18, and 24 using DLW, changes in body composition, and dual x-ray absorptiometry (DEXA) scan. CALERIE did not prescribe a “one size fits all” diet plan. Individuals worked with investigators to make dietary selections to help them reach their 25% calorie restriction goal. Participants were able to adjust their diet plan over the course of the study to maintain nutritional adequacy. The intervention employed an intense behavioral approach monitored by psychologists and nutritionists to modify diet in the hopes of enhancing calorie restriction adherence. Individual counseling was also provided to assist with reaching a participant’s calorie restriction goal.

For the first 28 days, the intervention group received detailed daily menus and full calorie restriction meals. They also received detailed training on portion sizes, how to keep a food journal, and are given a personal data assistant device to help analyze their diet. After the initial 28 days, participants were able to self-select foods where they are advised to follow the Acceptable Macronutrient Distribution Ranges of the Dietary Reference Intakes set by the Institute of Medicine’s Food and Nutrition Board (ie, 45%–65%, 20%–35%, and 10%–35% for carbohydrate, fat, and protein, respectively). Weighed 6-day food diaries were completed every 6 months via self-monitoring reports and nutrient intakes were monitored by registered dieticians.

A web-based tracking system was utilized to monitor calorie restriction adherence. If a participant fell outside of expected weight loss trajectories, the counselors were alerted.

Control Group

Participants assigned to the ad libitum control group were instructed to carry on their normal dietary patterns and were not given any dietary counseling [13]. The control group was meant to represent natural fluctuations in diet patterns over two years. Controls had quarterly contact with researchers and with outcome assessments at the same timepoints as the intervention group.

Hand Grip Strength Assessment

Hand grip strength was measured at three timepoints (baseline, month 12, and month 24) with peak force determined by a hand dynamometer in both the intervention and control groups. At each timepoint, participants performed three grip strength trials for each hand from which a mean peak force was calculated. This analysis utilized measurements from baseline and month 24 (end of intervention).

Data Analysis

Our analytic sample included 184 (96%) participants out of the 191 participants with month 24 data. We excluded 3 individuals who were missing either baseline or month 24 data for hand grip strength as well as 4 individuals with peak force grip strength that was greater than 3 standard deviations from the mean.

We assessed differences in baseline characteristics between the intervention and control groups using basic descriptive statistics. Backwards stepwise selection was utilized to determine any significant associations between baseline characteristics and average grip strength at baseline for each hand for the intervention and control groups combined.

Our primary outcome, percent grip strength change, was calculated by comparing peak force at baseline (PFBL) to peak force at month 24 (PF24): ([PF24 - PFBL] / PFBL) *100. This was calculated separately for each hand.

Independent sample t-tests were utilized to determine differences in mean grip strength at baseline, month 24, and percent change from baseline to month 24 between the calorie restriction intervention group and ad libitum control group. To adjust for any characteristics that differed by study arm at baseline, we conducted an ANCOVA, but the results did not change. Finally, we conducted stratified analyses by variables that were associated with baseline grip strength for both hands at $P<0.05$ as well as the following potential effect modifiers: handedness and physical activity level.

Intervention adherence was calculated as % calorie restriction from baseline to month 24, using energy intake (EI) at month 24 subtracted from total energy expenditure at baseline (TEEBL) and divided by TEEBL to determine adherence: ([TEEBL-EI] / TEEBL) *100. Percent calorie restriction was then categorized into 3 levels: 1. ≤10%, 2. 10% - 20%, 3. ≥20%. A one-way ANOVA was conducted to determine differences in percent change in grip strength by levels of calorie restriction (≤10%, 10% - 20%, ≥20%) among those in the intervention group only.

All data analysis was conducted using SAS Version 9.3 with a two-sided alpha of 0.05.

RESULTS

At baseline, age, caloric intake, weight, sex, BMI, race, ethnicity, marital status, and education did not differ significantly between groups for the 184 individuals with hand grip strength measures at baseline and 24 months (Table 1). There was a statistically significant difference between the intervention and control groups for handedness (p-value = 0.002).

Male sex was statistically significantly positively associated with mean baseline right hand peak force grip strength (p-value < 0.001). Both higher self-reported calorie intake (p-value = 0.004) and male sex (p-value < 0.001) were positively associated with baseline left hand peak. (data not shown).

At baseline, there was no difference in average peak force hand grip strength for the left (p-value=0.714) or right hand (p-value=0.971) between the intervention and control groups (Table 2). Over the 24 months, both groups experienced a decline in peak force for both left (p-value =0.658) and right (p-value=0.821) hands; however, this decline was not different by study arm.

There were no statistically significant differences in percent change of peak force grip strength from baseline to 24 months for left (p-value=0.633) or right (p-value=0.710) hands between the intervention and control group (Table 2). When adjusting for dominant hand status, which differed by study arm at baseline, and baseline grip strength the results were similar (Supplemental Table 1).

Among those in the intervention arm, there was a suggestion of greater decline in percent change peak force for the left hand with increasing calorie restriction, but this pattern was not apparent for the right hand (Table 3).

When stratified by sex was there was no evidence of an effect of the intervention on percent change in grip strength in men or women (Table 4). There was also no evidence of an interaction by handedness or physical activity level (data not shown)

DISCUSSION

In this relatively large intervention study of long-term calorie restriction in humans, there was no impact of the intervention on change in hand grip strength over two years compared to the control arm. We also did not see any potential dose-response relationship between level of calorie restriction and hand grip strength among those in the intervention. Since calorie restriction has been associated with improvements in other biomarkers of aging, we had hypothesized declines in grip strength seen over time as individuals age might have been mitigated in the calorie restricted group compared to controls.

Even though we were not able to observe an effect of calorie restriction on preservation or improvement of hand grip strength, as a marker of aging, other data from CALERIE supports that calorie restriction without nutrient deficiency does not compromise aerobic capacity or muscle strength in healthy nonobese adults. Specifically, VO_2 max, relative to body weight, increased in the calorie restriction group at timepoints one and two (1 year: +2.2 ± 0.4; 2 year: +1.9 ± 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$) compared to the ad libitum group [12]. Strength tests yielded similar results as absolute knee flexor and extensor strength increased relative to body mass [12]. Additionally, within the CALERIE study, calorie restriction significantly improved in c-reactive protein, insulin sensitivity index, metabolic syndrome score and persistent/significant reduction in LDL cholesterol, total cholesterol to HDL ratio, and systolic/diastolic blood pressure compared to control [11].

Among the intervention group only, we looked at a potential dose-response relationship between caloric restriction and grip strength. We observed the opposite direction of association (though not statistically significant) than what we had hypothesized evident for the left hand, but no clear pattern for the right hand. However, due to our limited sample size these results should be interpreted with caution.

Sex was associated with grip strength in both hands at baseline, so we investigated this a potential effect modifier, but there was no evidence of interaction. We also assessed potential differences by handedness, but similarly saw no evidence of interaction.

We explored if grip strength did not differ between groups due to decreased physical activity levels in the intervention group leading to muscle atrophy. We found that mean physical activity levels in the intervention group decreased statistically significantly from baseline to month 24, while the control group had not statistically significant changes in activity. There was no evidence of effect modification by physical activity levels, but our sample size was limited for assessing interactions.

The basic principle as to why calorie restriction works to improve aspects of longevity and aging is known as the disposable soma theory of aging. This evolutionary theory poses a trade off in resource allocation between somatic/cellular maintenance and reproductive fitness [14]. A higher proportion of energy resources are allocated to somatic/cellular maintenance in response to calorie restriction as it is evolutionary unsound to put too high of an investment in reproductive fitness. By putting energy towards reproduction in a period of fasting, or what the body perceives as an environment of “scarce resources”, it would be likely that one’s offspring would not survive to reproductive age given the harsh environment. Due to this environmental stressor, more energy is allocated to somatic maintenance so one can survive to a point where it would be safe to reproduce. We can then measure these changes in muscular and neural function through hand grip strength measurements as an outcome of muscle strength capacity to gauge improvements in longevity, health, and age-related diseases.

One strength of this study is that the CALERIE study had a diverse study population recruited by three study sites which would enhance generalizability of these findings. Additionally, hand grip strength was assessed by gold standard methods and the vast majority of participants had measure across the two time points under study. We also had data on numerous potential covariates in relation to baseline grip strength as potential effect modifiers and confounders for the main effect of the intervention.

An important limitation of CALERIE was the lack of adherence to the prescribed 25% calorie restriction in the intervention group, as the mean calorie restriction achieved (11.7%) was less than half the goal. Thus, it is possible hand grip strength could have been impacted had the full 25% calorie restriction been achieved. Overall we did observe small declines in hand grip strength overtime in the study, which are typically expected when one ages [1-3]. Since we did observe these expected declines our finding of no change by study arm could indicate a true null association between caloric restriction and grip strength. However, as this was not the primary outcome of the original trial we may have been underpowered to detect small changes in hand grip strength.

Given the health benefits found from prior research, it is important to continue investigating the role calorie restriction has in relation to longevity and aging via novel biomarkers. Moreover, additional research will allow us to understand how much calorie restriction is necessary to elicit potential health benefits. Calorie restriction studies in humans are still quite limited, so additional studies are needed to understand long term effects of calorie restriction (greater than 2 years) on many outcomes, including a range of biomarkers of aging.

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Table 1. Baseline description characteristics by study Arm (N=220)

Characteristic	Study Arm: **Intervention** 25% calorie restriction (N = 145)	Study Arm: **Control** Ad Libitum (N = 75)	P-Value*
Age (years), mean ± SD	37.9 (7.3)	37.9 (6.9)	0.975
Energy Intake, mean Kcal ± SD	2127.7 (557.2)	2044.9 (477.5)	0.460
Clinic Weight, mean kg ± SD	72.0 (9.4)	71.4 (8.7)	0.402
Sex, n (%)			
Male	45 (31.0)	22 (29.3)	0.795
Female	100 (69.0)	53 (70.7)	
Dominant Hand, n (%)			
Left	7 (4.8)	14 (18.7)	0.002
Right	131 (90.3)	60 (80.0)	
Ambidextrous	7 (4.8)	1 (1.33)	
BMI, n (%)			
22-24.9	70 (48.3)	37 (49.3)	0.881
25-27.9	75 (51.7)	38 (50.7)	
Sex-specific BMI, n (%)			
Female 22-24.9	59 (40.7)	32 (42.7)	0.990
Female 25-27.9	41 (28.3)	21 (28.0)	
Male 22-24.9	11 (7.6)	5 (6.7)	
Male 25-27.9	34 (23.5)	17 (22.7)	
Race, n (%)			
White	111 (76.6)	57 (76.0)	0.570
Black or African American	16 (11.0)	11 (14.7)	
Asian	12 (8.3)	3 (4.0)	
Other	6 (4.1)	4 (5.3)	
Ethnicity, n (%)			
Hispanic or Latino	3 (2.1)	4 (5.3)	0.155
Not Hispanic or Latino	138 (95.2)	71 (94.7)	
Unknown	4 (2.8)	0 (0.0)	
Marital Status, n (%)			
Married	86 (59.3)	44 (58.7)	0.894
Single, Never Married	41 (28.3)	21 (28.0)	
Not Married, Living with partner	8 (5.5)	3 (4.0)	
Previously Married	10 (6.9)	7 (9.3)	
Education Level, n (%)			
12^{th} grade/GED or less	2 (1.4)	6 (8.0)	0.131
Some College/Associates degree	21 (14.5)	10 (13.3)	
College	67 (46.2)	36 (48.0)	
Non-doctoral graduate degree	37 (25.5)	17 (22.7)	
Doctoral degree	18 (12.4)	6 (8.0)	

* p-values for continuous variables were calculated via t-tests and p-values for categorical variables were calculated via chi-square test

Table 2. Average* peak hand grip force at baseline, 24 months, and % change from baseline to 24 months (N=184) by study arm

Hand Grip Test	Intervention	Controls	P-value**
Left hand average Peak force ± SD			
Baseline	32.75 ± 10.02	32.22 ± 10.54	0.714
24 Month	31.08 ± 10.24	30.37 ± 11.25	0.658
% Change	-3.53 ± 18.92	-5.08 ± 24.69	0.633
Right hand average Peak force ± SD			
Baseline	33.70 ± 9.86	33.75 ± 10.57	0.971
24 Month	33.00 ± 10.58	32.63 ± 11.32	0.821
% Change	-1.58 ± 19.25	-2.77 ± 23.41	0.710

*Average of 3 measurements at each timepoint.

** T-test

Table 3. Average* % change in peak force hand grip strength from baseline to 24 months in the intervention group by calorie restriction level (N=112)

Percent Change from Baseline to 24 Months	**≤ 10% (N=37)**	**10% – 20% (N=54)**	**≥ 20% (N=21)**	**P-value****
Left % Change ± SD	-0.58 ± 18.77	-5.02 ± 19.52	-6.11 ± 15.02	0.435
Right % Change ± SD	-2.01 ± 20.15	-4.36 ± 18.42	-1.27 ± 17.18	0.286

*Average of 3 measurements at each timepoint.
**ANOVA

Table 4. Average* peak hand grip force at baseline, 24 months, and % change from baseline to 24 months by study arm stratified by sex; males (N=54) and females (N=130)

	Hand Grip Test	Intervention (n=33)	Controls (n=21)	P-value**
Males	Left hand average Peak force ± SD			
	Baseline	45.43 ± 7.35	43.62 ± 7.99	0.398
	24 Month	42.85 ± 7.74	42.82 ± 8.67	0.992
	% Change	-4.64 ± 15.79	-0.99 ± 16.42	0.419
	Right hand average Peak force ± SD			
	Baseline	46.71 ± 7.82	45.06 ± 7.86	0.454
	24 Month	45.45 ± 7.40	44.53 ± 8.81	0.680
	% Change	-1.51 ± 15.19	-0.23 ± 16.96	0.774

	Hand Grip Test	Intervention (n=84)	Controls (n=48)	P-value**
Females	Left hand average Peak force ± SD			
	Baseline	27.26 ± 5.23	27.65 ± 7.46	0.750
	24 Month	26.02 ± 5.82	24.91 ± 7.18	0.341
	% Change	-3.08 ± 20.11	-6.86 ± 27.51	0.408
	Right hand average Peak force ± SD			
	Baseline	28.60 ± 5.51	29.16 ± 7.56	0.653
	24 Month	27.66 ± 6.02	27.42 ± 7.83	0.854
	% Change	-1.61 ± 20.75	-3.88 ± 25.82	0.584

*Average of 3 measurements at each timepoint.
**T-test

Supplemental Table 1. Average* peak hand grip force at baseline, 24 months, and % change from baseline to 24 months (N=184) by study arm adjusted for handedness and baseline grip strength

Hand Grip Test	Intervention	Controls	P-value**
Left hand average Peak force ± SE			
Baseline	32.78 ± 0.86	32.17 ± 1.20	0.915
24 Month	30.96 ± 0.60	30.57 ± 0.78	0.693
% Change	-3.76 ± 1.94	-4.69 ± 2.51	0.769
Right hand average Peak force ± SE			
Baseline	33.66 ± 0.85	33.83 ± 1.19	0.938
24 Month	32.73 ± 0.61	32.69 ± 0.79	0.969
% Change	-1.95 ± 1.90	-2.15 ± 2.45	0.949

*Average of 3 measurements at each timepoint.
** ANCOVA