Original Investigation

Effect of Calorie Restriction on Mood, Quality of Life, Sleep, and Sexual Function in Healthy Nonobese Adults
The CALERIE 2 Randomized Clinical Trial

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IMPORTANCE Calorie restriction (CR) increases longevity in many species and reduces risk factors for chronic diseases. In humans, CR may improve health span, yet concerns remain about potential negative effects of CR.

OBJECTIVE To test the effect of CR on mood, quality of life (QOL), sleep, and sexual function in healthy nonobese adults.

DESIGN, SETTING, AND PARTICIPANTS A multisite randomized clinical trial (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy Phase 2 [CALERIE 2]) was conducted at 3 academic research institutions. Adult men and women (N = 220) with body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 22.0 to 28.0 were randomized to 2 years of 25% CR or an ad libitum (AL) control group in a 2:1 ratio favoring CR. Data were collected at baseline, 12 months, and 24 months and examined using intent-to-treat analysis. The study was conducted from January 22, 2007, to March 6, 2012. Data analysis was performed from July 18, 2012, to October 27, 2015.

INTERVENTIONS Two years of 25% CR or AL.

MAIN OUTCOMES AND MEASURES Self-report questionnaires were administered to measure mood (Beck Depression Inventory-II [BDI-II], score range 0-63, higher scores indicating worse mood, and Profile of Mood States [POMS], with a total mood disturbance score range of −32 to 200 and higher scores indicating higher levels of the constructs measured), QOL (Rand 36-Item Short Form, score range 0-100, higher scores reflecting better QOL, and Perceived Stress Scale, score range 0-40, higher scores indicating higher levels of stress), sleep (Pittsburgh Sleep Quality Index [PSQI], total score range 0-21, higher scores reflecting worse sleep quality), and sexual function (Derogatis Interview for Sexual Function–Self–report, total score range 24-188, higher scores indicating better sexual functioning).

RESULTS In all, 218 participants (152 women [69.7%]; mean [SD] age, 37.9 (7.2) years; mean [SD] BMI, 25.1 [1.6]) were included in the analyses. The CR and AL groups lost a mean (SE) of 7.6 (0.3) kg and 0.4 (0.5) kg, respectively, at month 24 ($P < .001$). Compared with the AL group, the CR group had significantly improved mood (BDI-II: between-group difference [BGD], −0.76; 95% CI, −1.41 to −0.11; effect size [ES], −0.35), reduced tension (POMS: BGD, −0.79; 95% CI, −1.38 to −0.19; ES, −0.39), and improved general health (BGD, 6.45; 95% CI, 3.93 to 8.98; ES, 0.75) and sexual drive and relationship (BGD, 1.06; 95% CI, 0.11 to 2.01; ES, 0.35) at month 24 as well as improved sleep duration at month 12 (BGD, −0.26; 95% CI, −0.49 to −0.02; ES, −0.32) (all $P < .05$). Greater percent weight loss in the CR group at month 24 was associated with increased vigor (Spearman correlation coefficient, $\rho = -0.30$) and less mood disturbance ($\rho = 0.27$) measured with the POMS, improved general health ($\rho = -0.27$) measured with the SF-36, and better sleep quality per the PSQI total score ($\rho = 0.28$) (all $P < .01$).

CONCLUSIONS AND RELEVANCE In nonobese adults, CR had some positive effects and no negative effects on health-related QOL.

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Invited Commentary

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Group Information: The CALERIE Study Group members are listed in the eAppendix in Supplement 1.

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Calorie restriction (CR) increases longevity in numerous species[1] and, in nonhuman primates, it increases health span (length of time the organism is free of disease).[2-4] To our knowledge, the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy Phase 2 (CALERIE 2) trial is the first study to examine the effects of long-term CR on disease risk factors and predictors of longevity in nonobese humans. The design[5] of CALERIE 2, recruitment methods,[6] baseline data,[7,8] and intervention used to promote long-term (2-year) CR[9] have been described elsewhere. Briefly, CR resulted in metabolic adaptation and improvements in chronic disease risk factors, indicating that CR may improve the health span of nonobese humans.[7] These results raise the possibility that more people, including normal-weight people, might attempt to practice CR in an effort to increase lifespan and health span, yet concerns remain about potential negative effects of CR on psychological and endocrine outcomes.

The purpose of the present analysis was to test the hypothesis that, compared with an ad libitum (AL) control group, 25% CR for 2 years would improve mood, quality of life (QOL), sleep, and sexual function (assessed by self-report and, in men, by reproductive hormones). These end points provide a direct test of the effects of CR on aspects of QOL that have been hypothesized to be negatively affected by CR, including decreased libido, lower stamina, depressed mood, and irritability[10]; in addition, the study extends the literature to a sample that includes nonobese individuals. The inclusion of both self-reported and biological (hormone) variables is novel since weight loss or CR among overweight and obese samples has been found to improve QOL,[11,12] sleep,[13] and sexual function,[14] although not all studies found improved sexual function,[15] and CR might transiently suppress the reproductive axis. In addition, sex hormone–binding globulin (SHBG) is inversely associated with risk of type 2 diabetes mellitus[16] and weight loss increases SHBG levels,[15,17] suggesting that SHBG may have biological functions beyond regulation of free sex hormone levels.

Key Points

Question What are the effects of 2 years of calorie restriction on the health-related quality of life of nonobese adults?

Findings In this randomized clinical trial that enrolled 220 healthy nonobese adults, long-term (2-year) calorie restriction had no negative effects and some positive effects on health-related quality of life.

Meaning In nonobese adults, calorie restriction, marked by approximately 10% weight loss, can be undertaken with little concern about negative effects on quality of life, mood, sexual function, and sleep.

Methods

Ethics and Trial Registration

CALERIE Phase 2 was a multisite single-protocol study that followed individual pilot studies that were conducted at 3 study sites during CALERIE Phase 1. CALERIE 2 was approved by the institutional review boards of Pennington Biomedical Research Center, Washington University, Tufts University, and Duke University. The coordinating center was at Duke University and data were collected at the other 3 sites. All participants provided written informed consent and received financial compensation. A data and safety monitoring board provided oversight of the study. The protocol of the study is available in Supplement 2.

Study Design

The study was a parallel-group, randomized clinical trial comparing 2 years of 25% CR with 2 years of habitual energy intake on an AL basis. The randomization ratio was 2:1 in favor of CR, and randomization was stratified by site, sex, and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) dichotomized as normal weight (22.0-24.9) or overweight (25.0-27.9). The intervention is described elsewhere[9]; it relied on a mathematical model built from our phase 1 studies to predict weight loss after 1 year assuming adherence to 25% CR[18] (during year 2, weight loss maintenance was promoted). To account for variability in weight loss, a zone of acceptable weight loss for individuals was created, and participants were considered adherent if their body weights were within this zone.[9,18] A weight graph illustrating participants' weight in relation to their zone was used to promote adherence and to trigger additional intervention strategies when needed.[9] In addition, CR participants received a manual-based curriculum and were provided food for the first 27 days of the intervention.

Participants

Participants were healthy men aged 20 to 50 years and women aged 20 to 47 years, with a BMI between 22.0 and 28.0. Screening occurred from January 22, 2007, to November 17, 2009, and the screening procedures are detailed elsewhere.[6] The study was completed on March 6, 2012.

Study Assessments

Details on the study procedures and assessments are provided elsewhere.[5] Self-report questionnaire data and reproductive hormones (men only) were measured at baseline, 12 months, and 24 months. Percent CR during the study was calculated using the intake balance method,[7] which relies on simultaneous measures of total daily energy expenditure by doubly labeled water and body composition changes.[19]

Assessment of Mood, Quality of Life, Perceived Sleep Quality, and Sexual Function

Mood was assessed with the Beck Depression Inventory II (BDI-II) and the Profile of Mood States (POMS).[20] The BDI-II is a reliable and valid measure of mood disturbance, with a score range of 0 to 63, where higher scores indicate worse mood.[21] The POMS has 6 subscales: tension (score range, 0-36), depression (score range, 0-60), anger (score range, 0-48), fatigue (score range, 0-28), vigor (score range, 0-32), confusion (score range, 0-28), and a total mood disturbance score (score

range, −32 to 200). The POMS is reliable and valid, and higher scores reflect higher levels of the construct being measured by the subscale.[22]

Quality of life was measured with the Rand 36-Item Short Form (SF-36)[23] and the Perceived Stress Scale (PSS).[24] The SF-36 has 8 subscales: 4 that measure mental aspects of QOL (role limitations due to emotional problems, vitality, social functioning, mental health) and 4 that measure physical aspects of QOL (physical functioning, role limitations due to physical problems, bodily pain, general health).[23] Scores on the SF-36 range from 0 to 100, with higher scores reflecting better QOL. The PSS assesses perceived stress and has a score range of 0 to 40, with higher scores indicating higher levels of perceived stress.[24]

Perceived sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI), a reliable and valid measure of sleep over a 1-month interval.[25] The questionnaire yields 7 subscales (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction) and a total score. The score range for the PSQI subscales is 0 to 3, and the PSQI total score range is 0 to 21; higher scores reflect worse sleep quality.

The Derogatis Interview for Sexual Function-Self-report (DISF-SR) is a reliable and valid measure of sexual function.[26] It has parallel forms for men and women, 5 subscales (sexual cognition and fantasy, sexual arousal, sexual behavior and experience, orgasm, and sexual drive and relationship), and a total score. Higher scores indicating better functioning and the ranges of scores are: 5 to 45 for the sexual cognition and fantasy subscale, the sexual arousal subscale, and the sexual behavior and experience subscale; 5 to 25 for the orgasm score; 4 to 28 for the sexual drive and relationship score; and 24 to 188 for the total score.

Assessment of Reproductive Hormones

To test the hypothesis that CR, in men, would result in increased SHBG levels and decreased luteinizing hormone, follicle-stimulating hormone, total testosterone, and free testosterone levels, these hormones were measured in the early morning after an overnight fast. Collection of reproductive hormones in women was not done because of difficulty in scheduling testing in the midluteal phase of their menstrual cycles and because many women were receiving hormonal contraception. Commercially available kits were used for the assays (ADVIA Centaur; Bayer Health Care, and Immulite 1000; Diagnostics Products Corp).

Data Analysis

All statistical tests were 2-tailed and, unless otherwise noted, $P < .05$ was considered the level of statistical significance. The statistical methodologies have been described.[7] An intent-to-treat (ITT) criterion was used. A repeated-measures analysis as implemented under mixed models was utilized, with the dependent variable being change to the follow-up time points. The independent variables were treatment and time (visit), and the treatment × time interaction. Participants were sampled by site, sex, and BMI stratum, and these variables, together with the baseline values of the outcome variable being evaluated, were included as covariates. Hypotheses of specific interest (eg, between-group differences [BGDs] on outcome variable changes at the individual time points) were tested by defining contrasts among the regression variables; the predicted mean (SE) changes are the adjusted values from this model. Type I error was controlled using a gatekeeping strategy.[27] A hierarchical structure was identified among the hypotheses of interest (ie, the treatment × time interaction) followed by the main effects, followed by specific within- and between-group comparisons. Comparisons were performed only at $\alpha = .05$ if significance was obtained at $\alpha = .05$ at the higher level in the hierarchy. Otherwise, the Bonferroni procedure was used. Main effects for sex were also examined, in addition to sex × treatment interactions, and sex × treatment × time interactions. A similar approach was adopted for the BMI strata. To evaluate the size of changes in health-related QOL between (and within) the groups, Cohen *d* effect size (ES)[28] was calculated, which reflects changes in SD units as estimated by the model.

Because of insufficient variability or floor or ceiling effects, 7 variables were converted to a binary outcome (ie, whether there was a negative change from baseline or not). For these, a generalized estimating equation model[29,30] was applied using the logit link and the Bernoulli variance, assuming the unstructured covariance structure, to determine whether there was a negative change from baseline that was related to treatment, time, and the interaction of these 2 predictors. In addition, 2 variables had limited variability due to a ceiling effect; thus, descriptive data are provided and statistical analysis was not conducted.

Spearman correlation coefficients were calculated in the CR group to determine whether the baseline values of the outcome variable were predictive of percent CR and weight change (kilograms and percent) from baseline to month 24 ($\alpha = .01$). Similar analyses determined whether percent CR and weight change from baseline to month 24 were associated with changes in the outcome variables from baseline to month 24. Data analysis was performed using SAS, version 9.2 (SAS Institute Inc). Data analysis was conducted from July 18, 2012, to October 27, 2015.

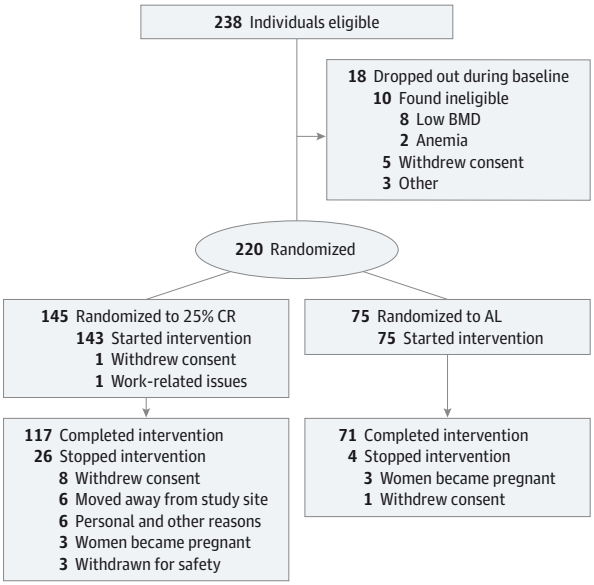
Results

Participant Characteristics

The screening process[6] and baseline data are detailed elsewhere[7,8] and illustrated in **Figure 1**.[6,7] A total of 220 participants were randomized, although data on 2 CR participants (0.9%) were not included in the analyses because they dropped out before starting the intervention. Thus, the ITT analyses included 218 participants (CR, 143 [65.6%]; AL, 75 [34.4%]). Most of the participants were women (152 [69.7%]) and white (168 [77.1%]). The mean (SD) age and BMI were 37.9 (7.2) years and 25.1 (1.6), respectively. There were no significant differences in the baseline demographic and anthropometric variables between the CR and AL groups overall or between the CR and AL groups for men and women separately (all $P > .15$) (**Table 1**).

Baseline values of the outcomes are presented in **Table 2**, **Table 3**, and eTable 1 in Supplement 1. There were no significant baseline CR and AL group differences (all $P > .22$). eTable 2 in Supplement 1 reports mean data at baseline and months 12 and 24, including the number of participants providing data at each time point. A total of 117 (81.8%) and 71 (94.7%) participants in the CR and AL groups, respectively, completed the study. The sample included normal-weight individuals, since the effect of CR on health-related QOL of these people is not well understood and the beneficial effects of CR on health span raise the possibility that more people will practice CR.

Figure 1. CONSORT Diagram



More than 10 000 people expressed interest in the study, and 238 people completed the screening process and were eligible. All 218 participants who started the intervention (calorie restriction [CR], 143; ad libitum [AL], 75) were included in the main study analysis. Adapted from Ravussin et al.[7]

Weight Change and Percent CR Achieved

Mean (SEM) percent CR achieved was 15.2% (0.7%) at month 12 and 11.9% (0.7%) at month 24.[7] The CR group lost 8.3 (0.3) kg (11.5% of initial weight) by month 12 and 7.6 (0.3) kg by month 24 (10.4%), with almost no weight change in the AL group (0.4 [0.5] kg at month 24) ($P < .001$ for CR vs AL at 24 months). In the CR group, BMI was reduced by 2.6 (0.1) at month 24; thus, the mean BMI for the CR group at the end of the trial was 22.6.

Mood

Compared with the AL group, the CR group experienced a significant improvement in mood (BDI-II: between-group difference [BGD], −0.76; 95% CI, −1.41 to −0.11; ES, −0.35) and tension (POMS: BGD, −0.79; 95% CI, −1.38 to −0.19; ES, −0.39) from baseline to month 24 (Table 2). A significant BMI × treatment × time interaction was found on the POMS depression subscale ($P = .03$). The AL group had worsening depression scores compared with the CR group (estimated change [SE], 0.92 [0.34] vs −0.30 [0.26]) only at month 24 in the overweight strata (**Figure 2**B). In addition, a significant sex × treatment interaction was present for the POMS depression subscale ($P = .01$), with men in the AL group having worse (higher) depression scores compared with men in the CR group (estimated change [SE], 0.53 [0.44] vs −0.63 [0.35]) (Figure 2C).

Quality of Life

Descriptive data are provided in eTable 1 in Supplement 1 for 2 SF-36 subscales (role limitations due to emotional problems and role limitations due to physical problems) that had

Table 1. Baseline Demographic, Anthropometric, and Clinical Characteristics

Characteristic	Men (n = 66)		Women (n = 152)		Total (N = 218)	
	AL (n = 22)	CR (n = 44)	AL (n = 53)	CR (n = 99)	AL (n = 75)	CR (n = 143)
Age, mean (SD), y	37.8 (7.1)	40.5 (7.2)	37.9 (6.9)	36.8 (7.2)	37.9 (7.0)	38.0 (7.3)
Race/ethnicity, No. (%)						
White	18 (81.8)	37 (84.1)	39 (73.6)	74 (74.7)	57 (76.0)	111 (77.6)
African American	1 (4.5)	2 (4.5)	10 (18.9)	13 (13.1)	11 (14.7)	15 (10.5)
Other[a]	3 (13.6)	5 (11.4)	4 (7.5)	12 (12.1)	7 (9.3)	17 (11.9)
Height, mean (SD), m	176.7 (5.3)	177.1 (7.2)	165.0 (6.8)	165.2 (6.4)	168.4 (8.3)	168.9 (8.6)
Weight, mean (SD), kg	79.8 (6.6)	81.6 (8.3)	68.0 (6.9)	67.7 (6.3)	71.5 (8.7)	72.0 (9.5)
BMI, mean (SD)	25.6 (1.7)	26.0 (1.6)	24.9 (1.6)	24.8 (1.7)	25.1 (1.6)	25.2 (1.8)
Body fat, mean (SD), %	25.7 (4.0)	26.1 (3.1)	36.8 (4.2)	36.0 (4.3)	33.6 (6.6)	32.9 (6.1)
Fat-free mass, mean (SD), kg	59.3 (5.2)	60.3 (6.0)	42.8 (3.6)	43.2 (4.1)	47.6 (8.6)	48.5 (9.2)
Fat mass, mean (SD), kg	20.5 (3.9)	21.3 (3.7)	25.2 (4.8)	24.4 (4.3)	23.8 (5.0)	23.5 (4.3)
Waist circumference, mean (SD), cm	88.5 (5.5)	89.0 (5.5)	78.3 (5.5)	77.0 (5.5)	81.3 (7.2)	80.7 (7.8)
Blood pressure, mean (SD), mm Hg						
Systolic	117.9 (7.6)	116.2 (8.2)	108.4 (9.4)	110.3 (10.1)	111.2 (9.9)	112.1 (9.9)
Diastolic	73.2 (7.6)	73.6 (7.5)	70.4 (6.8)	71.4 (7.5)	71.2 (7.1)	72.1 (7.5)

Abbreviations: AL, ad libitum; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CR, caloric restriction.

[a] Included American Indian/Alaska Native, Asian, more than one race, and unknown.

Table 2. Baseline Values and Estimated Change in the Mood, Quality of Life, and Sleep Variables in the CR and AL Groups at 12 and 24 Months

	AL Within Group			ITT Analysis of CR Within Group			Between Group			
Test	Mean (SE)[a]	*P* Value[b]	ES	Mean (SE)[a]	*P* Value[b]	ES	Difference	*P* Value[b]	95% CI	ES
Mood										
BDI-II[c]										
Baseline	1.55 (0.27)			1.55 (0.24)				.45		
Δ Month 12	0.49 (0.34)	.30	0.17	0.43 (0.25)	.19	0.15	−0.07 (0.42)	>.99	−0.88 to 0.75	−0.02
Δ Month 24	0.67 (0.27)	.03	0.30	−0.10 (0.21)	>.99	−0.04	−0.76 (0.33)	.04	−1.41 to −0.11	−0.35
POMS, tension[c]										
Baseline	2.19 (0.26)			2.21 (0.19)				.96		
Δ Month 12	0.42 (0.30)	.32	0.17	0.44 (0.22)	.10	0.18	0.01 (0.36)	.97	−0.70 to 0.73	0.01
Δ Month 24	0.63 (0.25)	.02	0.31	−0.16 (0.19)	.83	−0.08	−0.79 (0.30)	<.01	−1.38 to −0.19	−0.39
POMS, depression[c]										
Baseline	0.71 (0.20)			0.77 (0.17)				.81		
Δ Month 12	0.40 (0.27)	.27	0.18	0.43 (0.20)	.07	0.20	0.03 (0.33)	>.99	−0.61 to 0.67	0.01
Δ Month 24	0.37 (0.26)	.31	0.17	0.12 (0.20)	>.99	0.06	−0.25 (0.31)	.86	−0.87 to 0.37	−0.12
POMS, anger[c]										
Baseline	0.39 (0.12)			0.50 (0.10)				.61		
Δ Month 12	0.42 (0.24)	.17	0.21	0.46 (0.18)	.02	0.23	0.04 (0.30)	>.99	−0.54 to 0.63	0.02
Δ Month 24	0.38 (0.19)	.09	0.24	0.29 (0.15)	.10	0.19	−0.09 (0.23)	>.99	−0.55 to 0.37	−0.06
POMS, fatigue[c]										
Baseline	1.81 (0.28)			2.30 (0.27)				.59		
Δ Month 12	0.51 (0.35)	.29	0.18	0.73 (0.26)	.01	0.26	0.22 (0.43)	>.99	−0.62 to 1.06	0.08
Δ Month 24	0.84 (0.39)	.06	0.26	0.50 (0.30)	.19	0.16	−0.34 (0.48)	.97	−1.29 to 0.61	−0.11
POMS, vigor[c]										
Baseline	18.51 (0.71)			18.69 (0.53)				.79		
Δ Month 12	0.16 (0.58)	>.99	0.03	0.05 (0.44)	>.99	0.01	−0.11 (0.70)	>.99	−1.50 to 1.27	−0.02
Δ Month 24	−0.44 (0.59)	.91	−0.09	0.83 (0.45)	.14	0.17	1.27 (0.72)	.16	−0.15 to 2.69	0.26
POMS, confusion[c]										
Baseline	2.26 (0.21)			2.35 (0.18)				.97		
Δ Month 12	0.27 (0.24)	.56	0.13	0.42 (0.18)	.04	0.21	0.16 (0.30)	>.99	−0.43 to 0.74	0.08
Δ Month 24	0.12 (0.20)	>.99	0.07	0.12 (0.16)	.91	0.07	−0.00 (0.25)	>.99	−0.49 to 0.49	−0.001
POMS, total score[c]										
Baseline	−11.21 (1.31)			−0.63 (1.09)				.93		
Δ Month 12	1.83 (1.37)	.37	0.17	2.29 (1.01)	.05	0.21	0.47 (1.66)	>.99	−2.81 to 3.74	0.04
Δ Month 24	2.53 (1.28)	.10	0.25	0.03 (0.97)	>.99	0.002	−2.50 (1.56)	.22	−5.57 to 0.57	−0.25
Quality of Life										
SF-36, vitality[c]										
Baseline	71.0 (1.71)			71.02 (1.09)				.64		
Δ Month 12	1.15 (1.43)	.85	0.10	0.07 (1.08)	>.99	0.01	−1.08 (1.73)	>.99	−4.50 to 2.34	−0.09
Δ Month 24	−2.16 (1.50)	.31	−0.17	1.11 (1.18)	.69	0.09	3.27 (1.86)	.16	−0.39 to 6.92	0.26
SF-36, mental health[c]										
Baseline	86.72 (1.0)			86.13 (0.67)				.47		
Δ Month 12	−0.53 (1.05)	>.99	−0.06	−1.95 (0.79)	.03	−0.22	−1.42 (1.28)	.54	−3.95 to 1.11	−0.16
Δ Month 24	−1.40 (1.04)	.36	−0.16	-0.19 (0.81)	>.99	−0.02	1.21 (1.28)	.70	−1.32 to 3.74	0.14
SF-36, bodily pain[c]										
Baseline	91.63 (1.32)			91.64 (0.84)				.68		
Δ Month 12	−2.59 (1.60)	.22	−0.20	−0.20 (1.21)	>.99	−0.02	2.39 (1.95)	.22	−1.45 to 6.23	0.18
Δ Month 24	−4.19 (1.74)	.03	−0.29	−1.17 (1.36)	.78	−0.08	3.02 (2.16)	.16	−1.24 to 7.28	0.21
SF-36, general health[c]										
Baseline	85.27 (1.24)			85.70 (0.97)				.64		
Δ Month 12	−1.10 (1.11)	.64	−0.12	5.23 (0.84)	<.001	0.57	6.33 (1.34)	<.001	3.68 to 8.98	0.69
Δ Month 24	-0.76 (1.05)	.94	−0.09	5.69 (0.81)	<.001	0.66	6.45 (1.28)	<.001	3.93 to 8.98	0.75

(continued)

Table 2. Baseline Values and Estimated Change in the Mood, Quality of Life, and Sleep Variables in the CR and AL Groups at 12 and 24 Months (continued)

	AL Within Group			ITT Analysis of CR Within Group			Between Group			
Test	Mean (SE)[a]	*P* Value[b]	ES	Mean (SE)[a]	*P* Value[b]	ES	Difference	*P* Value[b]	95% CI	ES
Perceived Stress Scale[c]										
Baseline	2.52 (0.24)			2.53 (0.17)				.82		
Δ Month 12	0.22 (0.26)	.82	0.10	0.76 (0.20)	<.001	0.35	0.54 (0.32)	.09	−0.09 to 1.18	0.25
Δ Month 24	0.55 (0.22)	.03	0.30	0.21 (0.17)	.46	0.11	−0.35 (0.27)	.21	−0.89 to 0.19	−0.19
Perceived Sleep Quality										
PSQI, subjective sleep quality[c]										
Baseline	0.57 (0.07)			0.62 (0.05)				.51		
Δ Month 12	0.02 (0.07)	>.99	0.04	−0.01 (0.05)	>.99	-0.01	−0.03 (0.09)	>.99	−0.20 to 0.14	−0.05
Δ Month 24	0.12 (0.07)	.14	0.22	0.11 (0.05)	.07	0.20	−0.01 (0.08)	>.99	−0.18 to 0.16	−0.02
PSQI, sleep duration[c]										
Baseline	0.68 (0.10)			0.74 (0.08)				.65		
Δ Month 12	0.26 (0.10)	.02	0.32	0.00 (0.07)	>.99	0.00	−0.26 (0.12)	.03	−0.49 to −0.02	−0.32
Δ Month 24	0.19 (0.09)	.08	0.25	0.06 (0.07)	.75	0.08	−0.13 (0.11)	.26	−0.35 to 0.09	−0.17
PSQI, total score[c]										
Baseline	3.39 (0.26)			3.85 (0.22)				.31		
Δ Month 12	0.65 (0.30)	.06	0.26	0.10 (0.23)	>.99	0.04	−0.55 (0.37)	.27	−1.28 to 0.17	−0.22
Δ Month 24	0.60 (0.26)	.04	0.29	0.24 (0.20)	.47	0.11	−0.36 (0.32)	.51	−0.99 to 0.26	−0.17

Abbreviations: AL, ad libitum; BDI-II, Beck Depression Inventory II; CR, caloric restriction; Δ, change; ES, effect size; ITT, intent-to-treat; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; PSS, perceived stress scale; SF-36, Rand 36-Item Short Form.

[a] Baseline values are the observed mean (SE). Estimated change in the outcome variables were obtained from analyses that used an ITT approach to determine whether change in the outcome variables differed between the CR and AL groups.

[b] All *P* values reflect Bonferroni correction, truncated at >.99, as appropriate.

[c] Higher scores on the BDI-II, PSS, and PSQI scales reflect worse mood, greater stress, and worse sleep quality, respectively. Higher scores on the POMS scale indicate higher levels of the construct being measured. Higher scores on the SF-36 reflect better quality of life. The range of scores for the instruments is provided in the Methods section under the subsection entitled Assessment of Mood, Quality of Life, Perceived Sleep Quality, and Sexual Function.

ceiling effects and very little variability. Two other SF-36 variables (social functioning and physical functioning) were analyzed as binary outcomes, and regression analyses indicated that there were no negative changes from baseline related to treatment (eTable 1 in Supplement 1). Intent-to-treat results for the remainder of the SF-36 subscales are provided in Table 2. Compared with the AL group, the CR group experienced significant improvement in general health at months 12 (BGD, 6.33; 95% CI, 3.68-8.98; ES, 0.69) and 24 (BGD, 6.45; 95% CI, 3.93-8.98; ES, 0.75; both $P < .001$). Change on the PSS did not differ by group.

Perceived Sleep Quality

Five subscales of the PSQI were analyzed as binary outcomes, and regression analysis indicated that there were no negative changes from baseline that were related to group assignment (eTable 1 in Supplement 1). The ITT analyses revealed that sleep duration worsened in the AL group compared with the CR group at month 12 (BGD, −0.26; 95% CI, −0.49 to −0.02; ES, −0.32; $P = .03$) (Table 2).

Sexual Function

The CR group experienced improvements on the sexual drive and relationship subscale compared with the AL group at month 24 (BGD, 1.06; 95% CI, 0.11-2.01; ES, 0.35; $P = .03$) (Table 3). A significant sex × treatment interaction was found for the sexual arousal subscale ($P = .02$), with men in the AL group having higher arousal scores compared with men in the CR group (Figure 2E).

Reproductive Hormones

From the ITT analysis, SHBG levels increased in men in the CR group compared with the AL group at months 12 (BGD, 0.76; 95% CI, 0.40-1.12 µg/mL; ES, 1.16) and 24 (BGD, 0.92; 95% CI, 0.58-1.26 µg/mL; ES, 1.49; to convert to nanomoles per liter, multiply by 8.896; all $P < .001$) (Table 3). Free testosterone levels decreased in the CR group compared with the AL group at month 12 (BGD, −2.98; 95% CI, −4.75 to −1.21 ng/dL; ES, −0.92]), but not month 24 (BGD, −0.96; 95% CI, −2.46 to 0.54 ng/dL; ES, −0.35]; $P = .21$ (to convert to nanomoles per liter, multiply by 0.0347). Changes in luteinizing hormone, total testosterone, and follicle-stimulating hormone levels did not differ significantly between the groups.

Correlation Analyses

All Spearman correlations in the CR group noted below were significant at $\alpha = .01$. Spearman correlations were assessed between baseline values of the outcome variables and percent CR and weight change (kilograms and percent) from baseline to month 24. Sexual behavior and experience was significantly and favorably correlated with percent CR and weight loss (kilograms) at month 24 ($\rho = 0.26$ and $\rho = -0.30$, respectively).

Table 3. Baseline Values and ES in the Sexual Function and Hormone Variables in the CR and AL Groups at 12 and 24 Months

	AL Within Group			ITT Analysis of CR Within Group			Between Group			
Test	Mean (SE)[a]	*P* Value[b]	ES	Mean (SE)[a]	*P* Value[b]	ES	Difference	*P* Value[b]	95% CI	ES
Reported Sexual Function										
DISF-SR, sexual cognition and fantasy[c]										
Baseline	17.38 (1.14)			17.57 (0.87)				.91		
Δ Month 12	−0.16 (0.80)	>.99	−0.03	−0.80 (0.59)	.36	−0.13	−0.64 (0.95)	>.99	−2.52 to 1.25	−0.10
Δ Month 24	−0.76 (0.93)	.82	−0.11	−0.38 (0.70)	>.99	−0.05	0.38 (1.13)	>.99	−1.85 to 2.62	0.05
DISF-SR, sexual arousal[c]										
Baseline	13.26 (0.71)			13.16 (0.47)				.86		
Δ Month 12	0.87 (0.56)	.25	0.20	0.43 (0.41)	.59	0.10	−0.44 (0.67)	>.99	−1.77 to 0.89	−0.10
Δ Month 24	0.30 (0.53)	>.99	0.07	0.85 (0.40)	.07	0.21	0.55 (0.64)	.79	−0.72 to 1.82	0.14
DISF-SR, sexual behavior and experience[c]										
Baseline	11.18 (0.65)			11.94 (0.47)				.27		
Δ Month 12	1.12 (0.54)	.08	0.27	0.027 (0.40)	>.99	0.01	−1.10 (0.65)	.19	−2.38 to 0.19	−0.26
Δ Month 24	0.78 (0.52)	.27	0.19	0.85 (0.40)	.07	0.21	0.07 (0.64)	>.99	−1.19 to 1.33	0.02
DISF-SR, orgasm[c]										
Baseline	15.40 (0.73)			15.34 (0.48)				.58		
Δ Month 12	0.44 (0.52)	.79	0.11	0.06 (0.38)	>.99	0.02	−0.38 (0.62)	>.99	−1.61 to 0.85	−0.10
Δ Month 24	−0.36 (0.52)	.98	−0.09	0.59 (0.40)	.28	0.15	0.95 (0.64)	.28	−0.31 to 2.22	0.24
DISF-SR, sexual drive and relationship[c]										
Baseline	14.21 (0.47)			14.62 (0.32)				.65		
Δ Month 12	0.39 (0.37)	.59	0.13	−0.32 (0.28)	.49	−0.11	−0.71 (0.45)	.12	−1.60 to 0.18	−0.25
Δ Month 24	−0.53 (0.39)	.35	−0.18	0.53 (0.30)	.15	0.18	1.06 (0.48)	.03	0.11 to 2.01	0.35
DISF-SR, total score[c]										
Baseline	69.83 (2.96)			70.84 (2.20)				.67		
Δ Month 12	2.67 (2.18)	.44	0.16	−0.53 (1.60)	>.99	−0.03	−3.20 (2.61)	.44	−8.35 to 1.95	−0.19
Δ Month 24	0 (2.14)	>.99	0	2.10 (1.63)	.40	0.13	2.10 (2.60)	.84	−3.02 to 7.22	0.13

(continued)

Spearman correlations were assessed between change in the outcome variables from baseline to month 24 and percent CR and weight change from baseline to month 24. Change in SHBG levels from baseline to month 24 was significantly correlated with change in weight at month 24 (ρ = −0.44 for weight change [kilograms] and ρ = −0.45 for percent weight loss). In addition, weight change (kilograms) at month 24 correlated significantly with change on the POMS vigor (ρ = −0.32), fatigue (ρ = 0.24), and mood disturbance (ρ = 0.31) subscales, as well as the total PSQI score (ρ = 0.31). Percent weight change correlated with change in the POMS vigor (ρ = −0.30) and mood disturbance subscales (ρ = 0.27), as well as the SF-36 general health (ρ = −0.27) subscale, the total score (ρ = 0.28) on the PSQI, and total testosterone (ρ = −0.43). Percent CR at month 24 was correlated with change in sleep duration (ρ = −0.30). The eFigure in Supplement 1 illustrates the association between the percent weight change and the change in the outcome variables at month 24.

Discussion

To our knowledge, this is the first study to determine whether long-term CR affects psychological well-being and reproductive hormones (men only) in a sample that includes normal-weight individuals. Calorie restriction had some favorable effects on the outcomes, and weight loss was associated with improvements in many of the end points. These findings are noteworthy because floor and ceiling effects limited the ability for some scores to improve, although these effects provided ample opportunity for scores to worsen.

Consistent with the hypothesis and sparse literature[22,23] from samples that include normal-weight individuals, CR improved mood (BDI-II) and reduced tension (POMS), although the ESs were modest. Levels of QOL were high at baseline, yet CR improved general health and the ESs approached the large range (0.80)[28] and represented approximately a 5.2 and 5.7 score improvement. This finding is consistent with studies[11,12] of overweight or obese individuals, as is the failure to find differences on change in stress from the PSS.[13]

Sleep duration worsened in the AL group; this finding is consistent with the only other study[13] that evaluated sleep quality during CR in a sample that included normal-weight and overweight individuals. Although the ES was modest, it suggests that CR might attenuate changes in sleep that occur with age. Calorie restriction improved one measure of sexual function, and an interaction indicated that AL men reported higher arousal compared with CR men. This finding was the

Table 3. Baseline Values and ES in the Sexual Function and Hormone Variables in the CR and AL Groups at 12 and 24 Months (continued)

	AL Within Group			ITT Analysis of CR Within Group			Between Group			
Test	Mean (SE)[a]	*P* Value[b]	ES	Mean (SE)[a]	*P* Value[b]	ES	Difference	*P* Value[b]	95% CI	ES
Reproductive Hormones[d]										
SHBG, µg/mL										
Baseline	2.92 (0.25)			2.74 (0.16)				.51		
Δ Month 12	0.32 (0.16)	.09	0.49	1.09 (0.12)	<.001	1.65	0.76 (0.18)	<.001	0.40 to 1.12	1.16
Δ Month 24	0.14 (0.15)	.66	0.23	1.06 (.011)	<.001	1.72	0.92 (0.17)	<.001	0.58 to 1.26	1.49
LH, mIU/mL										
Baseline	3.43 (0.35)			3.13 (0.23)				.46		
Δ Month 12	0.26 (0.32)	.84	0.19	0.11 (0.24)	>.99	0.08	−0.15 (0.38)	>.99	−0.92 to 0.61	−0.11
Δ Month 24	0.10 (0.31)	>.99	0.08	0.36 (0.24)	.27	0.27	0.25 (0.36)	.98	−0.48 to 0.98	0.19
Total testosterone, ng/dL										
Baseline	485.23 (38.53)			467.82 (25.80)				.53		
Δ Month 12	67.72 (30.63)	.06	0.52	10.87 (22.95)	>.99	0.08	−56.85 (35.59)	.23	−128.19 to 14.50	−0.44
Δ Month 24	7.86 (30.69)	>.99	0.06	20.52 (23.50)	.77	0.16	12.65 (35.90)	>.99	−59.32 to 84.62	0.10
Free testosterone, ng/dL										
Baseline	11.42 (0.67)			11.5 (0.59)				.66		
Δ Month 12	0.71 (0.74)	.68	0.22	−2.27 (0.56)	<.001	−0.70	−2.98 (0.88)	<.01	−4.75 to −1.21	−0.92
Δ Month 24	−1.73 (0.64)	.02	0.63	−2.69 (0.50)	<.001	−0.98	−0.96 (0.75)	.21	−2.46 to 0.54	−0.35
FSH, mIU/mL										
Baseline	4.79 (0.70)			3.80 (0.30)				.29		
Δ Month 12	0.46 (0.26)	.16	0.41	0.54 (0.19)	.01	0.49	0.09 (0.30)	>.99	−0.52 to 0.70	0.08
Δ Month 24	0.82 (0.24)	<.01	0.79	0.80 (0.19)	<.001	0.77	−0.02 (0.29)	>.99	−0.60 to 0.56	−0.02

Abbreviations: AL, ad libitum; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CR, caloric restriction; DISF-SR, Derogatis Interview for Sexual Function–Self-report; ES, effect size; FSH, follicle-stimulating hormone; ITT, intent-to-treat; LH, luteinizing hormone; SHBG, sex hormone–binding globulin.

SI conversion factors: To convert LH to international units per liter, multiply by 1; SHBG to nanomoles per liter, multiply by 8.896; and total testosterone to nanomoles per liter, multiply by 0.0347.

[a] Baseline values are the observed mean (SE). Estimated change in the outcome variables were obtained from analyses that used an ITT approach to determine whether change in the outcome variables differed between the CR and AL groups. The ITT analyses included 218 participants (CR, 143; AL, 75). Baseline values of the variable being evaluated and the stratification variables of site, sex, and body mass index (BMI) stratum (22.0 ≤ BMI < 25.0 vs 25.0 ≤ BMI < 28.0) were included as covariates.

[b] All *P* values reflect Bonferroni correction, truncated at >.99, as appropriate.

[c] Higher scores on the DISF-SR reflect better sexual function. The range of scores for the instrument is provided in the Methods section.

[d] Reproductive hormones were collected only in men.

only occurrence of the AL group having a more positive outcome than the CR group. The association between obesity and sexual dysfunction is well established, and weight loss improves sexual function[14] in obese women[31] and obese men with type 2 diabetes mellitus,[32] and the present study provides data on a sample that included normal-weight healthy individuals.

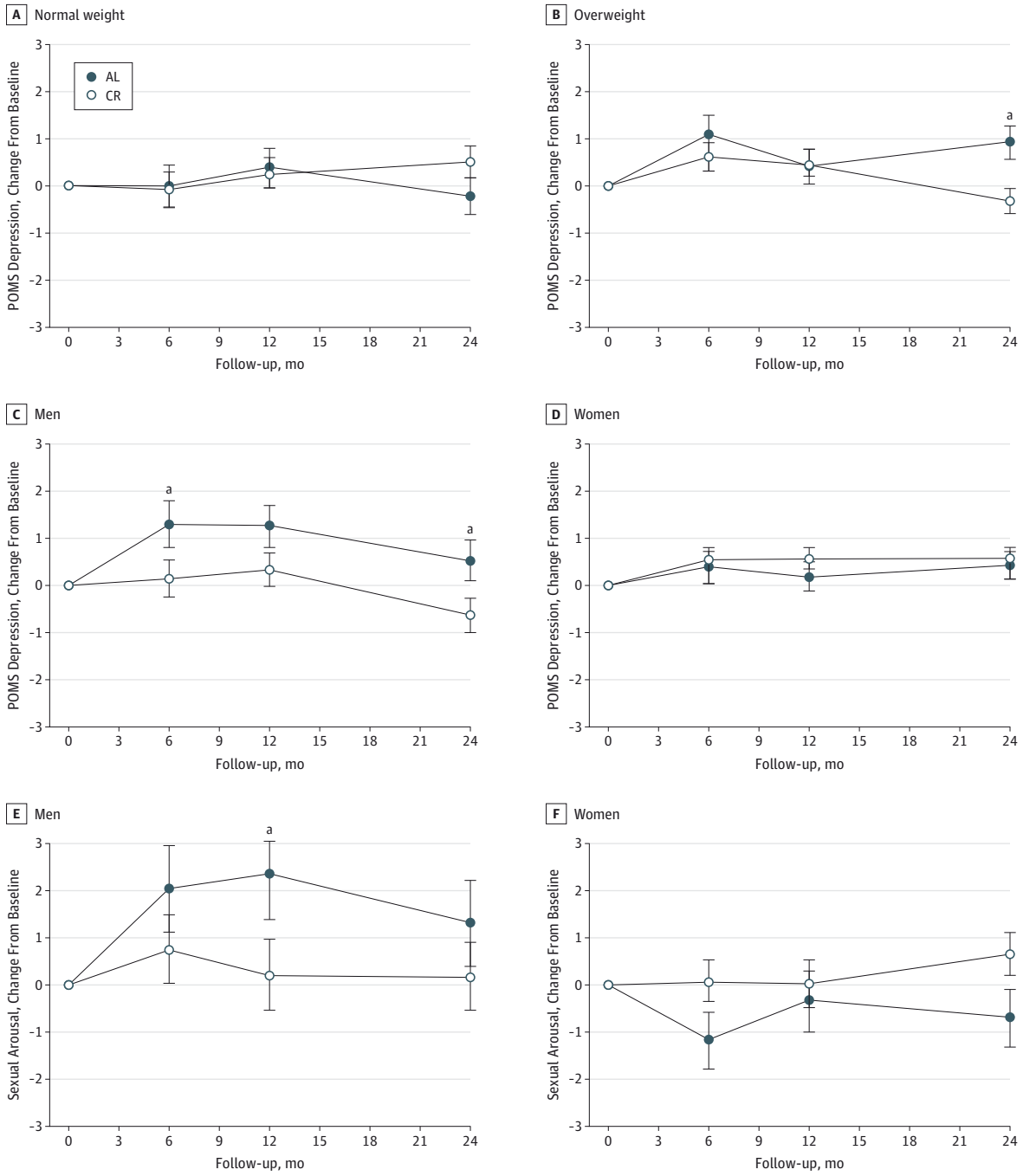
Consistent with the hypothesis, SHBG levels increased and free testosterone levels decreased in men of the CR group. The luteinizing hormone, follicle-stimulating hormone, and total testosterone hypotheses were not supported. The SHBG results are consistent with those previously reported, although those studies enrolled obese diabetic men,[17] obese nondiabetic men,[15] or obese men with and without type 2 diabetes mellitus.[32] The decrease in free testosterone levels in the CR group adds to the literature. The failure to find a change in total testosterone levels is consistent with Khoo et al,[17] but inconsistent with Kaukua et al[15] and another study of Khoo et al,[32] which found total testosterone levels to increase in obese nondiabetic men. Increased SHBG levels[17] and increased total testosterone levels[32] have been found to correlate with weight change, which is consistent with the present study's findings.

Strengths of this randomized clinical trial include the amount of weight loss achieved, maintenance of weight loss through 24 months, inclusion of normal-weight people, and the sample size. Limitations include selection of a healthy sample, which limited variability and contributed to ceiling and floor effects. In addition, the sample was predominantly female and white, which limits generalizability. Finally, differential attention between the groups could have influenced change in health-related QOL since the CR group met more frequently with study staff, although participating in the intervention also added burden to CR participants.

Conclusions

Calorie restriction had some positive effects and no negative effects on health-related QOL, and correlation analyses supported the association between weight loss and improved health-related QOL.[10] The results from this study are helpful to health care professionals because they provide data on the effect of CR on health-related QOL overall and sex hormones in men in a sample that included normal-weight individuals.

Figure 2. Illustration of Interaction Effects



Estimated changes in the end points for the ad libitum (AL) group are represented by solid circles. Estimated change in the end points for the calorie restriction (CR) group are represented by open circles. Illustrations of a body mass index × treatment × time interaction (A and B) and a sex × treatment interaction (C and D) for the Profile of Mood States (POMS) depression subscale[20] are provided. In addition, a sex × treatment interaction on the sexual arousal subscale of the Derogatis Interview for Sexual Function–Self-report[26] is illustrated (E and F). Error bars indicate SE.

[a] Significant differences between the AL and CR groups are denoted at the specified time point, with $P = .005$ for the difference between the AL and CR overweight participants at month 24 on the POMS depression scale; $P = .03$ and $P = .02$ for the difference between the AL and CR men on the POMS depression scale at months 6 and 12, respectively; and $P = .04$ for the difference between the AL and CR men at month 12 on the sexual arousal scale.

Calorie restriction among primarily overweight and obese persons has been found to improve QOL,[11,12] sleep,[13] and sexual function,[14] and the results of the present study indicate that 2 years of CR is unlikely to negatively affect these factors in healthy adults; rather, CR is likely to provide some improvement.

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Study concept and design: Martin, Das, Williamson, Scott, Redman, Stein, Gilhooly, Stewart, Roberts.
Acquisition, analysis, or interpretation of data: Martin, Bhapkar, Pittas, Pieper, Das, Williamson, Scott, Redman, Stein, Stewart, Robinson, Roberts.
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Group Information: The CALERIE Study Group members are listed in the eAppendix in Supplement 1.

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