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Authors

Mason, Ashley E
Hecht, Frederick M
Daubenmier, Jennifer J
et al.

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Weight Loss Maintenance and Cellular Aging in the Supporting Health Through Nutrition and Exercise Study

Ashley E. Mason, PhD, Frederick M. Hecht, MD, Jennifer J. Daubenmier, PhD, David A. Sbarra, PhD, Jue Lin, PhD, Patricia J. Moran, PhD, Samantha G. Schleicher, BA, Michael Acree, PhD, Aric A. Prather, PhD, and Elissa S. Epel, PhD

ABSTRACT

Objective: The aim of the study was to determine, within a weight loss clinical trial for obesity, the impact of intervention arm, weight change, and weight loss maintenance on telomere length (TL).

Methods: Adults ($N = 194$) with a body mass index between 30 and 45 were randomized to a 5.5-month weight loss program with ($n = 100$) or without ($n = 94$) mindfulness training and identical diet-exercise guidelines. We assessed TL at baseline and 3-, 6-, and 12-month postbaseline in immune cell populations (primarily in peripheral blood mononuclear cells [PBMCs], but also in granulocytes and T and B lymphocytes). We defined weight loss maintenance as having lost at least 5% or 10% of body weight (tested in separate models) from preintervention to postintervention, and having maintained this loss at 12 months. We predicted that greater weight loss and weight loss maintenance would be associated with TL lengthening.

Results: Neither weight loss intervention significantly predicted TL change nor did amount of weight change, at any time point. Across all participants, weight loss maintenance of at least 10% was associated with longer PBMC TL ($b = 239.08$, 95% CI = 0.92 to 477.25, $p = .049$), CD8+ TL ($b = 417.26$, 95% CI = 58.95 to 775.57, $p = .023$), and longer granulocyte TL ($b = 191.56$, 95% CI = -4.23 to 387.35, $p = .055$) at 12 months after accounting for baseline TL. Weight loss maintenance of 5% or more was associated with longer PBMC TL ($b = 163.32$, 95% CI = 4.00 to 320.62, $p = .045$) at 12 months after accounting for baseline TL. These tests should be interpreted in light of corrections for multiple tests.

Conclusions: Among individuals with obesity, losing and maintaining a weight loss of 10% or more may lead to TL lengthening, which may portend improved immune and metabolic function. TL lengthening in this study is of unknown duration beyond 12 months and requires further study.

Trial Registration: Clinicaltrials.gov identifier NCT00960414; Open Science Framework (OSF) preregistration: <https://osf.io/t3r2g/>.

Key words: behavioral intervention, mindfulness, telomere length, weight loss maintenance.

INTRODUCTION

Telomeres are hexameric (TTAGGG) nucleotide sequences at the ends of eukaryotic chromosomes that play important roles in diseases of aging (1). DNA polymerases are unable to completely replicate the ends of chromosomes with each cellular division, which leads to shorter TL over time. When TL is critically shortened, its associated proteins can no longer fully form the protective cap that promotes chromosomal stability, ultimately leading to cellular senescence. Telomerase, a cellular ribonucleoprotein enzyme, can add hexameric repeats to the telomeric ends of chromosomes, thereby increasing TL (2,3). Thus, TL can serve as a bidirectional index of physiological and psychological factors on aging over time (4), and studies linking shorter TL with cardiovascular diseases and diabetes (5–7) and mortality (8,9)

provide evidence that TL is also related to a range of important health outcomes.

Obesity may be an important determinant of associations between TL and disease states. Oxidative stress and systemic inflammation, which are both elevated in the context of obesity (10,11), shorten TL, and these findings form the basis for the hypothesis

BMI = body mass index, **CD4+** = cluster of differentiation 4 (indicating a CD4+ T lymphocyte), **CD8+** = cluster of differentiation 8 (indicating a CD8+ T lymphocyte), **CD19+** = cluster of differentiation 19 (indicating a B lymphocyte), **CI** = confidence interval, **HBME** = human brain microvascular endotheliocyte, **MET** = metabolic equivalent of task, **MIN** = minutes, **PBMC** = peripheral blood mononuclear cell, **RBC** = red blood cell, **TL** = telomere length, **T/S ratio** = telomere to single-copy gene ratio, **WBC** = white blood cell

SDC Supplemental Content

From the UCSF Department of Psychiatry (Mason, Schleicher, Prather, Epel), Center for Health and Community, San Francisco, California; UCSF Osher Center for Integrative Medicine (Mason, Hecht, Moran, Schleicher, Acree, Epel), San Francisco, California; Department of Health Education (Daubenmier), SF State University, Institute of Holistic Health Studies, San Francisco, California; Department of Psychology (Sbarra), The University of Arizona, Tucson; and UCSF Department of Biochemistry and Biophysics (Lin), San Francisco, California.

Address correspondence to Ashley E. Mason, PhD, University of California, San Francisco Osher Center for Integrative Medicine, 1545 Divisadero St, Suite 301, San Francisco, CA 94115. E-mail: ashley.mason@ucsf.edu

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that obesity might promote accelerated TL shortening (12,13). Indeed, more than 30 cross-sectional studies report associations between TL and adiposity (as indexed by body mass index [BMI]), and meta-analyses have reported that greater adiposity is associated with shorter TL (14,15).

Few studies, however, have examined associations between TL and weight loss in terms of nationally recommended weight loss guidelines, such as 5% (16–18) and 10% (19,20) of total body weight. One study found that in individuals with obesity treated with a bioenteric intragastric balloon, weight loss was associated with TL lengthening (21). In other research, individuals with obesity who underwent bariatric surgery evidenced TL lengthening 10 years later relative to age- and sex-matched normal-weight controls (22). In a prospective cohort study, an analysis of 2912 Chinese women of obese or overweight status who reduced their weight to a normal BMI (<25) showed TL lengthening in comparison with their counterparts who gained weight (23). Self-reported weight cycling, defined as losing and regaining 20 lb, has also been associated with TL shortening (24). Thus, a small but methodologically diverse body of literature suggests that weight loss may either reduce TL shortening and/or increase TL lengthening.

A second mediator of associations between TL and disease states may be psychological stress (25,26). Greater psychological stress is associated with shorter TL (27,28), through mechanisms related to exposure to cortisol, inflammation, and oxidative stress (29). Thus, interventions targeting both psychological stress and metabolic health may best promote TL lengthening. For example, one small pilot study found that men with prostate cancer who received an intensive lifestyle intervention targeting decreased stress, increased exercise, and improved nutrition showed TL lengthening 5 years later relative to a control group (30). Thus, the combined effects of decreased stress, increased exercise, and improved nutrition may have promoted the observed TL lengthening, although participants were not randomized to condition.

Interventions targeting weight loss and stress reduction may hold promise for slowing TL shortening. For example, a pilot intervention that preceded the present trial randomized women who were overweight or obese to a waitlist control or a mindfulness intervention that focused on reducing stress and increasing mindful eating. “As treated” participants who received a minimum dose of the mindfulness intervention (>40%) showed an 18% greater increase in telomerase activity than those randomized to the waitlist control group, although this was not a significant difference (31). In addition, greater reductions in stress and fasting glucose levels were associated with greater increases in telomerase activity. Mindful eating may lead to reductions in binge eating (32,33), which may promote weight loss. Mindfulness-based stress reduction (34) can lead to reductions in psychological stress. Hence, a behavioral intervention that combines mindfulness training for stress reduction and mindful eating with dietary recommendations may address two targets—stress reduction and metabolic health—which slow TL shortening and/or promote TL lengthening.

Present Study

We analyzed data from a randomized controlled trial testing the effects of a 5.5-month mindfulness-based weight loss intervention versus an active control intervention in which both intervention arms included the same standard diet and exercise guidelines. We examined the effects of (1) intervention arm, (2) weight

change, and (3) weight loss maintenance (defined using national guidelines of 5% and 10% or more) on changes in TL (peripheral blood mononuclear cells [PBMCs], granulocytes, CD4+ and CD8+ T-cells, and CD19+ B-cells) within a 12-month period. We hypothesized in preregistered analyses on the Open Science Framework (<https://osf.io/t3r2g/>) that (1) participants randomized to the mindfulness arm (relative to those randomized to the active control arm) would experience larger increases (or smaller decreases) in TL from baseline to 12-month postbaseline and (2) that greater weight loss from baseline to mid-intervention (3 months), postintervention (6 months), and follow-up (12 months) would be associated with larger increases (or smaller decreases) in TL during those respective time periods. Finally, we explored whether individuals who maintained weight loss over time, as defined by guidelines of 5% and 10% of body weight loss (relative to those who do not), would show larger increases (or smaller decreases) in TL at 12 months. We defined weight loss maintenance using the previously mentioned guidelines: specifically, we examined groups of participants who lost 10% or more (Status A) or 5% or more (Status B) of their body weight from baseline to 6-month postbaseline and who maintained this loss at 12 months. Our prespecified primary outcome variables were PBMC and granulocyte TL, and our prespecified secondary outcome variables included TL in CD4+ and CD8+ T-cells as well as CD19+ B-cells.

METHOD

Design

The current analyses used data from the Supporting Health by Integrating Nutrition and Exercise (SHINE) clinical trial (Clinicaltrials.gov registration: NCT00960414). Adults with obesity (BMI range = 30–45) were randomized in a 1:1 ratio to a 5.5-month diet and exercise weight loss program with or without mindfulness training that included mindfulness training targeting eating behavior, stress management, emotion regulation, and exercise. The study design and methods are reported in detail elsewhere (35). The University of California, San Francisco Institutional Review Board approved all study procedures. All participants provided informed consent.

Participants

Participants learned of the study through newspaper advertisements, flyers, online postings, and referrals made within university medical clinics. The study was advertised as a comparison of two weight loss interventions that each involved changes in diet, exercise, and stress management yet differed in the emphasis placed on each. To avoid selective attrition post-randomization due to any disappointment upon not being randomized to a preferred trial arm and to mask participants to study hypotheses regarding mindfulness practices, recruitment materials did not specifically advertise that mindfulness training would be taught in one of the arms. Inclusion criteria included abdominal obesity (waist circumference >102 cm for men and >88 cm for women) and age of 18 years or older. Exclusion criteria included types 1 and 2 diabetes mellitus (fasting glucose ≥ 126 or hemoglobin A1C >6.5 or between 6.0% and 6.5% with an abnormal oral glucose tolerance test); pregnancy, breastfeeding, or fewer than 6-month postpartum; use of corticosteroid and/or immune-suppressing or immune-modulating medications; use of prescription weight loss medications; untreated hypothyroidism; history of or active bulimia; current meditation or yoga practice; engagement in any other structured weight-management or weight loss program; or having participated in a mindfulness-based stress reduction course.

Procedures

Each intervention arm included 12 weekly group evening sessions (2–2.5 h), followed by 3 biweekly sessions, followed by 1 follow-up session 4 weeks

later (5.5 months total). Participants completed an all-day weekend session near the eighth week (5.0 hours for the active control arm, 6.5 hours for the mindfulness intervention arm). Registered dietitians taught the control arm sessions. Different registered dietitians and experienced mindfulness instructors taught the mindfulness arm sessions. See Daubenmier et al. (35) for intervention details.

Interventions

Mindfulness Arm

Intervention content included mindfulness training for eating behavior, stress management, emotion regulation, and exercise. Mindful eating practices targeted awareness of physical hunger, stomach fullness, taste satisfaction, food cravings, and other eating triggers (33). Instructors did not teach participants to avoid particular foods but rather encouraged them to eat favorite foods in smaller portions that fit with their calorie goals. Instructors encouraged participants to become aware of and to savor food tastes and textures, with the intention of deriving satisfaction from smaller amounts of favorite foods that tended to be of higher caloric density (e.g., sweets and desserts). Mindfulness training targeting stress management and emotion regulation incorporated components of mindfulness-based programs (34,36) including seated meditation, mindful yoga and walking, and loving-kindness meditations. Instructors also led extended exhalation breathing practices to promote initial physiological relaxation. Home-based activities included sitting meditation for up to 30 minutes a day/6 days a week, eating meals mindfully, minimeditations before meals, and mindful (chi) walking (37).

Active Control Arm

Intervention content accounted for the additional time, attention, social support, and expectations of benefit that the mindfulness participants may have experienced by providing additional group curricula about nutrition and physical activity. This included presentations about nutritional choices, discussion of sociopolitical issues that affect food choice, how to make well-informed decisions about diet products, and tutorials on strength training with exercise bands. To address participant expectations of receiving stress management tools, intervention content included instruction in progressive muscle relaxation and cognitive-behavioral skills, although at a lower dose than in the mindfulness intervention. To reduce participant burden while ensuring perceptions of benefit, sessions were reduced from 2.5 to 2.0 hours after session 9. Home-based activities reinforced diet and exercise lessons.

Diet-Exercise Guidelines

Diet and exercise components were the same for each intervention arm. Intervention instructors encouraged participants to focus on decreasing consumption of calorically dense, nutrient-poor foods such as refined carbohydrates, and increasing consumption of fresh fruits and vegetables, healthy oils, and proteins. To this end, participants set a goal of reducing daily food intake of their choice by 500 calories. The exercise component focused on increasing physical activity throughout the day as well as initiating structured aerobic and anaerobic exercise, such as bicycling, swimming, strength training, and walking.

Measures

Weight

We assessed weight in-person at all time points (baseline, 3, 6, and 12 months) and height at baseline. For all study visits, we used the same calibrated digital scale (Wheelchair Scale 6002; Scale-Tronix, Carol Stream IL), which rounded to the nearest 0.1 kg. Participants wore a hospital gown for all weight assessments. We rounded height to the nearest 0.1 cm.

Cell Processing

We assayed TL in PBMCs (baseline, and 3-, 6-, and 12-month time points), sorted PBMCs (baseline and 12-month postbaseline), and granulocytes (baseline,

and 3-, 6-, and 12-month postbaseline). Because of financial and timeline constraints (this study component was funded by a supplement with a shorter timeline than the parent study), we (1) assayed TL in PBMCs among all participants who provided at least one follow-up time point (3-, 6-, or 12-month postbaseline), (2) assayed TL in sorted PBMC cells (CD4+, CD8+ T-cells, and B-cells) only among participants in the first four (of six) waves who provided data at both baseline and 12-months postbaseline, and (3) assayed TL in granulocytes in all but the first wave (of six) waves, as we did not begin collecting red blood cells (RBCs) until the second wave. See the study by Prather et al. (38) for further details.

Fluorescence-Activated Cell Sorting

Cryopreserved PBMCs were thawed, washed, counted, and stained for sorting as previously described (39). Before staining, an aliquot of 1 million of PBMCs was removed, pelleted, and frozen at -80°C to assess PBMC TL. Thawed cells were first stained with LIVE/DEAD Fixable Aqua Dead Cell Stain Kit (Invitrogen) for exclusion of nonviable cells and were then stained with the following fluorescently conjugated monoclonal antibodies: anti-CD4-PE-Texas Red (Invitrogen); anti-CD3-V450, anti-CD19 PE-CyTM5, anti-CD28-PE, anti-CD45 FITC, and anti-CD8-APC (all from BD Biosciences). Stained cells were sorted on a customized BD FACSAriaTM II into the following fractions, using standard gating strategies: CD4+ T-cells (CD45 + CD3 + CD4+), CD8+ T-cells (CD45 + CD3 + CD8+), and CD19+ B-cells (CD45 + CD3-CD19+). Cells were collected into AIM V serum-free media (Invitrogen), pelleted by centrifugation, and stored at -80°C .

Granulocyte Preparation

Immediately after Ficoll preparation of PBMCs, the RBC/granulocyte pellet was removed from the Ficoll tube, mixed with three volumes of ACK lysis buffer (QIAGEN, Cat#158902) to lyse the RBCs, and incubated at room temperature for 10 minutes, with inversion every 2 minutes. Cells were then washed twice in phosphate-buffered saline, pelleted, and stored at -80°C .

Assay of TL

Total genomic DNA was purified using QIAamp DNA Mini kit (QIAGEN, Cat#51104) and stored at -80°C for batch TL measurement. The TL assay was adapted from the originally published method by Cawthon (39,40). The telomere thermal cycling profile comprised: cycling for T (telomeric) PCR at 96°C for 1 minute, denaturing at 96°C for 1 second, and annealing/extending at 54°C for 60 seconds with fluorescence data collection for 30 cycles, and cycling for S (single-copy gene) PCR at 96°C for 1 minute, denaturing at 95°C for 15 seconds, annealing at 58°C for 1 second, and extending at 72°C for 20 seconds for 8 cycles. This was followed by denaturing at 96°C for 1 second, annealing at 58°C for 1 second, extending at 72°C for 20 seconds, and holding at 83°C for 5 seconds for 35 cycles. The primers for the telomere PCR are tel1b (5'-CGGTTT(GTTTGG)5GTT-3'), used at a final concentration of 100 nM, and tel2b (5'-GGCTTG(CCTTAC)5CCT-3'), used at a final concentration of 900 nM. The primers for the single-copy gene (human beta-globin) PCR are hbg1 (5'-GCTTCTGACACAAGTGT GTTCACTAGC-3'), used at a final concentration of 300 nM, and hbg2 (5'-CACCAACTTCATCCACGTTACC-3'), used at a final concentration of 700 nM. The final reaction mix contains 20 mM of Tris-HCl, pH 8.4; 50 mM of KCl; 200 IM each dNTP; 1% DMSO; 0.4 Syber Green I; 22 ng *Escherichia coli* DNA per reaction; 0.4 U of Platinum Taq DNA polymerase (Invitrogen Inc) per 11 μl of reaction; 0.5–10 ng of genomic DNA. Tubes containing 26, 8.75, 2.9, 0.97, 0.324, and 0.108 ng of a reference DNA (from HeLa cancer cells) were included in each PCR run so that the quantity of targeted templates in each research sample could be determined relative to the reference DNA sample by the standard curve method. We used the same reference DNA for all PCR runs.

To control for interassay variability, we included eight control DNA samples in each run. We measured the telomere to single-copy gene ratio (T/S ratio) for each sample twice. When the duplicate T/S value and the

initial value varied by more than 7%, we ran the sample a third time and used the two closest values. In each batch, we divided the T/S ratio of each control DNA by the average T/S for the same DNA from 10 runs to get a normalizing factor. We repeated this for all eight samples and used the average normalizing factor for all 8 samples to obtain the final T/S ratio. We used the same assay plate for each participant when measuring sorted cell TL (CD4+, CD8+ T-cells and B-cells). In this sample, the average coefficient of variation was 3.4% for sorted cell TL data, 3.1% for granulocyte TL data, and 2.2% for PBMC TL data. Technicians were masked to intervention condition.

To determine the conversion factor for the calculation of approximate base pair TL from the T/S ratio, we measured T/S ratios for a set of genomic DNA samples from the human fibroblast primary cell line IMR90 at different population doublings, as well as in the telomerase protein subunit gene (hTERT) transfected into a lentiviral construct. We determined the mean terminal restriction fragment length from these DNA samples using Southern blot analysis. Comparison between T/S ratios and base pairs derived from Southern blot analysis generated the following formula to convert T/S ratios to base pairs: base pairs = 3274 + 2413 × (T/S) (41).

Covariates

We assessed participants' age (years), cigarette use (average number of cigarettes in last week), alcohol use (0 = none; 1 = once/month, 2 = 2-3×/month, 3 = 1×/wk, 4 = 2×/wk, 5 = 3-4×/wk, 6 = 5-6×/wk), educational attainment (0 = less than a Bachelor's degree; 1 = Bachelor's and above), and race (white, black, Latino/a, Asian or Pacific Islander, Native American, other) in-person at baseline. We assessed participants' physical activity using the International Physical Activity Questionnaire long form (42), which is a self-report measure that captures physical activity completed in the past week. From this, we computed the total prorated metabolic equivalent of task (METs (43)) as (3.3*m walking/wk + 4*m moderate

activity/wk + 8*m vigorous activity/wk), where m for each activity are prorated down to 180 if the reported m exceeded the cut-off of 180.

Statistical Analysis

We tested each hypothesis using models that included either (1) age and any covariates that were statistically significantly associated with outcomes or (2) intervention arm as well as any covariates that were statistically significantly associated with outcomes. We also report unadjusted models, which included only the predictors and outcomes. To ascertain whether to include a given covariate in adjusted models, we examined bivariate associations between each covariate and each outcome metric at 12 months. If a covariate was statistically significantly associated with an outcome (assessed at the final time point examined in each model), we retained this covariate in the final adjusted model. If a covariate was associated with some cell types, but not all, we retained it in all models to maximize consistency in interpretation. We used SAS PROC MIXED (fixed effects only) to test each hypothesis and modeled change in an outcome from baseline to 3, 6, or 12 months by including the latter time point as the outcome variable and accounting for baseline as a covariate, rather than modeling a change score directly (44). Models testing intervention effects accounted for baseline BMI. Models testing effects of weight loss and weight loss maintenance did not include baseline BMI as a covariate, as baseline BMI is a component of the primary predictor variable (weight change from baseline to subsequent time point). We defined two types of weight loss maintenance: having lost 10% of body weight from baseline to 6 months and having maintained this loss at 12 months (Status A), and having lost 5% of body weight from baseline to 6 months and having maintained this loss at 12 months (Status B). We report scale-dependent betas, standard errors, 95% confidence intervals, and *p* values in narrative and tables. As we conducted statistical tests using four primary predictors (intervention arm, weight change, weight loss maintenance of 10%, and weight loss maintenance of 5%) and five outcomes (PBMC, granulocytes, CD4+, CD8+, and

TABLE 1. Participant Characteristics on all Study Variables by Intervention Arm and Entire Sample

	Total Sample	Active Control	Mindfulness	Maintainer Status A (≥10%)		Maintainer Status B (≥5%)	
				Maintainers	Nonmaintainers	Maintainers	Nonmaintainers
<i>n</i> (%)	162 (100.0%)	74 (45.7%)	87 (54.3%)	17 (11.7%)	126 (88.3%)	50 (35.0%)	93 (65.0%)
Biol. sex (female), <i>n</i> (%)	162 (79.0%)	61 (82.4%)	67 (76.1%)	12 (70.6%)	102 (81.0%)	37 (74.0%)	77 (82.8%)
Age, M (SD), y	48.2 (12.5)	48.7 (12.0)	47.8 (13.0)	50.2 (13.5)	49.0 (12.3)	51.2 (11.8)	48.1 (12.6)
Race/ethnicity, <i>n</i> (%)							
White	99 (61.5%)	43 (58.1%)	56 (64.4%)	14 (82.4%)	78 (62.4%)	36 (72.0%)	56 (60.9%)
Black	20 (12.4%)	10 (13.5%)	10 (11.5%)	1 (5.9%)	18 (14.4%)	6 (12.0%)	13 (14.1%)
Latino	20 (12.4%)	13 (17.6%)	7 (8.0%)	1 (5.9%)	13 (10.4%)	1 (2.0%)	13 (14.1%)
Asian or Pacific Islander	14 (8.7%)	7 (9.5%)	7 (8.0%)	0 (0.0%)	12 (9.6%)	5 (10.0%)	7 (7.6%)
Other	8 (5.0%)	1 (1.4%)	7 (8.0%)	1 (5.9%)	4 (3.2%)	2 (4.0%)	3 (3.3%)
Educational attainment (Bachelor's degree+), <i>n</i> (%)	112 (69.6%)	48 (64.9%)	64 (73.6%)	10 (58.8%)	92 (73.6%)	37 (74.0%)	65 (70.6%)
Physical activity METs, M (SD)	2564.2 (2618.7)	2506.8 (2917.2)	2612.4 (2354.7)	2197.1 (2161.3)	2588.3 (2709.8)	2625.4 (2208.1)	2496.8 (2865.5)
Cigarette use, M (SD)	0.2 (1.2)	0.1 (0.5)	0.2 (1.5)	0 (0.0%)	0.1 (1.0)	0.2 (1.4)	0.1 (0.4)
Alcohol use, M (SD)	2.1 (1.9)	2.2 (1.8)	2.1 (1.9)	2.3 (2.1)	2.2 (1.8)	2.4 (1.9)	2.2 (1.8)
Randomized to mindfulness intervention arm, <i>n</i> (%)	—	—	—	9 (11.5%)	69 (88.5%)	33 (42.3%)	45 (57.7%)
BMI, M (SD), kg/m ²	35.4 (3.7)	35.1 (3.8)	35.3 (3.5)	35.7 (4.6)	35.3 (3.5)	35.0 (3.5)	35.5 (3.7)
Weight change, baseline to 12 mo, M (SD)	-4.1 (6.9)	-3.0 (6.5)	-5.1 (7.1)	-16.4 (6.2)	-2.6 (5.1)	-11.1 (5.8)	-0.6 (4.0)

BMI = body mass index; Biol. sex = biological sex; Physical activity METs = physical activity metabolic equivalent of task; Maintainer Status A = ≥10% body weight lost from baseline to 6 mo and maintenance of this loss at 12 mo; Maintainer Status B = ≥5% body weight lost from baseline to 6 mo and maintenance of this loss at 12 mo.

CD19+ cells), we interpreted statistical significance using a Bonferroni correction for 20 tests (p value criterion computed as $.05/20 = .0025$).

RESULTS

Participant Characteristics

Participants randomized to each arm were similar on baseline characteristics (Table 1), session attendance was similar for the

mindfulness and control arms (74.7% versus 71.2%, respectively), and researchers observed no serious adverse events in either intervention arm. See the study by Daubenmier et al. (35) and Mason et al. (45) for further details on intervention engagement, attrition, compliance, and changes in other factors, such as stress. Figure 1, Panels A and B, depict weight loss for participants who lost and maintained a loss of 10% ($n = 17$) and participants who lost and maintained a loss of 5% ($n = 51$).

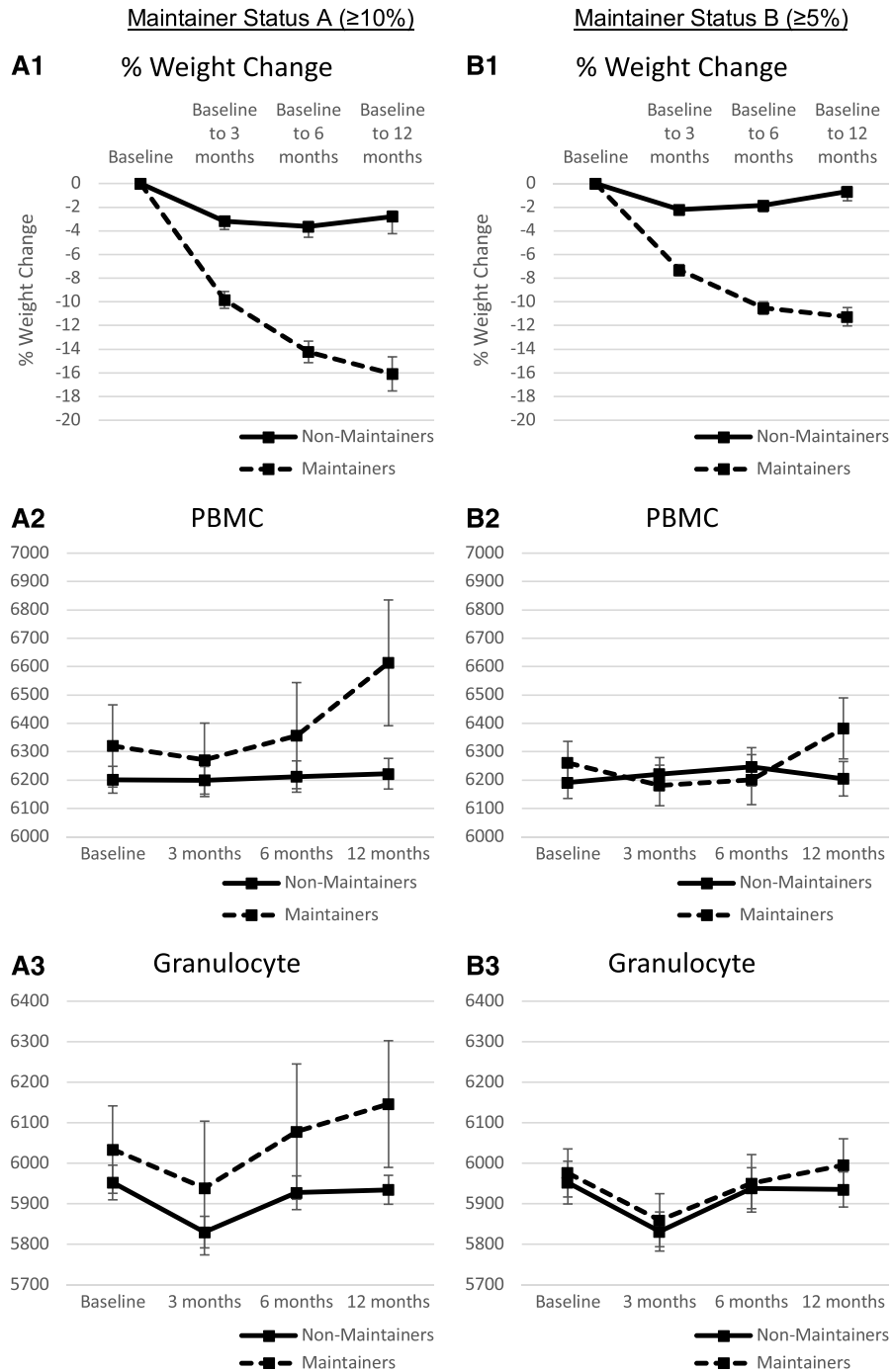


FIGURE 1. Percentage weight change from baseline to 3-, 6-, and 12-month postbaseline and TL in PBMCs (base pairs) and granulocytes (base pairs) at each time point by maintainer status type (left: Status A, 10% weight loss maintenance; right: Status B, 5% weight loss maintenance). Error bars reflect standard errors derived from within-time point t tests.

Candidate covariates (cigarette use, alcohol use, educational attainment, and race) did not significantly correlate with TL (PBMC, granulocytes, and sorted cells) at 12 months, and therefore, we did not retain them in adjusted models. Intervention arms (mindfulness versus active control) did not differ in METs at any time point (baseline, and 3, 6, or 12 months, $ps > .38$), in change between baseline and any time point, or in change between 6 and 12 months ($ps > .25$). This pattern and statistical significance of results was identical for weight loss maintenance of 10% or more (Status A; maintainers versus nonmaintainers; all $ps > .18$) and also for seven of eight tests for weight loss maintenance of 5% or more (Status B; maintainers versus nonmaintainers; all $ps > .18$). Given the well-known association between age and TL (26,46,47), we included age as a covariate in all models (see Supplementary Tables S1 and S2 for models excluding age, Supplemental Digital Content, <http://links.lww.com/PSYMED/A489>). We also note that correlations between baseline TL and 12-month TL were high ($ps < .000$) for each cell type and appear in Supplementary Table S3, Supplemental Digital Content, <http://links.lww.com/PSYMED/A489>.

Intervention Effects

Age was statistically significantly associated with 12-month PBMC, CD4+, and CD8+ TL and was therefore retained in all adjusted models. No other assessed covariates (cigarette use, alcohol use, educational attainment, and race) demonstrated this significant association; hence, we did not include others in adjusted models. As shown in Table 2, intervention arm did not statistically significantly predict 12-month TL change in any cell type. Greater baseline BMI, however, was associated with decreased PBMC (b (SE) = -26.89 (9.75), 95% CI = -46.17 to -7.71 , $p = .007$) and

B-cell TL (b (SE) = -46.53 (21.32), 95% CI = -89.03 to -4.04 , $p = .032$); however, these p values exceed the Bonferroni-corrected threshold of a p value of .0025.

Weight Change Effects

Weight Loss

In both unadjusted models and models adjusted for age and intervention arm, weight change from baseline to each subsequent time point was not associated with change in TL in those respective periods: baseline to 3 months (adjusted models: PBMC: b (SE) = -3.88 (7.54), 95% CI = -18.79 to 11.04 , $p = .608$; Granulocytes: b (SE) = 3.59 (8.35), 95% CI = -12.99 to 20.17 , $p = .668$); baseline to 6 months (adjusted models: PBMC: b (SE) = -0.57 (6.57), 95% CI = -13.56 to 12.42 , $p = .931$; granulocyte: b (SE) = 4.99 (6.27), 95% CI = -7.47 to 17.44 , $p = .428$), and baseline to 12 months (adjusted models: PBMC: b (SE) = -10.58 (6.43), 95% CI = -10.58 to 6.43 , $p = .102$; granulocyte: b (SE) = 0.30 (5.64), 95% CI = -10.91 to 11.51 , $p = .957$; CD4+ T-cell: b (SE) = 9.19 (7.56), 95% CI = -5.86 to 24.25 , $p = .228$; CD8+ T-cell: b (SE) = -11.64 (10.49), 95% CI = -32.55 to 9.26 , $p = .271$; CD19+ B-cell: b (SE) = -18.99 (14.74), 95% CI = -48.40 to 10.42 , $p = .202$).

Weight Loss Maintenance of 10% of Body Weight

As shown in Table 3, associations between weight loss maintenance status and changes in TL varied by cell type. Weight loss maintenance of 10% or more (Status A) was associated with longer 12-month PBMC TL (b (SE) = 239.08 (120.35), 95% CI = 0.92 to 477.25 , $p = .049$) after accounting for age, intervention arm, and baseline PBMC TL and trended toward association with longer

TABLE 2. Models Predicting 12-mo TL (TL)

Outcome (12 mo)	Effect	<i>b</i>	95% CI = Lower to Upper	<i>p</i>
PBMC	Intervention arm	0.70	(-138.44 to 139.84)	.992
	Baseline PBMC	0.68	(0.54 to 0.82)	<.000
	Age	-11.02	(-17.39 to -4.65)	.001
	Baseline BMI	-26.89	(-46.17 to -7.61)	.007
Granulocyte	Intervention arm	44.75	(-76.07 to 165.57)	.464
	Baseline granulocyte	0.49	(0.32 to 0.65)	<.000
	Age	-2.70	(-8.09 to 2.68)	.321
	Baseline BMI	-5.58	(-22.98 to 11.81)	.525
CD4+ T-cell	Intervention arm	78.45	(-70.88 to 227.79)	.299
	Baseline CD4+	0.66	(0.49 to 0.83)	<.000
	Age	-11.96	(-19.35 to -4.57)	.002
	Baseline BMI	-15.86	(-37.34 to 5.62)	.146
CD8+ T-cell	Intervention arm	18.09	(-193.33 to 229.51)	.865
	Baseline CD8+	0.49	(0.31 to 0.67)	<.000
	Age	-17.52	(-27.36 to -7.68)	.001
	Baseline BMI	-27.41	(-56.95 to 2.14)	.069
B-cell (CD19+)	Intervention arm	-134.57	(-440.72 to 171.58)	.384
	Baseline CD19+	0.49	(0.23 to 0.75)	<.000
	Age	-8.52	(-22.41 to 5.37)	.226
	Baseline BMI	-46.53	(-89.03 to -4.04)	.032

Intervention arm: 0 = active control, 1 = mindfulness; CI = confidence interval; PBMC = peripheral blood mononuclear cell; CD4+ = cluster of differentiation 4 (indicating a CD4+ T lymphocyte); CD8+ = cluster of differentiation (indicating a CD8+ T lymphocyte); B-cell = cluster of differentiation (indicating B lymphocyte).

TABLE 3. Models Predicting 12-mo TL From Weight Loss Maintenance Status A ($\geq 10\%$ of Initial Body Weight)

Outcome (12 mo)	Model Type	Effect	<i>b</i>	95% CI	<i>p</i>
PBMC	Adjusted for age	Maintainer Status A	238.81	(1.54 to 476.07)	.049
		Baseline PBMC	0.66	(0.51 to 0.82)	<.000
		Age	-11.86	(-18.50 to -5.23)	.001
	Adjusted for age and intervention arm	Intervention arm	-19.51	(-166.93 to 127.91)	.794
		Maintainer Status A	239.08	(0.92 to 477.25)	.049
		Baseline PBMC	0.66	(0.51 to 0.82)	<.000
Granulocyte	Adjusted for age	Maintainer Status A	192.49	(-1.54 to 386.53)	.052
		Baseline granulocyte	0.41	(0.25 to 0.58)	<.000
		Age	-4.69	(-9.93 to 0.55)	.079
	Adjusted for age and intervention arm	Intervention arm	6.90	(-113.46 to 127.26)	.910
		Maintainer Status A	191.56	(-4.24 to 387.36)	.055
		Baseline granulocyte	0.42	(0.25 to 0.59)	<.000
CD4+ T-cell	Adjusted for age	Maintainer Status A	-36.77	(-330.38 to 256.84)	.803
		Baseline CD4+	0.70	(0.51 to 0.89)	<.000
		Age	-11.34	(-19.42 to -3.27)	.009
	Adjusted for age and intervention arm	Intervention arm	52.36	(-107.81 to 212.54)	.517
		Maintainer Status A	-40.34	(-335.35 to 254.67)	.786
		Baseline CD4+	0.70	(0.51 to 0.90)	<.000
CD8+ T-cell	Adjusted for age	Maintainer Status A	414.83	(58.57 to 771.08)	.023
		Baseline CD8+	0.51	(0.33 to 0.68)	<.000
		Age	-15.58	(-25.10 to -6.06)	.002
	Adjusted for age and intervention arm	Intervention arm	-51.24	(-259.31 to 156.82)	.625
		Maintainer Status A	417.26	(58.95 to 775.57)	.023
		Baseline CD8+	0.51	(0.34 to 0.69)	<.000
B-cell (CD19+)	Adjusted for age	Maintainer Status A	47.04	(-491.80 to 585.87)	.862
		Baseline CD19+	0.54	(0.27 to 0.80)	<.001
		Age	-7.85	(-21.86 to 6.16)	.267
	Adjusted for age and intervention arm	Intervention arm	-93.07	(-413.69 to 227.55)	.564
		Maintainer Status A	46.76	(-494.82 to 588.35)	.864
		Baseline CD19+	0.53	(0.26 to 0.80)	<.000
		Age	-8.58	(-22.88 to 5.72)	.236

PBMC = primarily in peripheral blood mononuclear cell; CD4+ = cluster of differentiation 4 (indicating a CD4+ T lymphocyte); CD8+ = cluster of differentiation 8 (indicating a CD8+ T lymphocyte); CD19+ = cluster of differentiation 19 (indicating a CD19+ T lymphocyte); Maintainer Status A = losing $\geq 10\%$ of body weight and maintaining this loss at 12 mo (0 = nonmaintainer; 1 = maintainer).

12-month granulocyte TL (*b* (SE) = 191.56 (98.56), 95% CI = -4.23 to 387.35, *p* = .055). Of note, these *p* values exceed the Bonferroni-corrected threshold of a *p* value of .0025. Granulocyte TL evidenced a slight decrease from baseline to 3 months, before increasing from 3 months to 6 and 12 months (Fig. 1, A3). Among sorted cells, weight loss maintenance of 10% or more (Status A) was associated with longer 12-month CD8+ T-cell TL before (*b* (SE) = 440.34 (189.74), 95% CI = 62.35 to 818.32, *p* = .023) and after (*b* (SE) = 417.26 (179.78), 95% CI = 58.95 to 775.57, *p* = .023) accounting for age, intervention arm, and baseline CD8+ T-cell TL (although this exceeded the Bonferroni-corrected threshold of *p* = .0025). Thus, weight loss maintenance of 10% or more of body weight may confer benefit in terms of longer PBMC TL (especially within CD8+ cells) and granulocyte TL (Fig. 1, Panels A2 and A3).

Weight Loss Maintenance of 5% of Body Weight

As shown in Table 4, weight loss maintenance of 5% or more (Status B) was associated with longer 12-month PBMC TL (*b* (SE) = 162.32 (80.00), 95% CI = 4.00 to 320.62, *p* = .045) after accounting for age, intervention arm, and baseline PBMC TL (although this exceeded the Bonferroni-corrected threshold of *p* = .0025). Weight loss maintenance of 5% or more did not evidence a similar association with 12-month granulocyte TL (*b* (SE) = 59.82 (66.58), 95% CI = -72.45 to 192.09, *p* = .371). Of note, granulocyte TL evidenced a slight decrease from baseline to 3 months, before increasing from 3 to 6 months and staying similar (nonmaintainers) or increasing (maintainers) from 6 to 12 months (Fig. 1, B3). Among sorted cells, weight loss maintenance of 5% or more (Status B) was positively associated with longer 12-month

TABLE 4. Models Predicting 12-mo TL From Weight Loss Maintenance Status B ($\geq 5\%$ of Initial Body Weight)

Outcome (12 mo)	Model Type	Effect	<i>b</i>	95% CI	<i>p</i>
PBMC	Adjusted for age	Maintainer Status B	153.75	(-1.63 to 309.13)	.052
		Baseline PBMC	0.67	(0.51 to 0.82)	<.000
		Age	-12.35	(-19.03 to -5.67)	<.000
	Adjusted for age and intervention arm	Intervention arm	-45.52	(-195.23 to 104.19)	.548
		Maintainer Status B	162.32	(4.00 to 320.63)	.045
		Baseline PBMC	0.66	(0.51 to 0.82)	<.000
Granulocyte	Adjusted for Age	Maintainer Status B	60.05	(-66.34 to 186.45)	.348
		Baseline granulocyte	0.42	(0.25 to 0.60)	<.000
		Age	-4.45	(-9.79 to 0.89)	.102
	Adjusted for Age and Intervention Arm	Intervention arm	0.81	(-126.03 to 127.64)	.990
		Maintainer Status B	59.82	(-72.45 to 192.09)	.371
		Baseline granulocyte	0.43	(0.25 to 0.59)	<.000
CD4+ T-cell	Adjusted for age	Maintainer Status B	-36.96	(-213.61 to 139.68)	.678
		Baseline CD4+	0.71	(0.52 to 0.89)	<.000
		Age	-11.09	(-19.29 to -2.88)	.009
	Adjusted for age and intervention arm	Intervention arm	57.89	(-103.82 to 219.60)	.478
		Maintainer Status B	-46.64	(-225.96 to 132.67)	.606
		Baseline CD4+	0.71	(0.52 to 0.90)	<.000
CD8+ T-cell	Adjusted for age	Maintainer Status B	190.86	(-32.06 to 413.78)	.092
		Baseline CD8+	0.50	(0.33 to 0.68)	<.000
		Age	-16.84	(-26.55 to -7.14)	.001
	Adjusted for age and intervention arm	Intervention arm	-66.98	(-279.58 to 145.62)	.532
		Maintainer Status B	199.34	(-26.16 to 424.84)	.082
		Baseline CD8+	0.51	(0.33 to 0.69)	<.000
B-cell (CD19+)	Adjusted for age	Maintainer Status B	248.02	(-78.47 to 574.51)	.134
		Baseline CD19+	0.54	(0.29 to 0.80)	<.000
		Age	-8.79	(-22.53 to 4.95)	.206
	Adjusted for age and intervention arm	Intervention arm	-116.31	(-432.70 to 200.08)	.466
		Maintainer Status B	259.28	(-69.82 to 588.37)	.121
		Baseline CD19+	0.54	(0.28 to 0.80)	<.000
		Age	-9.73	(-23.76 to 4.29)	.171

PBMC = primarily in peripheral blood mononuclear cell; CD4+ = cluster of differentiation 4 (indicating a CD4+ T lymphocyte); CD8+ = cluster of differentiation 8 (indicating a CD8+ T lymphocyte); CD19+ = cluster of differentiation 19 (indicating a CD19+ T lymphocyte); CI = confidence interval; Maintainer Status B = losing $\geq 5\%$ of body weight and maintaining this loss at 12 mo (0 = nonmaintainer; 1 = maintainer).

CD8+ T-cell TL (b (SE) = 199.34 (113.14), 95% CI = -26.15 to 424.83, $p = .082$) after accounting for age, intervention arm, and baseline CD8+ TL (although this exceeded the Bonferroni-corrected threshold of $p = .0025$). Thus, weight loss maintenance of 5% or more of body weight may confer benefit in terms of longer PBMC TL (especially CD8+ T-cells; Fig. 1, Panels B2 and B3).

DISCUSSION

Although healthy lifestyle factors are associated with longer TL (e.g., (48,49)), few studies have documented telomere lengthening. Here, we examined a sample of healthy men and women with obesity who were randomized to receive a diet and exercise program with or without added mindfulness training. To our

knowledge, this is the first randomized controlled trial testing a weight loss intervention that examined TL as an outcome.

As reported in previous research (14), we found a positive cross-sectional association between greater BMI and shorter PBMC TL. We did not observe differential effects of the two weight loss intervention arms on 12-month TL, nor did we observe significant associations between simultaneous changes in weight and TL. We did, however, observe that successful weight loss maintenance of 10% was associated with greater TL lengthening within PBMCs, granulocytes (Fig. 1, Panels A2 and A3), and CD8+ T-cells at 12 months. Successful weight loss maintenance of 5% or more showed a similar pattern, although these effects were smaller and did not reliably differ from zero. Of

note, all observed associations exceeded the Bonferroni-corrected threshold of a p value of .0025 and should be interpreted in light of correction for multiple testing.

TL has primarily been examined in whole blood or in PBMCs; however, in this study, we examined TL in both granulocytes and PBMCs, as well as different subtypes of lymphocytes that make up much of the PBMC population. Although characterizing TL in white blood cell (WBC) subsets is more expensive and complex, this approach adds potentially important detail to understanding changes in TL (39,50,51). Because TL can systematically vary among different WBC types, changes in whole blood or PBMC TL may reflect actual changes in TL or may simply reflect changes in the distribution of specific WBC populations in the blood, such as shifts between the blood and tissue compartments. Granulocytes are typically the most common WBC, and granulocyte TL is thus most highly correlated with whole blood TL (mature RBCs do not have nuclei and thus do not have telomeres; hence, measures of TL in whole blood only reflect TL in WBCs; (52)). In contrast, PBMCs reflect longer-lived WBC populations (53,54).

Within PBMCs, T-cell TL tends to shorten more rapidly than B-cell TL (55,56). Here, we observed increased CD8+ T-cell TL among individuals with the most successful weight loss maintenance (10% of initial body weight). CD8+ T-cells are the main effector cells in adaptive, or “learned,” cellular immune responses, and shortened TL and replicative immunosenescence (inability to replicate) in CD8+ T-cells are associated with poorer immune responses to immunologic challenges, including poorer vaccine responses (57–59). Hence, this begins to suggest a pathway through which weight loss maintenance among individuals with obesity may reduce immune system aging.

The clinical significance of TL is becoming more well established. Large studies have linked shorter TL with greater likelihood of psychiatric disorders (60), greater psychosocial stress (61), and greater depressive symptoms (62). Large observational studies have also linked shorter TL to increased risk of ischemic heart disease (63), and recent research suggests a causal role of TL in Alzheimer disease (64) and cardiovascular disease (65). Although population studies reporting associations linking TL to components of metabolic health do not show causality (66), pilot data have implied that intensive lifestyle interventions may affect TL (30); hence, healthy lifestyle factors may improve TL. Longitudinal data have demonstrated that shorter TL may confer additional risk in the development of insulin resistance (67). Other work has shown that fasting insulin may mediate an association between TL and coronary heart disease (68). The clinical significance of telomere lengthening, however, has not been determined and may also depend on stability of this improvement. Future studies should test causal associations between TL and components of metabolic health that influence aging-related disease.

In the current study, TL seemed stable from baseline to 6 months, and we observed TL lengthening at 12 months among individuals who maintained a weight loss of 10% (7.5 kg). Notably, this was merely 17 participants (8.76% of the total sample). Thus, results may be interpreted as a proof of concept that successful weight loss up to a year later may confer beneficial effects on TL, although this magnitude of weight loss maintenance (10%) may be difficult for most people to achieve. However, 51

participants (26.29%) maintained a weight loss of 5%, which has clear beneficial effects on metabolic health (69) and may connote some beneficial effect on TL. We conclude that the overall pattern of results indicates that more than 10% weight loss maintenance may be associated with longer TL in PBMCs and CD8+ T-cells. We do apply caution to this conclusion; future work should seek to replicate this pattern of results. Of note, in these analyses, we prespecified our intention to include covariates that were associated with outcomes, and although we ultimately included only age, which is a robust correlate of TL (26,46,47), we may have increased the risk of overfitting our models (70). Future work should a priori select covariates for inclusion regardless of correlation with the outcome variables being examined.

Of note, although health behavior such as exercise is associated with longer TL (71,72), there was no evidence of systematic differences in exercise across intervention arms (mindfulness *versus* active control) or weight loss maintenance groups (Status A, $\geq 10\%$; Status B, $\geq 5\%$). Thus, the observed benefits may be more attributable to metabolic benefit derived from weight loss rather than those achieved through cardiovascular conditioning, etc. Preventing TL shortening may theoretically positively affect immune function and reduce risk for age-related diseases. It is unclear why we observed a short-term decrease in TL at the 3-month time point. Although this may have been a chance finding and requires future investigation, one hypothesis is that initial weight loss may have induced a catabolic state that represented a physiological stressor that contributed to initial TL shortening.

Mindfulness-based interventions have traditionally focused on stress reduction as a pathway to psychological and physiological health benefits. Notably, this sample had, on average, lower Perceived Stress Scale scores (M (SD) = 14.41 (5.76)) than national averages (73). Although psychological stresses, particularly work-related and family-related stresses, have been associated with obesity (74–76), in this study's sample, stress may not have been high enough such that stress reduction would have conferred benefit, or the intervention may not have engaged stress as an intervention target. Indeed, as reported elsewhere (45), participants in the mindfulness and active control groups did not experience significant differences in stress reduction. In contrast, participants in this sample had an average baseline BMI of 35.5, and weight loss was large enough that maintenance of such losses, which ostensibly occurred via changes in dietary intake, may have led to TL lengthening. Participants in this trial were encouraged to reduce caloric intake and to increase intake of foods traditionally recommended in Mediterranean diets (e.g., fresh fruits and vegetables, nuts, olive oil, fish). Indeed, previous work has shown that adherence to a Mediterranean diet, which has been shown to reduce cardiovascular risk factors (77), is associated with longer TL (78).

Conclusions

Contrary to our initial hypothesis, we did not find evidence that the mindfulness-based weight loss intervention differed from the control group in terms of change in TL. Additionally, we did not find evidence to suggest weight loss to be contemporaneously associated with TL change. We did, however, find support for the hypothesis that weight loss maintenance of 10% or more (of initial

body weight) was associated with TL lengthening 12 months later. Overall, results suggest a model in which initial weight loss may represent a physiologic stress for TL (resulting in shortening or no change), but that maintaining weight loss may produce longer-term benefits in TL (resulting in lengthening). Future research should further test this model.

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