Independent and Combined Effects of Dietary Weight Loss and Exercise on Leukocyte Telomere Length in Postmenopausal Women

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Abstract

Objective—Investigate the effects of 12 months of dietary weight loss and/or aerobic exercise on leukocyte telomere length in postmenopausal women.

Design and Methods—439 overweight or obese women (50–75 y) were randomized to: i) dietary weight loss (N=118); ii) aerobic exercise (N=117), iii) diet + exercise (N=117), or iv) control (N=87). The diet intervention was a group-based program with a 10% weight loss goal. The exercise intervention was 45 mins/day, 5 days/week of moderate-to-vigorous aerobic activity.

Fasting blood samples were taken at baseline and 12 months. DNA was extracted from isolated leukocytes and telomere length was measured by quantitative-polymerase chain reaction (qPCR). Mean changes were compared between groups (intent-to-treat) using generalized estimating equations.

Results—Baseline telomere length was inversely associated with age ($r=-0.12$ $p<0.01$) and positively associated with maximal oxygen uptake ($r=0.11$, $p=0.03$), but not with BMI or %body fat. Change in telomere length was inversely correlated with baseline telomere length ($r=-0.47$, $p<0.0001$). No significant difference in leukocyte telomere length was detected in any intervention group compared to controls, nor was the magnitude of weight loss associated with telomere length at 12 months.

Conclusions—Twelve-months of dietary weight loss and exercise did not change telomere length in postmenopausal women.

Keywords

INTRODUCTION

Telomeres are repetitive DNA sequences that comprise the molecular caps of chromosomes and help maintain genetic stability (1). With successive cell division, telomeres undergo incomplete replication leading to gradual shortening; thus, telomere length has been proposed as a useful marker of biological ageing (2, 3). Indeed, short telomeres have been associated with several pathologies of ageing including cancer, cardiovascular disease and dementia (4–7), as well as with early mortality (6, 7).

Inflammation and oxidative stress are known to accelerate telomere length shortening (8); however the effect of obesity has not been firmly established. Leukocyte telomere length has been negatively associated with obesity in some (9–13), but not all (14–16), cross-sectional studies. Telomere lengths appear shorter in physically inactive adults compared to active peers, and are significantly preserved among physically fit older adults (17). However, little is known about the effect of weight loss or exercise change on telomere length.

Our purpose was to determine the separate and combined effects of 12 months of dietary weight loss and/or aerobic exercise on leukocyte telomere length in overweight and obese postmenopausal women.

METHODS & PROCEDURES

Participants & Interventions

The Nutrition and Exercise in Women (NEW) study was a 12-month randomized controlled trial testing the effects of caloric restriction and/or exercise on circulating hormones and other outcomes. Study procedures were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board in Seattle, WA. All participants provided informed written consent.

The study methods have been previously described (18). Briefly, participants were postmenopausal women (50–75 y) with a body mass index (BMI) 25.0 kg/m^2 or 23.0 kg/m^2 if Asian-American, recruited through media and mass mailings. Exclusion criteria included: >100 min/week of moderate physical activity; diagnosed diabetes or other serious medical condition(s); postmenopausal hormone use; >2 alcoholic drinks/day; current smoking; participation in another structured weight loss program; contraindication to participation (e.g. abnormal exercise tolerance test, inability to attend sessions).

Eligible women were randomized to one of: i) reduced-calorie dietary modification (N=118); ii) moderate-to-vigorous intensity aerobic exercise (N=117); iii) combined diet and exercise (N=117); or iv) control (no intervention) (N=87) (Figure 1). Computerized random assignment, using permuted blocks randomization to achieve a proportionally smaller control group, was stratified according to BMI (or <30kg/m^2) and race/ethnicity.

The dietary intervention was a modification of the Diabetes Prevention Program (DPP) (19) and Look AHEAD (Action for Health in Diabetes) (20) lifestyle behavior change programs with goals of: 1200–2000 kcal/day, <30% daily calories from fat, and 10% weight loss. The exercise intervention goal was 45 minutes of moderate-to-vigorous (4 metabolic equivalents [METs]) intensity exercise at a target heart rate of 70–85% observed maximum, 5 days/week. Participants attended three facility-based supervised sessions/week and exercised 2 days/week at home.

Measures

All study measures were obtained and analyzed by trained personnel who were blinded to participants' randomization status.

At baseline (pre-randomization) and 12-months, demographic information, height, weight, medical history, dietary intake, supplement use and physical activity data were collected. Body composition was measured by DXA whole-body scanner (GE Lunar, Madison, WI). Cardiorespiratory fitness (VO$_2$max) was assessed using a maximal graded treadmill test according to a modified branching protocol (21).

Fasting venous blood (50 mL) was collected during clinic visits (no exercise or non-steroidal anti-inflammatory medications within 24 hours, no alcohol within 48 hours). Blood was processed within 1 hour and samples were stored at −80°C. DNA was extracted from isolated leukocytes using the Qiagen Midi Kit (Qiagen, Valencia, CA). Telomere length was measured by the quantitative-polymerase chain reaction (qPCR) method (22) (University of Washington Cytometry and Telomere Cost Center). For each sample, two PCRs were performed: the first one to amplify the telomeric DNA and the second one to amplify a single-copy control gene (36B4, acidic ribosomal phosphoprotein PO). This provided an internal control to normalize the starting amount of DNA. Telomere length was calculated as the ratio of telomeric DNA divided by the single-copy control gene. All samples were run in triplicate; the median was used for calculations. For quality assurance, duplicate DNA samples were included in each batch. Potential outlier samples with extreme long or short telomeres were repeated to confirm measurements. Inter- and intra-assay variability for qPCR were 6% and 7%, respectively. Samples were analyzed in batches such that each

participant's samples were assayed simultaneously, the number of samples from each study arm were approximately equal, participant randomization dates were similar, and sample order was random. Two participants (1 control; 1 exercise) were excluded at baseline because telomere length could not be measured. A comparative analysis of telomere length measured by qPCR and Southern blot previously reported a high correlation between both methods (r=0.847, p<0.0001) (23).

Statistical Analysis

All available data were used, without imputation for missing values. Pearson correlation coefficients were performed between baseline measures. The mean 12-month change in telomere length in each intervention group was computed and compared to controls using the generalized estimating equations (GEE) modification of linear regression to account for intra-individual correlation over time. Intervention effects were examined based on the assigned treatment at randomization, regardless of adherence or study retention (i.e. intent-to-treat). Assuming 80% power to make three primary pairwise comparisons (diet+exercise vs. exercise; diet+exercise vs. diet; and diet vs. exercise), the minimum detectable difference in telomere length was estimated at 0.082 (type I error=0.05). Based on regression between baseline age and telomere length, a mean change of −0.005 could be expected in our control group. Adjustment for multiple comparisons was made using Bonferroni correction (two-sided alpha=0.05/3). The main analyses were also repeated after stratification by median split of baseline telomere length. The effect of weight loss on telomere length was examined using a stratified analysis (<5%, 5–9.9%, and ≥10%) performed within each group and after combining all intervention groups together. All analyses were adjusted for age and baseline telomere length (23). Additional confounding by baseline BMI, race/ethnicity or smoking status (never, former) were also examined. Analyses were performed using SAS software version 9.2.

RESULTS

At 12-months, 399 participants completed a physical exam, provided a blood sample and underwent a DXA scan; 40 did not complete the study (Figure 1). Participant characteristics, intervention adherence, weight loss and body composition changes over 12 months have been previously published (18). The mean age and BMI were 58.0 years and 30.9 kg/m^2. Most women (65%) were college graduates and 85% were non-Hispanic white. Mean weight changes were −2.4% (p=0.03) in the exercise group, −8.5% (p<0.001) in the diet group, and −10.8% (p<0.001) in the diet + exercise group, compared to −0.8% among controls.

Women randomized to exercise participated in moderate-to-vigorous activity for a mean (SD) 163.3 (70.6) mins/wk (exercise), and 171.5 (62.9) mins/wk (diet+exercise). Both groups significantly increased average pedometer steps/day (+2416 and +3471 steps/d, respectively) and VO$_2$max (+0.17 and +0.12 L/min, respectively) compared to baseline (18). In both diet groups, women attended an average of 27 diet counseling sessions (86%).

Telomere Length

At baseline, leukocyte telomere length was inversely associated with age ($r=-0.12$ $p<0.01$) (Figure 2) and positively associated with VO_2max ($r=0.11$, $p=0.03$). Telomere length was not significantly correlated with BMI ($r=0.02$, $p=0.68$) nor % body fat ($r=-0.003$, $p=0.95$). Mean telomere length (SD) was not significantly different between overweight and obese women (1.045 (0.184) vs. 1.057 (0.201); $p=0.63$).

The 12-month change in leukocyte telomere length was significantly inversely correlated with baseline telomere length ($r=-0.47$, $p<0.0001$) (Figure 3). However, compared to controls, there were no significant changes in leukocyte telomere length over 12 months in any intervention group (Table 1). When the main analyses were stratified according to baseline telomere length (median split), women with shorter baseline telomere lengths had a greater mean increase in telomere length over 12 months than those with longer baseline telomere lengths; however, no interaction effects were statistically significant in any intervention arm compared to controls (diet: $p=0.99$; exercise: $p=0.32$; diet+ex: $p=0.63$).

The magnitude of weight loss did not significantly affect the 12-month change in telomere length in any intervention group, or when all intervention arms were combined (Table 2). Change in telomere length was not associated with baseline VO_2max, nor with the 12-month change in VO_2max among women randomized to exercise. Further adjusting the models for baseline BMI, race/ethnicity or smoking status (never, former) did not meaningfully change any of the results.

Over 12-months there was a net increase (mean leukocyte telomere length: 0.124, range: 0.002–0.736) in telomere length among 48% (n=190) of women. The proportion of women who experienced a net 12-month increase was not significantly different between groups ($\chi 2$ $p=0.90$).

DISCUSSION

The predominant mechanisms through which obesity may shorten telomere length and increase risk of ageing-related diseases include heightened oxidative stress, which increases telomere erosion, and inflammation, which accelerates leukocyte turnover (2). Weight loss has demonstrated effects on both of these processes (24, 25). However, our results suggest that 12 months of dietary weight loss and/or aerobic exercise sufficient to yield clinically meaningful weight loss in a majority of women, did not alter telomere length compared with controls.

Only a few observational studies have examined the association between adult weight and telomere length prospectively. Two studies, one including 647 women (35–74 y) (26) and the other including 70 young African American and white men and women (27) reported reduced telomere length associated with weight gain over 10 years or more follow-up, while waist-to-hip ratio was significantly associated with greater rate of telomere shortening over the subsequent 5 years in 608 patients with stable coronary artery disease (28). Results from the Finnish Diabetes Prevention Study randomized controlled trial showed only a weak inverse association ($r=-0.12$, $p=0.03$) between leukocyte telomere length and change in BMI

over a mean 4.5 year follow-up in 311 middle-aged adults with impaired glucose tolerance, with no significant difference between the lifestyle intervention group and controls (29). Lee et al. (11) previously reported a stronger negative association between obesity and telomere length in younger compared with older persons. Thus, it is possible that the ability to detect a significant effect of weight loss was diminished in our relatively homogeneous sample of postmenopausal women.

A previous study by LaRocca et al. (17) found that leukocyte telomere length was greater in a small sample (n=17) of endurance-trained older adults (who performed regular vigorous exercise 5 days/week for 5 years or longer) compared to inactive peers (n=15), and was not significantly different from young exercise-trained adults (n=10). Physical fitness has also been associated with telomere length in patients with coronary heart disease, such that patients with low fitness had more than a 2-fold greater odds of having telomere lengths in the lowest quartile compared to those with high fitness (30). We did not observe a significant difference in telomere length between controls and women randomized to exercise for 12 months, despite significant improvements in cardiorespiratory fitness. This suggests that the exercise dose or duration may have been insufficient to alter telomere dynamics in our population. It is also possible that underlying genetic factors could predispose individuals with longer telomeres to exercise or that the underlying biology of individuals with a history of being overweight and inactive (as our participants were) may render telomeres less responsive to lifestyle intervention in contrast to the endurance trained athletes previously studied.

Additionally, our study may have been underpowered to detect significant changes in telomere length between groups. Given the paucity of available data and the difficulty directly comparing relative leukocyte telomere length data across studies because of differences in qPCR methodology, further research is needed to confirm our results. However, the current results should provide valuable guidance in estimating anticipated effect sizes in future studies. Although telomeres gradually shorten with age, telomere length is active and dynamic (31). Thus, 12 months of behavioral intervention may have been too short a period over which to capture significant change in telomere length. Furthermore, we did not measure telomerase in this study- a critical enzyme that maintains telomere length and cellular replicate potential (32). Results from an uncontrolled pilot study in prostate cancer patients demonstrated a significant increase in telomerase activity after 3 months of intervention involving dietary modification, moderate aerobic activity, stress management and group support (33). Thus, telomerase may be more sensitive to lifestyle changes as it also has independent effects on cell and immune function (34).

Although telomere shortening represents a compelling link between genetics, accumulated lifestyle exposures, obesity and ageing-related diseases, continued research is needed to determine the degree to which telomere length may be responsive to change through specific lifestyle interventions.

Acknowledgements

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What is already known about this subject

- Although dynamic, telomeres undergo progressive shortening with age. They are proposed as a marker of biological ageing and are associated with outcomes including cardiovascular diseases and certain cancers.

- Inflammation and oxidative stress accelerate telomere length shortening. Leukocyte telomere length has been negatively associated with obesity in some, but not all, cross-sectional studies. Telomere lengths are shorter in physically inactive adults and are preserved in physically fit adults.

- The degree to which telomere length is amenable to change remains a question of great interest.

What this study adds

- A 12-month randomized intervention trial to test the separate and combined effects of dietary weight loss and/or aerobic exercise on leukocyte telomere length in overweight and obese postmenopausal women.

- Adds significantly to limited available data on prospective changes in leukocyte telomere length in response to lifestyle behavior change.

- Demonstrates that twelve months of weight loss and/or exercise is not sufficient to yield significant changes in telomere length in postmenopausal women.
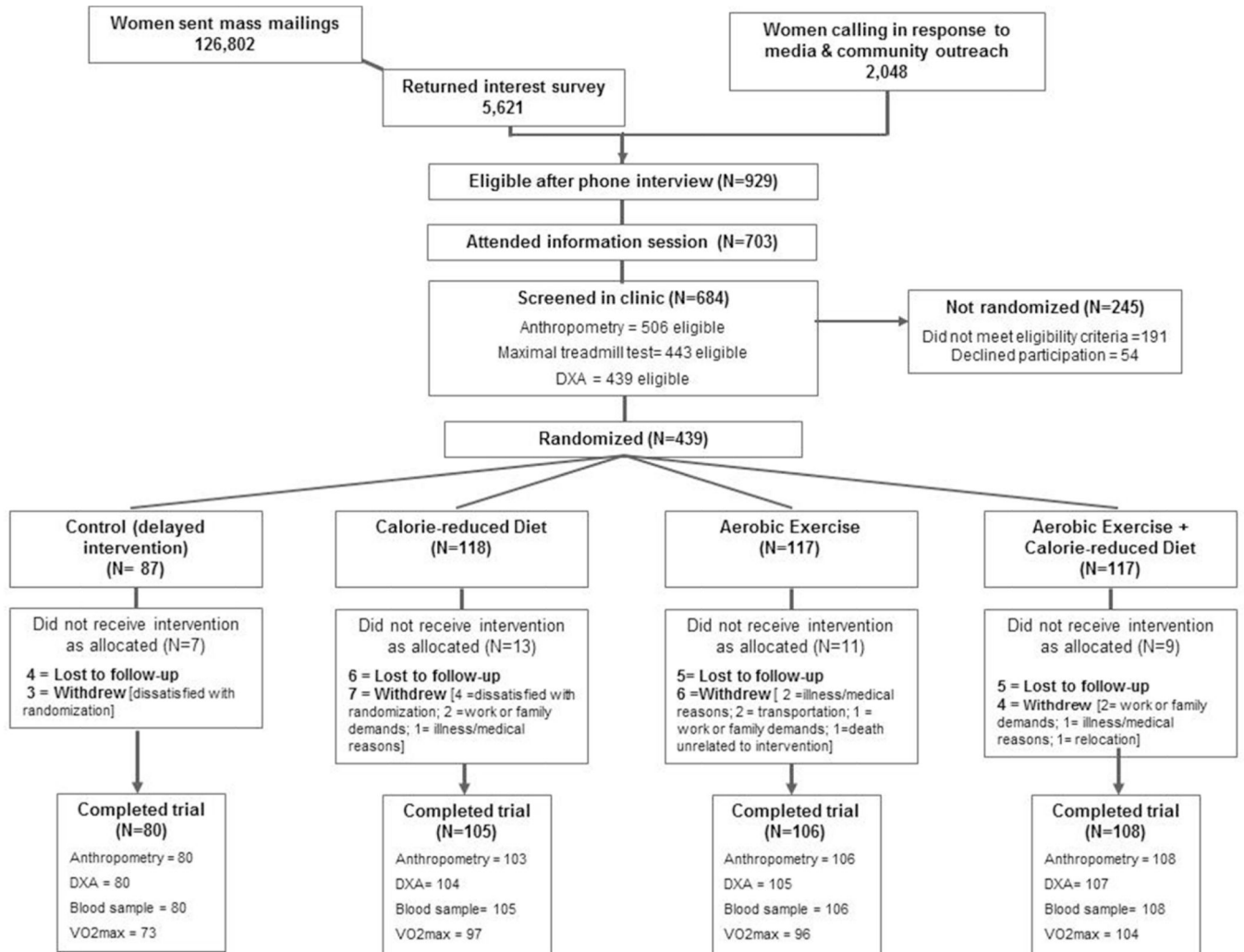

Figure 1.
Flow of participants through the Nutrition and Exercise in Women (NEW) study.

Figure 2.
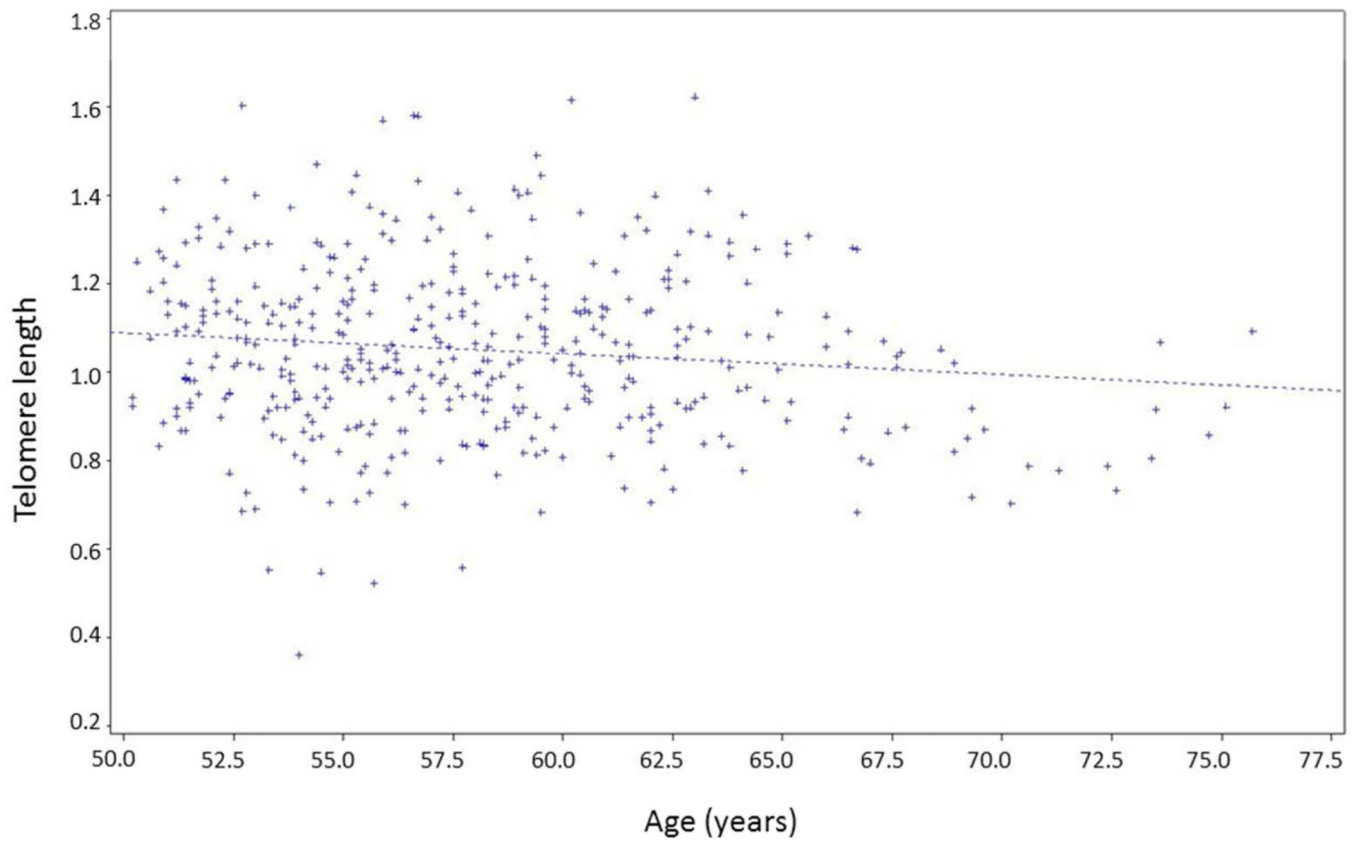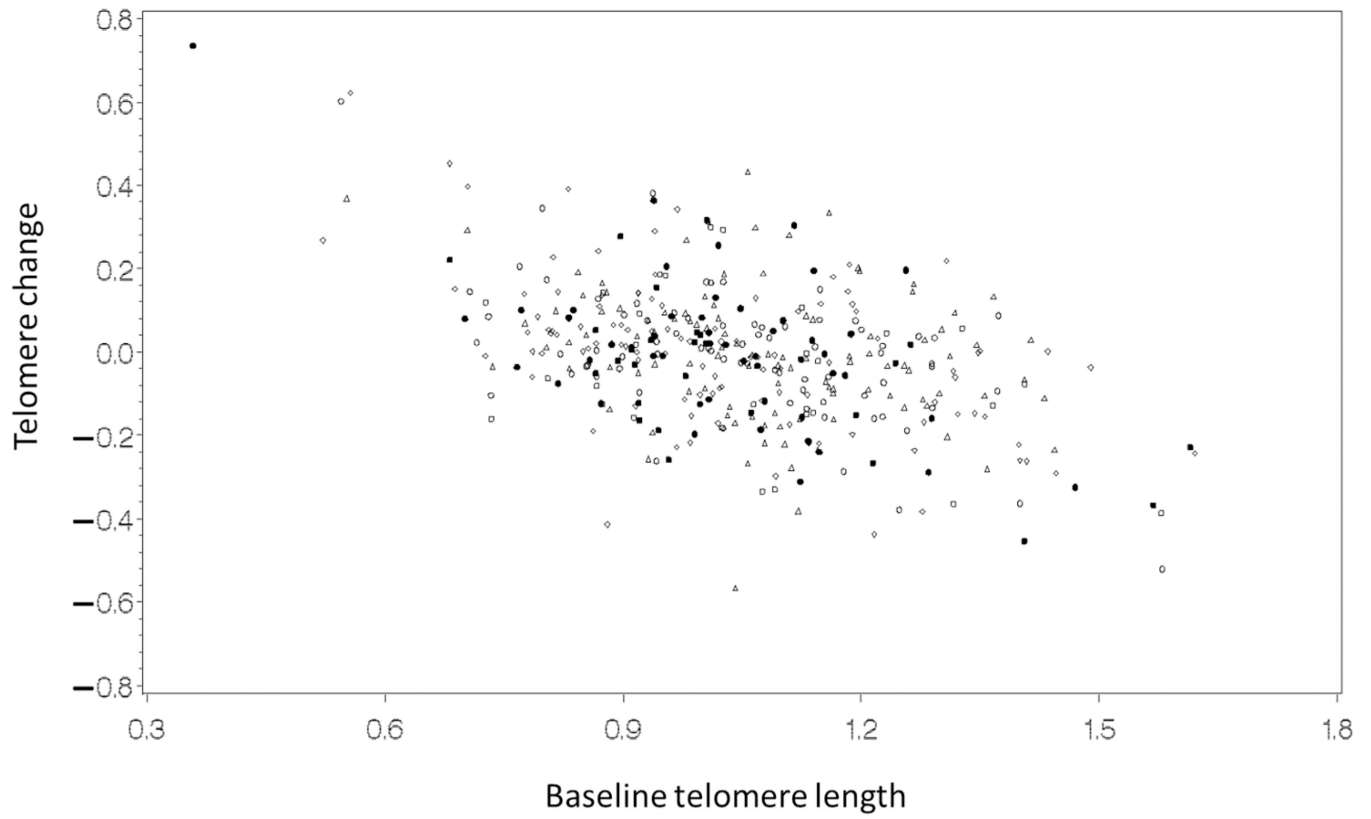Scatterplot diagram of baseline leukocyte telomere length vs. age. r=−0.12 p<0.01.

Figure 3.
Scatterplot diagram of baseline leukocyte telomere length vs. 12-month change in leukocyte telomere length, by intervention group. Control (black circle), Diet (open circle), Exercise (diamond), Diet + Exercise (triangle). r=0.47, p<0.0001.

Table 1

Baseline and 12-mo leukocyte telomere length in overweight and obese postmenopausal women, according to intervention assignment.

| | | Telomere length | | | | | |
| | | Baseline | | 12 mo | | | |
	N	Mean (SD)	N	Mean (SD)	Change	Change %	*p**
Control	86	1.042 (0.197)	79	1.015 (0.171)	−0.027	−0.3	ref
Exercise	116	1.027 (0.213)	106	1.025 (0.192)	−0.002	−0.2	0.51
Diet	118	1.058 (0.190)	105	1.040 (0.179)	−0.018	−1.6	0.53
Diet + Ex	117	1.074 (0.170)	108	1.075 (0.200)	0.001	0.1	0.14

*
P represents comparison of change within each intervention group compared to controls, adjusted for age and baseline telomere length.

Two participants (1 control; 1 exercise) were excluded at baseline because telomere length could not be measured.

Table 2

12-month change in telomere length, stratified by %weight loss in overweight and obese postmenopausal women randomized to dietary weight loss and/or aerobic exercise.

	N	Baseline	N	12 mo	Change	% Change
CONTROL	86	1.042 (0.197)	79	1.015 (0.171)	−0.027	−2.6
EXERCISE						
0% loss (no change or gain)	29	1.041 (0.156)	29	1.047 (0.174)	0.006	0.5
<5% loss	46	1.013 (0.217)	46	1.011 (0.188)	−0.002	−0.2
5–10% loss	29	1.044 (0.257)	30	1.029 (0.219)	−0.015	−1.5
Ptrend						*0.81*
DIET						
0% loss (no change or gain)	10	1.028 (0.195)	10	1.115 (0.221)	0.087	3.1
<5% loss	18	1.043 (0.200)	18	1.038 (0.180)	−0.005	−0.5
5–10% loss	27	1.043 (0.181)	27	1.031 (0.153)	−0.012	−1.2
10% loss	49	1.056 (0.201)	49	1.028 (0.185)	−0.028	−2.6
Ptrend						*0.22*
DIET+EXERCISE						
0% loss (no change or gain)	4	1.170 (0.102)	4	1.156 (0.083)	−0.014	−1.2
<5% loss	14	1.084 (0.141)	13	1.032 (0.245)	−0.052	−4.8
5–10% loss	21	1.081 (0.160)	21	1.083 (0.187)	0.002	0.2
10% loss	70	1.075 (0.183)	70	1.076 (0.201)	0.001	0.1
Ptrend						*0.57*
ALL INTERVENTIONS						
0% loss (no change or gain)	43	1.063 (0.163)	43	1.073 (0.181)	0.010	1.0
<5% loss	78	1.033 (0.201)	77	1.021 (0.195)	−0.012	−1.1
5–10% loss	73	1.035 (0.191)	74	1.034 (0.183)	−0.001	−0.1
10% loss	123	1.078 (0.198)	123	1.062 (0.198)	−0.016	−1.5
Ptrend						*0.51*

Ptrend across weight loss groups, within each intervention group, adjusted for age and baseline telomere length.

Analyses based on all available data. In total, 396 women had complete baseline and 12-month data for analysis.