ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Genomics, Proteomics, and Metabolomics

Longer Leukocyte Telomere Length Predicts Stronger Response to a Workplace Sugar-Sweetened Beverage Sales Ban: An Exploratory Study

Janet M Wojcicki,[1,2] Robert H Lustig,[1,3] Laurie M Jacobs,[3] Ashley E Mason,[4,5] Alison Hartman,[6] Cindy Leung,[7] Kimber Stanhope,[8] Jue Lin,[9] Laura A Schmidt,[3,10] and Elissa S Epel[4,6]

[1]Department of Pediatrics, University of California, San Francisco, CA, USA; [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA; [3]Philip R Lee Institute for Health Policy Studies, University of California, San Francisco, CA, USA; [4]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, USA; [5]Osher Center for Integrative Medicine, University of California, San Francisco, CA, USA; [6]Center for Health and Community, University of California, San Francisco, CA, USA; [7]Department of Nutritional Science, School of Public Health, University of Michigan, Ann Arbor, MI, USA; [8]Department of Molecular Biosciences, University of California, Davis, CA, USA; [9]Department of Biophysics and Biochemistry, University of California, San Francisco, CA, USA; and [10]Department of Anthropology, History and Social Medicine, University of California, San Francisco, CA, USA

ABSTRACT

Background: Shorter leukocyte telomere length (LTL) is associated with increased risk of a number of metabolic diseases including insulin resistance and the development of type 2 diabetes mellitus. Shorter LTL is also associated with stress reactivity suggestive of a possible role for LTL to predict response to behavioral interventions. However, few studies have evaluated how interventions, such as weight loss or dietary changes, are associated with LTL changes or whether LTL can predict behavioral responses to interventions.

Objectives: We evaluated metabolic changes in relation to LTL changes and LTL at baseline in a cohort of at-risk adults in response to a 10-mo workplace-based sugar-sweetened beverage (SSB) intervention.

Methods: At baseline, metabolic health and LTL measurements were assessed through standard blood draws on 212 participants. Multivariable linear regression models were used to assess changes in anthropometrics, SSB consumption, and 13 blood-based metabolic risk factors, in relation to LTL at baseline and changes in LTL.

Results: Longer LTL at baseline was associated with decreases in SSB consumption over the 6-mo follow-up period (B = −29.67; $P = 0.04$). Slower LTL attrition rates were associated with decreases in waist circumference (B = −0.27; $P = 0.03$), HDL cholesterol (B = −0.20; $P = 0.05$), and apoA1 (B = −0.09; $P = 0.01$).

Conclusions: Longer LTL at baseline predicted a favorable overall response to a behavioral intervention: decreases in SSB consumption. Abdominal adiposity losses paralleled slower declines in LTL suggestive of overall health benefits, but we found differences in the relations between metabolic changes and LTL at baseline compared with LTL attrition rates. Longer LTL may be a proxy marker of a positive behavioral response. This trial was registered at clinicaltrials.gov as NCT02585336. *Curr Dev Nutr* 2021;5:nzab084.

Keywords: telomere, SSB, sugar-sweetened beverages, lipids, adiposity, waist circumference, community level intervention

Manuscript received December 15, 2020. Initial review completed March 17, 2021. Revision accepted May 19, 2021. Published online May 26, 2021.
Supported by the University of California Office of the President (to LAS), the University of California San Francisco Office of the Executive Vice Chancellor/Provost, School of Medicine Dean's Office and University of California San Francisco Health, the Anne Wojcicki Foundation, the Robert Wood Johnson Foundation, and the Laura and Arnold Foundation.
Author disclosures: The authors report no conflicts of interest.

Address correspondence to JMW (e-mail: janet.wojcicki@ucsf.edu).

Abbreviations used: LTL, leukocyte telomere length; SSB, sugar-sweetened beverage; T/S, telomere over single copy gene; UCSF, University of California, San Francisco.

Introduction

Telomeres are the caps on the edges of chromosomes that protect the DNA from damage. Telomeres are particularly sensitive to oxidative stress, and leukocyte telomere length (LTL) has been shown to be a surrogate marker of cellular aging. Telomere length gets shorter with cell division and cross-sectional and population-based studies have found that telomere length is progressively shorter with advancing age (1, 2). The greatest amount of telomere length attrition happens in the first years of life as growth is accelerated during this time period (1, 3, 4). Telomeres are also particularly sensitive to reactive oxygen species damage and, as such, disease conditions associated with inflammation such as chronic stress, metabolic diseases, and cardiovascular diseases are associated with shorter telomere length (5, 6).

Previous longitudinal studies have found that shorter LTL is predictive of incident diabetes mellitus (7, 8) and cardiovascular disease (9). Reactive oxidative species exposure can result in leukocyte telomere damage setting in motion a cascade of events leading up to increased risk of disease states. Shorter telomere length and cellular senescence may result in impaired insulin secretion and insulin resistance as

well as the accumulation of senescent cells common in atherosclerosis (7, 9).

Leukocyte telomere length, weight, and metabolic health

Lifestyle factors and genetics both contribute to LTL maintenance suggesting a complex interface between environmental exposures, LTL, and disease states. Meta-analyses show cross-sectional relations between higher BMI and certain dietary factors [e.g., sugar-sweetened beverages (SSBs), processed meats] with shorter LTL (10, 11). In addition to shorter LTL, the pace of LTL attrition may be correlated with metabolic health, although few studies have examined this over time. Our previous study with obese and overweight Latina women found that rapid LTL shortening was associated with incident hypertension (12).

In addition, our clinical trial of weight loss found that individuals who lost ≥10% of their body weight and maintained it for 1 year had greater telomere lengthening than those who did not maintain weight loss (13). Other longitudinal studies with overweight and obese participants have similarly found that weight loss can result in telomere lengthening (14–16). These studies suggest that changes in nutritional status or adiposity may influence telomere stability.

Leukocyte telomere length, psychological health, and behavior change

Many studies have shown that longer LTL is associated with better psychological and mental health (17, 18), yet few studies, however, have tested whether LTL affects behavior or if LTL can be a predictor of behavior change during interventions. Studies suggest that longer LTL is associated with optimism and higher emotional intelligence (19, 20), potentially positive indicators for response to behavior interventions. There is some evidence that longer LTL may predict better responses to weight loss or nutrition-focused interventions (15) and more salutary stress response reactivity during emotional challenges (21). Given the growing accessibility of measures of telomere length in large populations, it is worth further exploring whether baseline longer TL indeed predicts positive outcomes from behavioral or medical interventions to identify high-resilience as opposed to high-risk groups.

In this exploratory study, we examined LTL in a racially and ethnically diverse adult cohort of workers at the University of California, San Francisco (UCSF) Medical Center who drank sugared beverages on a daily basis. This group tended to have obesity and insulin resistance at baseline (22). We initially tested the impact of exposure to a workplace-based SSB elimination on metabolic health over a 10-mo interval. We previously documented a decrease in overall workplace SSB consumption and a reduction in waist circumference (22). We also measured LTL before and after the intervention allowing us to assess any LTL changes during the intervention. Further, we asked whether baseline LTL predicts positive behavioral and metabolic outcomes.

We hypothesized that an individual's reductions in SSB consumption and improvements in metabolic health would correlate with slower decline in LTL during this period. We also hypothesized, based on prior data demonstrating longer LTL with better mental health (17, 23), that longer LTL would be associated with a better behavioral response to the intervention.

Methods

Study design

The study team enrolled 214 employees at the UCSF Medical Center into a metabolic substudy (NCT02585336) before the roll-out of a university-wide SSB ban beginning on 1 November, 2015 (22). We oversampled lower-income service and manual workers for the study because we anticipated that this group would be at higher risk of baseline SSB consumption and could benefit more from the proposed intervention. The inclusion criteria included self-reported daily SSB consumption over the last 3 mo of ≥360 mL or ≥12 fl oz (16). Men and women of all BMI groups (underweight, normal weight, overweight, and obese) were eligible for participation in the study. Of the 699 potentially eligible participants, 214 were able to participate in the metabolic substudy based on availability and campus location. Half of the participants were then randomly assigned to an additional brief motivational intervention session focused on SSB reduction which included goal setting and health knowledge as part of the study ($n = 109$). The other half of the participants did not receive any additional intervention beyond exposure to the university-wide SSB ban ($n = 105$). All participants were exposed to the university-wide SSB ban (22). We included the motivational intervention condition as a covariate in this study as described below.

The UCSF Committee on Human Research approved all aspects of the study and participants provided written signed consent before participation (22). As per the study protocol, participants were assured that their response to surveys and all data would not be shared with their supervisors or be associated with any university record. Participants received $125 ($50 for the baseline visit and $75 for follow-up).

Health and SSB assessments

At baseline, before the rollout of the UCSF SSB sales ban, and 10 mo after the intervention, participants completed 2 in-person health visits at UCSF where 30 mL fasting blood was drawn by trained research staff. The blood sample was then assayed for 13 lipid and metabolic biomarkers including triglycerides, total cholesterol, HDL-cholesterol concentration, LDL-cholesterol concentration, apoA1, apoB-100, uric acid, γ-glutamyl transferase, alanine aminotransferase, glycated hemoglobin, insulin, glucose, and homeostasis model assessment. During the same research visit, trained staff measured weight, waist circumference, height for BMI (in kg/m^2), and drew additional blood for future LTL analysis. After the research visit, samples were immediately processed and divided into aliquots of serum, plasma, and whole blood, and frozen at −80°C for analysis by the research laboratory of Peter Havel, DVM, University of California, Davis and the Blackburn Lab at UCSF. SSB consumption at baseline and 6 months later was measured using the modified Beverage Intake Questionnaire-15 (24), which was then used to estimate ounces of SSB intake. Two hundred and two participants (94.4%) completed both study visits. There were 182 participants who had LTL and other biological markers measured at baseline and subsequently at follow-up. As previously described (22), reasons for incomplete follow-up for blood draw were schedule conflicts or lack of interest. There were no statistically significant differences in age, gender, race/ethnicity, or BMI at baseline between those who completed both blood draws and those who did not. Further details of the methodology used are included in the online supplement of the published trial (22).

Leukocyte telomere length measurement

LTL was measured from the whole blood collected during the study visit. The UCSF telomere measurement laboratory uses a qPCR method adapted from Cawthon(25) to measure LTL (26). The method represents a ratio of 2 qPCR reactions—telomere over single copy gene (T/S) ratio—and had an interassay CV of 3.4% ± 3.0%.

Statistical analysis

We assessed the normality of our outcomes of interest—baseline LTL, changes in LTL, and changes in SSB consumption—using graphical assessments of normality as well as statistical tests such as Shapiro–Wilk using a cutoff of $P < 0.05$ to reject the null hypothesis that the data were normally distributed. LTL at baseline was normally distributed, but changes in LTL and SSB from baseline to follow-up were not normally distributed. As such, we assessed SSB consumption patterns and metabolic changes in relation to LTL at baseline and changes in LTL and SSB over time using parametric and nonparametric tests to assess associations, including the following parametric tests: Student's *t* test for categorical predictors, Pearson's *r* for continuous predictors and the respective nonparametric equivalents, the Spearman rank-order correlation test, and the Mann–Whitney *U* test. Specifically, we assessed SSB consumption patterns and metabolic changes in relation to LTL at baseline and changes in LTL over time, and LTL and metabolic changes in relation to SSB consumption. Variables that were significant at $P < 0.10$ and associated with changes in LTL and SSB consumption were included in multivariable linear regression models.

All statistical models were adjusted for participant age, sex, and race/ethnic background, given the associations between these demographic factors and LTL in prior studies (21). Models were also adjusted for intervention group in multivariable analyses because those who were randomly assigned to the brief motivational intervention aforementioned reported lower SSB intake at baseline. Multivariable linear regression was used to assess risk factor changes in SSB consumption over the follow-up period and leukocyte telomere attrition rate over 10 mo. A sensitivity analysis was conducted by comparing results with those obtained from robust linear regression to ensure that outliers were not driving the associations.

Multivariable linear regression residuals for LTL change were not normally distributed. As such, we used bootstrapping to increase the overall sample size to 1000 to assess the normality of the distribution with bootstrapped data, finding that the data were normally distributed and results were unchanged in the larger, bootstrapped sample. We used similar graphical assessments of normality and statistical tests (Shapiro–Wilk) as aforementioned in the bivariate analyses. We concluded that the nonnormality of the original distribution was related only to our sample size and not to other aspects of the data structure. Therefore, we opted for multivariable linear regression in our analyses.

Change in LTL from baseline to follow-up was adjusted for baseline LTL by assessing percentage change from baseline. We also compared findings with change from baseline to follow-up adjusted for length of follow-up and baseline LTL because not all participants had blood drawn on the exact same day. As there were no significant differences in findings, we present percentage change from baseline as our outcome of interest. Also, HDL cholesterol and apoA1 were not included in the same multivariable models owing to collinearity between these variables ($r > 0.8$). Collinearity was assessed using all pairwise correlation coefficients. Data were analyzed using Stata 15.0 (StataCorp LLC) and results are presented as means ± SDs.

Results

The current study included participants of a mean age of 41.20 ± 11.04 y. The cohort was 57.94% female, 14.95% non-Hispanic African American, 21.96% non-Hispanic white, 27.10% non-Hispanic Asian, and 19.63% Latinx (**Table 1**). At baseline, mean BMI was 29.39 ± 6.548, and 33% were overweight (25 ≤ BMI < 30) and another 39.5% were obese (BMI ≥ 30) with the remainder being in the normal-weight and underweight category of BMI < 25. Participants in the current study reported a reduction in SSB intake from 1052.8 ± 804.4 mL (35.6 ± 27.2 fl oz) per day at baseline to 558.9 ± 615.1 mL (18.9 ± 20.8 fl oz) per day, 6 mo after the sales ban: a decline of 48.6% (16). As reported earlier (16), there was no weight loss or BMI loss (0.03 ± 1.32) on average across the sample; however, there was a significant decrease of 2.19 ± 4.97 cm in mean waist circumference from baseline to follow-up (Table 1).

Telomere length at baseline

As expected, longer LTL at baseline was associated with younger age ($r = -0.49$; $P < 0.10$) and LTL was longer for women than for men (1.07 ± 0.16 compared with 1.01 ± 0.17 T/S; $P < 0.01$) (Table 1). Longer LTL at baseline was not associated with SSB intake at baseline ($r = 0.06$, $P = 0.41$) (Table 1). Longer LTL at baseline was associated with lower waist-to-hip ratio ($P < 0.001$) and trended toward lower waist circumference ($P = 0.10$) and BMI ($P = 0.10$) (Table 1), but these associations were no longer significant in the multivariable model adjusting for age, race/ethnicity, and gender.

BMI, waist circumference, and sagittal diameter at baseline were negatively correlated with changes in SSB consumption over the follow-up period ($\rho = -0.16$, $P = 0.04$; $\rho = -0.14$, $P = 0.06$; and $\rho = -0.013$, $P = 0.08$, respectively) (**Table 2**). LTL at baseline was negatively correlated with changes in SSB consumption and trended toward statistical significance ($\rho = -0.12$, $P = 0.10$) (Table 2). In a multivariable model adjusting for variables with $P \leq 0.10$ including race/ethnicity, age, gender, study assignment, apoB protein at baseline, and LTL at baseline, only LTL at baseline was associated with SSB reduction during the follow-up period (B = −29.67; 95% CI: −57.82, −1.51) (**Table 3**).

Telomere length attrition and changes in SSB consumption and metabolic health

Mean LTL at baseline was 1.05 ± 0.17 T/S and at follow-up was 1.04 ± 0.17 T/S, and mean attrition was −0.004 ± 0.07 T/S. Thus, there were no mean changes in LTL over the 10 mo, despite the group's overall improvement in SSB intake and waist circumference due to the environmental intervention. We also categorized by level of change: 44 participants (24.2%) reported LTL gain (defined as change > 5%) with a mean increase of 10.8% ± 5.7%; 86 participants (47.3%) reported LTL maintenance (change ≥ −5% and ≤5%) with mean maintenance being < 1% change (−0.79% ± 2.7%); and 52 participants (28.6%) reported LTL loss (change < −5%) with a mean loss of −9.2% ± 3.1%.

LTL attrition rate was associated with metabolic changes. In bivariate analysis, decreases in waist circumference were associated with reduced LTL attrition rate ($\rho = -0.17$, $P = 0.03$) and decreases in HDL choles-

TABLE 1 Demographics, metabolic markers and relations to baseline leukocyte telomere length[1]

	Baseline values Mean ± SD or %	Change[2] over time Mean ± SD	Baseline Leukocyte Telomere (T/S ratio) Mean ± SD or *r*	*P* value for Basetime Leukocyte Telomere Length
Demographics				
Age, y	41.20 ± 11.04*		−0.49*	<0.01*
Gender				0.01*
Female	57.94		1.07 ± 0.16	
Male	42.06		1.01 ± 0.17	
Race/ethnicity				0.67
Caucasian	21.96		1.03 ± 0.18	
African American	14.95		1.02 ± 0.16	
Latinx	19.63		1.04 ± 0.17	
Asian	27.10		1.07 ± 0.17	
Other or unknown	16.36		1.06 ± 0.15	
Adiposity				
BMI, kg/m^2	29.39 ± 6.48	0.03 ± 1.32	−0.05	0.51
Waist circumference, cm	98.65 ± 16.71*	−2.19 ± 4.97*	−0.12*	0.10*
Sagittal diameter, cm	24.69 ± 5.54*	−0.40 ± 2.23*	−0.12*	0.10*
Waist-to-hip ratio	0.93 ± 0.09*	0.003 ± −0.06*	−0.19*	<0.001*
Metabolic control				
Uric acid, mg/dL	6.11 ± 1.88	−0.13 ± 1.08	−0.04	0.53
GGT, U/L	37.34 ± 40.61	0.67 ± 35.08	−0.06	0.40
ALT, U/L	33.60 ± 20.18	2.17 ± 27.10	−0.02	0.79
HbA1c, %	5.91 ± 0.88	0.04 ± 0.42	−0.06	0.39
Insulin, mL U/L	19.23 ± 12.97	0.30 ± 11.05	−0.05	0.51
Glucose, mg/dL	97.11 ± 12.46	0.39 ± 8.17	−0.09	0.20
HOMA	4.74 ± 3.60	0.11 ± 3.54	−0.06	0.42
Lipids				
Triglycerides, mg/dL	110.4 ± 62.28	−2.11 ± 50.64	0.11	0.12
Total cholesterol, mg/dL	185.4 ± 36.0	3.85 ± 23.1	0.01	0.84
HDL-C, mg/dL	45.9 ± 12.3	1.53 ± 6.4	0.05	0.50
LDL-C, mg/dL	117.0 ± 29.1	3.10 ± 21.2	−0.03	0.68
ApoA1, mg/dL	148.0 ± 30.0*	3.21 ± 17.6*	0.03*	0.01*
ApoB-100, mg/dL	71.8 ± 19.3	1.32 ± 11.6	0.007	0.92
SSB consumption, fl oz	35.6 ± 27.1	−17.04 ± 28.9	0.06	0.41
Study assignment				
Intervention			1.08 ± 0.18	<0.01*
Control			1.02 ± 0.16	

[1] 1 fl oz = 29.6 mL. *statistical significance <0.05. ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; SSB, sugar-sweetened beverage; T/S, telomere over single copy gene.
[2] Change is defined as follow-up value − baseline value.

terol and apoA1 neared statistical significance for association with reduced attrition ($\rho = -0.14$; $P = 0.07$; and $\rho = -0.14$, $P = 0.05$, respectively) (**Table 4**). There was no association between LTL attrition rate and change in BMI over the follow-up period ($P = 0.37$) (Table 4).

In a multivariable analysis adjusting for participant's age, gender, and race/ethnicity and group assignment, variables that were independently associated with increases in LTL or slower rates of attrition were decreases in waist circumference (B = −0.27, $P = 0.03$), decreases in HDL cholesterol (B = −0.20, $P = 0.05$), and decreases in apoA1 (B = −0.09, $P = 0.01$) (**Table 5**).

Discussion

This exploratory study examined baseline LTL and 10-mo change in LTL in relation to changes in SSB consumption, waist circumference, weight, and metabolic change during a healthy beverage initiative intervention. This is the first study that we know of that has evaluated LTL changes in the context of an SSB intervention. We evaluated the relation between LTL and metabolic changes over 10 mo in a group of middle-aged adults, the majority with obesity or overweight. In the context of studies that suggest longer LTL may be a marker of psychological health and optimism (17–20), this is the first study to evaluate the role of LTL to predict behavioral response to an SSB intervention (reduction in SSB consumption).

There was no mean change in LTL and no association between change in SSB intake and change in LTL. Approximately half of participants showed LTL maintenance (within 5% of their baseline; 86 of 182, 47%), which is similar to other studies that have assessed short-term LTL change over a 1-y time period (27) and over 2.5 y (28). Our previous studies using 24-h dietary recalls have found cross-sectional associations between higher SSB consumption and shorter LTL (29, 30)

TABLE 2 Baseline metabolic markers, LTL with changes in SSB consumption over 6 months[1]

	SSB change over 6 months Mean ± SD or ρ (Spearman correlation)	*P* value
Demographics		
Age, y	−0.07	0.31
Gender		0.55
Female	−14.47 ± 27.14	
Male	−20.88 ± 31.03	
Race/ethnicity		0.47
Caucasian	−13.99 ± 19.28	
African American	−16.88 ± 29.81	
Latinx/Hispanic	−25.78 ± 31.22	
Asian	−14.38 ± 34.25	
Other or unknown	−15.88 ± 28.80	
Adiposity		
BMI, kg/m^2	−0.16*	0.04*
Waist circumference, cm	−0.14*	0.06*
Sagittal diameter, cm	−0.13	0.08
Waist-to-hip ratio	−0.08	0.26
Metabolic control		
Uric acid, mg/dL	−0.01	0.89
GGT, U/L	−0.10	0.15
ALT, U/L	−0.01	0.86
HbA1c, %	−0.09	0.22
Insulin, mL U/L	0.02	0.73
Glucose, mg/dL	−0.09	0.23
HOMA-IR	−0.04	0.60
Lipids		
Triglycerides, mg/dL	−0.09	0.24
Total cholesterol, mg/dL	0.11	0.14
HDL-C, mg/dL	0.04	0.60
LDL-C, mg/dL	−0.08	0.24
ApoA1, mg/dL	0.05	0.51
ApoB-100, mg/dL	−0.12*	0.10*
LTL (baseline) (T/S ratio)	−0.12*	0.10*

[1]*statistical significance <0.05. ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTL, leukocyte telomere length; SSB, sugar-sweetened beverage; leukocyte telomere length (measured by T/S ratio, telomere over single copy gene).

TABLE 3 Baseline adiposity, metabolic markers, and LTL in relation to SSB changes over 6 months: multivariable linear regression model[1]

	Unstandardized Beta/B (95% CI)	*P* value
Demographics		
Age	−0.27 (−0.72, 0.19)	0.25
Female	−7.82 (−16.35, 0.72)	0.59
Study assignment	−13.98 (−22.37, −5.58)*	<0.01*
Race/ethnicity		
Caucasian	1.0	
African American	−1.49 (−15.52, 12.53)	0.83
Latinx/Hispanic	−3.06 (−16.16, 10.04)	0.65
Asian	−1.08 (−12.30, 10.14)	0.85
Other/unknown	−1.21 (−14.68, 12.27)	0.86
Adiposity		
BMI, kg/m^2	−0.40 (−1.08, 0.27)	0.12
Lipids		
ApoB-100, mg/dL	−0.06 (−0.29, 0.17)	0.62
Baseline LTL (T/S ratio)	−29.67 (−57.82, −1.51)*	0.04*

[1]All variables in the table were included in the multivariable regression model. *statistical significance <0.05. Leukocyte telomere length (measured by T/S ratio, telomere over single copy gene); SSB, sugar-sweetened beverages.

and longitudinal associations between reductions in SSB consumption and LTL lengthening (31). It is possible that differences in the methods used (dietary recall compared with beverage frequency questionnaire) could explain the disparate findings. Alternatively, we purposively sampled a population with a high reported consumption of SSBs and we may have less variance in overall SSB consumption patterns than our previous studies.

However, slower attrition (or lengthening) was associated with decreases in waist circumference (B = −0.27, P = 0.03) and decreased apoA1 (B = −0.09, P = 0.01), as well as decreased HDL cholesterol (B = −0.20, P = 0.05) (Table 5). A number of cross-sectional studies have found shorter LTL to be associated with greater abdominal adiposity (32, 33) as did one of our previous longitudinal studies (34). Attenuated LTL loss or slowed aging is an important, underrecognized benefit of waist circumference loss. Furthermore, waist circumference loss is correlated with important metabolic changes and benefits, more so than loss of BMI (35). LTL is sensitive to inflammatory processes and reactive oxygen species damage and as such waist circumference changes may be more reflective of metabolic impact on LTL. The slower attrition patterns associated with decreases in HDL cholesterol and ApoA1, although seemingly counterintuitive, could be metabolic responses to the SSB intervention, which we speculate on below.

LTL as a predictor of response to an SSB intervention

Secondly, we asked whether having long telomeres may be a proxy factor for having a greater ability to benefit from an intervention, as suggested by several earlier studies.

Longer LTL was predictive of lower SSB consumption in our cohort over the follow-up, independently of whether they were assigned to the brief motivational intervention or not.

Other intervention studies have found that long LTL is associated with a better intervention/treatment effect, including studies that have focused on weight loss (15), reduction in metabolic markers such as fasting glucose (36), the impact of statins on cardiovascular disease (37), as well as studies that evaluated the role of selective serotonin reuptake inhibitors and other treatments of depression (38, 39). In other prospective studies, longer LTL has been found to be associated with slower progression of the metabolic syndrome (5) and reduced risk of new-onset diabetes mellitus (40). It is possible that any inflammatory or procytokine processes that shorten LTL may have an impact on mood and function, including impetus for behavioral and dietary change. Alternatively, longer baseline telomere length may be suggestive of a strong immune system and is associated with lower prevalence of clinical depression and depressive symptoms (17, 23).

A recent experimental study found that longer buccal telomere length was associated with activation in the amygdala and cuneus region of the brain related to an emotional cue, suggesting that telomere length predicts emotional brain activity and connectivity (41). Longer telomere length could be a crude proxy for a greater potential for learning.

TABLE 4 Change in metabolic markers and SSB consumption in relation to LTL percentage attrition[1]

	LTL percentage attrition, mean ± SD or Spearman ρ	*P* value
Demographics		
Age, y	−0.08	0.26
Gender		0.10*
Female	−1.17 ± 8.07	
Male	0.71 ± 8.22	
Race/ethnicity		0.69
Caucasian	−0.43 ± 7.46	
African American	0.25 ± 9.87	
Latinx/Hispanic	0.80 ± 8.27	
Asian	−0.56 ± 6.95	
Other or unknown	−1.88 ± 9.18	
Adiposity		
BMI, kg/m^2	−0.07	0.37
Waist circumference, cm	−0.17*	0.03*
Sagittal diameter, cm	−0.12	0.13
Waist-to-hip ratio	−0.08	0.29
Metabolic control		
Uric acid, mg/dL	−0.12	0.12
GGT, U/L	0.03	0.73
ALT, U/L	0.02	0.77
HbA1c, %	0.04	0.62
Insulin, mL U/L	−0.001	0.98
Glucose, mg/dL	−0.04	0.57
HOMA	−0.02	0.83
Lipids		
Triglycerides, mg/dL	0.08	0.27
Total cholesterol, mg/dL	−0.07	0.32
HDL-C, mg/dL	−0.14*	0.07*
LDL-C, mg/dL	−0.11	0.13
ApoA, mg/dL	−0.14*	0.05*
ApoB-100, mg/dL	−0.07	0.37
Change in SSB consumption, fl oz	0.10	0.22

[1]Percentage attrition is (LTL Follow-Up − TL Baseline) / TL Baseline × 100. 1 fl oz = 29.6 mL. *statistical significance <0.05. ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; LTL, leukocyte telomere length; SSB, sugar-sweetened beverage.

TABLE 5 Change in metabolic markers and leukocyte telomere length percentage attrition: multivariable linear regression model[1]

	Unstandardized Beta/B (95% CI)	*P* value
Demographics		
Age, y	−0.10 (−0.22, 0.02)	0.10
Female	−1.86 (−4.43, 0.71)	0.15
Race/ethnicity		
Caucasian	1.00	
African American	0.66 (−3.55, 4.87)	0.31
Latinx/Hispanic	1.08 (−2.95, 5.10)	0.53
Asian	−0.04 (−3.76, 3.29)	0.98
Other	−1.55 (−5.16, 2.98)	0.46
Group assignment	−2.48 (−5.02, 0.06)	0.06
Adiposity		
Waist circumference, cm	−0.27 (−0.52, −0.02)*	0.03*
Lipids		
HDL-C, mg/dL	−0.20 (−0.39, 0.002)*	0.05*
ApoA1, mg/dL	−0.09 (−0.16, −0.02)*	0.01*

[1]All variables in the table were included in the multivariable model with the exception of HDL and apoA1 protein, which were included in separate models due to collinearity. Percentage attrition is (TL Follow-Up − TL Baseline) / TL Baseline × 100. *-statistical significance <0.05. HDL-C, high-density lipoprotein cholesterol.

Further, additional studies are needed to assess the role that leukocyte and other telomere lengths could play to inform behavioral responses.

Consistency with the metabolic attrition hypothesis

The relation between telomere change and HDL and ApoA1 is worth some speculation. Our results may fit with the speculations made by Casagrande and Hau (42) on the role of telomere length attrition processes in the regulation of metabolic signaling and function. They hypothesize that in times of emergency, energy demands such as increased exercise, caloric restriction, or disease states, telomeres are shortened as a way to redirect energy to critical processes. For instance, increased apoA1 and HDL cholesterol in relation to accelerated LTL loss may signal increased energy demands related to the physiological stress of waist circumference loss in the context of SSB reduction. Alternatively, short-term intense stress exposure can increase HDL cholesterol in contrast with longer-term chronic stress exposures increasing cortisol, LDL, and triglycerides (43, 44). Previous studies have shown that in the context of active weight or adiposity loss, there is reduced lipoprotein synthesis with impaired VLDL-cholesterol catabolism resulting in decreased plasma HDL concentrations (45). It is possible that in the context of waist circumference loss due to declines in SSB intake, our participants were in the stage of active adiposity loss. Previous studies have also found reduced HDL concentrations in the context of SSB or fructose reduction (46). Alternatively, HDL and components such as apoA1, as part of the innate immune system, can also become proinflammatory or dysfunctional in the context of increased inflammation (47). Unfortunately, we did not assess changes in inflammatory markers.

Limitations

Future studies evaluating LTL in the context of SSB or other dietary interventions should assess inflammatory changes including C-reactive protein and α-1-acid glycoprotein and provide a more detailed assessment of dietary intake including total energy intake and overall diet quality. Whereas our study focused on heavy adult SSB consumers, future studies should also assess the impact of SSB interventions in children, adolescents, and among adults with varying amounts of consumption. Lastly, we conducted a number of statistical tests of association as an exploratory approach to understanding the relation between an SSB intervention and LTL changes. As such, our findings may be at risk of Type I error and all interpretation of our conclusions should take this into consideration.

Conclusions

Baseline LTL may be useful in predicting behavioral response for dietary interventions. In our study, longer baseline LTL predicted greater reported reductions in SSB intake. Abdominal weight loss, a significant finding of our SSB intervention, also paralleled attenuated declines in

LTL, emphasizing the important role of adiposity loss in the context of whole-body health.

Future studies with more comprehensive nutritional and inflammatory assessments will be necessary to evaluate how LTL, stressors, biomarkers, energy demands, and changes in these parameters affect long-term health.

Acknowledgments

The authors' responsibilities were as follows—JMW, ESE, CL, RHL, KS, and LAS: designed the research; AH and AEM: conducted the research; JL: did the laboratory analysis; JMW and LMJ: did the statistical analysis; and all authors: read and approved the final manuscript.

References

1. Frenck RW, Blackburn EH, Shannon KW. The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci USA 1998;95(10):5607–10.
2. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviv A, Spector TD. Obesity, cigarette smoking and telomere length in women. Lancet 2005;366(9486):662–4.
3. Gorenjak V, Petrelis AM, Stathopoulou MG, Visvikis-Siest S. Telomere length determinants in childhood. Clin Chem Lab Med 2020;58(2):162–77.
4. Wojcicki JM, Shiboski S, Heyman MB, Elwan D, Lin J, Blackburn E, Epel E. Telomere length change plateaus at 4 years of age in Latino children: associations with baseline length and maternal change. Mol Genet Genomics 2016;291(3):1379–89.
5. Révész D, Milaneschi Y, Verhoeven JE, Penninx BWJH. Telomere length as a marker of cellular aging is associated with prevalence and progression of metabolic syndrome. J Clin Endocrinol Metab 2014;99(12):4607–15.
6. Epel ES, Blackburn EH, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA 2004;101(49):17312–15.
7. Willeit P, Raschenberger J, Heydon EE, Tsimikas S, Hun M, Mayr A, Weger S, Witzlum JL, Butterworth AS, Willeit J, et al. Leucocyte telomere length and risk of type 2 diabetes mellitus: new prospective cohort study and literature-based meta-analysis. PLoS One 2014;9(11):e112483.
8. Zhao H, Han L, Chang D, Ye Y, Shen J, Daniel CR, Gu J, Chow W-H, Wu X. Social-demographics, health behaviors and telomere length in the Mexican American Mano a Mano Cohort. Oncotarget 2017;8(57):96553–67.
9. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systemic review and meta-analysis. BMJ 2014:349(7966):g4227.
10. Gielen M, Hageman GJ, Antoniou EE, Nordfjall K, Mangino M, Balasubramanyam M, de Meyer T, Hendricks AE, Gitay EJ, Hunt SC, et al. Body mass index is negatively associated with telomere length: a collaborative cross-sectional meta-analysis of 87 observational studies. Am J Clin Nutr 2018;108(3):453–75.
11. Canudas S, Becerra-Tomás N, Hernández-Alonso P, Galié S, Leung C, Crous-Bou M, De Vivo I, Gao Y, Gu Y, Meinilä J, et al. Mediterranean diet and telomere length: a systematic review and meta-analysis. Adv Nutr 2020;11(6):1544–54.
12. Wojcicki JM, Elwan D, Lin J, Blackburn E, Epel ES. Chronic obesity and incident hypertension in Latina women are associated with accelerated telomere length loss over a one year period. Metab Syndr Relat Disord 2018;16(6):262–6.
13. Mason AE, Hecht FM, Daubenmeier JJ, Sbarr DA, Lin J, Moran PJ, Schleiche SG, Acree M, Prather AA, Epel ES. Weight loss, weight-loss maintenance, and cellular aging in the Supporting Health Through Nutrition and Exercise (SHINE) Study. Psychosom Med 2018;80(7):609–19.
14. Carulli L, Anzivino C, Baldell E, Zenobii MF, Rocchi MBI, Bertolotti M. Telomere length elongation after weight loss intervention in obese adults. Mol Genet Metab 2016;118(2):138–42.
15. Garcia-Calzón S, Moleres A, Marcos A, Campoy C, Moreno LA, Azcona-Sanjulián MC, Martínez-González MA, Martínez JA, Zalba G, Marti A. Telomere length as a biomarker for adiposity changes after a multidisciplinary intervention in overweight/obese adolescents: the EVASYON Study. PLoS One 2014;9(2):e89828.
16. Morton JM, Garg T, Leva N. Association of laparoscopic gastric bypass surgery with telomere length in patients with obesity. JAMA Surg 2019;154(3):266–8.
17. Vakonaki E, Tsiminikaki K, Plaitis S, Fragkiadaki P, Tsoukalas D, Katsikantami I, Vaki G, Tzatzarakis MN, Spandidos DA, Tsatsakis AM. Common mental disorders and association with telomere length. Biomed Rep 2018;8(2):111–16.
18. Starnino L, Busque L, Tardif J-C, D'Antono B. Psychological profiles in the prediction of telomere length in healthy individuals. PLoS One 2016;11(10):e0165482.
19. Schutte NS, Palanisamy SKA, McFarlane JR. The relationship between positive psychological characteristics and longer telomeres. Psychol Health 2016;31(12):1466–80.
20. Ikeda A, Schwartz J, Peters JL, Baccarelli AA, Hoxba M, Dioni L, Spiro A, Sparrow D, Vokonas P, Kubzansky LD. Pessimistic orientation in relation to telomere length in older men: the VA Normative Aging Study. Psychoneuroendocrinology 2014;42:68–76.
21. Lucas T, Pierce J, Lumley MA, Granger DA, Lin J, Epel ES. Telomere length and procedural justice predict stress reactivity responses to unfair outcomes in African Americans. Psychoneuroendocrinology 2017;86: 104–9.
22. Epel ES, Hartman A, Jacobs LM, Leung C, Cohn MA, Jensen L, Ishkanian L, Wojcicki J, Mason AE, Lusting RH, et al. Association of a workplace sales ban on sugar-sweetened beverages with employee consumption of sugar-sweetened beverages and health. JAMA Intern Med 2020;180(1): 9–16.
23. Epel ES, Prather AA. Stress, telomeres, and psychopathology: toward a deeper understanding of a triad of early aging. Annu Rev Clin Psychol 2018;14(1):371–97.
24. Hendrick VE, Salva J, Comber DL, Flack KD, Estabrooks PA, Nsiah-Kumi P, Ortmeier S, Davy BM. Development of a brief questionnaire to assess habitual beverage intake (BEVQ-15): sugar-sweetened beverages and total beverage energy intake. J Acad Nutr Diet 2012;112(6):840–9.
25. Cawthon RM. Telomere measurement by quantitative PCR. Nucleic Acids Res 2002;30(10):e47.
26. Lin J, Epel E, Cheon J, Kroenke C, Sinclair E, Bigos M, Wolkowitz O, Mellon S, Blackburn E. Analyses and comparisons of telomerase activity and telomere length in human B and T cells: insights for epidemiology of telomere maintenance. J Immunol Methods 2010;352(1–2):71–80.
27. Puterman E, Lin J, Krauss J, Blackburn EH, Epel ES. Determinants of telomere attrition over one year in healthy older women: stress and health behaviors matter. Mol Psychiatry 2015;20(4):529–35.
28. Epel ES, Merkin SS, Cawthon R, Blackburn EH, Adler NE, Pletcher MJ, Seeman TE. The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men. Aging 2008;1(1):81–8.
29. Leung CW, Laraia BA, Needham BL, Rehkopf DH, Adler NE, Lin J, Blackburn EH. Soda and cell aging: associations between sugar-sweetened beverage consumption and leukocyte telomere length in healthy adults from the National Health and Nutrition Examination Surveys. Am J Public Health 2014;104(12):2425–31.
30. Wojcicki JM, Medrano R, Lin J, Epel E. Increased cellular aging by 3 years of age in Latino preschool children who consume more sugar sweetened beverages: a pilot study. Child Obes 2018;14(3):149–57.
31. Leung CW, Laraia BA, Coleman-Phox K, Bush NR, Lin J, Blackburn EH, Adler NE, Epel ES. Sugary beverage and food consumption, and leukocyte telomere length maintenance in pregnant women. Eur J Clin Nutr 2016;70(9):1086–8.
32. Lee M, Marin H, Firpo MA, Demerath EW. Inverse association between adiposity and telomere length: the Fels Longitudinal Study. Am J Hum Biol 2011;23(1):100–6.
33. Chen S, Yeh F, Lin J, Matsuguchi T, Blackburn E, Lee ET, Howard BV, Zhao J. Short leukocyte telomere length is associated with obesity in American Indians: the strong heart family study. Aging 2014;6(5):380–9.

34. Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. Telomere length trajectory and its determinants in persons with coronary artery disease: longitudinal findings from the Heart and Soul study. PLoS One 2010;5(1):e8612.
35. Rothberg AE, McEwen LN, Kraftson AT, Aijuni N, Fowler CE, Nay CK, Miller NM, Burant CF, Herman WH. Impact of weight loss on waist circumference and the components of the metabolic syndrome. BMJ Open Diabetes Res Care 2017;5(1):e000341.
36. Morell-Azana L, Ojeda-Rodríguez A, Azcona-SanJulián MC, Zalba G, Marti A. Associations of telomere length with anthropometric and glucose changes after a lifestyle intervention in abdominal obese children. Nutr Metab Cardiovasc Dis 2020;30(4):694–700.
37. Brouilette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ; West of Scotland Coronary Prevention Study Group. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. Lancet 2007;369(9556):107–14.
38. Hough CM, Bersani FS, Mellon SH, Epel ES, Reus VI, Lindqvist D, Lin J, Mahan L, Rosser R, Burke H, et al. Leukocyte telomere length predicts SSRI response in major depressive disorder: a preliminary report. Mol Neuropsychiatry 2016;2(2):88–96.
39. Ragson N, Lin KW, Lin J, Epel E, Blackburn E. Telomere length as a predictor of response to Pioglitazone in patients with unremitted depression: a preliminary study. Transl Psychiatry 2016;6(1):e709.
40. Verhulst S, Dalgård C, Labat C, Kark JD, Kimura M, Christensen K, Toupance S, Aviv A, Kyvik KO, Benetos A. A short leucocyte telomere length is associated with development of insulin resistance. Diabetologia 2016;59(6):1258–65.
41. Powell TR, De Jong S, Breen G, Lewis CM, Dima D. Telomere length as a predictor of emotional processing in the brain. Hum Brain Mapp 2019;40(6):1750–9.
42. Casagrande S, Hau M. Telomere attrition: metabolic regulation and signaling function. Biol Lett 2019;15(3):20180885.
43. Steptoe A, Brydon L. Associations between acute lipid stress responses and fasting lipid levels 3 years later. Health Psychol 2005;24(6):601–7.
44. Buitenwerf E, Kerstens MN, Links TP, Kema IP, Dullart RPF. High-density lipoproteins and adrenal steroidogenesis: a population-based study. J Clin Lipidol 2017;11(2):469–76.
45. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992;56(2):320–8.
46. Gugliucci A, Lustig RH, Caccavello R, Erkin-Cakmak A, Noworolski SM, Tai VW, Wen MJ, Mulligan K, Schwarz J-M. Short term isocaloric fructose restriction lowers apoC-III and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome. Atherosclerosis 2016;253;171–7.
47. Bindu GH, Rao VS, Kakkar VV. Friend turns foe: transformation of anti-inflammatory HDL to proinflammatory HDL during acute-phase response. Cholesterol 2011;274629.