Longitudinal Associations Between Metabolic Syndrome Components and Telomere Shortening

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Context: Deterioration of metabolic syndrome (MetS) has been associated with short telomere length (TL). Large-scale longitudinal studies with repeated measures of MetS and TL are lacking.

Objectives: We examined whether baseline MetS components predict TL over time, and whether deteriorations in MetS parallel telomere attrition.

Design and Setting: Participants were part of The Netherlands Study of Depression and Anxiety, an ongoing prospective cohort study.

Participants: This study included 1808 participants age 18–65 years.

Main Outcome Measures: Leukocyte TL (using qPCR) and MetS components (waist circumference, triglycerides, high-density lipoprotein [HDL] cholesterol, systolic blood pressure, and fasting glucose) were determined at baseline and after 6 years. Generalized estimated equation models were used to examine the associations between baseline MetS and TL over time, and linear regressions were used to associate 6-year changes in both MetS components and TL, while adjusting for sociodemographic and lifestyle factors.

Results: Higher baseline waist circumference (B = −29.7; $P = .006$) and glucose (B = −26.4; $P = .02$), and lower HDL (B = 25.5; $P = .03$) were consistently associated with shorter TL over followup. Greater 6-year increase in waist circumference was associated with larger telomere attrition (B = −41.8; $P = .01$), and similar but nonsignificant associations were observed for larger increase in triglycerides and glucose levels.

Conclusions: Metabolic dysregulations are associated with shorter telomeres over two time points. In particular, increasing abdominal adiposity is accompanied by accelerated telomere attrition. Future studies should elucidate underlying mechanisms of this bidirectional relationship and investigate whether targeting obesity may reduce telomere attrition to prevent further deterioration toward cardiovascular and aging-related complications. **(*J Clin Endocrinol Metab* 100: 3050–3059, 2015)**

Metabolic syndrome (MetS) is a constellation of interrelated risk factors (ie, abdominal obesity, dyslipidemia including low high-density lipoprotein [HDL] cholesterol and high triglycerides, hypertension, and hyperglycemia) for aging-related conditions such as cardiovascular diseases and diabetes (1). Mean leukocyte telomere length (TL) is considered a marker for cellular aging (2, 3). Telomeres are DNA-protein complexes that protect chromosomal stability (4). Cells lose telomeric repeats during each cell division, which eventually leads to replicative cell senescence or apoptosis (5–7). Normal telomeric maintenance requires the cellular enzyme telomer-

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Abbreviations: ATC, Anatomical Therapeutic Chemical; bp, base pairs; CV, coefficient of variation; GEE, generalized estimating equations; HDL, high-density lipoprotein; MetS, metabolic syndrome; NESDA, The Netherlands Study of Depression and Anxiety; SBP, systolic blood pressure; TL, telomere length; Y0, baseline; Y6, 6-year followup.

ase, which synthesizes telomeric DNA repeats, thereby preserving healthy cell function (8). Although approximately 70% of TL is explained by genetic factors (9), telomere attrition is accelerated by cumulative exposure to oxidative stress, proinflammatory mediators, and endocrine and autonomic dysfunction (10–13). Short TL has been associated with advancing chronological age (14) and with the onset of various aging-related diseases such as cardiovascular diseases, diabetes, cancer, and dementia, and even premature death (15–19).

MetS and its separate components were shown to be associated with shorter TL cross sectionally (20–25), with inflammation and oxidative stress as potential mediators (12, 26). A limited number of longitudinal studies has examined associations between MetS dysregulations and TL, showing that short baseline TL is associated with worse metabolic outcomes at followup, or vice versa, baseline MetS components predict a higher TL attrition rate. For instance, one large-scale cohort study (N = 8074) reported that baseline MetS dysregulations were associated with short TL after a 7-year followup (27). Conversely, a study in 2721 elderly participants reported that short baseline TL was associated with 7-year changes in adiposity measures, but did not have any information about the other MetS components (28). In our previous study within this topic, we only had baseline TL available and examined the opposite direction of this relationship: the associations between baseline TL and MetS at two time points (N = 2842) (20). We found that short baseline TL was associated with lower HDL cholesterol, and higher waist circumference, triglycerides, and glucose, and a higher overall number of MetS dysregulations both at baseline and at the 6-year followup (20). Only a small cohort study (N = 50) with repeated measurements of both MetS and TL reported that TL attrition was correlated with increases in insulin resistance and body mass index (29). Few experimental weight-loss studies have also measured TL in a subsample at multiple time points, and some have seen parallel telomere lengthening (30, 31), but others have not (32). Until now large-scale studies with repeated measures of all MetS components, TL, and relevant confounding factors have not been available. Whether changes in metabolic components truly parallel change in TL over time remains to be established.

The present study aimed to shed light on the longitudinal associations between MetS dysregulations and TL changes in a large sample from The Netherlands Study of Depression and Anxiety (NESDA), for which measurements of MetS and TL were performed at baseline and at 6-year followup. We examined whether baseline MetS components were consistently associated with TL over the followup, and correlated 6-year changes in MetS components with the 6-year change in TL. We hypothesized that, over time, worse baseline metabolic status would be associated with shorter TL and larger metabolic deterioration would be accompanied by higher 6-year telomere attrition.

Materials and Methods

Study population

Participants were from NESDA, a large, ongoing longitudinal cohort study among 2981 adults (age 18–65 y), as described elsewhere (33). Briefly, respondents were recruited between September 2004 and February 2007 from community, primary care, and specialized mental health care, including persons with a lifetime diagnosis of a depressive and/or anxiety disorder (74%) and healthy controls (26%). Baseline (Y0) data collection consisted of a medical examination, a blood draw, self-report questionnaires, and a detailed interview. Medication use in the previous month was derived from medication container inspection and interview, and reported medications were subsequently coded with the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. Of these participants, 2256 subjects (75.7%) were evaluated again after 6 years (Y6). Of the entire cohort, 1808 subjects (60.7%) had complete data on TL on both time points and MetS components at baseline, and were included in the first part of our analyses. Compared with those with complete data (N = 1808), those who dropped out (N = 1173) had longer TL at baseline (5518 vs 5437 bp; $P = .001$), were slightly younger (40.8 vs 42.6 y; $P < .001$), had less educational years (11.7 vs 12.5 y; $P < .001$), were less often Northern European (38.6 vs 61.4%; $P < .001$), less physical activity (3439 vs 3733 1000 metabolic equivalent [MET] min; $P = .009$), and were more often nondrinker (46.6 vs 53.4%; $P < .001$) or never smoker (37.1 vs 62.9%; $P = .001$), but were not different regarding sex and MetS components. The research protocol was approved by the ethical committee of participating universities and all respondents provided written informed consent.

Measurement of TL

TL was determined at baseline and 6 years. A more extensive description of TL assessment in our study has been reported before (20, 34). In short, DNA was prepared from fasting blood samples and stored in a −20°C freezer afterward. Subsequently, in 2012 ($N_{Y0} = 2936$) and 2014 ($N_{Y6} = 1883$), TL was determined at the laboratories of Telomere Diagnostics, Inc. (Menlo Park, CA) and University of California–San Francisco using qPCR (35). Telomere sequence copy number in each patient's sample (T) was compared with a single-copy gene copy number (S), relative to a reference sample. The resulting T/S ratio is proportional to mean TL (35). The reliability of the assays was adequate at baseline and followup: interassay coefficient of variation (CV) was sufficiently low ($CV_{Y0} = 4.6\%$; $CV_{Y6} = 3.0\%$). The follow-up T/S ratios were adjusted relative to the baseline visit samples for systematic differences caused by different reference samples, by rerunning and comparing various samples from baseline sample plates (N = 226, up to eight samples from each of the baseline visit plate), together with follow-up samples. As previously described (11, 20), we converted T/S ratios to base

pairs with the following formula: base pairs = 3274 + 2413 × ([T/S − 0.0545]/1.16). DNA samples were deidentified and the labs that performed the assays were blind to all the other measurements.

MetS components

All five MetS components were measured at baseline and 6 years. Waist circumference was measured with a tape measure at the central point between the lowest front rib and the highest front point of the pelvis, over light clothing. HDL cholesterol, triglycerides, and glucose levels were determined from fasting blood samples using routine standardized laboratorial methods. To incorporate information on medication use into the continuous MetS measures, adjustments were made as performed and described before (20, 36–38). According to the standards of medical care in diabetes (39), antidiabetic medication aims to lower the fasting glucose level to less than 7.0 mmol/L. Therefore, for persons using antidiabetic medication (N_{Y0} = 55; N_{Y6} = 83; ATC-code A10) when glucose level was less than 7.0 mmol/L, a value of 7.0 mmol/L was assigned. According to the average decline in triglycerides and increases in HDL cholesterol in fibrate trials, 0.10 mmol/L was subtracted from the HDL cholesterol level and 0.67 mmol/L was added to the triglyceride level of persons using fibrates (N_{Y0} = 4; N_{Y6} = 5; ATC-code C10AB) (40). Average systolic blood pressure (BP) (SBP) was calculated from two measurements during supine rest on the right arm with the Omron M4-I, HEM 752A (Omron, Healthcare Europe BV). For persons using antihypertensive medication (N_{Y0} = 262; N_{Y6} = 386; ATC-codes C02-C03/C07-C09), 10 mm Hg was added to the SBP according to the average decline in BP in antihypertensive trials (41).

We calculated a summarizing variable (range, 0–5), reflecting MetS severity (20), from the number of MetS dysregulations: 1) abdominal obesity: waist circumference at least 102 cm in men and at least 88 cm in women; 2) hypertriglyceridemia: triglycerides at least 1.7 mmol/L or medication for hypertriglyceridemia; 3) low HDL cholesterol less than 1.03 mmol/L in men and less than 1.30 mmol/L in women or medication for reduced HDL cholesterol; 4) hypertension: BP: systolic at least 130 and/or diastolic at least 85 mm Hg or antihypertensive medication; 5) hyperglycemia: fasting plasma glucose at least 5.6 mmol/L or antidiabetic medication (1).

Covariates

All covariates were recorded at baseline and 6-year followup. Sociodemographic factors included sex, age, years of attained education, and Northern-European ancestry. Lifestyle variables included alcohol consumption (no drinker, mild–moderate drinker [1–14 drinks/wk for women or 1–21 drinks/wk for men], heavy drinker [> 14 drinks/wk for women or > 21 drinks/wk for men), smoking (never, former, current), and physical activity [International Physical Activity Questionnaire (42), expressed in MET min in the past wk]. Persons with a depressive or anxiety disorder were oversampled in our study, and our earlier research has indicated that depression and anxiety disorders—but not antidepressant medication—are associated both with shorter TL (34, 43) and with MetS (38). Therefore, we considered the presence of a current (6-mo recency) depressive and/or anxiety disorder as a covariate.

Statistical analyses

Sample characteristics were described as means and SDs, or percentages. For nonnormally distributed factors the median and interquartile range were calculated. Differences between baseline and year 6 were determined with χ^2 test for categorical or dichotomous factors. For continuous factors this was done with paired *t* tests, or Wilcoxon signed-rank tests for nonnormally distributed factors.

Associations between baseline MetS components (per SD increase) and TL at year 0 and year 6 were analyzed using generalized estimating equations (GEE) with an exchangeable correlation structure. This takes into account the within-person correlations when examining multiple observations per subject and can handle missing observations. In separate GEE models with baseline and follow-up TL as the outcome, each baseline MetS component (or the total number of MetS dysregulations) was initially entered as predictor together with the main term for time (coded as 0 = baseline vs 1 = followup), baseline age, sex, race, and time-varying education, smoking, alcohol, and physical activity. Subsequently, MetS-by-time interaction terms were added to these models to investigate whether there is a differential slope of telomere shortening according to baseline MetS components. Sensitivity analyses were then performed to test the influence of psychopathology (depressive and/or anxiety disorders) on the association between baseline MetS dysregulations and TL. MetS-by-psychopathology interaction terms were entered into the models (including the main terms) to test whether the associations between baseline MetS components and TL were different across persons with psychopathology or healthy subjects.

Next, we calculated change scores of MetS components and TL by subtracting baseline values from follow-up values for all the participants with available MetS and TL at both time points. The total sample size ranged from 1702 for waist circumference to 1799 for triglycerides. To examine the importance of covariates for TL change, we conducted separate linear regression analyses including each baseline covariate as a predictor and TL change as the outcome. Then, we investigated the associations between changes in MetS components and TL change (both per SD increase in change) with linear regression analyses. Changes in MetS components or changes in the number of MetS dysregulations were entered into separate models as predictors, and 6-year TL change as the outcome, while adjusting for baseline covariates. In addition, we corrected each model for baseline TL, and baseline values of MetS components or the baseline number of MetS dysregulations. All analyses were conducted using SPSS version 20.0 (IBM). Statistical significance level was set at $P < .05$, two tailed.

Results

Table 1 shows the sample characteristics at baseline and followup. MetS severity increased over time, as shown by the larger number of MetS dysregulations and the deteriorations in the separate MetS components. Only SBP decreased slightly during followup. Overall, mean TL decreased from baseline to followup ($P < .001$), and the two measurement of TL were highly correlated ($r = 0.481$; $P < .001$).

Table 1. Sample Characteristics at Year 0 and Year 6 (n = 1808)

Sample Characteristics	Year 0	Year 6	P[c]
Demographics			
Age, y, mean (SD)	42.6 (12.9)	48.6 (12.9)	<.001
Female, %	65.6	65.6	
Education, y, mean (SD)	12.5 (3.3)	12.9 (3.3)	<.001
Northern European ancestry, %	95.9	95.9	
Lifestyle factors			
Smoking status, n (%)			<.001
Never	525 (29.0)	537 (29.7)	
Former	642 (35.5)	757 (41.9)	
Current	641 (35.5)	511 (28.3)	
Alcohol consumption, n (%)			<.001
Nondrinker	270 (14.9)	308 (17.0)	
Mild–moderate drinker	1308 (72.3)	1256 (69.5)	
Heavy drinker	230 (12.7)	169 (9.3)	
Physical activity, ×1000 MET-min/wk, M (IQR)	3.7 (3.1)	3.9 (3.5)	.182
MetS (components)			
Waist circumference, cm, mean (SD)	89.0 (14.1)	92.6 (13.9)	<.001
Triglycerides, mmol/L, M (IQR)	1.10 (0.79)	1.10 (0.80)	.002
HDL cholesterol, mmol/L, mean (SD)	1.63 (0.44)	1.56 (0.44)	<.001
SBP, mm Hg, mean (SD)	136.3 (19.8)	135.4 (20.2)	.001
Glucose, mmol/L, M (IQR)	5.00 (0.80)	5.38 (0.80)	<.001
No. of MetS abnormalities, M (IQR)[a]	1.0 (2.0)	2.0 (2.0)	<.001
0 abnormalities, n (%)	487 (26.9)	405 (22.4)	
1 abnormalities, n (%)	567 (31.4)	473 (26.2)	
2 abnormalities, n (%)	378 (20.9)	367 (20.3)	
3 abnormalities, n (%)[b]	223 (12.3)	281 (15.5)	
4 abnormalities, n (%)	113 (6.3)	145 (8.0)	
5 abnormalities, n (%)	40 (2.2)	87 (4.8)	
Telomere length			
T/S ratio, mean (SD)	1.09 (0.29)	1.07 (0.21)	<.001
Base pairs, mean (SD)	5437 (602)	5384 (432)	<.001

Abbreviations: IQR, interquartile range (for nonnormally distributed factors); M, median (for nonnormally distributed factors).

[a] Abnormalities defined as: 1) waist circumference > 102 cm (men) and > 88 cm (women); 2) triglycerides > 1.7 mmol/L (150 mg/dL) or medication for hypertriglyceridemia; 3) HDL cholesterol < 1.03 mmol/L (40 mg/dL, men) and < 1.30 mmol/L (50 mg/dL, women) or medication for reduced HDL cholesterol; 4) BP: systolic > 130 and/or diastolic > 85 mm Hg or antihypertensive; 5) fasting plasma glucose > 5.6 mmol/L (100 mg/dL) or antidiabetic medication.

[b] MetS defined as having ≥ three abnormalities.

[c] For categorical or dichotomous factors χ^2 tests were used; for continuous factors paired *t* tests were used or Wilcoxon signed-rank tests when nonnormally distributed.

Baseline MetS components and TL at two time points

Associations between baseline MetS dysregulations and repeatedly measured TL are shown in Table 2. First, lower baseline HDL (B = 25.45; SE = 12.0; $P = .03$) and higher waist circumference (B = −29.68; SE = 10.9; $P = .006$) and glucose (B = −26.38; SE = 11.0; $P = .02$) were consistently associated with short TL across the entire followup. A higher number of MetS dysregulations was associated to shorter TL across the entire followup, although this association was not significant (B = −15.63; SE = 8.51; $P = .07$). Next, MetS-by-time interaction terms were added to the models and found to be nonsignificant (Table 2), indicating no substantial difference in slopes of TL change over time according to baseline MetS levels. The overall picture emerging from these analyses is that baseline MetS dysregulations—especially high waist circumference, high glucose and low HDL—are consistently associated with shorter TL across the entire followup, and this relationship remains constant over time. These associations were not altered by incorporation of information on medication use (antidiabetics, fibrates, antihypertensives) within the levels of glucose, HDL cholesterol, triglycerides, and BP as findings were consistent when we did not incorporate this information. To visually illustrate the relationships between baseline MetS and longitudinal TL, we plotted the estimated means from the GEE models of TL at both time points according to different baseline MetS values (Figure 1).

Finally, in sensitivity analyses, MetS-by-psychopathology interaction terms that were entered in GEE models (including also the main terms) and were found to be nonsignificant (all $P < .10$), illustrating that the associations between baseline MetS dysregulations and TL change over

Table 2. Baseline MetS Components (per SD increase) as Predictors for TL at Year 0 and Year 6 (n = 1808)

	Model With Time			Model With Time + Time Tnteraction		
Baseline MetS Component	**B**	**SE**	***P*[b]**	**B**	**SE**	***P*[b]**
Waist circumference[a]	−29.68	10.86	.006	−46.49	24.84	.06
Time	−59.16	13.41	<.001	−59.04	13.40	<.001
Time × waist circumference				11.56	13.41	.39
Triglycerides[a]	−17.10	10.24	.10	−46.51	24.86	.06
Time	−59.21	13.42	<.001	−58.73	13.41	<.001
Time × triglycerides				20.22	12.97	.12
HDL cholesterol[a]	25.45	11.95	.03	25.16	26.78	.35
Time	−59.22	13.41	<.001	−59.23	13.41	<.001
Time × HDL cholesterol				0.19	14.00	.99
SBP[a]	15.33	11.75	.19	0.40	24.86	.99
Time	−59.98	13.43	<.001	−60.09	13.43	<.001
Time × SBP				10.15	12.69	.42
Fasting glucose[a]	−26.38	11.00	.02	−59.81	23.96	.01
Time	−59.61	13.42	<.001	−59.01	13.37	<.001
Time × fasting glucose				22.73	13.11	.08
No. MetS dysregulations[a]	−16.21	8.50	.06	−31.38	20.04	.12
Time	−59.15	13.41	<.001	−74.23	20.99	<.001
Time × No. MetS dysregulations				10.44	10.81	.33

[a] SD waist circumference, 14.06; SD triglycerides, 0.86; SD HDL, 0.44; SD SBP, 19.84; SD glucose, 0.91.

[b] Generalized estimated equation models adjusted for baseline age, sex and race, and for time-varying education, smoking, alcohol, and physical activity.

time were not different for those with and without a depressive and/or anxiety disorder.

Changes in MetS components and change in TL

Over the 6-year followup the absolute TL change was −50bp (SD = 536), and the relative TL change was −0.22% (SD = 9.31). Of all subjects, 27% had greater than 5% telomere shortening over time, 26% had greater than 5% telomere lengthening, and 47% had a relatively stable TL (ie, between 5% shortening and 5% lengthening). Longer baseline TL (B = −0.69; SE = 0.02; $P < .001$) and older age (B = −7.86; SE = 0.69; $P < .001$) were significant and independent predictors of 6-year TL attrition. Other sociodemographic and lifestyle factors were not associated significantly with TL change.

Fully adjusted associations between 6-year change in MetS components (per SD increase in change) or the number of MetS dysregulations and 6-year change in TL are shown in Table 3. Increasing waist circumference during 6-year followup was associated with larger 6-year telomere attrition (B = −41.8; SE = 16.4; $P = .01$). For other changes in MetS dysregulations, although going in a similar direction, the associations with TL change were nonsignificant. Figure 2 shows that, compared with the first quintile of 6-year change in waist, the third, fourth, and fifth quintiles of waist change (ie, > 2-cm waist gain) were associated with greater 6-year TL attrition. Mean TL attrition was comparable in the last three quintiles above the 2-cm waist gain, although there was a lower attrition in the fourth quintile compared with the third and fifth quintiles.

Discussion

This large-scale study investigated the longitudinal associations between MetS dysregulations and TL over a 6-year period. We found that higher baseline waist circumference and blood glucose, and lower HDL cholesterol were consistently associated with shorter TL throughout the entire followup. Furthermore, we found that greater 6-year increase in waist circumference was associated with greater 6-year telomere attrition. Similar, but nonsignificant trends were observed between increases in triglycerides and in glucose and telomere attrition. To our knowledge, this is the first large-scale study with repeated measurements of MetS and TL, showing the parallel between metabolic deterioration and TL changes.

We found that subjects had a mean telomere attrition rate of approximately 8 bp per year, a lower rate than described before in a systematic review, where yearly telomere attrition rate was 32–46 bp in longitudinal studies, and 20–30 bp in the larger cross-sectional studies. Possible explanations for this might be the relatively young and somatically healthy sample in our study, as most of the longitudinal studies consisted of small samples of elderly subjects with higher morbidity and mortality rates during followup. However, many studies reported steady or elongated telomeres in a subset of their sample as well, displaying similar variance in TL change to our sample (14). However, the longitudinal studies in this review were conducted within smaller samples (N = 75–510), and in older populations

(> 50 y), whereas our sample consisted of relatively young individuals (14). In line with earlier research, we found that the strongest predictors of larger telomere attrition rate over time were higher baseline TL and older age, whereas sex, education, and lifestyle did not influence the attrition rate significantly (44).

Overall, findings from the present study support the notion that TL and metabolic status go hand in hand.

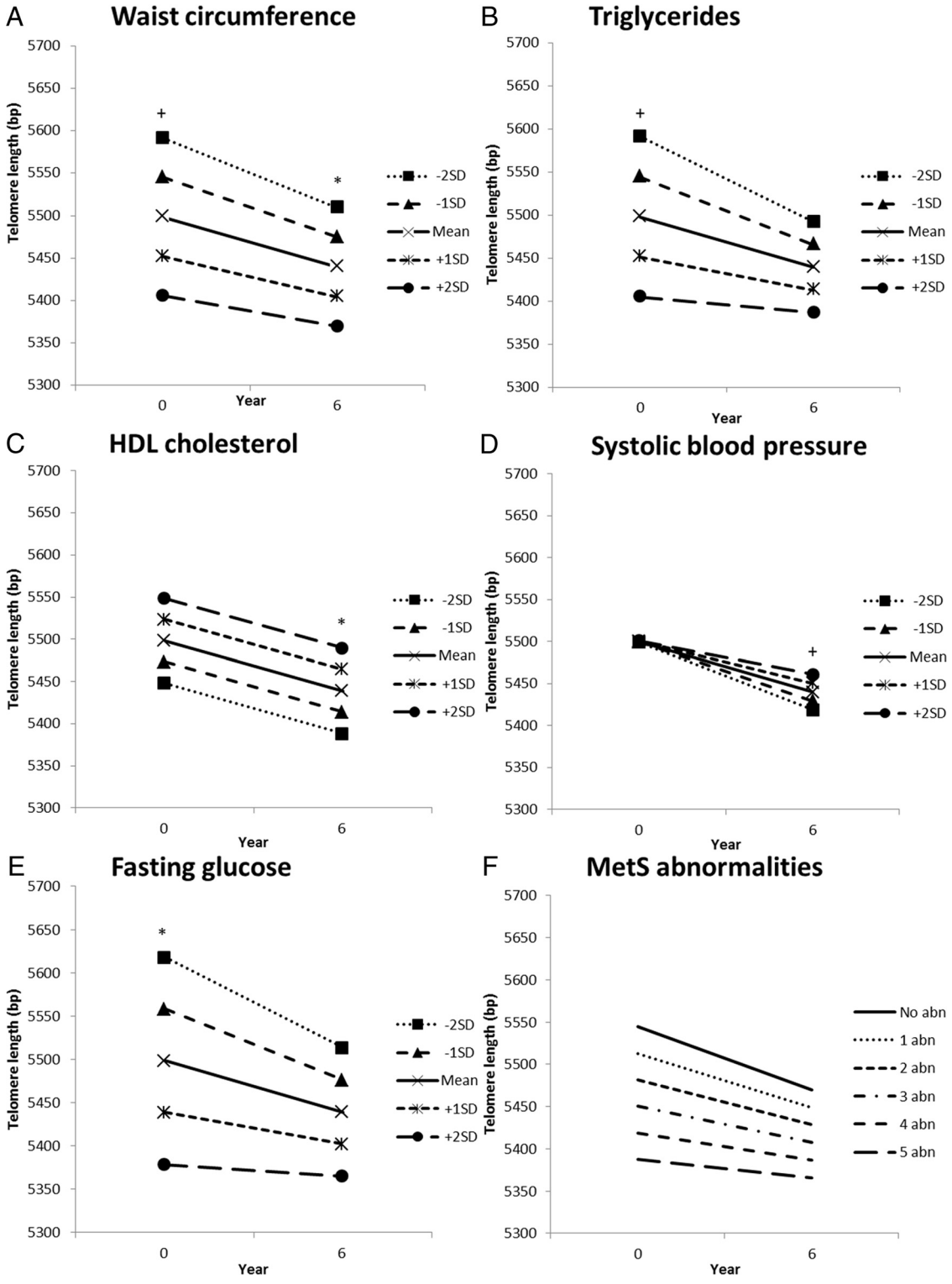

Figure 1. Estimated mean TL at Y0 and Y6 for the baseline levels of A, waist circumference; B, triglycerides; C, HDL cholesterol; D, SBP; E, fasting glucose; and F, number of MetS dysregulations. Means were estimated from GEE models (Table 2) including baseline MetS components, time, MetS components-by-time interactions, baseline age, sex, and race, and time-varying education, smoking, alcohol, and physical activity. From the same model we derived the association between continuous baseline MetS components and TL at baseline and at 6-year followup; *, $P < .05$; +, $P < .10$.

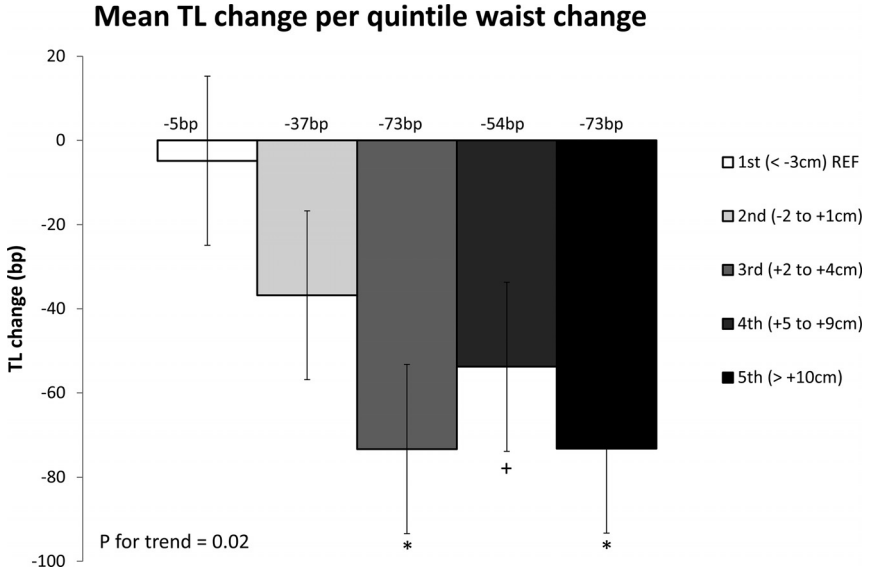

Figure 2. Associations (mean differences and SE bars) between 6-year change in waist circumference (per quintile change, lowest quintiles is the reference) and 6-year change in TL, adjusted for baseline age, sex, education, race, smoking, alcohol, physical activity, baseline TL, and baseline MetS component (N = 1702). *, $P < .05$; +, $P < .10$.

Waist circumference, blood glucose, and HDL cholesterol measured at baseline were associated with longitudinal trajectories of TL over 6 years. Consistently, a previous study by Huzen et al (27) showed that waist-to-hip-ratio, glucose, and HDL cholesterol were independently associated with telomere dynamics over a followup of similar length. More interestingly, the present findings showed that an increase over time, particularly in waist circumference, and to a lesser extent but not significantly in triglycerides and glucose, parallel telomere shortening over the same time span. Until now, only one small-scale study (N = 50) reported that a higher telomere shortening rate was correlated with increases in body mass index and insulin resistance (29). However, within our current findings we do not see a linear increase in telomere attrition with increased waist circumference because the fourth quintile of waist increase is associated with less telomere attrition than the fifth quintile. Potentially, there might be a floor effect of telomeric attrition when a certain threshold of adipocyte size is reached in cells (ie, adipocytes overflow) (45, 46), and simultaneously, compensatory mechanisms may be counterbalancing the attrition rate.

The present results strengthen the hypothesis of a link between telomere biology and MetS dysregulations, in particular abdominal adiposity, as a precursor of cardiovascular diseases, in line with the accumulating research (20, 28). The question remains how MetS components are associated with short TL. Adipose tissue, especially in the visceral domain, has been considered not only as a simple energy depository tissue, but also as an active endocrine organ (47, 48). Intriguingly, significant associations in adipocytes were found between large cell size and short TL (49). One explanatory hypothesis in this field is the so-called adipocyte overflow hypothesis, which suggests that when adipocytes enlarge, they reach their fat storage capacities, causing an overflow of fatty acids into sites such as the liver and muscle (50). These fatty acids not only promote deteriorations of other MetS components (eg, dyslipidemia, insulin resistance), but they also increase systemic inflammation and oxidative stress, both catalysts of telomeric attrition (47, 50–52). Our current findings support the earlier proposed concept that TL is the canary in the coal mine, displaying the accumulations of metabolic dysregulations and physiological dis-

Table 3. Six-Year Changes in MetS components (increase per SD) and the Number of MetS Dysregulations Associated With 6-Year Change in TL in Base Pairs (Year 6 Minus Year 0)

		Model 1[b]			Model 2[d]		
Six-Year Change	**N**	**B**	**SE**	***P*[c]**	**B**	**SE**	***P*[c]**
Δ Waist circumference[a]	1702	−39.83	16.17	.01	−41.84	16.39	.01
Δ Triglycerides[a]	1799	−14.12	8.65	.10	−12.94	8.75	.14
Δ HDL cholesterol[a]	1798	2.52	13.24	.85	4.08	13.47	.76
Δ SBP[a]	1707	6.10	12.98	.64	7.72	13.27	.56
Δ Fasting glucose[a]	1785	−16.38	9.72	.09	−16.31	9.85	.10
Δ No. MetS dysregulations	1758	−8.95	8.45	.29	−9.23	8.64	.29

[a] SD waist circumference, 14.06; SD triglycerides, 0.86; SD HDL, 0.44; SD SBP, 19.84; SD glucose, 0.91.

[b] Adjusted for baseline age, baseline TL, and baseline MetS component.

[c] Linear regression models.

[d] Additional adjustment for baseline sex, education, race, smoking, alcohol, and physical activity.

turbances such as inflammation, autonomic dysregulations, oxidative damage, and hormonal imbalances (11, 53).

Strengths of the current study were its large sample size and the repeated measurements of MetS, TL, and all covariates. Moreover, TL has been measured reliably with qPCR and interassay CVs were sufficiently low. However, a limitation was that TL was measured only in leukocytes, whereas the lymphocyte subsets vary in TL and telomere attrition rates, and TL changes might have been caused by redistributions of cell types (54, 55). Besides, even though qPCR is currently the only high-throughput strategy available, one might argue that it measures the mean bulk TL instead of the amount of short telomeres in single cells (56). Moreover, as described earlier, TL at baseline and 6 years was measured separately in two different labs. Although the assay conditions and the data analysis methods were the same, different reference standard DNA samples were used to calculate T and S concentrations. We adjusted this difference by rerunning 226 baseline samples together with the 6-year samples. However, we cannot officially rule out the possibility that adjustments do not fully correct the systematic difference. At last, telomerase activity and dietary intake were not recorded in this study.

Future therapeutic interventions in subjects with MetS should not only aim for abdominal fat reduction, but should also target broader improvements in physiology, ie, reduced inflammation and oxidative stress, and telomere lengthening. For instance, the few weight-loss studies that aimed to improve metabolic outcomes showed parallel telomere lengthening in adolescents (30) or elderly (31), although other studies have not observed any effects on TL (32). As adipose tissue hypertrophy and overflow is primarily due to metabolic oversupply (ie, high caloric intake and low physical activity) interventions should create metabolic undersupply (ie, caloric restriction and increased physical activity) to decelerate telomere attrition and to promote healthy aging (51, 52).

To conclude, baseline MetS components (waist circumference, glucose, and HDL cholesterol) were prospectively associated with TL over a 6-year follow-up period. Greater 6-year increase in waist circumference was associated with larger telomere attrition. Results from our previous study showed that, the other way around, baseline TL was associated with a higher metabolic risk status and with less favorable trajectories of metabolic outcomes over time. Taken together, these findings portrait a relationship between MetS and TL that can be best described as a process whereby MetS dysregulations, in particular abdominal adiposity, and TL interact to cause a progressive downward spiral. To our knowledge, this is the first large-scale study that showed that metabolic deterioration runs parallel to telomere attrition. Future well-designed multifaceted interventions studies should take into account this bidirectional relationship, and investigate whether targeting obesity may reduce, arrest, or even reverse telomere attrition to prevent further deterioration toward cardiovascular and aging-related complications.

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