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Leukocyte Telomere Length and Carotid Artery Intimal Medial Thickness

The Framingham Heart Study

Christopher J. O'Donnell, Serkalem Demissie, Masayuki Kimura, Daniel Levy, Jeffery P. Gardner, Charles White, Ralph B. D'Agostino, Philip A. Wolf, Joseph Polak, L. Adrienne Cupples, Abraham Aviv

Background and Purpose—Leukocyte telomere length (LTL) is relatively short in individuals who have evidence of cardiovascular disease. The purpose of this study was to examine the link between LTL and the predisposition to atherosclerosis, as determined by carotid artery intimal medial thickness (IMT) in participants of the Framingham Offspring Study.

Methods and Results—LTL was assayed by the mean length of the terminal restriction fragments and carotid artery IMT by B-mode ultrasonography in 1062 individuals (496 men, 566 women) aged 33 to 86 years. In the whole sample, there was a significant association of age-and sex-adjusted LTL with internal carotid artery IMT (ICA-IMT) ($r=-0.07$, $P=0.02$). In sex-stratified analysis, this association remained significant for men ($r=-0.11$, $P=0.02$) but not for women ($r=-0.04$, $P=0.36$). After further adjustment for cigarette smoking and BMI, a borderline significant association persisted in men ($P=0.06$). In secondary analysis, the age-adjusted LTL was significantly (and negatively) associated with ICA-IMT ($r=-0.28$, p=0.0006) in obese (BMI $>30 kg/m^2$) men but not in nonobese (BMI ≤ 30 kg/m^2) men. In addition, age-adjusted LTL was significantly shorter in men (6.89±0.02 kb) than women (7.01±0.02 kb; $P<0.0009$) and in current cigarette smokers (6.87±0.05 kb) than never smokers (6.99±0.03 kb; $P=0.0006$). Although there was no significant association of LTL with common carotid artery-IMT or with carotid artery stenosis, there was a significant inverse association of LTL with common carotid artery IMT in obese men.

Conclusion—In obese men, shortened LTL is a powerful marker of increased carotid IMT. Given the public health impact of atherosclerosis and in particular the current epidemic of obesity, the associations noted in obese men warrant further confirmation. **(*Arterioscler Thromb Vasc Biol*. 2008;28:1165-1171)**

Key Words: telomeres ■ atherosclerosis ■ leukocytes ■ obesity ■ sex ■ smoking

Leukocyte telomere length (LTL) is shorter in individuals with atherosclerotic cardiovascular disease (CVD) than in their peers.[1–5] In addition, individuals with increased CVD risk display relatively short LTL, particularly men (compared with women),[4,6–8] cigarette smokers,[8,9] and individuals with insulin resistance and high BMI.[4,9–11] These observations support the thesis that relatively short LTL is an index of both subclinical and overt atherosclerotic CVD. One measure of atherosclerosis that has been studied extensively is carotid intimal medial thickness (IMT) determined by B-mode ultrasound. The IMT of both internal carotid artery (ICA) and common carotid artery (CCA) are associated with incident myocardial infarction and stroke, after adjustment for major cardiovascular risk factors.[12–14] However, increased IMT of the ICA differs from that of the CCA in that it primarily represents atherosclerotic plaques,[15] whereas in the CCA such an increase may represent vascular hypertrophy in response to shear stresses.[16,17] Indeed, thickening of the intima of the ICA appears to be more strongly associated than that of the CCA with increased risk for incident atherosclerotic CVD.[15,18]

Atherosclerosis and vascular aging in general are protracted processes in which inflammation[19] and oxidative stress[20] play central roles. Most indices of inflammation and oxidative stress derived from blood samples are snapshots of the metabolic status at the time of sample collection. In contrast, LTL is apparently a record of the cumulative burden of inflammation and oxidative stress over the individual's life course.[21] This is the key reason for the use of LTL as a gauge of a host of aging-related disorders, including atherosclerotic CVD.

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Two studies have examined the association of LTL with carotid IMT,[4,22] but the sample sizes of these studies were relatively small and there were no significant multivariable-adjusted associations between LTL and measures of IMT in either study. Thus, a detailed larger study is warranted to further characterize the nexus between LTL and the IMT of the ICA and the CCA. To this end, we studied participants of the Framingham Offspring Study with available LTL and carotid artery IMT parameters.

Methods

Study Sample

The Framingham Offspring Study began in 1971 with the enrollment of 5124 men and women. It comprised offspring of the Original Cohort of the FHS and the spouses of the offspring. The members of the Framingham Offspring Study underwent repeated examinations every 4 to 8 years, and details of the selection of these participants have been previously described.[23,24] A total of 3532 participants of the Offspring Cohort attended examination cycle 6 (1995 to 1998) and underwent carotid ultrasonography. LTL was measured in 1244 subjects. Of these, we excluded 105 subjects who did not have IMT measurement data. As insulin resistance is associated with LTL[10,11] and treatment of hyperglycemia may impact this association, we also excluded 77 subjects who were treated for diabetes. Thus, data from 1062 subjects were analyzed for this report.

Carotid Ultrasonography

Ultrasonographic measurements were performed using a Toshiba SSH-140A imaging unit with a 7.0-MHz transducer for the common carotid artery (CCA) and a 5.0-MHz transducer for the internal carotid artery (ICA), as previously described.[25] Measurements of the right and left arteries were obtained from longitudinal views of both the distal CCA (at end-diastole and end-systole) and the ICA at end-diastole (each measured twice). Measurements performed by the sonographer were reread by a radiologist, with both individuals blinded to clinical information.

Interpretation and quantitative measurement of imaging studies was performed using a standardized protocol. Near- and far-wall IMT, lumen diameter, and vessel width were calculated at the ICA and CCA using high-resolution images uploaded into a specialized computer software analysis package as previously described.[14,25] IMT of the CCA and the ICA were defined as the mean of the mean IMT measurements for the right and left sides, as reported previously. Replicate readings (n=25) by 2 independent interpreters showed intraclass correlation coefficients for mean maximum ICA and CCA IMT of 0.74 and 0.90, respectively.[26,27]

Determination of LTL

LTL was derived from the mean of the terminal restriction fragment length (TRFL), measured by Southern blot analysis. Samples were digested overnight with restriction enzymes digest set, *Hin*fI (5.2 U)/*Rsa*I (5.2 U) (Roche). DNA samples (2 μg each) and DNA ladders (1 kb DNA ladder plus 23.1kb fragment of λ DNA/*Hind*III fragments [Invitrogen]) were resolved on a 0.5% agarose gel (20 cm×20 cm) at 50 V (GNA-200 Pharmacia Biotech). After 16 hours, the DNA was depurinated for 15 minutes in 0.25 N HCl, denatured 30 minutes in 0.5 mol/L NaOH/1.5 mol/L NaCl, and neutralized for 30 minutes in 0.5 mol/L Tris, pH 8/1.5 mol/L NaCl. The DNA was transferred for 1 hour to a positively charged nylon membrane (Roche) using a vacuum blotter (Boeckel Scientific). The membranes were spotted at 4 sites with diluted telomeric probe [digoxigenin 3′-end labeled 5′-$(CCTAAA)_3$] and then hybridized at 65°C with the probe overnight in 5× standard saline citrate (SSC), 0.1% Sarkosyl, 0.02% SDS, and 1% blocking reagent (Roche). The membranes were washed 3 times at room temperature in 2× SSC, 0.1% SDS each for 15 minutes and once in 2× SSC for 15 minutes. The digoxigenin-labeled probe was detected by the digoxigenin luminescent detection procedure (Roche) and exposed on X-ray film. After scanning the terminal restriction fragment signal by densitometry, the membrane was stripped and reprobed with a molecular weight marker probe. The merging of the 2 x-ray films using the 4 spotted sites of telomeric probe yields minimized variation in DNA migration in different lanes. The coefficient of variation (CV) for this approach (for samples measured in duplicate or triplicate on different gels and occasions and by two researchers) was 2.4%. All measurements of LTL were performed "blindly." On completion of the measurements, the LTL data were electronically transmitted to the FHS and merged with relevant parameters.

Clinical and Environmental Measurements and Definitions

At examination 6, offspring participants underwent a physician-administered history and physical examination that included standardized measurements of blood pressure in an upright seated position, after a period of rest, using a mercury sphygmomanometer. Systolic and diastolic blood pressures were the average of 2 separate readings performed by a physician. Pulse pressure (mm Hg) was calculated as the differences between the systolic and diastolic blood pressures. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications. Fasting blood was used for measurements of lipids, including total cholesterol, HDL cholesterol, and serum triglyceride concentration. Body mass index (BMI) was calculated as the weight in kilograms measured in light clothing, divided by the height in meters squared. Cigarette smoking status was defined as current (having smoked at least one cigarette per day over the past year before the examination), past (past smokers), and never (subjects who had never smoked cigarettes). Diabetes was defined as a fasting blood glucose ≥126 mg/dL or treatment with oral hypoglycemic agents or insulin.

Statistical Analysis

The values of mean ICA and CCA thicknesses were log-transformed to normalize their distributions. Sex-specific and sex-pooled analyses were performed to describe the data and to test the association of LTL with log CCA or log ICA IMT thickness. Means±SD, for continuous variables, and proportions, for categorical variables, were computed for all study subjects and for men and women, separately. Variables were compared between men and women using 2-sample t tests for continuous variables and χ^2 tests for categorical variables. To evaluate the relationships between LTL and IMT measures we performed linear regression analyses using LTL as a dependent variable; log CCA or log ICA IMT thickness as predictor variables; and age, sex (in combined analyses), BMI, cigarette smoking status, pulse pressure, diabetic status, total cholesterol, high density lipoprotein cholesterol, triglycerides, cholesterol treatment, C-reactive protein, and hormone replacement therapy and oral contraceptive use in women as candidate covariates. To describe these associations we also computed partial correlation coefficients. Our final regression models included the following covariates: (1) age and sex adjusted; (2) age, sex, smoking status; (3) age, sex, smoking status, and BMI; (4) age, sex, smoking status, BMI, and pulse pressure. The other covariates were excluded because they were not significant contributors independent of the other covariates in the multivariable model. Given the existence of marginally significant associations of LTL with IMT measures, secondary stratified analyses were performed by clinically important variables hypothesized to be potentially important modifiers of the association between LTL and carotid IMT based on prior literature, in particular, CVD status,[1,4] current smoking, and obesity status.[9] Results with probability values less than 0.05 were considered to be statistically significant. Analyses were performed using SAS version 8.12 (SAS Institute Inc).

Results

General Characteristics

The baseline characteristics of the 1062 FHS Offspring men (n=496) and women (n=566) in the current study are

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Table 1. General Characteristics of Study Subjects

	Men and Women (n=1062)				Men (n=496)		Women (n=566)		
Characteristic	Mean±SD or n (%)	Min	Max	n	Mean±SD or n (%)	n	Mean±SD or n (%)	n	*P* Value**
Age, y[a]	59.1±9.4	33	86	1062	59.6±9.6	496	58.6±9.2	566	0.08
Smoking									0.01
Current[b]	143 (13.5)			1062	63 (12.7)	496	80 (14.1)	566	
Past[b]	545 (51.3)			1062	280 (56.5)	496	265 (46.8)	566	
Never[b]	374 (35.2)			1062	153 (30.8)	496	221 (39)	566	
Body mass index, kg/m^2 [a]	27.8±5.2	17.2	53	1061	28.2±4.5	496	27.2±5.7	565	<0.001
Obese (BMI ≥30 kg/m^2)[b]	285 (26.9)			1061	144 (29)	496	141 (25)	565	0.14
Systolic blood pressure, mm Hg[a]	129.2±18.9	77	212	1062	130.5±17.7	496	128.1±19.9	566	0.04
Diastolic blood pressure, mm Hg[a]	75.5±9.3	49	106	1062	77.5±9	496	73.7±9.3	566	<0.001
Pulse pressure, mm Hg[a]	53.7±16	16	132	1062	53±15.3	496	54.4±16.6	566	0.16
Hypertension[b]	436 (41.2)			1058	220 (44.6)	493	216 (38.2)	565	0.04
Hypertension treatment[b]	287 (27.1)			1059	146 (29.6)	494	141 (25)	565	0.09
Diabetes[b]	79 (7.4)			1062	42 (8.5)	496	37 (6.5)	566	0.23
Total cholesterol, mg/dL[a]	205.8±36.9	93	330	1062	199.7±35.2	496	211.1±37.5	566	<0.001
High-density lipoprotein cholesterol, mg/dL[a]	51.7±15.9	11	122	1060	44.5±12.3	494	58±16.1	566	<0.001
Triglycerides, mg/dL[a]	135.3±84.8	29	822	1062	143.8±101.4	496	127.8±66.2	566	0.002
Log (triglycerides)[a]	4.8±0.5	3.4	6.7	1062	4.8±0.6	496	4.7±0.5	566	0.04
Cholesterol treatment[b]	132 (12.4)			1062	74 (14.9)	496	58 (10.2)	566	0.02
Prevalent cardiovascular disease[b]	106 (10)			1062	68 (13.7)	496	38 (6.7)	566	<0.001
C-reactive protein[a]	4.5±9.7	0.2	250.5	1029	4.3±12.6	481	4.7±6.2	548	0.49
Hormone replacement therapy[a]							175 (31)	565	
Oral contraceptives[a]							6 (1.1)	564	

[a]Mean±SD; [b]n (%); **Comparing men and women.

described in Table 1. Men in the cohort were slightly older than women (mean age 59.2 years for men and 58.6 years for women, respectively). Current cigarette smoking was observed in 14% of the overall cohort and there were significant sex differences: current smoking was slightly lower in men compared with women (13% versus 14%, respectively), but rates of past smoking were substantially higher in men versus women (56% versus 47%, respectively). In addition, men had a modest but significantly higher BMI than women (28.5 versus 27.4 kg/m^2, respectively).

Carotid Artery Characteristics

As shown in Table 2, men had higher ICA-IMT and CCA-IMT than women. In addition, men displayed a higher prevalence of carotid artery stenosis than women.

Relations of Leukocyte Telomere Length With Risk Factors

Sex-adjusted LTL was inversely correlated with age ($r=-0.34$, $P<0.0001$), displaying attrition at a rate of 21.1±1.78 (SE) bp/yr. There was no statistically significant difference in age-

Table 2. Distribution of Primary Variables of Study

	Men and Women (n=1062)				Men (n=496)		Women (n=566)		
Characteristic	Mean±SD or n (%)	Min	Max	n	Mean±SD or n (%)	n	Mean±SD or n (%)	n	*P* Value**
Age-adjusted TRFL,[a] bp	6.97±0.55	5.58	8.51	1062	6.89±0.02*	496	7.04±0.022*	566	<0.001
Stenosis[b]	221 (20.8)			1062	130 (26.2)	496	91 (16.1)	566	<0.001
ICA-IMT,[a] mm	0.56±0.36	0.21	3.94	1062	0.63±0.39	496	0.49±0.33	566	<0.001
Log (ICA-IMT)[c]	0.49±0.47	0.48	0.50	1062	0.55±0.49	496	0.44±0.42	566	<0.001
CCA-IMT,[a] mm	0.61±0.14	0.35	1.79	1058	0.64±0.13	493	0.58±0.13	565	<0.001
Log (CCA-IMT)	0.59±0.20	0.59	0.60	1058	0.62±0.20	493	0.57±0.20	565	<0.001

[a]Mean±SD; [b]n (%), [c]Mean value=geometric mean and Min and Max values=95% confidence bounds; *Standard error; **Comparing men and women. TRFL indicates terminal restriction fragment length; bp, base pair; ICA, internal carotid artery; CCA, common carotid artery; IMT, intimal medial thickness.

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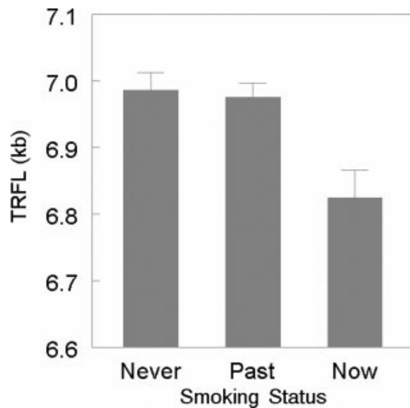

Figure 1. Leukocyte telomere length in never-smokers, past-smokers, and present-smokers.

dependent LTL attrition between women (21.5±2.5 bp/yr) and men (20.7±2.5 bp/yr; sex-age interaction P=0.815). However, age-adjusted LTL was significantly shorter in men (6.89±0.02 kb) than in women (7.01±0.02 kb; P<0.0001) and in current cigarette smokers (6.80±0.05 kb; P=0.0008), but not past smokers (6.97±0.02 kb; P=0.93), compared with never smokers (6.99±0.03 kb; Figure 1). Additionally, an inverse association was observed for age- and sex-adjusted LTL with BMI (r=−0.08, P=0.01). There were no significant associations of LTL with pulse pressure, total cholesterol, HDL cholesterol, or triglycerides (data not shown).

Associations Between Leukocyte Telomere Length and Carotid Artery Parameters

In the whole sample, age-adjusted LTL displayed significant association with ICA-IMT (r=−0.09, P=0.003). Tables 3 and 4 provide beta coefficients for regression analyses of LTL; in the text below, we provide the respective correlation coefficients. As women have longer LTL and lower ICA-IMT, we adjusted LTL for both age and sex. Age- and sex-adjusted LTL also showed significant association with ICA-IMT (r=−0.07, P=0.02). In further analyses, conducted separately by sex, this association remained significant for men (r=−0.13, P=0.02) but not for women (r=−0.04, P=0.36).

The associations of LTL with ICA-IMT after further multivariable-adjustment are presented in Table 3. For the entire sample, in a model adjusted for age, sex, and cigarette smoking, the association between LTL and ICA-IMT was of borderline significance (r=−0.06, P=0.07). This association was borderline significant in men (r=−0.09, P=0.05) but not women (r=−0.02, P=0.58). When BMI was added to the model, the association between LTL and ICA-IMT was unchanged in men (r=−0.09, P=0.05) and women (r=−0.01,

Table 3. Linear Regression Analysis of LTL on R^2 Individual Covariates and on ICA-IMT

	All				Men				Women			
	Beta Coefficient	*P* Value	Cumulative R^2	n	Beta Coefficient	*P* Value	Cumulative R^2	n	Beta Coefficient	*P* Value	Cumulative R^2	n
Intercept	8.004			1062	7.903			496	8.195			566
Age, y	−0.020	<0.001	0.12		−0.018	0.001	0.12		−0.021	<0.001	0.12	
Female	0.093	0.01	0.13									
Log (mean ICA IMT)	−0.090	0.02	0.13		−0.125	0.02	0.13		−0.052	0.36	0.12	
Intercept	8.096			1062	8.044			496	8.281			566
Age, y	−0.021	<0.001	0.12		−0.020	0.00	0.12		−0.021	<0.001	0.12	
Female	0.099	0.004	0.13									
Current smoking status	−0.162	0.003	0.14		−0.219	0.01	0.14		−0.121	0.10	0.12	
Past smoking status	0.004	0.91	0.14		0.037	0.50	0.14		−0.028	0.58	0.12	
Log (mean ICA IMT)	−0.071	0.07	0.14		−0.103	0.05	0.15		−0.032	0.58	0.12	
Intercept	8.335			1061	8.048			496	8.636			565
Age, y	−0.021	<0.001	0.12		−0.020	<0.001	0.12		−0.022	<0.001	0.12	
Female	0.092	0.01	0.13									
Current smoking status	−0.162	0.003	0.14		−0.219	0.01	0.14		−0.119	0.10	0.12	
Past smoking status	0.003	0.94	0.14		0.037	0.50	0.14		−0.032	0.53	0.12	
BMI, kg/m^2	−0.007	0.03	0.14		0.000	0.98	0.14		−0.012	0.01	0.13	
Log (mean ICA IMT)	−0.059	0.14	0.15		−0.103	0.06	0.15		−0.012	0.84	0.13	
Intercept	8.450			772	8.336			348	8.671			424
Age, y	−0.021	<0.001	0.12		−0.018	<0.001	0.11		−0.023	<0.001	0.12	
Female	0.105	0.01	0.13									
Current smoking status	−0.162	0.01	0.14		−0.248	0.01	0.14		−0.083	0.32	0.12	
Past smoking status	−0.014	0.75	0.14		−0.013	0.84	0.14		−0.016	0.78	0.12	
BMI, kg/m^2	−0.010	0.01	0.15		−0.005	0.39	0.14		−0.015	0.01	0.14	
Pulse Pressure	−0.001	0.37	0.15		−0.004	0.07	0.15		0.001	0.60	0.14	
Log (mean ICA IMT)	−0.055	0.29	0.15		−0.054	0.44	0.15		−0.055	0.479	0.14	

ICA indicates internal carotid artery; IMT, intimal medial thickness; BMI, body mass index.

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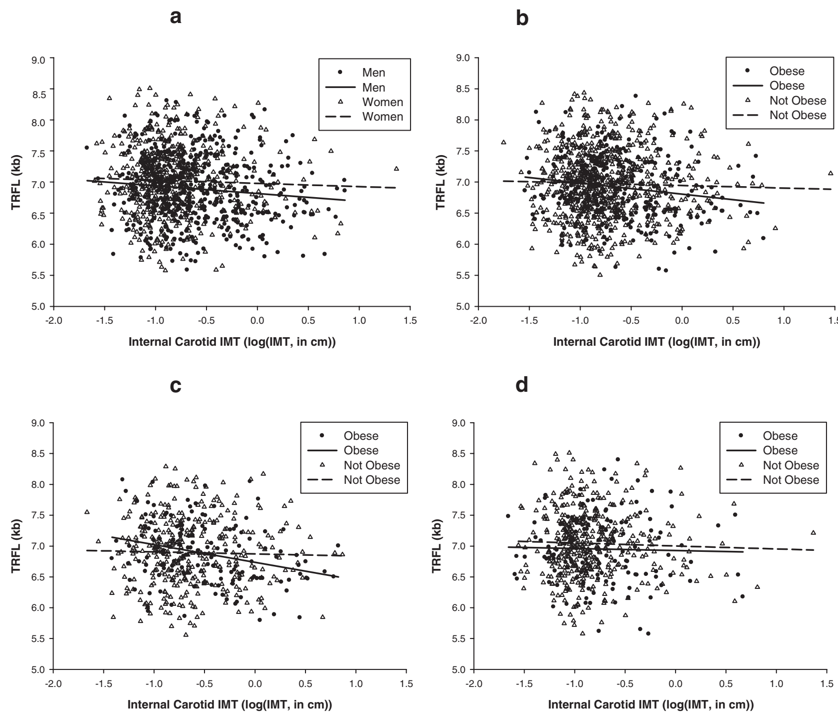

Figure 2. Age-adjusted LTL and ICA-IMT in men and women (a), obese vs nonobese subjects (b), obese vs nonobese men only (c), and obese vs nonobese women only (d).

P=0.84). There was further attenuation of the association by the further adjustment for pulse pressure (Table 3), and the overall association was similarly attenuated in separate models adjusting for hypertension drug treatment, total or HDL cholesterol or triglycerides (data not shown).

Given the consistent, albeit borderline significant, association between LTL and ICA-IMT in men but not women, we undertook secondary analyses to examine for associations in subjects with obesity, cigarette smoking, or prevalent CVD and for evidence of effect modification by these parameters. For obese (BMI $>$30kg/m^2) compared with nonobese (BMI $\leq$30 kg/m^2) men, age-adjusted LTL displayed a highly significant, negative association with ICA-IMT (r=−0.28, P=0.0005). This association remained highly significant after adjustment for smoking (r=−0.23, P=0.006). Further adjustment for other variables did not significantly alter the association. No significant associations between LTL and the ICA-IMT were observed in nonobese men or in women (obese and nonobese). However, in a test of interaction between obesity and ICA-IMT in men (see Figure 2c), there was no significant interaction (P=0.14). Figure 2 displays the results of these associations as scatter plots in the combined sample, men alone and women alone, by obese and nonobese subjects. There was no evidence of strongly increased associations between LTL and ICA-IMT in those with CVD or current cigarette smoking.

There was no significant association of LTL with the CCA-IMT or with carotid artery stenosis in multivariable-adjusted models in men or women. In men but not women, there was a significant association with CCA-IMT in obese but not nonobese subjects, and the association remained significant in multivariable-adjusted models (r=−0.53, P=0.03).

Discussion

In our community-based cohort, we found that men and current smokers had shorter age-adjusted LTL than women and never smokers, respectively. These findings are in line with previous research reporting sex[4,7,8] and smoking[8,9] effects on LTL. In the entire cohort, a modest inverse association was noted between LTL and ICA-IMT. On secondary analysis for evidence of effect modification by obesity status, we found that the inverse association between LTL and ICA-IMT was highly significant in obese men, even after adjustment for BMI and cigarette smoking. The strength of such an association in obese men is underscored by the fact that age—the main determinant of LTL shortening—accounted for 12.9% of the interindividual variation in LTL in the entire cohort and age and ICA-IMT combined accounted for 13.3% of LTL. Thus, ICA-IMT explained only 0.4% over and above age the interindividual variation in LTL (Table 3). In obese men, however, age accounted for only 8.9%, whereas age and ICA-IMT combined accounted for 16.4% of the interindividual variation in LTL (Table 4). Accordingly, increased ICA-IMT explained a substantial 7.5% over and above age of the interindividual variation in LTL.

At any given time, LTL reflects birth LTL, which is highly variable among newborns,[28,29] and age-dependent LTL attrition afterward. Cross-sectional evaluation of LTL at a single point in time would, therefore, understate the effect of a given variable on LTL attrition rate. The link between insulin resistance and LTL dynamics illustrates this concept. Insulin resistance explains 28% of the variation in LTL attrition rate in a longitudinal evaluation,[11] but it accounts for only 2.5% of the variation in LTL in a cross-sectional study.[10] Accordingly, factors that increase the predilection of obese men to atherosclerosis, as expressed in the ICA-IMT, apparently exert a profound effect on LTL attrition rate.

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Table 4. Results of Linear Regression Analysis of LTL on Individual Covariates and on ICA-IMT for Obese Men

	Beta Coefficient	*P* Value	Cumulative R^2	n
Intercept	7.393			144
Age, y	−0.011	0.02	0.09	
Log (mean ICA IMT)	−0.287	0.001	0.16	
Intercept	7.606			144
Age, y	−0.014	0.01	0.09	
Current smoking status	−0.196	0.15	0.14	
Past smoking status	0.042	0.65	0.14	
Log (mean ICA IMT)	−0.240	0.01	0.19	
Intercept	7.360			144
Age, y	−0.014	0.01	0.09	
Current smoking status	−0.193	0.15	0.14	
Past smoking status	0.044	0.64	0.14	
BMI, kg/m²	0.006	0.60	0.14	
Log (mean ICA IMT)	−0.240	0.01	0.19	
Intercept	7.522			91
Age, y	−0.014	0.06	0.11	
Current smoking status	−0.196	0.24	0.17	
Past smoking status	−0.022	0.86	0.17	
BMI, kg/m²	0.006	0.64	0.17	
Pulse Pressure	−0.003	0.53	0.18	
Log (mean ICA IMT)	−0.206	0.12	0.20	

ICA indicates internal carotid artery; IMT, intimal medial thickness; BMI, body mass index.

Two studies have examined the association of LTL with carotid artery IMT, but they were limited to either a small number of hypertensive men or a small to modest sized elderly cohort of both men and women. In their study of 166 hypertensive men, Benetos et al observed shorter LTL in men who displayed atherosclerotic plaques in the CCA and ICA compared with those without detectable plaques.[22] Fitzpatrick et al examined 419 randomly selected elderly participants of the Cardiovascular Health Study (average age 74.2 years), observing shortened LTL in individuals with increased ICA-IMT ($P=0.07$).[4] However, these cohorts are distinct from the Framingham Offspring Study cohort with respect to age distribution and demography. Nonetheless, our findings further extend those of these smaller studies in indicating that after age-adjustment shortened LTL is associated with increasing carotid IMT in men, particularly obese men.

The effect of sex on the association between LTL and the ICA-IMT is poorly understood. Sexual dimorphism is displayed in cardiovascular risk factors and CVD.[6,30–32] More importantly, in women, a host of variables, including menopause, might impact the association between LTL and cardiovascular risk factors.[33]

The mechanism underlying the association between age-adjusted LTL and ICA-IMT in obese men is not understood. However, given the growing prevalence of overweight and obesity in the United States[27] and the significant proportion of deaths attributable to obesity,[34] further research is warranted to confirm and decipher the link between LTL and atherosclerosis in obese persons. It is possible that the metabolic consequences of obesity provoke parallel changes in processes that are engaged in atherosclerosis and LTL dynamics to the extent that they are detectable in the shortening of LTL in obese individuals. Obesity is marked by insulin resistance, inflammation, and oxidative stress.[35–37] Insulin resistance,[10,11] oxidative stress,[10,38] and inflammation[4,33] are associated (inversely) with LTL. In obese men, the combined input of these factors on LTL dynamics might be of a magnitude that is reflected by the shortening of LTL in concert with increased ICA-IMT.

The same considerations might apply with regard to the shortened LTL in current smokers than in never smokers, as smoking increases the oxidative stress and inflammatory burden in the body.[39–43] Interestingly, we did not observe shortened LTL in past smokers as opposed to never smokers. Several possibilities may account for this finding. First, survivorship bias may play some role, because past smokers who survive may be genetically different from those who have died as a result of smoking. Second, the characterization of individuals as current smokers, past smokers, and never smokers is often imprecise and highly subjective, as it relies on the accounts of smoking provided by the subjects, which are often inaccurate. This is particularly applicable to past smokers. Third, it may be that cessation of smoking leads to LTL attrition that is markedly slower than the rate in nonsmokers because the antioxidant and antiinflammatory pathways were upregulated by the chronic exposure to cigarette smoke.

The strengths of this work include its conduct in a well characterized community-based sample, the highly accurate measurements of the IMT and LTL, and their blinded assessments. However, because of the cross-sectional design, evidence for association may not be equated with evidence for causality, and these findings warrant follow-up confirmation in longitudinal studies of both LTL dynamics and indices of atherosclerosis. In addition, the FHS comprises predominantly middle-class whites who may or may not be generalizable to other ethnicities of different socioeconomic backgrounds.

In conclusion, we observed an (inverse) association between LTL and the ICA-IMT, which in secondary analyses appeared particularly strong in obese men but not in women or nonobese men. In addition, we confirmed previous findings of shortened LTL in men versus women and in cigarette smokers versus never smokers. Our findings support further investigation of the relationships of LTL dynamics and 2 major risk factors, obesity and cigarette smoking, in the development of atherosclerosis.

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Disclosures

None.

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