JAMA Internal Medicine | Original Investigation

Association of Telomere Length With Risk of Disease and Mortality

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IMPORTANCE Telomeres protect DNA from damage. Because they shorten with each mitotic cycle, leukocyte telomere length (LTL) serves as a mitotic clock. Reduced LTL has been associated with multiple human disorders.

OBJECTIVE To determine the association between LTL and overall as well as disease-specific mortality and morbidity.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, community-based cohort study conducted from March 2006 to December 2010 included longitudinal follow-up (mean [SD], 12 [2] years) for 472 432 English participants from the United Kingdom Biobank (UK Biobank) and analyzed morbidity and mortality. The data were analyzed in 2021.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) and odds ratios for mortality and morbidity associated with a standard deviation change in LTL, adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and ethnicity.

RESULTS This study included a total of 472 432 English participants, of whom 54% were women (mean age, 57 years). Reduced LTL was associated with increased overall (HR, 1.08; 95% CI, 1.07-1.09), cardiovascular (HR, 1.09; 95% CI, 1.06-1.12), respiratory (HR, 1.40; 95% CI, 1.34-1.45), digestive (HR, 1.26; 95% CI, 1.19-1.33), musculoskeletal (HR, 1.51; 95% CI, 1.35-1.92), and COVID-19 (HR, 1.15; 95% CI, 1.07-1.23) mortality, but not cancer-related mortality. A total of 214 disorders were significantly overrepresented and 37 underrepresented in participants with shorter LTL. Respiratory (11%), digestive/liver-related (14%), circulatory (18%), and musculoskeletal conditions (6%), together with infections (5%), accounted for most positive associations, whereas (benign) neoplasms and endocrinologic/metabolic disorders were the most underrepresented entities. Malignant tumors, esophageal cancer, and lymphoid and myeloid leukemia were significantly more common in participants with shorter LTL, whereas brain cancer and melanoma were less prevalent. While smoking and alcohol consumption were associated with shorter LTL, additional adjustment for both factors, as well as cognitive function/major comorbid conditions, did not significantly alter the results.

CONCLUSIONS AND RELEVANCE This cohort study found that shorter LTL was associated with a small risk increase of overall mortality, but a higher risk of mortality was associated with specific organs and diseases.

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Supplemental content

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JAMA Intern Med. 2022;182(3):291-300. doi:10.1001/jamainternmed.2021.7804
Published online January 18, 2022.

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Telomeres are DNA structures at the end of chromosomes that protect them from damage and instability.[1] In most cells, telomeres shorten with each cell cycle; thus, telomere shortening indicates the proliferative history of the cell.[2] When telomeres become critically short, cells enter senescence cell cycle arrest or undergo apoptosis.[2] Telomere attrition is largely associated with age and genetic determinants but is modulated by host-related genetic (such as male sex) as well as lifestyle factors (eg, smoking, physical activity, and stress).[3] Leukocyte telomere length (LTL) serves as a biomarker for telomere length of the individual organism, and shortening of LTL has been associated with a broad range of pathologies, including lung, liver, hematologic, and cardiovascular diseases, as well as multiple cancer entities.[4-6] Despite that, to our knowledge, the prognostic value of LTL remains to be comprehensively characterized,[7] as most studies have either relatively small sample sizes, short follow-up duration, or insufficient power to detect clinically meaningful associations.

Using the well-characterized, community-based UK Biobank (UKB), which comprises the largest data set of directly measured LTL consisting of more than 472 000 participants, we analyzed the association between LTL and overall as well as disease-specific mortality. Additionally, we explored the association between LTL and 1847 phenomewide association study codes (phecodes) available in the data set. The outcomes of this approach suggest that participants with shorter telomeres are predisposed to specific organ dysfunctions, including cardiovascular, digestive, respiratory, musculoskeletal, or hematopoietic diseases. While these data highlight the association of proliferative history of leukocytes with specific human disorders, further studies are needed to dissect the underlying mechanisms.

Key Points

Question Is telomere length associated with mortality and development of specific diseases?

Findings In this cohort study, UK Biobank data from more than 450 000 individuals found that reduced baseline leukocyte telomere length was associated with increased overall and various disease-specific mortalities. The study identified more than 200 disorders that were significantly overrepresented or underrepresented in participants with shorter leukocyte telomere length.

Meaning The study findings suggest the relevance of telomere shortening for several diseases and warrant further mechanistic and therapeutic studies.

Methods

Data and Code Availability

The data sets used in this study have not been deposited in a public repository but are available after approval of a reasonable application at https://www.ukbiobank.ac.uk. All participants provided written informed consent for the study. The UKB study has approval from the Northwest Multicenter research ethics committee.

UKB Participants

The UKB is a population-based cohort study conducted in the UK from March 2006 to December 2010 that recruited 502 511 volunteers aged 37 to 73 years at baseline. All participants were registered with the UK National Health Service and attended an initial examination, which was followed by a long-term follow-up that takes place continuously. All participants gave written informed consent for genotyping and data linkage to medical reports. For definition of outcomes and covariates, see eTable 1 in the Supplement.

Ongoing inpatient hospital records beginning in 1996 until May 2021 were used to identify diagnoses according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes. Participants who underwent stem cell transplant (Z94.8) before the baseline examination were excluded (n = 158). The UKB receives death notifications (age at death and primary *ICD-10* diagnosis associated with death) through linkage to national death registries. *End of follow-up* was defined as death or end of hospital inpatient data collection in May 2021. Heavy alcohol consumption was defined as more than 60 g of alcohol per day for men and more than 40 g of alcohol per day for women, while moderate alcohol consumption was defined as more than 24 g of alcohol per day for men and more than 12 g of alcohol per day for women. The study has been approved by the UKB access committee (project 47527).

Telomere Measurements

The UKB extracted DNA from peripheral blood leukocytes as part of a cohortwide array genotyping project. Research staff at the University of Leicester (Leicester, England) conducted LTL measurements using the multiplex quantitative polymerase chain reaction (PCR) methods that were masked to phenotypic information. They compared the amplification of a telomere length PCR product (T) against a PCR product (S) of a reference single copy gene to produce a T/S ratio.[8] T and S were calculated relative to a calibrator sample (pooled DNA from 20 individuals) that was included in every run. In this study, the $\log_e$-transformed z score-adjusted T/S ratio (ie, UKB data field 22192) was used, which is the relative LTL adjusted for the effect of technical parameters. For the analyses using the first percentile of telomere length, the 1% of the participants with the shortest telomere length per each age/sex group were analyzed.

Phenomewide Association Study Analysis

The coding for clinical diagnoses in the data set followed the World Health Organization's *ICD-10* coding systems. For each study participant, *ICD-10* codes from the electronic health record diagnoses throughout the study period were collated and duplicates removed. We converted the *ICD-10* codes to 1847 associated phecodes using the PheWAS package, version 0.99.5.5.[9] Using a continuous model, we examined the association of decreased telomere length (per SD) with the development of each phecode.

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Primary Care Records

To ensure the validity of the hospital records, we repeated the analyses using the primary care records available for a subset of patients (more information available at https://www.ukbiobank.ac.uk). The CTV3 or Read, version 3, codes were converted to *ICD-10* codes. In the confirmatory analysis, we included only phecodes that were diagnosed at least 1 year after the baseline examination.

Analysis of Genetic Proxies for LTL (rs10936599 and rs2736100)

For the first 50 000 participants, genotyping was performed using the UK BiLEVE Axiom array, while the Affymetrix UK Biobank Axiom array was used for the remaining 450 000 participants. Two common genetic proxies for LTL were analyzed (rs10936599 and rs2736100).[10]

Statistical Analysis

The results of continuous variables are presented as mean (SD) (normal distribution). All categorical variables were displayed as relative (%) frequencies and the corresponding contingency tables. Univariate analysis of variance was used to determine overall differences between the 4 quartiles of telomere length. The primary outcomes of this study were estimates of the probability of overall and cause-specific mortality per SD telomere shortening, adjusted for age, sex, ethnicity, and objectively measured body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) at baseline. Self-reported alcohol use and smoking behavior at baseline were included in further analyses.

For the competing risk analyses, we tabulated the numbers of death per *ICD-10* code and compared them with those who were deceased of other causes as well as survivors. Hazard ratios (HRs) or odds ratios per SD of telomere shortening were presented with their corresponding 95% CIs. All multivariable analyses were adjusted for age, sex, ethnicity, and BMI at baseline. To account for major comorbidities, as well as physical and cognitive function, Charlson Comorbidity index[11] (CCI) scores and Phenotypic Age (PhenoAge[12]) were incorporated (eTables 2 and 3 in the Supplement). The PheWAS analysis was performed using the PheWAS R package (R Foundation).[9] For PheWAS and mortality analyses, Bonferroni correction was performed to account for multiple testing for the number of the major *ICD-10* phecodes (1847) analyzed ($P < .05$). The reference groups in this association study for analyzing any specific *ICD-10* code were participants without the specific *ICD-10* phecode. Differences were considered to be statistically significant with a 2-tailed $P < .05$. The data were analyzed using R version, 4.0.2 (R Foundation for Statistical Computing); SPSS, version 26 (IBM); and Prism, version 8 (GraphPad). eFigures 1, 4, and 5 in the Supplement were generated with Biorender software.

Results

Association of Telomere Length With Overall and Cause-Specific Survival

The UKB data set comprises 472 432 individuals with valid LTL measurements (eFigure 1 in the Supplement). Their telomere length distribution is depicted in eFigure 2A in the Supplement. As expected, higher age, male sex, obesity, alcohol consumption, and smoking were associated with shorter LTL; however, all parameters displayed only a weak association with LTL (eTable 4; eFigure 2, B-D in the Supplement). During the median (IQR) follow-up of 12 (11-13) years, 32 491 participants died (mortality rate, 5.7 per 1000 person-years; eTable 4 in the Supplement). Baseline telomere length was significantly shorter in participants who died within the follow-up period (mean telomere length, −0.23) than in those who survived (mean telomere length, 0.02; *P* value adjusted for age, sex, BMI, and ethnicity, <.001). Compared with participants in the highest LTL quartile, individuals in the lowest LTL quartile displayed 76% higher mortality (eFigure 3 and eTable 4 in the Supplement). The univariate analysis revealed a significant increase in the overall mortality per SD telomere shortening (HR, 1.27; 95% CI, 1.25-1.29), and while the HR dropped after adjustment for age, it remained highly significant (HR, 1.12; 95% CI, 1.10-1.13). Even after adjustment for age, sex, BMI, and ethnicity, shorter LTLs still conferred a significantly elevated overall death rate (HR, 1.08; 95% CI, 1.07-1.09; eTable 5 in the Supplement). Inclusion of additional covariates had only a negligible association with the HR per SD telomere shortening (eTable 5 in the Supplement).

Shorter LTLs were associated with significantly increased organ-specific mortalities in the univariate analysis (eTable 6 in the Supplement). After adjustment for age, sex, BMI, and ethnicity, 1-SD shorter LTL was associated with a higher risk of death of cardiovascular (HR, 1.09; 95% CI, 1.06-1.12), respiratory (HR, 1.40; 95% CI, 1.34-1.45), digestive (HR, 1.26; 95% CI, 1.19-1.33), and musculoskeletal diseases (HR, 1.51; 95% CI, 1.35-1.68) as well as of COVID-19 (HR, 1.15; 95% CI, 1.07-1.23), but neither of cancer nor neurological disorders (**Figure 1**; eFigure 4 in the Supplement). Among the specific entities, a particularly high HR was seen for mortality because of emphysema, chronic obstructive pulmonary disorder, (alcoholic) liver disease, and rheumatoid arthritis (Figure 1). Additional adjustment for smoking, alcohol consumption, PhenoAge, and CCI score did not significantly change the associations of LTL with overall mortality or mortality because of specific diseases, as well as cancers (eTables 7 and 8 in the Supplement).

Overrepresentation of Respiratory, Hepatic, and Hematologic Phecodes in Individuals With Shorter LTL

To obtain insight into conditions associated with shorter LTL (per SD telomere shortening), we conducted a multivariable PheWAS analysis. Of 1847 phecodes available in the UKB (eFigure 1 in the Supplement), 214 were significantly overrepresented and 37 underrepresented in participants with shorter LTLs (**Figure 2** and **Figure 3**; eTables 9 and 10 and eFigures 5 and 6 in the Supplement). The results were robust even when considering different methods used for LTL presentation. In particular, a PheWAS analysis using a non-$\log_e$-corrected non-z score-corrected T/S ratio shared 230 significantly associated phecodes with the z-transformed depiction that was used in this study.

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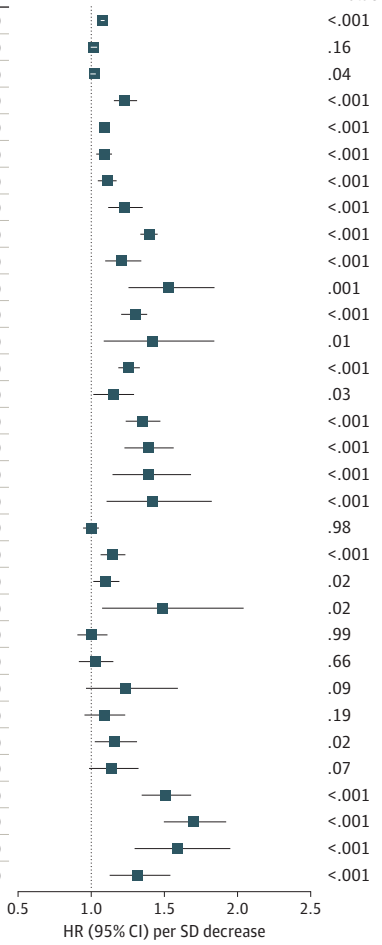
Figure 1. Association of Overall and Cause-Specific Mortality With Leukocyte Telomere Shortening Adjusted for Age, Sex, Body Mass Index (BMI), and Ethnicity

Disease (*ICD-10* code)	Total deaths	HR (95% CI)	*P* value
Overall mortality	32 491	1.08 (1.07-1.09)	<.001
Neoplasm (C00-C49)	16 603	1.02 (1.00-1.04)	.16
Malignant (C00-C99)	16 384	1.02 (1.00-1.03)	.04
Hematopoietic (C80-97)	1171	1.23 (1.16-1.31)	<.001
Cardiovascular (I)	6636	1.09 (1.06-1.12)	<.001
Chronic ischemic (I25)	2072	1.09 (1.04-1.14)	<.001
Acute myocardial infarction (I21)	1386	1.11 (1.05-1.17)	<.001
Stroke (I64)	387	1.23 (1.12-1.35)	<.001
Respiratory (J)	2328	1.40 (1.34-1.45)	<.001
Pneumonia (J18)	487	1.21 (1.10-1.34)	<.001
Emphysema (J43)	51	1.53 (1.26-1.84)	.001
COPD (J44)	862	1.30 (1.21-1.38)	<.001
Asthma (J45)	42	1.42 (1.09-1.84)	.01
Digestive (K)	1261	1.26 (1.19-1.33)	<.001
Intestine (K5)	305	1.15 (1.02-1.29)	.03
Liver (K7)	507	1.35 (1.24-1.47)	<.001
Alcoholic liver (K70)	277	1.39 (1.23-1.56)	<.001
Fibrosis and cirrhosis (K74)	114	1.39 (1.15-1.68)	<.001
Cholangitis (K83)	41	1.42 (1.11-1.82)	<.001
Neurological (G)	1762	1.00 (0.95-1.05)	.98
COVID-19 (U07)	994	1.15 (1.07-1.23)	<.001
Psychiatric (F)	670	1.10 (1.02-1.19)	.02
Alcohol-related (F10)	29	1.49 (1.08-2.04)	.02
Poisoning and external causes (X)	387	1.00 (0.91-1.11)	.99
Endocrine (E)	370	1.03 (0.92-1.15)	.66
Benign diseases of the blood (D50-D99)	286	1.24 (0.97-1.59)	.09
Infections (A00-B99)	273	1.09 (0.96-1.23)	.19
Injuries (W)	259	1.16 (1.03-1.31)	.02
Urogenital (N)	217	1.14 (0.99-1.32)	.07
Musculoskeletal (N)	173	1.51 (1.35-1.68)	<.001
Rheumatoid arthritis (M06)	39	1.70 (1.50-1.92)	<.001
Diseases of connective tissue (M35)	18	1.59 (1.30-1.95)	<.001
Drugs and biological substances (Y)	1171	1.32 (1.13-1.54)	<.001



All major *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* categories, as well as selected cause-specific mortalities, were analyzed. Hazard ratios (HRs) per *ICD-10* codes were generated from competing risk regression models, accounting for the risk of death through other causes; HRs (95% CI) per SD decrease of telomere length are shown. COPD indicates chronic obstructive pulmonary disease. BMI was calculated as weight in kilograms divided by height in meters squared.

Postinflammatory pulmonary fibrosis constituted the most prominent association that remained highly significant even after adjustment for a reported smoking/drinking behavior, PhenoAge, and CCI score (eFigure 7 in the Supplement). Even after this adjustment, 116 phecodes remained significantly overrepresented, while 38 were underrepresented in individuals with reduced LTL (eTables 11 and 12 in the Supplement). In line with the mortality analyses, respiratory and liver-related phecodes, together with hematologic disorders, were most prominently overrepresented in individuals with shorter LTLs (Figure 3; eFigure 5 in the Supplement). The association between LTL and respiratory disorders was only marginally affected by additional adjustment for smoking and alcohol consumption. Similarly, associations with liver diseases remained significant after correction for drinking and smoking behavior and after exclusion of moderate and heavy drinkers. Multiple cardiovascular phecodes, particularly those associated with arterial disease, were also enriched in participants with shorter LTL (Figure 3; eFigures 5 and 8 in the Supplement). In addition to malignant hematologic disorders, cancers that are associated with smoking and alcohol consumption (ie, cancer of the larynx, [oro]pharynx, and nasal cavities) were significantly associated with short LTLs (Figure 3 and **Figure 4**).

To avoid biases through the use of inpatient hospital records, we repeated the PheWAS analysis in a subset of UKB participants who were connected to their primary health records using only diagnoses that were reported at least 1 year after the measurement of the telomere length. Despite the limited power, we were able confirm 52 phecodes (eTables 13 and 14 in the Supplement).

To further ensure the robustness of our data, we performed a time-to-event analysis. Notably, the top 10 phecodes that were associated with LTL all remained significant in this assessment (eTables 15 and 16 in the Supplement). Finally, to determine the association of extremely short telomeres, we looked at a subcohort of subjects who fell into the shortest (first) percentile of LTL. While the overall pattern of associated disorders remained similar, extremely short LTL was associated with markedly increased mortality of hematopoietic neoplasms, cholangitis, musculoskeletal diseases (particularly rheumatoid arthritis), and deaths associated with drugs and biological substances (**Figure 5**).

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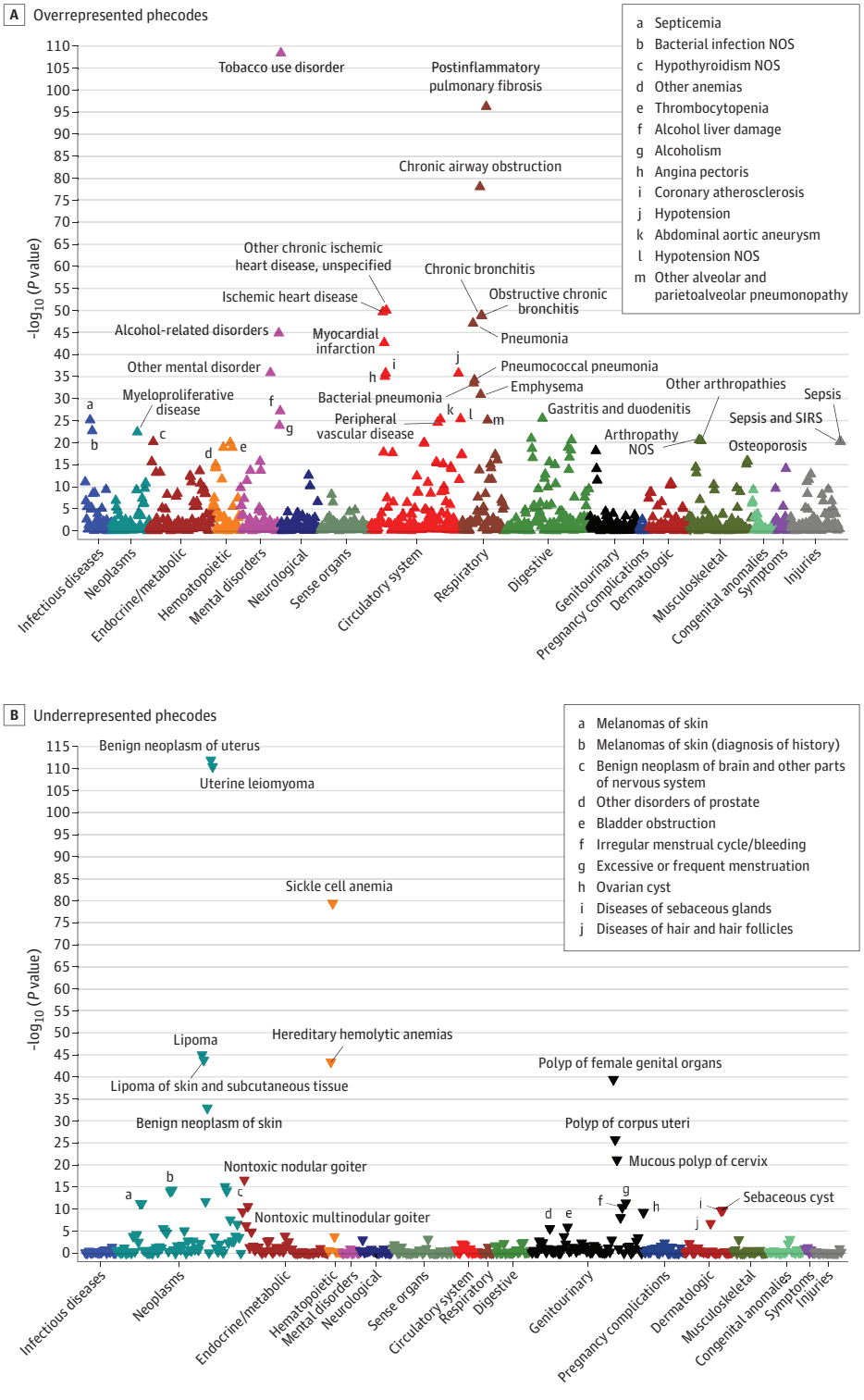
Figure 2. Multivariable Phenomewide Association Study Corrected for Age, Sex, Body Mass Index (BMI), and Ethnicity



Manhattan plot of adjusted log10 (*P* values) for all phecodes comparing their occurrence per SD telomere shortening. Highlighted are associations results with −log10 *P* values between 10 and 120. A and B, Upwards/downwards pointing triangles refer to phecodes that are over and/or underrepresented. NOS indicates not otherwise specified; SIRS, systemic inflammatory response syndrome. BMI was calculated as weight in kilograms divided by height in meters squared.

To dissect the association of well-known genetic variants associated with telomere length, we performed PheWAS analyses for the rs10936599 variant of TERC and the lead single-nucleotide variation for the 5p15.33 (*TERT*). In this analysis, we found several phecodes that were over and underrepresented that were also associated with direct measured LTL, including sickle cell anemia and postinflammatory pulmonary fibrosis (eFigures 9 and 10 in the Supplement).

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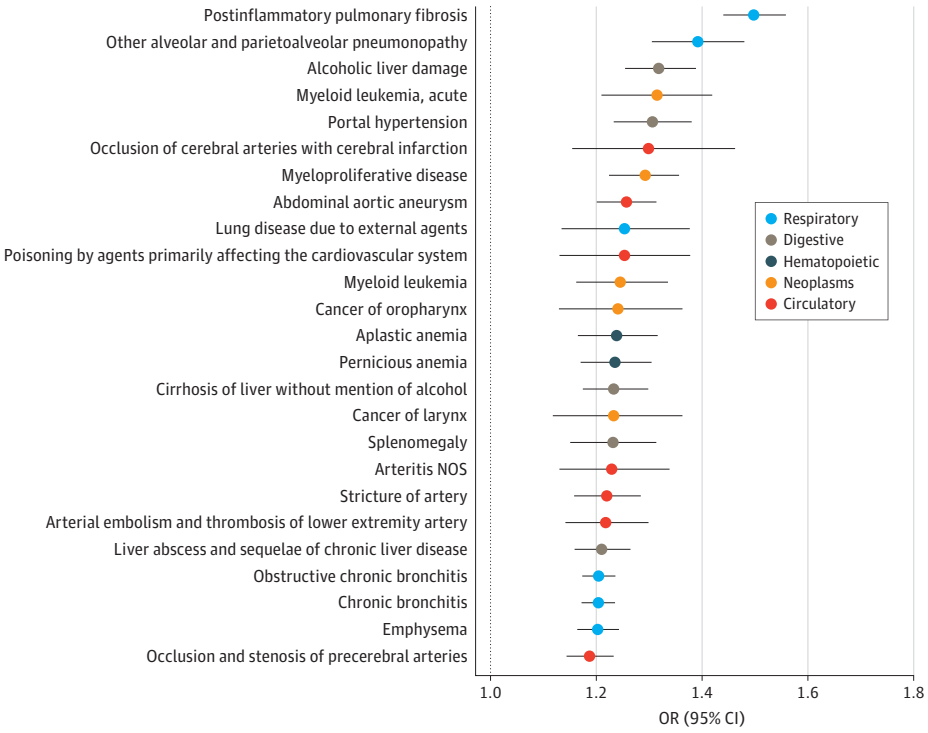
Figure 3. Most Overrepresented Phecodes in Patients With Shorter Telomeres



Adjusted for age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and ethnicity. Odds ratios (ORs) and 95% CIs per SD decrease of telomere length are given. Only phecodes that remained significant after adjustment for multiple testing are displayed. NOS indicates not otherwise specified.

Figure 4. Association Between Telomere Length and the Top 25 Cancers That Lead to Death, Sorted by Descending Hazard Ratio (HR), and Adjusted for Age, Sex, Body Mass Index (BMI), and Ethnicity

Top 25 cancers leading to death (*ICD-10* code)	HR (95% CI)	*P* value
Overall mortality of malignant neoplasms (C00-99)	1.02 (1.00-1.03)	.04
Lymphoid leukemia (C91)	1.64 (1.43-1.88)	<.001
Myeloid leukemia (C92)	1.34 (1.20-1.49)	<.001
Non-Hodgkin lymphoma (C85)	1.20 (1.06-1.36)	.01
Nonfollicular lymphoma (C83)	1.18 (1.02-1.36)	.03
Malignant neoplasm of esophagus (C15)	1.12 (1.05-1.20)	<.001
Malignant neoplasm of bladder (C67)	1.10 (0.99-1.22)	.07
Malignant neoplasm of prostate (C61)	1.07 (1.00-1.14)	.04
Malignant neoplasm of liver and bile ducts (C22)	1.06 (0.97-1.16)	.20
Hepatocellular carcinoma (22.0)	1.13 (0.99-1.29)	.08
Malignant neoplasm of pancreas (C25)	1.02 (0.97-1.08)	.43
Malignant neoplasm of colon (C18)	1.02 (0.95-1.10)	.52
Cancer of unknown origin (C80)	1.02 (0.95-1.10)	.62
Malignant neoplasm of the lung (C34)	1.02 (0.98-1.06)	.41
Malignant neoplasm of stomach (C16)	1.01 (0.91-1.11)	.88
Malignant neoplasm of breast (C50)	0.98 (0.92-1.03)	.38
Malignant neoplasm of rectum (C20)	0.97 (0.86-1.08)	.57
Malignant neoplasm of intestinal tract (C26)	0.97 (0.86-1.09)	.61
Malignant neoplasm of rectosigmoid (C19)	0.96 (0.86-1.06)	.40
Malignant neoplasm of kidney (C64)	0.96 (0.87-1.07)	.45
Malignant neoplasm of ovary (C56)	0.94 (0.86-1.02)	.12
Multiple myeloma (C90)	0.92 (0.82-1.02)	.10
Malignant neoplasm of uterus (C54)	0.88 (0.76-1.01)	.06
Malignant neoplasm of other connective and soft tissue (C49)	0.88 (0.74-1.04)	.13
Malignant neoplasm of brain (C71)	0.87 (0.81-0.94)	<.001
Mesothelioma (C45)	0.87 (0.78-0.96)	.01
Melanoma (C43)	0.80 (0.71-0.89)	<.001

Hazard ratios per *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* code were generated from competing risk regression models, accounting for the risk of death through other causes. The HRs (95% CI) per SD decrease of telomere length are shown. BMI is calculated as weight in kilograms divided by height in meters squared.

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Figure 5. Association of Overall and Cause-Specific Mortality for the First Percentile of Telomere Length Corrected for Age, Sex, Body Mass Index (BMI), and Ethnicity

Disease (*ICD-10* code)	HR (95% CI)	*P* value
Overall mortality	1.54 (1.42-1.66)	<.001
Neoplasms (C00-C49)	1.41 (1.25-1.58)	<.001
Malignant (C00-C99)	1.39 (1.23-1.56)	<.001
Hematopoietic (C80-97)	3.79 (2.91-4.94)	<.001
Cardiovascular (I)	1.40 (1.18-1.67)	<.001
Chronic ischemic (I25)	1.42 (1.04-1.92)	.03
Acute myocardial infarction (I21)	1.23 (0.82-1.84)	.32
Stroke (I64)	1.83 (0.98-3.43)	.06
Respiratory (J)	2.86 (2.31-2.53)	<.001
Pneumonia (J18)	1.96 (1.13-3.40)	.02
Emphysema (J43)	1.48 (0.20-10.70)	.70
COPD (J44)	2.26 (1.53-3.34)	<.001
Asthma (J45)	NA	.99
Digestive (K)	2.10 (1.49-2.97)	<.001
Intestine (K5)	0.73 (0.23-1.28)	.59
Liver (K7)	2.41 (1.42-4.11)	.001
Alcoholic liver (K70)	2.75 (1.36-5.58)	.01
Fibrosis and cirrhosis (K74)	2.79 (1.03-7.60)	.04
Cholangitis (K83)	7.38 (2.62-20.80)	<.001
Neurological (G)	0.82 (0.52-1.29)	.39
COVID-19 (U07)	2.18 (1.51-3.16)	<.001
Psychiatric (F)	0.89 (0.46-1.73)	.74
Alcohol-related (F10)	3.14 (0.42-23.20)	.26
Poisoning and external causes (X)	1.08 (0.40-2.89)	.88
Endocrine (E)	0.75 (0.87-3.53)	.12
Benign diseases of the blood (D50-D99)	2.63 (0.64-10.70)	.18
Infections (A00-B99)	NA	.92
Injuries (W)	NA	.91
Urogenital (N)	2.01 (0.89-4.52)	.09
Musculoskeletal (N)	6.39 (3.62-11.20)	<.001
Rheumatoid arthritis (M06)	17.10 (7.49-39.20)	<.001
Diseases of connective tissue (M35)	4.82 (0.64-36.40)	<.001
Drugs and biological substances (Y)	3.34 (1.36-8.19)	.008

All major *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* categories, as well as selected cause-specific mortalities, were analyzed. Hazard ratios (HRs) per *ICD-10* code were generated from competing risk regression models, accounting for the risk of death of other causes. The HRs (95% CI) per SD decrease of telomere length are shown. COPD indicates chronic obstructive pulmonary disease; NA, not applicable.

Differential Association of Telomere Shortening With Occurrence of Tumors

In line with the mortality analyses described previously that did not reveal a significant association between LTL and the overall cancer death rate, the cancer occurrence was mostly independent on LTL. Among the 25 most common cancers, only esophageal cancer and lymphoid and myeloid leukemia were more common in participants with shorter LTLs (Figure 4). However, brain cancer and melanoma were significantly underrepresented in individuals with shorter LTLs (Figure 4). Longer telomeres were associated with increased risk of benign neoplasms (eFigure 11 in the Supplement).

Discussion

We analyzed the UKB database to explore the relevance of LTL for human health. Given the large number of recruited individuals, the long follow-up period (>5 000 000 person-years), and a precise collection of disease phenotypes, we were able to gain insights and discovered more than 200 phecodes that are significantly associated with LTL.

We confirmed earlier findings that found an association of shorter LTL with modestly increased overall mortality.[13,14] Still, the prognostic relevance of LTL seems limited compared with other clinical factors, and it is unlikely that LTL alone will become a meaningful marker for overall mortality. On an organ level, we observed increased mortality of respiratory and digestive disorders as well as hematopoietic neoplasms, which resemble the phenotype caused by genetic defects in telomere maintenance.[2] Leukocyte telomere length also associated with several lifestyle-related factors. While the study suggested an association of BMI and smoking with shorter LTL,[15-18] studies on alcohol and LTL are scarce and indicate a complex association that needs further exploration.[18] Collectively, the study data extend earlier findings and indicate that organs may vary in their susceptibility to organismal telomere shortening, as reflected by LTL. We found no association between LTL and overall cancer-related and neurological disease-related mortality, contradicting earlier reports.[4,5]

Among the specific mortality causes, the most significant association was seen for respiratory diseases and persisted after adjustment for smoking. Emphysema-related deaths were particularly overrepresented in individuals with

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reduced LTL. This association was supported by experimental data that demonstrated that mice with shorter telomeres are susceptible to emphysema development.[19] Although chronic obstructive pulmonary disease–related deaths were significantly enriched in participants with reduced LTL, the HR was lower, which aligned with several studies indicating a modest association.[13,20] As potential underlying mechanisms, reduced LTL was not only associated with oxidative stress and a higher rate of pneumonia, but was also directly associated with an increase in the susceptibility of participants to an experimentally-induced respiratory infection.[14,21,22]

We detected a clear association between shorter LTL and excess mortality related to digestive disorders. It was attributed primarily to increased liver-related fatalities and remained significant after adjusting for multiple factors, including alcohol consumption. Although genetic and experimental studies demonstrated the negative association of short telomeres with development of liver disease,[23,24] to our knowledge, a direct association with LTL remained to be demonstrated, likely because liver-related death represents less than 5% of overall mortality. A possible explanation is the major role the liver plays in immune and inflammatory responses.[25]

Among other death causes, a modest but highly significant association between shorter LTL and increased cardiovascular mortality was seen, which is supported by previous reports.[26,27] This is unsurprising, because a healthy lifestyle with abundant physical activity attenuates telomere attrition,[16,18] while hypertension and insulin resistance promote it.[21] The observed surplus mortality from hematopoietic neoplasms in individuals with reduced LTL is plausible because shorter LTL indicates increased leukocyte stress. Moreover, LTL was diminished in participants with acute myeloid leukemia or aggressive non-Hodgkin lymphoma,[28,29] for which reduced LTL previously associated with stronger chromosomal aberrations.[28]

Lastly, we detected a clear association between shorter LTL and death of musculoskeletal diseases, such as rheumatoid arthritis. While previous reports about LTL in rheumatoid arthritis are unequivocal,[30,31] increased inflammation was associated with shorter LTL.[32,33] This is interesting, because reduced LTL may identify a subset of patients with poorly controlled rheumatoid arthritis and persistent inflammation, as suggested for participants with asthma or periodontitis.[33,34]

Because of the large data set, we explored the association of LTL with individual phecodes. The study results confirmed a strong association with specific disorders, such as pulmonary fibrosis or aortic aneurysm, that is well documented in the literature.[20,35,36] The study data demonstrate that the association with LTL may markedly differ within the same disease group, which is best exemplified by the assessed cancer entities. In these, a positive association between shorter LTL and esophageal/oropharyngeal cancer was seen, which corroborates previous observations and may be associated with a strong negative effect of smoking and alcohol consumption.[37,38] Moreover, hematopoietic neoplasms were enriched in people with shorter LTL, which is consistent with a previous report.[39] In contrast, but in line with the literature,[40] this study revealed a negative association between shorter LTL and occurrence of melanoma or lung cancer, which seems contraintuitive given its association with smoking. Notably, earlier studies were inconclusive, and the association may depend on the histological subtype.[41]

Finally, a limited number of phecodes are overrepresented in individuals with longer LTL, including various benign neoplasms. Because several of them have been associated with longer telomeres,[42,43] it is tempting to hypothesize that increased LTL either protect from the emergence of malignant tumors, possibly because of increased chromosomal stability, or promote benign lesions growth by reduced senescence.

Limitations

While the PheWAS analysis is well suited to identify many LTL-associated conditions, the missing temporal information may introduce reverse causation bias. To address that, we validated the top hits in a time-to-event assessment. The UKB is not an entirely representative population sample, as 94% of participants are White, high-income British individuals.[44] Moreover, outcomes based on *ICD-10* codes may have some degree of misclassification or underdiagnosis.

Conclusions

This cohort study, which to our knowledge is the largest study of telomere length, found that LTL is associated with specific human diseases and organ manifestations. In particular, individuals with short LTL were susceptible to similar disorders as participants with inherited telomere diseases, suggesting that LTL may contribute to specific illnesses irrespectively of the biology of different genetic variants. However, an association study cannot distinguish between causes and consequences. Shorter LTL may indicate a stressed bone marrow rather than per se predisposing to hematologic disorders. Further studies are needed to identify the underlying mechanisms and to delineate the relative contribution of genetic vs lifestyle-related factors.

ARTICLE INFORMATION

Accepted for Publication: October 7, 2021.

Published Online: January 18, 2022. doi:10.1001/jamainternmed.2021.7804

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Conflict of Interest Disclosures: Dr Strnad reported grants and personal fees from Arrowhead Pharmaceuticals, Vertex Pharmaceuticals, CLS Pharmaceuticals, and Grifols and personal fees from Dicerna Pharmaceuticals and Takeda outside the submitted work. No other disclosures were reported.

Funding/Support: This research was conducted using the UK Biobank Resource. Dr C. V. Schneider is supported by Walter-Benjamin Fellowship from German Research Foundation (SCHN-1640/1-1). Dr K. M. Schneider is supported by the German Research Foundation consortium (SCHN 1626/1-1). Dr Strnad is supported by grants from the German Research Foundation consortium (SFB 1382 "Gut-liver axis"; STR 1095/6-1 [Heisenberg professorship]).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Lev Litichevsky and Claudia Kraft, Perelman School of Medicine, for their consultation regarding computational techniques without compensation.

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Invited Commentary

Interpreting Geroscience-Guided Biomarker Studies

Scott R. Bauer, MD, ScM; John C. Newman, MD, PhD

Should I pay out of pocket *to have my telomeres measured? My telomeres are shorter than average—what does that mean? Are there treatments to lengthen my telomeres?*

These questions from patients will become increasingly common with the growing access to commercial putative aging biomarker products. Although offering these products directly to consumers is surely premature, the basic and translational science that inspires these products is a serious and exciting endeavor with immense potential.[1,2]

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Chronological aging is a major risk factor for most chronic diseases, multimorbidity, and geriatric syndromes, and progresses at the same rate for everyone. Conversely, biological aging, the mechanism by which chronological age affects risk of age-related conditions, changes at different rates based on individual genetics, environmental and early life exposures, and health-related behaviors. Clinicians already use clinical surrogates of biological age, including physical and cognitive function, functional status, and frailty, which increase with age at the population level but vary widely within individuals of the same chronological age. Advances in basic science have led to the identification of multiple biological mechanisms, or "hallmarks" of aging, including genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, and telomere attrition or shortening.[3] The geroscience hypothesis posits that modulating these biological mechanisms of aging will delay, prevent, or treat multiple age-related diseases and conditions simultaneously, prolonging the healthy years of life.[1] As part of the effort to test this hypothesis in humans, the development of measures of biological aging (geroscience-guided biomarkers) has become an explicit goal of researchers on aging and geroscience experts.[2,4] They argue that geroscience-guided biomarkers could inform the understanding of pathophysiologic mechanisms of aging in disease, act as surrogate end points in interventional clinical trials, guide therapies targeting these mechanisms, and strengthen individual age-related risk prediction models. As a growing chorus of thought leaders advocate that both researchers on aging[2] and clinicians who treat older patients[1] embrace geroscience, those new to the field may not be aware of the multiple potential uses of geroscience-guided biomarkers.

In this issue of *JAMA Internal Medicine*, Schneider et al[5] report that mean leukocyte telomere length (LTL), a geroscience-guided biomarker candidate, is associated with overall and disease-specific mortality in a large prospective cohort study. Mean LTL was measured at a single baseline visit for more than 470 000 UK BioBank participants who were enrolled at a median (range) age of 56 (37-73) years and followed up for a mean of 12 years. The authors found that shorter mean LTL was associated with a small but statistically significant increased risk of all-cause mortality, particularly for respiratory disease, liver disease, and hematopoietic cancers, as well as COVID-19. The associations were independent of sex, body mass index, ethnicity, health-related behaviors, and, importantly, chronological age. Mean LTL was not associated with risk of death from neurological and endocrine diseases or other cancers. This study is notable for several reasons. First, the findings support the premise, based on the geroscience hypothesis,[1] that a single biomarker based on a biological mechanism of aging could be associated with numerous causes of death, particularly from age-related conditions. Second, an association between mean LTL and all-cause mortality has been inconsistently observed in prior studies; indeed, the ability of mean LTL to predict death has been appropriately questioned.[6] Lastly, observed associations between mean LTL and death due to pulmonary diseases is supported by the mechanistic link between telomere gene mutations and idiopathic pulmonary fibrosis.[7] To help readers interpret and contextualize these results, we will describe our approach to evaluating the geroscience-guided biomarker literature based on both research and clinical uses.

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