ARTICLE

Shorter leukocyte telomere length is associated with higher risk of infections: a prospective study of 75,309 individuals from the general population

Jens Helby,[1,2,3] Børge G. Nordestgaard,[1,2,3,4] Thomas Benfield[3,5] and Stig E. Bojesen[1,2,3,4]

[1]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital; [2]The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital; [3]Faculty of Health and Medical Sciences, University of Copenhagen; [4]The Copenhagen City Heart Study, Bispebjerg and Frederiksberg Hospital, Copenhagen University Hospital and [5]Department of Infectious Diseases, Hvidovre Hospital, Copenhagen University Hospital, Denmark

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ABSTRACT

In the general population, older age is associated with short leukocyte telomere length and with high risk of infections. In a recent study of allogeneic hematopoietic cell transplantation for severe aplastic anemia, long donor leukocyte telomere length was associated with improved survival in the recipients. These findings suggest that leukocyte telomere length could possibly be a marker of immune competence. Therefore, we tested the hypothesis that shorter leukocyte telomere length is associated with higher risk of infectious disease hospitalization and infection-related death. Relative peripheral blood leukocyte telomere length was measured using quantitative polymerase chain reaction in 75,309 individuals from the general population and the individuals were followed for up to 23 years. During follow up, 9228 individuals were hospitalized with infections and infection-related death occurred in 1508 individuals. Shorter telomere length was associated with higher risk of any infection (hazard ratio 1.05 per standard deviation shorter leukocyte telomere length; 95% confidence interval 1.03-1.07) and pneumonia (1.07; 1.03-1.10) after adjustment for conventional infectious disease risk factors. Corresponding hazard ratios for infection-related death were 1.10 (1.04-1.16) for any infection and 1.11 (1.04-1.19) for pneumonia. Telomere length was not associated with risk of skin infection, urinary tract infection, sepsis, diarrheal disease, endocarditis, meningitis or other infections. In conclusion, our findings indicate that leukocyte telomere length may be a marker of immune competence. Further studies are needed to determine whether risk of infections in allogeneic hematopoietic cell transplantation recipients can be reduced by considering donor leukocyte telomere length when selecting donors.

Correspondence:
stig.egil.bojesen@regionh.dk

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Introduction

Telomeres are located at the chromosome tips and are composed of protein and tandem repeats of the nucleotide sequence TTAGGG.[1] In most cell types, the telomeric DNA becomes shorter with each mitotic cell division due to the end replication problem.[2,3] If telomeres reach a critically short length, further cell divisions may not be possible and cells become senescent or undergo apoptosis.[1,4]

In the general population, older age is associated with short telomere length in peripheral blood leukocytes and with high risk of infections,[5-7] but it is currently unknown whether short leukocyte telomere length is a cause of impaired immune competence.[8] In a recent study of allogeneic hematopoietic cell transplantation (allo-HCT) for severe aplastic anemia, long donor leukocyte telomere length was

Table 1. Baseline characteristics of 75,309 individuals from the general population according to age-adjusted quartiles of leukocyte telomere length.

Characteristic	Telomere length quartiles 1st (longest)	2nd	3rd	4th (shortest)
Individuals, n.	18,800	18,834	18,816	18,859
Relative telomere length, T/S-ratio	0.79 (0.74-0.88)	0.65 (0.61-0.68)	0.56 (0.52-0.59)	0.45 (0.41-0.50)
Age, years	57 (47-67)	57 (47-67)	57 (47-67)	57 (47-67)
Male sex, n.	7875 (42)	8295 (44)	8547 (45)	9059 (48)
Ever smokers, n.	11,091 (59)	11,415 (61)	11,646 (62)	11,984 (64)
Cumulative smoking[#], pack-years	17 (7-31)	18 (7-33)	19 (8-34)	20 (9-35)
Alcohol consumption >168/84 g/week[†], n.	7047 (37)	7279 (39)	7301 (39)	7027 (37)
Body mass index, kg/m^2	25.4 (23.0-28.2)	25.5 (23.2-28.5)	25.7 (23.2-28.5)	25.8 (23.3-28.8)
Any comorbidity[§], n.	3549 (19)	3721 (20)	3820 (20)	3898 (21)
Previously hospitalized[‡], n.	8138 (43)	8092 (43)	8078 (43)	8306 (44)
C-reactive protein, mg/L	1.4 (1.0-2.5)	1.5 (1.1-2.5)	1.5 (1.1-2.6)	1.6 (1.1-2.7)

Number (n.) (%) is shown for categorical variables and median (interquartile range, IQR) is shown for continuous variables. [#]Ever smokers only. [†]>168 g/week for men and >84 g/week for women. [§]As defined by the Charlson comorbidity index. [‡]Defined as any inpatient hospitalization within ten years before study enrollment for any cause other than infections.

associated with improved long-term survival in the recipients.[9] Due to insufficient statistical power in the analysis of cause-specific deaths, the study could not identify the reason why survival was higher in patients receiving transplants from donors with long leukocyte telomere length. Since infections are among the leading causes of death in aplastic anemia patients treated with allo-HCT,[10,11] a possible explanation could be that leukocyte telomere length is a marker of overall immune competence in the donor. However, no previous studies have examined the association between telomere length and risk of hospitalization for infectious disease in the general population, and studies on telomere length and risk of infection-related death have produced conflicting results.[12-15] If leukocyte telomere length is a marker of overall immune competence in the general population, it would indicate that shortening of telomeres may be one of the biological mechanisms underlying age-related decline in adaptive immunity and increase in infectious disease susceptibility. It is currently unknown whether a marker of immune competence can be useful for making decisions on treatment or other health interventions in individuals from the general population, but such a marker may potentially be useful when selecting donors for allo-HCT. Therefore, examination of the possible association between leukocyte telomere length and immune competence could provide important information of clinical as well as biological relevance.

Given this, we studied 75,309 individuals from the general population to test the hypothesis that shorter telomere length in leukocytes is associated with higher risk of hospitalization for infectious disease and higher risk of infection-related death. All individuals had telomere length measured in peripheral blood leukocytes at study enrollment and the participants were prospectively followed for up to 23 years for hospitalization for infectious disease and death.

Methods

Participants

We studied 75,309 individuals from two studies of the general population: 8681 individuals from the Copenhagen City Heart Study[16,17] (enrolled between 1991 and 1994) and 66,628 individuals from the Copenhagen General Population Study[18,19] (enrolled between 2003 and 2012). Using the Danish Civil Registration System,[20] which includes a unique identification number for all individuals with permanent residence in Denmark, the participants were randomly invited to represent the general population aged 20-100 years. In the Copenhagen City Heart study, 61% of the invited individuals participated, and in the Copenhagen General Population Study, 46% participated. At the day of examination, all participants completed a questionnaire on lifestyle and health, underwent a physical examination, and had blood samples drawn. None of the individuals participated in both studies. Among the participants, more than 99% were white and of Danish descent. No participants were lost to follow up. The studies were approved by Danish ethical committees and all participants provided written, informed consent.

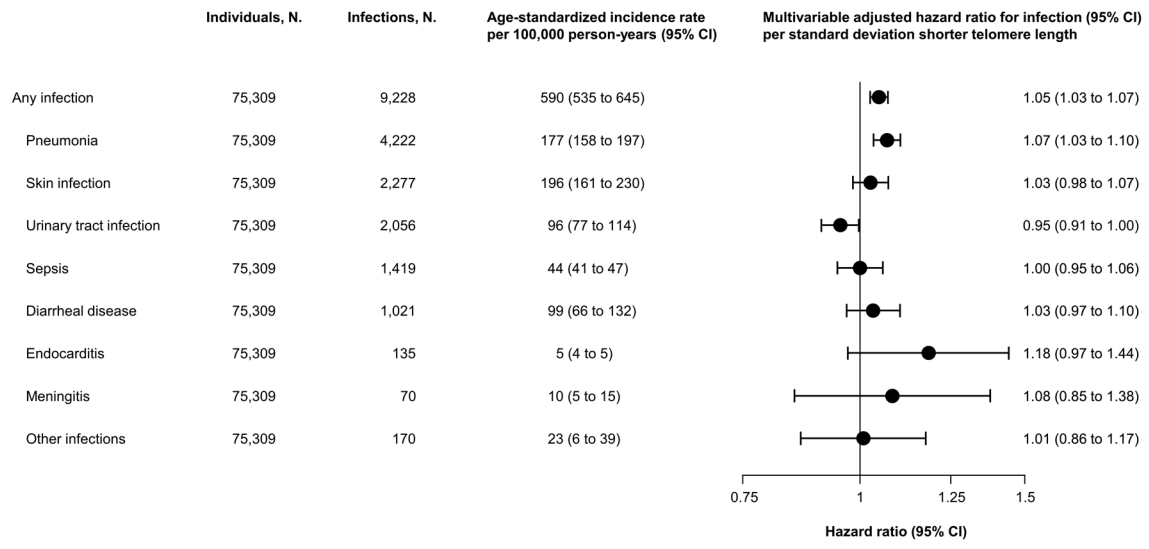

Figure 1. Risk of first hospitalization for any infection and specific infections in the general population per standard deviation shorter telomere length. The sum of specific infections exceeds the number of any infection since some individuals had more than one type of infection. Multivariable models were adjusted for values at study enrollment of age, sex, smoking status, cumulative smoking in pack-years, alcohol consumption, body mass index, plasma C-reactive protein level, Charlson comorbidity index, number of non-infectious disease hospitalizations within ten years before study enrollment, and study cohort. CI: confidence interval

Covariates

All included covariates were chosen *a priori* based on previous studies reporting them to be associated with telomere length and risk of infections.[19,21-24] Information on age and sex was obtained from the Danish Civil Registration system, while information on smoking status (current/former/never), cumulative smoking in pack-years (with one pack-year defined as 20 cigarettes or equivalent per day for a year), alcohol consumption (none/moderate/heavy, with heavy defined as >168 g/week for men and >84 g/week for women, as recommended by The Danish Health Authority), and body mass index (measured weight in kilograms divided by measured height in meters squared) was derived from the questionnaire and physical examination. As a marker of inflammation, plasma high-sensitivity C-reactive protein level at study enrollment was measured using standard hospital assays.

Telomere length measurements

After isolation of DNA from peripheral blood leukocytes using the Qiagen blood kit,[25] relative telomere length was measured by a modified monochrome multiplex quantitative polymerase chain reaction (qPCR) method,[26] as previously described in detail elsewhere.[19,21] The qPCR method was chosen since this is the only available method for high-throughput measurements of telomere length.[1,27] In short, the telomere template was amplified simultaneously with the single copy gene for albumin in the same well to adjust for different amounts of DNA in the samples. All samples were run in quadruplicates. For each sample, we calculated the ratio between telomere (T) repeat copy numbers and single gene (S) copy numbers, and the relative telomere length expressed as the T/S ratio was derived through calibration with measurements on K562 cell line DNA, which was included in each plate. Using this method, the T/S ratio of the K562 cell line DNA is by definition set to 1, so samples with shorter telomere length than K562 cell line DNA have T/S ratios below 1 while samples with longer telomere length than K562 cell line DNA have T/S ratios above 1.[26] To obtain a functional single-calibrator measurement, telomere length measurements were adjusted across calibrator lots, as described in detail in the *Online Supplementary Methods*. The laboratory technician performing all measurements was blinded to infectious disease endpoints and deaths.

Genotypes

An inherent limitation of observational studies on biomarkers and risk of disease is their inability to determine whether a biomarker are having a causal effect on the risk of disease, or if any found associations could be due to confounding or reverse causation. A way of overcoming this limitation is to study whether single nucleotide polymorphisms (SNPs) that influence the level of a biomarker are also associated with risk of disease. Using this approach, we genotyped participants for the three SNPs, rs1317082, rs7726159, and rs2487999, to examine whether a genetic predisposition to shorter telomere length is associated with risk of infections. The 3 SNPs were chosen based on a genome wide association study including 26,089 individuals, which found they were the SNPs most strongly associated with measured leukocyte telomere length.[28] The three genotypes were combined into an overall unweighted allele score, taking values from 0 to 6, which was calculated as the sum of the number of telomere length shortening alleles for each of the three genotypes. Since there were only 68 individuals with 0 telomere length shortening alleles, individuals with an unweighted allele score of 0 and 1 were combined into a single group. Similarly, a weighted allele score was constructed by first assigning each SNP a weight according to the SNPs average per allele effect size on measured T/S ratio, and then calculating the sum of weighted telomere shortening alleles for the three SNPs combined. To increase power, genotyping was also performed on participants from the two general population studies for whom measured telomere length was not available, leading to a total of 107,693 individuals genotyped.

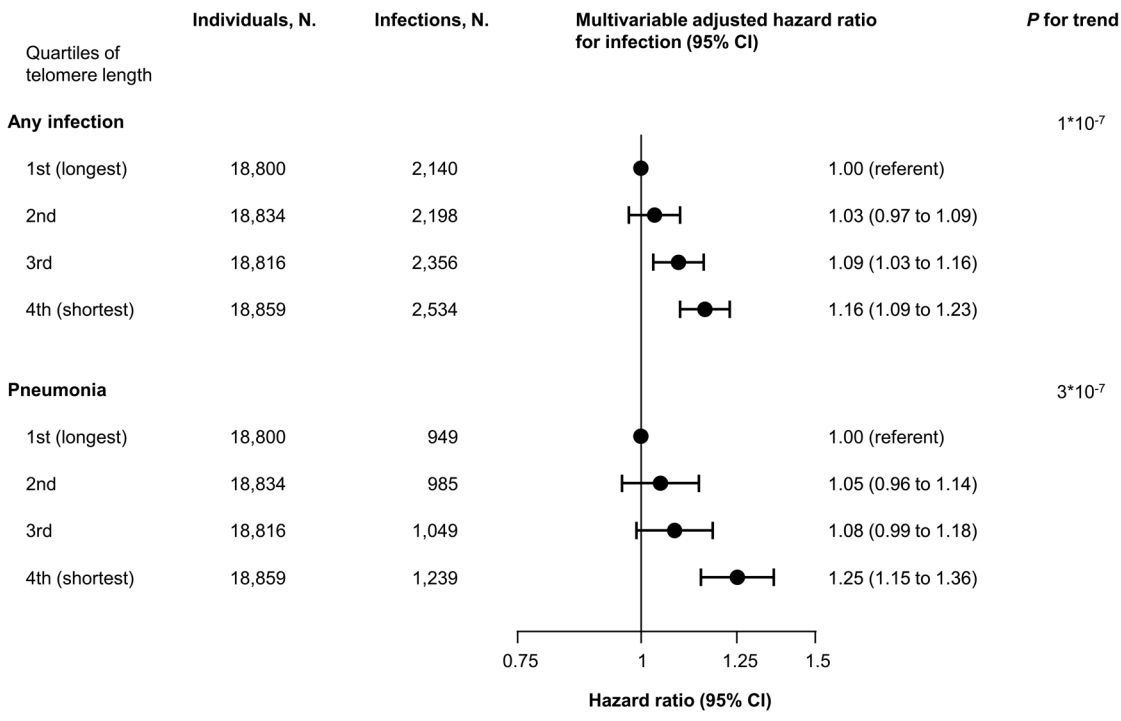

Figure 2. Risk of first hospitalization for any infection and pneumonia in the general population according to age-adjusted quartiles of telomere length. Multivariable models were adjusted for values at study enrollment of age, sex, smoking status, cumulative smoking in pack-years, alcohol consumption, body mass index, plasma C-reactive protein level, Charlson comorbidity index, number of non-infectious disease hospitalizations within ten years before study enrollment, and study cohort. CI: confidence interval.

More details on genotyping are described in the *Online Supplementary Methods.*

Infectious disease endpoints

Using the national Danish Patient Registry,[29] which covers all Danish hospitals, we obtained information for each individual participant on inpatient hospitalizations with a primary discharge diagnosis of an infectious disease from January 1st 1977 until November 5th 2014. Likewise, we obtained information from the national Danish Patient Registry on emergency room visits with a primary diagnosis of an infectious disease from January 1st 1994 until November 5th 2014. Information on vital status and date of death until November 5th 2014 was retrieved from the Danish Civil Registration system. For participants who died before December 31st 2012, information on infection-related deaths was obtained from the national Danish Register of Causes of Death,[30] which covers all deaths in Denmark and registers all diagnoses that a physician has listed on the death certificate as contributing to the cause of death. More details on classification of infectious disease endpoints are described in *Online Supplementary Table S1* and in the *Online Supplementary Methods.*

Comorbidities

Non-infectious comorbidities could possibly confound the association between telomere length and risk of infections, since short leukocyte telomere length has been found in individuals with chronic conditions such as heart failure[31] and chronic obstructive pulmonary disease,[32] and individuals with these conditions are also at high risk of infections.[22,24] To reduce such confounding, comorbidities at study enrollment were assessed using the Charlson comorbidity index,[33] which is a severity weighted measure of comorbid conditions that has been validated for its ability to predict mortality.[34,35] Individuals at high risk of undiagnosed comorbidities were identified using measurements of white blood cell differential count, platelet count, blood hemoglobin, plasma alanine aminotransferase, plasma creatinine, and non-fasting plasma glucose at study enrollment. These measurements were chosen as a broad screening for hematologic, hepatic, renal, and metabolic diseases. More details on assessment of comorbidities are described in the *Online Supplementary Methods.*

Statistical analysis

Statistical analyses were performed with Stata v. 13.1. All statistical tests were two-sided. Since several studies have documented a strong association between higher age and shorter telomere length,[5,6,19] calculation of telomere length quartiles was adjusted for age by computing quartiles of telomere length separately for each one-year age span. To reduce risk of reverse causation (i.e. that subclinical infections already present at date of examination may influence leukocyte telomere length), individuals were only included in the analyses if they were not hospitalized with any infection during the first 180 days after the date of examination. Risk of infectious disease hospitalization and risk of infection-related death were modeled separately by Cox proportional hazards regression using left-truncated age as the timescale, as described in detail in the *Online Supplementary Methods.* For the analyses on measured telomere length and risk of hospitalization for infectious disease, and for risk of infection-related death, follow up began 180 days after the date of examination. Multivariable models were adjusted for values at study enrollment

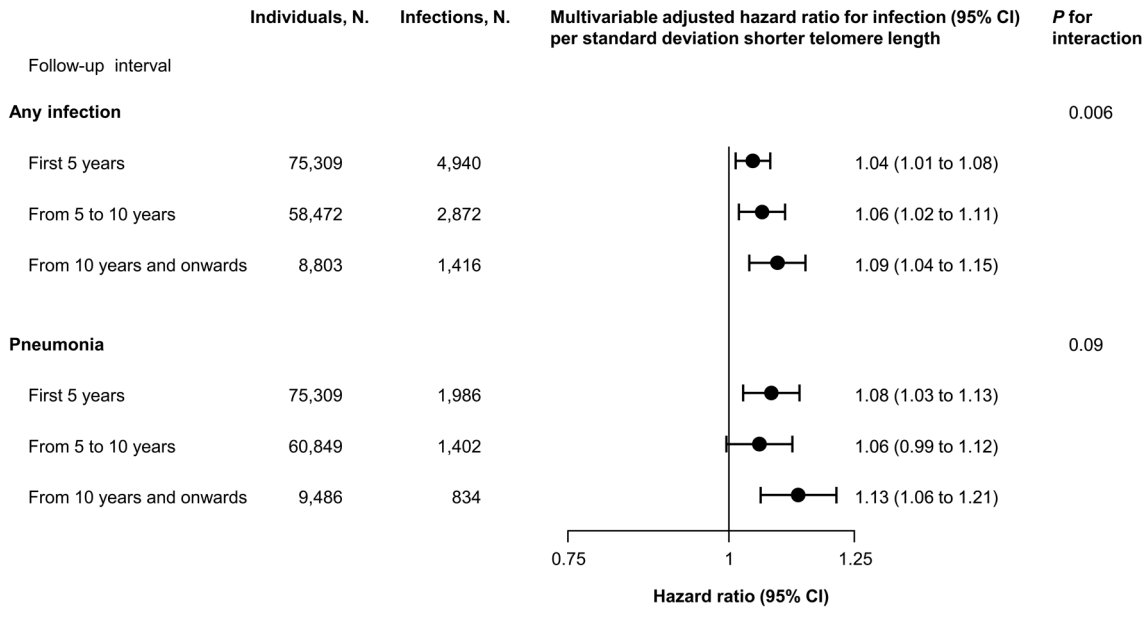

Figure 3. Risk of first hospitalization for any infection and pneumonia in the general population per standard deviation shorter telomere length stratified according to follow-up interval. Multivariable models were adjusted for values at study enrollment of age, sex, smoking status, cumulative smoking in pack-years, alcohol consumption, body mass index, plasma C-reactive protein level, Charlson comorbidity index, number of non-infectious disease hospitalizations within ten years before study enrollment, and study cohort. *P* for interaction was calculated using a likelihood ratio test, comparing models with and without an interaction term. CI: confidence interval.

of age, sex, smoking status, cumulative smoking in pack-years, alcohol consumption, body mass index, plasma C-reactive protein level, Charlson comorbidity index, number of non-infectious disease hospitalizations within ten years before study enrollment, and study cohort.

Results

Among 75,309 individuals from the general population, older age was strongly associated with shorter leukocyte telomere length with a mean lower T/S ratio of 0.0032 [95% confidence interval (CI): 0.0032-0.0033; linear regression $P<1*10^{-300}$; R-squared=0.073] for each year of older age. Therefore, baseline characteristics are shown after adjustment for age by calculation of age-adjusted quartiles of telomere length (Table 1).

Telomere length and risk of infections

During a median follow up of seven years (range 0-23 years), 9228 individuals were hospitalized due to infections. When examining risk of first hospitalization for infection after study enrollment, a one standard deviation shorter leukocyte telomere length was associated with higher risk of any infection [hazard ratio (HR) 1.05; 95%CI: 1.03-1.07] and pneumonia (HR 1.07; 95%CI: 1.03-1.10) (Figure 1). We found no association between telomere length and risk of skin infection, urinary tract infection, sepsis, diarrheal disease, endocarditis, meningitis, or other infections. Similarly, when examining risk of first hospitalization for infection according to age-adjusted quartiles of telomere length, increasing quartiles of telomere length were associated with higher risk of any infection (*P* for trend=$1*10^{-7}$) and pneumonia (*P* for trend=$3*10^{-7}$) (Figure 2). Hazard ratios for the shortest *versus* the longest quartile of telomere length were 1.16 (95%CI: 1.09-1.23) for any infection and 1.25 (95%CI: 1.15-1.36) for pneumonia.

When including both first and recurrent infectious disease hospitalizations (*Online Supplementary Figure S1*), risk estimates per standard deviation shorter telomere length were similar to those from the analysis on risk of first hospitalization for infectious disease (Figure 1).

Stratified analyses on risk of infections

To investigate whether the association between shorter telomere length and higher risk of any infection and pneumonia may be due to reverse causation, we performed stratified analyses according to follow-up interval. We found no indication of reverse causation, as risk estimates for any infection became more pronounced as more time elapsed after study enrollment (*P* for interaction with follow-up interval=0.006), while risk estimates for pneumonia were largely stable across follow-up intervals (*P* for interaction with follow-up interval=0.09) (Figure 3).

To further examine the robustness of the association between shorter telomere length and higher risk of any infection and pneumonia, we performed stratified analyses according to strata of the covariates that were included in the multivariable models (Figure 4 and *Online Supplementary Figure S2*). To additionally reduce confounding by comorbidities that may be undiagnosed at study enrollment, we also performed stratified analyses according to whether or not participants had normal blood laboratory tests at study enrollment. In all of the above mentioned strata, risk estimates remained stable for any infection (Figure 4) and pneumonia (*Online Supplementary Figure S2*).

As previous studies have found that shorter telomere

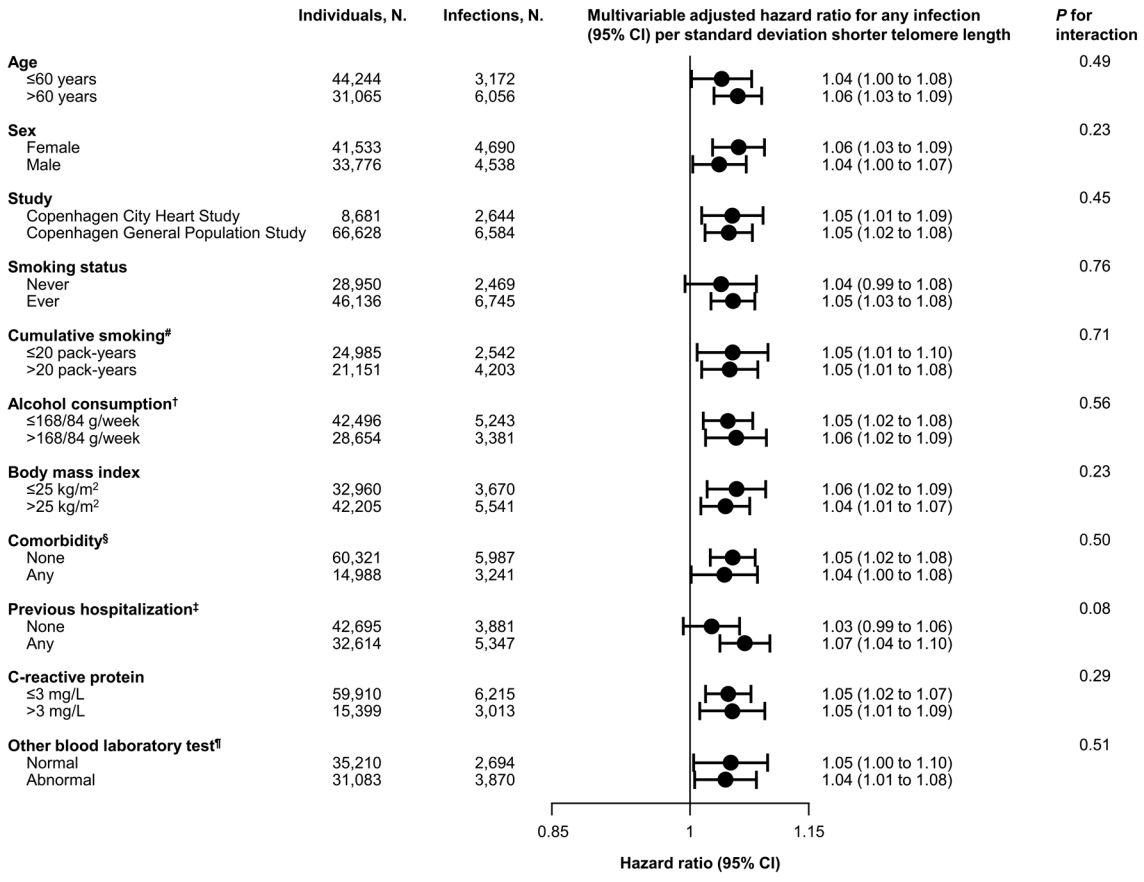

Figure 4. Stratified analyses for risk of first hospitalization for any infection per standard deviation shorter telomere length. Number of individuals at risk and number of infections vary slightly among the stratifications due to varying numbers of individuals with missing data on each of the covariates. Multivariable models were adjusted for values at study enrollment of age, sex, smoking status, cumulative smoking in pack-years, alcohol consumption, body mass index, plasma C-reactive protein level, Charlson comorbidity index, number of non-infectious disease hospitalizations within ten years before study enrollment, and study cohort. *P* for interaction was calculated using a likelihood ratio test, comparing models with and without an interaction term. CI: confidence interval. #Ever smokers only. †>168 g/week for men and >84 g/week for women. §As defined by the Charlson comorbidity index. ‡Defined as any inpatient hospitalization within ten years before study enrollment for any cause other than infections. ¶Includes measurements of white blood cell differential count, platelet count, blood hemoglobin, plasma alanine aminotransferase, plasma creatinine, and non-fasting plasma glucose.

length was associated with higher risk of cardiovascular disease,[21,36-39] and since cardiovascular disease is associated with high risk of infections,[22,24] we investigated whether the observed association between shorter telomere length and risk of infections may be secondary to cardiovascular disease. Risk estimates for any infection and pneumonia remained stable when the analyses were stratified according to whether or not individuals were diagnosed with any type of cardiovascular disease at study enrollment or during follow up (*Online Supplementary Figure S3*). Similarly, risk estimates for any infection and pneumonia were stable when including cardiovascular disease diagnosed at study enrollment or during follow up as a time-dependent variable in the multivariable model (*Online Supplementary Figure S4*).

Telomere length and risk of infection-related death

One standard deviation shorter telomere length was associated with higher risk of death related to any infection (HR 1.10; 95%CI: 1.04-1.16) and pneumonia (HR 1.11; 95%CI: 1.04-1.19) (Figure 5). We found no association between shorter telomere length and risk of death related to sepsis, urinary tract infection, diarrheal disease, endocarditis, skin infection, or other infections. For meningitis, exact calculations of risk estimates were not possible since there were only 2 meningitis-related deaths. Since previous studies on telomere length and risk of infection-related death have produced conflicting results which could potentially be explained by limited statistical power,[12-15] we performed power calculations based on the risk estimates from our present study and the number of participants and deaths reported in previous studies (*Online Supplementary Table S2*). All four previous studies each had less than 15% power to detect a hazard ratio for any infection-related death of 1.10 per standard deviation shorter telomere length at two-sided $P<0.05$.

Genetic predisposition to shorter telomere length and risk of infections

Among the 107,693 genotyped individuals, 21,317 individuals were hospitalized due to any infection during follow up (see *Online Supplementary Table S3* for baseline characteristics). Mean T/S ratio decreased by 0.012 (95%CI: 0.011-0.014) per telomere length shortening allele among the 75,018 individuals who had both leukocyte telomere length measurements and genotyping performed (linear regression on telomere length as a function of unweighted allele score: standardized β=-0.076; $P=2*10^{-97}$; R-squared=0.0058; same regression for weighted allele score: standardized β=-0.077; $P=6*10^{-99}$; R-squared=0.0059). For

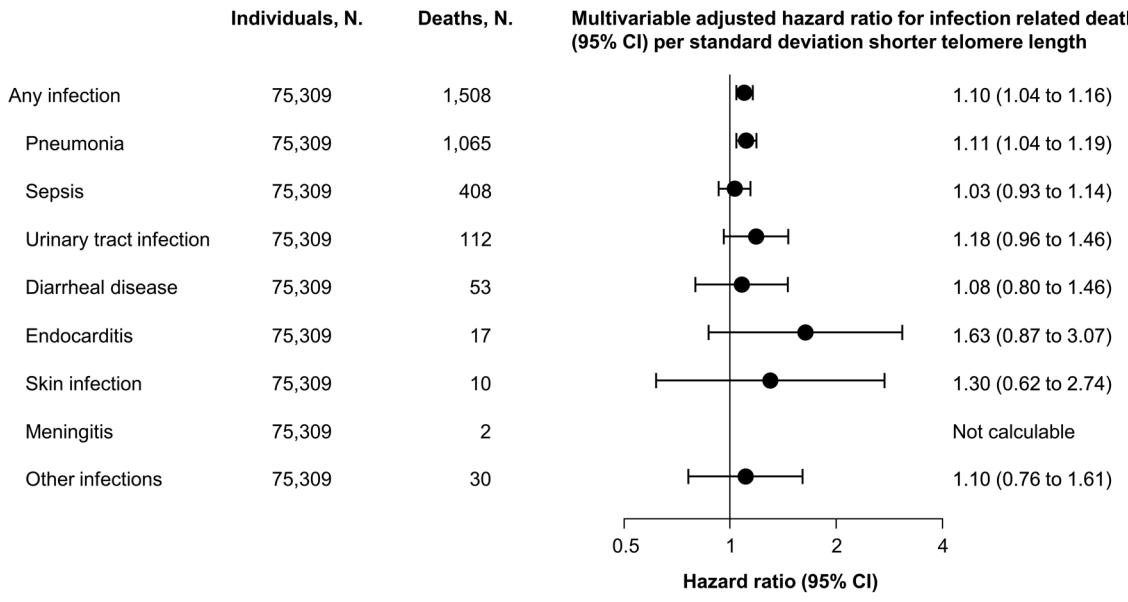

Figure 5. Risk of death related to any infection and death related to specific infections in the general population per standard deviation shorter telomere length. The sum of deaths related to specific infections exceeds the number of deaths related to any infection since some individuals had more than one type of infection listed on the death certificate. For meningitis, exact calculations of risk estimates were not possible since there were only 2 meningitis-related deaths. Multivariable models were adjusted for values at study enrollment of age, sex, smoking status, cumulative smoking in pack-years, alcohol consumption, body mass index, plasma C-reactive protein level, Charlson comorbidity index, number of non-infectious disease hospitalizations within ten years before study enrollment, and study cohort. CI: confidence interval.

both the unweighted and the weighted allele score, we found no association between a genetic predisposition to shorter telomere length and risk of hospitalization for any infection, pneumonia, skin infection, urinary tract infection, diarrheal disease, sepsis, meningitis, endocarditis or other infections (*Online Supplementary Figures S5-S7*). Importantly, however, genetic risk estimates did not differ from observational estimates, but as seen from the power calculation in the *Online Supplementary Results*, the rather modest influence of the SNPs on telomere length leads to very limited power in the analyses on a genetic predisposition to shorter telomeres and risk of infections, despite the large number of individuals genotyped.

Discussion

In this prospective study of 75,309 individuals from the general population, we found that shorter leukocyte telomere length was associated with higher risk of hospitalization due to any infection and pneumonia. Likewise, shorter leukocyte telomere length was associated with higher risk of death related to any infection and pneumonia. Our findings on telomere length and risk of hospitalization for infectious disease are novel, while our findings on risk of infection-related death corroborate the previous studies on this subject, which had produced conflicting results.[12-15] The higher risk of infections in individuals with shorter leukocyte telomere length could possibly be caused by impaired adaptive immune function as a consequence of short lymphocyte telomere length. This possible mechanism is supported by a study on the immune response after influenza vaccination,[40] which found that individuals with long telomere length in B-lymphocytes produced a more robust antibody response when compared to individuals with short B-lymphocyte telomere length. Likewise, when presented with a synthetic influenza peptide *in vitro*, influenza-specific $CD8^+$ T-lymphocytes with long telomere length showed higher proliferative capacity than those with short telomere length.[40] This indicates that telomere length in subtypes of lymphocytes may be directly related to the effectiveness of the adaptive immune response. Furthermore, aging leads to increasing numbers of $CD8^+$ T-lymphocytes undergoing replicative senescence, and these senescent lymphocytes are characterized by short telomere length and no expression of the co-stimulatory molecule CD28 which is necessary for proliferation.[41-44] Combined with our results, these findings suggest that shortening of telomeres is likely to be one of the mechanisms underlying age-related decline in adaptive immunity and increased susceptibility to infectious disease.[7,8]

Our finding that shorter leukocyte telomere length was associated with higher risk of hospitalization due to any infection and pneumonia is novel, as no previous studies have examined the association between leukocyte telomere length and risk of hospitalization for infectious disease in the general population. Nonetheless, our results are supported by a study on 152 individuals,[45] which found that shorter telomere length in peripheral blood mononuclear cells was associated with higher risk of rhinovirus infection in healthy volunteers who were quarantined and experimentally exposed to nasal drops containing rhinovirus. When we investigated risk of specific types of infection, shorter telomere length was associated exclusively with higher risk of pneumonia. However, hazard ratios per standard deviation shorter telomere length was consistently above 1 for skin infection, diarrheal disease, endocarditis and meningitis, although these findings were not statistically significant at a level of $P<0.05$. Hypothetically, our finding that pneumonia was the only specific type of infection with higher risk in individuals with shorter telomeres could

simply be due to the high number of hospitalizations for pneumonia in the general population, leading to more statistical power in the analysis on risk of pneumonia than for other infections. Somewhat similar to our findings, individuals with humoral immunodeficiencies such as X-linked agammaglobulinemia, common variable immunodeficiency, and selective immunoglobulin A deficiency have especially pronounced risk of bacterial respiratory tract infections, often caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.[46] We did not have information on specific causative pathogens for hospitalizations for pneumonia in the present study, but other studies have found *Streptococcus pneumoniae* and *Haemophilus influenzae* to be among the most common causes of bacterial pneumonia in the general population.[47,48] Hence, the pattern of risk of infectious disease associated with shorter telomere length may to some degree resemble what has been reported for specific deficiencies of the humoral immune response.

Our finding that shorter leukocyte telomere length was associated with higher risk of death related to any infection is supported by two independent prospective cohort studies, which together included a total of 1260 individuals, of whom 83 died from infectious diseases.[12,13] However, two other prospective cohort studies including a total of 3319 individuals and 90 infectious disease deaths found no association between telomere length and risk of death due to infectious disease.[14,15] When calculating power based on the risk estimates from our present study and the number of participants and deaths reported in previous studies, the four previous studies each had less than 15% power to detect the risk estimate for any infection-related death found in the present study. This suggests that the conflicting results from previous studies could possibly be related to limited statistical power because of the modest number of deaths from infectious disease in the study populations, which is less of a concern in our present study with 75,309 individuals and 1508 infection-related deaths. Importantly, the precision of the telomere length measurements also affects power, which is especially relevant since studies on telomere length and infection-related death have used different methods for measuring telomere length, and since the precision of the measurements may differ substantially between methods.[49,50]

The results from our study and those from previous studies suggest that leukocyte telomere length may be a marker of overall immune competence in the general population. It is still not known whether such a marker can be useful for making decisions on treatment or other health interventions in individuals from the general population. However, a marker of overall immune competence could potentially be useful when selecting donors for allogeneic hematopoietic cell transplantation (allo-HCT), where infections are among the leading causes of death in the recipients.[10,11] Theoretically, it may be possible to reduce the risk of serious infections and infection-related death in allo-HCT recipients by including donor telomere length in the selection criteria when selecting donors. Obviously, this hypothesis cannot be tested in a study of the general population, so further studies on donor telomere length and the risk of serious infections and infection-related death in allo-HCT recipients are needed.

Among the strengths of the current study is the prospective general population design, the large number of individuals studied, and the availability of detailed information on possible confounders such as smoking, alcohol intake, body mass index, hospital diagnosed comorbidities, and measurements of C-reactive protein as a marker of inflammation. Furthermore, as we have performed measurements of white blood cell differential count, platelet count, blood hemoglobin, plasma alanine aminotransferase, plasma creatinine, and non-fasting plasma glucose in a large subgroup of 66,818 individuals, we were also able to minimize confounding by undiagnosed comorbidities by stratifying the analyses on whether individuals had normal or abnormal values of these biomarkers. Due to the observational nature of the study, we are unable to determine with any certainty whether the association between leukocyte telomere length and risk of infections are due to a causal effect. In an attempt to investigate the question of causality, we examined the association between a genetic disposition to shorter telomere length and risk of infections in 107,693 individuals genotyped for the three SNPs that were reported to be most strongly associated with leukocyte telomere length in a genome wide association study of 26,089 individuals.[28] We found no association between a genetic predisposition to shorter telomere length and risk of any infection or any type of specific infections, which in principle indicates that the observational association between shorter telomere length and higher risk of infections is not due to a causal effect. However, these results should be interpreted with caution, as the rather modest influence of the SNPs on telomere length leads to low statistical power despite the large number of individuals genotyped, and this limits our ability to confirm or disprove any hypotheses of causality. Another limitation of our study is that we only have information on hospitalizations for infectious disease while information on cases of less serious infections that are typically treated by general practitioners is lacking. In theory, our findings could be biased if individuals with short telomere length appear frailer than other individuals, which could lead general practitioners to have a lower threshold for admitting these patients for hospital treatment. However, it is unlikely that our findings are caused solely by such a differential referral bias, as shorter telomere length was also associated with higher risk of death related to any infection and pneumonia.

In conclusion, we prospectively followed 75,309 individuals from the general population for up to 23 years and found that shorter leukocyte telomere length was associated with higher risk of any infection and pneumonia. These findings indicate that leukocyte telomere length may be a marker of immune competence among individuals from the general population. Further studies are needed to determine whether risk of infections in allo-HCT recipients can be reduced by considering donor leukocyte telomere length when selecting donors.

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