SUPPLEMENTARY APPENDIX

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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Correspondence: stig.egil.bojesen@regionh.dk

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

Authors: Jens Helby, Børge G. Nordestgaard, Thomas Benfield, and Stig E. Bojesen

Supplementary material:

Supplementary methods

Telomere length measurements

We used K562 cell line DNA as calibrator for all telomere length measurements and due to the large number of individuals with measurements performed (n=75,309), it was nessecerary to replenish supplies of the calibrator on several occasions. Hence, measurements were performed using 5 separate calibrator lots, each used for measurements on approximately 10,000-25,000 individuals. To obtain a functional single calibrator measurement, the measured T/S ratio from each individual was therefore adjusted to compensate for varying telomere length in the five calibrators. For each calibrator lot, we first calculated the mean T/S ratio of all samples measured using that calibrator lot, and for calibrator lots 2 to 5, the difference between the mean T/S ratio in each lot and the mean T/S ratio for calibrator lot 1 was calculated ($difference_{lotX}=mean_{lot1}-mean_{lotX}$). Each sample in calibrator lots 2 to 5 was then adjusted by adding the lot specific difference to the measured T/S ratio ($T/S\text{-}ratio_{adjusted}=T/S\text{-}ratio_{measured}+difference_{lotX}$). This adjustment improved overall correlation between T/S ratio and age in the study population (R-squared=0.025 for linear regression on unadjusted T/S-ratios as a function of age vs. R-squared=0.073 for adjusted T/S ratios). Likewise, the adjustment improved overall correlation between T/S ratio and allele score (R-squared=0.0044 for linear regression on unadjusted T/S-ratios as a function of unweighted allele score vs. R-squared=0.0058 for adjusted T/S ratios).

As a sensitivity analysis, we performed analyses on risk of infections using unadjusted T/S ratios and stratified according to calibrator lot number, which produced stable risk estimates per standard deviation shorter telomere length across all calibrator lots (Supplementary Figure S8). Similarly, results for the overall study population were similar to those presented in Figure 1 when using unadjusted T/S ratios but including calibrator lot number as a categorical variable with values 1 to 5 in the multivariable adjusted model (Supplementary Figure S9).

To assess precision of the measurements[1,2], telomere length was measured twice on separate dates in samples from 238 individuals with a mean T/S ratio of 0.64. Based on a one-way random-effects model[3], the individual intraclass correlation coefficient for repeated measurements of unadjusted T/S ratios on the same samples was 0.76 (95% CI 0.70-0.81).

Genotypes

A total of 107,693 individuals were genotyped for the three SNPs rs1317082, rs7726159, and rs2487999. All three SNPs are located in or near genes involved in the regulation of telomere length[4-6]: rs1317082 is located at the 3q26.2 locus which contains the TERC gene, rs7726159 is located at the 5p15.3 locus which contains the TERT gene and rs2487999 is located at the 10q24.3 locus which contains the OBCF1 gene. Individuals from the Copenhagen City Heart Study (n=9,430) were genotyped using an Illumina custom genotyping chip[7], while the Taqman method was used to genotype individuals from the Copenhagen General Population Study (n=98,263), as described in detail previously[8]. The distributions of all genotypes were in Hardy-Weinberg equilibrium when tested by chi^2-test (P=0.81 for rs1317082, P=0.86 for rs7726159 and P=0.77 for rs2487999).

Infectious disease endpoints

Classification of infectious disease events happening until December 31, 1993 was done using the World Health Organization's International Statistical Classification of Diseases, 8th revision (ICD-8), while the 10th revision (ICD-10) was used for events after this date. Based on the ICD-8 and ICD-10 codes listed in Supplementary Table S1, infectious diseases were sorted into the following 8 categories: Pneumonia, skin infection, urinary tract infection, sepsis, diarrhoeal disease, endocarditis, meningitis, and other infections. We have previously validated infectious disease diagnoses from the national Danish Patient Registry through a medical doctor specialized in infectious diseases reviewing detailed clinical information from hospital charts

on 141 admissions coded as infections in the registry[9]. In 139 of 141 admissions (99%), the hospital charts documented relevant signs and symptoms of infection, a positive culture from a sterile site or relevant specimen, and/or treatment with antibiotics.

Comorbidities

Based on previously published ICD-8[10] and ICD-10[11] codes for the Charlson comorbidity index, we retrieved information from the national Danish Patient Registry on inpatient hospitalizations, emergency room visits and outpatient hospital visits due to the following 17 disease categories: AIDS/HIV, any malignancy (including lymphoma and leukemia), cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes with complications, diabetes without complications, hemiplegia/paraplegia, metastatic solid tumors, mild liver disease, moderate/severe liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease, and rheumatic disease. As hospitalization in itself may increase risk of certain infections, we also retrieved information from the national Danish Patient Registry on the number of inpatient hospitalizations for any cause other than infections within 10 years before study enrollment.

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 hematological, hepatic, renal, and metabolic diseases. Among individuals who had these measurements performed (n=66,293), those with all of the above mentioned measurements within standard hospital reference ranges were classified as normal, while individuals were classified as having abnormal blood laboratory tests if at least one of the measurements were outside the reference range.

Statistical analysis

Infectious disease incidence rates were calculated per 100,000 person-years, and standardized according to 5-year age-groups with the World Health Organization world standard population[12].

Risk of infectious disease hospitalization and risk of infection-related death were modelled separately by Cox proportional hazards regression using left-truncated age as the timescale. For the analysis on measured telomere length and risk of first infectious disease hospitalization, follow-up began 180 days after date of examination and ended on date of infectious disease hospitalization, death due to any cause, emigration (n=343) or November 5, 2014, whichever came first. In the analysis on a genetic predisposition to short telomere length and risk of first infectious disease hospitalization, follow-up began on the participants 20th birthday or January 1, 1977, whichever came last, and follow-up ended on date of infectious disease hospitalization, death due to any cause, emigration or November 5, 2014, whichever came first. Events prior to start of follow-up were ignored in all analyses. For the analysis on measured telomere length and risk of infection related death, follow-up began 180 days after date of examination and ended on date of infection related death, death due to other causes, emigration or December 31, 2012, whichever came first. The proportional hazards assumption was assessed using Schoenfeld residuals and by plotting –ln(-ln(survival)) against ln(analysis time) without any mayor violations observed.

When analyzing combined risk of first and recurrent infectious disease hospitalizations, we used the conditional risk set model as described by Prentice, Williams and Peterson[13], with follow-up suspended at the time of each hospitalization and resumed 180 days after hospital discharge. For the analysis stratified according to follow-up interval, each participants follow-up was split into three time intervals: in the first interval, participants were followed from study enrollment until 5 years later, in the second interval, participants were followed from 5 until 10 years after study enrollment, and in the third interval, participants were followed from 10 years after study enrollment and onwards. To test whether risk estimates from two

models were different, the Z-test described by Altman and Bland was used[14]. For interaction analyses, P for interaction was calculated using a likelihood ratio test, comparing models with and without an interaction term.

For the multivariable models, sex , smoking status, alcohol consumption, body mass index, and study cohort was included as categorical variables, while age, cumulative smoking in pack-years, C-reactive protein level, Charlson comorbidity index and number of non-infectious disease hospitalizations within 10 years before study enrollment was included as continuous variables. We observed a J-shaped association between alcohol consumption and risk of any infection, as risk estimates were lowest for individuals with moderate alcohol consumption and higher for individuals with no alcohol consumption and for individuals with heavy alcohol consumption. Therefore, alcohol consumption was categorized into three groups: No alcohol consumption (0 gram/week), moderate alcohol consumption (1-168 g/week for men and 1-84 g/week for women, as recommended by The Danish Health Authority) and heavy alcohol consumption (>168 g/week for men and >84 g/week for women). Similarly, as we observed that individuals with body mass index 18.5-25 kg/m^2 had lower risk of infections than individuals who were underweight or overweight, body mass index was categorized into the following 6 groups: <18.5 kg/m^2, 18.5-25 kg/m^2, 25-30 kg/m^2, 30-35 kg/m^2, 35-40 kg/m^2 and >40 kg/m^2, respectively.

Information on age, sex, Charlson comorbidity index and number of non-infectious disease hospitalizations was available on all participants. For the remaining covariates, information was more than 98% complete. Missing data was coded as missing for the categorical variables smoking status, alcohol consumption and body mass index. For the continuous variable cumulative smoking, 1911 individuals had missing information, and these missing values were imputed based on a linear regression on cumulative smoking as a function of age, sex, smoking status and study cohort. Likewise, 1003 individuals had missing information on the continuous variable C-reactive protein level, and these missing values were imputed based on a linear

regression on C-reactive protein level as a function of age, sex and study cohort. However, after exclusion of participants with any missing values, all analyses gave results similar to those presented.

Supplementary results

Power calculation for a genetic predisposition to short telomeres and risk of infections

In the analysis on measured leukocyte telomere length and risk of first hospitalization for infection, the hazard ratio for any infection was 1.05 (95% CI 1.03-1.07) for a one standard deviation shorter telomere length (Figure 1). When performing a power calculation for the genetic analyses based on the weighted allele score and the Cox-model of 107,693 genotyped individuals and 21,317 first hospitalizations with any infection, we had only 8% power to detect a hazard ratio of 1.05 for a genetic predisposition to a one standard deviation shorter telomere length at two-sided $P<0.05$. Based on our observed incidence of hospitalization due to any infection, it would have required us to include 2.8 million individuals to have 80% power to detect a hazard ratio of 1.05 for a genetic predisposition to a one standard deviation shorter telomere length.

Supplementary Table S1: Categorization of infectious diseases according to the World Health Organization's International Statistical Classification of Diseases, revision 8 (ICD-8) and revision 10 (ICD-10)

Infectious disease category	ICD-8 codes	ICD-10 codes
Pneumonia	481xx-486xx	A481, J13-J16, J170, J18
Skin infection	03599, 680xx-684xx, 68501, 68509, 68600, 68608, 68609, 68690, 68691, 68692, 68695, 68696, 68699	A46, L00-L08, L303, L308F
Urinary tract infection	5900x, 5901x, 59099, 59500-59502, 59508, 59509, 59906	N109A-N109C, N110-N118B, N118D, N119, N12, N300, N308A-N308C, N309, N390
Sepsis	03610, 038xx	A021, A282B, A327, A392-A394, A40-A41, A427, A483, A499A, R572
Diarrhoeal disease	003xx-005xx, 008xx-009xx	A020, A022-A029, A03-A05, A08-A09
Endocarditis	421xx	I33, I38, I398
Meningitis	02701, 03609, 045xx, 05403, 07929, 320xx,	A390, A87, B003, B004A, G00-G01, G020, G039, G042
Other infections:		
Mycoses	110xx-112xx, 114xx-117xx	B35-B49
Hepatitis	070xx	B15-B19, Z225
Imported & parasitic infections	000xx-002xx, 006xx-007xx, 060xx-061xx, 084xx-087xx, 129xx-130xx, 13600, 13603	A00-A01, A06-A07, A90-A96, B50-B64
Influenza and viral lower respiratory tract infections	470xx-472xx, 48099	J09-J101C, J12, J171
HIV/AIDS	07983	B20-B24, F024, Z21
Tuberculosis	010xx, 011xx, 01200, 01208, 01209, 0121x-0129x, 013xx-018xx	A15-A19, N330, N740-N741
Parasitic worm diseases	120xx-128xx	B65-B83, N308J
Pertussis	03309, 03319	A37

Infectious disease categories are ranked according to the number of events in each category (highest to lowest).

Supplementary Table S2: Power calculations for the present study and previous studies on leukocyte telomere length and risk of death related to any infection.

	No. of participants	No. of infection related deaths	Power to detect a hazard ratio of 1.10 per standard deviation shorter telomere length at two sided p<0.05	Reported risk estimate for infection related death (95% confidence interval) from most adjusted model
Present study	75 309	1508	96%	Hazard ratio 1.10 (1.04-1.16) per standard deviation shorter telomere length
Previous studies				
Cawthon et al.[15]	124	8	5%	Mortality rate ratio 8.54 (1.52-47.9) for individuals from the bottom 25% of the telomere length distribution versus the top 75%
Njajou et al.[16]	2721	23	7%	Hazard ratio 0.8 (0.5–1.1) per 1000 base pair longer telomere length
Martin-Ruiz et al.[17]	598	67	12%	Hazard ratio 1.30 (0.72-2.39) for individuals in the tertile with longest telomeres vs. the tertile with shortest telomeres
Fitzpatrick et al.[18]	1136	75	13%	Hazard ratio 1.82 (1.12-2.96) per 1000 base pair shorter telomere length

Power calculations for the four previous studies were based on the risk estimate for death related to any infection from the present study and the number of participants and deaths reported in each of the previous studies.

Supplementary Table S3: Baseline characteristics of 107,693 genotyped participants from the general population according to number of telomere length shortening alleles (unweighted allele score)

	Number of telomere length shortening alleles (unweighted allele score)					
Characteristic	**0-1**	**2**	**3**	**4**	**5**	**6**
Individuals, No.	1731	11957	34521	40067	17075	2342
Relative telomere length[¶], T/S-ratio	0.64 (0.54-0.75)	0.62 (0.53-0.73)	0.61 (0.52-0.72)	0.60 (0.51-0.70)	0.59 (0.50-0.69)	0.58 (0.49-0.68)
Age, years	58 (47-68)	58 (48-67)	58 (47-67)	58 (48-67)	58 (48-67)	58 (48-67)
Male sex, No.	754 (44)	5400 (45)	15334 (44)	18169 (45)	7654 (45)	1068 (46)
Ever smokers, No.	1025 (59)	7173 (60)	20676 (60)	23951 (60)	10194 (60)	1395 (60)
Cumulative smoking[#], pack-years	18 (7-32)	17 (7-32)	17 (7-32)	17 (7-32)	17 (7-32)	19 (8-33)
Alcohol consumption >168/84 g/week[†], No.	658 (38)	4570 (38)	13336 (39)	15398 (38)	6599 (39)	911 (39)
Body mass index, kg/m^2	25.3 (23.0-28.2)	25.6 (23.2-28.4)	25.5 (23.1-28.4)	25.6 (23.2-28.4)	25.5 (23.1-28.5)	25.7 (23.2-28.6)
Any comorbidity[§], No.	357 (20.6)	2423 (20.3)	7149 (20.7)	8233 (20.5)	3487 (20.4)	460 (19.6)
Previously hospitalized[‡], No.	760 (43.9)	5172 (43.3)	15082 (43.7)	17061 (42.6)	7304 (42.8)	962 (41.1)
C-reactive protein, mg/L	1.4 (1.0-2.3)	1.5 (1.0-2.4)	1.5 (1.0-2.4)	1.5 (1.0-2.4)	1.5 (1.0-2.4)	1.5 (1.0-2.4)

No. (%) is shown for categorical variables and median (interquartile range, IQR) is shown for continuous variables.

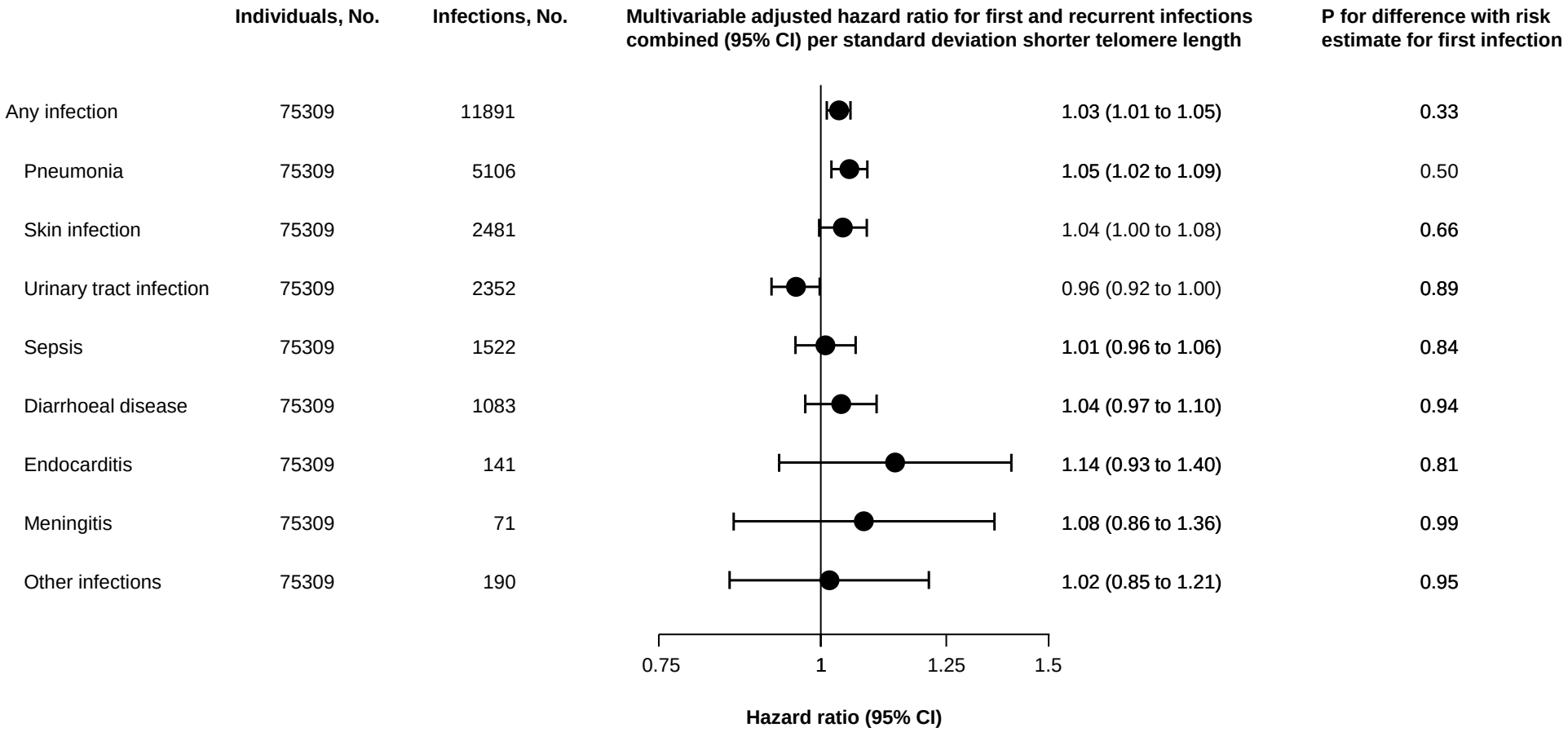
[¶] Based on 75,018 individuals who had both leukocyte telomere length measurements and genotyping performed

[#] Ever smokers only.

[†] >168 g/week for men and >84 g/week for women.

[§] As defined by the Charlson comorbidity index.

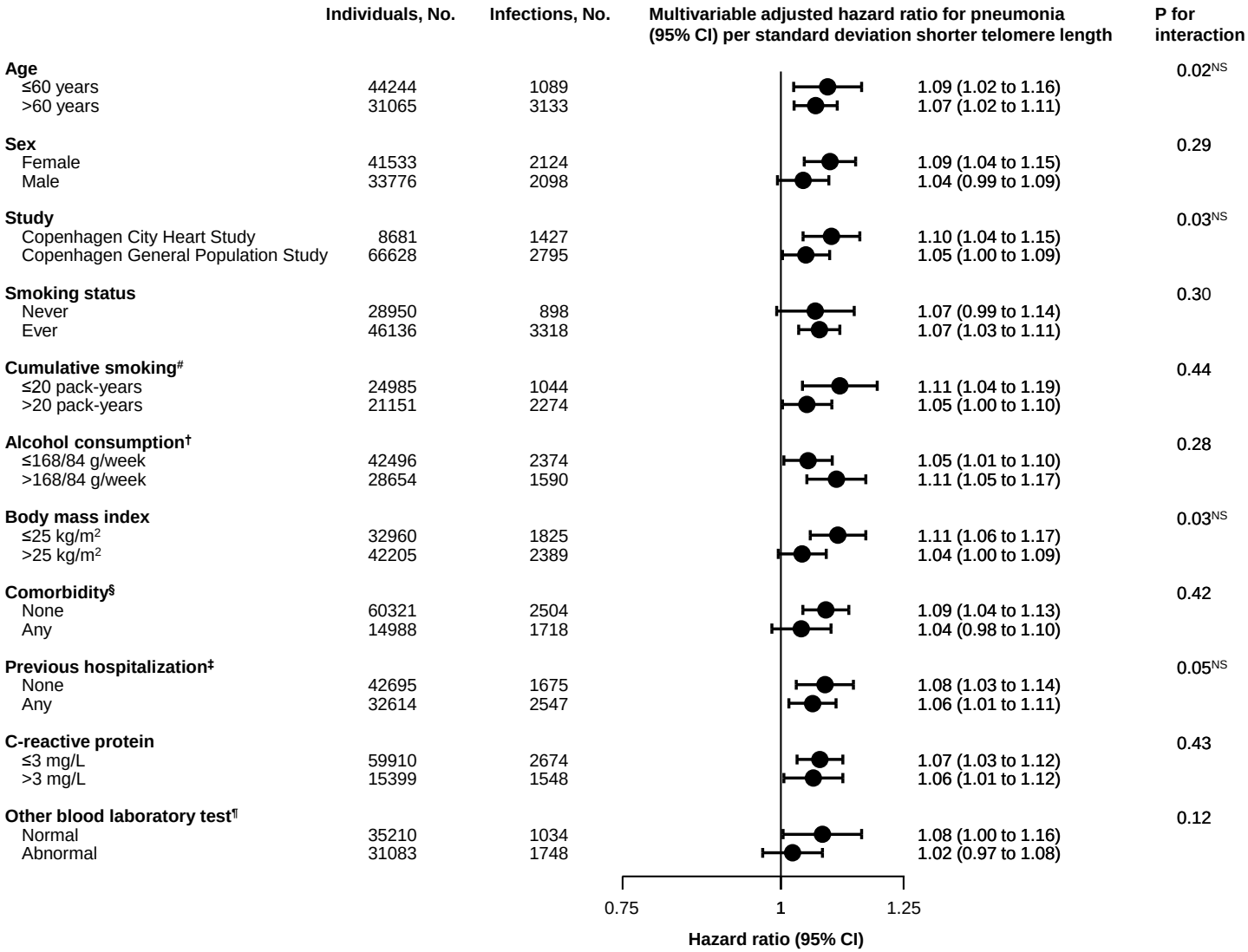
[‡] Defined as any inpatient hospitalization within 10 years before study enrollment for any cause other than infections.



Supplementary Figure S1: Combined risk of first and recurrent hospitalizations 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 10 years before study enrollment, and study cohort. P for difference is from Altman and Bland's Z-test, comparing risk of first infection with combined risk of first and recurrent infections.

CI: confidence interval



Supplementary Figure S2: Stratified analyses for risk of first hospitalization for pneumonia 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 10 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.

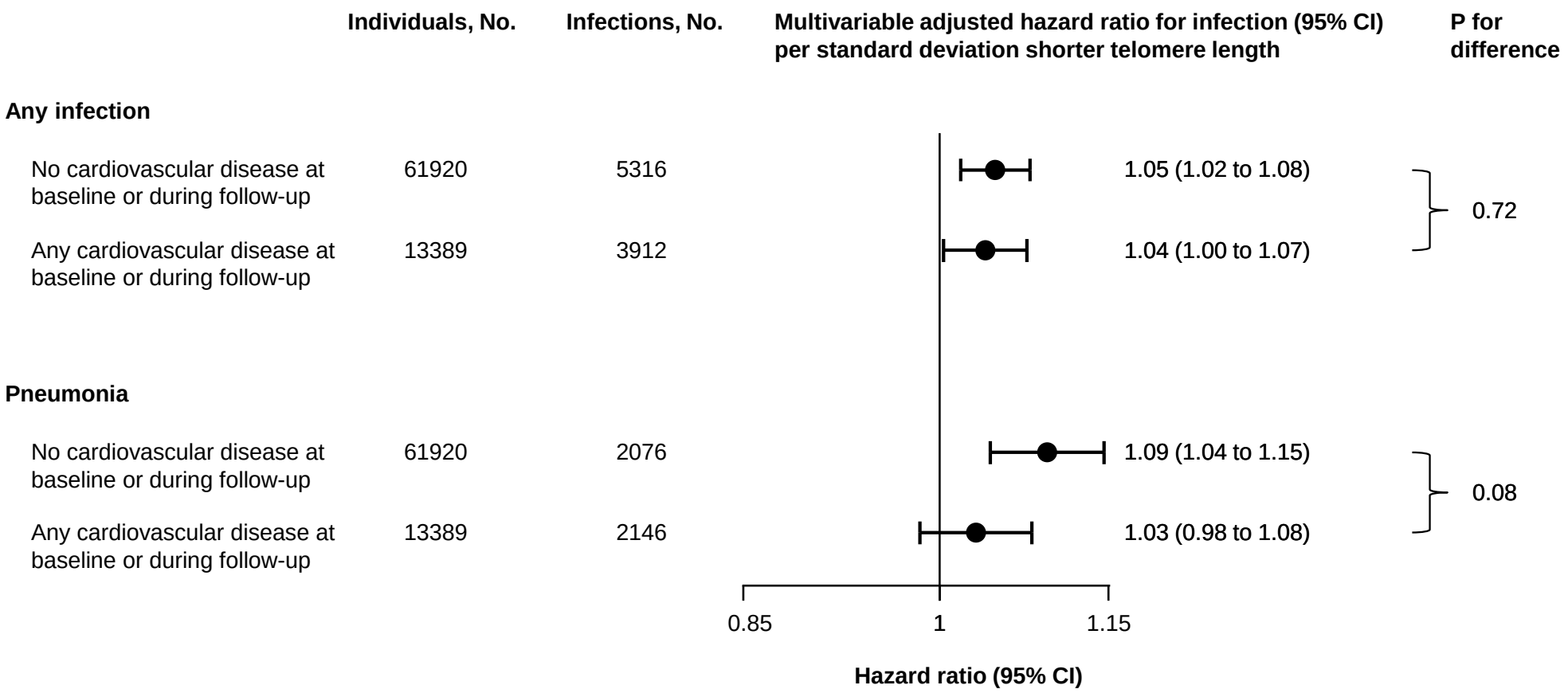
[†] >168 g/week for men and >84 g/week for women.

[§] As defined by the Charlson comorbidity index.

[‡] Defined as any inpatient hospitalization within 10 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.

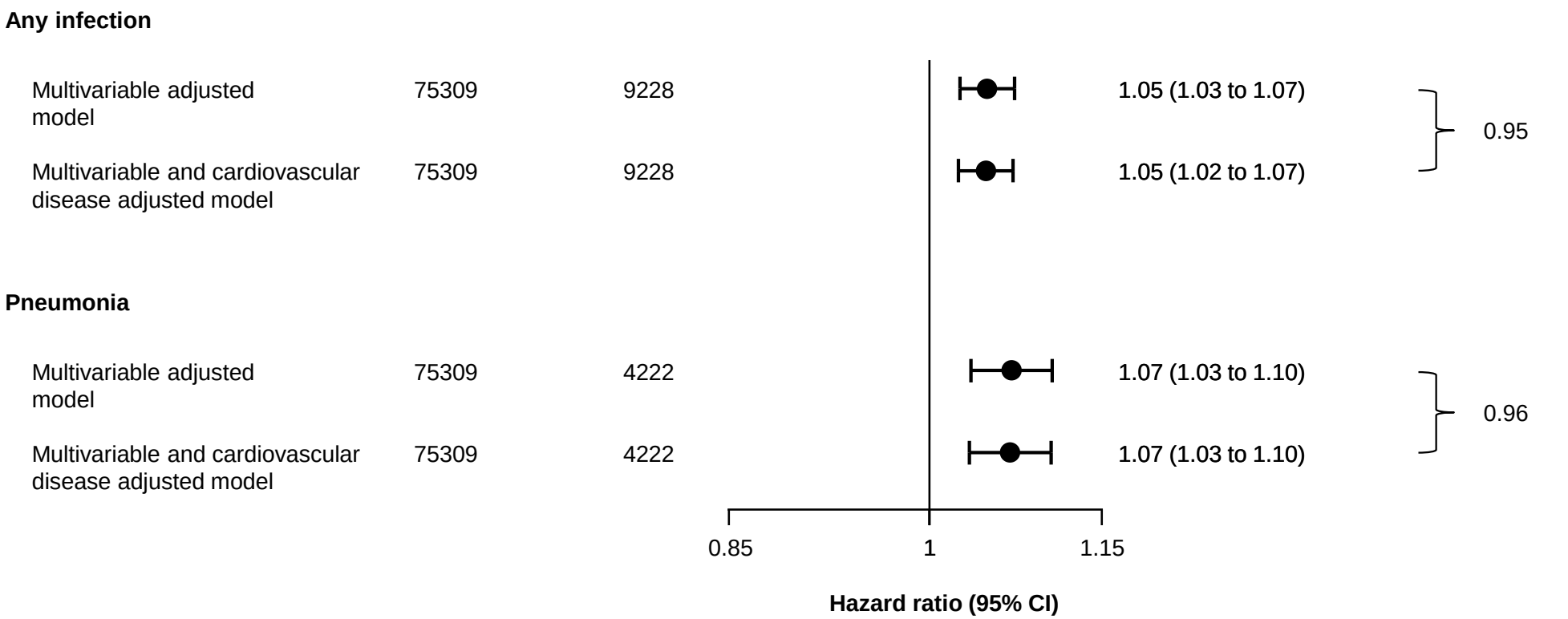
[NS] P-value for interaction was not statistically significant at <0.05 level after adjustment for 11 multiple comparisons using the Bonferroni method (required P-value less than 0.05/11=0.0045).



Supplementary Figure S3: Risk of first hospitalization for any infection and pneumonia per standard deviation shorter telomere length stratified according to whether or not individuals were diagnosed with any type of cardiovascular disease at study enrollment or during follow-up. Cardiovascular disease was defined as any diagnosis of cerebrovascular disease, congestive heart failure, myocardial infarction or peripheral vascular disease, as described for the Charlson comorbidity index. 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 10 years before study enrollment, and study cohort. P for difference is from Altman and Bland's Z-test.

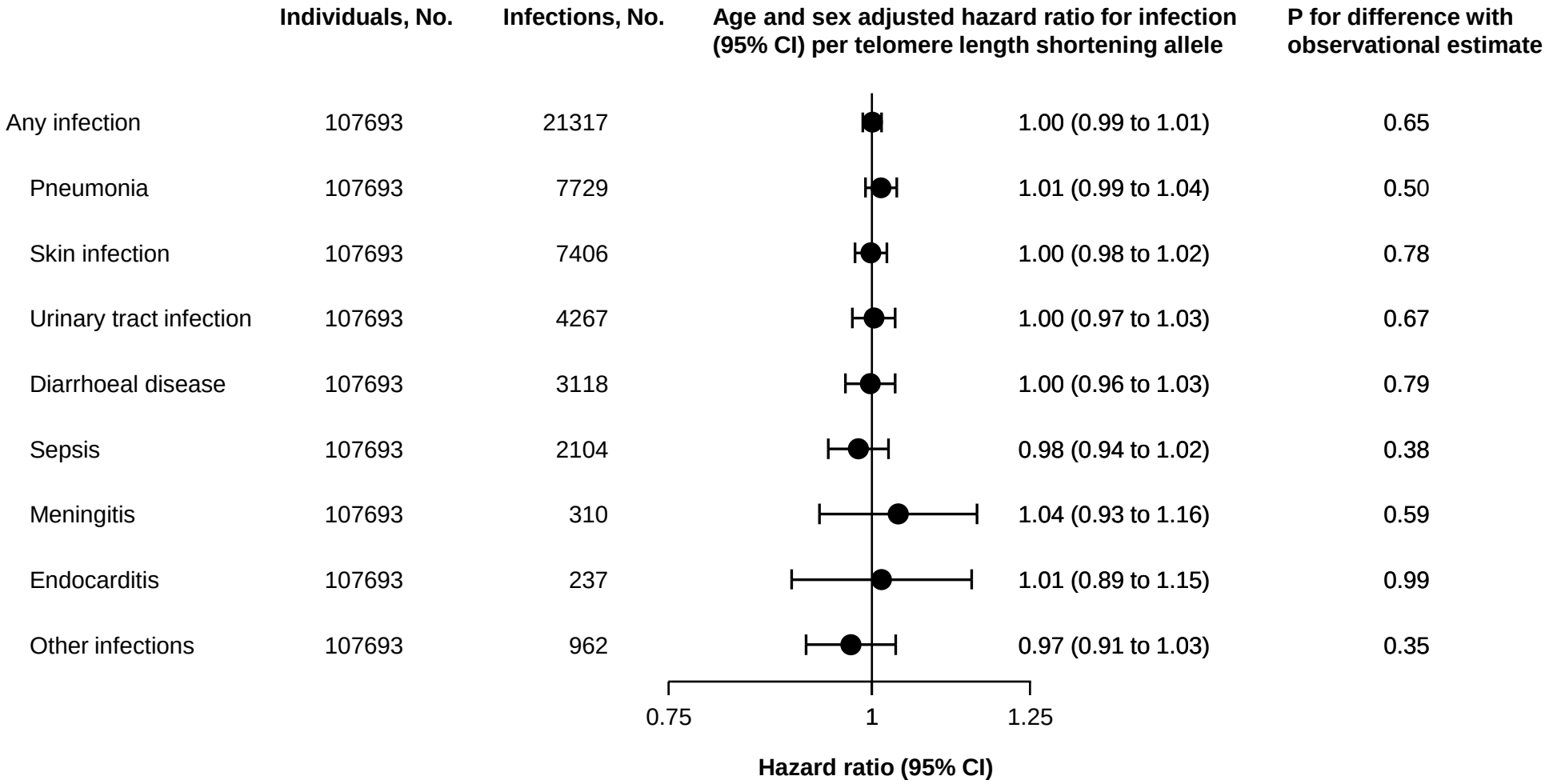
CI: confidence interval



Supplementary Figure S4: Risk of first hospitalization for any infection and pneumonia per standard deviation shorter telomere length comparing the multivariable model to the multivariable and cardiovascular disease adjusted model. 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 10 years before study enrollment, and study cohort. The multivariable and cardiovascular disease adjusted models were adjusted for

cardiovascular disease at baseline and during follow-up and for all the variables included in the multivariable model except Charlson comorbidity index. Cardiovascular disease was included in the model by including time-dependent binary variables on diagnoses of cerebrovascular disease, congestive heart failure, myocardial infarction, and peripheral vascular disease, as described for the Charlson comorbidity index. P for difference is from Altman and Bland's Z-test.

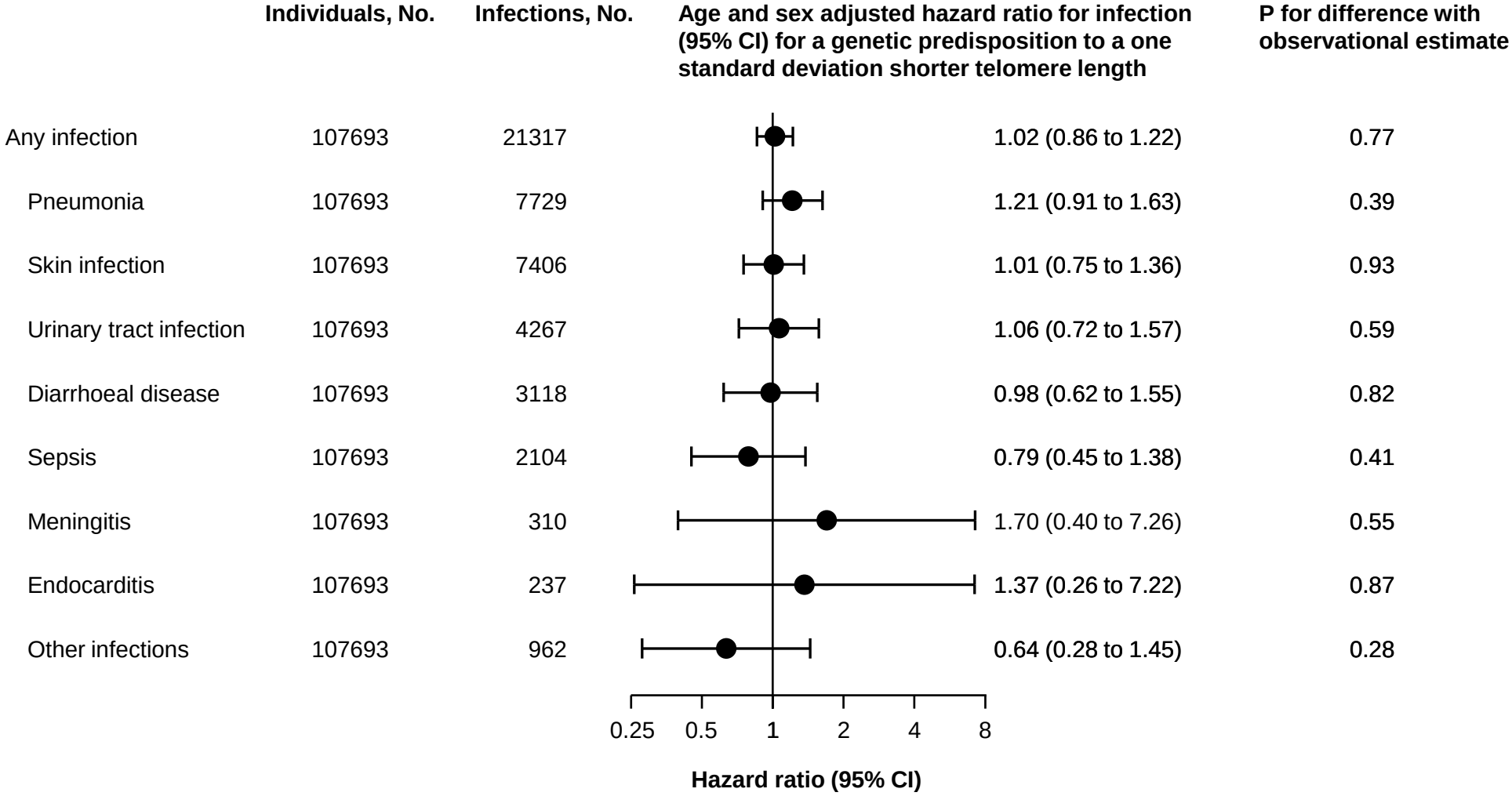
CI: confidence interval



Supplementary Figure S5: Risk of first hospitalization for any infection and specific infections in the general population per telomere length shortening allele using the unweighted allele score. The sum of specific infections exceeds the number of any infection since some individuals had more than one type of infection. P for

difference is from Altman and Bland's Z-test, comparing the genetic risk estimate per telomere length shortening allele with the observational risk estimate for a 0.012 unit lower T/S ratio, as the mean decrease in T/S ratio was 0.012 per telomere length shortening allele.

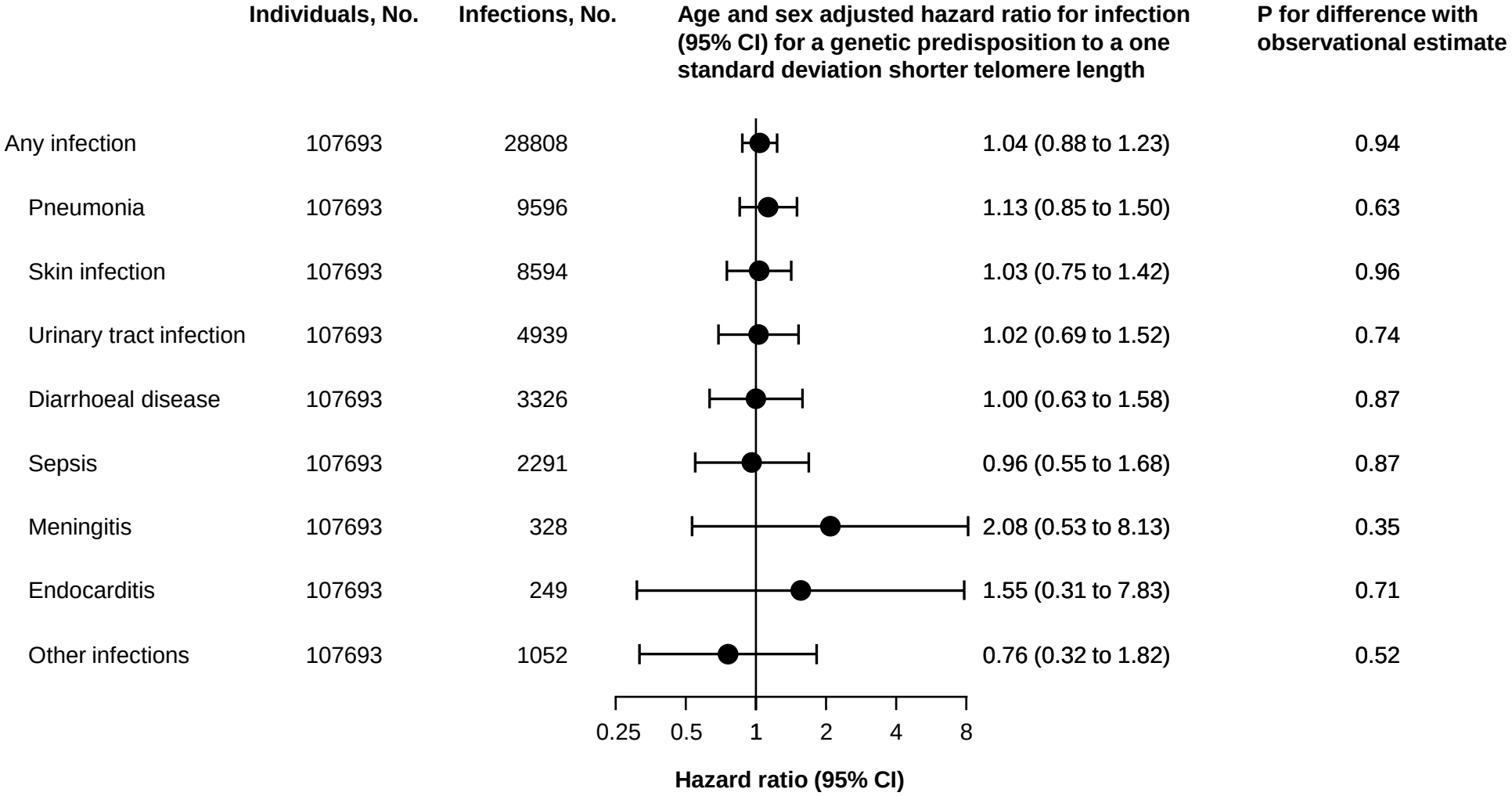
CI: confidence interval



Supplementary Figure S6: Risk of first hospitalization for any infection and specific infections in the general population for a genetic predisposition to a one standard deviation shorter telomere length using the weighted allele score. The sum of specific infections exceeds the number of any infection since some individuals

had more than one type of infection. P for difference is from Altman and Bland's Z-test, comparing the genetic risk estimate to the observational risk estimate for a one standard deviation shorter telomere length.

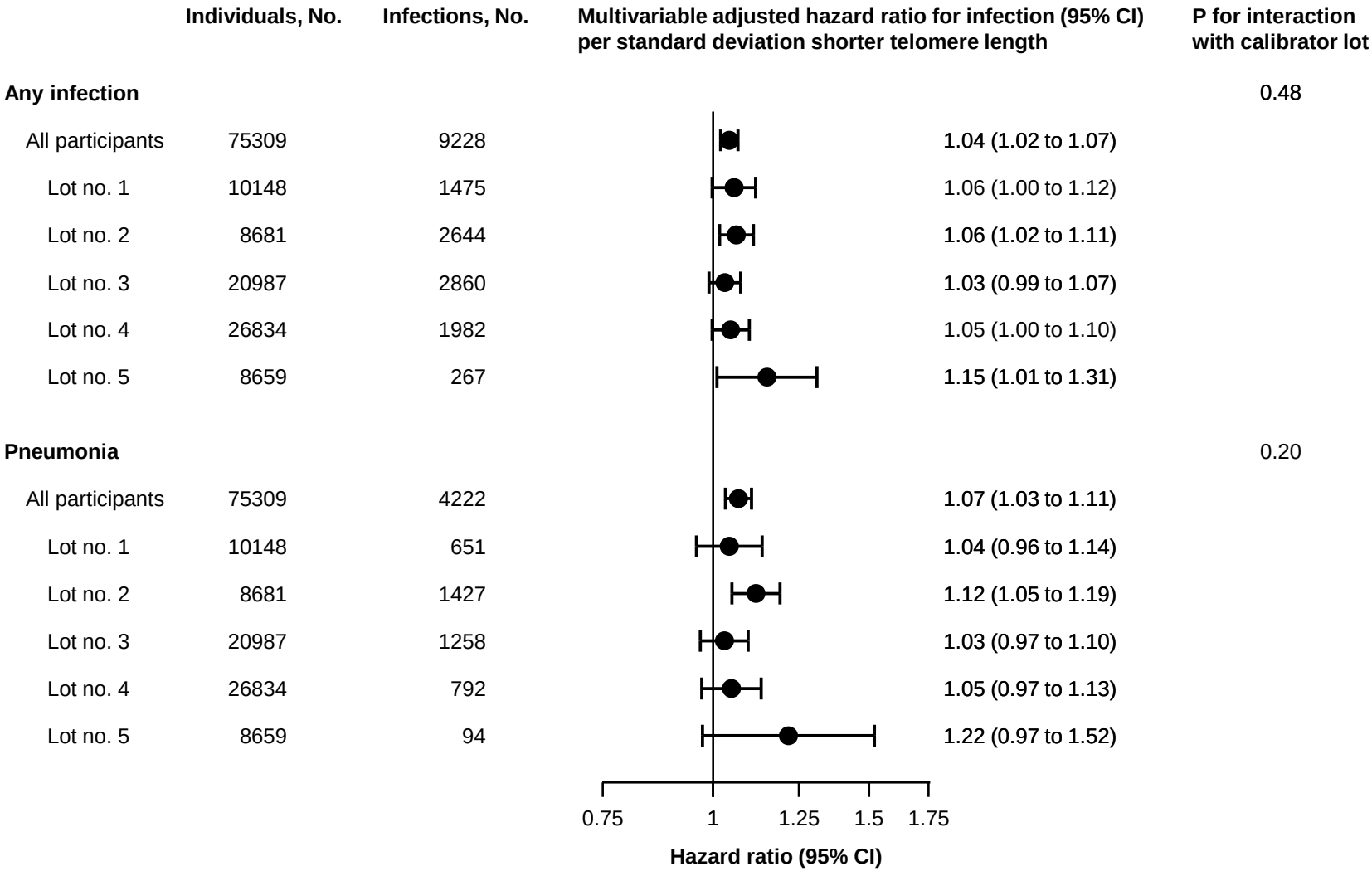
CI: confidence interval



Supplementary Figure S7: Combined risk of first and recurrent hospitalizations for any infection and specific infections in the general population for a genetic predisposition to a one standard deviation shorter telomere length using the weighted allele score. The sum of specific infections exceeds the number of any infection

since some individuals had more than one type of infection. P for difference is from Altman and Bland's Z-test, comparing the genetic risk estimate to the observational risk estimate for a one standard deviation shorter telomere length.

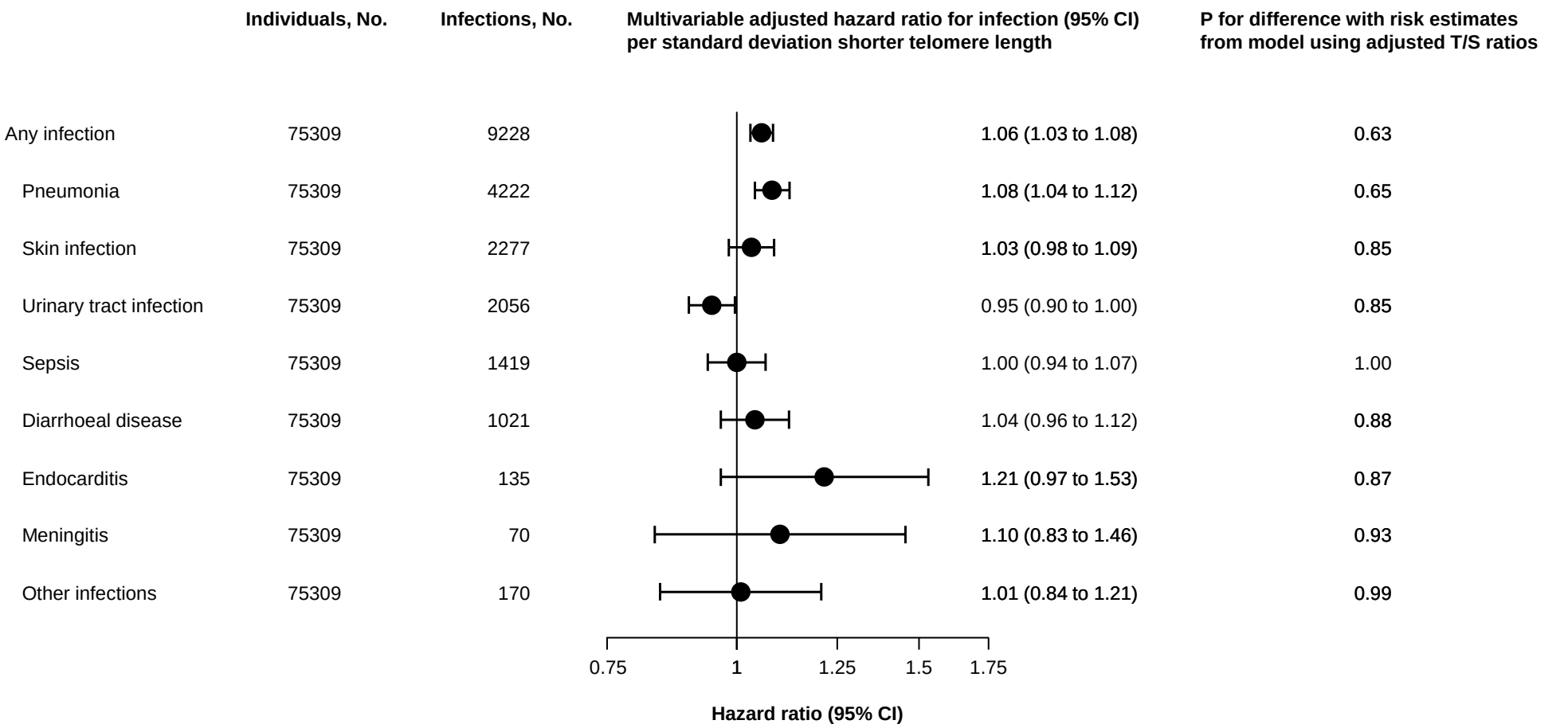
CI: confidence interval



Supplementary Figure S8: Risk of first hospitalization for any infection and pneumonia per standard deviation shorter telomere length using unadjusted T/S ratios and stratified according to which calibrator lot was used for the telomere length measurements. 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 10 years before study enrollment, and study cohort. For the interaction analysis, calibrator lot was included in the model as a categorical variable with values 1 to 5 and P for interaction was calculated using a likelihood ratio test, comparing models with and without the interaction term.

CI: confidence interval



Supplementary Figure S9: Risk of first hospitalization for any infection and specific infections per standard deviation shorter telomere length using unadjusted T/S ratios but including calibrator lot in the multivariable model as a categorical variable with values 1 to 5. 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 10 years before study enrollment, study cohort and calibrator lot. P for difference is from Altman and Bland's Z-test, comparing the risk estimates obtained using unadjusted T/S ratios to the risk estimates obtained using adjusted T/S ratios as shown in Figure 1.

CI: confidence interval

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