ARTICLE

Annual space weather fluctuations and telomere length dynamics in a longitudinal cohort of older men: the Normative Aging Study

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BACKGROUND: Space weather has been associated with increased risk of cardiovascular diseases in space and flight crew. However, limited research has focused on the ground population, particularly among the elderly who are vulnerable to aging-related diseases.
OBJECTIVE: We evaluated the association between space weather alterations and biological aging using leukocyte telomere length as a biomarker in healthy elderly men.
METHODS: We used data from the Normative Aging Study, a longitudinal cohort of healthy elderly men in Massachusetts, USA. Leukocyte telomere length and health information were measured at in-person examinations approximately every three years, contributing to a total of 1,850 visits from 791 participants. Regional space weather information was collected daily, including cosmic ray-induced ionization, neutrons, sunspot number, interplanetary magnetic field, and Kp-index as our exposure of interest. We used mixed-effects models with a random intercept per individual to evaluate the associations between annual averages of space weather indicators and relative telomere length while accounting for participant demographics, environmental parameters, and secular trends.
RESULTS: The mean age at baseline was 72.36 years. A one-year increment in age is associated with a 1.21% reduction in leukocyte telomere length. In the fully adjusted model accounting for individual and environmental factors, an interquartile range (IQR) increase of annual cosmic ray induced ionization (110.0 ion pairs cm^{-3} sec^{-1}) was associated with a 17.64% (95%CI: −27.73%, −7.55%) decrease in leukocyte telomere length, equivalent to 15-years age increment. Solar and geomagnetic activities were associated with increased leukocyte telomere length, but the association became absent after adjusting for cosmic ray indicators.

IMPACT:

- Galactic cosmic rays may accelerate the aging process in populations on the Earth, despite the protection by the Earth's atmosphere and magnetic field. This research enhances our understanding of how changes in space weather can impact health, highlights potential risks from space to Earth's inhabitants, and helps inform health strategies for vulnerable populations.

Keywords: Radiation; Epidemiology; Population Based Studies; Vulnerable Populations

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INTRODUCTION

Exposure to radiation associated with space weather, including galactic cosmic rays (GCRs) and solar and geomagnetic activities (SGAs), is associated with increased risk of cardiovascular diseases (CVDs) morbidity and mortality in space and flight crew who are exposed to relatively high levels of space weather, and the general population who are exposed to relatively low levels [1–4]. Primary GCRs continuously penetrate the Earth's atmosphere, which induce ionization through a nuclear-electromagnetic-muon cascade resulting in high energy secondary particles composed by muons, neutrons, and Cosmic Ray Induced Ionization (CRII). The primary and secondary GCRs are modulated by solar activity [5]. When solar activity is strong, CRII intensity is reduced, and this phenomenon is also referred to as the Forbush decrease [6]. GCRs have been consistently linked to increased incidence of skin cancers among airline cabin crew [7] and increased risk of leukemia and central nervous system tumors in children [4, 8]. Solar activity represents a broad range of electromagnetic

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radiation emission from the sun, in which solar ultraviolet radiation is a well-established risk factor for melanoma and non-melanoma skin cancers through its effect on DNA damage [9, 10], and other multiple cancers [11]. Given the well-established role for DNA damage in telomere loss and aging-related diseases [12, 13], we tested the hypothesis that exposure to ionizing radiation associated with space weather affects biological aging.

Telomere length is considered a genome biomarker of cancer incidence and aging processes [14, 15]. Telomeres are repetitive G-rich sequences on terminal chromosomes that maintain genome integrity by preventing double-strand breaks (DSBs) on chromosome ends [16]. With each cell division, telomere length shortens, and this shortening is correlated across tissues, with most tissues showing a correlation with age. Leukocyte telomere length, in particular, is an established biomarker of normal aging [14]. An increasing number of factors have been reported to influence telomere length including cellular factors [e.g., chronic inflammation [17], oxidative stress [18]], lifestyle [e.g., smoking [19], obesity [20], cardiovascular diseases [CVDs] [21], cancer [15]), and environmental exposures [e.g., air pollution [22, 23], and ionizing radiation [24]]. The results of animal and population studies on the impact of radiation on telomere length remain controversial. In cell experiments, both shortening [25] and lengthening [26, 27] have been observed in normal human cells after ionizing irradiation. For population studies [28], elongated telomere was found along with increased DNA damage responses among NASA astronauts during their space mission [29–31]. But one study found no changes in telomere length in association with background radiation in a dose much lower than the space environment [32–34]. One study reported shortened telomere length only associated with low exposed dose but not high dose [35], while another study reported inverse relationship between telomere length and lifetime dose [36].

The associations between space weather with CVD and cancer risk have been widely reported in occupational studies [4, 7]. In this study, we are thus interested in the association between space weather and leukocyte telomere length in the Normative Aging Study (NAS), a well-established cohort of healthy men living in Massachusetts. As the elderly population are at higher risks for CVD and cancer, investigating the relationship between space weather and leukocyte telomere length in this vulnerable population is important with respect to understanding aging processes, disease development and prevention. We also investigated the potential confounding impact of air pollution. To our knowledge, this is the first study to investigate the relationship between SGAs and secondary GCRs (e.g., CRII and neutrons) with leukocyte telomere length.

METHODS

Study population

NAS is a longitudinal cohort of healthy older men for aging research established in 1963 by the U.S. Department of Veterans Affairs. All participants were free of chronic diseases at the time of enrollment. Our study was restricted to 827 participants who remained in NAS from January 1999 to December 2010, during which period the DNA collection took place. We identified 791 participants with at least one measurement of telomere length during the study period, contributing to in total 1850 visits. During the study period, space weather indicators were consistently measured and available, and follow-up visits for participants occurred approximately every 3 years for health evaluations, from which demographic and clinical characteristics of participants were collected through routine physical examinations (height and weight), laboratory tests (fasting blood glucose, white blood cell count, percent neutrophils, percent lymphocytes), collection of medical history information (treatment with statin medication, treatment with hypertension, diagnosis of diabetes), and completion of questionnaires on smoking history, education level, and other factors that may affect health. Body mass index (BMI) was computed as the weight in kilograms divided by the square of the height in meters based on height and weight measurements at each visit. This study was approved by the institutional review boards of the Harvard T.H. School of Public Health and the Veterans Administration Boston Healthcare System, and all participants provided written informed consent.

Space weather assessment

We used sunspot number and interplanetary magnetic field (IMF) intensity as indicators of solar activity along with K_p-index as an indicator of geomagnetic disturbances. These data were obtained from the NASA Goddard Space Flight Center and were converted from Coordinated Universal Time to Eastern Time, the time zone in Boston, MA, as these exposures vary based on geographic location and day. GCRs at the ground level were estimated by the sum of paired ions cm^{-3} sec^{-1} produced by primary and secondary GCRs in atmospheric reactions with the CRII model as previously described by Usoskin and Kovaltsov [37, 38]. Neutrons were estimated from the neutron monitors in the Bartol Research Institute, University of Delaware, USA [39]. SGAs are inversely associated with CRII and Neutrons (Figure S1). The annual moving averages for the space weather indicators were calculated by taking the average of the 365 daily measures before the date of each telomere length measurement.

Weather and air pollution assessment

Measurements of black carbon (BC) were obtained from the Harvard Air Pollution Monitoring Supersite in Boston, MA. Daily, 24-hour averaged BC was measured using an Aethalometer (Model AE-16; Magee Scientific Corp., Berkeley, California), daily temperature (°C) and relative humidity in Boston MA were collected from the National Oceanic Atmospheric Administration's National Centers for Environmental Information. Seasonality was defined in sine and cosine terms: $\sin(2\times\pi\times\frac{day}{365})$ *and* $\cos(2\times\pi\times\frac{day}{365})$. Similar to space weather indicators, daily measures of the environmental assessments were converted into annual moving averages till the day of telomere length measurement for long-term predictions.

Telomere length measurement

The detailed measurement for leukocyte telomere length in the NAS cohort has been previously described [23]. Briefly, DNA of each participant was extracted from stored frozen buffy coat using QiAmp DNA blood kits (Qiagen, Germantown, MD, USA). Telomere length was measured by a standardized quantitative polymerase chain reaction method [40]: beta-globin was used as the single-copy gene (S) and relative leukocyte telomere length was measured by determining the ratio of the telomere (T) repeat copy number to the S copy number (T:S ratio) and reported as relative units expressing the ratio between telomere length in the test DNA and standard DNA. The standard DNA was pulled from DNAs of 475 random participants (50 ng for each sample) and used to generate a standard curve in each PCR run ranging from 20 to 0.25 ng/μL. The PCR runs were performed in 384-well plates on a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The PCR reaction was conducted with 2 μL (2 ng/μL) DNA in 5 μL reaction mix, using PCR primer sets and PCR mix composition as previously described [41]. After PCR amplification, the specificity of the product was confirmed by dissociation curve analysis. All samples were run in triplicates, and the average T:S ratio was obtained over the three measurements. The intra-assay coefficient of variation for the T/S ratio was 8.1% [42]. To evaluate the reproducibility of this measurement, we amplified T and S in 15 samples in triplicate over 3 consecutive days; the coefficient of variation for the average T:S ratio was calculated to be 8.7%, which was close to the original method [40]. The telomere length dynamics in the study population during 1999–2010 among participants with at least 4 follow-up visits were provided in Figure S2.

Statistical analysis

In our primary analysis, we examined the relationship between each space weather indicator and telomere length using multivariate regression. We employed a mixed-effects model with a subject-specific intercept to account for the correlation among repeated measures within the same participant. The dependent variable was the log-transformed telomere length for normal distribution of data. Due to the high correlation among space weather indicators, we included only one indicator at a time in the respective mixed-effects model.

To evaluate the linearity of the continuous space weather indicators, we used natural cubic spline models with 3 degrees of freedom (df). The

dfs of the models were determined by approximating the effective number of df for each model. We evaluated the models through visual inspection of the response function. Since all models displayed consistent trends, we modeled all space weather indicators with linear functions for interpretability.

In the first model, age and the year of telomere length measurements were adjusted to account for the shortening nature of telomere length with age and secular trend:

$$Y_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 Year_{ij} + \beta_3 S_{ij} + b_i + \varepsilon_{ij}$$

Where for individual i at clinical visit j, Y_{ij} is the log transformed outcome (relative telomere length), S_{ij} is one of the annual moving average of space weather indicators (IMF, sunspot number, K_p-index, CRII, or neutrons), b_i is the subject-specific intercept that allows for correlation of measurements within participants, and ε_{ij} denotes the random error.

In the second model, clinical characteristics were additionally adjusted to account for potential confounding from individual level covariates, because we assumed that these variables influenced participation of the study and were likely determinants of telomere length, independent of space weather. This adjustment helped to eliminate non-causal paths through participation:

$$Y_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 Year_{ij} + \beta_3 C_{3ij} + \ldots + \beta_k C_{kij} + \beta_{k+1} S_{ij} + b_i + \varepsilon_{ij}$$

Where C_{3ij} to C_{kij} denote the clinical characteristics including BMI, smoking status and packyears, white blood cell count, percent neutrophils, percent lymphocytes, treatment with statin medication, treatment with hypertension, diagnosis of diabetes, fasting blood glucose, years of education, which were selected a priori as potential confounders with their effects on telomere length [23].

In the third model, environmental parameters were additionally adjusted under the assumption that these variables are either opening a non-causal path between space weather and telomere length through confounding or selection on participation.

$$Y_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 Year_{ij} + \beta_3 C_{3ij} + \ldots + \beta_k C_{kij} + \beta_{k+1} E_{1ij} + \ldots + \beta_{k+z} E_{zij} + \beta_{k+z+1} S_{ij} + b_i + \varepsilon_{ij}$$

Where E_{1ij} to E_{zij} denote environmental covariates including annual moving averages of black carbon, temperature, relative humidity, and seasonality.

Estimated association between each space weather indicator with telomere length was reported by exponentiating the multiplication of the coefficient with IQR of space weather variable. We reported associations per IQR increase to enable comparison across the different types of space weather indicators. We calculated IQRs by taking the difference between the 75th and 25th percentile of the annual moving average of indicators before telomere measurement. All analyses were done by complete-case analysis because the missing value rates for all variables were less than 2%.

Sensitivity analyses

In the NAS population, the number of follow-up visits varied across participants, which might cause selection bias if the data are not missing at random. Therefore, we repeated the analyses using inverse probability weighting (IPW) for follow-up visits. The logistic regression model was used to model the followed response (followed=1, censored=0) with covariates from the previous visit: telomere length, annual moving averages of sunspot number, IMF, Kp_index, CRII, neutrons, black carbon, temperature, relative humidity, sine and cosine terms for seasonality, age, BMI, smoking status, pack-years of cumulative smoking, physician-diagnosed diabetes, fasting blood glucose, statin use, hypertensive drug use, white blood cell counts, percent neutrophils and lymphocytes, and years of education. The earliest visit for everyone was assigned with a weight of 1. If a previous visit had missing values in the covariates, making it unavailable to estimate the follow-up probability, the weight from earlier visits was retained. To stabilize the estimated probabilities and avoid potentially biased results from extreme weights of a small number of participants, the weights were trimmed at the 0.5 and 99.5 percentile (Figure S3).

Further sensitivity analysis was conducted to explore the potential mediation of CRII and neutrons or SGA on each other's association with telomere length. The effect estimates of space weather variable of interest were evaluated before and after adjusting for the potential mediator. Causal Directed Acyclic Graphs (DAGs) were employed to evaluate the mediation role with prior knowledge regarding the relationship between solar activities and CRII (Figure S4).

Table 1. Characteristics of Normative Aging Study (NAS) participants included in the analysis across visits between 1999–2010.

	Baseline Visit	All	Missing
No of observations	791	1850	–
Age [years (mean ± SD)] [a]	72.36 ± 6.87	74.42 ± 6.76	–
BMI [kg/m2(mean ± SD)] [b]	28.21 ± 4.09	27.96 ± 4.07	–
Smoking status [n(%)]			6 (0.32)
Never smoker	240 (30.57)	593 (32.11)	–
Current smoker	34 (4.33)	79 (4.28)	–
Former smoker	511 (65.10)	1175 (63.62)	–
Pack-years [median (IQR)] [b]	12 (35)	11 (30.94)	–
Leukocyte count [cells/cm^3 (mean ± SD)]	6.51 ± 2.90	6.57 ± 3.52	15 (0.81)
Neutrophils [% (mean ± SD)]	61.94 ± 8.65	62.15 ± 8.99	33 (1.78)
Lymphocytes [% (mean ± SD)]	25.72 ± 8.06	25.51 ± 8.36	33 (1.78)
Statin use [n(%)] [a]	264 (33.38)	829 (44.74)	-
Hypertension medicine [n(%)] [a]	458 (57.90)	1192 (64.33)	-
Diabetes [n(%)]	111 (14.03)	280 (15.11)	-
Fasting blood glucose [n(%)] [b]			-
<110 mg/dL	532 (67.26)	1305 (70.43)	-
>110 or <126 mg/dL	150 (18.96)	319 (17.22)	-
>126 mg/dL	109 (13.78)	229 (12.36)	-
Education [years (mean ± SD)]	14.96 ± 2.95	15.07 ± 2.95	6 (0.32)
Telomere length (mean ± SD) [a]	1.25 ± 0.47	1.17 ± 0.49	-

NAS Normative Aging Study, *BMI* body mass index, *SD* standard deviation, *IQR* interquartile range.
[a]$p < 0.001$ for comparison between baseline and all visits.
[b]$p < 0.01$ for comparison between baseline and all visits.
[c]$p < 0.05$ for comparison between baseline and all visits.

By including participants who had at least one telomere length measurement, we might introduce selection bias if the included participants were different than the study base population in terms of risk factors of telomere length changes. Therefore, we conducted additional sensitivity analysis by comparing the characteristics during follow-up between the 791 subjects included in the study and the rest of 36 non-included among the 827 eligible NAS participants during 1999–2010.

All analyses were conducted in R version 4.1.2.

RESULTS

791 participants with at least one measurement of telomere length during 1999–2010 were included in the current study from NAS. The participants were all male, with a mean age of 72.36 years at baseline (Table 1). During the study period, the number of visits per participant ranged from 1 to 5. Of the participants, 227 had only 1 visit, 203 had 2 visits, 232 had 3 visits, 124 had 4 visits, and 5 had 5 visits. Telomere length decreased among participants during 1999–2010 (Figure S2), and one-year increment in age is associated with a 1.21% reduction in telomere length ($p < 0.0001$). We confirmed a depression of GCRs with increased SGAs: secondary GCR decreased from 1999–2000 and increased after 2005, while sunspot number, IMF intensity, and Kp-index were at their highest levels during 2000–2005 (Fig. 1; Figure S1). Moreover, we observed decreased telomere length with increases in CRII and neutrons, and increased telomere length with increases in sunspot number, IMF and Kp_index (Fig. 2).

We further modeled the associations through linear mixed effect models with log transformed telomere length as the dependent variable and controlled for shortening patterns of telomere with age and secular trend, clinical and demographic characteristics [i.e., BMI, smoking status (e.g., packyears), white blood cell count, percent neutrophils, percent lymphocytes, treatment with statin medication, treatment with hypertension medication, diagnosis of diabetes, fasting blood glucose, years of education)], and environmental risk factors (i.e., annual moving averages of black carbon, temperature and relative humidity, and seasonality). Natural cubic splines with 3 degrees of freedom displayed overall consistent changing trends of telomere length associated with space weather indicators (Fig. 3). Despite the association flattening or slightly inverting when there are fewer data with wide confidence intervals, this provides further evidence that non-linearity is unlikely. Therefore, the main associations are presented in the form of an interquartile range increase of space weather fluctuations (Table 2).

Besides sunspot number, all other selected indicators of space weather showed significant associations with telomere length. Secondary GCRs were associated with a decrease in telomere length. The IQR for the annual moving average in CRII was 110.0 ion pairs cm^{-3} sec^{-1}. An increase of this magnitude of CRII is associated with a 17.64% (95%CI: −27.73%, −7.55%) decrease in telomere length in the fully adjusted model. For neutrons the IQR was 305.7 ion pairs cm^{-3} sec^{-1}. An increase of this magnitude was associated with a 15.73% (95%CI: −24.68%, −6.78%) decrease in telomere length after adjustments.

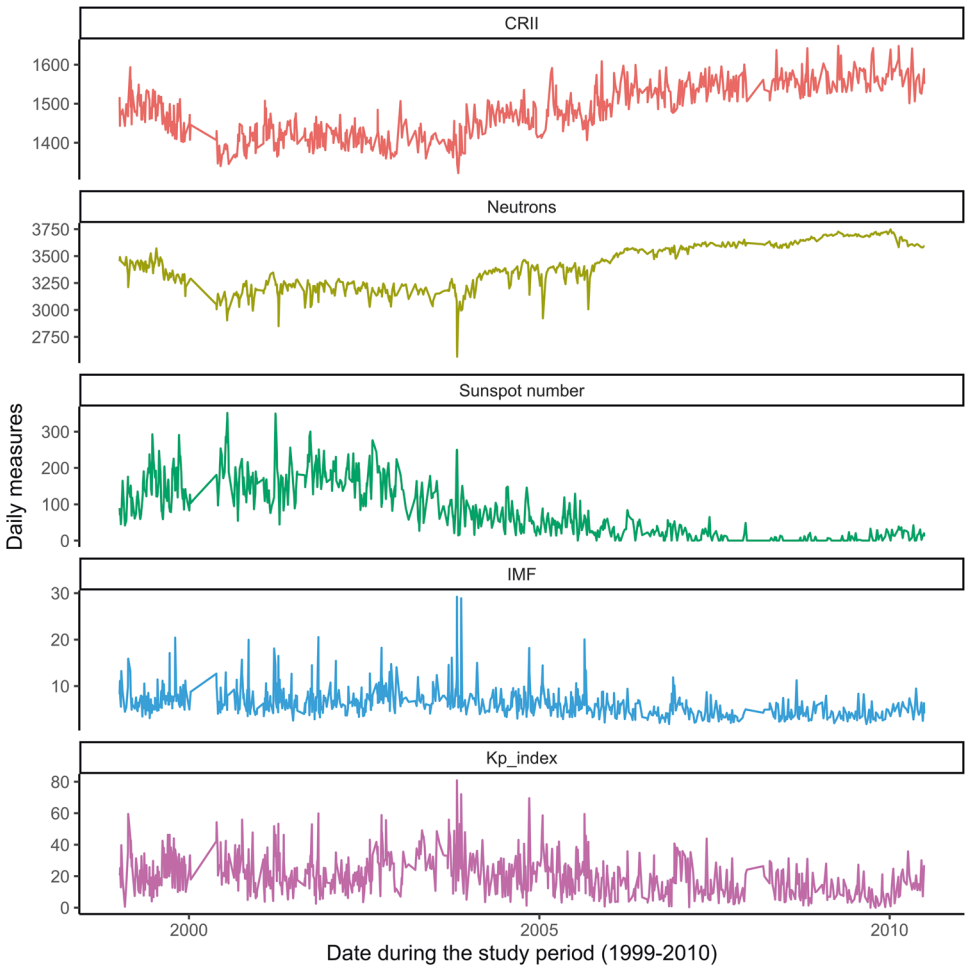

Fig. 1 Daily cosmic rays and solar and geomagnetic activities between 1999 and 2010. CRII, cosmic ray induced ionization (ion pairs cm^{-3} sec^{-1}); IMF, interplanetary magnetic field (nT).

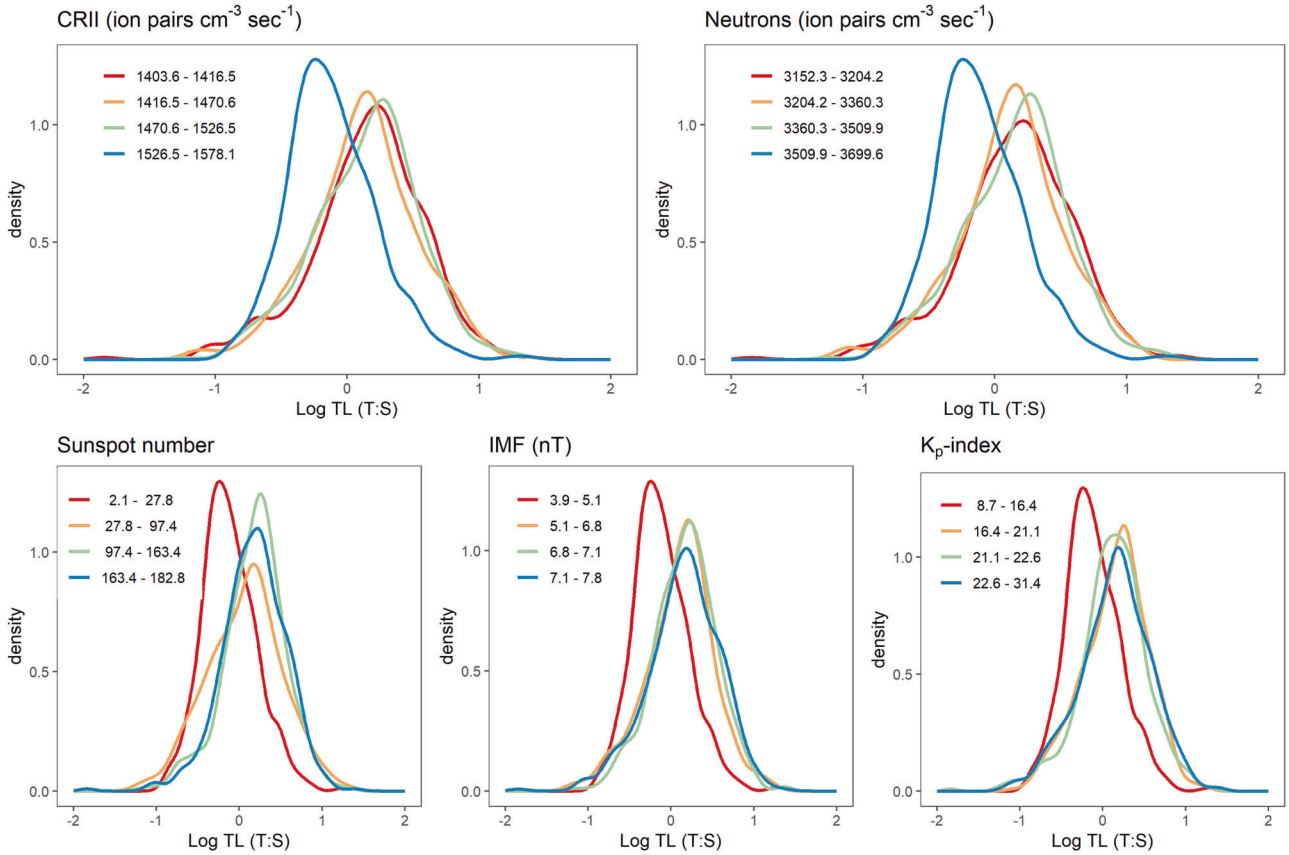

Fig. 2 Distribution of log-transformed relative telomere length (T:S) by quartiles of cosmic rays and solar activities. CRII, cosmic ray induced ionization (ion pairs cm^{-3} sec^{-1}); IMF, interplanetary magnetic field (nT).

Similar results were obtained after accounting for potential selection bias from loss to follow-up through IPW (Table 2) with weights trimmed at the 0.5th percentile (0.27) and 99.5th percentile (1.84).

Because of the Forbush decrease, wherein solar activity is anti-correlated with secondary GCR intensity [6], the changes of telomere length associated with SGA were, as expected, in the opposite direction as compared to GCRs. IQR increases of annual moving averages in IMF (IQR = 2.01 nT) and K_p_index (IQR = 6.20) were associated with 12.56% (95%CI: 5.31%, 19.82%) and 7.02% (95%CI: 2.93%, 11.11%) increases in telomere length, respectively.

We further explored the potential mediation effect of CRII and neutrons or SGA on the relationship with telomere length. Adjusting for sunspot number in the GCR secondary models did not impact the associations between CRII or neutrons with telomere length (Table 3a). However, after adjusting for CRII or neutrons in the SGA models, the associations between each SGA and telomere length became not significant (Table 3b). These findings supported the role of CRII and neutrons on reduced telomere length independently of SGA intensity (Figure S4), implying that the positive associations between SGA and telomere length were due to the anticorrelated nature of SGA and GCRs, rather than the direct effects of SGA.

There were no significant differences in characteristics between included subjects and those NAS participants not included in the analysis during the same time-period except in age (Table S1).

DISCUSSION

These findings provide the first evidence for potential effects of space weather on telomere length in an elderly healthy men cohort living in Massachusetts, suggesting that GCRs may accelerate population aging processes. IQR increases in the annual moving average of CRII were related to a significant decrease in telomere length, which was equivalent to the changes associated with 15 years of age increment. Elongation and shortening of telomeres are both significant biomarkers for disease as telomere lengthening is a precursor for cancer, while shortening of telomeres in noncancerous cells is a well-established aging biomarker and precursor for CVD. Shortening of telomeres, which is a hallmark of biological aging, is widely reported to be influenced by lifestyle and environmental exposures [19–23]. The relationship between GCRs and telomere shortening may indicate direct DNA damage caused by the impact of GCRs high-energy secondary participles, which induce directly and indirectly complex DNA lesions that are harder for cells to repair [43, 44]. In addition to direct DNA damage, GCR exposures could also cause damage DNA through oxidative stress and genome instability, which has been consistently linked to shortened telomere length [12, 45]. In both scenarios, the DNA damage induced by ionizing radiation outweighs the cell's ability to maintain telomere integrity, resulting in telomere shortening.

We found positive associations between SGAs and telomere elongation, which is likely due to their negative correlation with GCRs. Consistent with this model, after controlling for GCRs in the SGA models, the association between SGAs and telomere elongation disappeared. Observational studies have reported inconsistent findings for the relationship between telomere length and cancer risks ("telomere paradox"): telomere elongation was linked to increased cancer risks while shorter telomeres were also found associated with increased risk of developing cancer [46]. Also, longer telomere length increased cancer risk was reported in several Mendelian randomization studies

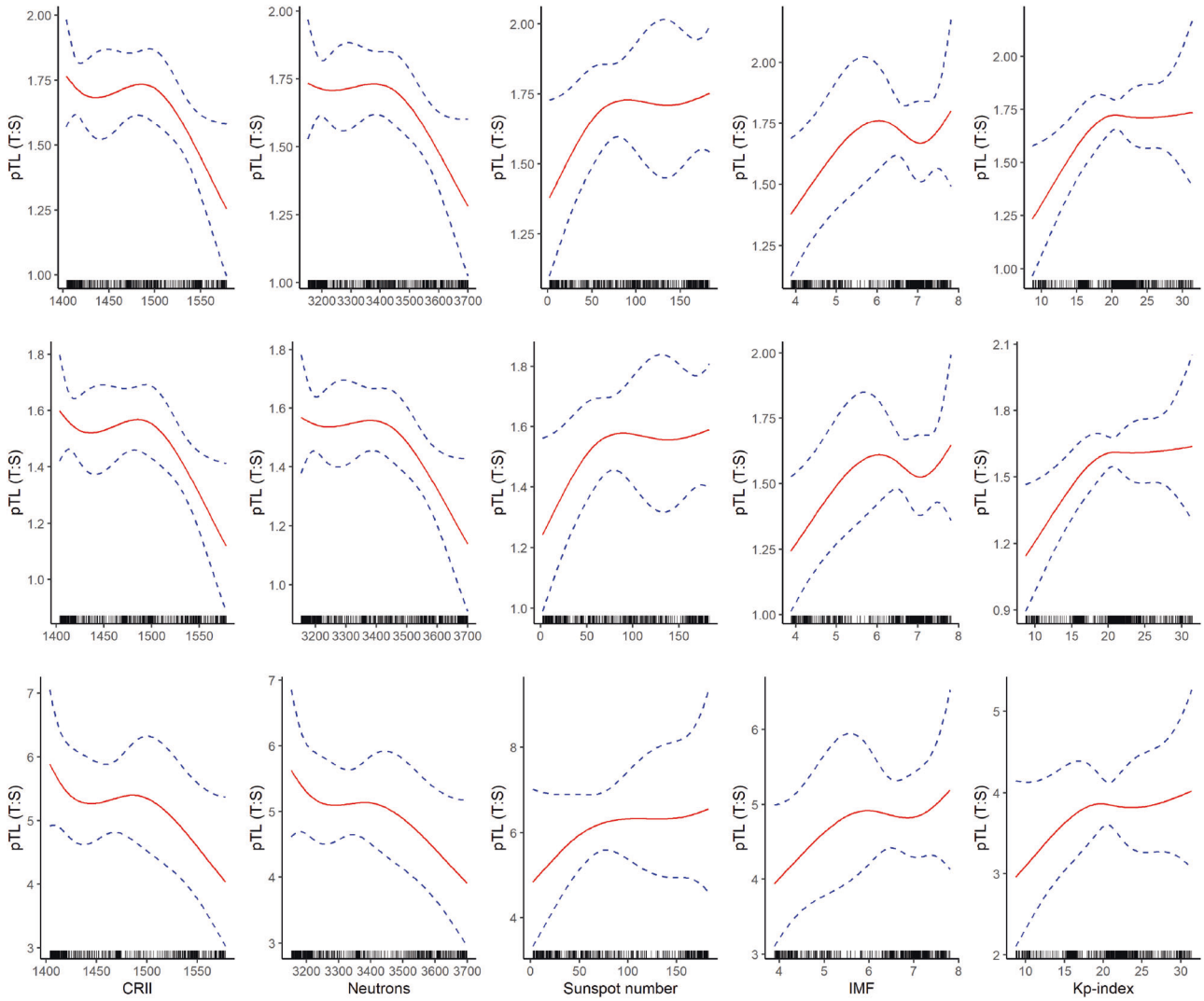

Fig. 3 Relationships between relative telomere length with annual moving averages of cosmic rays and solar activities during 1999–2010. Natural cubic splines with 3 degrees of freedom (solid red line) and 95% confidence intervals (dashed blue lines) were plotted with each space weather parameters on the x-axis and predicted telomere length (T:S ratio) on the y-axis. Results presented as age and year adjusted models (top); multivariable models additionally adjusted for clinical characteristics including BMI, smoking status and packyears, white blood cell count, percent neutrophils, percent lymphocytes, treatment with statin medication, treatment with hypertension, diagnosis of diabetes, fasting blood glucose, years of education (middle); and multivariable models additionally adjusted for environmental covariates including seasonality, annual moving averages of temperature, relative humidity, and black carbon (bottom). The vertical cyan lines along the *x*-axes show the distribution of the corresponding space weather parameter. CRII, cosmic ray induced ionization (ion pairs cm^{-3} sec^{-1}); IMF, interplanetary magnetic field (nT); pTL, predicted telomere length.

[47, 48], implying a causal relationship free of confounding from observational studies. Several previous studies about radiation effects in normal human cells [26, 27] and biological samples obtained from astronauts [29–31] have found lengthening of telomere post X-ray irradiation or background radiation. This is in line with our finding for the associations between SGAs and telomere elongation, as X-rays mainly are related to solar activity. From there, we hypothesized that observational studies about astronauts conducted during the solar cycle when solar activities are strong and, therefore, suppress GCR intensity, resulted in elongation effects of SGAs outweighing the shortening effects of GCR. DNA repair plays a key role in genome maintenance and genetic variants in DNA repair pathways were found to influence telomere length [24, 49]. Examining relationships between space weather and genetic variants in telomere length regulation and DNA repair pathways could be one approach to explore the mechanisms behind telomere elongation, given that insufficient DNA repair is also a risk factor for multiple cancers [4, 50–52].

Our study was conducted among the healthy elderly men from NAS, which is a valuable resource to study biomarkers in populations subjected to accelerated aging. We only looked at an elderly, male population living in Boston MA, who were mostly white, which might limit our generalizability to other populations with different demographics including sex, age, race, and location. The observed association between a IQR (110.0 ion pairs cm^{-3} sec^{-1}) increase of CRII moving average and telomere shortening is equivalent to 15-years age increment, and further research is warranted to evaluate the association scale in a younger population, as all lives on Earth are exposed to space weather and thus subject to its telomere-shortening threats. Our study is benefited from the longitudinal nature of NAS, and we were able to collect up to five repeated measures of telomere length (Figure S2), rendering us the opportunity to

Table 2. Associations between annual moving-averages of space weather indicators and telomere length, expressed as difference in telomere length per interquartile range (IQR) increases in each measure ($n = 791$ subjects).

	N	Percent Change (95% CI)
+ *age and year*		
CRII	1850	−9.28 (−13.78, −4.79)
Neutrons	1850	−8.45 (−12.51, −4.39)
Sunspot number	1850	7.41 (0.36, 14.46)
IMF	1850	11.64 (6.33, 16.95)
Kp_index	1850	6.35 (3.41, 9.29)
+ *clinical characteristics* [a]		
CRII	1806	−9.61 (−14.20, −5.02)
Neutrons	1806	−8.80 (−12.95, −4.65)
Sunspot number	1806	6.68 (−0.50, 13.86)
IMF	1806	12.24 (6.80, 17.67)
Kp_index	1806	6.91 (3.93, 9.90)
+ *environment* [b]		
CRII	1570	−17.64 (−27.73, −7.55)
Neutrons	1570	−15.73 (−24.68, −6.78)
Sunspot number	1570	0.63 (−17.82, 19.09)
IMF	1570	12.56 (5.31, 19.82)
Kp_index	1570	7.02 (2.93, 11.11)
+ *inverse-probability weighting* [c]		
CRII	1570	−18.04 (−28.09, −7.99)
Neutrons	1570	−16.54 (−25.44, −7.63)
Sunspot number	1570	−2.06 (−20.42, 16.30)
IMF	1570	13.10 (5.86, 20.34)
Kp_index	1570	7.58 (3.46, 11.70)

IQR interquartile range, *CI* confidence interval, *CRII* cosmic ray induced ionization, *IMF* interplanetary magnetic field.
[a]Additionally adjusted for BMI, smoking status and packyears, white blood cell count, percent neutrophils, percent lymphocytes, treatment with statin medication, treatment with hypertension, diagnosis of diabetes, fasting blood glucose, years of education.
[b]Additionally adjusted for seasonality, annual moving averages of temperature, relative humidity, and black carbon.
[c]Accounted for lost to follow-up by inverse probability follow-up response weighting.

Table 3. a. Independent associations between galactic cosmic rays and telomere length, adjusted for solar and geomagnetic activities and expressed as difference in telomere length per interquartile range (IQR) increases in each measure ($n = 791$ subjects) (first 3 rows). b. Independent associations between solar and geomagnetic activities and telomere length, adjusted for galactic cosmic rays and expressed as difference in telomere length per interquartile range (IQR) increases in each measure ($n = 791$ subjects) (last 3 rows).

	CRII	Neutrons
Sunspot number [a]	−19.94 (−30.71, −9.18)	−16.90 (−26.21, −7.60)
IMF	−10.04 (−32.97, 12.88)	−9.44 (−30.99, 12.12)
Kp_index	−10.70 (−25.51, 4.12)	−9.60 (−23.54, 4.34)
Sunspot number	−12.04 (−31.65, 7.56)	−8.86 (−27.96, 10.24)
IMF	6.08 (−10.39, 22.56)	5.60 (−11.87, 23.07)
Kp_index	3.84 (−2.16, 9.85)	3.65 (−2.72, 10.03)

IQR interquartile range, *CRII* cosmic ray induced ionization, *IMF* interplanetary magnetic field.
[a] Significant adjusted associations between CRII or Neutrons with telomere length, accounting for sunspot number.

study the dynamic relationship between space weather and telomere over follow-up, with a complete set of measurements for SGAs and GCRs during the study period. We eliminated potential bias through IPW, where the statistical models were weighted by the weights for the inverse of probability of remaining in the cohort given characteristics in the previous visit and were thus able to evaluate the association between space weather and telomere length in a counterfactual world had everyone been followed. Another potential selection bias comes from enrolling only participants who provided DNA samples. We compared the personal characteristics between included subjects and those NAS participants not included in the analysis during the same time-period and found no significant differences except in age.

Our findings provided that, although lives on Earth are protected from the extraterrestrial radiation sources by the atmosphere and the Earth's magnetic field, like the astronauts, our health is still potentially threatened by the ionizing radiation associated with space weather. Extraterrestrial radiation appears to exert biological effects on the general population and may thus modulate the aging process. Further studies are warranted to clarify the role of telomere in space weather induced diseases.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: PK, CLZV, JS. Methodology: TZ, CLZV. Investigation: AAB. Formal analysis: TZ. Visualization: TZ. Funding acquisition: JS, AAB, ZDN, PV, PK. Project administration: PV. Supervision: PK, CLZV, ZDN. Writing – original draft: TZ, CLZV. Writing – review & editing: all authors

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The VA normative aging study was approved by the institutional review boards of the Harvard T.H. School of Public Health and the Veterans Administration Boston Healthcare System, and all participants provided written informed consent.

ADDITIONAL INFORMATION

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