Archival Report

Biological Psychiatry

Physician-Training Stress and Accelerated Cellular Aging

Kathryn K. Ridout, Samuel J. Ridout, Constance Guille, Douglas A. Mata, Huda Akil, and Srijan Sen

ABSTRACT

BACKGROUND: Stress is a key precipitant for many common diseases, but established biological markers to track stress and guide investigations into mechanisms linking stress and disease are lacking. Cross-sectional studies have identified correlations between stress and telomere attrition, but no large, longitudinal studies examining the impacts of chronic stress on telomere length exist. Residency training for physicians is a well-established stressful experience and can be used as a prospective stress model.

METHODS: In a longitudinal cohort study of 250 interns (first-year residents) at 55 United States hospital systems serving during the 2015–2016 academic year, we examined associations between measures of the residency experience and saliva-measured telomere attrition.

RESULTS: Telomere length shortened significantly over the course of internship year, from mean ± SD of 6465.1 ± 876.8 base pairs before internship to 6321.5 ± 630.6 base pairs at the end of internship (t_{246} = 2.69; p = .008). Stressful early family environments and neuroticism were significantly associated with shorter preinternship telomere length. Longer work hours were associated with greater telomere intern telomere loss over the year (p = .002). Of note, the mean telomere attrition during internship year was six times greater than the typical annual attrition rate identified in a recent meta-analysis.

CONCLUSIONS: This work implicates telomere attrition as a biologically measurable consequence of physician training, with the magnitude of attrition associated with workload. Identification of an objective, biological sequela of residency stress may help to facilitate the development of effective interventions. Further, the findings implicate telomere attrition as an objective biomarker to follow the pathologic effects of stress, in general.

Keywords: Aging, Education, Graduate, Medical, Residency, Telomere

https://doi.org/10.1016/j.biopsych.2019.04.030

Medical residency, the first phase of professional medical training in the United States, is a stressful period in the career of physicians. Residents are faced with long work hours, sleep deprivation, and a new degree of responsibility for patients (1–4). Despite efforts from the accrediting agencies and training institutions to limit work hours, ensure adequate supervision, and implement programs to monitor and promote wellness, residents continue to report high stress and burnout (1,3,5–7). In addition to precipitating mental health problems (8,9), stress exposure is an important risk factor for systemic diseases such as obesity, type 2 diabetes, and cardiovascular disease (10). To date, studies of physician-training stress have largely focused on self-report measures of perceived stress, mental health, and well-being (2,4,6,11). Direct assessment of the objective, biological effects of physician training hold the promise to broaden our understanding of the effects of the training on health and more precisely identify targets for intervention.

Telomeres are complexes consisting of tandem DNA nucleotide TTAGGG repeats complexed with proteins found at the ends of chromosomes that help ensure stability and maintenance of the nuclear genome (10,12). Telomere length decreases with each cell replication cycle (12), and once telomeres reach a critically shortened length, cells enter a state of replicative senescence (12). A recent systematic review of 129 primary studies found that telomeres shorten at a rate of 24.7 base pairs per year in somatic tissues on average (13). In cross-sectional studies, shorter telomere length has been correlated with multiple forms of stress exposure, including psychological stress, perceived stress, social stress, caregiver stress, posttraumatic stress, and childhood maltreatment (10,14–18). Telomere attrition is also a predictor of somatic disease risk, including heart disease and diabetes, as well as of general senescence and mortality (10,12). However, no large, longitudinal studies examining the impacts of chronic stress on telomere length have been reported.

The objective of this study was to examine the biological impacts of residency training by longitudinally assessing telomere-length attrition across the internship year and how

ISSN: 0006-3223

this marker of cellular aging relates to factors of the training experience.

METHODS AND MATERIALS

Participants

The Intern Health Study is a multisite prospective cohort study that aims to assess stress and mood during medical internship. Training physicians ($N = 4904$) who were beginning internship at one of 55 institutions (see the Supplement for a list of institutions) in 2015 were sent an e-mail 8 to 10 weeks prior to commencing the internship and invited to participate in the study (Figure 1) (9,19). For 44 subjects, the e-mail invitations were returned as undeliverable and we were unable to obtain a valid e-mail address. Of the remaining invited subjects, 64.3% (3127/4860) agreed to participate. The first 250 subjects to enroll in the parent study were included in the current analysis of telomere length. Subjects were given $50 Amazon gift cards for participation. The Institutional Review Board at the University of Michigan approved the study. Power analysis estimated that 76 subjects would allow detection of a moderate effect size change in telomere length over the intern year ($d \geq 0.5$) with $\alpha = .05$ and a power of 0.99.

Baseline Assessment

All surveys were conducted through a secure, web-based platform designed to maintain confidentiality. Subjects completed a baseline survey upon study enrollment prior to commencing the internship. The survey assessed general demographic factors (age, gender, and marital status), specialty, self-reported history of depression, and various psychological measures. Depressive symptoms were measured with the nine-item Patient Health Questionnaire (PHQ-9), which scores each of the nine criteria for depression from 0 (not at all) to 3 (nearly every day), with PHQ-9 scores ≥10 having a sensitivity of 81.3% (95% confidence interval, 71.6%–89.3%) and specificity of 85.3% (95% confidence interval, 81.0%–89.1%) for major depressive disorder (20). Early-life stress has been strongly implicated with telomere attrition in prior studies (18). Neuroticism has been associated with telomere attrition in some but not all prior studies (21,22). Neuroticism [defined as tendency for quick arousal, slow relaxation from arousal, and tendency to respond with negativity (23)] was assessed using the NEO Five-Factor Inventory, which comprises 12 questions scored on a scale from 1 (disagree strongly) to 5 (agree strongly) (24). Early family environment was assessed using the Risky Families Questionnaire, which scores the extent to which respondents felt loved, were shown affection, were abused, lived with a substance abuser, lived in an organized and well-managed household, and had adults who "knew what they were up to" from 1 (rarely or none of the time) to 4 (most or all of the time) (25).

Within-Internship Assessments

Participants were contacted via e-mail at months 3, 6, 9, and 12 of their internship year and asked to complete a web-based survey that included the PHQ-9, average daily work and sleep hours over the past week, and outside-residency stressful life events (defined as experiencing a serious illness, going through death or serious illness in a close family member or friend, experiencing financial problems, undergoing the end of a serious relationship, or becoming a victim of crime or domestic violence) during the past 3 months (9). These measures have previously been shown to be associated with increased subjective and objective markers of residency stress (9).

DNA Collection and Telomere-Length Analysis

Subjects submitted Oragene OG-500 salivary DNA self-collection kit (DNA Genotek Inc., Ottawa, ON, Canada) saliva samples via postal mail for telomere assessment 2 to 6 weeks before their internship and at the completion of their internship (26). For each individual subject, baseline and follow-up samples were extracted and assayed for telomere length on the same plate. Telomeres were measured relative to a single copy gene (human beta-globin) using an assay adapted from previously published methods (27). Telomere primer sequences were [5′-CGGTTT(GTTTGG)$_5$GTT-3′] and [5′-GGCTTG(CCTTAC)$_5$CCT-3′] at final concentrations of 100 and 900 nmol/L, respectively. Beta-globin primer sequences were [5′-GCTTCTGACACAACTGTGTTCACTAGC-3′] and [5′-CACCAACTTCATCCACGTTCACC-3′] at final concentrations of 300 and 700 nmol/L, respectively. The final reaction mix contained 20 mmol/L Tris, pH 8.4; 50 mmol/L potassium chloride; 200 μmol/L each of deoxynucleotide; 1% dimethylsulfoxide; and 0.4 × concentration SYBR Green I (Invitrogen, Carlsbad, CA); 22 ng *Escherichia coli* DNA (MP Biomedicals, Solon, OH); 0.4 unit Platinum Taq DNA polymerase (Invitrogen); and 0.5 to 10 ng genomic DNA per 11-μL reaction. Reference DNA from HeLa cancer cells was used to generate a standard curve for all polymerase chain reaction runs using a LightCycler 480 real-time polymerase chain reaction machine (Roche Diagnostics, Indianapolis, IN). The interassay coefficient of variation for telomere-length measurement was 4%. Samples were run in duplicate. If the results for the same sample varied by >7%, the sample was run a third time and the average of the two closest values was used. Telomere-to–single copy gene (T/S) ratio was converted to base pairs using the formula T/S × 2413 + 3274, which was based on comparison of the ratio to Southern blot analysis (28,29).

Statistical Analysis

Pre- to postinternship change in telomere length was assessed using a paired-samples *t* test. Relationships between demographic characteristics and telomere length were assessed using bivariate correlation analysis. Associations between other independent variables and telomere length were examined using Pearson correlations. Univariate generalized linear models were used to examine the effects of the following within-internship variables on telomere attrition: 1) average intern-year work hours (calculated by averaging reported hours for each quarter), 2) stressful life events (calculated by averaging reported events for each quarter), 3) PHQ-9 depressive symptoms scores (calculated by averaging reported PHQ-9 for each quarter), 4) sleep length (calculated by averaging reported average sleep for each quarter), and 5) specialty. We created quartiles for work hours by derived work-shift length, calculated by dividing the reported average

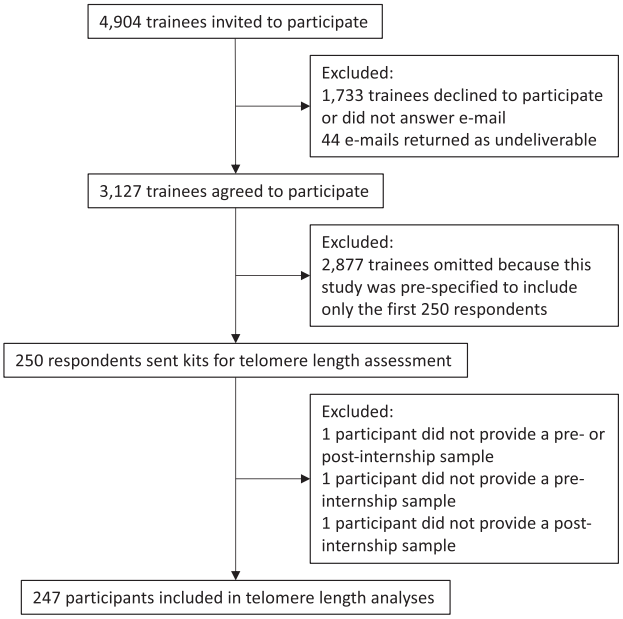

Figure 1. Flow of participants through the study.

number of work hours each quarter by 5 (assuming a 5-day work week). As prior literature has identified age and gender as significant predictors of telomere length (10,13), we adjusted for these variables in all Pearson correlations and generalized linear models. Missing telomere data from three subjects were dealt with by listwise deletion. Statistical significance was defined as a two-tailed p value of $< .05$. All p values in this study were subjected to the Benjamini-Hochberg procedure; reported significant p values were significant at the Benjamini-Hochberg calculated critical value (calculated using the formula $(i/m)Q$, where i is the individual p value's rank, m is the total number of tests, and Q is the false discovery rate) with the false discovery rate set to 0.15. Data conformed to the assumptions of normality of distribution. Analyses were performed using IBM SPSS Statistics Software Version 24.0 (IBM Corp., Armonk, NY). Summary data are presented as mean (SD) unless otherwise indicated.

College Student Control Sample

In order to gain additional insight into the expected telomere attrition rate in young adults, we assessed a sample of 84 University of Michigan students who were incoming as first-year undergraduate students in the 2016/2017 academic year (average age, 18.3 years [0.8 SD] at baseline), who provided DNA samples for longitudinal analysis in the August before starting college and then again in August after their first year. Telomere length in these samples proceeded as described above.

RESULTS

Participant Characteristics

In all, 250 medical interns agreed to participate in this 1-year study of telomere attrition during the intern year, of which 98.8% (247/250) provided salivary DNA samples for both pre- and postinternship analysis of telomere length. The mean age of the interns at baseline was 27.4 (2.9) years, and 52.6% (130/247) were women (Table 1). The subjects taking part in the present telomere study ($n = 247$) did not differ significantly from those in the overall 2015 Intern Health Study Cohort ($N = 3127$) on gender, age, history of depression, neuroticism, work hours, baseline depressive symptom score, or internship depressive symptom score (all p values $> .05$). Compared with all individuals in the American Association for Medical Colleges database who were beginning internship, this sample was slightly younger (27.4 vs. 28.8 years of age) and included a slightly higher percentage of women (52.6% vs. 48.6%).

Telomere Attrition With Intern Year

The mean gap between collection of the baseline and follow-up samples was 385.2 (11.6) days. There was significant attrition of telomere-length base pairs from the start of internship (6465.1 [876.8]; T/S ratio 1.32 [0.36]) to follow-up (6321.5 [630.6]; T/S ratio 1.26 [0.26]), amounting to a loss of 143.5 (839.1) base pairs (−0.060 [0.35] T/S ratio) over the course of intern year ($t_{246} = 2.69$, 95% confidence interval 38.4–248.7, $p = .008$).

Correlates of Baseline Telomere Length

Neither age ($r = -.04$, $p = .58$) nor gender ($r = -.12$, $p = .07$) was significantly correlated with preinternship telomere length (Table 2). Controlling for age and gender, a more stressful early family environment ($r = .13$, $p = .04$) and higher levels of neuroticism ($r = .18$, $p = .006$) were significantly associated with preinternship telomere length. Personal or family history of depression, depressive symptom scores prior to intern year, and sleep were not associated with preinternship telomere length on age- and gender-adjusted analysis ($p > .05$ for all comparisons).

Predictors of Telomere Attrition

There was a significant correlation between baseline and follow-up telomere length ($r = .418$, $p < .0001$). Among demographic variables, older age ($r = -.15$, $p = .02$), but not

Table 1. Resident Characteristics ($n = 247$)

Characteristic	Value[a]
Age, Years	27.4 (2.9)
Male, *n* (%)	117 (47.4)
Hours Worked per Week	64.5 (9.2)
PHQ-9 Score at Baseline	2.6 (2.6)
PHQ-9 Score at Follow-up	5.2 (3.6)
Positive History of Depression, *n* (%)	138 (55.9)
Positive Family History of Depression, *n* (%)	121 (49.0)
Risky Families Questionnaire Score	11.8 (8.4)
Neuroticism Score	21.2 (8.6)
Number of Stressful Life Events During Intern Year	0.8 (1.0)
Telomere Length at Baseline	6465.0 (876.8)
Telomere Length at Follow-up	6321.5 (630.5)

PHQ-9, nine-item Patient Health Questionnaire.
[a]Summary data are presented as mean (SD) unless otherwise indicated.

Table 2. Correlation Coefficients Between Baseline Preinternship Characteristics and Telomere Length (n = 247)

	Preinternship Telomere Length		Change in Telomere Length	
Baseline Characteristic	Correlation Coefficient	p Value	Correlation Coefficient	p Value
Age	.04	.58	−.15	.02
Gender	−.12	.07	.03	.62
Baseline Depressive Symptom (PHQ-9) Score[a]	.07	.31	−.07	.28
Personal History of Depression[a]	−.01	.84	−.03	.58
Family History of Depression[a]	.04	.63	−.04	.59
Early Family Environment (RFQ) Score[a]	.13	.04	−.04	.53
Neuroticism Score[a]	.18	.006	−.09	.15
Sleep Hours	−.09	.15	.10	.14

PHQ-9, nine-item Patient Health Questionnaire; RFQ, Risky Families Questionnaire.

[a]Analysis performed while adjusting for age and gender.

gender (r = .03, p = .62), was significantly associated with telomere-length attrition over the internship year. Early family environment and neuroticism were not significantly associated with telomere attrition over the year ($p > .05$ for both comparisons). Interns reported working a mean (SD) of 64.5 (± 9.1) hours per week. Currently, the American Council for Graduate Medical Education requires medical interns work shifts that are no longer than 16 hours a day. We categorized average work hours by projected shift length to gain insight regarding a potential dose response to working shifts below this threshold (shifts of ≤16 hours) compared with working at or above this threshold (16 hours or more). When controlling for age and gender, there was a main effect of work hours on telomere attrition ($F_{3,236}$ = 5.20, p = .002, Cohen's d = −.51) (Figure 2), such that working more hours, and potentially more shifts, at or above the American Council for Graduate Medical Education threshold was associated with greater telomere attrition (Supplemental Table S1). These results remained significant when we included preinternship telomere length, early family environment, and neuroticism in the models (F = 2.93, p = .034; F = 5.18, p = .002; and F = 5.03, p = .002, respectively). Other within-internship variables were not significantly correlated with telomere attrition ($p > .05$, data not shown).

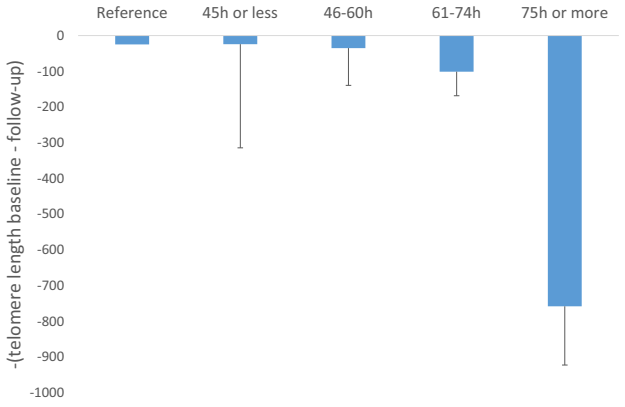

Figure 2. Univariate generalized linear model of telomere length change with internship stress stratified by work hours. The categorization of average work hours was structured to examine the impact of projected shift hours below (9, 12, or 15) or above (16 or above) the American Council for Graduate Medical Education–required threshold for interns. There was a main effect of work hours on telomere attrition ($F_{3,236}$ = 5.20; p = .002), such that working more shifts at or above the American Council for Graduate Medical Education threshold was associated with increased telomere attrition. Data are presented as mean (SE). The reference telomere loss is the expected average telomere loss per year from the article of Epel *et al.* (14).

Comparison to Normative and Control Sample Attrition Rates

In the meta-analysis (13) used to establish the typical annual telomere attrition of 25 base pairs per year, the average age of subjects was substantially higher than the average age of subjects in the current study. Thus, we obtained access to a control sample of young adults to gain additional insight into the expected telomere attrition in our sample. In contrast to the intern sample, telomere length did not decrease over the year. In fact, there was a nonsignificant increase in telomere length across the first year of undergraduate studies (t_{83} = −2.026, p = .05).

DISCUSSION

This prospective cohort study of 250 medical interns demonstrated that physician training is associated with a significant decrease in telomere length, with an average telomere attrition of 143.5 (839.1) base pairs over the course of the intern year. Telomere shortening remained significant after we accounted for previously reported predictors of telomere attrition, such as personality traits and number of stressful life events outside of residency training. The rate of attrition was related to work hours, with higher work hours associated with greater telomere attrition (Figure 2). Further, the rate of attrition during internship was substantially larger than the typical attrition of 25 base pairs per year in a recent systematic review and meta-analysis of >100 studies and in a control sample of college students (13).

The longitudinal model of this study provides a powerful within-subject design that suggests that, in this relatively homogeneous group in regard to age and education level, workload predicts accelerated attrition of telomeres, which can have long-lasting consequences on an individual's health. These are the first data showing a link between the subjectively stressful experience of physician training and an objective marker of cellular stress exposure. By identifying a relation between work hours and telomere attrition, these results demonstrate that a quantifiable marker, such as telomere length, can facilitate the identification of the critical components of physician stress that may have long-lasting consequences for physical health and well-being, which are critical to target for intervention. Potentially, telomere length may help evaluate the effectiveness of such interventions. While our results indicate that internship is associated with accelerated telomere attrition, the mechanisms underlying the association

between stress and telomere length are unknown. Telomeres shorten after repeated cellular divisions and cellular stress exposures (10). It is possible that the stress associated with the experience of intern year directly activates or is associated with mechanisms activating increased cellular stress and replication, resulting in accelerated telomere shortening (30). Immune cell replication could also have been increased through infectious agent exposure in health care settings. Decreased telomerase activity, a key regulator of telomere length, has been associated with stress exposure, and it may play a role in linking internship and telomere attrition (10).

A large and growing body of work has identified that physician training and practice adversely affect a range of mental health outcomes, including burnout, depression, and suicide risk (1,31,32). The present findings complement and extend this body of work. First, the identification of an objective, biological marker of physician-training stress further substantiates the harmful consequences of this stress on well-being and mental health and adds urgency to the case that reform in graduate medical education is needed. Further, the identified telomere attrition raises concern that the consequences of physician-training stress extend beyond well-being and include increased risk for systemic, chronic diseases previously associated with shortened telomeres (10,18,30,33). Future studies are needed to assess whether the telomere attrition associated with internship persists through training and practice and, if it does, what its relationship with disease is.

Beyond physician-training stress specifically, this study suggests that telomere length may be useful as a biomarker for stress in general. Chronic activation of the stress-response system is a leading cause of death and disability, through increasing the risk of psychiatric disorders such as depression and anxiety as well as systemic diseases such as obesity, type 2 diabetes, and cardiovascular disease. In cross-sectional studies, shorter telomere length has been correlated with multiple forms of stress exposure, including psychological stress, perceived stress, social stress, caregiver stress, post-traumatic stress, and childhood maltreatment (10,14–18). Demonstrating accelerated telomere attrition in a longitudinal study and identifying workload as a critical component of the stress impact substantially adds to the evidence supporting telomere length as a stress marker.

Our study has a number of limitations. First, the sample was restricted to interns, so results may not be generalizable to all training physicians or fully representative of all residents. Relatedly, training physicians differ from the general population in important ways. The longitudinal association between stress and telomere attrition should be replicated in other population samples. Second, while our study measured many factors previously reported to affect resident perceived stress and mental health, we were unable to measure other potential confounders such as smoking, weight, diet, and exercise (12,34). Of note, effect sizes reported for telomere length and smoking ($d = -.011$) (35), diet (no significant effect size found) (36,37), and exercise (no significant effect size found) (34,38) have typically been in the small to nonsignificant range, while the effect found here was in the medium range ($d = -.051$). However, such variables may be helpful in understanding behavioral mechanisms linking the internship experience and telomere attrition. Third, the data that we used to establish normative telomere attrition rates are imperfect. Most notably, most prior studies include samples that are, on average, substantially older than the intern sample. However, evidence indicates that typical telomere attrition is low to absent in young adults (13), a conclusion consistent with the findings of no telomere attrition in our control sample of college students. Together, these findings raise confidence that the annual telomere attrition identified in interns is substantially accelerated compared with the expected attrition in young adults. Finally, this study measured telomere length from saliva, which is considered a relatively new measure compared with blood telomere length. However, there is good correlation between saliva and blood telomere-length measurements (39), and previous literature suggests that telomeres isolated from saliva samples show consistent results with stress exposure compared with telomeres from samples isolated from blood (18).

In summary, the present study identified telomere attrition with residency training and found that extended work hours were associated with accelerated rates of attrition. These results underscore the need to improve resident health and well-being during training. Further, the findings identify a quantifiable, objective biological marker that holds the promise to track physician stress and, potentially, stress more generally.

ACKNOWLEDGMENTS AND DISCLOSURES

This research was supported by the National Institute of Mental Health (Grant No. MH101459 [to SS]), the American Foundation for Suicide Prevention (Grant No. LSRG-0-059-16 [to CG and SS]), and the Office of Naval Research (Grant No. ONR N00014–12–1-0366 [to HA]).

We thank the training physicians who participated in the study. We also thank Drs. Jack Barchas, William Bunney, Francis Lee, Richard Myers, Alan Schatzberg, and Stanley Watson for valuable input.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (KKR, SJR), Kaiser Permanente, San Jose, California; Department of Psychiatry and Human Behavior (KKR), Alpert Medical School of Brown University, Providence, Rhode Island; Brain Research and Integrative Neuropsychopharmacology Division (CG), Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina; Department of Pathology (DAM), Brigham and Women's Hospital, Harvard Medical School and Brigham Education Institute (DAM), Boston, Massachusetts; and Molecular and Behavioral Neuroscience Institute (HA, SS) and Department of Psychiatry (HA, SS), University of Michigan, Ann Arbor, Michigan.

Address correspondence to Srijan Sen, M.D., Ph.D., 1066 Molecular and Behavioral Neuroscience Institute, 205 Zina Pitcher Place, Ann Arbor, MI 48109; E-mail: srijan@umich.edu.

Received Dec 26, 2018; revised Apr 25, 2019; accepted Apr 26, 2019.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2019.04.030.

REFERENCES

1. Baker K, Sen S (2016): Healing medicine's future: Prioritizing physician trainee mental health. AMA J Ethics 18:604–613.
2. Mata DA, Ramos MA, Bansal N, Khan R, Guille C, Di Angelantonio E, *et al.* (2015): Prevalence of depression and depressive symptoms among resident physicians: A systematic review and meta-analysis. JAMA 314:2373–2383.
3. Wilkinson H, Whittington R, Perry L, Eames C (2017): Examining the relationship between burnout and empathy in healthcare professionals: A systematic review. Burn Res 6:18–29.

4. Yaghmour NA, Brigham TP, Richter T, Miller RS, Philibert I, Baldwin DC Jr, *et al.* (2017): Causes of death of residents in ACGME-accredited programs 2000 through 2014: Implications for the learning environment. Acad Med 92:976–983.
5. Dewa CS, Loong D, Bonato S, Thanh NX, Jacobs P (2014): How does burnout affect physician productivity? A systematic literature review. BMC Health Serv Res 14:325.
6. Dyrbye LN, West CP, Satele D, Boone S, Tan L, Sloan J, *et al.* (2014): Burnout among U.S. medical students, residents, and early career physicians relative to the general U.S. population. Acad Med 89:443–451.
7. Hall LH, Johnson J, Watt I, Tsipa A, O'Connor DB (2016): Healthcare staff wellbeing, burnout, and patient safety: A systematic review. PLoS One 11:e0159015.
8. Grant F, Guille C, Sen S (2013): Well-being and the risk of depression under stress. PLoS One 8:e67395.
9. Sen S, Kranzler HR, Krystal JH, Speller H, Chan G, Gelernter J, *et al.* (2010): A prospective cohort study investigating factors associated with depression during medical internship. Arch Gen Psychiatry 67:557–565.
10. Ridout SJ, Ridout KK, Kao HT, Carpenter LL, Philip NS, Tyrka AR, *et al.* (2015): Telomeres, early-life stress and mental illness. Adv Psychosom Med 34:92–108.
11. Daneshvar F, Weinreich M, Daneshvar D, Sperling M, Salmane C, Yacoub H, *et al.* (2017): Cardiorespiratory fitness in internal medicine residents: Are future physicians becoming deconditioned? J Grad Med Educ 9:97–101.
12. Blackburn EH, Epel ES, Lin J (2015): Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. Science 350:1193–1198.
13. Muezzinler A, Zaineddin AK, Brenner H (2013): A systematic review of leukocyte telomere length and age in adults. Ageing Res Rev 12:509–519.
14. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, *et al.* (2004): Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 101:17312–17315.
15. Li X, Wang J, Zhou J, Huang P, Li J (2017): The association between post-traumatic stress disorder and shorter telomere length: A systematic review and meta-analysis. J Affect Disord 218:322–326.
16. Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, *et al.* (2016): Perceived stress and telomere length: A systematic review, meta-analysis, and methodologic considerations for advancing the field. Brain Behav Immun 54:158–169.
17. Oliveira BS, Zunzunegui MV, Quinlan J, Fahmi H, Tu MT, Guerra RO (2016): Systematic review of the association between chronic social stress and telomere length: A life course perspective. Ageing Res Rev 26:37–52.
18. Ridout KK, Levandowski M, Ridout SJ, Gantz L, Goonan K, Palermo D, *et al.* (2017): Early life adversity and telomere length: A meta-analysis. Mol Psychiatry 23:858–871.
19. Guille C, Zhao Z, Krystal J, Nichols B, Brady K, Sen S (2015): Web-based cognitive behavioral therapy intervention for the prevention of suicidal ideation in medical interns: A randomized clinical trial. JAMA Psychiatry 72:1192–1198.
20. Mitchell AJ, Yadegarfar M, Gill J, Stubbs B (2016): Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: A diagnostic meta-analysis of 40 studies. BJPsych Open 2:127–138.
21. van Ockenburg SL, de Jonge P, van der Harst P, Ormel J, Rosmalen JG (2014): Does neuroticism make you old? Prospective associations between neuroticism and leukocyte telomere length. Psychol Med 44:723–729.
22. Savolainen K, Eriksson JG, Kajantie E, Pesonen AK, Räikkönen K (2015): Associations between the five-factor model of personality and leukocyte telomere length in elderly men and women: The Helsinki Birth Cohort Study (HBCS). J Psychosom Res 79:233–238.
23. Lahey BB (2009): Public health significance of neuroticism. Am Psychol 64:241–256.
24. Costa PT Jr, McCrae RR (1997): Stability and change in personality assessment: the revised NEO Personality Inventory in the year 2000. J Pers Assess 68:86–94.
25. Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE (2004): Early environment, emotions, responses to stress, and health. J Pers 72:1365–1393.
26. Rogers NL, Cole SA, Lan HC, Crossa A, Demerath EW (2007): New saliva DNA collection method compared to buccal cell collection techniques for epidemiological studies. Am J Hum Biol 19:319–326.
27. Lin J, Epel E, Cheon J, Kroenke C, Sinclair E, Bigos M, *et al.* (2010): Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. J Immunol Methods 352:71–80.
28. Entringer S, Epel ES, Lin J, Blackburn EH, Buss C, Shahbaba B, *et al.* (2015): Maternal folate concentration in early pregnancy and newborn telomere length. Ann Nutr Metab 66:202–208.
29. Goglin SE, Farzaneh-Far R, Epel ES, Lin J, Blackburn EH, Whooley MA (2016): Change in leukocyte telomere length predicts mortality in patients with stable coronary heart disease from the Heart and Soul Study. PLoS One 11:e0160748.
30. Ridout KK, Carpenter LL, Tyrka AR (2016): The cellular sequelae of early stress: Focus on aging and mitochondria. Neuropsychopharmacology 41:388–389.
31. Rotenstein LS, Ramos MA, Torre M, Segal JB, Peluso MJ, Guille C, *et al.* (2016): Prevalence of depression, depressive symptoms, and suicidal ideation among medical students: A systematic review and meta-analysis. JAMA 316:2214–2236.
32. Dzau VJ, Kirch DG, Nasca TJ (2018): To care is human—Collectively confronting the clinician-burnout crisis. N Engl J Med 378:312–314.
33. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR (2016): Depression and telomere length: A meta-analysis. J Affect Disord 191:237–247.
34. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L (2017): Physical activity and telomere length: Impact of aging and potential mechanisms of action. Oncotarget 8:45008–45019.
35. Astuti Y, Wardhana A, Watkins J, Wulaningsih W, Network PR (2017): Cigarette smoking and telomere length: A systematic review of 84 studies and meta-analysis. Environ Res 158:480–489.
36. Perez LM, Amaral MA, Mundstock E, Barbe-Tuana FM, Guma F, Jones MH, *et al.* (2017): Effects of diet on telomere length: Systematic review and meta-analysis. Public Health Genomics 20:286–292.
37. Rafie N, Golpour Hamedani S, Barak F, Safavi SM, Miraghajani M (2017): Dietary patterns, food groups and telomere length: A systematic review of current studies. Eur J Clin Nutr 71:151–158.
38. Mundstock E, Zatti H, Louzada FM, Oliveira SG, Guma FT, Paris MM, *et al.* (2015): Effects of physical activity in telomere length: Systematic review and meta-analysis. Ageing Res Rev 22:72–80.
39. Stout SA, Lin J, Hernandez N, Davis EP, Blackburn E, Carroll JE, *et al.* (2017): Validation of Minimally-Invasive Sample Collection Methods for Measurement of Telomere Length. Front Aging Neurosci 9:397.