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Tired Telomeres: poor global sleep quality, perceived stress, and telomere length in immune cell subsets in obese men and women

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Abstract

Poor sleep quality and short sleep duration are associated with increased incidence and progression of a number of chronic health conditions observed at greater frequency among the obese and those experiencing high levels of stress. Accelerated cellular aging, as indexed by telomere attrition in immune cells, is a plausible pathway linking sleep and disease risk. Prior studies linking sleep and telomere length are mixed. One factor may be reliance on leukocytes, which are composed of varied immune cell types, as the sole measure of telomere length. To better clarify these associations, we investigated the relationships of global sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), and diary-reported sleep duration with telomere length in different immune cell subsets, including granulocytes, peripheral blood mononuclear cells (PBMCs), CD8+ and CD4+ T lymphocytes, and B lymphocytes in a sample of 87 obese men and women (BMI mean = 35.4, SD = 3.6; 81.6% women; 62.8% Caucasian). Multiple linear regression analyses were performed adjusting for age, gender, race, education, BMI, sleep apnea risk, and perceived stress. Poorer PSQI global sleep quality was associated with statistically significantly shorter telomere length in lymphocytes but not granulocytes and in particular CD8+ T cells (b = −56.8 base pairs per one point increase in PSQI, SE = 20.4, p=0.007) and CD4+ T cells (b = −37.2, SE = 15.9, p = 0.022). Among separate aspects of global sleep

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quality, low perceived sleep quality and decrements in daytime function were most related to shorter telomeres. In addition, perceived stress moderated the sleep-CD8+ telomere association. Poorer global sleep quality predicted shorter telomere length in CD8+ T cells among those with high perceived stress but not in low stress participants. These findings provide preliminary evidence that poorer global sleep quality is related to telomere length in several immune cell types, which may serve as a pathway linking sleep and disease risk in obese individuals.

Keywords

sleep quality; sleep duration; telomere length; stress; obesity

Introduction

Growing epidemiologic evidence links short sleep (i.e., sleeping 6 or fewer hours per night) and poor sleep quality with increased incidence and progression of several chronic medical conditions observed at greater prevalence among overweight and obese individuals, including type 2 diabetes, coronary heart disease, and metabolic syndrome (Ayas et al., 2003; Cappuccio et al., 2010a; Gangwisch et al., 2007; Grandner et al., 2013; Grandner et al., 2012; Hall et al., 2008; Jennings et al., 2007). Sleep complaints and clinical sleep disorders such as obstructive sleep apnea (OSA) are common among the overweight and the obese (Beccuti and Pannain, 2011). However, the underlying biological mechanisms linking sleep and disease risk remain to be elucidated. In this regard, researchers have turned their attention to the role of accelerated cellular aging, as indexed by immune cell telomere length, as a plausible pathway.

Telomeres are DNA-protein complexes at the ends of eukaryotic chromosomes that protect the DNA that encodes genetic information from loss or instability (Blackburn, 1991; Lin et al., 2010). In adult human mitotic cells telomeres shorten with successive cell divisions. Critically short telomeres can send cells into replicative senescence, causing cell cycle arrest and malfunction as well as potential genomic instability. The contributors to accelerated cellular aging are complex and multifaceted; however, there is growing acceptance that telomere shortening in immune cells is a marker, and possibly a mechanism (Codd et al., 2013; Guo et al., 2011; Sahin et al., 2011), underlying premature morbidity and mortality in humans. Numerous clinical studies link short telomere length, measured primarily in leukocytes, with increased rates and risks of age-related diseases (Epel et al., 2009; Fitzpatrick et al., 2007; Franceschi and Campisi, 2014; Haycock et al., 2014; McElhaney and Effros, 2009; Zee et al., 2010; Zhao et al., 2014). Investigations of pathways through which short telomeres contribute to disease pathogenesis are topics of active scientific inquiry. Senescent cells show increased secretion of proinflammatory cytokines and extra cellular matrix-degrading enzymes, which may, in turn, drive accelerated disease progression (Blackburn, 2005; Effros et al., 2005). With respect to psychosocial predictors, short telomere length has been associated with a variety of psychological and behavioral factors, including psychological stress, depression, tobacco use, sedentary behavior, and obesity (Prather et al., 2013a; Puterman and Epel, 2012; Shalev et al., 2013; Starkweather et

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al., 2014; Verhoeven et al., 2013). Investigation of the relationship between telomere length and sleep, however, has been limited.

A handful of studies have investigated associations between sleep and telomere length (Cribbet et al., 2014; Jackowska et al., 2012; Lee et al., 2014; Liang et al., 2011; Prather et al., 2011a). Overall, these studies support associations of short sleep duration and poor subjective sleep quality with shorter leukocyte telomere length. One limitation of this literature, however, has been the reliance on measures of telomere length in heterogeneous leukocyte populations, which include granulocytes and peripheral mononuclear cells (PBMCs). PBMCs can be further subdivided into lymphocytes (e.g., T cells, B cells and natural killer cells) and monocytes. With advancing age, the shortening of telomeres occurs primarily in CD8+ cells (Effros et al., 2005; McElhaney and Effros, 2009; Posnett et al., 1999), particularly those that have lost CD28 expression. CD28 is co-stimulatory molecule important for proliferative capacity. CD8+CD28− T lymphocytes are terminally differentiated effector CD8+ T lymphocytes that lose telomerase activity and secrete excess proinflammatory cytokines (Effros et al., 2005; McElhaney and Effros, 2009). An increased proportion of CD8+CD28− T cells predicts poorer antibody response (Effros et al., 1994), increased susceptibility to the common cold (Cohen et al., 2013), and early mortality in elderly adults (Wikby et al., 2002). To date, it remains unclear whether poor sleep is differentially associated with telomere length across different cell types. Given the importance of CD8+CD28− T cells in the aging immune system, an association of poor sleep with shortened telomeres in CD8+ T lymphocytes might be particularly significant.

Another limitation of the existing sleep-telomere literature is that there has been little investigation of the role stress plays in the associations between sleep and telomere length. Individuals experiencing elevated levels of stress regularly also experience poor sleep. Existing literature also suggests that sleep modulates the stress response. In this regard, experimental studies employing sleep deprivation demonstrate that sleep loss lowers one's threshold for what is perceived as stressful (Minkel et al., 2012) and leads to enhanced amygdala activation, a brain region critical to processing emotion and regulating stress physiology, in response to threatening stimuli (Yoo et al., 2007).

The aims of the present study were to investigate the associations between self-reported sleep duration, measured via daily diary reports, and subjective global sleep quality, assessed using the Pittsburgh Sleep Quality Index, with telomere length in granulocytes, PBMCs and sorted cells (CD4+ and CD8+ T lymphocytes, and B lymphocytes) in a sample of obese men and women. As a secondary exploratory analysis, we examined whether levels of perceived stress moderated associations between sleep and telomere length. Based on the existing literature, we hypothesized that shorter sleep duration and poorer global sleep quality would be associated with shorter telomere length, particularly in CD8+ T lymphocytes. Further, we hypothesized that these sleep-telomere relationships would be stronger in participants experiencing higher levels of perceived stress.

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Methods

Participants

Study participants from the San Francisco Bay Area were recruited for a randomized controlled trial comparing a standard diet and exercise weight loss program to an enhanced program incorporating mindfulness-based eating and stress management techniques. Data for the present analysis come from the baseline assessment of this trial prior to randomization. To be eligible to participate in the study, individuals had to have a body mass index (BMI) score between 30 and 45, be 18 years old or older, and non-diabetic. The latter criterion was verified by fasting glucose (< 126 mg/dl) and hemoglobin A1c (< 6.0%, or 6.0% but < 6.5% with a normal oral glucose tolerance test). Additional exclusion criteria included untreated hypothyroidism, use of immunomodulatory medications in the past 6 months (e.g., corticosteroids), being pregnant or planning to become pregnant in the next 12 months, presence of a psychiatric or medical condition that would preclude participation in the group intervention, current bulimia and/or weight loss of 15lbs or more in the past 3 months, and participation in mindfulness-based therapies in the past 2 months prior to enrollment. Informed consent was obtained from each participant prior to carrying out the study protocols. This study was approved by the Institutional Review Board of the University of California, San Francisco.

Study Procedures

Participants completed sociodemographic and psychological questionnaires at home using a web-based platform and at their clinic assessment, which also included a blood draw and anthropometric measurement. Blood was drawn under 12-hour fasting conditions between 8 AM and 12 PM into acid citrate dextrose venous vacuum collection tubes. PBMCs were isolated from whole blood by Ficoll-Hypaque density gradient centrifugation within 6 hours of blood drawing, cryopreserved in liquid nitrogen, and stored at the UCSF Biological Specimen Bank until testing. Height and weight measures were obtained and BMI was calculated as weight (in kilograms) divided by height squared (in meters^2).

Sleep Measures—Participants completed the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a widely used and well-validated measure of global sleep quality. This 19-item measure yields seven component scores that reflect sleep difficulties in subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. A higher PSQI global score is indicative of poorer overall sleep quality. Participants also completed a daily activity diary over three consecutive days. As part of this diary, participants were asked “Around what time did you fall asleep last night?” and “What time did you wake up today?” This information was used to estimate each participant’s average diary-reported sleep duration. Participants were required to have at least two nights of data to be included in the average. Risk for obstructive sleep apnea (OSA) was assessed using the Berlin Sleep Questionnaire (Netzer et al., 1999), which is a well-validated self-report measure characterizing individuals at “high risk” versus “low risk” for OSA.

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Perceived Psychological Stress—Participants completed the Perceived Stress Scale (Cohen et al., 1983) to assess levels of psychological stress. This 10-item measure is widely used for assessing global stress perceptions, including ratings of feeling overwhelmed, out of control, and stressed over the past month. This measure was included because higher levels of perceived stress have been associated with telomere attrition in several studies (Epel et al., 2004; Shalev et al., 2013).

Immune cell and telomere processing

FACS sorting—Cryopreserved PBMCS were thawed, washed, counted and stained for sorting as previously described (Lin et al., 2010). Before staining, an aliquot of 1 million PBMCs was removed, pelleted and frozen at −80°C to assess telomere length measurement on total PBMC. For staining, briefly, thawed cells were first stained with LIVE/DEAD® Fixable Aqua Dead Cell Stain Kit (Invitrogen) for exclusion of non-viable cells, and then with the following fluorescently conjugated monoclonal antibodies: anti-CD4-PE-Texas Red® (Invitrogen); anti-CD3-V450, anti-CD19 PE-Cy™5, anti-CD28-PE, anti-CD45 FITC and anti-CD8-APC (all from BD Biosciences). Stained cells were sorted on a customized BD FACSAria™ II into the following fractions: CD4+ T cells (CD3+CD4+), CD8+ T cells (CD3+CD8+) and B cells (CD3-CD19+) using standard gating strategies. Cells were collected into AIM V serum-free media (Invitrogen) pelleted by centrifugation and stored at −80°C.

Granulocyte preparation—Immediately following Ficoll preparation of PBMCs, the red blood cell/granuloctye pellet was removed from the Ficoll tube, mixed with 3 volumes of ACK lysis buffer (QIAGEN, cat #158902), to lyse the red blood cells and incubated at room temperature for 10 minutes with inversion every 2 minutes. Cells were then washed twice in PBS, pelleted and stored at −80°C.

Assay of telomere length—Total genomic DNA was purified using QIAamp® DNA Mini kit (QIAGEN, Cat#51104) and stored at −80°C for batch telomere length measurement. The telomere length assay is adapted from the published original method by Cawthon (Cawthon, 2002; Lin et al., 2010). The telomere thermal cycling profile consists of: Cycling for T(telomic) PCR: 96°C for 1 minute; denature at 96°C for 1 second, anneal/extend at 54°C for 60 seconds, with fluorescence data collection, 30 cycles. Cycling for S (single copy gene) PCR: PCR: 96°C for 1 minute; denature at 95°C for 15 seconds, anneal at 58°C for 1 second, extend at 72°C for 20 seconds, 8 cycles; followed by denature at 96°C for 1 second, anneal at 58°C for 1 second, extend at 72°C for 20 seconds, hold at 83°C for 5 seconds with data collection, 35 cycles. The primers for the telomere PCR are *tel1b* [5'-CGGTTT(GTTTGG)5GTT-3'], used at a final concentration of 100 nM, and *tel2b* [5'-GGCTTG$(CCTTAC)_5$CCT-3'], used at a final concentration of 900 nM. The primers for the single-copy gene (human beta-globin) PCR are *hbg1* [5' GCTTCTGACACAACTGTGTTCACTAGC-3'], used at a final concentration of 300 nM, and *hbg2* [5'-CACCAACTTCATCCACGTTCACC-3'], used at a final concentration of 700 nM. The final reaction mix contains 20 mM Tris-HCl, pH 8.4; 50 mM KCl; 200 μM each dNTP; 1% DMSO; 0.4x Syber Green I; 22 ng E. coli DNA per reaction; 0.4 Units of Platinum Taq DNA polymerase (Invitrogen Inc.) per 11 microliter reaction; 0.5 – 10 ng of

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genomic DNA. Tubes containing 26, 8.75, 2.9, 0.97, 0.324 and 0.108ng of a reference DNA (from Hela cancer cells) are included in each PCR run so that the quantity of targeted templates in each research sample can be determined relative to the reference DNA sample by the standard curve method. The same reference DNA was used for all PCR runs.

To control for inter-assay variability, 8 control DNA samples are included in each run. In each batch, the T/S ratio of each control DNA is divided by the average T/S for the same DNA from 10 runs to get a normalizing factor. This is done for all 8 samples and the average normalizing factor for all 8 samples is used to correct the participant DNA samples to get the final T/S ratio. The T/S ratio for each sample was measured twice. When the duplicate T/S value and the initial value varied by more than 7%, the sample was run the third time and the two closest values were reported. For telomere length measurement of the CD4+ and CD8+ T lymphocytes and B lymphocytes, cell types of the same participant were always run on the same assay plate. The average CV for sorted cell telomere length data was 3.4%. The average CV for granulocyte telomere length data was 3.1%. The average CV for the PBMC telomere length data was 2.2%.

Statistical Analyses

All analyses were performed using SPSS for Macintosh (Version 21). Pearson product-moment correlations and independent t-tests were conducted to examine associations between sociodemographic characteristics, psychosocial factors, and telomere length. Age-adjusted partial correlations were performed to examine associations between sleep measures and telomere length in all cell types. These were followed by multiple linear regressions controlling for the effects of age, gender, race, education, BMI, perceived stress, and sleep apnea risk.

To clarify associations between PSQI global sleep quality and telomere length, we employed an empirically validated 3-factor scoring model for the PSQI to decompose the measure into three factors: Sleep Efficiency (composed of PSQI sleep duration and habitual sleep efficiency components), Perceived Sleep Quality (comprised of PSQI subjective sleep quality, sleep latency, and sleep medication use components), and Daily Disturbance (comprised of PSQI sleep disturbance and daytime dysfunction components) (Cole et al., 2006). Because prior evidence has linked shorter telomere length to specific subscales of the PSQI (e.g., habitual sleep duration, subjective sleep quality (Cribbet et al., 2014; Prather et al., 2011b)), analyses using these subscales were also conducted.

As a secondary analysis, we also investigated the moderating effect of perceived stress on the relationship between sleep and telomere length. In this regard, interaction analyses were performed according to the guidelines of Hayes and Matthes (Hayes and Matthes, 2009). The main effects of the sleep measures and perceived stress, and the interaction terms of sleep-perceived stress were entered into regression models predicting telomere length. Study covariates (age, gender, race, BMI, education, and sleep apnea risk) were included in all interaction analyses. Interactions were probed and simple slopes were computed for all interactions that had $p<0.10$.

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Telomere length values, originally expressed in T/S ratios, were converted to base pairs prior to analyses (Lin et al., 2010). One hundred ninety four participants enrolled in this study; however, analyses were restricted to participants who had complete data on sleep measures and telomere length in sorted cells (n=87). There were no statistically significant differences between included and excluded participants on any of the sleep measures, perceived stress, or sociodemographic characteristics. Measurement of granulocyte telomere length was added after data collection began, yielding 73 study participants with granulocyte telomere length for these analyses.

Results

Descriptive statistics and correlations with telomere length

Sociodemographic and psychosocial characteristics for this study sample are presented in Table 1. Bivariate correlational analyses revealed that granulocytes, PBMCs, and sorted cell telomere lengths were inversely associated with age (r's= −0.39 to −0.60, p's<0.001). In addition, higher BMI scores were associated with shorter telomere length measured in granulocytes (r= −0.24, p=0.040) and CD4+ T lymphocytes (r= −0.26, p=0.015). Independent t-tests revealed that men had statistically significantly shorter telomere lengths compared to women in granulocytes (men: 5,669, SD= 341; women: 5995, SD=441, p=0.015), PBMCs (men: 5,911, SD=315; women: 6,336, SD=585, p=0.006), CD8+ T lymphocytes (men: 5,472, SD=419; women: 6,097, SD=677, p< 0.001), and CD4+ T lymphocytes (men: 5,429, SD=439; women: 5,759, SD=561, p=0.030) but not B lymphocytes (men: 6,357, SD=564; women: 6,560, SD=661, p=0.19). There were no statistically significant differences in telomere length between participants who had graduated college and those who did not (p's>0.05) or those at high and low risk for sleep apnea in this sample (all p's>0.40). As expected (Lin et al., 2010), telomere lengths were inter-correlated across cell populations (r's= 0.31 to 0.69, p's<0.01)

Is sleep associated with CD8+ T lymphocyte telomere length?

As displayed in Table 2, unadjusted and age-adjusted partial correlations revealed that PSQI global sleep quality scores, where higher scores are indicative of poorer overall sleep, and shorter diary-reported sleep duration were associated with shorter telomere length in CD8+ T cells as well as other sorted cells. However, after adjusting for age, only the associations between PSQI global sleep quality and CD8+ T lymphocytes telomere length (r=-0.26, p=0.015) and diary-reported sleep duration and granulocyte telomere length (r= 0.24, p=0.044) were statistically significant.

Multiple linear regressions were computed to estimate associations of PSQI global sleep quality and diary-reported sleep duration with telomere length in sorted cells after accounting for possible confounders in addition to age, including gender, race, education, BMI, perceived stress, and sleep apnea risk. As displayed in Table 3, poorer overall PSQI global sleep was statistically significantly associated with shorter telomere length in CD8+ T lymphocytes while a smaller, though statistically significant, relationship was observed for CD4+ telomere length. In contrast, diary-reported sleep duration in hours was not statistically significantly related to telomere length. Figure 1 summarizes the linear

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relationships between PSQI global sleep quality and CD8+ and CD4+ T lymphocyte telomere lengths.

To further clarify the relationship between PSQI global sleep quality scores and telomere length, we decomposed the PSQI global score based on an empirically validated 3-factor scoring model (Cole et al., 2006). Adjusting for covariates, shorter telomere lengths in CD8+ and CD4+ T lymphocytes were associated with higher, i.e., poorer, scores on the Perceived Sleep Quality (CD8+: b=-70.5, SE=35.4, p=0.050; CD4+: b=-66.8, SE=26.8, p=0.015) and Daily Disturbance factors (CD8+: b=-186.8, SE=57.6, p=0.002; CD4+: b=-92.6, SE=45.9, p=0.047). When exploring associations using the subjective sleep quality and habitual sleep duration subscales from the PSQI, which have previously been linked to telomere length (Cribbet et al., 2014),, we found that poorer PSQI subjective sleep quality (CD8+: b=-187.9, SE=95.1, p=0.052; CD4+: b=-165.2, SE=72.3, p=0.025) but not PSQI sleep duration (p's>0.10) was associated with shorter CD8+ and CD4+ T lymphocyte telomere length in this sample. These findings raise the possibility that associations between sleep and telomere length may be due more to psychological or affective phenomena than lack of sleep per se. Accordingly, in secondary analyses, perceived stress was tested as potential moderator of the sleep-telomere relationship.

Does perceived stress influence the sleep-telomere relationship?

Perceived stress was essentially unrelated to the sleep measures (PSQI: r=0.03, p=0.754; sleep duration: r=0.08, p=0.482). Further, bivariate correlations revealed that levels of perceived stress were not strongly related to telomere length in any of the cell types (r's 0.06 to 0.12, p's>0.20). Nevertheless, after adjusting for covariates, interaction analyses revealed that perceived stress moderated the relationship between sleep and CD8+ T lymphocyte telomere length (interaction: b=-6.37, SE=3.28, p=0.056; R^2=0.03). Interactions between sleep and stress in predicting telomere length in other cell types were below statistical significance (p's>0.10).

To better understand the pattern of results, simple slopes were calculated. As displayed in Figure 2, among participants reporting higher perceived stress (i.e., those 1 SD above the mean on the Perceived Stress Scale (PSS)) poorer PSQI global sleep quality was associated with shorter CD8+ T lymphocytes telomere length (b= −110.79 SE= 34.26, p=0.002). Conversely, PSQI global sleep quality was much less related to CD8+ T lymphocyte telomere length in low stress participants (i.e., 1 SD below the mean on the PSS) (b= −34.22, SE= 23.21, p=0.145).

Discussion

Immune cell telomere length has emerged as a marker, and putative mechanism, linking a variety of psychosocial and behavioral factors with premature morbidity and mortality (Puterman and Epel, 2012; Shalev et al., 2013). Sleep has gained prominence as an important behavioral contributor to physical health and well-being (Buysse, 2014; Cappuccio et al., 2010b), yet only a handful of studies have investigated sleep's role in telomere length attrition (Cribbet et al., 2014; Jackowska et al., 2012; Lee et al., 2014; Liang et al., 2011; Prather et al., 2011a). In this study of obese men and women, we investigated

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the cross-sectional associations between PSQI global sleep quality and diary-reported sleep duration with telomere length measured in granulocytes, PBMCs and sorted immune cell types, namely T and B cells. In this regard, after controlling for potential confounders (age, gender, race, education, BMI, sleep apnea risk, and perceived stress), poorer PSQI global sleep quality was statically significantly associated with shorter telomere lengths in CD8+ and CD4+ T lymphocytes. Diary-reported sleep duration, in contrast, was not related in adjusted analyses to telomere length in any of the immune cell types examined.

PSQI global sleep quality score was statistically significantly related to telomere length only in T lymphocytes, but much smaller in other cell subsets, and within the T cell subset, association was stronger for CD8+ cells. This observation is intriguing in the context of existing research on immunosenescence where age-related impairment of CD8+ T lymphocyte responses is a hallmark (Chou and Effros, 2013). CD8+ T cells are critical to cell-mediated immunity; however, a lifetime of antigen elicited clonal expansion can result in exhaustion of replicative capacity and subsequent senescence (Effros, 2009). Telomerase, an enzyme that restores telomere base pairs, plays an important role in differential telomere length shortening across cell types (Blackburn, 2005). Indeed, in vitro studies demonstrate antigen activated CD8+ T lymphocytes have an attenuated capacity to produce telomerase following repeated stimulation compared to CD4+ cells, yielding a more rapid shortening of telomere length in CD8+ T lymphocytes (Effros et al., 2005). Whether telomerase levels play a role in the link between sleep quality and telomere length in CD8+ T lymphocytes remains an open question. However, given that poorer sleep quality was also associated with shorter telomere length in CD4+ T lymphocytes, it is likely that the influence of sleep on telomere attrition is multiply determined. Notably, we also observed that shorter diary-based sleep duration was associated shorter telomere length in granulocytes in age-adjusted analyses. Granulocytes, including basophils, neutrophils and eosinophils, are derived from the stem cells residing in bone marrow. As such, the telomere length shortening of these cells is not a result of excess replication in peripheral circulation. Future research is warranted to identify psychological and behavioral contributors to telomere attrition in these varied cell types.

An analysis using the 3-model structure of the PSQI global sleep quality (Cole et al., 2006) provided some newfound clarity to the sleep-telomere length relationship. The Perceived Sleep Quality and Daily Disturbances factors were associated with telomere length in CD8+ and CD4+ cell types while Sleep Efficiency was not substantially related to telomere length. Given that the Sleep Efficiency factor is composed of PSQI subscales that reflect habitual sleep efficiency and sleep duration, it is possible that much of the influence of global sleep quality on telomere attrition is driven by the consequences of sleep loss, such as daytime sleepiness and the subjective experience of poor sleep rather than indices of sleep behavior per se. This may explain why the PSQI global sleep quality measure predicted telomere length while self-reported sleep duration was much less related. Shorter sleep duration, assessed by daily diary, was associated with shorter telomere length in unadjusted analyses; however, these relationships were largely attenuated when adjusting for age. This is not particularly surprising given the well-documented changes in sleep that occur with aging (Ohayon et al., 2004). While speculative, the fact that the Perceived Sleep Quality and Daily Disturbance factors appear to play an important role fits with a growing literature that

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demonstrates the modulatory role of sleep on heightened stress perception, stress reactivity and concomitant stress physiology (Franzen et al., 2009; Minkel et al., 2012; Prather et al., 2013b), including biological mechanisms implicated in the cell aging process.

Perceived psychological stress appeared to moderate the association between PSQI global sleep quality and CD8+ T cell telomere length such that poorer overall sleep was more related to shorter telomere length in high than in low stress individuals. There were no substantial main effects of perceived stress on telomere length in any subset. A possible implication is that perceived stress may impact telomeres only when health behaviors are also dysregulated (e.g., (Puterman et al., 2014)). It was surprising that levels of perceived stress were unrelated to the sleep measures in this study. The PSQI global sleep quality score is composed of multiple sleep facets, some of which might be more strongly related to stress than others. In this regard, higher levels of stress were statistically significantly related to the Sleep Disturbance factor of the 3-factor PSQI scoring model ($r=0.27$, $p=0.012$), but essentially unrelated to the other two factors. It is plausible that larger moderating effects of stress on the sleep-CD8+ telomere length would have been observed if additional, more rigorous stress measures were incorporated. For instance, individual differences in stress reactivity have been shown to predict a number of biological outcomes (Jennings et al., 2004; Marsland et al., 2002). Further, stress hormones, such as cortisol, have been implicated with telomere biology (Choi et al., 2008; Tomiyama et al., 2012). Accordingly, more robust characterization of stress is required in future studies to better clarify the interaction between sleep and stress in predicting telomere length.

The biological pathways through which poor global sleep quality relates to telomere length need to be elucidated. In this regard, enhanced sympathetic arousal and dysregulation of the hypothalamic pituitary adrenal (HPA) axis have been observed in sleep-disturbed populations (Backhaus et al., 2004; Irwin et al., 2003). Elevated levels of nocturnal catecholamines have been linked to shorter leukocyte telomere length (Epel et al., 2006) and in vitro data suggest that T cells treated with cortisol show downregulated telomerase activity (Choi et al., 2008). Inflammation is likely another mediating pathway, particularly given that higher levels of systemic inflammation are consistently observed in obese compared to non-obese individuals (Mohamed-Ali et al., 1997; Ouchi et al., 2011; Zeyda and Stulnig, 2009). Epidemiologic and some laboratory-based studies support associations between short or disrupted sleep with increased levels of proinflammatory mediators (e.g., interleukin-(IL)-6 and tumor necrosis factor (TNF)-α) (reviewed in (Solarz et al., 2012). Furthermore, acute IL-6 reactivity has been found to be enhanced in individuals characterized as both poor sleepers and having excess visceral adiposity compared to leaner, better sleepers (Prather et al., 2013b).

There is growing evidence from observational and experimental sleep studies relating sleep with weight gain and obesity (Cappuccio et al., 2008; Markwald et al., 2013). To date, few studies have incorporated markers of cellular aging, such as telomere length. Some but not all studies suggest that telomere length shortens with increasing body mass (Muezzinler et al., 2014), raising the possibility that sleep-related changes in obesity may drive accelerated aging. The cross-sectional nature of the present study cannot address this possibility, but this

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is something that could be efficiently tested in ongoing trials exploring sleep effects on weight.

There are several limitations of the present findings that should be considered in interpreting these results. First, the sample comprised of primarily women (81.6%) and only obese participants, thus restricting our ability to generalize beyond this population. Obesity is often associated with metabolic dysfunction, which may affect both sleep and telomere length. Accordingly, we do not know if the same relationships would exist in a normal weight sample. Normal weight individuals tend to have longer telomeres than obese (Muezzinler et al., 2014) and often report higher sleep quality. While it is likely that a similar association would be observed, it may be attenuated due to a smaller range of sleep quality in a normal weight sample. Future studies exploring these associations in non-obese individuals and men are warranted. Second, sleep was assessed by self-report, and while the Pittsburgh Sleep Quality Index is well-validated, it remains unclear whether similar associations with telomere length would emerge using objective measures (e.g., polysomnography). In this regard, shorter leukocyte telomere length was associated with shorter sleep duration, measured using wrist actigraphy, in a large sample of HIV+ patients (Lee et al., 2014). Third, obstructive sleep apnea (OSA) was not assessed directly. Recent evidence demonstrated shorter leukocyte telomere length in participants with a history of OSA (Savolainen et al., 2014). Fourth, while one of the clear strengths of this investigation was the ability to examine telomere length in multiple immune cell subsets, the fact that many of the findings were observed in CD8+ cells raises the question of whether additionally subsetting into CD8+CD28+ and CD8+CD28-cells would have further illuminated sleep effects. As noted, CD28 is a co-stimulatory factor whose absence is a marker of immunosenescence. Whether the associations between sleep quality and CD8+ T lymphocytes would be stronger in the CD8+CD28-subset remains an open question. Finally, the cross-sectional nature of these data cannot rule out the possibility that shorter telomere length results in poorer sleep quality. For example, shorter telomere length has been related to elevations in inflammation (Effros et al., 2005; O'Donovan et al., 2011; Revesz et al., 2013), which has, in turn, been implicated in sleep regulation (Bryant et al., 2004).

In sum, these findings provide novel evidence that poorer global sleep quality is associated with shorter telomere length in CD8+ and CD4+ T lymphocytes. In addition, analyses revealed that links between poor sleep quality and shorter telomere length, specifically in CD8+ T cells, are strengthened in individuals reporting higher perceived psychological stress. Future research studies on cell type specific telomere length and age-related disease will benefit from the incorporation measures of sleep and stress, separately and in combination.

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Highlights

- Poor global sleep quality is associated with shorter telomere length in CD8+ and CD4+ T lymphocytes.
- Associations between global sleep quality and telomere length were driven by poorer subjective sleep quality and daytime dysfunction.
- PSQI global sleep quality and CD8+ T lymphocyte telomere length was more strongly associated in those reporting higher perceived stress.

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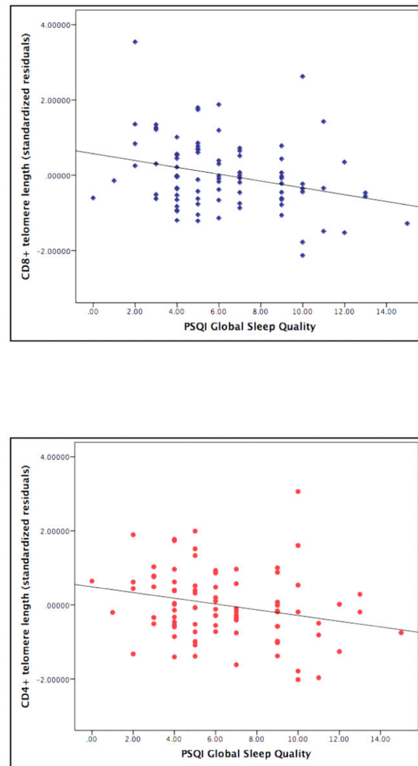

Figure 1.

Associations between PSQI global sleep quality scores and CD8+ (top panel) and CD4+ (bottom panel) T lymphocyte telomere lengths. Telomere length presented as standardized residuals following adjustment for age, gender, race, education, BMI, perceived stress, and sleep apnea risk.

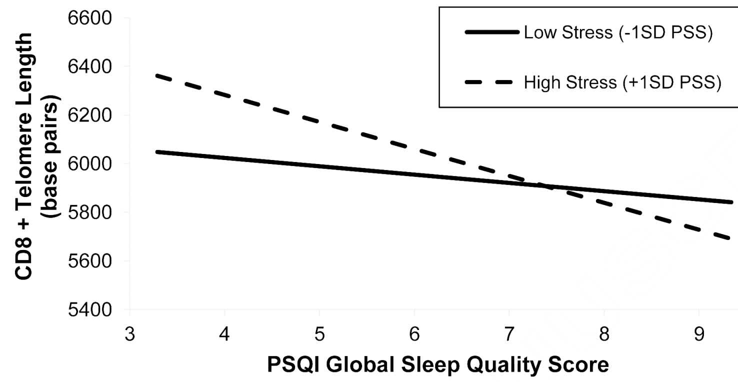

Figure 2.

Poorer PSQI global sleep quality is associated with shorter CD8+ T lymphocyte telomere length in high but not low stress participants. Analyses adjusted for age, gender, race, education, BMI, and sleep apnea risk.

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Table 1

Sample characteristics. Values expressed as means (standard deviations) or percentages.

Variable (n=87)	Mean (Standard Deviation) or %
Age (years)	48.0 (12.5)
Gender (% female)	81.6%
Race (% Caucasian)	62.8%
Body mass index (kg/m^2)	35.4 (3.6)
Education (% with Bachelor's degree)	72.1%
Perceived Stress Scale	15.1 (6.0)
Berlin Questionnaire Sleep Apnea (% high risk)	72.4%
PSQI global sleep quality score	6.3 (3.0)
Diary-reported sleep duration (hours)	7.1 (1.2)
Telomere Length	
Granulocytes* (base pairs)	5936.9 (440.9)
Peripheral Blood Mononuclear Cells (PBMCs) (base pairs)	6,257.4 (568.1)
CD4+ T lymphocyte (base pairs)	5,698.2 (553.7)
CD8+ T lymphocyte (base pairs)	5,982.2 (680.4)
B lymphocyte (base pairs)	6,557.3 (648.9)

*n=73

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Table 2

Unadjusted and age-adjusted telomere length with PSQI global sleep quality scores and diary-reported sleep duration.

	Granulocytes	PBMC	CD8+	CD4+	CD19+
Unadjusted					
PSQI global sleep quality	–0.19, p=0.106	–0.16, p=0.150	–0.27, p=0.013	–0.197, p=0.067	–0.15, p=0.165
Diary sleep duration	0.316, p=0.006	0.25, p=0.018	0.19, p=0.078	0.26, p=0.014	0.10, p=0.343
Age-adjusted					
PSQI global sleep quality	–0.14, p=0.253	–0.13, p=0.226	–0.26, p=0.015	–0.18, p=0.09	–0.13, p=0.243
Diary sleep duration	0.24, p=0.044	0.16, p=0.151	0.09, p=0.414	0.17, p=0.127	0.01, p=0.939

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Table 3

Associations between sleep measures and telomere length (TL) in sorted cells after controlling for covariates.

Predictor[a]	Granulocytes b (SE)	p-value	PBMC b (SE)	p-value	CD8+ b (SE)	p-value	CD4+ b (SE)	p-value	CD19+ b (SE)	p-value
PSQI global sleep quality	−25.15 (16.98)	0.143	−22.88 (17.10)	0.185	−56.83 (20.44)	0.007	−37.20 (15.87	0.022	−28.87 (23.12)	0.216
Diary sleep duration	42.48 (42.12)	0.317	20.35 (47.26)	0.668	−15.86 (58.62)	0.787	39.18 (44.71)	0.384	−20.06 (63.43)	0.753

[a] all models computed separately controlling for age, gender, race, education, BMI, sleep apnea risk, and perceived stress