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Sleep Variability, Health-Related Practices and Inflammatory Markers in a Community Dwelling Sample of Older Adults

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Abstract

Background—Low-grade chronic inflammation is an important risk factor for age-related morbidity. Health behaviors, including average aggregate measures of sleep, have been linked to increased inflammation in older adults. Variability in sleep timing may also be associated with increased inflammation. This study evaluated relationships among several health behaviors and circulating proinflammatory cytokines (IL-6 and TNF- α).

Method—Participants were community dwelling older adults >60 years (N = 222: 39 bereaved, 55 caregivers, 52 with insomnia, and 76 good sleepers). Mean values and intra-individual variability in sleep, as well as caffeine and alcohol use, exercise, and daytime napping were assessed by sleep diaries. Blood draws were obtained in the morning.

Results—Several interactions were noted between sleep behaviors, inflammatory markers, and participant group. Greater variability in wake time and time in bed was associated with higher IL-6 among good sleepers relative to caregivers and older adults with insomnia. Good sleepers who consumed moderate amounts of alcohol had the lowest concentrations of IL-6 compared to the other three groups who consumed alcohol. Insomnia subjects, but not good sleepers, showed increased concentrations of IL-6 associated with caffeine use. Caregivers showed increased concentrations of TNF- α with alcohol use relative to good sleepers. Greater variability in bedtime, later wake times and longer time in bed was associated with higher TNF- α regardless of group.

Conclusions—Moderation and regularity in the practice of certain health behaviors, including sleep practices, were associated with lower plasma levels of inflammatory markers in older adults. Life circumstances and specific sleep disorders may modify these associations.

Keywords

sleep variability; health-related behaviors; inflammatory markers; aging; caffeine; alcohol; cytokine; sleep timing

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Conflict of Interest The other authors report no disclosures.

Introduction

Virtually all physiological processes change with aging. One consistent observation is a decline in the ability of the immune system to function optimally in response to physiological challenge which can result in poor fever response, diminished leukocyte response to infections (1) or increased risk for infectious disease.(2, 3) One marker of an aging immune system is the subsequent increase in basal levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α). Indeed, IL-6 and TNF- α concentrations show an over 2-fold increase in healthy older adults compared to young controls.(4–7). Increased concentrations of these proinflammatory cytokines are often referred to as low-grade chronic inflammation (3, 7) which is thought to increase susceptibility to several age-related diseases, such as Alzheimer's Disease, arthritis and atherosclerosis. (1, 6, 7) Evaluating behaviors that may influence and modify the production of inflammatory cytokines, thereby promoting healthy aging, is important (8), particularly given that the population > 60 years of age is growing more rapidly than any other age group (9).

The majority of investigations that have examined relationships among health behaviors and inflammation in the context of aging have focused on poor health behaviors such as excessive alcohol use, smoking, lack of physical activity and short sleep duration (8, 10–12). More recently, however, there has been a paradigm shift in health behaviors research to focus on positive health behaviors, defined as voluntary and modifiable actions that help prevent illness and promote health, and their associated health benefits. In addition, the prevailing notion that one must engage or abstain in a behavior in order to receive its associated health benefits is being challenged by new evidence which suggests that moderate practice of certain health behaviors may be *more* beneficial than abstinence, particularly among older adults.(8, 13) For instance, moderate use of alcohol (1–7 drinks per week), (14, 15) caffeine (1–2 cups per day),(16–18) and regular exercise of moderate intensity (2–3 times per week)(7) are associated with successful aging. It has been postulated that these positive behaviors contribute to successful aging by reducing low-grade chronic inflammation (1, 19, 20).

Similar to physical activity, sleep is a modifiable behavior critical to health and functioning. Reliable associations have been reported for short and/or fragmented sleep duration and a host of adverse health outcomes such as hypertension, obesity, Type 2 diabetes, the metabolic syndrome, and all-cause mortality. (21–28) Similarly short and/or fragmented sleep has been associated with increased levels of inflammatory markers. (29, 30) Although we know that sleep behaviors may fluctuate widely across nights (31–35), little is known about the influence of night-to-night, or intra-individual, variability in sleep behaviors on health and functioning. We know from shift work research that extreme variability in sleep timing, duration and/or fragmentation affects behavior, affect, physiology and disease risk. (36) (37–39) Although the shift work data are intriguing, study outcomes may relate to abnormal circadian timing as well as night-to-night variability. Recent studies have shown that associations between night-to-night, or intra-individual, variability in sleep and increased morbidity are observed in non-shiftworkers as well. (33, 34) These data suggest that the study of variability in sleep behaviors may provide new perspectives on the physiological effects of sleep and its relevance to health and functioning.

Even though age-related sleep problems are prevalent (40–42) and associated with adverse health outcomes (28, 43–45), variability in age-related sleep has not been linked to either chronic inflammation or subsequent disease risk. The purpose of this study was to explore associations between wake- and sleep-related health behaviors and circulating concentrations of inflammatory markers in a diverse elder population. In particular, we

explored relationships between intra-individual variability in sleep and circulating concentrations of inflammatory markers in a cohort of community dwelling older adults. The cohort consisted of four groups of older adults: Bereaved, Caregivers, Insomniacs, and Good Sleepers. In general, this cohort represents community dwelling elders experiencing a variety of age-related psychosocial stresses and sleep problems, which may be associated with increased circulating inflammatory markers. Given our emphasis on health behaviors, we tested measures of sleep most likely to be under voluntary control, i.e., sleep timing (bedtime, waketime and time in bed) and daytime napping. We hypothesized that: (1) individuals with less intra-individual variability in sleep timing would have lower circulating levels of IL-6 and TNF- α compared to those with greater variability; and (2) older adults who practiced traditionally-evaluated, positive health behaviors, including napping, alcohol and caffeine use and exercise (in moderation) would have lower circulating concentrations of IL-6 and TNF- α compared to those who abstained. Lastly, given the distinct characteristics of the groups included in this cohort, we explored whether associations among sleep timing and traditional health behaviors and markers of inflammation differed among groups.

Methods

Participants were part of the program project “Aging Well, Sleeping Efficiently: Intervention Studies” (AgeWise) (1 PO1 AG020677, PI Monk) which focused on behavioral sleep therapies to improve health and functioning in older adults experiencing various late-life challenges. The program included four individual research projects which shared assessment methods, but had different target samples and behavioral interventions. Detailed descriptions of the program, exclusion criteria, and recruitment procedures have been published elsewhere.(44, 46) Briefly, AgeWise participants (total n = 222) included bereaved older adults (n = 39: 8M, 31F), caregivers to spouses with dementia (n = 55: 11M, 44F), individuals with insomnia (n = 52: 18M, 34F), and good elderly sleepers (n = 76: 36M, 40F). Bereaved, caregiver and insomnia participants were aged 60 and older. “Good elderly sleepers” were aged 75 and older. All participants completed a standardized data collection protocol, in addition to specific procedures for their project. None had significant unstable or untreated medical conditions or psychiatric disorders, however many were taking medications and reported co-morbid illnesses. All bereaved, caregivers, and adults with insomnia had to meet study specific sleep disturbances to be included in each respective study. The bereaved and caregiver groups had to have at least a score of 6 on the Pittsburgh Sleep Quality Index (PSQI) (47) and polysomnographically determined sleep efficiency of 90% or worse, and the insomnia group had to meet DSM-IV criteria for primary insomnia. Good elderly sleepers, on the other hand, were required to have no significant sleep disturbances and no current psychiatric disorder as determined by the SCID (48). Data for the overall program project were collected from July 2003 through January 2009 with each participant enrolled for a 1-year period. Only baseline data relevant to this paper, including demographics, endorsement of health behaviors, sleep, selected covariates and inflammatory markers are presented below. Written, informed consent was obtained from individual participants prior to collection of data and the study was approved by the Institutional Review Board at the University of Pittsburgh.

Measurements

Upon entry into the study, participants completed a battery of questionnaires. Relevant to this report are data obtained from the *Pittsburgh Sleep Diary (PghSD)*.(49) Participants completed the PghSD for 7 or 14 consecutive days depending on the protocol. To assess variability in sleep timing we considered three diary-assessed sleep timing variables: bedtime (BT), waketime (WT) and duration of time in bed (TIB). We chose these sleep

measures as they best reflect an accurate definition of a sleep-related health behavior: “an action taken by a person to maintain, attain, or regain good health and to prevent illness.” Within-individual mean estimates for sleep timing (BT, WT, and TIB) were obtained by averaging the values from all 7 or 14 nights. Estimates of intra-individual variability in these measures were obtained by calculating the within-subjects standard deviation (SD) across all 7 or 14 nights for each individual. We also examined whether these indices of intra-individual variability were stable over time by examining the variability from week one to week two. Paired t-tests were conducted for 123 subjects who had at least 6 days of BT and WT information in each of the two weeks. There were no statistically significant differences between variability in week one compared to week two, thus these measures were considered stable over time.

Information on daily use of caffeine, alcohol, tobacco, naps and exercise were also obtained from the PghSD. As a result of study design and inclusion/exclusion criteria, the frequency of both caffeine and alcohol use indicated that consumption among the participants could be considered moderate (caffeine: 0–8 cups per day with the mean = 1.7/day; alcohol: <1 – 3 drinks per day for alcohol with approximately 70% consuming < 1 drink/week); thus, we dichotomized participants into moderate users and abstainers. The frequency of smoking was so low (3%) that it was not evaluated in analyses. The frequency of naps indicated that approximately 60% napped 1–11.5x/week and 40% did not nap at all; thus, we dichotomized participants into nappers and non-nappers. Lastly, at least some exercise was endorsed by 78% of the participants. Thus, we dichotomized participants into exercisers and non-exercisers.

Psychosocial variables examined as possible covariates in the analyses included physical and mental status assessed via the Medical Outcome Survey (MOS)-Short Form (SF)-36(50), depressive symptomatology assessed by the Hamilton Rating Scale for Depression 25-item (HRSD)(51), and stress measured by the Perceived Stress Scale 4-item (52). Not surprisingly given the populations evaluated, these covariates significantly differed by group. Good sleepers had fewer depressive symptoms than the other three groups ($p < .001$), better mental health status ($p < .001$) and the lowest amount of perceived stress ($p < .001$). Participants were asked to report on current medication use and medical conditions. Medications were classified and counted into classes such as analgesics, anti-hypertensives, benzodiazepines, antidepressants, corticosteroids, and hormones and over-the-counter medications. Medical conditions were similarly classified and counted into classes such as arthritis, cancer, coronary heart disease, COPD/asthma, and digestive disorders.

Assay of Cytokines

Blood samples (20mls) were obtained from participants during the physical examination between 7:00 –10:00 AM for assay of IL-6 and TNF- α . Samples were collected within 14 days prior to the commencement of recording data in sleep diaries. Samples were centrifuged, aliquoted and stored at –80 until assay. Plasma levels of IL-6 and TNF- α were determined by ELISA (R & D Systems) according to the manufacturer's instructions. The range for IL-6 was between 0.156 pg/ml - 10 pg/ml and for TNF- α the range was between 0.5 pg/ml - 32 pg/ml. All samples were run in duplicate and coefficient of variation between samples was < 10%.

Statistical Analyses

Prior to statistical testing, the data were examined for normality and transformations were used where necessary. Descriptive statistics were generated to characterize the entire study sample and group sub-samples (bereaved, caregivers, older adults with insomnia or good sleepers). Bivariate correlations were used to evaluate the associations between the

covariates and outcomes. HRSD scores, perceived stress scores and MOS-mental scores were not significantly associated with IL-6 or TNF- α . MOS-physical scores, number of medication classes endorsed, and co-morbid illnesses were modestly associated with IL-6 ($r = -0.20$, $p = 0.003$, $r = .20$, $p = .003$ and $r = .15$, $p = .03$, respectively), but not TNF- α . Given the collinearity among MOS-physical score, medications, and illnesses, we limited covariate selection to the MOS-physical score. ANOVAs were used to test for group differences. Significant differences were followed by Tukey post-hoc tests to identify which specific groups differed. Linear regression models were conducted to test the hypotheses that health behaviors were associated with IL-6 and TNF- α . Participants were dichotomized in order to examine whether endorsement of a specific health behavior was associated with circulating levels of inflammatory markers. Sleep and sleep variability were evaluated as continuous measures. The practice of each health behavior was examined separately with age, BMI, gender, MOS-physical score, group and the respective group by health behavior interactions in the model. Group was dummy coded (0/1) in all the analyses with the good sleeper group used as the reference group. Statistics were run using SAS v 9.2. Variables were considered significant at $p < .05$ (2-tailed).

Results

Demographic characteristics of the sample are shown in Table 1. The majority of participants endorsed the use of an average of 2–3 medication classes such as analgesics, anti-hypertensives, benzodiazepines, antidepressants, corticosteroids, and hormones. Participants also reported an average of four co-morbid conditions such as arthritis, gastrointestinal issues, hypertension/cardiovascular disease, and osteoporosis. There were small, but significant differences in the number of medication classes endorsed as well as the number of co-morbid diagnoses reported. Over two-thirds of the sample consumed caffeine on a daily basis, while more than half of the sample consumed alcohol. The groups did not differ in either caffeine or alcohol consumption. Almost 80% of this sample exercised somewhat regularly, with the exception of the bereaved group, of whom only 10% exercised regularly. About 60% napped within the 2-week sleep diary recording period, again with the exception of the bereaved group, of whom only 7% reporting napping.

Table 1 also shows sleep data. Sleep diary data indicate that the cohort spent approximately 7 hrs per night in bed with no group differences. Total sleep time, on the other hand, was only 6 ½ hrs per night with distinct group differences. Good sleepers slept the longest whereas those with insomnia slept the least, which is consistent with study definitions and eligibility criteria. With respect to the cytokines, the mean and range of values were well within normal limits for the age of the sample (19) and did not differ among groups. A small percentage (10%) had elevated levels of both cytokines (> 2 SD above the mean).

Linear regression models were run to test the hypotheses that positive health-related behaviors were associated with lower levels of the inflammatory markers IL-6 and TNF- α . Age ($p < .001$) was a significant correlate of IL-6 and TNF- α in all models, except BT and variability in wake time. BMI and gender were not significant covariates in any of the models controlling for age and MOS-physical score. All of the models examining IL-6 were significant (all $R^2 = .13-.20$) (Table 2a). A significant interaction effect showed that greater variability in WT was associated with higher IL-6 among good sleepers compared to caregivers or adults with insomnia, (standardized $\beta = -.671$, $p < .004$; standardized $\beta = -.70$, $p < .009$) (Table 2a). Greater variability in mean TIB was also associated with increased IL-6 concentrations among good sleepers compared to caregivers (standardized $\beta = -1.09$, $p < 0.02$) or older adults with insomnia (standardized $\beta = -0.96$, $p < 0.03$) (Figure 1) (Table 2a). No significant interaction effects were observed for IL-6 and the bereaved groups on any sleep behavior. Three models examining sleep and TNF- α were significant ($R^2 = .11-.13$).

12). There were no significant interaction effects, but greater variability in BT, later wake times and longer time in bed were associated with significantly greater concentrations of TNF- α regardless of group (standardized $\beta = -0.41$, $p < .02$, standardized $\beta = 0.40$, $p < .02$ and standardized $\beta = 0.47$, $p < .004$) (Table 2b).

We also found significant interaction effects between traditional health-related behaviors, inflammatory markers, and group. An interaction was observed between use of caffeine and group for IL-6. Moderate caffeine use was associated with higher IL-6 concentrations among the older adults with insomnia (mean = 2.10 ± 2.14 pg/ml) relative to the good sleepers (mean = 1.85 ± 3.11 pg/ml) who showed lower levels of IL-6 associated with caffeine use (standardized $\beta = 0.37$, $p < 0.01$) (Table 2a). There was also a group $\times$ alcohol interaction for IL-6 and TNF- α . Alcohol use in good sleepers ($1.25 \pm .87$ pg/ml) was associated with lower circulating levels of IL-6 but it was associated with higher levels among users in the bereaved (mean = 1.78 ± 1.81 pg/ml) (standardized $\beta = 0.31$, $p < 0.02$), caregivers (mean = 1.65 ± 1.13 pg/ml) (standardized $\beta = 0.34$, $p < 0.005$), and older adults with insomnia (mean = 1.79 ± 1.78 pg/ml) (standardized $\beta = 0.33$, $p < 0.02$) groups. The same pattern of relationship for alcohol was seen for TNF- α in the good sleepers (mean = 1.62 ± 2.14 pg/ml) versus the caregivers (2.38 ± 3.60 pg/ml) (standardized $\beta = 0.40$, $p < 0.002$) (Tables 2a and 2b).

Discussion

This study evaluated whether sleep and variability in sleep patterns were associated with circulating concentrations of inflammatory cytokines similar to other traditional health behaviors among a community dwelling elderly cohort. The most novel and important findings of the study were the significant associations between several sleep-related behaviors and the inflammatory markers IL-6 and TNF- α . Interestingly, many of the relationships varied significantly by group suggesting that age-related events or the presence of insomnia may moderate these relationships. These data are consistent with a recent report that elders with insomnia have more variable sleep than controls(31); however, this is the first report, to our knowledge to show that greater intra-individual variability in sleep-related behaviors is associated with higher levels of circulating IL-6 and TNF- α . Our findings, are also consistent with previous work, which indicate moderate caffeine and alcohol consumption are associated with lower levels of inflammatory markers, but primarily in good sleepers (12, 17, 53, 54).

We propose that among older adults with psychosocial and medical challenges such as bereavement, caregiving, and insomnia, greater daily variability in sleep timing may pose a risk for higher circulating concentrations of inflammatory cytokines. In conjunction with other risk factors including perceived stress and low social support, sleep variability could increase the risk for inflammatory related diseases, such as cardiovascular disease, depression and Type 2 diabetes,(1, 30, 55–58) especially given the link between average aggregate measures of sleep disturbance and disease.(59–61) Recent research relating variability in bed time to higher Hamilton Rating Scale for Depression scores among elders with insomnia supports this hypothesis.(31) Additional research is needed to evaluate the relationship between variability in sleep measures, levels of inflammatory markers and risk for adverse health outcomes.

In the current study only a small percentage of participants (10%) had cytokine concentrations that may be considered elevated. While there are no established cutoffs for IL-6 or TNF- α to indicate increased risk for disease, as there are with CRP (4, 58, 62), there are several studies that support the hypothesis that higher cytokine concentrations do confer an increased risk for disease development, including cardiovascular disease and stroke,

particularly in the healthy old compared to young volunteers. (5) This is further indicated by the fact that inflammatory cytokines increase as a function of age, regardless of health status. (1, 7) There is also a strong relationship between increased IL-6 and TNF- α and CRP levels, of which there is extensive evidence of increased levels and risk for morbidity (58, 62–66) Dissecting the complex relationship of age-related, disease-related and behaviorally-related increases in inflammatory cytokines will undoubtedly be a challenge. We propose that future studies should examine the physiological effects of variations in daily sleep patterns in addition to simple average aggregate measures in adults with and without current illness. Since poor sleep is associated with altered activity and reactivity of the stress response system, (67, 68) we hypothesize that sleep variability is an index of physiological stress that can independently as well as dynamically influence the inflammatory response. Data from behavioral sleep interventions support this hypothesis since the primary aim of behavioral interventions is to reduce the variability of sleep behaviors (e.g. waking at the same time each day). Such interventions may ultimately improve health and functioning.

Understanding behavioral mechanisms that affect inflammation among aging individuals is important. Given that increasing age is associated with changes in functioning of the immune system, which can result in low-grade chronic inflammation (20), and increased IL-6 and TNF- α are implicated in the pathogenesis of various age-associated diseases including osteoporosis, cardiovascular disease, Alzheimer's Disease, and frailty (5, 69–71), moderate practice of certain health-related behaviors may stave off morbidity and contribute to successful, healthy aging and longevity via reductions in inflammation. Consumption of caffeine, for example, may confer protective effects from Alzheimer's Disease, depression, anxiety, cognitive impairment, cardiovascular disease, and cancer (72, 73) through a reduction in systemic inflammation. (17, 18, 54) The relationship between the majority of health behaviors evaluated and inflammation suggests a "J shaped curve". Those that practice in moderation have lower concentrations than those who abstain or practice in excess (74). However, current age-related events or other psychosocial factors may influence relationships. The biological significance of caffeine or alcohol consumption on these pathways within healthy and diseased older individuals requires further evaluation.

In contrast to previous data, we did not find relationships between exercise or napping and inflammation. (7, 75, 76) This may however, be a reflection of the cohort or study design. The average BMI of the sample (mean = 26) puts them in the slightly overweight range. Since fat tissue produces about 40% of the circulating cytokines measured in plasma (77), it is plausible that some of the variance in higher circulating cytokine concentrations are a consequence of larger fat stores. However, the majority of participants, except for the bereaved cohort, endorsed regular exercise. Epidemiological data on exercise in older adults indicate that less than 10% of individuals older than 75 years of age exercise at least once per week, even though 5 times per week is recommended. (78) Almost 80% of our sample reported exercising in a 2-week period, with 55% reporting exercise at least 5x/week. Even though the majority of the sample was between 60–75yrs, 59.2% of the good sleepers (> 75 years) reported some physical activity at least 5x/week suggesting that this cohort may be different than other samples. In the same way, one must consider how the effect of exercise on inflammatory markers depends on defined criteria such as frequency and intensity, as well as age. (75) We contend that our findings may differ from other published reports due different methodologies used to assess physical activity. In our study, participants were asked to report on any daily activity, and whether it was light, medium or heavy. In the report by Davis et al., (78) physical activity was determined using an accelerometer. These authors note that accelerometry does not distinguish the type of activity, but it does provide minute-by-minute counts of activity. Subjective perceptions of activity and its degree of intensity could explain the contrary results. Little data are available regarding napping behavior and inflammatory markers. (76) Naps are considered counterproductive for older

adults individuals with sleep disorders such as insomnia.(79) However, among those with healthy sleep patterns, naps, when timed appropriately, have the potential to improve the quality of life and possibly physical health outcomes.(80)

We are unable to comment on or test causality with these data since it is a correlational study. However, the results suggest that certain health-related practices and stable sleep patterns are associated with lower circulating concentrations of inflammatory markers. Evaluation of prospective relationships may better inform how these variables are associated. There are also several limitations that preclude our ability to generalize to all older adults. We recognize that the results regarding sleep variability were driven primarily by the good sleepers and reflect inter-individual variability. However, we examined intra-individual variability: the range or spread that an individual has with regards to one's own mean. This measure may proffer additional information as to which individuals are more susceptible to immune alterations. Other variables could also account for positive as well as null findings including participant's characteristics, particularly life circumstances, depressive symptomatology, health status or inclusion/exclusion criteria. For example, to be included in the good sleeper group individuals had to report no significant sleep problems. They could have however, been a caregiver or bereaved thereby introducing additional variability. Our findings do not appear to corroborate the existing literature which suggests that older individuals endorse a wider distribution of each health behavior than we observed in our study.(8) In our cohort, few individuals consumed > 3 cups of caffeine per day or drank > 1 alcoholic beverage per day. Almost no one smoked and a large percentage exercised regularly. This is likely a result of selection or participation bias. These relationships also need to be evaluated in younger and middle-aged populations, given the evidence of heavy caffeine and alcohol use to either postpone or induce sleep in those groups. Additionally, the sleep patterns of our cohort may not reflect the *general* elderly population. The bereaved, caregiver and insomnia groups only included those who had significant sleep complaints, but without significant sleep disordered breathing; whereas those in the good sleeper group had to have *no* significant sleep complaints. However, the large number of participants (n = 222) reflect the common occurrence of these age-related life situations and suggest that the findings may be generalizable. Another significant limitation is having only one blood sample. Given the multiple sources of cytokine production, we cannot identify the origin of measured cytokines. We suggest that the effects of health behaviors on reduced low-grade chronic inflammation may best be understood through *repeated* samplings, and possibly stimulation assays, since the immune system is dynamic and a single circulating measure does not provide a comprehensive perspective of long-term functioning.

In summary, improving the health and well-being of our older adult population is an important goal. One way to accomplish this goal is by understanding the moderators of successful aging. These findings suggest that certain health-related practices in moderation and regular sleep patterns are associated with lower circulating levels of inflammatory markers among older adults experiencing various age-related events. Moreover, given the increased morbidity among bereaved,(81) spouses providing care,(82) and those with insomnia,(83) encouraging health practices that may offset the increases in inflammation commonly observed among these groups(84, 84, 84, 84, 85, 85, 85, 85, 86, 86, 86, 86) may prove beneficial to overall health. Prospective controlled trials are needed to test possible causal pathways between these behaviors, inflammatory markers, and ultimately, successful aging.

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Glossary

WT	wake time
BT	bed time
TIB	time in bed
SD	standard deviation

Reference List

1. Bruunsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. *Immunol Allergy Clin North Am*. 2003; 23(1):15–39. [PubMed: 12645876]
2. Hinojosa E, Boyd AR, Orihuela CJ. Age-associated inflammation and toll-like receptor dysfunction prime the lungs for pneumococcal pneumonia. *J Infect Dis*. 2009; 200(4):546–554. [PubMed: 19586419]
3. Mazzeo RS. Aging, immune function, and exercise: hormonal regulation. *Int J Sports Med*. 2000; 21 Suppl 1:S10–S13. [PubMed: 10893018]
4. Bruunsgaard H, Andersen-Ranberg K, Hjelmberg JB, Pedersen BK, Jeune B. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. *Am J Med*. 2003; 115(4):278–283. [PubMed: 12967692]
5. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med*. 2000; 51:245–270. [PubMed: 10774463]
6. Maggio M, Guralnik JM, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci*. 2006; 61(6):575–584. [PubMed: 16799139]
7. Pedersen BK, Bruunsgaard H, Ostrowski K, Krabbe K, Hansen H, Krzykowski K, Toft A, Sondergaard SR, Petersen EW, Ibfelt T, Schjerling P. Cytokines in aging and exercise. *Int J Sports Med*. 2000; 21 Suppl 1:S4–S9. [PubMed: 10893017]
8. Peel NM, McClure RJ, Bartlett HP. Behavioral determinants of healthy aging. *Am J Prev Med*. 2005; 28(3):298–304. [PubMed: 15766620]
9. Goldacre MJ. Demography of aging and the epidemiology of gastrointestinal disorders in the elderly. *Best Pract Res Clin Gastroenterol*. 2009; 23(6):793–804. [PubMed: 19942158]
10. Cardi M, Munk N, Zanjani F, Kruger T, Schaie KW, Willis SL. Health Behavior Risk Factors Across Age as Predictors of Cardiovascular Disease Diagnosis. *J Aging Health*. 2009
11. Helmersson J, Larsson A, Vessby B, Basu S. Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis*. 2005; 181(1):201–207. [PubMed: 15939073]
12. Szabo G, Mandrekar P, Oak S, Mayerle J. Effect of ethanol on inflammatory responses. Implications for pancreatitis. *Pancreatology*. 2007; 7(2–3):115–123. [PubMed: 17592223]
13. Rowe JW, Kahn RL. Human aging: usual and successful. *Science*. 1987; 237(4811):143–149. [PubMed: 3299702]
14. Crews FT, Bechara R, Brown LA, Guidot DM, Mandrekar P, Oak S, Qin L, Szabo G, Wheeler M, Zou J. Cytokines and alcohol. *Alcohol Clin Exp Res*. 2006; 30(4):720–730. [PubMed: 16573591]

15. Volpato S, Pahor M, Ferrucci L, Simonsick EM, Guralnik JM, Kritchevsky SB, Fellin R, Harris TB. Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitor-1 in well-functioning older adults: the Health, Aging, and Body Composition study. *Circulation*. 2004; 109(5):607–612. [PubMed: 14769682]
16. Hamer M, Williams ED, Vuononvirta R, Gibson EL, Steptoe A. Association between coffee consumption and markers of inflammation and cardiovascular function during mental stress. *J Hypertens*. 2006; 24(11):2191–2197. [PubMed: 17053540]
17. Horrigan LA, Kelly JP, Connor TJ. Caffeine suppresses TNF-alpha production via activation of the cyclic AMP/protein kinase A pathway. *Int Immunopharmacol*. 2004; 4(10–11):1409–1417. [PubMed: 15313438]
18. Zampelas A, Panagiotakos DB, Pitsavos C, Chrysoshoou C, Stefanadis C. Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am J Clin Nutr*. 2004; 80(4):862–867. [PubMed: 15447891]
19. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol*. 2004; 39(5):687–699. [PubMed: 15130663]
20. Ostan R, Bucci L, Capri M, Salvioli S, Scurti M, Pini E, Monti D, Franceschi C. Immunosenescence and immunogenetics of human longevity. *Neuroimmunomodulation*. 2008; 15(4–6):224–240. [PubMed: 19047800]
21. Ayas NT, White DP, Al Delaimy WK, Manson JE, Stampfer MJ, Speizer FE, Patel S, Hu FB. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care*. 2003; 26(2):380–384. [PubMed: 12547866]
22. Cappuccio FP, Stranges S, Kandala NB, Miller MA, Taggart FM, Kumari M, Ferrie JE, Shipley MJ, Brunner EJ, Marmot MG. Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. *Hypertension*. 2007; 50(4):693–700. [PubMed: 17785629]
23. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension*. 2006; 47(5):833–839. [PubMed: 16585410]
24. Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. *Sleep*. 2008; 31(5):635–643. [PubMed: 18517034]
25. Jennings JR, Muldoon MF, Hall M, Buysse DJ, Manuck SB. Self-reported sleep quality is associated with the metabolic syndrome. *Sleep*. 2007; 30(2):219–223. [PubMed: 17326548]
26. Nock NL, Li L, Larkin EK, Patel SR, Redline S. Empirical evidence for "syndrome Z": a hierarchical 5-factor model of the metabolic syndrome incorporating sleep disturbance measures. *Sleep*. 2009; 32(5):615–622. [PubMed: 19480228]
27. Patel SR, Ayas NT, Malhotra MR, White DP, Schernhammer ES, Speizer FE, Stampfer MJ, Hu FB. A prospective study of sleep duration and mortality risk in women. *Sleep*. 2004; 27(3):440–444. [PubMed: 15164896]
28. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care*. 2006; 29(3):657–661. [PubMed: 16505522]
29. Vgontzas AN, Zoumakis M, Bixler EO, Lin HM, Prolo P, Vela-Bueno A, Kales A, Chrousos GP. Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications. *J Clin Endocrinol Metab*. 2003; 88(5):2087–2095. [PubMed: 12727959]
30. von Kanel R, Dimsdale JE, Ancoli-Israel S, Mills PJ, Patterson TL, McKibbin CL, Archuleta C, Grant I. Poor sleep is associated with higher plasma proinflammatory cytokine interleukin-6 and procoagulant marker fibrin D-dimer in older caregivers of people with Alzheimer's disease. *J Am Geriatr Soc*. 2006; 54(3):431–437. [PubMed: 16551309]
31. Buysse DJ, Cheng Y, Germain A, Moul DE, Franzen PL, Fletcher M, Monk TH. Night-to-night sleep variability in older adults with and without chronic insomnia. *Sleep Med*. 2009

32. Edinger JD, Marsh GR, McCall WV, Erwin CW, Lininger AW. Sleep variability across consecutive nights of home monitoring in older mixed DIMS patients. *Sleep*. 1991; 14(1):13–17. [PubMed: 1811313]
33. Knutson KL, Rathouz PJ, Yan LL, Liu K, Lauderdale DS. Intra-individual daily and yearly variability in actigraphically recorded sleep measures: the CARDIA study. *Sleep*. 2007; 30(6): 793–796. [PubMed: 17580601]
34. Mezick EJ, Matthews KA, Hall M, Kamarck TW, Buysse DJ, Owens JF, Reis SE. Intra-individual variability in sleep duration and fragmentation: Associations with stress. *Psychoneuroendocrinology*. 2009
35. Van Hilten JJ, Braat EA, van der Velde EA, Middelkoop HA, Kerkhof GA, Kamphuisen HA. Ambulatory activity monitoring during sleep: an evaluation of internight and intrasubject variability in healthy persons aged 50–98 years. *Sleep*. 1993; 16(2):146–150. [PubMed: 8446834]
36. Vokac Z, Magnus P, Jebens E, Gundersen N. Apparent phase-shifts of circadian rhythms (masking effects) during rapid shift rotation. *Int Arch Occup Environ Health*. 1981; 49(1):53–65. [PubMed: 7298214]
37. Berger AM, Hobbs BB. Impact of shift work on the health and safety of nurses and patients. *Clin J Oncol Nurs*. 2006; 10(4):465–471. [PubMed: 16927899]
38. Gander P, Signal L. Who is too old for shift work? Developing better criteria. *Chronobiol Int*. 2008; 25(2):199–213. [PubMed: 18484361]
39. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Speizer FE, Hennekens CH. Prospective study of shift work and risk of coronary heart disease in women. *Circulation*. 1995; 92(11):3178–3182. [PubMed: 7586301]
40. Ancoli-Israel S. Sleep and aging: prevalence of disturbed sleep and treatment considerations in older adults. *J Clin Psychiatry*. 2005; 66 Suppl 9:24–30. [PubMed: 16336039]
41. Blois R, Feinberg I, Gaillard JM, Kupfer DJ, Webb WB. Sleep in normal and pathological aging. *Experientia*. 1983; 39:551–686. [PubMed: 6343111]
42. Fok M, Stewart R, Besset A, Ritchie K, Prince M. Incidence and persistence of sleep complaints in a community older population. *Int J Geriatr Psychiatry*. 2009
43. Dew MA, Hoch CC, Buysse DJ, Monk TH, Begley AE, Houck PR, Hall M, Kupfer DJ, Reynolds CF. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosom Med*. 2003; 65:63–73. [PubMed: 12554816]
44. Driscoll HC, Serody L, Patrick S, Maurer J, Bensasi S, Houck PR, Mazumdar S, Nofzinger EA, Bell B, Nebes RD, Miller MD, Reynolds CF III. Sleeping well, aging well: a descriptive and cross-sectional study of sleep in "successful agers" 75 and older. *Am J Geriatr Psychiatry*. 2008; 16(1):74–82. [PubMed: 18070833]
45. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: A prospective perspective. *Am J Psychiatry*. 2000; 157(1):81–88. [PubMed: 10618017]
46. Hall M, Buysse DJ, Nofzinger EA, Reynolds CF III, Thompson W, Mazumdar S, Monk TH. Financial strain is a significant correlate of sleep continuity disturbances in late-life. *Biol Psychol*. 2008; 77(2):217–222. [PubMed: 18055094]
47. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28:193–213. [PubMed: 2748771]
48. First, MB.; Gibbon, M.; Spitzer, RL.; Williams, JBW. User's Guide for the Structured Interview for DSM-IV Axis I Disorders - Research Version (SCID-1, version 2.0, February 1996 final version). New York: Biometrics Research; 1996.
49. Monk TH, Reynolds CF, Kupfer DJ, Buysse DJ, Coble PA, Hayes AJ, Machen MA, Petrie SR, Ritenour AM. The Pittsburgh Sleep Diary. *J Sleep Res*. 1994; 3:111–120.
50. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care*. 1988; 26(7):724–735. [PubMed: 3393032]
51. Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology*. 1967; 6:278–296. [PubMed: 6080235]
52. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983; 24:385–396. [PubMed: 6668417]

53. Mandrekar P, Catalano D, White B, Szabo G. Moderate alcohol intake in humans attenuates monocyte inflammatory responses: inhibition of nuclear regulatory factor kappa B and induction of interleukin 10. *Alcohol Clin Exp Res*. 2006; 30(1):135–139. [PubMed: 16433741]
54. Ritter M, Hohenberger K, Alter P, Herzum M, Tebbe J, Maisch M. Caffeine inhibits cytokine expression in lymphocytes. *Cytokine*. 2005; 30(4):177–181. [PubMed: 15863391]
55. Batuman O, Go D, Clark LT, Smith EL, Clements P, Feit A, Lederer D. Relationship between cytokine levels and coronary artery disease in women. *Heart Dis*. 2001; 3(2):80–84. [PubMed: 11975775]
56. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Tracy RP, Rubin SM, Harris TB, Pahor M. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). *Am J Cardiol*. 2003; 92(5):522–528. [PubMed: 12943870]
57. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. *Psychosom Med*. 2005; 67(2):187–194. [PubMed: 15784782]
58. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001; 286(3):327–334. [PubMed: 11466099]
59. Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Nieto FJ. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med*. 2005; 165(8):863–867. [PubMed: 15851636]
60. Leineweber C, Kecklund G, Janszky I, Akerstedt T, Orth-Gomer K. Poor sleep increases the prospective risk for recurrent events in middle-aged women with coronary disease. The Stockholm Female Coronary Risk Study. *J Psychosom Res*. 2003; 54(2):121–127. [PubMed: 12573733]
61. Meisinger C, Heier M, Lowel H, Schneider A, Doring A. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. *Sleep*. 2007; 30(9):1121–1127. [PubMed: 17910384]
62. Benderly M, Haim M, Boyko V, Tanne D, Behar S, Matas Z, Zimlichman R, Goldbourt U. C-Reactive Protein Distribution and Correlates among Men and Women with Chronic Coronary Heart Disease. *Cardiology*. 2007; 107(4):345–353. [PubMed: 17283424]
63. Albert MA, Ridker PM. C-reactive protein as a risk predictor: do race/ethnicity and gender make a difference? *Circulation*. 2006; 114(5):e67–e74. [PubMed: 16880331]
64. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol*. 2004; 43(4):678–683. [PubMed: 14975482]
65. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000; 342(12):836–843. [PubMed: 10733371]
66. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999; 19(4):972–978. [PubMed: 10195925]
67. McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism*. 2006; 55(10 Suppl 2):S20–S23. [PubMed: 16979422]
68. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev*. 2008
69. Fisman EZ, Adler Y, Tenenbaum A. Biomarkers in cardiovascular diabetology: interleukins and matrixins. *Adv Cardiol*. 2008; 45:44–64. [PubMed: 18230955]
70. Kuiper J, van Puijvelde GH, van Wanrooij EJ, van Es T, Habets K, Hauer AD, van den Berkel TJ. Immunomodulation of the inflammatory response in atherosclerosis. *Curr Opin Lipidol*. 2007; 18(5):521–526. [PubMed: 17885422]
71. Ramos AM, Pellanda LC, Gus I, Portal VL. Inflammatory markers of cardiovascular disease in the elderly. *Arq Bras Cardiol*. 2009; 92(3):221–234. [PubMed: 19390712]
72. Bonita JS, Mandarano M, Shuta D, Vinson J. Coffee and cardiovascular disease: in vitro, cellular, animal, and human studies. *Pharmacol Res*. 2007; 55(3):187–198. [PubMed: 17368041]

73. Daly JW. Caffeine analogs: biomedical impact. *Cell Mol Life Sci.* 2007; 64(16):2153–2169. [PubMed: 17514358]
74. O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun.* 2009; 23(7):887–897. [PubMed: 19389469]
75. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* 2005; 98(4): 1154–1162. [PubMed: 15772055]
76. Vgontzas AN, Pejovic S, Zoumakis E, Lin HM, Bixler EO, Basta M, Fang J, Sarriannidis A, Chrousos GP. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *Am J Physiol Endocrinol Metab.* 2007; 292(1):E253–E261. [PubMed: 16940468]
77. Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW, Gimble JM. Cytokine profile of human adipose-derived stem cells: expression of angiogenic, hematopoietic, and pro-inflammatory factors. *J Cell Physiol.* 2007; 212(3):702–709. [PubMed: 17477371]
78. Davis MG, Fox KR. Physical activity patterns assessed by accelerometry in older people. *Eur J Appl Physiol.* 2007; 100(5):581–589. [PubMed: 17063361]
79. Buysse DJ. Insomnia, depression and aging. Assessing sleep and mood interactions in older adults. *Geriatrics.* 2004; 59(2):47–51. [PubMed: 14989593]
80. Takahashi M. The role of prescribed napping in sleep medicine. *Sleep Med Rev.* 2003; 7(3):227–235. [PubMed: 12927122]
81. Carter PA. Bereaved caregivers' descriptions of sleep: impact on daily life and the bereavement process. *Oncol Nurs Forum.* 2005; 32(4):741. [PubMed: 15990901]
82. Beeson RA. Loneliness and depression in spousal caregivers of those with Alzheimer's disease versus non-caregiving spouses. *Arch Psychiatr Nurs.* 2003; 17(3):135–143. [PubMed: 12840806]
83. Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care.* 2006; 12(8 Suppl):S221–S229. [PubMed: 16686592]
84. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A.* 2003; 100(15):9090–9095. [PubMed: 12840146]
85. O'Connor MF, Irwin MR, Wellisch DK. When grief heats up: Pro-inflammatory cytokines predict regional brain activation. *Neuroimage.* 2009
86. Savard J, Laroche L, Simard S, Ivers H, Morin CM. Chronic insomnia and immune functioning. *Psychosom Med.* 2003; 65(2):211–221. [PubMed: 12651988]

Figure 1.

Table 1

Sample Descriptors for the Full Sample of Older Adults as well as by Group.

	Individual Groups					
	Full Sample N=222	Bereaved (a) N = 39	Caregiver (b) N = 55	Good Sleepers (c) N = 76	Insomnia (d) N = 52	p-value*
Demographics						
Age ^ (years)	73.7 (7.1)	71.6 (7.0)	73.7 (7.2)	76.5 (6.3)	71.1 (7.0)	<0.001, c > a, d
% Female	67.1	79.5	80.0	52.6	65.4	0.003 a, b > c
% White	94.1	92.3	98.2	93.4	92.3	0.48
BMI	26.8 (4.3)	27.6 (5.4)	27.7 (4.1)	25.8 (3.4)	26.3 (4.5)	0.054
# of Medications	2.8 (1.7)	2.4 (1.8)	3.0 (1.5)	2.3 (1.4)	3.6 (1.8)	< .001, a < c; d < b, d
# of Co-morbid Diagnoses	4.6 (2.4)	3.8 (2.1)	4.5 (2.3)	4.6 (2.2)	5.5 (2.7)	= .01, a, b < d
HRS25 Total#	6.9 (5.3) n=218	9.2 (6.0)	9.1 (5.6)	2.3 (2.0) n=72	9.2 (3.0)	<0.001 c < a, b, d
MOS Mental	53.1 (9.9) n=214	48.2 (12.4) n=33	48.7 (10.9) n=54	58.2 (5.8) n=75	53.4 (8.4)	<0.001 c > a, b, d d > b
MOS Physical	46.4 (9.7) n=214	44.7 (11.1) n=33	45.5 (10.2) n=54	49.1 (6.9) n=75	44.6 (10.9)	=0.03 c > d
PSS4 Total	3.2 (2.7) n=219	3.6 (2.7) n=37	4.7 (2.7) n=54	2.1 (2.3)	3.2 (2.6)	<0.001 a>c, b>c, d
Sleep-related Health Behaviors						
%Naps (yes)	59.5	7.7	69.1	73.7	67.3	<0.001 b, c, d > a

	Individual Groups					p-value *
	Full Sample N=222	Bereaved (a) N = 39	Caregiver (b) N = 55	Good Sleepers (c) N = 76	Insomnia (d) N = 52	
Mean BT	11:27 (0:52)	11:24 (0:49)	11:29 (0:55)	11:24 (0:50)	23:32 (0:52)	0.81
Variability BT [^]	38.73 (26.13)	38.91 (23.36)	35.02 (16.84)	35.52 (18.20)	46.55 (40.03)	0.42
Mean WT	6:48 (1:01)	6:35 (0:59)	6:52 (0:57)	6:52 (1:00)	6:49 (1:09)	0.52
Variability WT	48.1 (22.87)	51.0 (21.51)	49.43 (19.00)	36.93 (18.93)	61.51 (25.12)	<0.001 a > c d > b > c
Mean TIB (minutes)	442.30 (57.69)	430.82 (59.17)	442.79 (61.21)	448.39 (48.70)	442.80 (63.15)	0.53
Variability TIB [^] (minutes)	57.62 (25.76)	58.10 (24.97)	56.60 (21.58)	48.37 (21.40)	69.80 (30.69)	<0.001 d > c
Mean TST	391.04 (66.89)	385.42 (66.00)	394.41 (61.41)	426.73 (48.81)	348.07 (68.32)	<0.001 d < a, b < c
Variability TST [^]	67.45 (31.70)	69.98 (34.77)	69.87 (31.26)	51.17 (22.81)	83.03 (30.84)	<0.001 c < a, b, d
Traditional Health Behaviors						
% Caffeine (yes)	70.1	69.2	69.1	78.7	59.6	0.15
% Alcohol (yes)	59.23	56.4	52.7	66.7	57.7	0.41
% Smoke (yes)	3.2	0.00	3.6	1.3	7.7	0.15
% Exercise (yes)	77.9	10.3	98.2	86.8	94.2	<0.001 b, c, d > a
Inflammatory Markers						
IL-6 [^] (pg/ml)	1.83 (2.18)	1.69 (1.47)	1.66 (1.13)	2.05 (3.13)	1.79 (1.74)	0.79
TNF alpha [^] (pg/ml)	1.68 (2.27)	1.47 (1.20)	1.73 (2.70)	1.82 (2.74)	1.59 (1.60)	0.99

Values are mean (SD) or percent.

HRSD-25 = 25-item Hamilton Rating Scale for Depression; MOS Mental = Medical Outcomes Survey-Mental status; MOS Physical = Medical Outcomes Survey-Physical Status; PSS4 = 4-item Perceived Stress Scale; BT = Bed time; WT = Wake time; TST = Total sleep time; TIB = Time in Bed all derived from PghSD

^ Means and standard deviations reported in the original units. Variability measures are average standard deviations and its subsequent SD. #Transformation used in the analyses.

* Statistical tests were Fisher's exact test or ANOVA followed by Tukey post-hoc tests where appropriate.

Table 2

a. Standardized betas from regression models examining relationship between health behaviors and sleep parameters with IL-6 [^]											
X	Age [^]	BMI	Male	MOS PCS	Berev	Care	Insom	X	Berev ^{*X}	Care ^{*X}	Insom ^{*X}
Healthy Behaviors											
Caffeine	0.32 ^{**}	0.12	-0.03	-0.19 [*]	-0.20	-0.09	-0.24	-0.16	0.24	0.11	0.37 [*]
Alcohol	0.32 ^{**}	0.12	-0.03	-0.16 [*]	-0.23	-0.27 [*]	-0.19	-0.39 [*]	0.31 [*]	0.35 [*]	0.33 [*]
Exercise	0.30 ^{**}	0.12	-0.03	-0.16 [*]	0.05	0.02	0.55 [*]	0.07	0.02	-0.02	-0.52
Naps	0.31 ^{**}	0.13	-0.02	-0.16 [*]	-0.02	0.02	0.12	-0.02	0.11	-0.01	-0.07
Diary Data											
Mean BT	0.31 ^{**}	0.11	-0.05	-0.15	2.15	2.29	1.54	0.21	-2.11	-2.27	-1.49
Variability BT [^]	0.31 ^{**}	0.12	-0.04	-0.16 [*]	0.19	0.55	0.68	0.16	-0.16	-0.54	-0.66
Mean WT	0.32 ^{**}	0.12	-0.05	-0.16 [*]	0.42	0.46	0.28	0.18	-0.36	-0.44	-0.22
Variability WT	0.33 ^{**}	0.12	-0.02	0.15	-0.19	0.53 [*]	0.42 [*]	0.56 ^{**}	-0.30	-0.71 [*]	-0.70 [*]
Mean TIB (minutes)	0.30 ^{**}	0.12	-0.03	-0.17 [*]	-0.20	-0.08	-0.28	-0.03	0.24	0.10	0.33
Variability TIB [^] (minutes)	0.34 ^{**}	0.12	-0.04	-0.16 [*]	0.47	-1.02 [*]	0.83 [*]	-0.39 [*]	-0.50	-1.09 [*]	-0.96 [*]
b. Standardized betas from regression models examining relationship between health behaviors and sleep parameters with TNF- α [^]											
X	Age [^]	BMI	Male	MOS PCS	Berev	Care	Insom	X	Berev ^{*X}	Care ^{*X}	Insom ^{*X}
Healthy Behaviors											
Caffeine	0.29 ^{**}	0.04	0.01	0.002	0.23	0.16	0.20	0.09	-0.19	-0.15	-0.13
Alcohol	0.30 ^{**}	0.04	0.004	-0.03	0.004	-0.25 [*]	0.05	-0.17	0.07	0.40 [*]	0.04
Exercise	0.26 [*]	0.03	0.02	0.004	0.02	0.004	0.42	-0.06	0.05	0.05	-0.33
Naps	0.28 ^{**}	0.04	0.004	0.005	0.02	-0.02	0.03	-0.11	0.05	0.09	0.08
Diary Data											
Mean BT	0.27 [*]	0.04	0.02	-0.01	0.10	1.03	-0.71	-0.03	-0.04	-0.99	0.78

b. Standardized betas from regression models examining relationship between health behaviors and sleep parameters with TNF- α

X	Age [^]	BMI	Male	MOS PCS	Berev	Care	Insom	X	Berev *X	Care *X	Inso m*X
Variability BT [^]	0.30 ^{**}	0.03	0.04	-0.002	0.74	0.97	0.82	0.41 [*]	-0.68	-0.93	-0.81
Mean WT	0.29 ^{**}	0.04	0.005	0.01	1.09	1.03	0.95	0.40 [*]	-0.98	-0.99	-0.87
Variability WT	0.27 [*]	0.03	0.04	0.02	0.08	-0.03	0.04	0.14	-0.04	0.05	-0.04
Mean TIB (minutes)	0.30 ^{**}	0.05	0.02	-0.01	1.32	1.20	1.27	0.47 [*]	-1.20	-1.14	-1.19
Variability TIB [^] (minutes)	0.28 ^{**}	0.03	0.03	0.005	0.23	0.53	0.21	0.23	-0.19	-0.55	-0.24

^{**} p < 0.001,

^{*} p < 0.05

X = Predictor (healthy behaviors or diary sleep data). Each group was compared to the Healthy Elders in the interactions

[^] transformed used in analyses

^{**} p < 0.001,

^{*} p < 0.05

X = Predictor (healthy behaviors or diary sleep data). Each group was compared to the Healthy Elders in the interactions

[^] transformed used in analyses