

Social relationships, sleep quality, and interleukin-6 in aging women

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This study examined the interplay of social engagement, sleep quality, and plasma levels of interleukin-6 (IL-6) in a sample of aging women ($n = 74$, aged 61–90, M age = 73.4). Social engagement was assessed by questionnaire, sleep was assessed by using the NightCap in-home sleep monitoring system and the Pittsburgh Sleep Quality Index, and blood samples were obtained for analysis of plasma levels of IL-6. Regarding subjective assessment, poorer sleep (higher scores on the Pittsburgh Sleep Quality Index) was associated with lower positive social relations scores. Multivariate regression analyses showed that lower levels of plasma IL-6 were predicted by greater sleep efficiency ($P < 0.001$), measured objectively and by more positive social relations ($P < 0.05$). A significant interaction showed that women with the highest IL-6 levels were those with both poor sleep efficiency and poor social relations ($P < 0.05$). However, those with low sleep efficiency but compensating good relationships as well as women with poor relationships but compensating high sleep efficiency had IL-6 levels comparable to those with the protective influences of both good social ties and good sleep.

social engagement

In this study, we probe an elderly population to identify social and behavioral factors that may characterize persons at reduced risk for negative health outcomes. In particular, we focus on sleep quality and its interactions with social engagement in predicting reduced plasma IL-6 levels in aging women. We select each of these factors because all have been linked with important health outcomes and with aging processes. For example, IL-6, an inflammatory factor whose concentration generally increases in the blood with age (1–6), has been linked with Alzheimer's disease, osteoporosis, rheumatoid arthritis, cardiovascular disease, and some forms of cancer (1, 2, 5–7), and it is prospectively associated with general disability (3) and mortality (8) in large population-based studies. In addition, progressive loss of sleep quality and complaints about poor sleep and fatigue are common in the elderly (9–11), and poor sleep quality increases the risk of mortality (12). Low sleep quality has also been linked to elevated IL-6 levels in patients with clinical sleep disorders (13) and experimental studies involving healthy volunteers (14–16). Social relationships, in addition, have been linked with sleep quality. Whether measured objectively or subjectively, sleep efficiency is lower and time awake during the night greater in individuals reporting higher levels of loneliness (17, 18). Self-reported sleep quality is also lower in married men and women who report higher levels of attachment anxiety, an effect that is independent of depressive affect (13). Potential links between social relationships and IL-6 are less well established, although we recently reported that positive relations with others significantly predicted lower plasma levels of IL-6 in aging women (19).

In this investigation, the objective was to put these various factors together to assess whether the optimally low IL-6 profile would be evident among aging women having both strong social relationships and good sleep quality and, conversely, whether those with high levels of IL-6 would lack both protective influences. Such inquiry

would document the additive effects of psychosocial and behavioral factors on a key biological measure associated with aging. However, we were also interested in possible compensatory (interactive) influences, for example, whether those with poor sleep quality who nonetheless had good quality relationships and those with poor quality relationships who had good quality sleep might also show lower levels of IL-6. A further possibility is that sleep quality mediates the association of social relations and plasma IL-6. Our analyses tested for both moderating and mediating influences (20).

Such inquiry responds to the growing interest in factors that prevent or delay functional declines in the elderly (14, 15) and to the call for integrative studies that combine influences on health across multiple domains (psychological, social, behavioral, and biological) (16). We tested these relationships by using self-reported and objective sleep assessments. The NightCap system provides objective measures of sleep latency, total sleep duration, duration of rapid eye movement (REM) and non-rapid eye movement (NREM) stages, and sleep efficiency. Use of the NightCap system facilitated data collection in participants' homes, and the data obtained previously has compared favorably to those gathered in the laboratory (21, 22). This method was used to examine the impact of loneliness on sleep (17). Participants also completed the Pittsburgh Sleep Quality Index (PSQI), a measure of self-rated sleep quality (19). Positive social engagement was operationalized by using the positive relations with others scale, one of Ryff's six dimensions of psychological well-being (23). This measure has been linked to several biological markers of health (24, 25), including plasma IL-6 (unpublished data).

Methods

Participants. Respondents from a prior longitudinal study of aging (see refs. 26 and 27) were contacted by mail and invited to participate in an additional study involving biomarker data collection, and volunteers were enrolled until a target number of 135 was reached. There were no inclusion or exclusion criteria, except the ability and willingness to travel to the General Clinical Research Center (GCRC) on the University of Wisconsin, Madison campus for an overnight stay. Consent for all procedures was obtained during the GCRC visit. Among those who did not participate, 16% were ineligible (because of death, severe morbidity, or moving out of the area), and 42% declined to participate (in some cases because of difficulties with travel or for reasons of health). However, this newly recruited biomarker sample of 135 participants was not significantly different from the original longitudinal sample with regard to health (chronic conditions and health symptoms), income, and marital status, but was significantly younger and had more education. The biomarker sample ranged in age from 61 to 90 with an average age of 73.4 years. Respondents had moderate

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Abbreviations: GCRC, General Clinical Research Center; HPA, hypothalamic-pituitary-adrenal; REM, rapid eye movement; NREM, non-REM; PSQI, Pittsburgh Sleep Quality Index.

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incomes and slightly more than a high school education, and more than half (55.1%) were widowed.

Self-Report Measures. Self-administered questionnaires were sent to respondents 3–4 weeks before their visit to the University of Wisconsin campus for the biomarker assessments. These questionnaires were completed independently and returned to investigators at the time of their campus visit.

Social engagement. Eudaimonic well-being refers to active engagement with the existential challenges of living (see ref. 28). Social engagement, one key aspect of well-being, was assessed by using the positive relations with others eudaimonic well-being scale (23), which was measured with 14 self-descriptive items (scale range = 14–84). Individuals scoring high on this scale report had satisfying and trusting relationships with others and concern for the welfare of others. For example, a high score on the item “I feel that I get a lot out of my friendships” would indicate higher levels of positive relations, whereas a high score on the item “I often feel as if I’m on the outside looking in when it comes to friendships” would indicate low levels. The positive relations scale has been used in conjunction with the five other scales of psychological well-being (23) in studies of marital transitions (20), community relocation (26), and biological markers of disease (29). The α coefficient for this scale, a measure of the internal consistency of the scale items, was 0.88. Previous publications have documented the validity of this scale (23, 30).

PSQI. The PSQI was included in the self-administered questionnaire packet that participants completed before their GCRC stay. Participants are asked about their sleep habits during the preceding month. The PSQI has 17 items, most of which are rated on a four-point Likert scale, designed to assess seven components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. These items generate a global score with a possible range of 0–21. Typically, a global sleep score >5 indicates significant sleep problems (19). The PSQI has well established reliability and validity and is widely used in clinical research.

Health behaviors. Tobacco and alcohol use are known to influence both sleep and plasma IL-6 levels (31–34). To control for potential confounding effects, smoking and alcohol consumption by study participants was determined from the self-administered questionnaires. None of the participants was a current smoker, whereas 36 (46.2%) had smoked at some time in their lives. For this reason, only smoking history was included in statistical analyses. Thirty-one participants (39.7%) responded that there was a time in their lives when they consumed at least one drink 3 days a week. This dummy-coded variable was also included in statistical analyses.

GCRC Health Assessments. Participants were admitted to the GCRC located within the University of Wisconsin Hospital and Clinics for an overnight stay. A trained nurse or physician took the respondent’s medical history and conducted a physical health examination.

To control for the potential effect of chronic illness on IL-6 levels, a summary variable was created from specific items related to overall health, inflammatory conditions, immune-related diseases, or conditions with which IL-6 has been linked. These items included medical history of allergies, asthma, diabetes, cancer or leukemia, hypertension, heart trouble or disease, or arthritis or rheumatism. Additional items from the physical examination and laboratory tests were also selected to control for potential effects on IL-6. Because IL-6 has been linked to obesity (35, 36), waist/hip ratio was measured in the respondents. Waist/hip ratio was calculated on the basis of waist circumference (measured at its narrowest point between the ribs and iliac crest), and hip circumference (measured at the maximal point of the buttocks).

During GCRC visits, use of prescription and over-the-counter medications was recorded and coded. To control for the possible effects of medications on IL-6 levels, a variable was created to

indicate the use of antiinflammatory and psychoactive medications and antihistamines, including salicylates and steroidal and nonsteroidal anti-inflammatory drugs (coded as use and nonuse of any of these drugs). This variable was entered into regression models at the first step along with other control variables. Because antioxidant vitamins (e.g., vitamins A, C, and E) were being used by $>90\%$ of participants, no variable was created to control for their impact on dependent measures.

Cytokine Measures. In-home resting blood samples were obtained from participants by trained nurses with standard phlebotomy techniques. Samples were centrifuged and the plasma fraction aliquoted and stored at -80°C until analyzed. IL-6 concentrations were measured in duplicate by using ELISA (Quantikine HS High Sensitivity human IL-6; R & D Systems, Minneapolis) according to the manufacturer’s directions. Blood samples were obtained as part of another study of immune responses to influenza vaccination, and because of the vaccination schedule, the period between each participant’s visit to the GCRC and the blood samples varied, although $>50\%$ of samples were collected within 9 months of the GCRC visit. To control for any systematic effects of these differences, the time elapsed between the GCRC visit and the blood draws for each individual was entered into regression models as a control variable. Immunizations were scheduled to coincide with flu season, and so all blood samples were obtained between October and December, and all sampling occurred after participants had visited the GCRC. Blood draws were scheduled at the convenience of the participants, and so time of day was not consistent (although all samples were obtained during daylight hours).

NightCap Sleep Recordings. Participants received instructions on using the NightCap and wore the NightCap for 1 night during their stay at the GCRC. They then collected sleep data for 4 consecutive nights at home immediately after their stay at the GCRC. Exploratory analyses showed that sleep parameters during the 4 nights at home were similar to one another and of better quality than the night in the GCRC.

The NightCap is a two-channel device that records eye and head movements by using sensors that are mounted in a bandana worn on the head during each night of sleep. The eye sensor consists of a piezoelectric self-adhesive mylar sensor that is attached to the left eyelid. Head motions are detected with a multipolar cylindrical mercury switch on the forehead. Activity in these sensors is recorded at 250-ms intervals and output to a small recording device. The algorithm used by the NightCap system, which is described in Ajilore *et al.* (22), essentially distinguishes three sleep/wake states across samples for each minute of sleep: wake (activity in both eye and head channels), NREM sleep (activity in neither channel), and REM (eyelid activity only).

Artifact prone data were discarded, as were the data from the first night of sleep at the GCRC, which was considered to be an accommodation night. Estimates of time in bed, sleep duration, sleep efficiency (sleep duration as a function of total time in bed), latency to sleep onset, total sleep duration, mean awake time, mean NREM time, and mean REM time were determined for each participant for each night of sleep. Subjects having at least two nights of good data after the accommodation night were retained for subsequent analyses. To adjust for individual differences in night length, different sleep states (awake, NREM, and REM) were expressed as a percent of total time in bed.

Statistical Analysis. Associations among sleep parameters, sociodemographic factors, health status, health behaviors, plasma IL-6, and positive relations with others were examined initially with bivariate analyses. Multivariate linear regression analyses were then used to examine the independent and interactive relationships among sleep parameters, positive relations with others, and plasma IL-6. Control

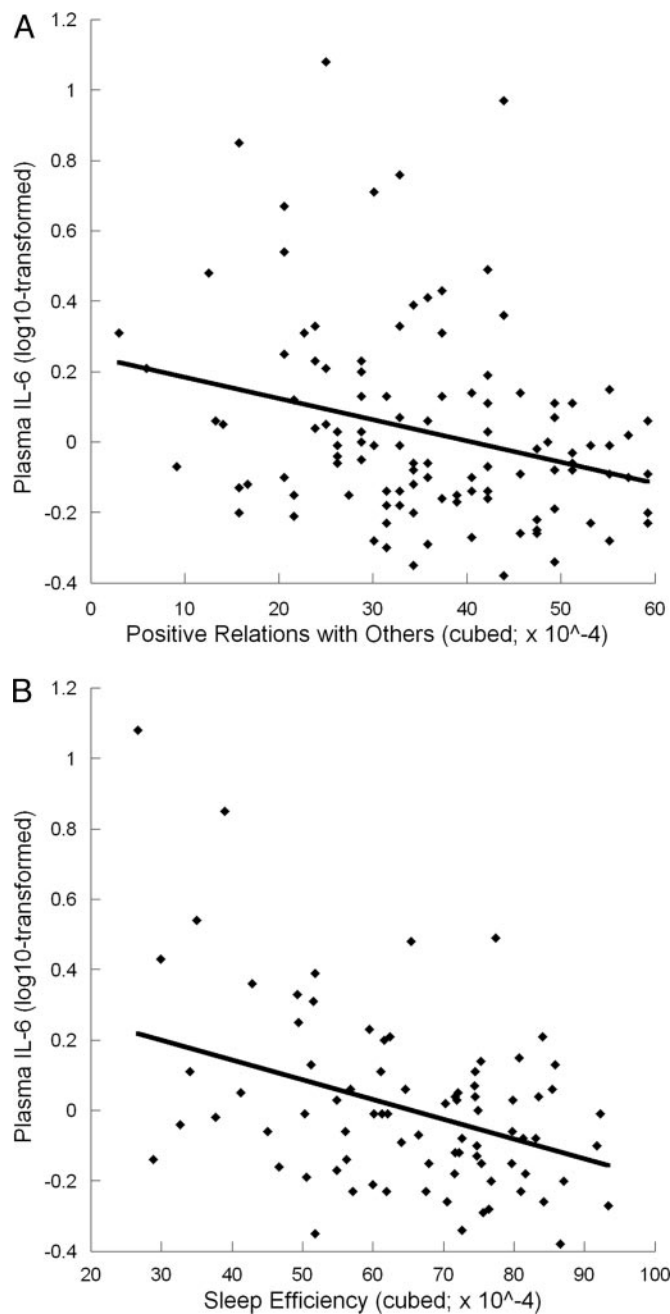


Fig. 1. Bivariate associations of positive relations with others and sleep efficiency with IL-6. (A) Bivariate scatter plot of the association of positive relations with others and plasma IL-6. There was a significant negative association between these variables, with higher scores on the positive relations measure predicting lower levels of IL-6 ($R = -0.34$, $P < 0.01$). Data transformations are indicated on the figure axis labels. (B) Bivariate scatter plot of the association of sleep efficiency and plasma IL-6. There was a significant negative association between these variables, with higher scores on the positive relations measure predicting lower levels of IL-6 ($R = -0.44$, $P < 0.001$). Data transformations are indicated on the figure axis labels.

IL-6 levels. Although latency to sleep onset predicted IL-6 levels at the bivariate level, the association was not significant once the control variables were included in the regression analysis (data not shown). PSQI global scores were also not significantly related to plasma IL-6 levels (data not shown).

To examine potential moderating influences, sleep efficiency and positive relations with others were entered into a regression model,

followed by the interaction term. This analysis revealed a significant interaction between these two measures (Table 3, Model 3; $P < 0.05$). As shown in Fig. 2, IL-6 levels were highest in women with poor sleep quality who also scored low on the positive relations scale; women with good sleep quality or strong social relationships or both all had lower IL-6 levels. In this last regression model, positive relations with others, sleep efficiency, and the interaction term accounted for 34% of the variance in plasma IL-6 (change in $R^2 = 0.34$, $P < 0.001$).

Finally, to test the possibility that sleep quality mediates the association between positive relations with others and plasma IL-6, sleep efficiency was entered into the regression model after positive relations (Table 3, Model 4). This analysis showed that when both terms were in the regression model, sleep efficiency and positive relations independently predicted IL-6 levels, suggesting that sleep efficiency did not mediate the association of positive relations and IL-6.

Discussion

This study tested the hypotheses that both social engagement and sleep quality would predict plasma IL-6 levels in aging women and further that there would be moderating or compensatory influences among these predictor variables. The results provided support for both hypotheses. Net of numerous control variables, sleep efficiency and positive relations with others significantly predicted levels of IL-6 in the hypothesized direction. These findings are consistent with previous research (38–42) but extend prior findings in important directions with regard to the size of the aging sample and the comprehensiveness of both the sleep assessments and the control variables (age, marital status, health problems, medication use, smoking, alcohol consumption, and subjective sleep quality). Regarding the interplay of social ties and sleep on IL-6 levels, we also found evidence of compensatory effects. That is, although women with both good social ties and good sleep efficiency had lower levels of IL-6, it was also the case that those who had good relationships but poor sleep efficiency, or had good sleep efficiency but poor social relations, had comparably low levels of IL-6. Such findings underscore the protective influence of psychosocial and behavioral factors; the strengths of one compensate for the deficiencies of the other. Clearly the most disadvantaged respondents were those with both poor sleep efficiency and low quality social connections with others, but focusing on only this outcome misses the important and frequently overlooked evidence regarding the factors that may protect against age-related increases in inflammation, even in the face of other psychosocial or behavioral risks. As such, the findings join a growing literature that is mapping diverse pathways toward the maintenance of health in aging individuals (43, 44).

The results also foreshadow further mechanistic relationships that may underlie the linkages among sleep quality, social engagement, and inflammation in aging women. One implication of the interaction between sleep efficiency and positive relations with others is that both may be linked to IL-6 by way of a common tertiary mechanism, possibly the hypothalamic–pituitary–adrenal (HPA) axis. Sleep disruption in the laboratory, for example, is associated with alterations in HPA activity (45), and age-related changes in sleep are linked to dysregulation of the HPA axis (46, 47). Psychological stress and clinical depression, both of which are associated with HPA dysfunction (48, 49), are also linked to impaired regulation of IL-6 production, at least in immunocompetent cells (50). The ability of glucocorticoids to restrain IL-6 production *in vitro*, for example, is impaired in individuals experiencing chronic stress (51). Significantly, however, social support partially restores sensitivity to regulation by glucocorticoids regulation (51). It is conceivable that sleep quality and social engagement converge in preserving HPA regulation in aging women and, thereby, regulation of IL-6 production. The potential for mechanistic links between social engagement and specific aspects of brain and neuroendocrine function is underscored by recent research

Table 3. Multivariate linear regressions of sleep parameters and positive relations with others on plasma IL-6 levels in aging women ($n = 78$)

Predictors	Model 1 (β)	Model 2 (β)	Model 3 (β)	Model 4 (β)
Positive relations with others, cubed	-0.31*		-1.21*	-0.31*
Sleep efficiency, cubed		-0.40 [†]	-0.98*	-0.38 [†]
Positive relations \times sleep efficiency interaction			1.13 [‡]	
Change in R^2	0.09*	0.13 [†]	0.34 [†]	0.22 [†]

Standardized regression coefficients are shown. All models included the control variables listed below, and the change in R^2 is net of the control variables. Models 1 and 2 show the individual contributions of positive relations and sleep efficiency to plasma IL-6 levels. Model 3 shows the interaction of sleep efficiency and positive relations in predicting IL-6. Model 4 tested the extent to which sleep efficiency and positive relations independently predicted IL-6 levels. Models controlled for age, marital status, years of education, pretax family income, chronic health conditions, medication use, alcohol consumption, and smoking. *, $P < 0.01$; [†], $P < 0.001$; [‡], $P < 0.05$.

showing that greater left frontal brain activation, measured by electroencephalography, is significantly associated with higher scores on the positive relations scale (52). This speculation suggests a number of testable hypotheses involving simultaneous assessments of sleep quality, social engagement, HPA function, and IL-6.

The relationship between sleep quality and IL-6 may be reciprocal; indeed, evidence is accumulating in both animal and human studies to suggest that IL-6 may modulate sleep. For example, IL-6 levels exhibit a circadian pattern that corresponds to the human sleep cycle, with peak values at night and nadirs during the day (53, 54). Endogenous IL-6 may contribute to excessive daytime sleepiness or altered nighttime sleep under adverse conditions when IL-6 is elevated. Evidence in mice probes underlying mechanisms, suggesting that IL-6 does not impact NREMs, possibly due to low levels of the protein in the brain, whereas knockout mice lacking genes for IL-6 were found to spend more time in REMs after sleep deprivation (55). These lines of research suggest that IL-6 may be involved in physiological sleep regulation.

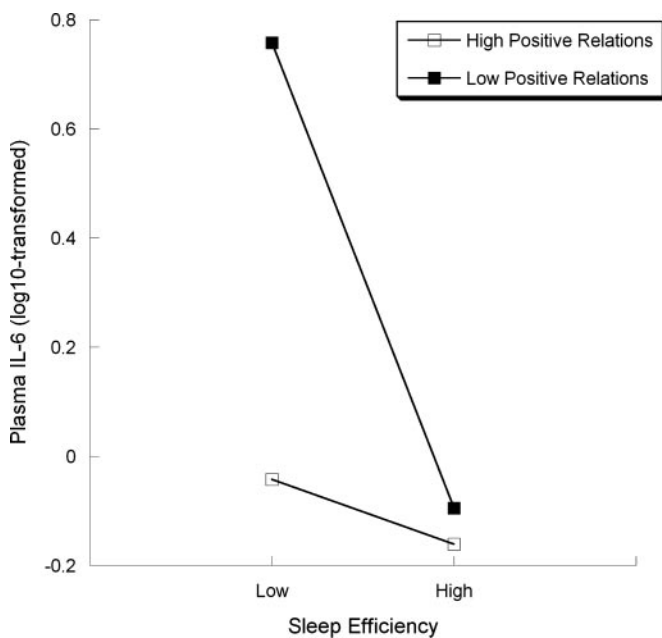


Fig. 2. Interaction of sleep efficiency and positive relations with others. The interaction significantly predicted plasma IL-6 levels ($\beta = 1.19$, $P < 0.05$). The data points shown were calculated from the same regression equation. Sociodemographic, health status, and health behavior control variables were set to their mean values. Maximal or minimal values for sleep efficiency and positive relations predictor variables were then added to the equation to generate the estimates shown here (37).

Aging processes set the context for this inquiry. As such, it is important to note that age alone significantly predicted both sleep quality and plasma IL-6 levels in this sample. At the bivariate level, advancing age was associated with decreased sleep efficiency, although not with subjective sleep quality. However, regression analyses showed that the association of age and sleep efficiency was mediated by the presence of chronic health conditions and health-driven limitations on activity (data not shown). These findings are consistent with the suggestion that age-related sleep impairments are not due to aging *per se* but rather to the presence of age-related diseases (10, 56, 57). In contrast, the association of age with plasma IL-6 levels was independent of the health indicators included in the regression models, an observation that is consistent with previous reports of age-related increases in IL-6 (1, 3, 4, 6). We probed for ill health in a number of ways (chronic conditions, number of sick days, visits to doctor in past year, and health problems in daily activities). These variables were all included in regression models and did not significantly affect the association of IL-6 with age (data not shown). Although it is still possible that undetected and unperceived disease processes, rather than aging, contributed to higher IL-6 levels in these older women, it seems likely that other factors also associated with aging, such as changes in psychological well-being, may have contributed to IL-6 levels. We hypothesize, for example, that the rate of IL-6 accumulation in the blood with age may be attenuated by positive social engagement. Resolution of this issue will require longitudinal collection of health and cytokine data.

Although the combined assessments of objective and subjective sleep quality, social engagement, and inflammation represent strengths of this study, interpretations of the findings should be tempered given the homogeneity of the sample, its relatively small size, and the cross-sectional design. Better understanding of these complex interactions, and the dynamics they imply, can be achieved through the application of longitudinal designs with larger and more diverse samples and time-coordinated assessments of key variables. Collection of behavioral, psychological, and biological data at multiple times, for example, will enable us to determine whether social relationships and sleep quality are predictive of IL-6 levels, or reciprocally, whether IL-6 predicts later sleep problems and/or poor quality social ties. An important contribution of animal studies to this topic would be investigations of the impact of disruption of social groups (e.g., removal of one member of a prairie vole couple) on changes in sleep character and quality. There is currently a lack of literature dealing with the nexus between social relationships and sleep in animals, despite the quite elaborate literature focused on the immune systems and sleep (58).

The length of time between collection of questionnaire and sleep data and the collection of blood samples for cytokine analyses was significant in some cases. This temporal slippage was not ideal, especially if any of the variables of interest showed limited stability over time. We reasoned, however, that if sleep quality, social

relations scores, or plasma IL-6 levels were highly fluctuating, time-dependent domains, it would reduce the likelihood of observing significant relationships among them. As such, the data we had available translated to a relatively conservative test of our hypotheses, and the results suggest, in part because of the temporal dissociation, that these relationships may be quite robust. Thus, this temporal slippage represents both a limitation and a strength of this study.

Increased variability in psychological and biological functioning with age is a key issue undergirding this study. Most research, however, has focused on changes in average levels of function. Increases in IL-6 that typically occur with age, for example, are linked to increased risk of disease, disability, and mortality (1–3, 6–8, 59–62). As a consequence, less attention has been paid to the variance in markers of aging (15). The results of this study indicate that although poor social relationships and poor sleep quality

independently predicted increased IL-6 levels in older women, high scores on either variable also compensate for the presence of low scores on the other and predict levels of IL-6 indistinguishable from those in women with both strong social relationships and high quality sleep. Thus, these findings suggest that strong social relationships and good quality sleep contribute, additively and interactively, to advantaged biological profiles in aging women. They also offer a potential target for interventions designed to increase the likelihood of successful aging, an issue of increasing importance given the steadily rising proportion of older adults in western countries, particularly the United States.

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