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Self-Rated Health and Inflammation: A Test of Depression and Sleep Quality as Mediators

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Abstract

Objective: Despite its simplicity, single-item measures of self-rated health have been associated with mortality independent of objective health conditions. However, little is known about the mechanisms potentially responsible for such associations. This study tested the association between self-rated health and inflammatory markers as biological pathways, and whether sleep quality and/or depression statistically mediated such links.

Method: Eighty-six heterosexual married couples completed a standard measure of self-rated health, the CES-Depression scale, and the Pittsburgh Sleep Quality Index. Participants also had blood drawn for determination of plasma levels of IL-6 and hs-CRP. The Monte Carlo method was used to construct confidence intervals for mediation analyses.

Results: Results indicated that poor self-rated health was associated with higher CRP levels ($B = .31$, $SE = .14$, $p = .028$). Importantly, Monte Carlo mediational analyses showed that these results were statistically mediated by sleep quality ($aXb = 0.10$, 95% CI [0.003, 0.217]) but not depressive symptoms ($aXb = 0.03$, 95% CI [-0.03, 0.10]).

Conclusions: These results highlight the biological and behavioral mechanisms potentially linking SRH to longer-term health outcomes. Such work can inform basic theory in the area as well as intervention approaches that target such pathways.

Keywords

Self-rated health; sleep quality; depression; inflammation

Self-Rated Health and Inflammation: A Test of Depression and Sleep Quality as Mediators

Self-rated health (SRH) is a single-item measure of one's perceived health and a robust predictor of morbidity and mortality [1,2]. In one meta-analysis, poorer SRH showed a graded association to higher mortality rates [3]. These associations held while also considering cognitive function and SES [4]. Although SRH is considered a subjective summary of one's physical health, statistical adjustments for functional status and co-morbid diseases attenuate, but do not eliminate, the association between SRH and mortality. In fact, there is still about a 2-fold increase in mortality risk that is not explained by these objective health indicators [3].

Most of the current work in the area has focused on the antecedent processes that influence SRH, especially cognitive representations and conscious/automatic decision-making about one's health status [2,5]. In contrast, very little work has examined the potential mechanisms responsible for links between SRH and mortality. This is important as mechanistic work can inform interventions even in the absence of a complete understanding of its precursors. In terms of biological mechanism, recent work has focused on inflammation as a pathway linking SRH to health. Studies in this area indicate a link between poorer SRH and higher level of inflammation as indexed by CRP, IL-6, and TNF-alpha [6–11]. This is important because chronic inflammation has been causally linked to a wide-range of health problems including diabetes, frailty, cognitive decline, and overall mortality [12,13], and inflammation can negatively affect every stage of cardiovascular disease progression [14].

Much less is known about intermediary psychological and behavioral mechanisms linking SRH to health outcomes. Of these, sleep quality and depression have emerged as two likely candidates. Both of these factors have also been linked to morbidity and mortality which highlights their potential role in the link between SRH and health outcomes. Depression is a reliable predictor of poor medical outcomes and mortality in both cardiovascular disease and cancer patients [15,16]. Sleep plays an important role in biological restoration and repair [17] and emerging research has linked poor sleep (e.g., duration, quality) to negative health outcomes [18–20].

There are important conceptual reasons to hypothesize that depression and sleep quality might be mediators of the link between SRH and inflammation. Health problems are stressful and requires considerable coping resources [21]. Perceptions of poor health may thus be linked to depression and several studies are consistent with this possibility [22,23]. For instance, a prospective study of 789 patients with a history of depression showed that

poor SRH predicted increases in depression 5 years later [23]. Inconsistent with aspects of mediation, however, several studies have found that the link between SRH and inflammation persist even when statistically adjusting for depression [7,9]. It is important to note that none of these studies have utilized more recent, sensitive tests of statistical mediation [24].

Although a more recent area of inquiry, SRH may also negatively influence health via poor sleep. The stress of perceiving poor health [25] might negatively affect one's sleep. Only a few studies have directly examined this association but they indicate that low SRH is associated with poor sleep outcomes [26–28]. Moreover, several studies found that the link between SRH and sleep was independent of depressive symptoms [26,29]. These data highlight the fact that depression and sleep quality, although related, might be distinct mediators of the link between SRH and inflammation.

The current study thus had several aims. The first was to replicate the link between SRH and the inflammatory markers CRP and IL-6. Both of these markers of inflammation predict future risk for cardiovascular disease and related mortality [30–32]. Based on prior work, it was predicted that SRH would predict both CRP and IL-6 levels. A second, major aim was to test depression and global sleep quality as potential pathways using more formal tests of mediation. It was hypothesized that sleep quality would mediate links between SRH and inflammation. Predictions for depression as a mediator were more tentative given studies suggesting the link between SRH and inflammation is statistically independent of depressive symptoms [9].

Method

Participants

Eighty-six relatively healthy long-term married middle-age to older adult couples ($M_{\text{age}}=56.3$, $SD=7.32$, range 42 to 78 years) were included in this study. The study was part of a larger study that investigated social interactions and cardiovascular health in middle-aged and older adults [33]. Most were White (94.2%) and had an income over \$40,000 per year (88.4%). Many older adults are on some form of medication so only individuals who (a) were on strong immunosuppressive treatment (e.g., corticosteroid therapy) and/or (b) had cancer or HIV were excluded due to concerns about potential effects of treatment on inflammation. Participants were not told to discontinue any medication use or screened for illnesses the day of their visit.

Procedure

This study was approved by the Institutional Review Board at the University of Utah. Eligible participants were screened via phone interviews and scheduled for a laboratory appointment during a three-hour late morning block (9 am to 12 pm) to control for diurnal influences on inflammation. Following informed consent, participants were first rechecked against the exclusion criteria upon their arrival for their session. Participants then completed background questionnaires (i.e., demographic, medication/health questionnaires) as well as a standard measure of self-rated health, the CES-depression scale, and the Pittsburgh Sleep Quality Index (see below). Twenty milliliters of blood were also drawn and treated with

EDTA to prevent clotting. Plasma was separated via centrifuge and levels of IL-6 and CRP were determined at the University of Amsterdam (see below). Couples were then debriefed and received \$60.00 each for their participation. Data collection for this study occurred during a 14-month span during the years 2008–2009.

Measures

Health Assessment.—A standardized health questionnaire provided information on medications being used for medical conditions (0=no, 1=yes). This questionnaire has been used in a large longitudinal study on the chronic stress of caregiving for a relative with Alzheimer's Disease and its effects on physiological function [34]. Body mass index (BMI) was calculated based on weight and height in kg/m^2 .

Self-Rated Health.—Participants were asked to rate their current health on a 1 to 5-point scale (1=excellent, 2=good, 3=fair, 4=poor, 5=bad). This simple measure of self-rated health has been shown to predict mortality above and beyond existing health conditions and physical limitations [3].

PSQI.—The Pittsburgh Sleep Quality Index (PSQI) assesses global sleep quality during the previous month [35]. The scale is comprised of 19 items which are used to derive a total of seven component scores: Sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction. Component scores are summed to produce an overall PSQI score with higher scores indicating poorer global sleep quality. This instrument has demonstrated good reliability ($\alpha = 0.83$) and validity [36]. Internal consistency in the present study was adequate (wives $\alpha = .69$; husbands $\alpha = .72$).

CES-D.—The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item scale that assesses depressive symptoms. The Cronbach's alpha was high in both patient and control samples (.90), with a 4 week test-retest correlation of .67 [37]. Importantly, the CES-D also has good sensitivity for detecting depressive symptoms [38]. The internal consistency of the CES-D in the current study was similarly high (wives $\alpha = .88$; husbands $\alpha = .85$).

Inflammation Assessments.—High sensitivity CRP (hsCRP) was measured by immunonephelometry using a Behring Nephelometer II. The limit of detection for C-reactive protein is 0.015 mg/L (High Sensitivity CRP, Dade Behring). All samples were assayed in the same run, yielding a within-assay CV% of <4.5% for hsCRP. IL-6 was determined using a commercially available high-sensitivity ELISA (hsIL-6 Quantikine, R&D systems), which has a lower detection limit of 0.15 pg/ml and yielded an intra-assay CV% of <6%. Consistent with prior work, CRP and IL-6 were natural log transformed to normalize the distribution prior to analyses [39]. The non-normality of the data was confirmed by significant Shapiro-Wilk tests for CRP ($W=.67, p<.001$) and IL-6 ($W=.83, p<.001$, [40]).

Statistical Model

Proc mixed (SAS institute) was utilized for the main analyses [41]. All factors were treated as fixed [42] and grand mean centered prior to analyses [43]. The covariance structure for the repeated measures factors of dyad (i.e., 1=husband, 2=wife) was modeled using the compound symmetry structure [41]. The outputs of these models were unstandardized parameter estimates (B) using the Satterthwaite approximation to determine the appropriate degrees of freedom [41]. Consistent with prior work, analyses statistically adjusted for age, sex, BMI, income, and medication use related to health conditions such as statins and anti-inflammatory agents [44]. Subsequent mediational analyses were conducted using the Monte Carlo method [24]. This method uses parameter estimates and standard errors from the main models above which account for the dependency within couples. These data points are then used in the MCMED macro [45] to construct 95% confidence intervals for each indirect effect using 5000 resamples.

Results

Descriptive Analyses

Descriptive data for the main study variables are detailed in Table 1. The average self-rated health was 1.65 ($SD=0.66$) while the mean untransformed CRP and IL-6 levels in the sample were .19 ($SD=.25$) and 1.57 pg/ml ($SD=1.06$), respectively. The average level of global sleep quality in the sample was 5.06 ($SD=3.08$) which is at the cut-off indicating poor overall sleep quality (i.e., 5.0, Buysse et al., 2008). Mean depression levels were moderate ($M=27.0$, sum of 1 to 4-point scale). Zero order correlations between the main study variables for wives and husbands are shown in Table 2. For both husbands and wives, SRH was significantly related to poorer sleep quality and depressive symptoms, whereas poor sleep quality was related to higher depression and higher CRP levels. Importantly, SRH was significantly associated with higher CRP levels for both husbands and wives in these unadjusted analyses.

Main Analyses

Analyses first focused on whether SRH was related to markers of inflammation. Consistent with prior work, poor SRH was associated with higher CRP levels ($B=.31$, $SE=.14$, $p=.028$) independent of demographic factors and medication use for chronic conditions (see Table 3). Poor SRH was not related to IL-6 levels ($B=.08$, $SE=.07$, $p=.217$). Ancillary analyses showed that these results were not moderated by sex for either CRP ($p>.17$) or IL-6 ($p>.37$).

Mediational analyses focused on the significant link between SRH and CRP. Replicating prior work, the link between SRH and global sleep quality was significant ($B=1.68$, $SE=.36$, $p<.0001$), and marginally significant for global sleep quality and CRP levels when including the covariates (e.g., age, medication use) and SRH in the model ($B=.06$, $SE=.03$, $p=.064$). Most important, the indirect (mediated) effect of SRH on CRP through sleep quality was significant ($aXb=0.10$, 95% CI [0.003, 0.217]). Mediational analyses were next conducted with depression. Replicating prior work, the link between SRH and depression was significant ($B=3.16$, $SE=.76$, $p<.0001$) even when including the covariates. However, depression was not related to CRP levels ($B=.01$, $SE=.01$, $p=.70$) when including covariates

and SRH in the model. As a result, the indirect influence of depression on the SRH – CRP association was not significant ($aXb=0.03$, 95% CI $[-0.03, 0.10]$).

Discussion

The main goals of the current study were to replicate the link between SRH and inflammation, and to model global sleep quality and depression as potential mechanisms. Consistent with prior research, poor SRH was associated with higher CRP levels [6,9]. SRH was not related to higher IL-6 levels, however. Importantly, this is one of the first studies to show that global sleep quality was a significant mediator of the association between SRH and CRP levels. In contrast, depression did not appear to mediate the link between SRH and CRP. These data inform theoretical models as SRH appears to be negatively associated with global sleep quality which in turn is related to higher CRP levels.

Depression and sleep quality were examined as potential mechanisms due to prior work linking them to SRH [23,27]. Consistent with hypotheses, global sleep quality was a statistical mediator of the association between SRH and CRP. These data are important because sleep is emerging as an important predictor of early morbidity and mortality [19,47]. It is important to note that poor SRH may have reciprocal links with global sleep quality. For instance, poor sleep may also contribute to lower SRH over time [48]. Nevertheless, the results can inform interventions as there are several approaches to treating sleep difficulties that might be used in populations with poor SRH to promote positive health outcomes. For instance, there is meta-analytic evidence linking cognitive-behavioral therapy to better sleep outcomes [49].

Depression, in contrast, did not appear to mediate links between SRH and CRP levels. These data are consistent with several studies that have found that SRH was independently related to inflammation even when statistically adjusting for depression (e.g., Christian et al., 2011). The current study did not detect a significant overall link between depression and inflammatory markers which is contrary to a meta-analysis on the topic [50]. However, the effect sizes linking self-reported depression to CRP and IL-6 were relatively small in this meta-analysis and influenced by statistical adjustments, especially BMI as adipose tissue is a significant source of inflammation [51]. The conceptual implications of whether one should statistically adjust for BMI is complicated by models suggesting that this might be a mechanism linking depression to health [52]. The current study did find that depression was marginally associated with CRP when BMI was not included in the model ($p=.063$) but not when also including SRH ($p=.54$). Combined with the results from the prior meta-analysis, these data suggest that larger samples will be needed to adequately test depression as a mediator.

More generally, these data highlight the importance of modeling potential mechanisms responsible for links between self-rated health and mortality. In the present study, more sensitive techniques for detecting mediation were utilized compared to prior work that simply adjusted for potential mediators [24,54]. Most of the work in this area has also focused on antecedent processes such as actual physical health conditions and/or cognitive processes that give rise to self-rated health above and beyond objective indicators of health

(e.g., symptom perception, [2,3]). Such work is certainly important, but data on biobehavioral mechanisms has lagged behind such questions and can inform theoretical models and intervention approaches. For instance, knowing that sleep is a potential mediator expands possible intervention approaches as there are well-documented behavioral interventions for sleep problems that might then mitigate the association between self-rated health and inflammation [53]. This is especially important because as noted above poor SRH may have reciprocal links with global sleep quality [48]. Future prospective work can better capture the likely complexity of such links and more accurately model reciprocal influences.

There are also important limitations of the current work. First, the results of this study were consistent with mediation. However, it is limited by the cross-sectional design so longitudinal studies will be needed for strong inference and to model more complex (e.g., reciprocal) links [55]. In addition, although the Pittsburgh Sleep Index is related to objective measures of sleep (e.g., actigraphy, [35,36]), such objective measures would have increased the construct validity of this project's sleep assessment. This study also included relatively healthy individuals so generalizations to clinical populations are limited. These limitations notwithstanding, this is one of the first papers demonstrating that sleep quality mediates the link between SRH and CRP and highlights the importance of future theoretical work focusing on pathways.

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Abbreviations:

SRH	self-rated health
SES	socioeconomic status
BMI	body mass index
CES-D	center of epidemiological studies depression scale
CRP	c-reactive protein
IL-6	interleukin-6
TNF-alpha	tumor necrosis factor-alpha
HIV	human immunodeficiency virus
PSQI	Pittsburgh sleep quality index

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Table 1.

Final sample characteristics (n=86 couples)

Variable	Sample
Mean (SD)	
Age in years	56.3 (7.32)
BMI in kg/m ²	26.3 (4.84)
Self-rated health	1.65 (0.66)
Sleep quality	5.06 (3.08)
CES-D	27.0 (6.47)
Raw IL-6 in pg/ml	1.57 (1.06)
Raw CRP in pg/ml	0.19 (0.25)
Frequency	
Ethnicity (% White)	94.2%
Income Over \$40,000	88.4%
Statin use (% yes)	8.1%
Anti-inflammatory use (% yes)	26.7%
Hormone replacement use (% yes)	5.2%

Table 2.

Zero order correlations (n=86 couples) among main study variables for wives (top panel) and husbands (bottom panel) as well cross-correlations between wives and husbands (diagonals).

Variable	1.	2.	3.	4.	5.
1. SRH	.28[*]	.40 ^{**}	.29 ^{**}	.11	.32 ^{**}
2. PSQI	.37 ^{**}	.20	.51 ^{**}	-.08	.29 ^{**}
3. CES-D	.42 ^{**}	.46 ^{**}	.24[*]	-.20	.07
4. IL-6	.28 ^{**}	.24 [*]	.23 [*]	.10	.47 ^{**}
5. CRP	.27 ^{**}	.28 ^{**}	.26 ^{**}	.59 ^{**}	.05

Note: SRH=self-rated health, PSQI=Pittsburgh sleep quality index, CES-D=Center for Epidemiological Studies – Depression scale, IL-6=Interleukin-6, CRP=C-reactive protein.

^{*}
p .05,

^{**}
p .01.

Table 3.

Main results of proc mixed models which included covariates and self-rated health on inflammatory markers (n=86 couples).

Variable	IL-6			CRP		
	B	SE	p	B	SE	p
BMI (kg/m ²)	.06	.01	<.001	.10	.02	<.001
Age (years)	.01	.01	.15	-.004	.01	.76
Sex (male-female)	.34	.08	<.001	.29	.19	.12
Income (\$)	.01	.04	.73	-.05	.08	.51
Statin (no-yes)	.14	.15	.34	.16	.32	.61
Anti-Inflammatory (no-yes)	-.20	.09	.029	.14	.20	.47
Hormone replacement (no-yes)	-.30	.18	.10	.71	.40	.073
Self-rated health	.08	.07	.22	.31	.14	.028