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Full-length Article

Self-rated health and interleukin-6: Longitudinal relationships in older adults

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ABSTRACT

Background: Both self-rated health (SRH) and inflammation are implicated in chronic diseases and premature mortality. Better SRH is associated with lower proinflammatory cytokines, but there is little evidence about whether this relationship is more stable or dynamic.
Objective: To study the between- and within-person associations between SRH and IL-6.
Methods: Older adults ($N = 131$; $M_{age} = 75$ years) rated their health and provided blood samples for analysis of IL-6 at separate occasions every 6 months over a period up to 5 years. Age, sex, BMI, neuroticism, and statin use were examined as covariates in multilevel models.
Results: In bivariate models, better SRH, lower BMI, younger age, and female sex correlated with lower IL-6. In multilevel models, stable SRH (between-person differences; $p < .001$) but not dynamic SRH (within-person changes; $p = .93$) correlated with IL-6. The stable relationship persisted with demographic and health covariates in the model.
Conclusions: Better stable SRH but not dynamic SRH was robustly associated with lower IL-6 among older adults, lending support to previous cross-sectional findings on the relation between inflammatory markers and SRH. The findings suggest that trait-like mechanisms, rather than changes over a time scale of 6-month waves, govern this association. To further investigate the mechanisms behind the SRH–IL-6 association, studies with different measurement frequencies, higher within-person variability, and experimental approaches are warranted.

1. Introduction

Self-rated health (SRH) predicts future objective health risks and summarizes health information in a way that goes beyond the biomedical model (Ganna and Ingelsson, 2015; Idler and Benyamini, 1997). It is not yet understood how this one subjective rating can explain outcomes such as cardiovascular events and mortality even after accounting for other risk factors. Inflammation is also implicated in premature mortality (Baune et al., 2011; Volpato et al., 2001) and may be a key biological corollary of SRH. Inflammation induces sickness behavior, including behavioral withdrawal, nonspecific symptoms of weakness, listlessness, changed sleep patterns, hyperalgesia and decreases in motivation and appetite (Dantzer and Kelley, 2007). These symptoms may affect subjective appraisals of health, even among generally healthy adults.

Indeed, low-grade inflammation as measured by elevated levels of pro-inflammatory cytokines, especially interleukin-6 (IL-6), correlates with poorer SRH (Andreasson et al., 2013; Cohen et al., 1997; Janszky et al., 2005; Lekander et al., 2004). However, these cross-sectional findings cannot distinguish to what extent changes in SRH and inflammation are correlated within individuals over time. Some authors have stressed the importance of changes in SRH (Gerber et al., 2009; Lekander et al., 2013; Lyyra et al., 2009). For example, prediction of mortality from SRH improved when changes in health ratings were included (Gerber et al., 2009). Because factors that co-vary with subjective health, such as disease, energy, sleep, and cytokines, are not stable over time (Jylhä, 2009; Lekander et al., 2013, 2004), it is reasonable to assume that health is actively appraised in a responsive and dynamic manner and therefore follows changes in its presumed determinants. Short-term changes in symptoms and affect were

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related to SRH in a group of older adults (Winter et al., 2007), and within-person changes in affect were likewise associated with changes in SRH in the present sample of older adults (Segerstrom, 2014). Similarly, experimental sleep restriction to 4 h/night for five nights caused gradually poorer SRH in healthy young adults (Lekander et al., 2013). However, that study assessed current rather than general SRH. Studies of the link between changes in inflammation and SRH over time are generally lacking: The sole cross-sectional study found that retrospective perceived change in health in the past year was unrelated to IL-6 and did not influence the significant cross-sectional relationship between current SRH and IL-6 (Christian et al., 2011).

Longitudinal research can elucidate the nature of relationships between SRH and inflammatory markers in ways that cross-sectional research cannot (Ryu et al., 2012). Ryu et al. (2012, p. 330) point out that in longitudinal health research, often "each person's mean level and the fluctuations from the mean (chronic) level are the important data of interest", a distinction that can only be made when people are measured repeatedly over time. SRH and inflammation are likely to be related over a very long time course (e.g., over years as a consequence of aging), creating relationships that emerge as between-person differences in studies with shorter time frames as well as cross-sectional designs. They also appear to be related over a short time course, e.g., within hours to days as a consequence of sleep restriction (Lekander et al., 2013) or injected endotoxins (Lekander et al., 2012; Lidberg et al., 2013). However, no studies to date have examined natural covariation between them over intermediate time frames (e.g., over months).

1.1. The present study

In the present study, we applied this longitudinal framework of stable mean levels and dynamic fluctuations to potential associations between SRH and inflammation in a sample of healthy older adults. The association between SRH and inflammatory cytokines is thought to be stronger with advancing age: partly because lower levels of inflammatory cytokines in younger adults (Knudsen et al., 2008) restrict the range and limit the ability to test relationships, and also perhaps due to an increased sensitivity to these cytokines with age (Unden et al., 2007). Studying older adults thus provides an excellent research model. Among proinflammatory cytokines, IL-6 is a suitable target as it is, as noted above, often related to SRH in cross-sectional studies, distributed in detectable ranges, and increases with age. We hypothesized that worse SRH would correlate with higher levels of the inflammatory marker IL-6 both between people and within people over time, reflecting relationships at the levels of (1) stable individual differences that emerge over very long time frames and (2) dynamic relationships that emerge as people change over shorter time frames. Additional sensitivity analyses assessed the roles of demographic and health covariates (age, sex, statin use, and BMI) and blood sample timing relative to SRH assessment. Finally, negative dispositional factors such as neuroticism are linked with inflammatory markers (Marsland et al., 2008; Roy et al., 2010) and may confound a potential association between SRH and inflammatory cytokines. Therefore, neuroticism was also included among the covariates.

2. Methods

2.1. Participants

Study participants were 131 community-dwelling, married older adults over the age of 60 (M_{age} = 74 years; range: 60–93 at study entry). No dyads were included in the sample to avoid dyadic dependencies in the data. Consistent with the sex ratio in older age, 41% of the sample was male, and 59% was female. The majority of the sample was White (96%), and the remainder was African American (4%). Median annual household income was $57,000 (range: $12,000–$400,000), and median education was 16 years (range: 7–22).

Exclusion criteria at enrollment included self-reported (a) diseases or disorders affecting the immune system, (b) chemotherapy or radiation treatment within the past 5 years, (c) unwillingness to undergo vaccination or venipuncture, (d) immunomodulatory medications including opiates and steroids, and (e) more than two of the following classes of medications: psychotropics, antihypertensives, hormone replacement, or thyroid supplements. Based on the clinician's judgement at screening and subsequent neuropsychological assessment, all participants were cognitively able to respond to questionnaires.

2.2. Procedure

Study participants were recruited from a volunteer subject pool maintained by the Sanders–Brown Center on Aging at the University of Kentucky. Prospective participants were contacted and screened by telephone. Those who were interested and eligible were enrolled and completed questionnaire measures verbally with the assistance of a research assistant and response cards. These interviews were undertaken at 6-month intervals over a period of up to 10 waves (5 years). Participants received a $20 gift card at each wave completed. Informed consent was obtained at the first interview, and all study procedures were approved by the University of Kentucky Institutional Review Board.

Blood samples were drawn in spring and fall. For the purposes of this study, we selected participants who had provided at least one valid IL-6 sample at any wave. In addition, twelve observations were excluded for elevated IL-6 values (range = 89–2048 pg/mL) due to current/recent sickness. The final sample included 131 out of 150 participants in the parent study. Of these, 131 completed Wave 1, 128 completed Wave 2; 121, Wave 3; 116, Wave 4; 110, Wave 5; 108, Wave 6; 102, Wave 7; 92, Wave 8; 57, Wave 9; and 34, Wave 10. Because some participants enrolled in the study later than others, they completed fewer waves before the end of the study; lower N in Waves 8, 9, and 10 are attributable to this mechanism. These missing data are missing completely at random and thus do not bias the parameter estimates (Fitzmaurice et al., 2011). There were in total 999 observations of SRH and 775 of IL-6 (due to, e.g., missing values due to sickness) that in combination yielded a final sample of 769 observations included for analysis.

2.3. Measures

2.3.1. Demographics

Demographic information was collected at the first interview. Date of birth and interview date were used to calculate exact chronological age at each interview.

2.3.2. Self-rated health

SRH was measured using a single item from the Medical Outcomes Study Health-Related Quality of Life scale (Ware and Sherbourne, 1992). The item reads: "In general, would you say your health is…" with responses *excellent*, *very good*, *good*, *fair*, *poor*. The variable was coded for analysis so that higher values represent better SRH.

2.3.3. Interleukin-6

Study nurses drew blood samples in fall and spring. The sample that was drawn closest to the interview was paired with that interview wave. The median interval from interview to blood draw was

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