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Is Inflammation a Link between Self-Reported Health and Infectious Disease Risk?

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Abstract

Self-reported health (SRH) has been consistently shown to predict morbidity and mortality. However, the mechanisms underlying this association are poorly understood. Cohen and colleagues' study reported in this issue of Psychosomatic Medicine fills this gap by examining a potential biological mechanism: alteration of immune system functioning. The study shows that SRH predicted common cold following experimentally controlled virus inoculation in healthy individuals. More specifically, SRH predicted the cold-related illness expression as measured by objective clinical signs, while it did not predict the infection rates as measured by pre-defined increases in specific antibodies. This editorial discusses the significance of this study and the possibility that inflammation, an innate immune response, is a link between SRH and common cold risk. Since the illness expression of cold is generally attributed to increased local inflammation, and SRH has been found associated with increased systemic inflammation, it is possible that SRH is a correlate of a heightened systemic inflammatory state and thus leads to increased local inflammatory responses after an exposure to a cold virus. SRH was also associated with well-known risk factors for inflammation in this study, such as overweight, perceived stress, and social isolation. Because of the strong predictive value of SRH for future morbidity and mortality and the simple low-cost tools that enable its assessment, SRH has the potential to identify high-risk individuals in various public health settings. Future research is needed to address the translational applicability of these findings and to further the mechanistic investigation in high-risk groups including older adults.

Keywords

self-reported health; common cold; immune system; inflammation

Self-reported health (SRH) is often assessed using a single question such as "In general, how would you rate your health?" with response options set out on a scale from excellent to good, fair, and poor. This simple approach has been consistently shown to predict morbidity and mortality, even after accounting for objective health status, behavioral risk factors, and sociodemographic characteristics (1, 2). Furthermore, data from the UK Biobank, a large epidemiological study following 500,000 men and women aged 40-70 years, have shown

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that SRH is one of the strongest predictors of 5 year all-cause mortality (3). The evidence that this single question has such a robust predictive capacity of health outcomes is remarkable in this era of technically sophisticated health management approaches. This simple approach has the appealing potential to identify those at risk and enables public health initiatives that increasingly require implementation of sensitive, efficient, and cost-effective approaches, especially in communities with limited resources such as developing countries and rural areas of developed countries.

However, despite this empirical evidence and implementation potential, questions on SRH have not been widely used in clinical settings. Furthermore, although some social and behavioral mechanisms have been postulated to explain the association between SRH and morbidity and mortality (1), its mechanisms are poorly understood in general, and especially regarding what physiological systems are involved. There have been suggestions on the biological mechanisms such as the involvement of systemic inflammatory markers (4-7), reproductive hormones (8), and 25-hydroxyvitamin D (9). However, all this evidence has been observational, limiting causal or mechanistic inferences.

Cohen et al.'s study reported in this issue of Psychosomatic Medicine is a human experimental investigation that fills this gap by examining a potential biological mechanism: alteration of immune system (10). The authors examined the aggregated data from their experimental studies of common cold where cold viruses were inoculated to healthy volunteers. SRH was an important predictor of common cold, more specifically illness expression as measured by objective clinical signs of common cold; while it did not predict the infection rates as measured by pre-defined increases in specific antibodies.

This study is significant because of its unique contribution to the understanding of biological mechanisms of the link between SRH and morbidity. The association between SRH and common cold was robust and independent of various confounders. Furthermore, the contribution from psychosocial factors to this association was modest and the association of SRH with common cold remained significant after adjustment for these factors. Additionally, using an independent study sample of cold induction, the authors also showed that the history of colds did not predict the development of clinical illness. Although SRH was not assessed in this independent sample, this finding suggests that history of having colds did not account for the association between SRH and colds. The significance of this study also lies in its extension of prior epidemiological research of prediction models by the use of experimental strategies to examine pathophysiological mechanisms, thus paving the way for future translational studies. Although SRH was not a randomly assigned variable and hence not interpretable as a direct causative factor in the strict sense, the current study used an experimental provocation of a disease process and took into account a variety of potential confounders (e.g., sociodemographics, body mass, and pre-challenge immunity) and mediators (e.g. psychosocial and behavioral factors). Thus, this is an important step forward from testing prediction models of SRH to examining causal mechanisms of SRH.

Prior SRH studies have primarily focused on older adults, and Cohen et al. expanded this knowledge base to younger adults by examining their susceptibility to upper respiratory infections, which have a huge economic impact in this active and productive population.

Non-influenza-related viral respiratory tract infection is estimated to cost $40 billion annually in the US due to medical costs and productivity loss, which is an economic burden comparable to or higher than many significant chronic conditions such as hypertension, chronic obstructive pulmonary disease, congestive heart failure, asthma, and migraine (11).

A limitation inherent to any research of SRH, including the study by Cohen et al., is that this approach relies on the use a self-reported subjective variable, without random assignment, hence subject to confounding. Additionally, as the authors noted, the study sample consisted of healthy younger adults, while the target population of most prior SRH studies has been older adults. This healthy state of the study sample was evident in the fact that no subject rated their health as poor and only 2% rated their health as fair, which indicates a restriction of range and limits the generalizability of the findings to those with poor health status, including older and younger adults.

Interestingly, the current study shows a lack of association between SRH and infection as measured by increases in virus-specific serum neutralizing antibodies; therefore a lack of association between SRH and adaptive immunity. What SRH robustly predicted was the illness expression of cold, which is generally attributed to increased local inflammation (12), for example as indexed by interleukin (IL)-1 (13) and IL-6 (14). Therefore, this pattern of results indicates an association between SRH and innate immunity. Furthermore, SRH has been found associated with increased systemic inflammation in observational studies (4-7). The ensuing question is then whether SRH is an indicator of a heightened systemic inflammatory state and thus leads to increased local inflammatory responses after an exposure to a cold virus. While the authors conclude “poorer SRH is associated with poorer immunocompetence, possibly reflecting sensitivity to sensations associated with premorbid immune dysfunction”, further research on the inter-relationships among SRH, systemic inflammation, viral exposure, and local inflammatory responses could lead to a more specific statement as follows: “SRH possibly reflects sensitivity to sensations associated with premorbid systemic inflammation”. Indeed, pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF)-α can activate the central nervous system to produce a broad array of ‘sickness behaviors’, which refer to the coordinated set of behavioral changes that develop in sick individuals during the course of an infection, including malaise, lassitude, fatigue, reduced appetite, anhedonia, dysphoria, social withdrawal, reduced reward-seeking motivation, and changes in sleep patterns (15). Sickness behaviors induced either by acute systemic inflammation or more commonly by chronic low-grade inflammation could be perceived and translated by the affected individuals as a subjective sensation of ill health, hence leading to the repeatedly shown association between SRH and increased systemic inflammation (4-7). In such a heightened inflammatory state, an exposure to a cold virus would lead to an amplified systemic and local inflammatory responses and therefore to exaggerated systemic and local symptoms of cold.

Another interesting observation is that less favorable SRH categories were characterized by higher body-mass index (BMI) and more negative socio-emotional factors (e.g., increases in perceived stress and decreases in social integration). High BMI, perceived stress, and social isolation have all been consistently associated with increased systemic inflammation

(16-18). Although no data on inflammation per se were available in this study, these findings suggest SRH might be related to systemic inflammation in this sample as well.

Although the current study by Cohen and colleagues did not detect any differences of adaptive immune responses according to SRH among healthy young adults, a future study of SRH and cold induction in older adults and those with inflammation-related diseases might reveal a somewhat different picture. As has been described by the perspective of 'inflammaging', the immune system in older adults is characterized not only by a hyperactive innate immune system with chronically increased systemic inflammation but also by a declining adaptive immunity. Thus, poor SRH might predict not only the illness expression of colds but also the infection itself in older adults, respectively influenced by altered innate and adaptive immunity. Future research should therefore replicate the current findings by Cohen et al. in high-risk groups such as older adults, with attention paid to both innate and adaptive immune responses. In addition to this mechanistic investigation, future research might also address translational applicability of the current findings. The following research questions may be worth investigating: whether SRH serves as a simple cost-effective screening tool for susceptibility to infectious or inflammatory disorders; and whether interventions that target immune/inflammatory mechanisms prevent development of disease processes and ultimately mortality in the risk groups identified by SRH.

References

1. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav. 1997:21–37. [PubMed: 9097506]
2. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality prediction with a single general self-rated health question. J Gen Intern Med. 2006; 21:267–75. [PubMed: 16336622]
3. Ganna A, Ingelsson E. 5 year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study. The Lancet. 2015; 386:533–40.
4. Leshem-Rubinow E, Shenhar-Tsarfaty S, Milwidsky A, Toker S, Shapira I, Berliner S, Benyamini Y, Melamed S, Rogowski O. Self-rated health is associated with elevated C-reactive protein even among apparently healthy individuals. Isr Med Assoc J. 2015; 17:213–8. [PubMed: 26040045]
5. Christian LM, Glaser R, Porter K, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK. Poorer self-rated health is associated with elevated inflammatory markers among older adults. Psychoneuroendocrinology. 2011; 36:1495–504. [PubMed: 21601365]
6. Tanno K, Ohsawa M, Onoda T, Itai K, Sakata K, Tanaka F, Makita S, Nakamura M, Omama S, Ogasawara K, Ogawa A, Ishibashi Y, Kuribayashi T, Koyama T, Okayama A. Poor self-rated health is significantly associated with elevated C-reactive protein levels in women, but not in men, in the Japanese general population. J Psychosom Res. 2012; 73:225–31. [PubMed: 22850264]
7. Shanahan L, Bauldry S, Freeman J, Bondy CL. Self-rated health and C-reactive protein in young adults. Brain Behav Immun. 2014; 36:139–46. [PubMed: 24513874]
8. Hsu B, Cumming RG, Blyth FM, Naganathan V, Le Couteur DG, Seibel MJ, Waite LM, Handelsman DJ. Longitudinal and cross-sectional relationships of circulating reproductive hormone levels to self-rated health and health-related quality of life in community-dwelling older men. J Clin Endocrinol Metab. 2014; 99:1638–47. [PubMed: 24552220]
9. Rafiq R, Swart KM, van Schoor NM, Deeg DJ, Lips P, de Jongh RT. Associations of serum 25-hydroxyvitamin D concentrations with quality of life and self-rated health in an older population. J Clin Endocrinol Metab. 2014; 99:3136–43. [PubMed: 24885628]
10. Cohen S, Janicki-Deverts D, Doyle WJ. Self-Rated Health in Healthy Adults and Susceptibility to the Common Cold. Psychosom Med. 2015

11. Fendrick A, Monto AS, Nightengale B, Sarnes M. The economic burden of non–influenza-related viral respiratory tract infection in the united states. Arch Intern Med. 2003; 163:487–94. [PubMed: 12588210]
12. Heikkinen T, Järvinen A. The common cold. The Lancet. 2003; 361:51–9.
13. Proud D, Gwaltney JM, Hendley JO, Dinarello CA, Gillis S, Schleimer RP. Increased levels of interleukin-1 are detected in nasal secretions of volunteers during experimental rhinovirus colds. J Infect Dis. 1994; 169:1007–13. [PubMed: 8169385]
14. Zhu Z, Tang W, Ray A, Wu Y, Einarsson O, Landry ML, Gwaltney J Jr, Elias JA. Rhinovirus stimulation of interleukin-6 in vivo and in vitro. Evidence for nuclear factor kappa B-dependent transcriptional activation. J Clin Invest. 1996; 97:421. [PubMed: 8567963]
15. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol. 2011; 11:625–32. [PubMed: 21818124]
16. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999; 282:2131–5. [PubMed: 10591334]
17. Black PH. Stress and the inflammatory response: A review of neurogenic inflammation. Brain Behav Immun. 2002; 16:622–53. [PubMed: 12480495]
18. Heffner KL, Waring ME, Roberts MB, Eaton CB, Gramling R. Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. Soc Sci Med. 2011; 72:1482–8. [PubMed: 21492978]