ORIGINAL ARTICLE

Mild Depressive Symptoms Are Associated With Amplified and Prolonged Inflammatory Responses After Influenza Virus Vaccination in Older Adults

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Background: Depression is associated with enhanced production of proinflammatory cytokines that influence a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes mellitus, certain cancers, periodontal disease, frailty, and functional decline. In this prospective community study, we assessed the relationship between depressive symptoms and changes in inflammatory response after an influenza virus vaccination.

Methods: To study the dynamics of interleukin (IL) 6 levels in plasma in response to an immunological challenge, we obtained blood samples in 119 older adults (mean age, 71.21 ± 8.68 years [SD]) immediately before an annual influenza vaccination and again 2 weeks later. The short form of the Beck Depression Inventory, completed at these same times, provided information on depressive symptoms.

Results: The number of depressive symptoms in this sample was low on average before vaccination (mean ± SD number of symptoms, 3.07 ± 3.09) and did not change significantly after vaccination. Participants with more depressive symptoms had higher levels of IL-6 before and after vaccination than did those who reported fewer symptoms; moreover, individuals reporting more depressive symptoms also showed an increase in plasma IL-6 levels 2 weeks later, while there was little change in IL-6 levels among those reporting few or no symptoms.

Conclusions: Even a modest number of depressive symptoms may sensitize the inflammatory response system in older adults and produce amplified and prolonged inflammatory responses after infection and other immunological challenges. Sustained and/or amplified inflammatory responses could accelerate a range of age-related diseases.

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BOTH MAJOR depression and subthreshold depressive symptoms are associated with a spectrum of health risks.[1-4] Depression can affect health through alterations in the functioning of the central nervous, immune, endocrine, and cardiovascular systems, as well as through adverse influences on health behaviors.[5-7] In this article, we focus on a central immunological mechanism that serves as a gateway for a variety of age-associated diseases—the dysregulation of proinflammatory cytokine production, particularly interleukin (IL) 6.[8]

The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma. Inflammation is an important and constructive consequence of infection and injury; proinflammatory cytokines including IL-1, IL-6, and tumor necrosis factor attract immune cells to the site of infection or injury and prime them to become activated to respond. Anti-inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13 dampen this immune response by decreasing cell function and synthesis of other cytokines. Broadly speaking, cytokines provide intercellular signals that help to regulate the immune system's response to injury and infection.

Although the mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage, chronic or recurring infections can provoke pathologic changes.[9] For example, low levels of persistent inflammation may result when chronic infectious processes such as periodontal disease, urinary tract infections, chronic pulmonary disease, and chronic renal disease persistently stimulate the immune system. Persistent stimulation of proinflammatory cytokine production has the greatest effect among older adults who already show age-related increases in IL-6 production.[10]

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Inflammation has been linked to a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes mellitus, certain lymphoproliferative diseases or cancers, Alzheimer disease, and periodontal disease.[8] The association between cardiovascular disease and IL-6 levels is related in part to the central role that this cytokine plays in promoting the production of C-reactive protein, an important risk factor for myocardial infarction[11]; high concentrations of C-reactive protein indicated the risk of future cardiovascular disease in apparently healthy men.[12]

In addition to its tie to cardiovascular disease, chronic inflammation has been suggested as a key biological mechanism that may fuel declines in physical function leading to frailty, disability, and death.[9,13] For example, elevated plasma IL-6 levels indicated future disability in older adults, a finding that may reflect the effects of the cytokine on muscle atrophy and/or the pathophysiologic role played by the cytokine in particular diseases.[14]

Heightened proinflammatory cytokines are a well-documented correlate of syndromic depressive disorders.[7,15-18] In addition, anxiety and depressive symptoms appear to have consequences for proinflammatory cytokine production.[17,19,20] These data suggest a key mechanism whereby syndromic depression and subthreshold depressive symptoms may serve as a key gateway to a broad array of health problems.

Cross-sensitization between cytokines and stressors has been well documented in rodents.[21,22] For example, exposure to a novel environment, foot or tail shock, or even exposure to conditioned stimuli that were present during foot shock all enhanced IL-6 production.[21,23] Furthermore, rats that had previously been stressed produced larger and more rapid proinflammatory cytokine responses to a bacterial endotoxin than did rats without prior stress exposure.[21]

With these issues in mind, we investigated changes in plasma IL-6 levels in response to a standard annual influenza virus vaccination. We hypothesized that more depressive symptoms would be associated with higher levels of IL-6, as well as with an amplified and prolonged inflammatory response after vaccination.

METHODS

SUBJECTS

The subjects were part of a larger longitudinal project on stress and health in older adults.[24,25] Subjects were recruited via notices placed in community, hospital, and university newspapers; senior citizen centers; and the newsletter for the Alzheimer Disease Association. The 119 participants included 23 spouses who were currently providing care for a spouse with Alzheimer disease or another progressive dementia, 24 former caregivers whose spouse had died (mean ± SD time since death, 25.03 ± 16.92 months), and 72 noncaregivers who were demographically indistinguishable from caregivers but had no similar responsibilities; current caregivers, former caregivers, and control subjects did not differ in age ($F_{2,116}=0.45$, $P=.64$), level of education ($F_{2,116}=1.62$, $P=.20$), distribution of men and women, ($\chi^2_2=0.65$, $P=.72$), or ethnic distribution ($\chi^2_2=2.01$, $P=.37$). Subjects with immunologically related health problems such as cancer or recent surgical procedures were excluded during recruitment, as were subjects with any medications with broad immunological consequences that might have been related to vaccine responses.

For this study, we included all individuals in the cohort who had provided 2 blood samples; the first was drawn just before an annual influenza vaccination in the fall, while the second sample was obtained 10 to 14 days later. The 43 men and 76 women in this sample ranged in age from 48 to 89 years (mean age ± SD, 71.21 ± 8.68 years), the median education was partial college, 100 were married, 6 were divorced, 12 were widowed, and 1 was never married. The Ohio State University Biomedical Research Review Committee approved the project; all subjects gave written informed consent before participation.

ASSESSMENT OF DEPRESSIVE SYMPTOMS AND HEALTH-RELATED BEHAVIORS

The Beck Depression Inventory–Short Form (BDI-SF) provided information on the severity of depressive symptoms.[26] The 13 items on the BDI-SF cover affective, cognitive, and vegetative depressive symptoms. Subjects rated the severity of each symptom from 0 to 3. Other authors have provided an empirically derived cutoff score of 5 to differentiate depressed from nondepressed older adults.[27]

We collected health-related data to assess the possibility that relationships between depressive symptoms and IL-6 levels might simply reflect the contribution of other variables. Assessment of health-related behaviors included recent medication use, hours of sleep in the last 24 hours and the last 3 days, and recent alcohol intake.[28] Two questions were used to assess exercise.[29] Plasma albumin levels and body mass data provided information on the nutritional status of subjects. Health questions from the Older Adults Resources Survey[30] were used to assess problems with the lungs, kidneys, liver, digestive system, heart, thyroid, teeth, and circulatory system, as well as high blood pressure; migraines; type 2 diabetes mellitus; hormonal conditions; cancer; cataracts; hernia; gout; hardening of the arteries; prostate, ovarian, and uterine disorders; and muscle-related disorders. Authors of several studies found excellent agreement between self-reports and hospital or physician records for specific conditions of interest to us, including heart attack, stroke, and type 2 diabetes mellitus.[31,32]

IMMUNOLOGICAL ASSAYS AND VACCINE

Levels of IL-6 were assayed by using a Quantikine High Sensitivity Immunoassay Kit (R&D Systems Inc, Minneapolis, Minn) according to kit instructions. Samples were run undiluted in duplicate. Samples that were out of range of the standard curve were retested after being diluted 1:10 with buffer included with the kit. Plates were read at a wavelength of 490 nm, with a correction wavelength of 690 nm, by using a Labsystems Multiscan MCC/340 plate reader (Labsystems, Helsinki, Finland). Sample concentrations were extrapolated from a standard curve calculated by using a 4-parameter logistic fit and multiplied by the dilution factor if necessary.

Fluzone vaccine was provided for this study (Connaught Laboratories Inc, Swiftwater, Pa). The vaccine contained zonally purified whole viruses inactivated with formaldehyde. The trivalent Fluzone vaccine was standardized to contain 45 µg of hemagglutinin per 0.5-mL dose (15 µg of hemagglutinin per virus strain). Antibody titers were determined as described previously.[25]

STATISTICAL METHODS

To test our primary hypotheses, we used a repeated-measures regression model (repeated-measures generalized linear model;

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SPSS 11.0 for Windows, SPSS Inc, Chicago, Ill). This procedure generalizes the standard multiple regression model to incorporate repeated measures of dependent variables.[33,34] For analysis of immune measures, the dependent measures of IL-6 levels were repeated across time (baseline and 2 weeks after vaccination). Sex was an independent variable, and BDI-SF score was a continuous independent variable. In addition to the repeated measures regressions, we used a Wilcoxon signed rank test to examine the distribution of IL-6 change from baseline. For these analyses, we computed simple change in IL-6 from baseline to 2 weeks after vaccination as dependent measures. We then compared the distribution of IL-6 change between subjects with a BDI-SF score of 2 or lower and those with a score of 3 or higher. All tests were 2-tailed; a .05 α level was used to indicate statistical significance. The IL-6 and influenza virus antibody data were subjected to logarithmic transformations with a base of 10 to normalize the distributions before analyses.

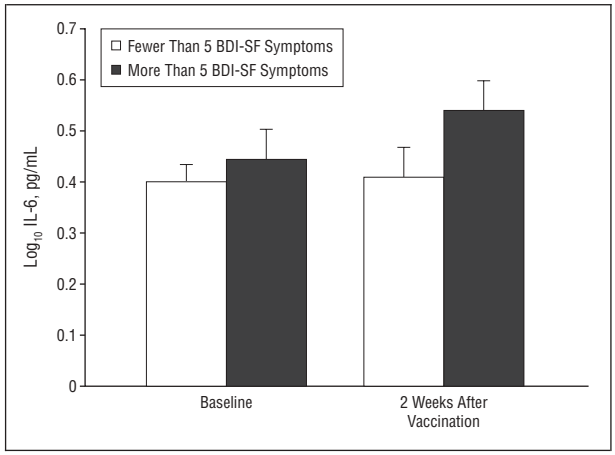
RESULTS

DEPRESSIVE SYMPTOMS AND CHANGES IN IL-6 LEVELS AFTER VACCINATION

A time × depressive symptoms interaction indicated that individuals who reported more depressive symptoms demonstrated an increase in plasma IL-6 levels 2 weeks after vaccination ($F_{1,116}$=7.42, P=.007) (**Figure**). Additionally, depressive symptoms were associated with elevated levels of IL-6 ($F_{1,116}$=4.78, P=.03). The IL-6 levels did not change during the 2-week interval ($F_{1,116}$=1.32, P=.25), indicating no main effect for change across time when depressive symptoms were held constant.

As expected, the correlation between the 2 IL-6 samples was substantial (r=0.74, P < .001), and 52 (44%) of 119 of the sample either stayed the same or had lower values at follow-up. However, a simple examination of the uniformity of the direction of change provided another view of the data. Among the 61 subjects who had a BDI-SF score of 2 or lower, 28 (46%) had lower IL-6 levels at follow-up, while 33 (54%) had levels higher than they did before vaccination, producing a nonsignificant Wilcoxon signed rank test z score of –0.18 (P=.86). In contrast, among the 58 individuals who scored 3 or higher on the BDI-SF, 2 (3%) were the same both times, 22 (38%) had lower levels at follow-up, and most 34 (59%) showed increased IL-6 production 2 weeks after vaccination (z=–2.37, P=.02). Thus, IL-6 changes related to depressive symptoms did not simply reflect changes in only a few outlying values. Throughout our data, we found no significant sex differences. Although sex was included as a variable in the first round of analyses, sex differences will not be reported.

We assessed the possibility that the persistent IL-6 response after vaccination associated with elevated depressive symptoms might be a function of differences in vaccine history or response. Depressive symptoms did not differ between the 77 subjects who had received an influenza virus vaccination in the past year and the 42 who had not ($F_{1,117}$=0.32, P=.57). Using the conventional 4-fold antibody increase as the standard for determining a significant response to viral vaccine,[35] we defined vaccine responders as those whose influenza virus antibody titers increased 4-fold or more to any 1 of the 3 individual vaccine components or to the total Fluzone vaccine when used as the antigen (ie, all 3 components combined). The 48 subjects who responded at 2 weeks did not differ in depressive symptoms, as compared with the 71 who did not respond ($F_{1,117}$=0.005, P=.94). Depressive symptoms were not associated with antibody titers to the vaccine ($F_{1,117}$=1.41, P=.24). After including the vaccine response in our primary analyses, the time × depressive symptoms interaction remained significant ($F_{1,115}$=7.73, P=.006). Thus, IL-6 changes associated with depressive symptoms did not appear to reflect vaccine history or response.



Participants were placed into nondepressed (open bars) and depressed groups (closed bars) on the basis of an empirically derived cutoff score of 5 symptoms on the Beck Depression Inventory–Short Form (BDI-SF)[27] to illustrate the relationship between depressive symptoms and interleukin (IL) 6 production at baseline and 2 weeks after vaccination (N=119). The time × depressive symptoms interaction indicated that individuals who reported more depressive symptoms demonstrated an increase in IL-6 level 2 weeks after vaccination ($F_{1,116}$=7.42, P=.007). Depressive symptoms were associated with elevated levels of IL-6 across baseline and after vaccination ($F_{1,116}$=4.78, P=.03). Log indicates logarithm, and error bars indicate SEM.

To assess the effect of the chronically stressed caregivers in the sample, in a further analysis we removed all caregivers, current and former; the removal of the latter also provided a correction for any effects associated with bereavement.[20,24,36] The time × depressive symptoms interaction was marginal after removal of these subjects ($F_{1,70}$=3.65, P=.06). These findings are not surprising, because depressive symptoms varied by group ($F_{2,116}$=6.06, P=.003). Pairwise comparisons indicated that current caregivers reported more depressive symptoms (mean ± SD number of symptoms, 5.00 ± 3.81) than did either control subjects (mean ± SD number of symptoms, 2.64 ± 2.63) or bereaved caregivers (mean ± SD number of symptoms, 2.50 ± 3.02). Higher levels of depressive symptoms in current caregivers were likely a key factor in their increased IL-6 levels after vaccination.

We also addressed changes in depressive symptoms across the 2 times and their relationship to baseline levels of IL-6. The number of depressive symptoms in this sample was low on average before vaccination (mean ± SD number of symptoms, 3.07 ± 3.09). Depressive symptoms showed no significant change from baseline to 2 weeks after vaccination ($F_{1,116}$=0.18, P=.67), and

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depressive symptoms across time were not related to baseline levels of IL-6 ($F_{1,116}$=0.98, P=.32).

DEPRESSIVE SYMPTOMS, IL-6 LEVELS, SOCIODEMOGRAPHIC DATA, AND HEALTH BEHAVIORS

Additional analyses were used to examine the possibility that the relationships between IL-6 levels and depressive symptoms might be a function of differences in sociodemographic variables, health behaviors, chronic health problems, or medication use. Depressive symptoms were not significantly related to sociodemographic data, including sex, age, ethnicity, or level of education (for all, $P>.07$). Baseline IL-6 levels were not significantly related to sociodemographic data, including sex, age, or level of education (for all, $P>.17$). Neither IL-6 levels across time nor changes in IL-6 levels were related to sex, as already mentioned. The IL-6 level was not significantly related to age (r=0.15, P=.11). Although nonwhite participants (n=3) had higher levels of IL-6, as compared with white participants (n=116, $F_{1,117}$=28.03, P=.03), change in IL-6 level was not significantly related to ethnicity; the small nonwhite group is clearly a limiting factor in this analysis. However, change in IL-6 level from baseline to 2 weeks after vaccination was related to education; individuals who had less education demonstrated greater increases in IL-6 level ($F_{4,113}$=2.89, P=.03), which is consistent with the ample literature on risks associated with lower socioeconomic status and health.

Depressive symptoms were not significantly related to key health behavior data, including alcohol use, smoking, weight, body mass index, caffeine intake, exercise, or serum albumin level (for all, $P>.13$). Plasma IL-6 levels were not significantly related to smoking, body mass index, caffeine intake, exercise, or serum albumin (for all, $P>.08$). Overall, higher levels of IL-6 were marginally related to higher weight (r=0.17, P=.06) and greater body mass index (r=0.17, P=.08) and significantly related to greater alcohol use (r=0.22, P=.02).

Depression and sleep difficulties are frequently associated, so it was not surprising that participants who reported less than adequate sleep during the past 3 days reported elevated depressive symptoms (N=18; mean±SD number of symptoms, 5.78±4.43), as compared with participants who reported adequate sleep (N=101; mean±SD number of symptoms, 2.58±2.53; $F_{1,117}$=18.72; $P<.001$). In analyses controlling for sleep adequacy, the time×depressive symptoms interaction remained significant ($F_{1,116}$=8.02, P=.005), and the main effect for depressive symptoms on IL-6 levels remained significant ($F_{1,116}$=4.26, P=.04), which suggests that sleep was not the primary factor. Moreover, IL-6 levels and change in IL-6 levels from baseline to 2 weeks after vaccination were not related to sleep adequacy (for all, $F<1.00$).

Finally, we included an analysis that controlled for all variables that were significantly related to IL-6 level or change in IL-6 level (ie, caregiver status, ethnicity, education, weight, and alcohol use). Even with these controls included, the time×depressive symptoms interaction remained significant ($F_{1,112}$=5.86, P=.02), and depressive symptoms were significantly related to IL-6 levels across time ($F_{1,112}$=6.94, P=.01). Although some health behaviors were related to IL-6 level, the key interaction was still significant when health behaviors were considered concurrently.

Prevalence of current chronic health problems was significantly associated with depressive symptoms ($F_{1,115}$=19.54, $P<.001$) and sex ($F_{1,115}$=9.72, P=.002), and a significant sex×depressive symptoms interaction indicated that depression was significantly related to prevalence of current chronic health problems for men (β=0.47) but not for women (β=0.11). However, examination of the data revealed 1 outlying value on current problems, with a number of chronic health problems greater than 4 SD from the mean. When this individual was removed, the sex×depressive symptoms interaction was not significant ($F_{1,114}$=0.18, P=.68). Women reported more current chronic health problems (mean±SD number of problems reported, 2.2±2.09) than did men (mean±SD number of problems reported, 1.26±1.45), but this finding was not significant ($F_{1,114}$=3.51, P=.06). A greater number of depressive symptoms was not significantly related to greater reporting of current chronic health problems ($F_{1,114}$=3.31, P=.07). Similar relationships were observed for past chronic health problems (data not shown).

The most common medications taken by subjects were analgesics (30 subjects), diuretics (29 subjects), cardiac medication (25 subjects), estrogen supplements (18 subjects), and β-blockers (17 subjects). To investigate the possibility that health problems were responsible for depressive symptoms and might be fueling changes in IL-6 levels as well, we compared depressive symptoms and IL-6 levels from baseline to 2 weeks between the 23 subjects who reported using no medications and the 96 subjects taking medications. Depressive symptoms, overall IL-6 levels, and IL-6 level change from baseline to 2 weeks were not related to medication status (for all, $F<1.00$).

Participants taking cardiac medication did not significantly differ in IL-6 level change from baseline to 2 weeks ($F<1.00$), but they showed elevated IL-6 levels across both times, as compared with participants not taking cardiac medication ($F_{1,117}$=10.48, P=.002). Participants taking β-blockers did not significantly differ in IL-6 level change from baseline to 2 weeks ($F<1.00$), but they showed elevated IL-6 levels across both times, as compared with participants not taking β-blockers ($F_{1,117}$=5.89, P=.02). Analyses that accounted for both these medications still showed a significant time×depressive symptoms interaction ($F_{1,115}$=7.25, P=.008). Thus, even after accounting for use of β-blockers and cardiac medication, increased depressive symptoms were related to increased IL-6 levels from baseline to 2 weeks. Although depressive symptoms were no longer related to IL-6 levels averaged across both times ($F_{1,115}$=1.96, P=.16), the key time×depressive symptoms interaction was significant even after removing participants taking any β-blockers or cardiac medications ($F_{1,80}$=4.10, P=.05). Although the number of analyses we conducted to evaluate other health-related variables substantially inflated the possibility of finding significance where null findings were desirable, we found no evidence that the significant

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time × depressive symptoms interaction for IL-6 was simply a function of chronic health problems, medications, or health habits.

COMMENT

Participants with more depressive symptoms had higher levels of IL-6 before and after vaccination than did those who reported fewer symptoms; moreover, individuals reporting more depressive symptoms also showed enhancement of IL-6 levels 2 weeks later, while there was little change in plasma IL-6 levels among those reporting few or no symptoms. These findings are particularly noteworthy because the number of depressive symptoms was low in this sample before vaccination and did not change significantly after vaccination.

The absence of an overall increase in IL-6 levels from baseline to 2 weeks after vaccination is consistent with what one would expect from a memory immune response; most of these subjects were older individuals seropositive for influenza virus. These data are in accord with results of previous studies that did not show a proinflammatory (IL-6) response 1 month after influenza vaccination.[37,38] We propose that depressive symptoms are associated with dysregulation of the normal cytokine response to the vaccine.

In data from Lutgendorf et al,[20] caregivers for family members with dementia had more depressive symptoms than did noncaregivers, and they also had higher levels of IL-6. A growing body of evidence has demonstrated that caregiving can dysregulate many aspects of the immune response.[39-43] For example, caregivers took 24% longer to heal small standardized wounds than did noncaregivers (48.7 ± 2.9 days vs 39.3 ± 3.0 days).[39] Moreover, caregivers for family members with dementia exhibited statistically significant deficits relative to well-matched noncaregivers in their immune responses to both influenza virus and pneumococcal pneumonia vaccines.[25,40,44] Vaccine responses provide a good proxy for novel exposure to antigens or pathogens: Adults who show poorer immune responses to vaccines also experience higher rates of clinical illness and infectious episodes that last longer.[45]

Increased susceptibility to infectious disease and poorer recovery from infection are substantial and important problems; however, they have additional risks. Repeated, chronic, or slow-resolving infections or wounds enhance secretion of proinflammatory cytokines, a process that can further inhibit certain aspects of immune responses (eg, production of IL-2, a cytokine important in protection against infection).[46] Depressive symptoms can directly affect the cells of the immune system and modulate the secretion of proinflammatory cytokines; in addition, depression may contribute to prolonged or chronic infections or delayed wound healing, processes that indirectly fuel proinflammatory cytokine production.[47]

As described earlier, cross-sensitization between cytokines and stressors has been well-documented in rodents[21,22]; in the animal model, both stress and administration of epinephrine elevated plasma IL-6 levels, which is consistent with evidence that IL-6 production is stimulated through β-adrenergic receptors, among other pathways.[11] Thus, production of IL-6 and other proinflammatory cytokines can be directly stimulated by negative emotions and stressful experiences, which is consistent with the conceptualization of major depression as a dysfunction in the stress response.[48] Results of animal studies also provide evidence that prior stress produces exaggerated proinflammatory cytokine responses to infection.[21] Similarly, evidence from human studies suggests that syndromic depression may sensitize the inflammatory response system. For example, among women who had just given birth, those who had a lifetime history of major depression showed greater increases in both plasma IL-6 and soluble IL-6 receptor levels after delivery than did women without a similar history of depression.[49] Data from the current study extend these previous observations in important ways; they suggest that even relatively modest levels of depressive symptoms may enhance and prolong alterations in the inflammatory response system when activated by modest infectious challenges.

Higher plasma IL-6 levels are associated with adverse health habits. Levels are higher in smokers than nonsmokers, in individuals who report less physical activity, in those whose sleep is impaired, and in those with a higher body mass index.[13,14,17,50] In our data, after accounting for demographic and health behavior variables, the links between depressive symptoms and IL-6 levels were still significant. Thus, health behaviors, although important, are not sufficient to explain the relationships.

We have argued that depressive symptoms prompt immune dysregulation, and these processes may lead to subsequent maladaptive immune and endocrine changes.[11,23,51-54] Production of IL-6 and other proinflammatory cytokines can be directly stimulated by depressive symptoms and stressors providing 1 direct link to chronic stress and health risk. In addition, depression and stress may contribute to prolonged infection or delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Research that addresses this dysregulation of the immune and endocrine systems associated with depression could substantially enhance our understanding of psychological influences on health, particularly among the elderly.[55]

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