

Plasma Interleukin-6 and Soluble IL-6 Receptors Are Associated With Psychological Well-Being in Aging Women

Elliot M. Friedman, Mary Hayney, and Gayle D. Love
University of Wisconsin—Madison

Burton H. Singer
Princeton University

Carol D. Ryff
University of Wisconsin—Madison

Objective: This study tested the hypothesis that psychological well-being would predict lower plasma levels of inflammatory factors in aging women. **Design:** One hundred thirty-five women ages 61–91 years ($M = 74.5$ years) participated in this study. After completing self-administered questionnaires in their homes, participants stayed overnight at the General Clinical Research Center (GCRC) at the University of Wisconsin—Madison. Blood samples for cytokine analyses were obtained in participants' homes after the GCRC visit. **Main Outcome Measures:** Psychological well-being and ill-being, history of health problems, and health behaviors were assessed via self-administered questionnaires. Detailed medical history and concurrent health measures were obtained during the GCRC stay. Enzyme-linked immunosorbent assays were used to determine interleukin-6 (IL-6) and soluble IL-6 receptor (sIL-6R) concentrations in plasma. **Results and Conclusion:** Regression analyses showed that plasma IL-6 levels were lower in women scoring higher on positive relationships, whereas sIL-6R levels were lower in women scoring higher on purpose in life, even after a variety of sociodemographic and health factors were controlled. These outcomes, combined with the absence of significant links with other measures of well-being and ill-being, suggest selective patterns of association between later life inflammatory processes and psychological factors, particularly those focused on positive ties with others and purposeful engagement.

Keywords: interleukin-6, social relationships, aging, women, well-being

Interleukin-6 (IL-6) is one of a family of inflammatory factors that are implicated in age-related disorders such as Alzheimer's disease, osteoporosis, rheumatoid arthritis, cardiovascular disease, and some forms of cancer (Ershler & Keller, 2000; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998; Volpato et al., 2001). Because IL-6 concentrations in peripheral blood also increase with age (Ershler, 1993), this cytokine has become a central focus of research into age-related inflammatory diseases. Regulation of IL-6 is sensitive to a range of psychological influences. Clinical depression and depressed mood in older participants are associated with elevated plasma levels of IL-6 (Dentino et al., 1999; Penninx

et al., 2003), as is the chronic stress of caring for a spouse with Alzheimer's disease (Kiecolt-Glaser et al., 2003), which suggests that negative psychological experiences may constitute a risk factor for elevated circulating levels of IL-6 in individuals already at risk because of advancing age. The aim of the present study is to test the hypothesis that the reverse might also be true: Positive psychological influences, operationalized with multiple indicators of well-being, may be associated with lower levels of IL-6 in otherwise healthy aging individuals.

As Keyes (2002) and others have argued, mental health and mental illness are best characterized as separate but related continua of psychological functioning. It is significant that mental health comprises the presence of well-being, not just the absence of mental distress or illness. Although the lion's share of attention has been given to the latter, increasing attention is now being given to the former (Keyes, 2002). From this perspective, evidence that IL-6 levels in the blood vary in relation to negative affective states and mental illness does not necessarily mean that IL-6 also varies with gradations of well-being and positive affective states, although some activities linked to positive psychological functioning, such as attending religious services regularly, have been associated with lower plasma levels of IL-6 (Lutgendorf et al., 2004). Moreover, well-being has been shown to be associated with lower levels of other disease-related biomarkers (Ryff, Singer, & Love, 2004) and other inflammatory factors, such as fibrinogen (Steptoe, Wardle, & Marmot, 2005). Given these previous studies,

Elliot M. Friedman, Department of Population Health Sciences, University of Wisconsin—Madison Madison, WI; Mary Hayney, School of Pharmacy, University of Wisconsin—Madison; Gayle D. Love and Carol D. Ryff, Institute on Aging, University of Wisconsin—Madison; Burton H. Singer, Office of Population Research, Princeton University.

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Correspondence concerning this article should be addressed to Elliot M. Friedman, Department of Population Health Sciences, 624 WARF Office Building, 610 North Walnut Street, University of Wisconsin—Madison, Madison, WI 53726-2397. Email: friedman1@wisc.edu

we hypothesized that higher levels of well-being would be associated with lower plasma levels of IL-6 in our sample.

We distinguish between two types of well-being, hedonic and eudaimonic, in accordance with contemporary theories about the nature of human happiness and life satisfaction (Ryan & Deci, 2001; Waterman, 1993). Hedonic well-being is associated with the pursuit of pleasure, including attainment of important life goals, contentment, and the avoidance of physical and psychic discomfort, and it is typically assessed with measures of the frequency and intensity of positive mood (Diener, 2000; Ryan & Deci, 2001). In contrast, eudaimonic well-being stems from the Aristotelian ideal of the pursuit of personal excellence rather than happiness or pleasure (Ryan & Deci, 2001; Waterman, 1993), and in the present study it was measured with Ryff and Keyes's (1995) six Scales of Psychological Well-Being (PWB).

Both hedonic and eudaimonic well-being have been linked to some health outcomes. Positive affect, for example, is associated with reduced stroke incidence (Ostir, Markides, Peek, & Goodwin, 2001; Ostir, Raji, Ottenbacher, Markides, & Goodwin, 2003), overall functional independence (Ostir, Markides, Black, & Goodwin, 2000), and lower stress-induced increases in fibrinogen (Step-toe et al., 2005). In a study of Swedish white-collar workers, higher levels of eudaimonic well-being were associated with lower levels of cortisol and fewer musculoskeletal symptoms but were unrelated to blood pressure or cardiovascular measures (Lindfors, 2002). Using the same participants as in the present study, Ryff et al. (2004) found that specific eudaimonic well-being measures were positively associated with high-density lipoprotein (HDL) cholesterol and sleep efficiency and negatively associated with diurnal salivary cortisol slope, body weight, waist-hip ratio, glycosylated hemoglobin, total cholesterol, and plasma levels of soluble IL-6 receptors (Ryff et al., 2004). Although there is some conceptual and statistical overlap in indexes of hedonic and eudaimonic well-being, important distinctions between them have been empirically demonstrated (Keyes, Shmotkin, & Ryff, 2002; Ryan & Deci, 2001; Ryff & Keyes, 1995; Waterman, 1993). In the present study, we contrasted the relations of each of these types of well-being to a specific biomarker of age-related disease, and we hypothesized that greater hedonic and eudaimonic well-being would be associated with lower levels of IL-6.

In addition to plasma IL-6, we measured plasma levels of soluble IL-6 receptors (sIL-6R). Unlike other soluble cytokine receptors, such as those for IL-2 or TNF- α , that serve to inhibit the actions of the related cytokines (Arend, Malyak, Bigler, Smith, & Janson, 1991), the sIL-6R amplifies the inflammatory actions of IL-6 by forming a complex with IL-6 that prolongs the biological activity of IL-6 and allows it to act on cells that are not normally responsive to IL-6 (Jones, Horiuchi, Topley, Yamamoto, & Fuller, 2001). For this reason, sIL-6R is also considered a proinflammatory factor (Jones et al., 2001). Like IL-6, levels of sIL-6R found in the peripheral blood are increased in response to strongly negative psychological experience, such as posttraumatic stress disorder (Sutherland, Alexander, & Hutchison, 2003). Plasma levels of sIL-6R were expected to be negatively related to well-being.

Finally, we also included measures of different aspects of ill-being, including depressive affect, anxiety, and anger, predicting that higher levels of ill-being would be associated with higher plasma levels of both IL-6 and sIL-6R. Because IL-6 levels have been linked to depression in particular (Dentino et al., 1999;

Penninx et al., 2003), an additional set of analyses included depressive affect as a control variable in analyses of the relation between well-being and IL-6. In this way, we tested the extent to which well-being and ill-being have distinct relations to later life inflammatory processes.

Method

Participants

Respondents came from a prior longitudinal study of aging women ($N = 301$) undergoing community relocation. About 5 years after the original study, additional research support allowed for a fifth wave of data collection that included psychosocial assessments and a comprehensive array of biomarkers on approximately half of the original sample ($N = 135$). Among those who did not participate, 16% were no longer eligible (because of death, severe morbidity, or relocation from the area), and another 42% declined to participate (for no stated reason or because of concerns about health and demands of the study). The newly recruited sample was not significantly different from the original sample with regard to health (chronic conditions, health symptoms), income, or marital status but was significantly younger, had more education, and had higher scores on four of six aspects of eudaimonic well-being (environmental mastery, personal growth, purpose in life, self-acceptance) compared with the original sample. No comparisons on hedonic well-being were available, as those scales were added to the study in Wave 5.

The participants in the present study ranged in age from 61 to 91 years ($M = 74.02$ years). Respondents had moderate incomes and slightly more than a high school education. Over half (55.6%) were widowed, with the rest married (17%), never married (8.9%), or divorced or separated (18.5%). One hundred thirty-five women completed self-administered questionnaires. Blood samples obtained for cytokine analyses were sufficient for IL-6 assays in 112 cases and for sIL-6R in 91 cases. Analyses showed that these subsamples did not differ significantly from the full sample of 135 women on any of the outcome measures, variables of interest, or covariates. For this reason, descriptive data for the full sample of 135 participants are shown in Table 1.

Well-Being and Ill-Being Measures

Self-administered questionnaires were sent to respondents 3–4 weeks prior to their visit to the University of Wisconsin—Madison campus for the biomarker assessments. These were completed independently and returned to investigators at the time of participants' campus visit. All alpha coefficients we present are based on responses from study participants.

Eudaimonic well-being. *Eudaimonic well-being* refers to active engagement with the existential challenges of living (see Keyes et al., 2002) and was operationalized with six PWB scales: Autonomy, Environmental Mastery, Personal Growth, Positive Relations With Others, Purpose in Life, and Self-Acceptance. These were based on Ryff's (1989) theoretical integration of numerous formulations of positive functioning. In this study, each well-being scale was measured with 14 self-descriptive items (scale range = 14–84). Internal consistency for the six scales ranged from .85 to .91. Previous publications have documented the

Table 1
Descriptive Statistics For Demographic, Health-Related, and Psychosocial Variables (N = 135)

Measure	<i>M</i>	%	<i>SD</i>	Range
Age (years)	74.02		7.08	61–91
Pretax family income (\$)	26,360		18,340	<8,000 to >100,000
Years of schooling	14.1		2.8	8–23
Married		17.0		
Widowed		55.6		
Weight (lbs.)	164.8		37.4	95–273
Waist–hip ratio	0.83		0.08	0.67–1.06
Hemoglobin A1C	5.6		1.2	0.0–13.0
Total/HDL cholesterol ratio	3.8		1.1	1.9–7.4
HDL cholesterol	56.9		14.4	24–99
Average systolic blood pressure	144.2		17.6	81–200
Average diastolic blood pressure	74.2		9.9	43–99
Urinary norepinephrine (μg/g creatinine)	40.6		85.1	9–1005
Urinary epinephrine (μg/g creatinine)	3.6		9.2	0.5–103.6
Urinary cortisol (μg/dL)	61.9		176.3	8.3–1684.2
Allergies or sinus problems		43.7		
Arthritis or rheumatism		54.8		
Asthma or wheezing		11.9		
Cancer or leukemia		19.3		
Diabetes		11.9		
Heart trouble or disease		28.9		
Hypertension		48.1		
Ever regularly drank three or more drinks per week		40.0		
Any alcoholic beverage in the past 3 months		67.4		
Ever smoked		40.0		
Currently smoke		1.5		
Taking anti-inflammatory medication		16.3		
IL-6 (pg/mL)	1.4 ^a		1.6	0.42–12.01
sIL-6R (pg/mL)	677.1		230.3	310.3–1594.0
Eudaimonic well-being (scale range 14–84)				
Positive Relations With Others	69.2		10.7	31–84
Personal Growth	69.7		9.0	36–84
Purpose in Life	66.4		10.6	21–84
Environmental Mastery	67.4		10.2	24–84
Self-Acceptance	65.4		11.6	15–84
Autonomy	63.6		10.1	36–84
MASQ (scale range 14–70)				
Depressive Symptoms	18.5		7.2	12–54
Anxious Symptoms	16.5		5.5	11–43
Loss of Interest	12.5		8.0	8–35
Anxious Arousal	23.1		6.7	17–65
Positive Affect	45.1		10.6	14–70
Spielberger Trait Anxiety (scale range 10–40)				
Anger	12.1		4.1	10–39

Note. Hemoglobin A1C = glycosylated hemoglobin; HDL = high-density lipoprotein; IL-6 = interleukin-6; sIL-6R = soluble IL-6 receptors; MASQ = Mood and Anxiety Symptom Questionnaire.

^a *Mdn* = 0.94.

reliability and validity of the scales (Ryff, 1989; Ryff & Keyes, 1995). Correlations among the scales averaged .52 (range = .38–.75). In spite of these intercorrelations, the hypothesized six-factor structure of well-being has been supported by confirmatory factor analyses on data from nationally representative samples in the United States (Brim, Ryff, & Kessler, 2004; Ryff & Keyes, 1995; Springer & Hauser, in press; Sweet, Bumpass, & Call, 1988) and Canada (Canadian Study of Health and Aging Working Group, 1994; Clarke, Marshall, Ryff, & Wheaton, 2001), as well as smaller samples in China (Cheng & Chan, 2005) and in the Netherlands (Van Dierendonck, 2004). Recent work has documented that eudaimonic well-being is empirically distinct from yet related to hedonic well-being (Keyes et al., 2002).

Hedonic well-being. Hedonic well-being was assessed with the Positive Affect scale of the short-form Mood and Anxiety Symptom Questionnaire (MASQ; Watson, Clark, et al., 1995). This scale includes 14 items that capture joy-in-living aspects of positive affect. The internal consistency of the MASQ Positive Affect subscale was .94.

Ill-being. Psychological ill-being was measured with the four depressive and anxiety symptom scales from the MASQ (Depressive Symptoms, Anxious Symptoms, Loss of Interest, and Anxious Arousal); these are based on *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000) symptom criteria for anxiety and depressive disorders. Internal consistencies for these scales range from .81 to .91, and the scales

correlate .85–.95 with other anxiety and depressive symptom scales, such as the Profile of Mood States and the Beck Depression Inventory (Watson, Weber, et al., 1995). Finally, anger and anxiety were measured with the trait form assessment developed by Spielberger (1983) and consisted of 10 items each. Alpha coefficients were .92 and .88, respectively, for anger and anxiety.

Health Measures

After completing the self-administered questionnaires, participants were admitted for an overnight stay to the General Clinical Research Center (GCRC) located within the University of Wisconsin Hospital and Clinics. A trained nurse or physician took the respondent's medical history and conducted a physical health examination. GCRC nursing staff obtained blood samples.

Specific self-reported items related to overall health, inflammatory conditions, immune-related diseases, and conditions with which IL-6 or sIL-6R have been linked were selected for preliminary correlational analyses. These included number of days sick in the foregoing 6 months; the degree to which illness inhibited daily activities; the number of nonroutine doctor visits in the preceding year; and medical history of allergies, asthma, diabetes, cancer or leukemia, hypertension, heart trouble or disease, or arthritis or rheumatism.

Specific items from the physical exam and laboratory tests were also selected for preliminary correlational analyses. As IL-6 has been linked to obesity and blood lipids (You, Yang, Lyles, Gong, & Nicklas, 2005), we measured weight, waist–hip ratio, HDL and total cholesterol, and glycosylated hemoglobin 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). Fasting blood samples for assays of HDL cholesterol, total cholesterol, and glycosylated hemoglobin were obtained prior to 7 a.m. during the participants' overnight stay at the GCRC.

Neuroendocrine and autonomic systems, which are known to influence IL-6 regulation, were assessed in a number of ways. Systolic and diastolic blood pressure were measured three times after 5 min of quiet sitting, and the average of the two most similar was calculated. As IL-6 and other inflammatory factors are associated with hypertension (Chae, Lee, Rifai, & Ridker, 2001), these blood pressure measures were also included in preliminary correlational analyses. Biomarkers linked to neuroendocrine function included overnight urinary cortisol, daily salivary cortisol, overnight urinary epinephrine and norepinephrine, and, from the fasting blood samples we have described, dehydroepiandrosterone sulfate. Urinary cortisol, epinephrine, and norepinephrine levels were adjusted for urine creatinine levels. Urinary free cortisol levels were measured via radioimmunoassay at the ARUP Laboratory (Salt Lake City, UT). Urinary epinephrine and norepinephrine levels were measured via liquid chromatography at the University of Wisconsin Hospital and Clinics Clinical Laboratory.

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 and sIL-6R levels, we created a variable to indicate the use of anti-inflammatory medications, 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 over 90% of participants, no variable was created to control for their impact on dependent measures.

Smoking and alcohol consumption were determined from the self-administered questionnaires. Only 2 participants were current smokers, whereas 54 (40%) had smoked at some time in their lives. For this reason, only smoking history was included in statistical analyses. Fifty-four participants (40%) reported consuming at least one drink 3 days a week at some time in their lives. This variable was also included in statistical analyses.

Cytokine Measures

Blood samples for cytokine and cytokine receptor analyses were obtained as part of a study of immune responses to influenza vaccinations, and the time between the GCRC visit and blood collection ranged from weeks to months. To ensure that any observed relations between psychosocial and immune markers could not be attributed to individual differences in time between phases of the study, we entered the time between GCRC visit and blood collection into all regression models as a control variable. Self-administered questionnaire data collection always preceded GCRC stays, which always preceded blood collection. Three samples were collected from each participant: before and 2 and 4 weeks after immunization. Preliminary analyses of these samples indicated no significant mean differences in IL-6 or sIL-6R levels, so the data from the three blood draws were combined and averaged to provide a more precise estimate of circulating levels of these inflammatory factors.

Blood samples were obtained from participants by standard phlebotomy techniques. All samples were obtained in participants' home. Plasma samples were stored at -80°C until analyzed. IL-6 and sIL-6R concentrations were measured in duplicate with enzyme-linked immunosorbent assay (Quantikine HS High Sensitivity human IL-6 and Quantikine human sIL-6R; R & D Systems, Minneapolis, MN), according to the manufacturer's directions. Because of low sample volumes in some cases, IL-6 and sIL-6R analyses were completed on 112 and 91 participants, respectively.

Any sample with an optical density greater than that correlating with the highest value on the standard curve was diluted and reassayed. Any sample with an optical density less than that correlating with the lowest value on the standard curve was assigned a value of 0.1 pg/ml (IL-6) or 1.0 pg/ml (sIL-6R). Inter- and intraassay coefficients of variation for all assays were less than 10%. Limits of detection were 0.1 pg/mL for the Quantikine HS IL-6 assay and 1.0 pg/mL for the Quantikine sIL-6R assay.

Statistical Analyses

Data analysis was conducted in three steps. First, frequency distributions for all measures (psychological and biological) were examined, trimmed for outliers (a winsorizing procedure was used to preserve data), and symmetrized (normalized) as needed. Transformations are noted in tables of reported results. Second, correlations were calculated between biomarkers and subjective and objective health measures. Two analyses were conducted, one for plasma IL-6 and the other for plasma sIL-6R. Using a per-

comparison error rate, we identified correlations that were significantly different from zero at levels of .05, .01, and .001.

Third, health items that were significantly related to immune measures in the bivariate analyses were then included in multivariate hierarchical regression analyses; separate analyses were conducted for the two dependent measures and for each measure of well-being or ill-being. Included as control variables in all analyses were age, years of education, average pretax household income, marital status, health status, health behavior, neuroendocrine measures, and anti-inflammatory medication use. It should be noted that because 75 (55%) participants were widows, two dichotomous variables were created for marital status: The first compared married and unmarried participants, and the second compared widows with others. Both of these dichotomous variables were entered into each regression equation.

Results

Table 1 shows the characteristics of the study sample. As we have noted, most of the women in the study were widowed, had some college education, and earned a modest income. Roughly half of the sample had problems with allergies, arthritis, or hypertension but were otherwise healthy. The participants also scored relatively high on measures of psychological well-being and low on measures of ill-being.

Table 2 shows the results of hierarchical regression analyses of measures predicting plasma IL-6. Bivariate analyses showed that waist-hip ratio, $r(111) = .30, p < .01$; HDL cholesterol, $r(111) = -.25, p < .01$; days sick in the past year, $r(111) = .19, p < .05$; health problems interfering with daily activities, $r(111) = .26, p < .01$; and history of hypertension, $r(111) = .28, p < .01$, were all

significantly related to plasma IL-6 levels. These variables were then entered into hierarchical regression analyses as control variables along with sociodemographic, health, and health behavior variables. Each of the well-being and ill-being measures was then added to the model individually, and only the eudaimonic well-being measure of positive relationships with others significantly predicted plasma IL-6 beyond control and health variables. The positive relationships score was negatively correlated with IL-6, suggesting that higher levels of social well-being were related to lower circulating levels of IL-6 (Table 2, Model 1). This association is also displayed graphically in Figure 1.

Following our goal of testing the effects of psychological well-being on inflammatory factors, net of the influence of psychological ill-being, the MASQ Depressive Symptoms scale, which had the strongest negative associations with the PWB scales overall, was added to the regression analyses in Model 2 (see Table 2). Inclusion of this measure did not affect the associations between any of the PWB measures and plasma IL-6, although multiple measures of ill-being were significantly correlated with multiple measures of well-being.

Table 3 shows the results of hierarchical regression analyses of factors predicting plasma sIL-6R levels. Waist-hip ratio, $r(87) = .250, p < .05$, and total/HDL cholesterol, $r(87) = .222, p < .05$, were the only health measures that were significantly correlated with plasma sIL-6R in preliminary bivariate analyses, and these were added to regression models as control variables along with the sociodemographic and health behavior variables we have mentioned. Addition of well-being and ill-being measures to the model showed that purpose in life was significantly negatively related ($\beta = -.22, p < .05$) and environmental mastery was marginally

Table 2
Hierarchical Regression Analyses of Well-Being and Ill-Being Measures on Plasma Interleukin-6
($n = 112$)

Variable	Model 1		Model 2	
	β	t	β	t
PWB				
Positive Relations With Others (cubed)	-.18	-2.02*	-.18	-2.00*
Personal Growth (cubed)	.09	0.94	.09	1.07
Purpose in Life (cubed)	-.05	-0.51	-.05	-0.05
Environmental Mastery (cubed)	-.13	-1.50	-.13	-1.27
Self-Acceptance (cubed)	-.03	-0.40	.01	0.04
Autonomy (cubed)	.01	0.15	.03	0.03
MASQ				
Positive Affect	-.06	-0.62	-.03	-0.32
Depressive Symptoms (log-transformed)	.06	0.71		
Anxious Symptoms (log-transformed)	-.06	-0.72		
Loss of Interest (log-transformed)	.11	1.30		
Anxious Arousal (log-transformed)	.08	0.88		
Spielberger Trait Anger	-.01	-0.04		

Note. In each case, Model 1 includes the well-being or ill-being predictor variable and all control variables. Full model effect sizes include control variables. To test the independence of well-being and ill-being measures in predicting plasma interleukin-6 levels, Model 2 includes the MASQ Depressive Symptoms scale. Control variables for statistical models were age, years of education, marital status (married vs. unmarried; widowed vs. other), pretax household income, anti-inflammatory medication, health status, smoking, and alcohol consumption. The degree of freedom for all t tests was 111. PWB = Scales of Psychological Well-Being; MASQ = Mood and Anxiety Symptom Questionnaire.

* $p < .05$.

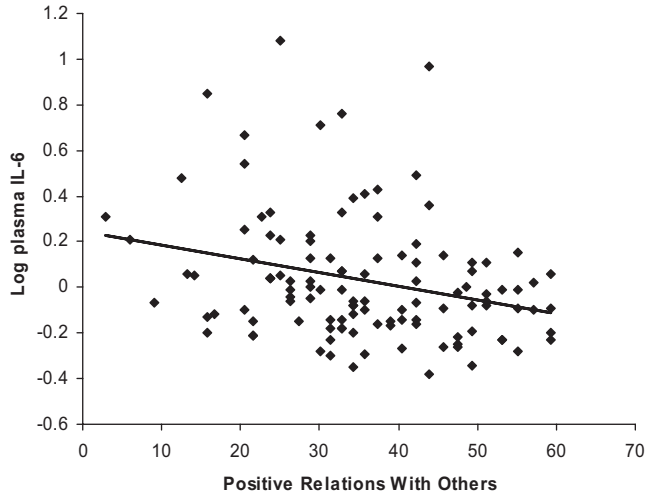


Figure 1. Scatterplot of scores on the Positive Relations With Others scale (cubed and then multiplied by 10^{-4}) and plasma interleukin-6 (IL-6 [pg/mL]; log-transformed) in a sample of aging women ($n = 112$). Positive relationships significantly predicted plasma IL-6 after sociodemographic variables, health status, smoking, alcohol consumption, and anti-inflammatory medication use were controlled ($p < .05$; $r = -.18$).

negatively related ($\beta = -.19, p < .07$) to plasma sIL-6R (Table 3, Model 1). Both of these relations were in the predicted direction.

As before, the MASQ Depressive Symptoms scale was added to regression analyses involving PWB measures at the last step. Not only did the addition of the MASQ scale fail to diminish the association of PWB measures and IL-6, but for many of the scales

there appeared to be suppressor effects present; regression coefficients for the Personal Growth, Purpose in Life, Environmental Mastery, and Self-Acceptance PWB scales and the MASQ High Positive Affect scale become larger once the Depressive Symptoms scale was included. Indeed, the association between plasma sIL-6R and Environmental Mastery, marginally significant without the depression scale, become statistically significant with its inclusion (Table 3, Model 2).

One question raised by these data is whether the associations between well-being measures and plasma levels of IL-6 in particular are meaningful for health. Previous research has suggested that the relation between IL-6 and general morbidity and disability is nonlinear, with risk of morbidity rising significantly above a threshold blood concentration of 2.5 pg/mL (Ferrucci et al., 1999). There were only 11 women in the current study whose IL-6 values exceeded 2.5 pg/mL, but compared with those below this threshold, they scored significantly lower on the Positive Relations With Others scale, $t(114) = 2.15, p < .05$. Moreover, women with Positive Relations With Others scores below the median were almost twice as likely to have plasma IL-6 concentrations above 2.5 pg/mL as women above the median. These data suggest that differences in plasma IL-6 levels based on social well-being are clinically meaningful. There is currently no similar standard of clinical significance for sIL-6R.

Discussion

This study examines the relations between different measures of psychological well- and ill-being and in vivo cytokine levels in aging women. Given past research on circulating levels of IL-6, we hypothesized that ill-being would be associated with higher plasma

Table 3
Hierarchical Regression Analyses of Well-Being and Ill-Being Measures on Plasma Soluble Interleukin-6 Receptors ($n = 91$)

Variable	Model 1		Model 2	
	β	t	β	t
PWB				
Positive Relations With Others (cubed)	-.15	-1.36	-.15	-1.32
Personal Growth (cubed)	-.14	-1.25	-.15	-1.22
Purpose in Life (cubed)	-.22	-2.06*	-.24	-2.10*
Environmental Mastery (cubed)	-.20	-1.89#	-.27	-2.09*
Self-Acceptance (cubed)	-.16	-1.49	-.21	-1.62
Autonomy (cubed)	-.10	-0.97	-.10	-0.92
MASQ				
Positive Affect	-.09	-0.85	-.12	-0.84
Depressive Symptoms (log-transformed)	.03	0.29		
Anxious Symptoms (log-transformed)	.02	0.15		
Loss of Interest (log-transformed)	.16	1.56		
Anxious Arousal (log-transformed)	-.03	-0.22		
Spielberger Trait Anger	-.14	-1.39		

Note. In each case, Model 1 includes the well-being or ill-being predictor variable and all control variables. Full model effect sizes include control variables. To test the independence of well-being and ill-being measures in predicting plasma soluble interleukin-6 receptor levels, Model 2 includes the MASQ Depressive Symptoms scale. Control variables for statistical models were age, years of education, marital status (married vs. unmarried; widowed vs. other), pretax household income, anti-inflammatory medication, health status, smoking, and alcohol consumption. The degree of freedom for all t tests is 90. PWB = Scales of Psychological Well-Being; MASQ = Mood and Anxiety Symptom Questionnaire.
* $p < .05$. # $p < .10$.

levels of IL-6 and sIL-6R and that well-being would be associated with lower levels. In fact, the only measures that were significantly related to IL-6 and sIL-6R were measures of eudaimonic well-being; neither hedonic well-being nor ill-being was associated with these inflammatory factors after health and sociodemographic factors were taken into account. These results suggest a number of things. First, in aging women who are generally healthy, biomarkers of inflammation are more closely related to gradations in specific aspects of eudaimonic well-being than they are to differences in positive or negative affective states. This appears to conflict with previous research in which negative affect has been associated with age-related increases in both IL-6 (Dentino et al., 1999; Kiecolt-Glaser et al., 2003; Maes et al., 1997; Penninx et al., 2003) and sIL-6R (Maes et al., 1997), although the absence of severe negative affect in this study may account for the lack of replication. The implication, however, is that specific aspects of well-being in aging individuals appear to be meaningfully related to biomarkers that have been linked to a range of age-related diseases.

The present finding that plasma IL-6 levels were lower in women with higher scores on positive relationships with others is consistent with studies showing that social integration and social support predict reduced morbidity and mortality (Cohen, 2004; House, Landis, & Umberson, 1988; Uchino, Cacioppo, & Kiecolt-Glaser, 1996) and can serve as buffers against the health impact of life stressors (Cohen, 2004). In one study, social support partially mitigated the impact of chronic stress on neuroendocrine regulation of *in vitro* IL-6 production in parents of children with cancer (Miller, Cohen, & Ritchey, 2002), although plasma levels of IL-6 in a study of older adults were unrelated to participation in social clubs, size of social network, perceived social support, and loneliness (Lutgendorf et al., 2004). The same measure of social ties used in the present study was previously linked to lower allostatic load scores in two age cohorts (Seeman, Singer, Ryff, Dienberg Love, & Levy-Storms, 2002). In general, social relationships are consistently associated with biomarkers of health (Ryff & Singer, 2000), and social isolation constitutes a major risk factor for morbidity and mortality, especially in older adults (House et al., 1988; Uchino et al., 1996). Indeed, some of the women who scored below the median on the positive relationships well-being scale had levels of IL-6 that predict increased risk of morbidity and disability (Ferrucci et al., 1999).

Plasma levels of sIL-6R, in contrast, were significantly negatively related to scores on the Purpose in Life and Environmental Mastery PWB scales. The Purpose in Life scale measures the extent to which individuals find meaning in their daily activities and life challenges (Ryff, 1989; Ryff & Keyes, 1995), and it has been linked to lower levels of salivary cortisol, lower waist-hip ratio, and higher levels of HDL cholesterol (Ryff et al., 2004). Other studies using related constructs have shown, for example, that striving to find meaning in life predicted greater natural killer cell activity in women who had experienced the death of a close relative (Bower, Kemeny, Taylor, & Fahey, 2003). Finally, the relation between environmental mastery and sIL-6R levels is consistent with previous work showing strong associations between health and mastery or related constructs, such as a sense of personal control over events, associations that are particularly strong in older adults (Rodin, 1986). Indeed, achieving high-quality social ties, finding meaning in one's endeavors, and feeling

a sense of control over one's life are all broadly linked to better physical and psychological health (Schneiderman, Antoni, Saab, & Ironson, 2001).

The results of this study underscore a number of important perspectives about the association of well-being and ill-being with one another and with biomarkers of disease. For example, although two of the ill-being scales (MASQ Loss of Interest, MASQ Anxious Arousal) significantly predicted IL-6 levels in the bivariate analysis, inclusion of sociodemographic and health control variables eliminated these associations. The reasons for this result are unclear, although one possibility is that poor health might simultaneously explain higher plasma IL-6 levels and higher levels of ill-being. Future efforts will focus on the potential associations of ill-being measures with health and sociodemographic factors. In contrast, the Positive Relations With Others PWB scale was significantly associated with plasma IL-6 even after control variables were taken into account. Moreover, inclusion of the MASQ Depressive Symptoms scale in regression analyses involving PWB measures did not affect the association of the PWB scales with IL-6 and even strengthened the associations between the PWB scales and sIL-6R. It should be noted that well-being variables were not similarly included in analyses involving ill-being measures, as no measure of ill-being was significantly associated with IL-6 in the multivariate analyses. Collectively, these results corroborate previous reports of significant differences in the ways well-being and ill-being are associated with a variety of biomarkers (Ryff et al., 2006).

The associations of well-being variables and inflammatory markers also appear to be complex. At the bivariate level, both positive relations with others and purpose in life significantly predicted plasma IL-6 and sIL-6R. After the inclusion of control variables in the regression analyses, however, the association of purpose in life and IL-6 became nonsignificant, indicating that this association may be linked to health status, whereas positive relations with others predicted IL-6 levels independently of health status. In contrast, even after the inclusion of control variables, the association of positive relations with others and sIL-6R was close to marginal significance, and this association might achieve statistical significance with a larger sample. Further research with larger samples will certainly illuminate these associations.

These were cross-sectional analyses, and the results do not establish that differences in psychological well-being produce different plasma levels of IL-6. Although plasma IL-6 levels are clearly responsive to psychological states (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004; Miller et al., 2002; Steptoe, Owen, Kunz-Ebrecht, & Mohamed-Ali, 2002), prospective studies have shown that IL-6 levels are elevated in healthy aging individuals who go on to develop disease or disability many years later (Ferrucci et al., 1999). Long-term studies in which psychological and biological factors are assessed at multiple times are necessary to examine the issue of causality more rigorously. That said, determining the direction of cause ultimately may be less important than determining which psychological and biological variables are associated and under which circumstances. One may also expect that the directions of influence will change, possibly multiple times in the same individual, with changing health and life circumstances. It should be noted that the relation between well-being measures and inflammatory factors in this study was preserved in spite of the variable time interval between questionnaire

completion and blood draws. As IL-6 and sIL-6R levels might be expected to fluctuate in response to life events or acute changes in the participants' health status, the relations between these factors and psychological well-being appear to be fairly robust. With that in mind, these data represent an initial step in establishing a relation between positive psychological states and inflammatory markers.

There are several important considerations that limit the generalizability of these data. In particular, this was a fairly small sample of generally healthy older women who, on average, had high levels of well-being and low levels of ill-being. Stronger relations might emerge between ill-being measures and proinflammatory factors, for example, in a more heterogeneous sample. That said, the associations of well-being and IL-6 and sIL-6R in the present study suggest that lack of well-being may put individuals at risk for age-related morbidity even in the absence of chronic stress or depression. In addition, it is possible that both well-being and plasma IL-6 levels are related to tertiary influences that were not assessed in this study. An equally plausible alternative interpretation of these results, for example, is that high levels of IL-6 and low scores on the positive relationships scale were both the result of age-related disease. Although we controlled for medical conditions and self-reported limitations on activity, it is entirely possible that subclinical conditions existed in this sample. Longitudinal examinations of psychological and biological processes are needed to resolve this issue. Finally, because the associations of well-being and inflammation have received minimal prior attention and because the eudaimonic well-being measures in particular have been shown to be distinct from one another (Ryff & Keyes, 1995), this study also contained a large number of regression analyses. The results thus should be interpreted with some caution, as preliminary findings in need of assessment with larger, more sociodemographically diverse samples.

In sum, these data suggest that psychological well-being, in particular purposeful engagement in living, being able to manage the demands of everyday life, and the pursuit of quality relationships with others, is a significant predictor of biological factors that are linked to age-related health outcomes, even after the influences of important sociodemographic and health variables have been considered. Although the literature on healthy aging has largely focused on minimizing the impact of maladjustment and adverse life events, these data are consistent with a growing literature highlighting the benefits for health of maximizing psychological well-being.

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