Short Communication

Pessimism correlates with leukocyte telomere shortness and elevated interleukin-6 in post-menopausal women

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A B S T R A C T

The combination of less positive and more negative expectations for the future (i.e., lower optimism and higher pessimism) increases risk for disease and early mortality. We tested the possibility that expectations might influence health outcomes by altering the rate of biological aging, specifically of the immune system (immunosenescence). However, no studies to date have examined associations between optimism or pessimism and indicators of immunosenescence such as leukocyte telomere length (TL) and interleukin-6 (IL-6) levels. We investigated whether dispositional tendencies towards optimism and pessimism were associated with TL and IL-6 in a sample of 36 healthy post-menopausal women. Multiple regression analyses where optimism and pessimism were entered simultaneously, and chronological age and caregiver status were controlled, indicated that pessimism was independently associated with shorter TL (β = −0.68, p = .001) and higher IL-6 concentrations (β = .50, p = .02). In contrast, optimism was not independently associated with either measure of immunosenescence. These findings suggest that dispositional pessimism may increase IL-6 and accelerate rate of telomere shortening. Mechanistic causal relationships between these parameters need to be investigated.

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1. Introduction

Expecting less positive and/or more negative outcomes in the future (i.e., lower optimism and/or higher pessimism) is associated with faster progression of diseases of aging (Allison et al., 2003; Matthews et al., 2004) and earlier mortality (Gilray et al., 2006), but the mechanisms underlying this association have been elusive. Immunosenescence (aging of the immune system) has been implicated in health defects associated with aging, including susceptibility to infectious disease, diseases of aging, and earlier mortality (Effros, 2004). Telomeres, consisting of repetitive DNA sequences complexed with proteins, cap chromosome ends and protect against chromosomal damage (Blackburn, 2001). Human population studies show a general decline of leukocyte telomeric DNA length (TL) with age, suggesting that leukocyte telomere shortness may serve as an indicator of immunosenescence (Effros, 2004).

Chronic psychological stress has been associated with accelerated leukocyte telomere shortening (Damjanovic et al., 2007; Epel et al., 2004). In one study, caregivers had shorter TL than controls (Damjanovic et al., 2007). In another study, caregivers and non-caregivers had similar mean TL, but perceived stress was a significant predictor of TL in both caregiving and non-caregiving women and across the combined sample (Epel et al., 2004). No studies have examined how individual differences in perceived stress vulnerability might promote telomere shortening.

An individual’s scores on optimism and pessimism measures generally remain stable across time (Gilray et al., 2006; Scheier et al., 1994), and the combination of low optimism and/or high pessimism is associated with more negative mood, less positive mood and poorer coping with stress (Carver et al., 1993; Scheier and Carver, 1985). Generalized negative expectations for the future could increase vulnerability to high perceived stress and consequently, accelerated telomere shortening.

Inflammatory cytokines including interleukin-6 (IL-6) can promote inflammatory processes, and both acute and chronic psychological stress have been associated with increased IL-6 (Kiecolt-Glaser et al., 2003; Steptoe et al., 2001). Repeated episodes of inflammation are associated with telomere shortening in leukocytes (Carrero et al., 2008; Wu et al., 2000). Thus, inflammatory processes may provide an important link between psychological stress and TL.

Positive and negative future thinking have different neural correlates (Sharot et al., 2007), and it has been suggested that optimism and pessimism have divergent genetic and environmental
determinants (Plomin et al., 1992). Thus, it is important to sepa-
renently examine associations between optimism, pessimism and
health-related variables. The primary goal of the current study
was to assess optimism vs. pessimism, in relation to TL, and in sec-
ondary analyses, whether this relationship might be mediated by
neuroticism, perceived stress, and health behaviors.

2. Methods

2.1. Participants and procedure

We recruited 36 healthy post-menopausal women aged be-
tween 50 and 80 years through flyers and posters in the com-
nunity, and from elderly service providers in the Bay Area,
California. This was a different sample from the premenopausal
sample in which we previously reported a link between stress
and telomere length (Epel et al., 2004). The post-menopausal sam-
ple described here included 30 White (81.1%), one Black, one His-
panic/Latina and four Asian women. Exclusion criteria included
the presence of major medical conditions such as heart disease,
cancer, or diabetes, use of medications containing agents known
to affect stress hormone levels, and regular smoking. Participants
underwent a fasting blood draw between 8.00AM and 10.00AM,
and completed self-report questionnaires within one week of the
blood draw. Blood was collected from the non-dominant arm using
an indwelling catheter, and processed within 1 h. The study proto-
col was approved by the Institutional Review Board of the Univer-
sity of California, San Francisco. Written, informed consent was
obtained from all participants.

2.2. Materials and measures

2.2.1. Optimism/pessimism

The Revised Life Orientation Test (LOT-R) was used to measure
optimism and pessimism (Scheier et al., 1994). The instrument
comprises three positively worded items, which comprise the optimism
scale (e.g., "In uncertain times, I usually expect the best"); three neg-
avely worded items, which comprise the pessimism scale (e.g., "If
something can go wrong for me, it will"); and four filler items. Partic-
ipants are asked to rate their agreement or disagreement with each
of the statements on a five-point scale from 0 ("strongly disagree") to
5 ("strongly agree"). Internal consistency for the optimism (α = .74)
and pessimism (α = .78) subscales was high.

2.2.2. Perceived stress

The 10-item Perceived Stress Scale was used to assess apprais-
als of psychological stress experienced during the last month,
including the extent to which situations are experienced as unpred-
dictable, uncontrollable and overwhelming (Cohen et al., 1983).
Participants are asked to rate the extent to which they felt or
thought a particular way in the previous month on a 5-point Likert
scale ranging from 0 ("never") to 4 ("very often"). Internal consist-
cy was high (α = .93).

2.2.3. Neuroticism

The Big Five Inventory was used to assess neuroticism (John
et al., 1991). This scale comprises eight items that assess emotional
stability or neuroticism (e.g., "I see myself as someone who worries
a lot"). Participants rate their agreement with the items on a 5-
point Likert scale ranging from 1 ("disagree strongly") to 5 ("agree
strongly"). Internal consistency for the scale was high (α = .84).

2.2.4. Health behaviors and demographics

Questions from the Yale Physical Activity Scale were used to as-
ess frequency and duration of vigorous activities during the previ-
ous month (Dipietro et al., 1993). Scores were computed by
multiplying frequency of vigorous activities by duration. The
Insomnia Severity Index (ISI), a valid and reliable measure in older
people, was used to assess sleep difficulties (Bastien et al., 2001).
Body mass index (BMI) was calculated as weight in kilograms
(measured on a balance beam scale in hospital gown) divided by
height in meters squared.

2.2.5. Telomere length (TL)

Samples were collected in 10-ml heparin tubes (Becton–Dickin-
sion, Franklin Lakes, NJ). Leukocytes were isolated using density-
gradient centrifugation (with Ficoll–Paque PLUS) and frozen at
−80 °C. DNA was extracted from leukocytes by the University of
California, San Francisco DNA bank. Genomic DNA isolation was
performed using a standardized and quality-controlled PureGene
DNA isolation system (Genta Systems, Minneapolis). The quantity
and quality of the genomic DNA isolate was determined by 260/
280 UV spectrophotometry. At regular intervals, the integrity of
isolated DNA was evaluated by agarose gel electrophoresis
performed on randomly selected isolates.

DNA was analyzed for TL using quantitative polymerase chain
reaction (qPCR) as previously described (Cawthon, 2002) with the
following modifications. The primers for the telomere qPCR were
tel1b (5′-GGCTTTG(TTGGTGGT)-3′) and tel2b (5′-
GGCTTC(TCTTAC)5CCT-3′), each used at a final concentration of
900 nM. Single-copy gene (human β-globin) qPCR primers were:
hbg1 (5′-GCTCTGACAGTACTGTTACAGC-3′), used at a final
concentration of 300 nM, and hbg2 (5′-CACACACTTACCGTT
CACC-3′), used at a final concentration of 700 nM. The final reac-
tion mix was: 20 mM Tris–HCl, pH 8.4; 50 mM KCl; 200 nM each
dNTP; 1% DMSO; 0.4× Sybr Green I; 44 ng Escherichia coli DNA;
0.8 U Platinum Taq DNA polymerase (Invitrogen) per 22 μl reac-
tion; 1.5–20 ng genomic DNA. Tubes containing 40, 13.3, 4.4, and
1.5 ng of reference DNA from Hela cells were included in each qPCR
run so that the quantity of targeted templates in each research
sample could be determined relative to a single reference DNA
sample by the standard curve method. All qPCRs were carried out
on a MX3000P (Stratagene, La Jolla, CA) real-time PCR
instrument.

To adjust for batch-to-batch variation, the same four control
DNA samples covering the normal range of T/S ratios were included
on each of six independent runs. A conversion factor was calcu-
lated based on the average T/S ratio of the four control DNA
samples in each run compared to the established T/S ratio.

To develop the conversion factor for the calculation of approxi-
mate base pair telomere length from the T/S ratio, the T/S ratios of a
set of genomic DNA samples from primary human cell line IMR90
at different population doubling were determined. The termin-
all restriction fragment length of these DNA samples was measured
by Southern blot analysis to create the TRF and T/S ratio plot. The
slope of the plot was used as the conversion factor. The CV of the
TL method was 6.7%.

2.2.6. IL-6

Samples were collected in 10-ml SST tubes (Becton–Dickinson,
Franklin Lakes, NJ). A high sensitivity enzyme-linked immunosor-
bent assay was used to quantify IL-6 (R&D Systems, Minneapolis,
MN) in the laboratory of Dr. Dhabhar. Assay sensitivity is
<0.1 pg/ml, and average intra- and inter-assay coefficients of vari-
ation were 7% and 8%, respectively. IL-6 levels were available for 21
participants.

2.3. Data analysis

Zero-order Pearson’s correlations were used to assess associa-
tions among optimism, pessimism, TL and IL-6. In a series of sepa-
rate hierarchical linear regression models for TL and IL-6, optimism and pessimism were entered simultaneously in the second step of the models, controlling for chronological age and caregiver status (caregiver/control) in the first step.

In secondary analyses, to demonstrate relationships between high and low pessimism and TL adjusted only for age, we examined differences between groups in the top and bottom tertiles for pessimism. Studies that examine telomere shortening across the lifespan indicate that approximately 31–63 base pairs are lost per year (Hastie et al., 1990; Iwama et al., 1998). We used these estimates of base pair loss per year to examine approximate differences in years of telomere shortening between participants scoring in the top and bottom tertiles for pessimism.

Secondary analyses were conducted to assess the contribution of potential mediating variables including perceived stress, neuroticism, BMI, sleep and exercise. In order to assess the contribution of these variables, we entered them in the first step of hierarchical linear regression equations with optimism and pessimism entered in the second step, and separate equations computed for TL and IL-6. We also controlled for these variables in ANCOVA to assess the difference in TL between participants in the top and bottom tertiles for pessimism. Because we did not have sufficient power to conduct these multivariate analyses, and health behaviors are current rather than reflecting lifetime (see Section 4), these secondary results should be interpreted with caution. SPSS software was used. Two-tailed p-tests were used throughout.

3. Results

The sample comprised 36 post-menopausal women ranging from 51 to 79 years (M age = 60.73, SD = 6.65; M BMI = 26.05, SD = 5.04). Of the women, 23 were caregivers for a relative with dementia and 13 were not caregiving and considered controls. Caregivers and controls were not significantly different on demographics, TL or IL-6, and the pattern of findings did not differ between groups. Accordingly, for the analyses reported here, we pooled data from caregivers and controls.

TL and IL-6 were significantly and negatively associated (r = −.51, p = .01). Optimism was marginally associated with longer TL (r = .31, p = .07), and there was no association between optimism and IL-6 (r = −.34, p = .14). In contrast, pessimism was strongly associated with shorter TL (r = −.55, p = .001; Fig. 1) and higher IL-6 (r = .43, p = .05). Controlling for age and caregiver status, and entering optimism and pessimism simultaneously, optimism was not uniquely associated with either TL or IL-6. Pessimism, on the other hand, remained significantly associated with both TL and IL-6 (Table 1). Comparing those participants with scores in the top and bottom tertiles for pessimism, and controlling for age, we found that participants with the highest pessimism scores had mean TL (M = 4697 bp, SD = 849 bp) 705 base pairs shorter than those participants with the lowest pessimism scores (M = 5402 bp, SD = 734 bp). This between group difference was significant, F(1,24) = 6.36, η² = .21, p = .02. Using the same methods as in previous work (Epel et al., 2004), we estimated that highly pessimistic participants demonstrated roughly 11–23 years’ equivalent of additional telomere shortening compared with non-pessimistic participants. Participants in the top tertile for pessimism also had significantly higher levels of IL-6 than participants in the bottom tertile, F(1,12) = 9.95, η² = .52, p = .01. Higher levels of perceived stress were associated with shorter TL (p = .01), which replicated our previous finding (Epel et al., 2004). Perceived stress was not associated with IL-6 (p = .31).

In the secondary analyses, the association between pessimism and TL remained significant when we controlled for age, caregiver status, optimism, perceived stress, neuroticism, BMI, exercise and sleep in multiple regression (β = −.66, t = −2.60, p = .02). However, the association between pessimism and IL-6 was not significant when these variables were included (β = .64, t = 1.93, p = .11). The between group (high vs. low pessimism) difference in TL also remained significant when we entered potential mediators as covariates, F(1,10) = 5.04, η² = .35, p = .049. The TL/pessimism effect sizes for both the correlation (Cohen’s d = 1.32) and the adjusted coefficient from the multiple regression (f = 1.32) were both large effects. However, given the small sample size, and multiple covariates these secondary analyses should be viewed as preliminary and true tests of mediation will require further studies.

4. Discussion

This study is the first demonstration that a personality trait, specifically higher pessimism, is associated with shorter TL in leukocytes. It is also the first demonstration that pessimism is associated with higher basal levels of IL-6, an indicator of systemic inflammation and possibly immune system aging (Effros, 2004; Franceschi et al., 2000). Diminished TL and higher IL-6 level each alone predict mortality (Cawthon et al., 2003; Kimura et al., 2008; Volpato et al., 2001). Hence, our data support the possibility

![Fig. 1. Scatterplot of dispositional pessimism and telomere length (r = −.55, p = .001).](image-url)
that immunosenescence, as measured by shorter TL and higher IL-6, is one of the mediators of the relationships between expectancies, disease risk (Allison et al., 2003; Matthews et al., 2004) and mortality (Giltay et al., 2006).

The combination of high optimism and/or low pessimism has previously been associated with markers of immune functioning (Crues et al., 2000; Segerstrom, 2005). Interestingly, in our study the absence of pessimism was more important than the presence of optimism in predicting a “younger”-appearing immune system; we found no unique association between optimism and either TL or IL-6. These results are consistent with previous studies that have distinguished between optimism and pessimism, in which linear associations were reported between pessimism, but not optimism, and objective indicators of health (Milam et al., 2004; Schulz et al., 1996).

Although pessimism could exert some of its effects on immunosenescence through perceived stress or health behaviors, the observed associations between pessimism and markers of immunosenescence were independent of current perceived stress and health behaviors as measured. While current perceived stress and health behaviors are likely to share variance with lifetime history, they will not fully estimate exposure over decades. Consequently, the current findings do not rule out the possibility that psychological stress and health behaviors mediate at least some of the relationships we have shown to exist between pessimism, shorter TL and higher IL-6.

Given observed associations between both acute and chronic psychological stress and raised IL-6 levels (Kiecolt-Glaser et al., 2003; Steptoe et al., 2001), we propose that exposure to psychological stressors in pessimists could contribute to chronic low-level increases in circulating pro-inflammatory cytokines, which may in turn contribute to telomere shortening across the lifespan. However, leukocytes with short telomeres tend to release greater quantities of pro-inflammatory cytokines, including IL-6 (Effros, 2004), and thus we cannot rule out the possibility that the direction of causality is from short telomeres to elevated IL-6 and not vice versa. Longitudinal research will be needed to assess causality.

References