

## Hostility and pain are related to inflammation in older adults <sup>☆</sup>

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### Abstract

Chronically elevated systemic inflammation has a dramatic impact on health for older individuals. As stress-related responses, both hostility and pain perception may contribute to inflammation which in turn may maintain negative emotion and pain over time. We used structural equation modeling to examine the degree to which trait hostility and pain were uniquely associated with C-reactive protein (CRP) and serum IL-6 levels over a 6-year span in a sample of older adults. The sample included 113 present or former caregivers of a spouse with dementia and 101 non-caregivers. After accounting for depression, health behaviours, and other risk factors, which were also assessed longitudinally, pain and, to a lesser extent, hostility were uniquely associated with plasma levels of CRP but not IL-6. When examined separately, the association between pain and CRP was significant only for caregivers, while the association between hostility and CRP was comparable for the two groups. These findings suggest that hostility may play a role in a cycle of inflammation among older adults, and that pain may be particularly problematic for those under chronic stress. Our results also shed light on inflammation as a mechanism underlying the effects of hostility on cardiovascular disease morbidity and mortality.

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### 1. Introduction

Chronically elevated systemic inflammation is implicated in mortality and morbidity from a range of age-related conditions, including diabetes, arthritis, and general disability (e.g., Ferrucci et al., 1999; Pradhan et al., 2001). Moreover, considerable evidence now suggests that atherosclerosis, a key component of coronary artery disease

(CAD), is the result of inflammatory processes (Black, 2003). Even among apparently healthy individuals, elevated levels of proinflammatory cytokines, such as interleukin-6 (IL-6), and other markers of systemic inflammation, such as C-reactive protein (CRP), are associated prospectively with an increased risk for myocardial infarction (Ridker et al., 2000a,b). There is now substantial evidence that chronic psychological stress can lead to inflammatory responses (Black, 2002), perhaps particularly for those with genetic predispositions to inflammation (Fishman et al., 1998; Jeanmonod et al., 2004), or dispositional characteristics, such as hostility (e.g., Suarez, 2004). Thus, it is important to isolate which, to what extent, and under what circumstances individual differences and other psychosocial factors contribute to systemic inflammation. At the same time,

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a related and vital area of research is to determine to what extent inflammation accounts for the association between psychosocial factors and health outcomes, such as CAD and chronic pain.

A substantial body of work now links health outcomes with hostility—a dispositional tendency characterized by behaviour (e.g., aggression) and attitudes (e.g., cynicism), as well as anger. Hostility is relatively stable across time, with some evidence for a heritable component (Iwata et al., 2004). In particular, hostility is strongly and independently associated with the development and progression of CAD (Boyle et al., 2004; Miller et al., 1996). Hostility, anger experience, and related behaviour (e.g., anger expression) also appear to be involved in the maintenance of chronic pain (Fernandez and Turk, 1995). Not only can pain cause anger and hostility but such reactions are associated with exacerbation of pain, disability, and depression (Duckro et al., 1994; Kerns et al., 1994). Studies linking hostility with health outcomes such as pain and cardiovascular disease have often not only controlled for biomedical risk factors but also for depression, which is associated with many aspects of immune function (Irwin, 2001) as well as with lower overall perceived health and increased pain (Wells et al., 1989).

One way in which hostility may be involved with both CAD and chronic pain is via long-term increases in systemic inflammation. Among younger adults, trait hostility has been uniquely associated with greater levels of CRP (Suarez, 2004), an acute phase protein induced primarily by IL-6 (Heinrich et al., 1990). Trait hostility, more so than self-reported anger and verbal aggression, has also been associated among healthy young men with lipopolysaccharide (LPS) stimulated TNF- $\alpha$  (Suarez et al., 2002), which triggers the production of IL-6 and promotes CRP production (Pang et al., 1994; Richards and Gauldie, 1995). There is less evidence to suggest a direct association between hostility and IL-6 levels. Another study of younger men found an independent association between hostility and IL-6 levels only among those not currently taking multi-vitamins (Suarez, 2003). Among a sample of relatively young women, the cynical component of hostility was associated with IL-6 levels only among those low in depressive symptoms (Miller et al., 2003a). To our knowledge, the association between hostility and either CRP or IL-6 has not been examined in older adults, for whom the effects of chronically elevated systemic inflammation are particularly problematic.

The association between pain and inflammatory markers is also not well understood, but recent research has made it clear that there is a connection (Watkins et al., 1995) and strongly supports the contention that the association is bi-directional. It seems likely that systemic inflammation contributes to general perceptions of pain, either indirectly by contributing to disease processes such as arthritis, or directly through soft tissue injury or increased pressure on nerve cells (Black, 2002; Sturmer et al., 2005). It is also likely that pain perception leads to an increase in systemic inflammation,

perhaps via stress responses. In laboratory animals, physical stressors such as footshock reliably increase IL-6 levels (Arimura et al., 1994; Zhou et al., 1993), and substance P can modulate immune function through multiple pathways, including stimulation of TNF- $\alpha$  (Black, 2002; Machelska et al., 2001). Independent of behavioural stress manipulations, humans injected with capsaicin (the active ingredient in red chili peppers) showed small but significant increases in plasma IL-6 (Lutgendorf et al., 2004). There is also evidence that chronic pain is associated with elevated CRP levels. For example, patients with osteoarthritis and acute sciatic pain—populations for whom inflammation may be a particularly important contributor to pain—evidence elevated levels of CRP (Sturmer et al., 2004, 2005). Among those with sciatic pain, serum IL-6 levels (but not CRP) were associated with time-dependent increases in pain perception over the course of a day (Geiss et al., 1997). Furthering our understanding of the bi-directionality of the association between pain and inflammation, there is now substantial evidence that spinal inflammation and other pain-inducing trauma can activate spinal glial cells which subsequently release proinflammatory cytokines that serve to enhance pain (Wieseler-Frank et al., 2005).

To our knowledge, the role of pain has not been examined in the context of hostility and inflammation in any population. Another important issue is how a cycle of inter-related pain and hostility would predict systemic inflammation under conditions of chronic stress. Chronic stress, such as can occur when providing care for an ailing relative, is associated with immune dysregulation, including elevated levels of IL-6 (Lutgendorf et al., 1999), faster increases in IL-6 over a span of years (Kiecolt-Glaser et al., 2003), and poorer wound healing (Kiecolt-Glaser et al., 2005). Preliminary evidence suggests that such responses may be exacerbated in individuals genetically predisposed to react to stress with increases in IL-6 or, over time, in CRP (Fishman et al., 1998; Jeanmonod et al., 2004). Similarly, stress may make more common hostile responses, which may thus be more strongly associated with inflammation in times of difficulty. On the other hand, hostility appears to be associated with inflammation in young, healthy subjects who are not experiencing chronic stressors like caregiving (e.g., Suarez, 2004). Because pain can be considered a chronic stressor itself, a pain and stress interaction may be even more likely: In addition to aggravation caused by pain directly, pain that persists over time can have a dramatically negative impact on relationships, finances, and work and social role participation (Robinson and Riley, 1999). Thus, it is likely that pain might be particularly problematic in terms of inflammation for those also experiencing other life stress. In support of this premise, a study of older women with arthritis found that the combination of depressive symptoms and perceived stress was a predictor of pain among those with rheumatoid arthritis but not osteoarthritis (Zautra and Smith, 2001); these authors speculated that this difference was due to stress-related influences on inflammatory processes among RA participants as well as

the greater and more prolonged pain-related stress experienced by those with RA (Zautra and Smith, 2001).

The primary goal of the current research was to examine the degree to which hostility and general bodily pain (as assessed over multiple years) are uniquely associated with CRP and IL-6 levels in older adults. This was examined in a model that allowed for bi-directionality between the key variables of bodily pain, hostility, depression, and inflammatory markers, thus testing a cycle likely to exist in reality. Depression was included to control for its possible impact on CRP and IL-6 levels, and was expected to be associated with hostility and pain. Hostility and bodily pain were both expected to be associated bi-directionally with CRP and IL-6 levels and also to be associated with each other. In addition to biomedical factors, such as gender, age, body mass index, and medication use, which have been associated with inflammation (e.g., Festa et al., 2001; Pearson et al., 2003), we also examined the role of health behaviours, such as sleep, exercise, alcohol and caffeine use, and smoking. Health behaviours such as these have been associated with hostility (see review by Williams, 2002) and depression (Kiecolt-Glaser and Glaser, 1988, 2002) as well as inflammatory markers (Albert et al., 2001; Danesh et al., 1999; Ferrucci et al., 1999; Taaffe et al., 2000).

Our sample of present and former (recently bereaved) caregivers of a spouse with dementia and well-matched, non-caregiving controls allowed us to examine secondary expectations regarding chronic stress. Caregiving for a spouse with a progressive dementing illness disease can be extremely stressful (Robinson-Whelen et al., 2001); although the perceived stress and negative affect commonly elevated among caregivers of spouses decline gradually after the death of the spouse (Robinson-Whelen et al., 2001), caregivers continue to show immune down-regulation for several years after bereavement (Esterling et al., 1996; Kiecolt-Glaser et al., 2003). We expected that bodily pain and, more tentatively, hostility would be more strongly linked with inflammation for caregivers.

## 2. Methods

### 2.1. Participants

Participants for whom we had hostility, IL-6, and CRP data across years were drawn from a larger study on the longitudinal effects of caregiving (Kiecolt-Glaser et al., 1991, 1996, 2005). The sample included 113 participants who were either present or former caregivers of a spouse with dementia and 101 control participants (non-caregivers). Spousal dementia caregivers were recruited from local dementia evaluation centers in area hospitals, neurologist's referrals, Columbus Alzheimer's Disease Association support groups and newsletters, and respite care programs. At the time of recruitment, caregivers were all providing five or more hours of care to a spouse with Alzheimer's or another progressive dementia. Control participants were recruited through a variety of sources, including newspaper advertisements, notices posted in senior centers, and referrals from other participants.

During recruitment we excluded those with certain health problems, such as diabetes, cancer, autoimmune disease, and recent surgery, and those taking any medications with broad immunological consequences. Inevitably, some participants developed chronic conditions over the

course of the 6 years; analyses described later control for new conditions. New caregivers and controls were regularly added during the course of the study to account for participants who died, moved, or dropped out over the course of the study (for more details, see Kiecolt-Glaser et al., 2003). Only participants with data from two or more years were included in the present analyses and 60% of participants provided eight or more blood draws; When average values were computed, only participants with data at two or more years were included.

### 2.2. Procedures

Participants were paid \$40 annually for their participation in the study, which included yearly interviews, concurrent with a blood draw, and a second blood draw later in the year. Blood draws were rescheduled if participants reported acute illness. Plasma samples were always taken between 8 and 11 a.m. to control for diurnal variation, and were frozen at  $-40^{\circ}\text{C}$  until analysis.

### 2.3. Measures

#### 2.3.1. CRP and IL-6

Plasma samples were thawed and run in duplicate, with all samples for an individual run in the same assay. CRP levels were determined by a high sensitivity rate nephelometric immunoassay using a Dade-Behring BN-100 nephelometer in the Special Functions Clinical Laboratory at Ohio State University Medical Center. IL-6 levels were assayed by a Quantikine High Sensitivity Immunoassay kit (R&D Systems). When blood draws from different times in the same year were available, which was the case for all years for IL-6 and for the first 2 years for CRP, average values across years were used.

#### 2.3.2. Pain

The bodily pain subscale from the RAND 36-Item Health Survey (Hays et al., 1993), which includes the same two items as the widely used SF-36 subscale with the same name (Ware and Sherbourne, 1992), were used to assess current pain in years 2–6. One item asked about magnitude of current pain over the past 4 weeks and the other about perceived interference from pain during the same time period, each on a scale from 1 to 100 (Hays et al., 1993). The items are scored such that lower scores indicate greater pain. This subscale is widely viewed as providing a measure of general bodily pain and has been shown to be distinct from physical functioning, physical limitation, and emotional functioning items in the SF-36 (Ware and Kosinski, 2001). Pain ratings were consistent across years (Chronbach's  $\alpha = .85$ ): Most individuals with high bodily pain in 1 year reported high bodily pain in other years. We thus combined yearly pain scores to create a measure of average bodily pain.

#### 2.3.3. Hostility

Observed measurements of hostility were made at years 1–5 with the Cook Medley Hostility scale (Ho scale: Cook and Medley, 1954), which assesses trait tendencies towards cynical attitudes, aggression, and anger responses. Fifty true/false questions are summed to form six subscales: cynicism, hostile affect, hostile attributions, aggression, social avoidance, and other. In the present study, averages for each of the subscales across years were used to form a latent factor, as described in detail below.

#### 2.3.4. Depressed mood

The Beck Depression Inventory-Short Form (BDI-SF) provided information on depressed mood (Beck et al., 1988). The 13 items in the BDI-SF describe affective, cognitive, and vegetative symptoms; participants rate their severity of each symptom on a scale 0–3. A cut-off score of 5 is typically used to differentiate depressed from non-depressed older adults (Scogin et al., 1988).

#### 2.3.5. Health behaviours

The Pittsburgh Sleep Quality Inventory (PSQI) provided a measure of overall sleep quality over the last month based on 19 items on a 0–3

scale, which are summed such that greater values indicate worse sleep quality (Buysse et al., 1989). Smoking (number of packs smoked a week) was assessed, although we found that very few participants in the study reported smoking at all over all years ( $n = 13$ ). We also assessed exercise (number of days per week in which the participant engaged in vigorous exercise), alcohol use (number of drinks in the past week), and caffeine use (number of drinks in the past 48 h). With the exception of sleep quality, which was assessed only in years 4–6, health behaviours were assessed at all 6 years and averaged across years.

### 2.3.6. Medication use

The use of major medication categories was assessed over the years of the study, with some individuals reporting use of cardiac medications ( $n = 56$ ), beta-blockers ( $n = 38$ ), estrogen ( $n = 54$ ), and hypolipidemic agents ( $n = 28$ ). Based on participant report of their current medications, medication use was coded as 0 (no) or 1 (yes) in each of these medication categories.

### 2.4. Data analysis strategy

We used structural equation modeling (SEM) to examine the unique effects of hostility and bodily pain on CRP and IL-6 levels. The use of SEM to operationalize and examine relationships between health relevant variables has been well established (Bentler and Stein, 1992). SEM offers the ability to examine several multiple regression equations simultaneously, identifying the unique associations between multiple variables while taking into account the degree to which they are intercorrelated (Byrne, 2001). Another major advantage of SEM over other statistical techniques such as multiple regression is that it allows the use of latent variables, which are constructs that are defined from a set of conceptually and empirically-related measures; at the same time, SEM also enables the specification of the error inevitable in measured variables. We used latent constructs in the present study to specify IL-6, CRP, and hostility.

SEM analyses were performed with AMOS 5.0.1 (Arbuckle, 1999), using its maximum likelihood estimation procedure. As is recommended (Anderson and Gerbing, 1988), we first examined measurement models using analyses equivalent to confirmatory factor analysis. To facilitate identification of the latent constructs, the factor loadings of one measured indicator in each model was set to 1.0. The second stage of analysis was to evaluate the predicted associations in a series of structural models. First, we evaluated a structural model with the key variables of interest: hostility, bodily pain, depression, IL-6, and CRP levels. Next, we added biomedical risk factors to the model, including age, gender, body mass, and medication use. Finally, we examined a structural model that also included health behaviours (e.g., sleep, exercise, and cigarette use). This final model was then tested using the group moderation feature in AMOS to examine the degree to which associations held for caregivers compared to controls.

In evaluating adequacy of all models, we primarily considered two fit indices: the comparative fit index (CFI) and the root-mean-square error of approximation (RMSEA). We also report the  $\chi^2$  statistic, which is useful for comparing models but not as valuable as an indicator of model fit because it is sensitive to sample size (Hu and Bentler, 1998). Based on stringent recommendations (Hu and Bentler, 1998), we considered a CFI value of .90 or greater to indicate good fit and values of .95 or greater to represent excellent fit. The 90% confidence interval around the RMSEA point estimate was considered to indicate good fit to the data if it included values of .10 or less, with values less than .06 representing excellent fit (Byrne, 2001; Hu and Bentler, 1998).

To report means and correlations among key variables, we used average values for hostility, IL-6 and CRP levels. To insure a normal distribution, IL-6 and CRP values were logarithmically transformed (base 10) and these values were used in all analyses. For simplification, the use of beta-blocker and cardiac medication was combined, after first examining them separately and determining that they operated in equivalent ways in the model.

## 3. Results

### 3.1. Preliminary analyses

The sample overall was predominately female (71.5%), Caucasian (87.4%), and the mean age at study entry was 69.05 ( $SD = 9.33$ ). Participants were well-educated, with 95.8% high school graduates and the majority with at least some college. The median household income at study entry of \$20–30,000 is not a good indicator of socioeconomic status, as many of participants were older women who had not worked outside the home. As shown in Table 1, demographic characteristics were similar for caregivers and controls with one exception: Caregivers were more likely to be currently married at the beginning of the study,  $\chi^2 = 34.64$  ( $df = 1$ ,  $N = 214$ ),  $p < .001$ , of potential concern given that married individuals tend to be advantaged compared to non-married, divorced, or bereaved individuals (Graham et al., 2005). Because marital status changed throughout the study (due to divorce and bereavement), we created a dummy-coded variable to indicate who was currently married at the beginning of the study, for use as a possible covariate in later analyses. As shown in Table 1, the two groups were also comparable on the majority of the other variables included in the study, including body mass, medication use, and most health behaviours. The health behaviours on which they differed (cigarette use and exercise) were included in the final structural model, along with sleep quality.

As has been reported elsewhere, caregivers in this study reported significantly higher perceived stress than non-caregivers and substantially higher perceived stress than national norms (Kiecolt-Glaser et al., 1995) which supports the conceptualization of caregiver status as a proxy for chronic stress. As shown in Table 1, caregivers also showed significantly higher depressed mood,  $t(212) = 3.08$ ,  $p < .01$ , bodily pain,  $t(208) = 2.02$ ,  $p < .05$ , and a non-significant trend towards higher overall hostility,  $t(212) = 1.67$ ,  $p = .10$ . Although the average caregiver just met criteria for depression based on the BDI-SF, the sample as a whole was relatively well-functioning and not clinically depressed. Average CRP levels for the overall sample (4.9 mg/L) are quite high, given that levels of 3 mg/L are considered high risk for cardiovascular disease (Pearson et al., 2003). There were 12 individuals in the current study with CRP levels greater than 10 mg/L in more than 1 year, which can indicate an inflammatory disease state or trauma (Pearson et al., 2003). These individuals were retained in the study after determining that their inclusion had no impact on the significance of key paths within the examined SEM models or on overall fit of these models to the data.

Table 2 presents the correlations among measured indicators for the sample as a whole, using averaged values across years for IL-6, CRP, and hostility. Hostility showed a trend toward higher CRP levels ( $r = .11$ ,  $p = .10$ ) but was not associated with IL-6 levels. Greater bodily pain was significantly associated with higher CRP levels ( $r = .31$ ,  $p < .01$ )

Table 1  
Sample characteristics

Variable	Overall (n = 214)	Caregivers (n = 113)	Controls (n = 101)
<b>Demographic</b>			
Age (years)	69.1 ± 9.3	69.8 ± 9.5	68.2 ± 9.5
Gender (% female)	71.5%	69.0%	74.0%
Ethnicity (% Caucasian)	87.4%	90.3%	84.2%
Currently married (%)	82.2%	97.3%	65.3%*
High school grad (%)	95.8%	95.5%	96.0%
Median income	20–30K	20–30K	30–40K
<b>Body mass</b>			
	26.3 ± 4.4	26.5 ± 4.3	26.1 ± 4.5
<b>Medication use (average all years of # participants using)</b>			
Cardiac/beta-blockers	0.3 ± 0.4	0.3 ± 0.4	0.3 ± 0.4
Hypolipidemic	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3
Estrogen	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4
<b>Health behaviours</b>			
Sleep quality <sup>a</sup>	6.1 ± 3.6	6.4 ± 3.7	5.7 ± 3.5
Exercise (dys/wk)	2.1 ± 1.9	1.8 ± 1.8	2.4 ± 1.9*
Cigarettes (pks/wk)	0.3 ± 1.5	0.1 ± 0.5	0.54 ± 2.0*
Caffeine (drinks past 48 h)	3.0 ± 2.7	3.0 ± 2.7	2.9 ± 2.8
Alcohol (drinks past wk)	1.8 ± 0.7	2.2 ± 4.1	1.8 ± 3.1
Hostility (overall Ho scale)	14.8 ± 6.9	15.6 ± 6.8	14.0 ± 6.9*
Pain <sup>b</sup>	71.5 ± 20.3	68.9 ± 20.5	74.5 ± 19.7*
Depressed mood	4.5 ± 3.5	5.2 ± 3.5	3.7 ± 3.3*
IL-6 (pg/ml) <sup>c</sup>	6.3 ± 29.7	7.8 ± 40.0	4.6 ± 8.9
CRP (mg/L) <sup>c</sup>	4.9 ± 5.1	5.1 ± 5.4	4.9 ± 4.6

Note. Values are expressed as means ± standard deviation. The groups are similar on all characteristics where noted.

<sup>a</sup> Lower scores are indicative of greater sleep quality.

<sup>b</sup> Lower scores are indicative of greater bodily pain.

<sup>c</sup> Although log-normed values are used in all analyses, raw values are provided here to aid in interpretation.

\* Those in the caregiver group were significantly more likely to have been married at beginning of the study,  $\chi^2 = 34.64$  ( $df = 1$ ,  $N = 214$ ),  $p < .001$ , and reported less vigorous exercise,  $t(212) = -2.27$ ,  $p < .05$ , and less use of cigarettes,  $t(212) = -2.32$ ,  $p < .01$ . Caregivers reported marginally more overall hostility,  $t(212) = 1.67$ ,  $p = .10$ , and significantly higher depressed mood,  $t(2, 212) = 3.08$ ,  $p < .01$ , and pain  $t(208) = 2.02$ ,  $p < .05$ .

Table 2  
Correlations among measured indicators

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. CRP	.27**	.11	-.31**	.06	-.12	.16*	-.07	.48**	.14*	-.05	.21**	.08	-.24**	.23**	.06	-.09
2. IL-6	—	-.01	-.09	-.07	.19**	-.19**	.02	.21**	.25**	.06	-.21**	.03	-.10	.09	-.10	.07
3. Hostility		—	-.25**	.40**	.04	-.14*	.11	.12	.13	.03	-.02	.22**	-.15*	-.03	-.01	-.04
4. Pain			—	-.49**	-.10	-.04	-.05	-.19**	-.20**	-.10	-.08	-.29**	.24**	.05	.07	.09
5. Depress.				—	-.04	.09	.01	.03	.21**	.11	.21**	.36**	-.21**	-.05	-.02	-.07
6. Age					—	-.33**	.13	-.24**	.18*	-.03	-.27**	.03	-.05	-.13	-.16*	-.05
7. Gender						—	-.27**	.02	-.13	-.06	.36**	.06	-.05	.12	-.05	-.19**
8. Married							—	.02	.06	-.03	-.10	.06	-.08	-.12	-.02	.11
9. BMI								—	.11	.01	-.09	-.05	-.23**	-.02	.07	-.03
10. Cardiac									—	.24**	-.05	.12	-.07	-.01	-.25**	-.04
11. Antilipid										—	.03	.15	-.02	-.08	-.08	-.02
12. Estrogen											—	.12	-.01	.14*	.01	-.07
13. Sleep												—	-.22**	-.01	-.21**	-.13
14. Exercise													—	.02	.02	.09
15. Cigarette														—	.21**	.12
16. Caffeine															—	.17*
17. Alcohol																—

Note. Pain, low pain; Depress., depressed mood; Married, married (no = 0, yes = 1); BMI, body mass index; Cardiac, cardiac and beta-blocker use; Antilipid, hypolipidemic agent use; Estrogen, estrogen use; Sleep, low sleep quality.

\*  $p < .05$ .

\*\*  $p < .01$ .

but also not with IL-6 values. To further explore the associations between hostility and pain with CRP, we created dummy-coded variables to distinguish participants with particularly low and high hostility and bodily pain, based

on plus or minus one standard deviation from the mean. The lowest pain group ( $n = 32$ ) had average CRP levels of 3.22 ( $SD = 2.77$ ) while the highest pain group had levels at 7.72 ( $SD = 6.22$ ); an ANOVA revealed that differences

between all three groups were significant,  $F(2,207) = 7.44$ ,  $p < .001$ , as was the difference between the two most extreme groups,  $t(207) = -3.74$ ,  $p < .001$ . The lowest hostility group had CRP levels at 3.40 ( $n = 35$ ), versus 5.27 for the highest hostility group ( $n = 34$ ); an ANOVA showed that differences between the averages of these groups approached significance,  $F(2,211) = 2.21$ ,  $p = .10$ , and the difference between the most extreme groups was marginally significant,  $t(211) = -1.86$ ,  $p = .06$ .

As expected, the key variables of interest were significantly correlated: Hostility was significantly associated with greater bodily pain ( $r = .25$ ,  $p < .01$ ) as well as depression ( $r = .40$ ,  $p < .01$ ), and depression was also strongly associated with greater bodily pain ( $r = .40$ ,  $p < .01$ ). CRP levels were also correlated with IL-6 levels, body mass, gender, cardiac/beta-blocker use, estrogen use, exercise, and cigarette use (see Table 2), while IL-6 levels were associated with age, gender, body mass, cardiac/beta-blocker use, and estrogen use. Importantly, marital status was not correlated with any variable other than gender.

### 3.2. Measurement model evaluation

#### 3.2.1. CRP and IL-6

Using log-transformed scores of mean values at each year, individual measurement models for IL-6 and CRP values were both a good fit to the data. Next, in addition to specifying an association between IL-6 and CRP levels, which are tightly correlated (Black, 2003), we allowed measurements of IL-6 and CRP in the same year to covary ( $B$ 's ranged from .24 to .47), which allowed us to account for the fact that the subset of participants at each given year was slightly different due to participant death and the addition of new participants. This final model with both IL-6 and CRP was an excellent fit to the data,  $X^2(47) = 48.76$ ,  $p = .40$ , CFI = .99, and RMSEA = .01 (90% CI = .00–.05). Each of the factor loadings relating each measured indicator to its latent construct (range  $-1.0$  to  $+1.0$ ) were significant ( $B$ 's between .67 and .86,  $p$ 's  $< .05$ ), further suggesting that the latent constructs of IL-6 and CRP were estimated successfully from the measured values.

#### 3.2.2. Hostility

Using means across all 5 years for the six Cook–Medley subscales, the predicted measurement model of hostility was also a good fit to the data despite a significant  $\chi^2$ ,  $X^2(9) = 18.72$ ,  $p < .05$ , CFI = .93, and RMSEA = .07 (90% CI = .02–.12). All factor loadings of the measured indicators to the latent construct were significant at  $p < .001$ ,  $B$ 's between .33 and .63.

### 3.3. Central analyses with structural models

#### 3.3.1. Model with hostility, pain, depressed mood, and inflammatory markers

Using only the key variables of interest, a model was evaluated (see Fig. 1) in which hostility and bodily pain

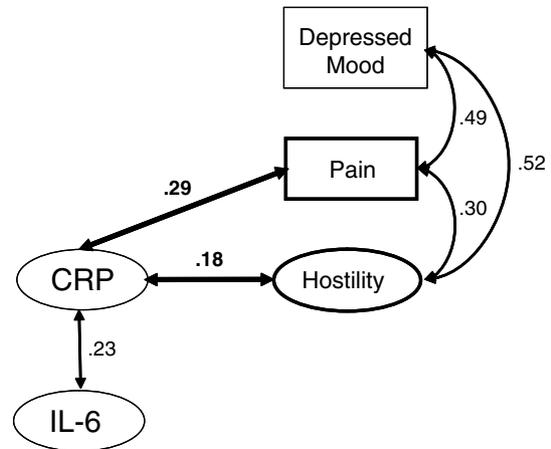


Fig. 1. Structural model associations among key variables,  $X^2(159) = 161.34$ ,  $p = .43$ ; CFI = 1.0, and RMSEA = .01 (95% CI = .00–.03). All coefficients significant at  $p < .05$  or better. For all variables, higher values indicate higher levels of the construct. The absence of a path indicates the lack of a significant association. The latent constructs are represented as ovals and the measured variables as rectangles. Key paths and variables are shown in boldface.

were bi-directionally associated with CRP levels; bi-directionality was specified to reflect the reality that an increase in inflammation may lead to increased pain and hostility, particularly over a span of years. A path was not specified between depressed mood and CRP levels based on examination of the correlation matrix and because depressed mood was included in the current study primarily to control for its association with other key constructs. Because of the non-significant correlation between any of the key variables and IL-6 levels, direct associations with IL-6 were not examined in this model. The overall fit of the model was excellent,  $X^2(159) = 161.34$ ,  $p = .43$ ; CFI = 1.0, and RMSEA = .01 (95% CI = .00–.03). As expected, hostility was associated with higher levels of CRP ( $B = .18$ ,  $p < .05$ ), as was greater bodily pain ( $B = .29$ ,  $p < .001$ ). Also as expected, hostility and higher pain were both associated with greater depressed mood ( $B = .52$  and  $B = .49$ , respectively,  $p$ 's  $< .01$ ) and hostility and greater pain were also positively related ( $B = .30$ ,  $p < .01$ ).

Exploratory analyses with the above model confirmed that depressed mood, bodily pain, and hostility were not associated with IL-6 levels and that depressed mood was not associated with CRP levels; the inclusion of these paths did not affect overall model fit. Marital status was not associated with any of the key variables in the model, and is not included in subsequent analyses.

#### 3.3.2. Model with addition of biomedical factors

Next, a model was examined that included the biomedical factors of gender, body mass index, age, and medication use. Only paths that were suggested by the correlation matrix and which made theoretical sense were examined. For example, a direct path between cardiac/beta-blocker medication and bodily pain was not specified as the correlation between these variables was not predicted; this path

was later examined on an exploratory basis within the final model and was confirmed to be non-significant in that context. As originally examined, the model was a good fit overall,  $X^2(275) = 318.71$ ,  $p < .01$ ; CFI = .96, and RMSEA = .03 (95% CI = .01–.04). To clarify the model, three non-significant paths were dropped: paths between gender and CRP and IL-6 values, and the path between cardiac medication use and age. This slightly trimmed model was also a good fit to the data,  $X^2(278) = 325.17$ ,  $p < .05$ ; CFI = .97, and RMSEA = .03 (95% CI = .01–.04). With these variables added to the model, hostility remained uniquely associated with CRP levels ( $B = .17$ ,  $p < .05$ ), as did greater bodily pain ( $B = .24$ ,  $p < .001$ ).

3.3.3. Final model including health behaviours

Finally, a model was examined that included the addition of health behaviours (see Fig. 2). To avoid adding more measured indicators than necessary to the model, only the health behaviours that were significantly correlated with either IL-6, CRP, hostility, or bodily pain were added (sleep quality, exercise, and cigarette use). Again, only paths that were suggested by the correlation matrix and theory were examined (for example, a path between hostility and exercise was not specified). A non-significant path between exercise and CRP levels was dropped from the model, with no impact on model fit. Despite a significant  $\chi^2$ ,  $X^2(351) = 428.25$ ,  $p < .01$ , the model was a good fit overall, CFI = .96, RMSEA = .03 (95% CI = .02–.04). In this model, greater bodily pain remained uniquely associated with higher CRP levels ( $B = .24$ ,  $p < .001$ ) and the unique association between hostility and CRP values decreased

only slightly to marginal significance ( $B = .16$ ,  $p = .07$ ). As expected, hostility was also uniquely associated with bodily pain ( $B = .25$ ,  $p < .01$ ).

Although depressed mood was not directly associated with CRP or IL-6 levels, it was indirectly associated with CRP via its strong association with hostility and pain ( $B$ 's .49 and .47, respectively,  $p$ 's < .001). Neither the inclusion of a path between depressed mood and CRP nor paths between the key variables and IL-6 were significant and did not change the fit of the overall model. In this final model, 38% of the variance of CRP levels was accounted for and was predicted directly by body mass, cardiac/beta-blocker use, estrogen use, cigarette use, hostility, pain, and IL-6, while 17% of the variance of IL-6 levels was accounted for and was predicted directly by body mass, age, cardiac/beta-blocker use, estrogen use, and CRP.

3.4. Moderation of effects by caregiver status

The model shown in Fig. 2 was tested for moderation by caregiver status using multi-sample structural equation modeling techniques provided in AMOS. First, all paths in the model were constrained to be equal for caregivers and controls (non-caregivers),  $X^2(735) = 969.46$ ,  $p < .001$ , CFI = .88, and RMSEA = .04 (95% CI = .03–.05). This model was compared to one in which no paths were constrained,  $X^2(702) = 907.71$ ,  $p < .001$ , CFI = .90, and RMSEA = .04 (95% CI = .03–.04). A difference test indicated that the fit of the constrained model was significantly worse  $\Delta X^2(33) = 61.75$ ,  $p < .01$ , suggesting that there were significant differences between the two groups. In the

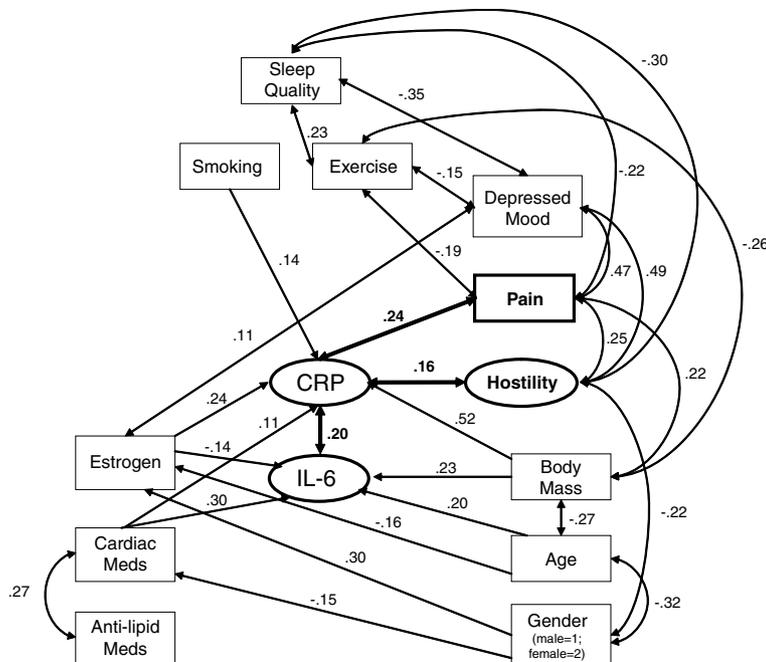


Fig. 2. Final model,  $X^2(351) = 428.25$ ,  $p < .01$ , CFI = .96, and RMSEA = .03 (95% CI = .02–.04). All coefficients significant at  $p < .05$  or better. For all variables, higher values indicate higher levels of the construct. The lack of a path indicates the lack of a significant association. The latent constructs are represented as ovals and the measured variables as rectangles. Key paths and variables are shown in boldface.

unconstrained model, we next examined differences in the key paths of interest. The path between bodily pain and CRP was significant for caregivers ( $B = .35, p < .001$ ) but not significant for non-caregivers ( $B = .05, p = .55$ ). A difference test comparing models with and without constraints on this path indicated that it was significantly different between the two groups,  $\Delta X^2(1) = 7.3, p < .01$ . The path between hostility and CRP levels was marginally significant for controls ( $B = .22, p = .10$ ) but non-significant for caregivers ( $B = .13, p = .24$ ); however, a difference test indicated that this path was not significantly different for the two groups,  $\Delta X^2(1) = .18, p > .10$ .

### 3.5. Presence of chronic disease

As noted earlier, some participants developed chronic diseases over the course of the 6 years. This was largely controlled for by including medication use in the models. For example, the use of cardiac/beta-blocker medication in the present study was correlated with cardiac problems that developed over the course of the study,  $r = .58, p < .001$ . In addition, we separately added to the final model a variable indicating the presence of self-reported cardiac problems over the years of the study, and a variable that indicated the presence of a broader range of chronic conditions, including osteoarthritis, high blood pressure, and diabetes. The inclusion of neither variable affected the key paths of interest (e.g., between hostility and CRP, or bodily pain and CRP), the moderation by caregiver status, or the overall variance of CRP predicted by the model overall.

## 4. Discussion

Based on longitudinal data assessed over 6 years, results of the current study indicate that average bodily pain, which was relatively consistent over time, plays a unique role in a bi-directional cycle of inflammation among older adults. To our knowledge, this is the first study to examine long-term pain and CRP levels in the context of other psychosocial factors in any sample. Independent from depression and hostility, as well as biomedical and health behaviour risk factors and the presence of chronic disease, greater perceived pain was associated with an increase in CRP levels (but not IL-6) for the overall sample. However, when caregivers were examined separately from control participants, pain was associated with higher CRP values only for caregivers. These findings suggest that pain may be associated with elevated inflammation primarily under conditions of chronic stress. When faced with additional stress, the stress, aggravation, and life impact of pain may cause systemic inflammation or may exacerbate inflammation already caused by underlying physical pathology. Other explanations for the interaction effect by caregiver status are possible. For example, there might not have been sufficient variability in pain scores in the control group to make observable an association between CRP levels and pain. However, any differences between the control and caregiver

ing populations are probably at least related to chronic stress, as great care was taken to recruit and maintain equivalent groups in this study.

Results of this study also indicate that hostility is uniquely associated with systemically elevated CRP levels, although less robustly so than was pain. Hostility was significantly associated with CRP levels after accounting for pain and depression. Even after taking biomedical risk factors and health behaviours into account, hostility was marginally associated with CRP levels in the present study. This finding is in concordance with research with younger adults, which has also showed a marginally significant association between hostility and CRP levels after controlling for similar risk factors (Suarez, 2004). The present work extends such findings by employing a sample of older adults, for whom chronically elevated inflammation is particularly dangerous, and using multivariate statistical techniques to examine the role of hostility separate from depressed mood and other risk factors, while accounting for the reality that they are correlated. A strength of the present study is that it enables understanding of how hostility may be indirectly associated with CRP levels, via associations with pain, health behaviours, and other factors that are associated with CRP levels.

To the extent that both pain and hostility are associated with systemic elevation of inflammation, they may contribute to a vicious cycle in which inflammation may increase pain directly (e.g., by nerve pressure or tissue damage (Black, 2002; Sturmer et al., 2005)) or indirectly via psychological responses such as hostility. Such a cycle of increased inflammation might dramatically decrease quality of life and overall health, particularly for older adults for whom elevated CRP is associated with mortality and the development of disability even in those without cardiovascular disease (Ferrucci et al., 1999; Kritchevsky et al., 2005).

As IL-6 is the primary inducer of CRP in the liver and appears to be the central mediator of the acute phase response (Black, 2003; Heinrich et al., 1990), it is somewhat surprising that both pain and hostility were associated with CRP but not serum IL-6 levels in the current study. However, this pattern of results is in concordance with studies of younger adults which have shown hostility to be associated with CRP (Suarez, 2004) but not with IL-6 except for certain subpopulations (Miller et al., 2003a; Suarez, 2003). The presence of CRP certainly indicates the presence of IL-6 (Black, 2003) and not only were the latent factors of CRP and IL-6 levels associated in the current study but the individual year averages of CRP and IL-6 were also separately associated. It is possible that chronically elevated CRP levels may be the primary and most visible end product of chronic over-stimulation of IL-6 (Black, 2003) in response to long-term pain and trait hostility.

Although depression is strongly associated with IL-6 (Irwin, 2001; Kiecolt-Glaser and Glaser, 2002; Miller et al., 2003b; Musselman et al., 2001), and has been associated with CRP levels (e.g., Miller et al., 2002b; Tiemeier et al., 2003), it is not very surprising that depressed mood was not

associated with either inflammatory marker in the present study. Depressive symptoms have been associated with IL-6 (Lutgendorf et al., 1999) as well as with CRP (Penninx et al., 2003); however, studies showing the most consistent association have been with clinically depressed samples or with samples with a larger percentage of depressed participants. Indeed, Suarez (2004) has shown that depressed versus non-depressed individuals (as determined by the clinical depression cutoff on the BDI) showed significantly greater levels of CRP. Participants in the current study overall were relatively well-functioning and not clinically depressed. It is likely that correlations between depressive symptoms and inflammatory responses in healthy populations are responses to stress as opposed to causally related. That said, a combination of hostility and depression appears to be a greater predictor of CRP levels among younger adults than hostility alone (Suarez, 2004). The present study is supportive of an indirect role of depression mood on CRP in that depressed mood was strongly associated with hostility, pain, and estrogen use, all of which were associated with CRP levels.

Although replication with prospective studies would be needed to determine the clinical impact of hostility and pain on CRP, the associations found in the present study may well be meaningful for overall health. As noted in the results, the overall mean CRP for the sample was elevated, at 4.9 mg/L, probably due to the mean age of 69 at study entry and increased stress due to caregiving activities among many participants. However, CRP levels were much higher among those with the highest pain (7.72 as compared to 3.22) and marginally significantly elevated among those with highest hostility (5.72 as compared to 3.40). Although CRP levels of 3.0 mg/L are often used as a cutoff to determine cardiovascular disease risk, most studies show a dose–response relationship (Pearson et al., 2003), indicating that such elevations may be damaging. Extremely high levels of CRP may be particularly dangerous for older adults, as they are at greater risk for serious complications and death associated with inflammatory diseases and related conditions. Moreover, as hostility has also been associated with CRP levels in younger adults, this trait tendency may be involved in a process that starts early in life, leading to the emergence of serious illness years later.

Additional research will be needed to understand the physiological mechanisms underlying associations between hostility, pain, and CRP. Hormonal changes in response to stress can induce inflammatory processes (Black, 2002; McEwen et al., 1997) and are likely to play a major role. Pain can initiate a systemic stress response by activating neuroendocrinological pathways, including the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, with accompanying release of stress hormones. Hostility is associated with exaggeration of such responses particularly in reaction to interpersonal stressors (Smith and Spiro, 2002). Although stress hormones typically have an inhibitory effect on proinflammatory cytokines in a local

environment, chronic stress may lead to dysregulation, resulting in a systemic and excessive immune response (Elenkov and Chrousos, 2002; Miller et al., 2002a). Among older adults, catecholamine driven increases in IL-6 may be further aggravated by age-related decreases in adrenal steroids that typically inhibit IL-6 production (Ershler, 1993). In addition, trait hostility is associated with tryptophan (a precursor of the neurotransmitter serotonin) and low brain serotonergic function (for a review, see Williams, 2002). As assessed with the Cook–Medley scale used in the current study, hostility has also been associated with blunted responsiveness of  $\beta$ -adrenergic receptors in both women and men (Sherwood et al., 2004), which is related to heightened sympathetic activity (Mills et al., 1997; Wood et al., 1982).

Genetic predispositions may also play a causative role in the associations observed in the present study. As multiple genetic loci appear to be involved in hostility, it is possible that the same areas may be relevant to both inflammation and hostility, potentially driving all or some of their association (Smith and Spiro, 2002). It is also possible that genetic and environmental factors interact to influence inflammation. Recent work suggests that psychological and pain-related stress may be particularly problematic for individuals with genetic predispositions to inflammatory responses. For example, industrial employees with the TNF- $\alpha$ -308 G/A gene polymorphism who self-reported high levels of sustained exhaustion evidenced greater CRP levels (Jeanmonod et al., 2004). Future investigations of genetic–environmental interactions in this area would be useful.

One limitation of the current research is that we did not have information about specific pain conditions affecting participants. Certain forms of pain, such as rheumatoid arthritis or sciatic pain, might be more strongly associated with inflammation than others. It is also unfortunate that we were not able to examine the role of statin use specifically in our final model. Statins were not widely used at the onset of the current study but have since been shown to have significant anti-inflammatory effects. However, we were able to control for hypolipidemic agents more generally, which would have included the use of statins by participants. Finally, the design of the current study does not allow us to make causal statements about the degree to which hostility and pain contribute to CRP or the extent to which CRP contributes to hostility and pain. However, it is likely that this association is bi-directional, and a strength of the current study is that we specified bi-directional paths among these variables in the examined models. Prospective studies to confirm causal directions would be helpful, but future research in this area should also include studies that can examine interactive, circular effects with other and larger samples.

Our findings contribute to a growing body of research demonstrating that psychological factors are associated with systemic inflammation (e.g., Kiecolt-Glaser and Glaser, 2002; Lutgendorf et al., 1999; Miller et al., 2003a; Suarez, 2004).

By examining a multivariate bi-directional model that included hostility, pain, and depression, the present study is supportive of a model in which pain and hostility contribute to a cycle of elevated inflammation, directly and indirectly, with a potentially significant health impact for older adults. Such research is particularly exciting because it suggests several areas for future research targeted at interventions to reduce systemic inflammation. For example, inflammation may be reduced by interventions to improve pain, particularly for those who report feeling unable to cope with the stress in their lives. In addition, those experiencing chronic pain, which is often under treated and difficult to manage with medication alone (Turk and Flor, 1999), may benefit from medical treatment to reduce inflammation or even psychological interventions to reduce hostility or better manage anger responses.

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