THE LONGITUDINAL ASSOCIATION OF SOCIAL RELATIONSHIP CHARACTERISTICS WITH CIRCULATING MARKERS OF INFLAMMATION AND POTENTIAL MECHANISMS IN HEALTHY OLDER ADULTS

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A large body of literature has established an association of social relationship characteristics with premature mortality and recent evidence suggests that systemic inflammation may mediate this association. However, the literature examining the link between social relationships and inflammation using healthy samples is limited by 1) the use of cross-sectional designs, 2) few methodologically rigorous longitudinal studies, 3) cursory measures of social relationships, and 4) failure to explore mechanisms accounting for any significant effects. To address these limitations, the current study used growth curve modeling to test the prospective association of perceived support, social integration, and marital satisfaction with the rate of change of inflammatory biomarkers, CRP and IL-6 in healthy, older adults. In the case of any significant effects, the study planned to test interpersonal (i.e. social interactions), affective (i.e. positive/negative affect), and behavioral (i.e. obesity, smoking, sleep duration) variables as mechanisms of overall effects using mediation analyses. Questionnaire measures of social integration, perceived social support, and marital satisfaction were collected at baseline, inflammatory biomarkers and health behaviors (with the exception of sleep duration) were measured at all 3 time-points, and social interaction characteristics and affect were measured using ecological momentary assessment (EMA) at baseline and 6-year follow up. Results showed no significant prospective association of social integration, perceived support, or marital quality with the rate of change in IL-6 and CRP over a 6-year period. Additionally, perceived

social support did not buffer the deleterious effect of chronic stress on the longitudinal changes in these biomarkers. Given lack of direct effects, longitudinal mediation analyses were not pursued. Exploratory analyses testing social interactions as independent predictors of the longitudinal changes in IL-6 and CRP showed that higher frequency of negative interactions with a spouse in daily life was associated with higher initial levels of IL-6, adding to the body of work examining the link between marital quality and inflammation. The non-significant prospective associations in the main analyses may, in large part, be due to the lack of power in the current study, as well as due to homogeneity in social behavior and health characteristics in this sample.

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PREFACE

To my grandfather and late grandmother: You created the optimal socioeconomic and familial conditions in place for generations ahead of you to prosper and I feel deeply indebted and grateful for that privilege. To my parents and brother: I acknowledge and appreciate your unwavering support throughout my graduate journey. To my father for his constant “can do” and “so what?” attitude. To my mother for being my biggest cheerleader and maintaining a great sense of humor. To my brother for allowing me to exercise my “older sibling” rights generously these past few years. To my brand-new husband for his unconditional love and commitment to our relationship, which has only strengthened with time. I am lucky to be your partner and on the receiving end of your selfless nature. To my new parents-in-law: the completion of my graduate journey would not have been possible without your love, support, and patience. To my milestone committee members: I would like to extend a heartfelt thanks to you all (Sheldon Cohen, Anna Marsland, Amanda Forest, Aidan Wright, and Karen Matthews) for your words of praise, encouragement, as well as constructive feedback on all projects. And last (but not least), I would like to thank my research advisor, Dr. Thomas Kamarck, for his ongoing guidance throughout my graduate journey and for making this possible.

1.0 INTRODUCTION

1.1 BACKGROUND AND SIGNIFICANCE

A large body of research has established an association of structural (i.e. quantitative) and functional (i.e. qualitative) features of social relationships with a variety of health outcomes (House et al., 1988), including premature mortality (Berkman & Syme, 1979; Holt-Lunstad et al., 2010; Holt-Lunstad et al., 2015). Social integration, a structural measure of social relationships, and perceived support, a functional measure, are two of the most widely studied relationship characteristics examined in relation to mental and physical health. Social integration is considered an objective measure of diversity of social roles and frequency of interactions with members of one's social network. Measures of social integration emphasize objective characteristics of one's global social network, rather than beliefs, attitudes, or perceptions about network members. While social integration indicates greater diversity in social roles and greater social participation, social isolation implies a lack of diversity in social roles and limited social engagement (Holt-Lunstad et al., 2015). In contrast, perceived social support is considered a subjective measure of perception of availability of 3 broad types of support: instrumental (e.g. financial aid), informational (e.g. advice or appraisal/cognitive support), and emotional support (e.g. perceived expression of empathy, care, etc.) (Cohen, 2004). The inverse association of both social constructs with premature mortality illustrates the salubrious effects of regular social

participation and perception of supportive ties, as well as the detrimental effects of social isolation and perception of lack of support.

In addition to these network-level characteristics of social relationships, characteristics of specific relational domains have also been studied in association with health outcomes. A recent meta-analysis examined the association of perceived social support with all-cause mortality and examined any moderators of this association, including the identity of support providers (e.g. family vs. friends vs. others) (Shor et al., 2013). Data were obtained from 50 published studies between 1989 and 2008. Studies showed equal representation of men and women and of various age groups above the age of 40; the median of studies' maximum follow-up duration was 6.12 years. Results showed that individuals with lower support levels had a significantly greater risk for mortality compared to those with higher ratings of support, and that individuals who received less or no support from family members had a higher mortality rate compared to those who received relatively high levels of family support. This finding was not replicated when examining support from friends or acquaintances, highlighting the importance of familial relationships in the association between perceived support and mortality This empirical evidence aligns with a recent theoretical model outlined by Feeney and colleagues (2015), which emphasizes the importance of well-functioning close relationships, such as with family members, in achieving psychological, social, and physical health.

Given that marriage is the central familial relationship in adulthood, and that it can be a source of both support and conflict, the association of marital quality with health outcomes has been of particular interest. A recent meta-analysis examined the association of marital quality with a variety of health outcomes, one of which included mortality, in a sample of 72,000 middle-aged individuals (Robles et al., 2014). A total of 128 cross-sectional and longitudinal

(with a median follow-up around 2-5 years) studies were included in the meta-analysis, out of which 112 included measures of various clinical endpoints, whereas the rest of the studies examined cardiovascular and neuroendocrine processes. Results showed that individuals with high marital quality (i.e. those reporting greater satisfaction with their relationship, positive attitudes toward one's partner, and low levels of hostile and/or negative behavior) tended to be at lower risk for cardiovascular disease, reported better self-rated health and/or lower self-rated symptoms, reported fewer cardiovascular disease-related events (e.g. cardiac events, rehospitalization, mortality etc.), and were at lower risk of premature mortality. Marital quality may be particularly important at older ages, given growth curve evidence that marital strain accelerates the typical decline in self-rated health that occurs over time, especially at older ages (Umberson et al., 2006). This evidence suggests that poor marital quality is related to a variety of physical health outcomes, the most important of which may be cardiovascular disease and premature mortality.

Given that cardiovascular disease (CVD) is a leading cause of mortality, it may be that the decline in health and elevated risk of mortality in distressed marriages may be partly due to subclinical progression of CVD. In fact, the quality of marital interactions in naturalistic settings, measured through ecological momentary assessment (EMA), has been related to subclinical measures of CVD. Specifically, mean negativity of marital interactions in daily life uniquely associates with extent of CVD, indicated by greater intima-media thickness (IMT), above and beyond the effect of negative interactions with others, in healthy middle-aged adults (Joseph et al., 2014). Overall, data reported from this study and those previously discussed from the meta-analysis highlight the unique importance of marital quality in association with risk for CVD and mortality.

1.2 SYSTEMIC INFLAMMATION AS A BIOLOGICAL MECHANISM

Systemic inflammation has garnered interest as a potential biological mechanism that may account for the association of social relationship characteristics with premature mortality. This has been substantiated by recent evidence suggesting that cumulative inflammatory burden may, in part, account for the association of social relationship characteristics with premature mortality (Yang et al., 2013). This particular study, using Cox regression for survival analysis, reported a positive prospective association of social isolation with premature mortality at 18 year follow up, with effects strongest for older men, in a sample of 6,729 participants that were aged 40 years and older. Follow-up analyses were conducted to test whether chronic inflammatory processes account for this association. An inflammatory burden variable, based on measures collected at baseline, was created to index high risk cut off scores of inflammatory biomarkers, including C-reactive protein (CRP), fibrinogen, and serum albumin. Inclusion of the inflammatory burden index reduced the sizes of coefficients linking social isolation with mortality across all regression models and eliminated the significance of the coefficients linking social isolation with cancer mortality, consistent with a potential mediating role.

Given this evidence and the fact that coronary artery disease (CAD) is one of the leading causes of mortality, there has been interest in studying the association of social relationship characteristics with specific inflammatory biomarkers implicated in future risk of CAD. CAD is increasingly viewed as an inflammatory process characterized by a number of localized events at the endothelium, such as increased production of proinflammatory cytokines, adhesion molecules, and endothelial dysfunction (Black & Garbutt, 2002). Early signs of atherosclerosis include lesions, consisting of blood-borne inflammatory and immune cells, lipids, and debris in thickened areas of the innermost layer of the artery, the intima. Lesions are preceded by fatty

streaks, characterized by lipid-laden cells beneath the endothelium (Hansson, 2005). While this process is localized to the endothelial lining in initial stages, the chronic production of pro-inflammatory cytokines by activated macrophagescy at the site of the endothelium can cause these cytokines to spill into circulation and initiate a systemic acute phase response (APR), leading to systemic inflammation in the periphery. The APR is characterized by 1) the prolonged presence of pro-inflammatory agents in peripheral circulation, and 2) the hepatic production of acute phase proteins (APPs), such as C-reactive protein (CRP). Elevated levels of these APPs, especially for prolonged periods, may be a precursor to a number of chronic diseases of aging.

The progression of CAD is often considered an inflammatory cascade of events, initiated by primary pro-inflammatory cytokines (e.g. IL-1). Primary cytokines catalyze the production of secondary pro-inflammatory cytokines, particularly interleukin (IL)-6. IL-6 forms a complex with sIL-6r, a soluble receptor for IL-6, in the blood that activates the inflammatory processes by prolonging the half-life of IL-6 (Jones et al., 2001). Elevated levels of circulating IL-6 have been previously associated with a variety of health outcomes, including cardiovascular (CV) morbidity and mortality (Van Gaal et al., 2006). However, interpretation of elevated levels of IL-6 should be made with caution, given that 1) IL-6 is largely considered a "messenger" molecule that can function as anti-inflammatory under certain conditions (e.g. physical activity), and 2) IL-6 production can be induced from multiple sources, such as smooth muscle cells and adipocytes (Hansel et al., 2010). Nevertheless, increases in IL-6, in part, trigger an APR, which is often measured by elevated levels of APPs, including CRP (Libby & Ridker, 2002). CRP is a non-specific, downstream, and stable marker of systemic inflammation and is known to reliably predict future risk of CVD (The Emerging Risk Factors Collaboration, 2013).

Notably, IL-6 has been shown to interact with the nervous system through the autonomic nervous system (by activation of the vagus nerve) and the central nervous system (by crossing the blood brain barrier) (Tracey, 2002). Through this interaction, IL-6 is able to uniquely initiate symptoms of "sickness behavior," which can affect quality and quantity of social participation. Physiological symptoms of sickness behavior include fever and increases in circulating white blood cells, while behavioral symptoms include increases in depressive symptoms and fatigue, and decreased cognitive function and social interaction (Maier & Watkins, 1998; Harrison et al., 2009). The bidirectional nature of the interaction between IL-6 and the nervous system, as one pathway, has implications for reverse causality in any associations observed with psychosocial factors.

In sum, the progression of CVD is described as an inflammatory process and elevated circulating levels of IL-6 and CRP in the periphery are associated with increased risk for CVD. Chronic psychosocial stress has been shown to induce production and elevation of inflammatory cytokines in the absence of injury or infection (Iwata et al., 2013), leading to the study of the link between psychosocial stress with circulating levels of inflammatory biomarkers (Black & Garbutt, 2002). In light of new evidence suggesting 1) a possible mediating role of systemic inflammation (Yang et al., 2013) in the association of social isolation with mortality, and 2) a link between social integration and social support with various pro-inflammatory biomarkers (Uchino et al., 2018), there has been an interest in the contribution of social relationship characteristics in determining circulating levels of inflammatory markers, as one pathway to heightened risk for premature mortality and CVD. However, the extant literature is limited in several ways and these limitations are discussed next.

1.3 SOCIAL RELATIONSHIPS AND INFLAMMATION

Social behavior and inflammation are increasingly being viewed as coregulators of each other. On the one hand, a wealth of evidence shows that social distress, conceptualized as loss, distress, separation, and rejection, associates with increased circulating levels of pro-inflammatory biomarkers across the lifespan in children (Slopen et al., 2013), adolescents (Fuligni et al., 2009), college students (Chiang et al., 2012), and older adults (Schultze-Florey et al., 2012). On the other hand, there is also evidence that increase in inflammatory activity shapes social behavior in an effort to avoid illness and aid recovery by increasing approach-related behavior to positive social stimuli and increasing avoidance of negative social stimuli (Eisenberger et al., 2017). For example, previous work has shown that individuals who experienced an inflammatory challenge to an endotoxin showed 1) a greater desire to be with close others during the peak inflammatory response, 2) greater neural activity in the ventral striatum (VS) in response to viewing images of their loved ones (Inagaki et al., 2015), and 3) greater activity in reward-related neural regions in response to positive social feedback (Muscatell et al., 2016). In contrast, greater inflammatory activity to endotoxin was associated with greater threat-related neural sensitivity to social exclusion (EisenbergerM et al., 2009), negative social evaluation (Muscatell et al., 2016), and to socially threatening images (Inagaki et al., 2012). Taken together, this evidence illustrates that systemic inflammation may be related to greater threat-related neural sensitivity to negative social stimuli and greater reward-related neural sensitivity to positive social stimuli (Eisenberger et al., 2017). Most importantly, it highlights the bidirectional effects between social behavior and inflammation, which have implications for study designs and in establishing directionality of any observed effects.

1.3.1 Social integration and inflammation

A large literature examines the association of structural aspects of social relationships with circulating markers of IL-6 and CRP in healthy samples. A qualitative review synthesizing this literature (Bajaj et al., unpublished) found a total of 16 studies that examined the association of social integration with circulating markers of inflammation, out of which 14 examined a cross-sectional association in healthy adults, and 2 examined a longitudinal association of child isolation with adult inflammation. This literature is characterized by relative consistency, as 12 of the 14 cross-sectional studies reported a significant positive association of social isolation with concentrations of inflammatory biomarkers (Loucks et al., 2006a; Loucks et al., 2006b; Ford et al., 2006; Loucks et al., 2005; Heffner et al., 2011; Hafner et al., 2011; Steptoe et al., 2003; Helminen et al., 1997; Glei et al., 2012; Shankar & McMunn, 2011; Kamiya et al., 2010; Seeman et al., 2014). Five of these 12 studies reported a gender-related effect, such that isolated men had higher concentrations of various circulating inflammatory markers than their more socially integrated counterparts, whereas there were no such associations shown among women (Loucks et al., 2006a; Loucks et al., 2006b; Ford et al., 2006; Loucks et al., 2005; Hafner et al., 2011). Moreover, one of these studies reported an additional age-related effect demonstrated by a positive association between isolation and CRP in older men only (Ford et al., 2006). Two studies out of the original 16 examined the longitudinal association of child isolation with adult inflammation and both reported a significant, positive association (Danese et al., 2009; Lacey et al., 2014); however, the measures of child isolation in these studies assessed social rejection and withdrawal, which may have limited comparability with measures of social isolation in adulthood.

Based on the quality criteria proposed in this qualitative review, studies reporting an association of social isolation with CRP were greater in quantity and quality than those reporting an association with IL-6. Specifically, 9 of the 14 studies that measured CRP as an outcome reported a significant positive association (Loucks et al., 2006b; Ford et al., 2006; Heffner et al., 2011; Glei et al., 2012; Shankar & McMunn, 2011; Kamiya et al., 2010; Danese et al., 2009; Lacey et al., 2014), while only 2 of the 6 studies that measured IL-6 as an outcome reported a significant positive association (Loucks et al., 2006a; Hafner et al., 2011). Studies reporting a significant association with CRP were also higher in quality based on pre-determined criteria that considered psychometric strength of questionnaire measures, adjustment for confounding variables, exclusion of participants with acute infections and/or exclusion of CRP values indicative of acute infections, and adequate report of detection sensitivity levels for all immunological assays.

Since this qualitative review, a meta-analysis (Uchino et al., 2018) was published with an updated record of this literature. The inclusionary criteria of this meta-analysis differed significantly from the previous qualitative review in a number of ways. In particular, the meta-analysis included 1) studies with stimulated measures of cytokines, 2) clinical samples, 3) studies with other pro-inflammatory biomarkers besides IL-6 and CRP, such as fibrinogen and TNF alpha, 4) studies with received support as a predictor, and 5) 13 new samples that were published after the previous qualitative review was completed. However, the conclusion drawn from this meta-analysis pertaining to the cross-sectional link between social integration and inflammation is consistent with the conclusion of the previous qualitative review. Specifically, both reviews concluded that there is a consistent, inverse association between social integration and IL-6 and CRP.

The consistency in the literature on social integration and inflammatory markers may be partly due to the homogeneity of measures used to assess social integration. Almost all studies that reported a significant association used Berkman & Syme's Social Network Inventory (SNI), or a measure based on this established instrument, in order to assess structural indices of social participation. This measure has been used in a variety of studies with reportedly high levels of predictive validity, with both inflammatory and mortality outcomes (Ford et al., 2006; Loucks et al., 2006; Berkman & Syme, 1979).

However, a major limitation of the literature examining the link between social integration and inflammation is its reliance on cross-sectional data due to limited prospective evidence. Uchino and colleagues (2018), in their meta-analysis, reported 6 samples that examined the association of social integration with inflammation longitudinally. However, 1 of these 6 samples examined this link with 12-month change in stimulated measure of TNF-alpha using a clinical sample of cancer patients, which precludes any comparison with circulating measures of IL-6 and CRP and in healthy samples (Marucha et al., 2005). The second sample (Cho et al., 2015) found a moderating effect of social isolation on the longitudinal association between sleep disturbance and CRP, but the study design did not include a baseline measure of social integration and therefore, did not allow for a test of a prospective main effect of social isolation with change in CRP. The last 4 samples examining the prospective link between social integration and inflammation were included in a study conducted by Yang and colleagues (2016). The study claimed to test the association of social integration with longitudinal change in CRP in 4 samples across the lifespan; however, 3 of their 4 samples lacked repeated longitudinal measures of biomarkers, thereby precluding any conclusions about an association with longitudinal <u>change</u> in biomarkers. Further, the 4th sample included CRP data from baseline only,

which also barred any conclusions about associations with change in biomarkers. In sum, while there seems to be a consistent inverse, cross-sectional association between social integration and IL-6 and CRP, the prospective evidence is limited by 1) its lack of study of circulating IL-6 and CRP, 2) its lack of study of this association prospectively in healthy samples, and 3) its inadequate measure of longitudinal change in IL-6 and CRP over the follow-up period.

Given the limitations associated with the extant prospective evidence, it is unknown whether the observed effects between social integration and IL-6 and CRP can be accounted for by the effect of change in these biomarkers on sickness behavior and the subsequent social withdrawal (Eisenberger et al., 2010). Further, it is also unknown whether socially integrated individuals show a slower increase, or even a decline, in these markers over time. The current study aims to address these limitations by 1) examining the longitudinal association of social integration, as assessed by the Social Network Inventory (SNI), with trajectory of circulating IL-6 and CRP over a 6-year period, ruling out reverse causality, and 2) exploring any moderation by age and gender in these associations.

1.3.2 Perceived support and inflammation

In contrast with the literature on social integration and inflammation, the cross-sectional literature on perceived social support and circulating IL-6 and CRP reports inconsistent findings. Nine total studies, in our initial qualitative review, tested the association of perceived support with circulating markers of inflammation and reported mixed evidence (Helminen et al., 1997; Glei et al., 2012; Kamiya et al., 2010; Davis et al., 1999; Hemingway et al., 2003; Mezuk et al., 2010; Runsten et al., 2014; Seeman et al., 2014; Nowakowski & Sumerau, 2015). While 3 studies reported significant associations (Mezuk et al., 2010; Glei et al., 2012; Runsten et al.,

2014), most studies report null associations (Bajaj et al., 2016; Hemingway et al., 2003; Kamiya et al., 2010; McDade et al., 2006; Helminen et al., 1997; Seeman et al., 2014; Nowakowski & Sumerau, 2015). Even in the 3 studies that reported significant findings, the associations varied by gender, measure of perceived support, and in direction of association. For example, Mezuk and colleagues (2010) reported an inverse main effect between emotional support and CRP in men but a stress buffering effect in women, while Runstein and colleagues (2014) reported an inverse association of global social support with CRP in a sample of women. And lastly, Glei and colleagues (2012) reported an unexpected positive association between social support and CRP in a sample of both men and women.

Three studies recently published in 2016, included in the meta-analysis by Uchino and colleagues (2018), further examined the cross-sectional association of perceived social support with IL-6 and/or CRP in healthy samples. Gouin and colleagues (2016) conducted a study to test whether dyadic coping, in parents of children on the autism spectrum disorder, associated with CRP cross-sectionally. While perceived support was not the main variable of interest, analyses included perceived social support as a covariate in the main effect between dyadic coping and CRP. Results showed that perceived support showed an inverse, cross-sectional association with CRP in parents with chronic caregiving stress. The second study examined the association of perceived social support with CRP and found no overall main effect but showed a moderating effect by race, such that high support was associated with lower CRP in African Americans (Uchino et al., 2016). And, the third study reported a negative correlation between perceived social support and CRP (not IL-6) but this finding was significant only in a small sample of breast cancer survivors (N=15), not in matched healthy controls (Muscatell et al., 2016).

The mixed nature of these cross-sectional findings may be, in large part, due to 1) limited measures of perceived support, and 2) the sample characteristics of these studies pertaining to chronic stress, ethnic composition, and chronic health conditions. Regarding the former, Helminen and colleagues (1997) used a measure of perceived availability of material, informational, and emotional support with low internal consistency and limited construct validity, while Kamiya and colleagues (2010) used a 3-item self-report assessment of perceived emotional support with no prior data attesting to its validity. Regarding the latter point of sample composition, studies that reported a main effect of social support and CRP differed in the ethnic and sample composition of their samples. Mezuk and colleagues reported a significant inverse association between emotional support and CRP in a sample that had one of the largest proportions of African Americans (i.e. 30%), whereas Glei and colleagues found social support to be unexpectedly associated with higher CRP in sample with relatively lower representation of ethnic minority in their sample (12% combined for both African Americans and Hispanic/Latino in Glei et al., 2012). Similarly, Gouin and colleagues (2016) found an inverse association between perceived support and CRP in a sample of chronically stressed parents and Muscatell and colleagues (2016) found this association in a clinical sample but not in a healthy sample. In sum, this cross-sectional literature lends limited support for an inverse association between global social support and IL-6 and CRP in healthy samples but suggests benefits of support in relation to these biomarkers using 1) specific subtypes of support (i.e. emotional support) and 2) in individuals with chronic medical conditions, of racial minority, and with chronic stress.

Further, as in the case of the social integration literature, prospective literature that examines the association of social support with longitudinal change in IL-6 and CRP also comes with significant limitations that prohibit any conclusions about such associations. For example,

Hughes and colleagues (2014) reported a significant association of social support with longitudinal change in IL-6 but this sample included breast cancer patients and results showed that pre-treatment support levels predicted a smaller increase in IL-6 from diagnosis to post-treatment. These results do not inform conclusions about a prospective association in a healthy, subclinical sample. Secondly, Yang and colleagues (2016) claimed to measure the prospective association of social support with change in CRP in 4 samples but as mentioned previously, 3 of the 4 samples lacked repeated measures of CRP and the 4th sample only included a baseline measure of CRP. Similarly, their earlier study (Yang et al., 2014) aimed to examine the longitudinal association of global support, family support, friend support, and spouse support with longitudinal change in CRP and IL-6 but analyses averaged the measures of social support across both waves to predict inflammation at wave 2 without any measure of inflammation at baseline. Thirdly, Eguchi and colleagues (2016) reported a significant inverse, prospective association of supervisor support with change in CRP over a period of 1-year but the effect was only found in women and the study did not test the role of global social support, irrespective of the source of support. Therefore, extant prospective literature has not adequately tested the association of global social support with longitudinal change in IL-6 or CRP in a healthy sample to examine subclinical processes in systemic inflammation that contribute to increased cardiovascular risk.

As a separate, but related issue, emerging evidence suggests that observed associations between perceived support and health outcomes may be specific to certain types of role relationships rather than one's entire social network. Existing theory supports the role of well-functioning close relationships (i.e. with family, spouse, and friends) in psychological, social, and physical wellbeing (Feeney et al., 2015), and empirical evidence suggests that relational

sources of support differentially associate with health outcomes, such that support from family members may be most protective against mortality risk (Shor et al., 2013) and support and strain from spouse, friends, and family significantly contribute to inflammatory risk (Yang et al., 2014). To examine whether close relationships may be specifically important in the association with inflammatory outcomes, we recently examined these associations in the context of two different samples of middle-aged and older adults using a cross-sectional design (Bajaj et al., 2016). Interactions within close relationships were measured using ecological momentary assessment (EMA) to collect repeated assessments of frequency and quality of interactions with spouse, friends, and family members. Results showed that the frequency of positive interactions with close others was particularly important, such that it inversely associated with IL-6 level in both middle-aged and older adults, after adjustment for demographic factors, body mass index, smoking, and alcohol intake. In contrast, global measures of perceived support and social integration were not associated with inflammatory markers in these cross-sectional samples. These results illustrate the importance of studying social behavior in daily life, as well as examining the quality of close relationships, as potential correlates of systemic inflammation.

In sum, the literature examining the association of perceived support with inflammatory markers is characterized by inconsistent findings that vary in direction and in significance. They also show considerable heterogeneity in the measure of support, as well as in the sample composition in the cross-sectional literature. Possibly due to these reasons, the bulk of the cross-sectional literature does not suggest an association between perceived support and IL-6 or CRP in healthy samples. Further, prospective studies examining the link between perceived support and inflammation are significantly limited in their study of healthy samples and in their operational measure of longitudinal change. Specifically, prospective evidence in the social

support-inflammation literature has not adequately examined the association of global social support with longitudinal change in inflammatory markers in heathy samples. This limitation does not address the potential of reverse causality nor does it address whether perceived support is related to the rate of change in inflammatory markers over time. There has also been an interest in whether any main effects between perceived support and health outcomes may be driven by the quality of a few close relationships, rather than one's entire social network. The current study aims to extend this literature by 1) using a well-validated and reliable measure of perceived support, namely the Interpersonal Support Evaluation List (ISEL), 2) examining the longitudinal association of perceived support with rate of change in IL-6 and CRP over a 6-year period, as well as any moderation by age and gender, and 3) examining the role of quality of close relationships through EMA measures of social interactions in daily life.

1.3.3 Marital quality and inflammation

Given the central role of marriage in adulthood and the association of marital quality with health outcomes (Robles et al., 2014), a growing area of research examines the association of marital quality with circulating markers of inflammation. Two studies tested the cross-sectional association of partner support and strain with IL-6 and CRP using the Midlife in the United States (MIDUS) cohort (Whisman & Sbarra, 2012; Donoho et al., 2013), with the latter study including a larger sample, including individuals married for $\geq$ 10 years, and adjusting for marital duration in analyses. Both studies reported an inverse association between partner support, measured through 6 supportive interaction items (e.g. "how much does your spouse really understand the way you feel about things?"), and circulating IL-6 in women, but Whisman & Sbarra (2012) found the effect only in younger women (i.e. below age 53). These findings

suggest that positive aspects of marriage may be more beneficial and especially in younger women. However, unpublished data, using the Dyadic Adjustment Scale to assess marital quality, show that marital quality does not associate cross-sectionally with circulating IL-6 or CRP in men or women in a sample of healthy older adults (Bajaj et al., unpublished manuscript). Although the sample size in the latter study was considerably smaller than in the previous 2 studies (N=542 in Donoho et al., 2013 and N=415 in Whisman & Sbarra, 2012), it is possible that marital quality does not robustly associate with circulating IL-6 or CRP cross-sectionally.

Although existing evidence does not provide strong support for a cross-sectional association of marital quality with circulating markers of inflammation, this literature is characterized by a few limitations. Firstly, it should be noted that this evidence is based on a small number of studies and only one sample (two, if unpublished data are counted). Secondly, it is based only on cross-sectional data to date, which does not rule out the effects of pro-inflammatory biomarkers on marital quality. The current study aims to extend this literature by examining the longitudinal association of marital adjustment with the rate of change in circulating IL-6 and CRP over a 6-year period, as well as any moderation by age and gender.

1.4 MECHANISMS OF THE ASSOCIATION BETWEEN SOCIAL RELATIONSHIPS AND INFLAMMATION

An important limitation of the extant literature is its failure to examine mechanistic pathways that may account for any observed effects of social relationship characteristics on circulating markers of inflammation. Although studies tend to control for confounding variables believed to alter the nature of social networks and contribute to inflammatory processes, any attenuation of

the main effect after this adjustment does not provide empirical support for mediation. Therefore, as an ancillary aim of this project, psychosocial mechanisms of the link between social relationship characteristics and circulating markers of inflammation will be explored in the case of any significant longitudinal main effects. These mechanisms include behavioral, affective, and interpersonal pathways.

1.4.1 Social relationships, health behaviors, and inflammation

Social connectedness is believed to be beneficial for health, regardless of the quality of social ties. This is thought to be due to, in part, the effects of "social control" processes, (Cohen, 2004; Cohen & Janicki-Deverts, 2009), which involve exposure to normative social controls and peer influence that guide one's health behaviors. Integration within one's social network may engender feelings of responsibility toward self and for others, which may promote engagement in healthy behaviors and/or avoidance of risky health behaviors. Isolated individuals may not be subject to these social controls, which could partly contribute to increased engagement in risky health behaviors among those low in social engagement. This theoretical rationale is supported by empirical evidence linking limited social participation with greater engagement in risky health behaviors, such as drinking, smoking, irregular diet and sleep habits, and substance use (Berkman & Syme, 1979; Umberson, 1987; Cohen, 1988; Trevino et al., 1990). Important evidence regarding possible mechanisms in the link between social integration and improved health practices is provided by Cohen and Lemay (2007). In this study, 193 adults (aged 21-54 years old) were interviewed on 14 consecutive evenings about their daily social interactions, affect, smoking behavior, and alcohol consumption. Results replicated earlier findings by showing that socially integrated individuals smoked fewer cigarettes and drank fewer drinks,

than their less integrated counterparts. However, interestingly, within-person analyses showed that in socially isolated individuals, the more people participants interacted with during a day, the greater their drinking and smoking behaviors. In contrast, individuals who were socially integrated reported fewer smoking and drinking behaviors irrespective of the number of interactants. Therefore, theoretical rationales based on the social control processes and empirical data support a positive association between social integration and better health practices, perhaps because socially integrated individuals may show greater resistance to negative peer influences.

In addition to social integration, characteristics of marriage, such as marital status and quality, also appear to be associated with better health practices. Regarding marital status, one prospective study, consisting of individuals aged 24 and older, showed that 1) married individuals tended to exert greater effort to control health behaviors than unmarried individuals, 2) social control exerted in a marriage at baseline prospectively predicted improved health practices 3 years later, and 2) the transition from married to unmarried status was associated with an increase in negative health behaviors (Umberson, 1992). Consistent with this finding, prospective data have also shown that the transition to marriage is associated with a reduction in risky health behaviors, such as excessive drinking, drug use, and smoking (Bachman et al., 2002; Chilcoat & Breslau, 1996). Duncan and colleagues (2006) replicated these findings by showing that in young adults, the transition to cohabitation or marriage is associated with a decrease in substance use, and Bachman and colleagues (2002) extended these findings to cohabitating couples who are planning to marry. The gain of an important social role upon the start of marriage may increase a sense of responsibility toward self and/or partner that may serve to regulate one's health behaviors.

In addition to marital status, marital quality may also facilitate engagement in health behaviors. This notion is supported by evidence showing that higher marital adjustment is associated cross-sectionally with better compliance to a blood pressure medication regimen in 200 married couples (Trevino et al., 1990), and that positive marital interactions are associated with reduced probability of engagement in risky health habits over time in a sample of 320 married men (Wickrama et al., 1995). In contrast to these positive characteristics, marital conflict is shown to be both a precursor and a consequence of alcohol and drug abuse (O'Farrell et al., 1998). Overall, marital status and quality may serve as motivating factors to increase engagement in healthy behaviors and/or decrease engagement in risky behaviors perhaps due to a greater sense of responsibility for self and spouse.

Similar to social integration and marital characteristics, perceived support has been associated with greater engagement in healthy behaviors. For example, one study used a sample of 180 undergraduate students and reported that students who rated themselves as low in perceived support showed increased engagement in health-compromising behaviors, such as smoking and alcohol consumption, during a 2-week period of academic stress, as compared to stressed students who perceived higher support (Steptoe et al., 1996). Other studies have shown an association of perceived support with increased physical activity in men and women (Treiber et al., 1991), and smoking cessation in men (Hanson et al., 1990; Murray et al., 1995). Therefore, social relationship characteristics, including social integration, perceived support, and marital quality, may relate to health outcomes through engagement in and regulation of health behaviors.

When considering inflammatory processes, three specific health behaviors may be particularly important: obesity, smoking, and sleep duration. In regards to obesity, two recent reviews have documented a large body of empirical data establishing a positive association of

obesity with inflammatory biomarkers (Mathieu et al., 2010; de Heredia et al., 2012), including a positive association of adipose tissue with IL-6, TNF-α, and CRP (Despres et al., 2003; Cartier et al., 2008; Blackburn et al., 2006). Given that adipocytes are one source of IL-6 production and that macrophages are present within adipose tissue, one potential mechanism through which obesity may influence systemic inflammation is through an increase in macrophages with increasing adipose tissue. Additionally, a second pathway has been proposed through the interaction between large adipocytes and free fatty acids (FFAs) to activate Toll-like receptors, which are pattern recognition receptors involved in the innate immune system and in the synthesis and production of inflammatory cytokines (Mathieu et al., 2010). Therefore, both of these pathways may be responsible, independently or synergistically, in the link between obesity and systemic inflammation.

Secondly, smoking behavior has also been shown to contribute to the inflammatory process. Various indices of smoking behavior (i.e. smoking status, cigarettes smoker per day, and time since quitting) were studied in association with inflammatory outcomes in a sample of older, long-term smokers, where results showed current smoking status to be associated with as many as 10 inflammatory markers, encompassing several components of the immune response (Shiels et al., 2014). Empirical studies have shown that adjustment for smoking behavior has often significantly attenuated any observed effects between perceived support and circulating levels of inflammatory biomarkers (e.g. Helminen et al., 1997), suggesting a mediational role.

And lastly, short sleep duration has been consistently linked with increased rate of CV morbidity and all-cause mortality (Solarz et al., 2011; Cappuccio et al., 2010), and inflammatory mechanisms that may account for these associations have garnered interest. A recent review documented the relatively consistent association of short sleep duration with elevated circulating

inflammatory biomarkers (Solarz et al., 2011). Particularly, controlled experimental studies have consistently shown increases in either TNF-α, IL-6 or CRP in participants subjected to sleep deprivation or restriction. Cohort studies show comparably more mixed findings but empirical evidence overall supports an association of shorter self-reported sleep duration with both CRP and IL-6 (Miller et al., 2009), and a positive association of light or disrupted sleep with IL-6 (Hong et al., 2005; Friedman et al., 2005). Greater sleep loss may relate to inflammatory processes through alterations in the autonomic nervous system (ANS), given that increased blood pressure has been observed as a consequence of sleep deprivation (Mullington et al., 2009).

Overall, this evidence suggests that obesity, smoking behavior, and sleep duration are importantly linked with both social relationship characteristics and biomarkers of systemic inflammation. Therefore, this study aims to examine whether these health behaviors mediate any significant, prospective association of perceived support, social integration, and marital satisfaction with circulating IL-6 and CRP.

1.4.2 Social relationships, affect, and inflammation

Social or interpersonal stress has been found to be, by far, one of the most distressing events when compared to other daily stressors in both men and women (Bolger et al., 1989); therefore, a long line of work has shown that social relationship characteristics are strongly linked to affective symptoms and perhaps in a bidirectional manner.

A longstanding area of research has examined the influence of social factors on depressive symptoms with reports that functional aspects of support (e.g. perceived support) are inversely associated with depressed mood (Lin et al., 1999), and that structural (i.e. degree of participation in social network) aspects of support are inversely associated with wellbeing,

depressed mood, and hopelessness (Lin et al., 1999; Golden et al., 2009). A recent review included 51 studies (28 cross-sectional and 23 prospective) from 2004-2014 to examine the association of various social relationship characteristics with depressive symptoms (Santini et al., 2015). These studies, based on community samples, showed a robust and consistent inverse association of perceived emotional support, perceived instrumental support, and large diverse social networks with presence, onset or development of depression and/or depressive symptoms. These effects have been replicated in marital relationships, with results showing that in 2 samples of newlywed and maritally distressed wives, participants reported worse depressive mood symptoms on days they experienced lower marital happiness (Smith et al., 2012). In sum, interpersonal stress at a network-level and in specific relational domains is associated with increases in negative affect.

Perhaps an even larger literature suggests a robust cross-sectional association of negative affect with poor health outcomes. This literature illustrates a reliable association between negative emotions, such as anxiety, guilty, and anger, with a variety of poor health outcomes, such as complaints of physical symptoms, lower physical health-related quality of life, and risk for CVD (see the following reviews: Mayne et al., 1999; Pandey & Choubey, 2010; Sirois & Burg, 2003; Gallo et al., 2004). A subset of this literature has further honed in on the association of negative emotions with systemic inflammation, due to its potential contribution to CV risk and premature mortality. For example, 4 notable reviews present a large body of evidence that has established an association of negative emotions, such as anxiety and depression, with elevated circulating levels of pro-inflammatory biomarkers that indicate the presence of systemic inflammation (see the following reviews: Gouin et al., 2011; Dowlati et al., 2010; O'Donovan et al., 2010), and explore the possibility of systemic inflammation as a mediator of the association

of negative emotions with measures of morbidity and mortality (Kiecolt-Glaser et al., 2002). This impressive body of evidence illustrates the importance of immune function in exacerbating risk for a variety of health outcomes through pathways such as prolonged infection, delayed wound healing, and increased cytokine production. Dysregulated inflammatory responses can be particularly impacted by negative emotion caused by interpersonal stress in troubled relationships (see review: Jaremka et al., 2013).

A critique of this literature has been the popular use of cross-sectional design, which is limited in ruling out the role of reverse causality in the association of negative affect and inflammatory risk (Messay et al., 2012). This is especially a concern given experimental evidence showing that increases in pro-inflammatory markers, such as IL-6 and TNF-α, induced by an injection of endotoxin causes significant increases in depressed mood (Eisenberger et al., 2010). As a result, to rule out reverse causality, a variety of empirical studies have examined the prospective association of negative emotion with pro-inflammatory biomarkers. For example, depressive symptoms have been shown to be associated with larger increases in CRP in a sample of healthy, older adults over a course of 6 years (Stewart et al., 2009), in middle-aged African Americans over a course of 5 years (Deverts et al., 2010), and in patients with acute coronary syndrome over 1 month (Shaffer et al., 2011). To further examine a bidirectional relationship using a prospective design, a large sample with a wide age range (N=73,131, age range = 20-100 years old) was used to explore the development of depressive symptoms based on baseline level of CRP (Wium-Andersen et al., 2013). Results showed that increasing CRP levels over time were associated with increasing risk for hospitalization for depression in this sample. The positive association of CRP with depressive symptoms was replicated in a longitudinal study using a sample of 1,791 women over 7-years (Matthews et al., 2010) and in a sample of 3,397

older adults, with some suggestion in the latter study that this association may be accounted for by metabolic and health factors (e.g. BMI, cholesterol, chronic health conditions) (Au et al., 2015). Overall, these studies suggest that negative affect, most commonly measured through depressive symptoms, is bidirectionally associated with CRP and IL-6 level in both cross-sectional and prospective designs.

Compared to the literature examining the association of negative affect with inflammation, a considerably smaller area of research examines the link between positive disposition and health outcomes. Pressman & Cohen (2012) reviewed the literature and showed that greater experience of positive emotions is associated with increased longevity, illustrating the importance of studying positive affect. To examine whether systemic inflammation may account for this effect with mortality, at least 3 recent reports have presented evidence of an inverse association between measures of positive affect and inflammatory outcomes. Middle-aged women who reported experiencing greater positive affect in daily life, by reporting how often they felt very or extremely happy using EMA over the course of 1 day, had lower levels of CRP and IL-6 in a cross-sectional study (Steptoe et al., 2008). This study replicated the inverse association found by an earlier study between positive affective resources, such as purposeful engagement, and lower IL-6 (Friedman et al., 2007). And most recently, the inverse association of positive affect with IL-6 was shown in a sample of 94 healthy undergraduate students, as well as in a sample of 105 undergraduate students, with the latter sample showing the same effect when positive affect was additionally measured through the experience of key positive emotions (e.g. joy, awe, amusement) in daily lives (Stellar et al., 2015). However, although extant literature suggests an association of both positive and negative affect (and their correlates) with

circulating markers of inflammation, more work is needed to determine if affect may explain the association of social relationship characteristics with inflammation.

Overall, this evidence suggests that the quantity and quality of social participation in one's social network, as well as in a marital relationship, correlates with measures of positive and negative mood, and that positive and negative affect associate with circulating markers of inflammation. This study aims to bridge these two independent literatures by examining whether positive and negative affect may mediate any significant, prospective association of perceived support, social integration, and marital satisfaction with circulating IL-6 and CRP.

1.4.3 Social relationships, social interactions, and inflammation

In addition to behavioral and affective pathways, social relationship characteristics may also exert their effect on circulating markers of inflammation through an interpersonal pathway by altering the nature of social interactions in daily life. Individuals who are more socially integrated, by definition, show greater social engagement and this may be captured through EMA by measuring frequency of social interactions in daily life. Similarly, it is likely that individuals who perceive greater support within their social network tend to have more frequent positive interactions with members of their social network, and that individuals who report greater marital satisfaction tend to have more frequent positive interactions with their spouse in daily life.

Empirical evidence supports this theoretical link between global measures of social relationships and quality of social interactions. Existing evidence shows that support between parent and child, within married couples, and between siblings is often conveyed through high quality social interactions, which tend to promote more benign interpretation of negative life

events and cognitively reframe problems as challenges (Gardner et al., 2004). Regarding marital relationships, a review conducted by Gottman & Notarious (2000) provides empirical evidence for the view that global marital satisfaction is associated with more constructive and positive marital interactions, characterized by greater problem-solving and positive affect, among other favorable outcomes. A recent example of this evidence is presented by Kiecolt-Glaser and colleagues (2005), who showed that married couples with greater marital satisfaction engaged in less hostile interactions with their spouses following a conflict-resolution task, compared with married couples with lower marital satisfaction. Therefore, global measures of social relationship characteristics may influence the quality of one's social interactions.

An emerging, but promising, area of research is examining the association between social interactions, as measured by daily diary and/or by EMA, and circulating markers of inflammation. For example, negative and competitive interactions, measured through daily diaries, were associated with higher levels of circulating IL-6 and sTNFαRII (a receptor for pro-inflammatory cytokine TNF-α) in a sample of undergraduate participants (Chiang et al., 2012). Further evidence suggests that the quality of social interactions with close others may be particularly important. For example, negative social interactions with friends and family, reported through daily diaries, were associated with higher levels of circulating CRP in a sample of adolescents (Fuligni et al., 2009). The importance of close relationships remains in middle-aged and older adults, given that greater frequency of total positive interactions in daily life was associated with lower IL-6 in older adults, and that greater frequency of positive interactions within close relationships was associated with lower IL-6 in both middle-aged and older adults (Bajaj et al., 2016). Therefore, an emerging area of literature suggests an association between daily social behavior and circulating markers of inflammation across the life span. Given that

global assessments of one's social relationships may reflect one's social interactions, and that social interaction characteristics may associate with circulating markers of inflammation, the study of daily social interactions may provide support for an interpersonal pathway in the association of social relationships with inflammation. As a next step, this study aims to test the mediating role of daily social interaction characteristics in any significant, prospective association of perceived support, social integration, and marital satisfaction with circulating IL-6 and CRP.

1.5 AIMS AND HYPOTHESES

To address the limitations of the extant literature as described above, the current study examined the prospective association of perceived support, social integration, and marital satisfaction with the rate of change in inflammatory biomarkers, CRP and IL-6, over a 6-year period in a sample of healthy, older adults. In the case of any significant longitudinal effects, it aimed to test behavioral (i.e. obesity, smoking, sleep duration), affective (i.e. positive/negative affect), and interpersonal (i.e. frequency and quality of daily social interactions) pathways as potential mechanisms of any observed effects using longitudinal mediation analyses. The proposed study used data from an existing study of a longitudinal design with time points at baseline, 3-year, and 6-year follow up. Questionnaire measures of social integration, perceived social support, and marital satisfaction were collected at baseline, inflammatory biomarkers and health behaviors (with the exception of sleep duration) were measured at all 3 time-points, and social interaction characteristics and affect were measured through multiple assessments using EMA at baseline and 6-year follow up.

This proposal presents features that are novel relative to the existing published literature, such as 1) the examination of the prospective association of social relationship characteristics with the rate of change in biomarkers using growth curve modeling, 2) examination of social relationship predictors that are structural vs. functional in nature, and those that are studied at a network-level vs. those that are specific to individual relationships, and 3) potential examination of interpersonal, affective, and behavioral pathways using longitudinal mediation in any significant prospective associations. The aims of the study are outlined below.

Aim 1: To examine whether perceived support, social integration, and marital adjustment associate with mean initial levels and the rate of change in IL-6 and CRP level over a 6-year period, and whether perceived support buffers the effect of chronic stress on trajectory of inflammatory outcomes.

Hypothesis 1a: 1) Greater perceived support, as measured by the Interpersonal Evaluation Support List (ISEL), 2) greater social integration, as measured by the Social Network Inventory (SNI), and 3) greater marital adjustment, as measured by the Dyadic Adjustment Scale (DAS), at baseline will associate with either a smaller increase or a larger decline in both IL-6 and CRP level over 6 years. Greater chronic stress, measured by the Chronic Stress Scale (CSS), will associate with a larger increase or a smaller decline in both IL-6 and CRP over 6-years but only in individuals with low perceptions of support.

Exploratory Hypothesis 1b: The associations above will be tested to examine whether they are moderated by gender.

Exploratory Hypothesis 1c: If there is a significant association of perceived support, social integration, and marital adjustment with rate of change in inflammatory outcomes, follow-

up analyses will adjust for perceived stress, personality variables (i.e. extraversion and agreeableness) and depressive symptoms.

Aim 2: To examine the mediating role of health behaviors in the case of any significant, prospective association of social relationships characteristics with 6-year changes in inflammatory outcomes, and where mediator of interest is correlated with both predictor and change in outcome.

Hypothesis 2a: Higher BMI, short self-reported sleep duration, and current smoking status will mediate the longitudinal association of perceived support, social integration, and marital satisfaction with both inflammatory markers.

Aim 3: To examine the mediating role of EMA measures of positive and negative affect in any significant, prospective association between social relationship characteristics at baseline and 6-year changes in inflammatory markers, and where mediator of interest is correlated with both predictor and change in outcome.

Hypothesis 3a: Mean positive and negative affect will mediate the longitudinal association of perceived support, social integration, and marital satisfaction with both inflammatory markers.

Aim 4: To examine the mediating role of social interaction characteristics in any significant, prospective association of social relationship characteristics at baseline with 6- year changes in inflammatory markers, and where mediator of interest is correlated with both predictor and change in outcome.

Hypothesis 4a: Greater frequency of social interactions will mediate the longitudinal association of social integration with change in inflammatory markers.

Hypothesis 4b: Greater frequency of positive social interactions and/or frequency of negative social interactions will mediate the longitudinal association of perceived social support with

change inflammatory outcomes. These results will be compared with measures of mean positivity and mean negativity in social interactions.

Exploratory Hypothesis 4c: If support for Hypothesis 4b is found, exploratory analyses will be conducted to test whether greater frequency of positive interactions and mean positivity of interactions with close others (i.e. spouse, friends, and family), and/or frequency of negative interactions and mean negativity of interactions with close others mediates the longitudinal association of perceived social support with 6-year changes in inflammatory markers, compared to interactions with non-close others (i.e. acquaintances, friends).

Hypothesis 4d: Greater frequency of positive marital interactions and/or frequency of negative marital interactions will mediate the longitudinal association of marital adjustment with changes in both inflammatory markers. These results will be compared with measures of mean positivity and mean negativity in marital interactions.

2.0 METHODS

2.1 PARTICIPANTS

Participants included men and women enrolled in the Pittsburgh Healthy Heart Project (PHHP), a prospective study of healthy, community-dwelling adults aged 50-70 years. Exclusionary criteria in this study included: (a) history of schizophrenia, bipolar disorder, chronic hepatitis, chronic lung disease, hypertension, and heart, renal, or neurological conditions; (b) drinking > 5 portions of alcohol, 3 times or more/week; (c) prescription of insulin, glucocorticoid or autonomically active drugs, prescription of anti-arrhythmic, antihypertensive, lipid-lowering, or weight-loss medications; (d) pregnancy or lactation. Although individuals with a history of chronic disease were generally excluded, people with diabetes who were not taking insulin, those with a history of cancer but no treatment in the past 6 months, and those with mild or moderate rheumatoid arthritis were eligible. Participants were recruited between September 1998 and April 2000. The current study was approved by the University of Pittsburgh Institutional Review Board and participants received $200 for participation in baseline measures and a total of $700 for attending two follow-up visits.

Data to be examined in this report were collected at the PHHP baseline, 3-year, and 6-year follow up visits. At baseline (1998-2000), participants attended 11 visits: a medical screen, seven visits for ambulatory monitoring training and questionnaire assessments, one visit for stress reactivity testing and two visits for ultrasound assessment of subclinical CVD. An average of 3 years later, participants returned for a second blood draw and ultrasound testing. An average of 6 years after baseline, participants attended six follow-up visits, during which they completed

a medical update, questionnaire assessments, and an additional round of ambulatory monitoring training, ultrasound assessments, and autonomic testing.

2.2 PROCEDURE

Participants completed multiple laboratory visits, some of which are not relevant to this report. Demographic assessments and a fasting blood draw were completed at Visit 1 of the baseline and 6-year protocol and measures of perceived support and social integration were assessed at Visit 2 of the baseline protocol. At baseline, ecological momentary assessments (EMA) were completed through interviews on an electronic diary (ED) (Palm™ Pilot Professional handheld, Palm, Inc., Santa Clara, CA). Interviews were completed every 45 minutes during the waking day over 6 days, in two 3-day periods, separated by four months. The EMA protocol was repeated at the 6-year follow up, at which point participants completed EMA every 45 minutes over one 3-day period. A subset of the EMA interview administered at both time points included the same items assessing the frequency and quality of social interactions, as well as measures of positive and negative affect in daily life. See Figure 1.

Both at baseline and at that 6-year time point, participants were trained to use the ED device and practiced using the device in the field for one day. Participants then returned for a "Shakedown" visit, where the participants' data were reviewed by a research assistant. If there were no questions or concerns, the monitoring period began the following day. The interview consisted of questions regarding mental state, mood, and the physical and social environment. A subset of the items assessed how the participant was feeling and whether the participant was currently in a social interaction, (if not) the interval since the most recent interaction, the

duration of interaction, the type of interaction (in person vs. phone, etc.), the quality of interaction, and the partners involved in the interaction. The protocol from this sample has provided valid measures of social interactions that associate in the expected direction with existing measures of social relationship characteristics (Janicki et al., 2006; Vella et al., 2008), and with various health outcomes (Janicki et al., 2005; Joseph et al., 2014).

2.3 INSTRUMENTS

2.3.1 Social integration

Social integration was assessed by the Social Network Inventory (SNI) at baseline. The SNI assesses participation in 12 types of relationships: one point is assigned for each role that the individual participates in within his or her social network at least once every 2 weeks (a measure of "network diversity" with a range of 1-12). Social integration was measured as the sum score on the SNI (Cohen et al., 1997). The SNI has shown consistent predictive validity in relation to many health outcomes, including health behaviors (i.e. smoking, drinking), susceptibility to colds, and immune response (Cohen & Lemay, 2007; Cohen et al., 1997; Pressman et al., 2005; Holt-Lunstad et al., 2010). See Appendix A.

2.3.2 Perceived social support

Perceived social support was measured by the Interpersonal Support Evaluation List (ISEL) at baseline, using the tangible, belonging, appraisal, and self-esteem scales. Respondents were

asked to indicate whether each statement, assessing perceived availability of social resources, is "probably true" or "probably false" about themselves. Each item was scored on a 4-point scale and scores were summed and averaged across the 4 subscales. Psychometric properties of the ISEL instrument are presented by Cohen and colleagues (Cohen et al., 1985).

The ISEL shows strong validity demonstrated by high correlations with the Family Environment Scale (assesses perceptions of family members), Partner Adjustment Scale (assesses quality of marital relationships), and the Rosenberg Self-Esteem Scale (r= .30, r=.31, r=.74, respectively). The ISEL has also shown evidence for discriminant validity, given its lack of correlation with measures of social desirability, such as the Crowne-Marlow Social Desirability Scale, and given its role in accounting for significant variance in the prediction of depressive symptoms above and beyond social anxiety, a related construct. Internal reliability of the ISEL in the general population ranges from .88 to .90, and the test-retest correlation was reported to be .70 over a 6-week interval and .74 over a 6-month interval (Cohen et al., 1985). See Appendix B.

2.3.3 Marital satisfaction

Marital satisfaction was measured by the widely-used Dyadic Adjustment Scale (DAS) (Spanier et al., 1976) at baseline. It is a 32-item self-report instrument which has been shown to discriminate between distressed and nondistressed married or cohabitating couples and concurrent validity by its association with the Marital Adjustment Scale (Locke & Wallace, 1959). It has also shown adequate internal consistency and test-retest reliability over a 3-week period (Carey et al., 1993). See Appendix C.

2.3.4 Chronic stress

Chronic stress was measured by the Chronic Stress Scale (CSS) at baseline. The CSS was developed by Norris & Uhl (1993) and is a 27-item scale comprised of multi-item subscales: marital stress, parental stress, filial stress, financial stress, ecological stress, and physical stress. These subscales were each scored using a Likert Scale of 0 – 4 (Never to Very Often) with a time frame of the past 6 months. Respondents who were unmarried or not living with a partner or who had no children or who were unemployed received scores of 0 on the applicable subscales. An aggregate chronic stress score was created as the average z-score across all applicable (non-zero) subscales. This method has been previously used in this dataset (Janicki, 2006). See Appendix D.

2.3.5 Ecological Momentary Assessment (EMA)

Participants were presented with electronic diary (ED) interviews every 45 minutes during waking hours at baseline and 6-year. A subset of these questions assessed the nature of social interactions and positive and negative affect. As mentioned previously, the EMA monitoring period occurred over two 3-day periods at baseline, separated by 4 months, and over one 3-day period at 6-year but included the same items assessing social interaction characteristics and positive and negative affect. Participants were presented with a visual analogue Likert scale ranging from 1-11 at baseline and from 1-10 at 6-year (i.e. at baseline: **NO** 1 2 3 4 5 6 7 8 9 10 11 **YES** and at 6-year: **NO** 1 2 3 4 5 6 7 8 9 10 **YES**). Therefore, scores $\geq$ 7 at baseline and $\geq$ 6 at 6-year indicated "yes" to the questions asked pertaining to social interactions and positive and negative affect. See Appendix E for baseline EMA items and Appendix F for 6-year EMA items.

Given the difference in scale used at baseline and 6-year, both scales were transformed to make them equivalent, and therefore, comparable in their mean ratings of social interactions and affect. Specifically, the 1-11 scale at baseline and the 1-10 scale at 6-year were both transformed to a 0-9 scale by subtracting values by 1 and multiplying by .9 in the case of baseline, and subtracting 1 from each score in the case of 6-year. Therefore, mean scores of these measures (from baseline and 6-year) follow a transformed Likert scale of 0-9.

2.3.6 EMA: Positive and negative affect

At both baseline and 6-year time-points, positive affect was assessed using 2 items and negative affect was assessed using 4 items. To assess positive affect, participants were asked how "energetic" or "happy" they were currently feeling (i.e. "How feeling?" preceded these items). To assess negative affect, participants were asked how "sad," "frustrated/angry," "nervous/stressed," they felt (again, "How feeling?" preceded these items) at the time of the blood pressure reading preceding the ED interview and whether they had "thought about things that upset [them]." Mean scores of positive and negative affect were created by averaging each participant's rating of mood across all ED interviews using the transformed 0-9 Likert scale. This approach yielded summary scores of mean positive and negative affect across the monitoring period at baseline and 6-year follow up.

2.3.7 EMA: Social interactions

The ED interview at both baseline and 6-year follow up used 3-item scales to assess positive social interactions and 2-items scales to assess negative social interactions. The 3 items that

assessed positive interactions were those that were "pleasant," "agreeable," and "friendly." The 2 items that assessed negative interactions were those where the participant reporting being "in conflict" and being "treated badly." Social interaction quality was scored in 2 ways: 1) frequency of positive and negative interactions, and 2) mean positivity and negativity in social interactions.

To measure frequency of positive and negative interactions, 3 summary scores were derived for each individual based on: 1) relative frequency of total interactions, defined as the proportion of all observations that were spent in social interactions at the time of the interview or within the 10 min prior to the interview (Range = 0-100%), 2) relative frequency of positive interactions, defined as the proportion of interviews that were rated as positive (i.e. proportion of interviews in which there was a current or recent interaction and in which all 3 items were rated $\geq$ the midpoint of the scale on items (indicating yes) regarding "pleasant," "agreeable" or "friendly" interactions), and 3) relative frequency of negative interactions (i.e. proportion of interviews in which there was a current or recent interaction and in which both items were rated $\geq$ the midpoint of the scale (indicating yes) on items regarding whether a participant was in "conflict, and "treated badly"). The relative frequency measure used here allows us to consider temporal exposure as a potentially important dimension of psychosocial risk (Kamarck et al., 2012).

We additionally examined the frequency of positive and negative interactions with close others (i.e. spouse, friends, family member) and those exclusively with spouses (among married individuals) by creating 3 summary scores, using the same method described above, for frequency of total, positive, and negative interactions with close others and exclusively with spouses. This approach has been used in our previous cross-sectional work with the same sample of older adults (see Bajaj et al., 2016).

The frequency measures were compared with mean quality of social interactions. To measure mean quality of interactions, a "mean positivity" score was created to average participant ratings on all current or recent interactions that were rated as yes on all 3 positive adjectives: "pleasant," "agreeable," and "friendly." Specifically, the 0-9 ratings were averaged across each of the 3 adjectives. Similarly, a "mean negativity" score was created to average participant ratings on all current or recent interactions, inquiring whether the participant was "in conflict," and "treated badly," that averaged the 0-9 ratings across both adjectives. The mean quality scores yielded 2 summary scores that reflect the mean positivity and negativity across all social interactions, as well as, when appropriate observations were selected, with close partners (i.e. spouse, friends, family member) at both baseline and 6-year follow-up.

2.3.8 Health behaviors

Obesity, self-reported sleep duration, and smoking status were health behaviors of interest. Obesity was measured as body mass index (BMI) at baseline, 3-year, and 6-year as weight/height^2. Sleep duration over a 1-month interval was assessed using an item from the Pittsburgh Sleep Quality Index (PSQI). In the proposed study, sleep duration was assessed at baseline and 6-year follow up through the question "During the past month, how many hours of actual sleep did you get at night?" Self-reported insufficient sleep has been previously associated with increased overall and cardiovascular morbidity (Solarz et al., 2011). Smoking status was measured at baseline, 3-year, and 6-year follow up using a subset of items from a 33-item Health Behavior Questionnaire. Smoking status was designated as never smoker, ex-smoker or current smoker through self-report.

2.3.9 Inflammation measures

During the initial visit at baseline and the 6-year follow up, blood was drawn between 8:30 am and 11:30 am. Participants were instructed to fast and to avoid caffeine for 12 hours prior to these visits. Blood samples, collected in tubes with no additives, were centrifuged within 3 hours of collection to isolate serum. Serum aliquots were frozen at -80 degrees Celsius until the time of assay. Serum samples were sent to the Laboratory for Clinical Biochemistry Research at the University of Vermont. There, IL-6 was measured using ultra-sensitive enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN), which have a detection range of 0.156-10.0 pg/mL. The interassay coefficient for this method is 6.3% at the University of Vermont. CRP was measured with a BNII nephelometer utilizing a particle-enhanced immunonephelometric assay (Dade Behring, Deerfield, IL). The detection range for this assay is 0.15-1100 mg/L, and the routine interassay coefficient of variation is 5% at the University of Vermont.

Consistent with current recommendations (Pearson et al., 2003), individuals with CRP $\geq$ 10 mg/L were excluded from analyses, due to assumption of recent acute infection. CRP and IL-6 values were log transformed to reduce skewness, as is customary in the literature.

2.3.10 Standard covariates

Standard covariates include age (in years), sex (0=male, 1=female), race (0=white, 1=non-white), and education level operationalized as years of education in growth curve analyses, and as categories (1=high school or less, 2=technical school or some college/Associate's,

3=Bachelor's degree, 4=Master's degree or higher) in regression models and in exploratory analyses pertaining to social interaction characteristics. See Figure 1 for protocol.

2.3.11 Psychosocial covariates

In the case of any significant main effects between baseline social relationship constructs and the rate of change in biomarkers using growth curve analyses in Aim 1, the study planned to include depressive symptoms, personality characteristics (i.e. agreeableness and extraversion), and perceived stress as covariates.

2.3.11.1 Depressive symptoms

The 21-item version of the Beck Depression Inventory (BDI) was used as a measure of depressive symptoms using the sum score. The internal consistency of the standard 21-item scale has been reported to be .85 and it related significantly with other measures of depressive symptoms, and its correlates, as seen by significant correlations between the BDI and the Zung Self-Rating Depression Scale and with the UCLA Loneliness Scale (Reynolds & Gould, 1981).

2.3.11.2 Agreeableness and extraversion

The agreeableness and extraversion components of the 60-item version of the NEO-FFI was used in this study. This is a widely-used tool to estimate stable measures of personality. The various subscales of this instrument have shown moderate correlations with other personality assessments, such as Jackson's Basic Personality Inventory (Costa & McCrae, 1992) and

moderate coefficient alphas and 6-year stability (Costa & McCrae, 1988). Previous data from a sample of university students have also shown acceptable measures of internal consistency of the agreeableness and extraversion subscales using the 60-item version (Anisi et al., 2011).

2.3.11.3 Perceived stress

The Perceived Stress Scale was designed to measure the degree to which situations in one's life were appraised as stressful over the past month in community samples. The original 14-item scale was used in the current study. This scale has shown high construct validity, as indicated by moderate correlations with other measures of appraised stress (e.g. number of life events, self-reported perceptions of events), and better predictive validity compared to life-event scale of psychological and physical symptoms, as well as health services utilization. Cronbach's alpha coefficient for internal reliability has reported to be .75 (Cohen & Williamson, 1988).

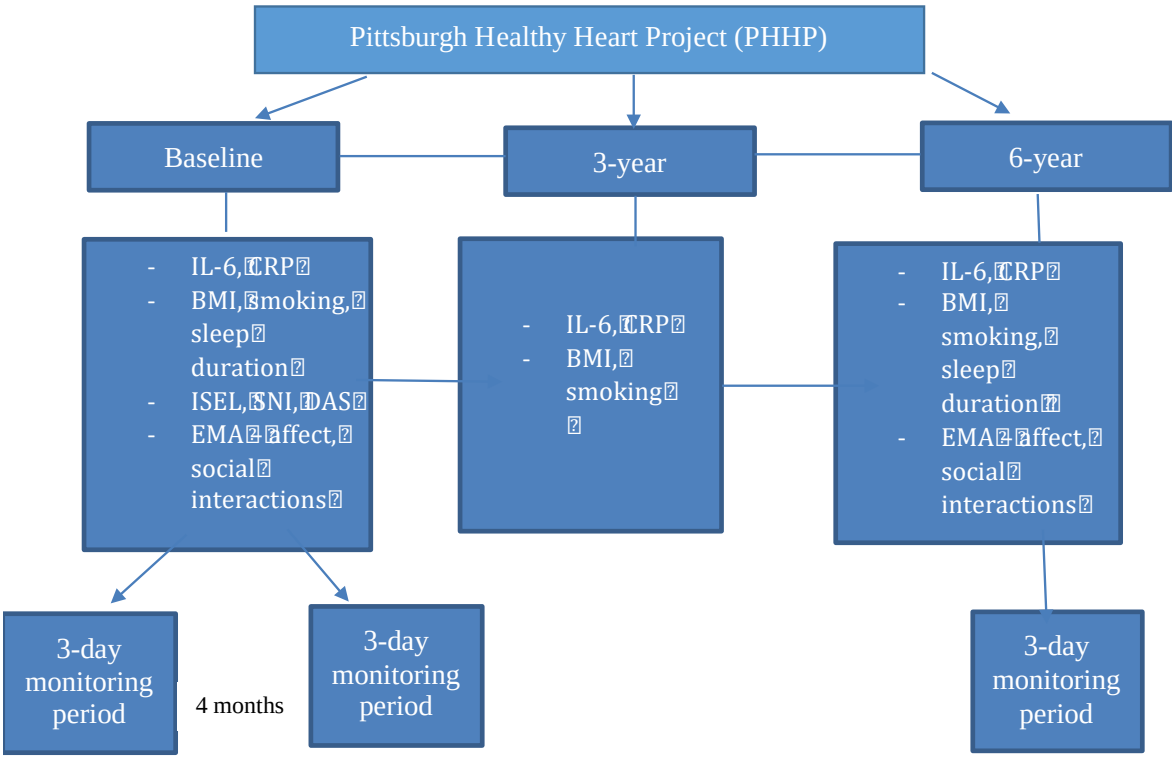

Figure 1. Flow Chart of Measures Collected at Baseline, 3-year, and 6-year follow-up. IL-6 = Interleukin-6; CRP = C-Reactive Protein; BMI = Body Mass Index; ISEL = Interpersonal Support Evaluation List; SNI = Social Network Inventory; DAS = Dyadic Adjustment Scale; EMA = Ecological Momentary Assessment.
Note: T1 = Baseline, T2= 3-year follow up, T3= 6-year follow up. All analyses were performed in MPlus 7.4 or SAS 9.4 as stated.

2.4 STATISTICAL APPROACH

Aim 1: To examine whether global measures of perceived support, social integration, and marital adjustment associate with rate of change in circulating IL-6 and CRP, and whether perceived support buffers the effect of chronic stress on change in IL-6 and CRP.

Analysis plan: Latent growth curve modeling (LGM) was used to examine whether social relationship characteristics at baseline predict trajectory of change in IL-6 and CRP over 6 years, using time invariant covariates (TIC) of age, sex, race, and education, and to test whether perceived support buffered the effects of chronic stress on the rate of change in IL-6 and CRP over 6 years. This modeling technique allowed for examination of between-person changes in mean values of IL-6 and CRP over time as they relate to T1 measures of social relationship characteristics and chronic stress. Several indices of overall model fit were used: comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA), and standard root mean square residual (SRMR). Good model fit was defined by the following criteria: CFI > .95, TLI > .95, RMSEA < .05, SRMR < .08 (Hu & Bentler, 1999). Adequate model fit was defined by the following criteria: CFI > .90, TLI > .90, RMSEA < .08, SRMR < .08 (Hu & Bentler, 1999). See Figure 2.

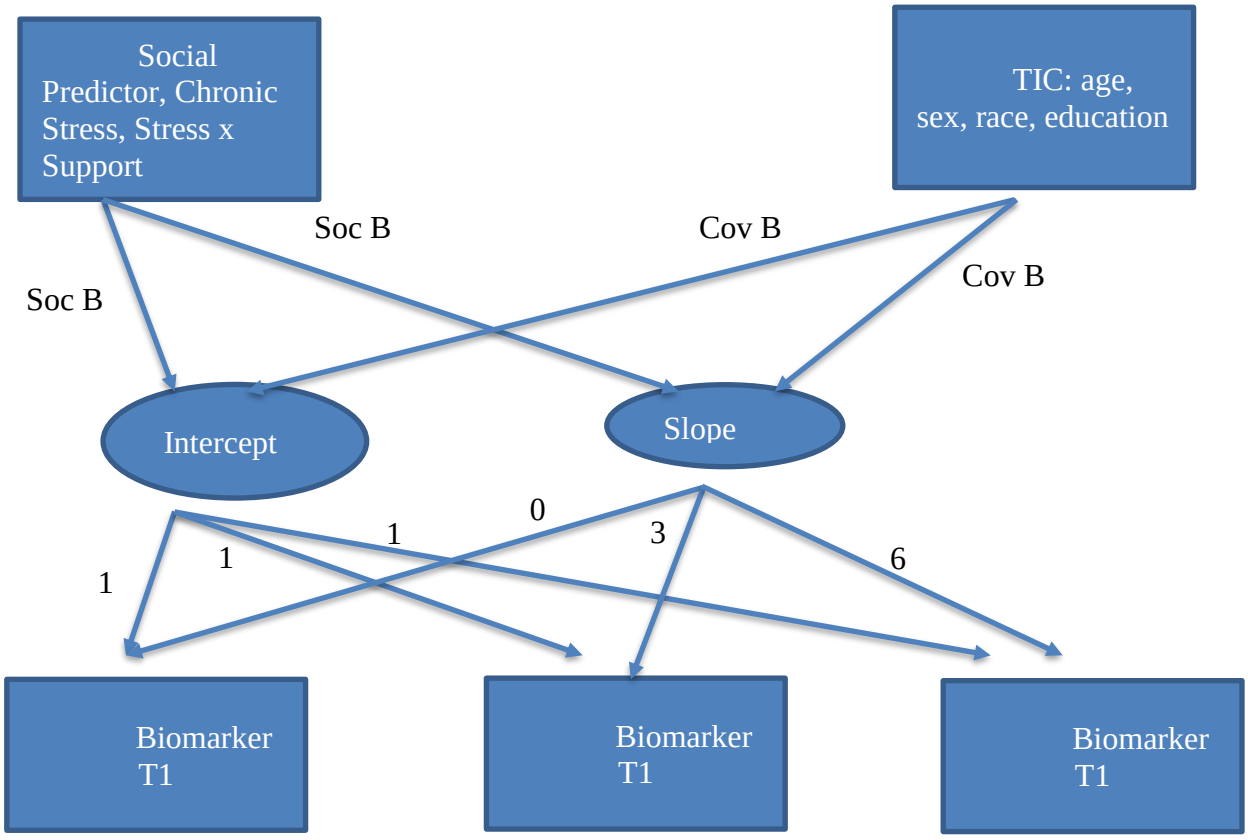

Figure 2. A Conceptual Latent Growth Curve Model for Aim 1. Predictors include social integration, perceived social support, marital quality, and chronic stress at baseline, as well as the interaction between chronic stress and perceived support. Time-invarying covariates include age, sex, race, and education. Biomarkers include CRP and IL-6 assessed at baseline, 3-year, and 6-year follow-up.

Aim 2: To examine the mediating role of health behaviors in any significant, prospective association of global social constructs with inflammatory biomarkers.

Analysis Plan: Prior to testing mediation, 2 screening tests were performed to test: 1) whether T1 social relationship characteristics showed significant prospective associations with residualized change in 6-year inflammatory outcomes, after adjustment for demographic covariates (i.e. age, sex, race, education), other social relationship characteristics, and baseline measures of inflammatory outcomes in multiple regression models, and 2) whether each health behavior was related to both predictor at baseline (i.e. social integration, social support, and marital quality) at baseline and change in outcome based on partial correlations.

In cases where conditions 1 and 2 were satisfied, a three-wave cross lagged panel (Cole & Maxwell, 2003) was proposed to test BMI and smoking status as mediators examining 1) whether X1 (i.e. social relationship characteristic) predicted M2 (i.e. each individual health behavior) while controlling M1 (i.e. health behavior at T1) (path a), 2) whether M2 (i.e. health behavior at T2) predicted Y3 (i.e. inflammatory outcome at T3) while controlling for Y2 (i.e. inflammatory outcomes at T2) (path b), and 3) whether the cross product term (ab) provided support for a significant indirect effect. Significance of ab product term was to be determined based on whether ab=0 (where a nonzero value indicates significance) by examining the confidence interval for the product term (Cole & Maxwell, 2003). It should be noted that since sleep duration was measured at T1 and T3, a separate two-wave model was proposed to examine this variable as a mediator (See Figure 4). See Figure 3 below for examination of BMI and smoking as mediators.

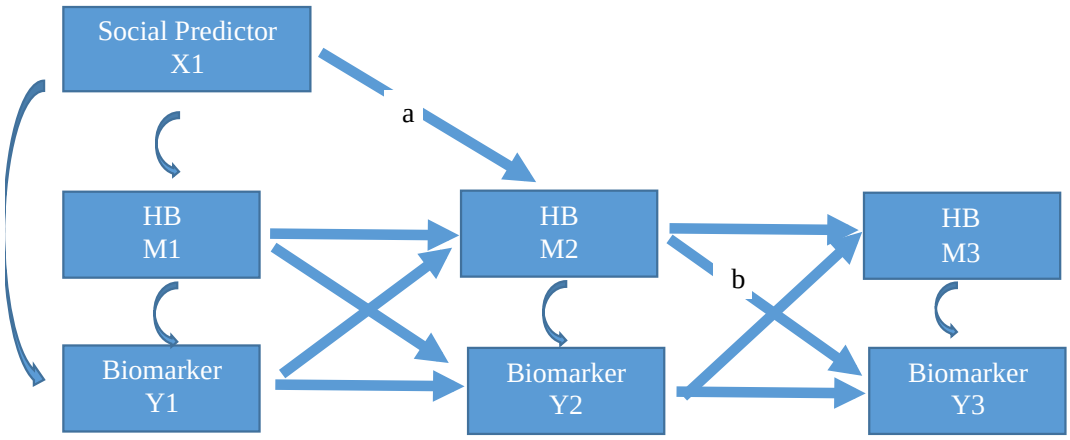

Figure 3. A Conceptual Three-Wave Cross-Lagged Panel for Aim 2 in the Case of a Significant Prospective Main Effect with Residualized Change. HB = Health Behavior; Social relationship predictors include social integration, perceived social support, and marital adjustment. Health behaviors for this model include obesity and smoking status. Biomarkers include CRP and IL-6.

Aim 3: To examine the mediating role of positive and negative affect, as measured by EMA monitoring, in any significant prospective association of global social constructs with inflammatory outcomes.

Analysis Plan: The same screening conditions described under Aim 2 applied here. If both conditions were satisfied, a two-wave cross-lagged panel was proposed to determine whether 1) X1 (i.e. social relationship characteristic at T1) predicted M3 (i.e. positive and/or negative affect at T3) while controlling for M1 (i.e. positive/negative affect at T1) (path a), 2) whether M1 (i.e. positive/negative affect at T1) predicted Y3 (i.e. biomarker at T3) while controlling for Y1 (i.e. biomarker at T1) (path b), and 3) whether the cross product term (ab) provided support for a significant indirect effect through positive and/or negative affect. This two-wave panel has been previously used to examine longitudinal mediation using the same 2 time points (i.e. baseline and 6-year) in this dataset (Kamarck et al., 2012). This strategy allowed for testing of partial mediation based on the assumption of stationarity (i.e. path b between M1 and Y2 would be equal to Path b between M2 and Y3), and is recommended as an alternative when only two-wave data are available (Cole & Maxwell, 2003). Note that this two-wave panel was also proposed to examine sleep duration as a potential behavioral mediator in the case of a significant prospective main effect, given that this data was only available at baseline and 6-year. See Figure 4.

Aim 4: To examine the mediating role of social interaction characteristics, as measured by EMA monitoring, in the case of any significant prospective association of global social constructs with inflammatory outcomes.

Analysis Plan: The same analysis plan as for Aim 3 (i.e. two-wave cross lagged panel) was proposed to test this aim should the same two screening conditions be satisfied. See Figure 4.

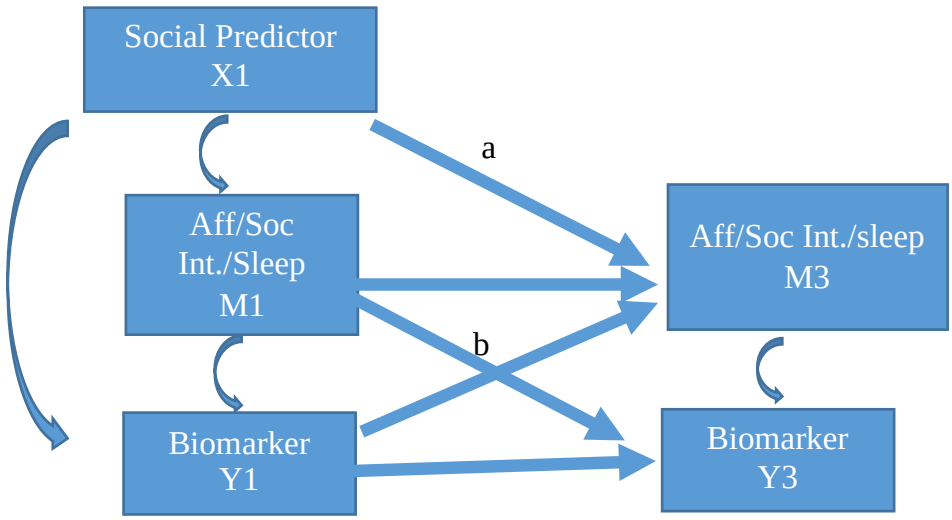

Figure 4. A Conceptual Two-Wave Cross Lagged Panel for Aims 3 and 4. Aff = Affective variables; Soc Int. = Social Interaction variables; Sleep = Sleep duration; Social relationship predictors include social integration, perceived social support, and marital quality; Affect variables include mean positive affect and mean negative affect assessed by EMA; Social interaction variables include EMA measures of frequency of total interactions, frequency of positive interactions (and with close others), frequency of negative interactions (and with close others), frequency of spousal interactions, mean positivity of total interactions (and with close others), mean negativity of total interactions (and with close others), and mean positivity and negativity in spousal interactions. Biomarkers include CRP and IL-6.

3.0 RESULTS

3.1 DESCRIPTIVE CHARACTERISTICS OF SAMPLE

All analyses below were conducted in SAS 9.4 and Mplus 7.4. Data from the 6-year follow-up was collected an average of 73 months after the baseline data (i.e. 6.08 years). At baseline, 344 cases provided IL-6 and/or CRP data, out of which 22 cases showed CRP values $\geq$ 10 mg/L and were excluded. At 3-year, 344 cases were available for IL-6 and/or CRP data, out of which 17 cases showed CRP values $\geq$ 10 mg/L and were excluded. And at 6-year, 293 cases provided IL-6 and/or CRP data, out of which 8 cases showed CRP values $\geq$ 10 mg/L and were excluded. This exclusionary criterion was used per the standard in the literature positing that CRP values greater than or equal to 10 mg/L indicate the presence of an acute infection. This resulted in a final sample of N=349 that consisted of valid data for both IL-6 and CRP on at least 1 out of the 3 time points: baseline, 3-year, and 6-year. Out of these 349 individuals, 258 reported being currently married and/or living with a partner in a married-like relationship. Out of the 258 married individuals, 254 completed a questionnaire assessing marital quality. Therefore, all independent variables of interest and covariates were examined in the whole sample of 349 individuals and 254 married individuals with valid biomarker data and available data on marital quality in the latter case.

There were no remarkable differences in demographic variables in the samples at the 3 different time points. Compared to the whole sample of N=349 at baseline, N=285 had complete and valid inflammation data at 6-year follow-up. Study dropouts were more likely to be younger than study participants (58.9 years vs. 60.85, $t(347) = 3.01$, $p = .003$) but there were no significant

differences in dropouts vs. study participants in sex, race, or education ($t(347) = 1.56$, $p= 12$; $t(347) = -1.87$, $p=.07$; $t(347) = .76$, $p= .44$, respectively). In the whole sample, mean IL-6 values were 1.80, 1.97, and 2.72 pg/mL at baseline, 3-year, and 6-year, respectively. Mean CRP values were 2.26, 1.97, and 1.66 mg/L at baseline, 3-year, and 6-year respectively, showing an apparent decline in CRP over time. IL-6 and CRP values were correlated at $r=.23$ ($p<.0001$) at baseline, $r=.22$ ($p<.0001$) at 3-year, and $r=.36$ ($p<.001$) at 6-year.

The decline in mean CRP values over the 3 time-points was unexpected and inconsistent with previous literature. As a result, we examined several possible explanations for this apparent decrease. One explanation is that perhaps there were random errors in the readings at one or more of the time-points. To test for this possibility, we calculated change scores as the raw difference between IL-6 scores at baseline and 6-year, as well as between CRP scores at baseline and 6-year, to see if they were appropriately correlated with each other. IL-6 change scores and CRP change scores were significantly correlated with each other in the positive direction ($r= .35$, $p<.0001$), indicating that the rank order of change for these two sets of measures appears to be similar over time. That is, those who show the largest increase in IL-6 are more likely to be those also showing the largest increase in CRP, consistent with expectation.

We also examined whether CRP at baseline was related to BMI at baseline, 3-year, and 6-year. Baseline CRP was significantly correlated with baseline BMI ($r=.27$, $p<.0001$), with 3-year BMI ($r=.25$, $p<.0001$), and with 6-year BMI ($r= .25$, $p <.0001$) all in the expected directions. CRP values were also significantly correlated with each other across the 3 time-points (baseline CRP and 3-year CRP: $r= .54$, $p<.0001$; 3-year CRP and 6-year CRP: $r= .45$, $p<.0001$; baseline CRP and 6-year CRP: $r= .33$, $p<.0001$). This is consistent with the possibility that CRP measures at each of the time-points are equally valid indices of inflammatory risk. These data,

then, are inconsistent with the possibility that there are random errors in our CRP measures at one or more of the time points.

If there are no random errors in our CRP measures, a second explanation for the unexpected decline in this measure over the 6-year follow-up could be that there were systematic improvements in health behaviors in this sample over time. To test this possibility, we examined whether there were significant changes in some of the health behaviors that may be correlated with CRP, namely BMI, smoking status, and sleep duration. None of these three measures showed significant changes over the 6-year follow-up ($t(338) = 1.44$, $p = .15$ for BMI; $t(287) = 1.35$, $p = .18$ for smoking; $t(280) = .46$, $p = .65$ for sleep duration). Furthermore, changes in these health behaviors were unrelated with 6-year changes in CRP. For example, 6-year CRP change was not significantly correlated with change in BMI from baseline to 3-year ($r = .11$, $p = .09$), with change in BMI from 3-year to 6-year ($r = .00$, $p = .99$), and with change in BMI from baseline to 6-year ($r = .09$, $p = .13$). Similarly, 6-year CRP change was not correlated with change in smoking status from baseline to 3-year, 3-year to 6-year, and baseline to 6-year ($r = .03$, $p = .66$; $r = -.06$, $p = .33$; $r = -.03$, $p = .61$, respectively). And lastly, change in sleep duration from baseline to 6-year also did not correlate significantly with CRP change from baseline to 6-year ($r = -.03$, $p = .69$). Therefore, the data are inconsistent with the possibility that the systematic changes in CRP were due to systematic improvements in relevant health behaviors.

Taken together, these analyses indicate stability of CRP over time, in its correlations with IL-6, and in its correlations with health behaviors. Further, the analyses above are inconsistent with the possibility of random errors in assay procedures at one or more time points and changes in health behaviors as possible explanations for the observed decline in CRP. Instead, all 3 measures of CRP appear to be valid indices of individual differences in chronic inflammation, at

least in terms of their association with other markers of inflammation. Therefore, rather than reflecting random error, any temporal changes in these values may reflect differences in measurement standards at the times they were assayed. This was confirmed with the laboratory staff at University of Vermont, who mentioned that immunological assays for CRP values at baseline and 3-year were run at a different time than the assay for 6-year CRP and that inconsistency of reagents used in CRP assays could plausibly have contributed to the systematic shift in mean CRP values. If so, these measures of CRP can be accurately used to assess changes over time in relative inflammatory risk, but not in absolute degree of change.

The sample characteristics of the total sample and the married subsample are shown in Table 1.

Table 1. Characteristics of sample used in growth curve models.

Sample Characteristic	Sample Size	Mean (SD) or % (n)
Mean Age (SD)	349	60.49 (4.78)
% male (n)	349	49 (171)
% non-White (*n*)	349	15.8 (55)
% bachelor's degree or higher (*n*)	349	51 (178)
% current smokers (*n*)	349	6.6 (23)
Perceived Social Support (ISEL)	347	137.65 (14.05)
Social Integration (SNI)	347	6.64 (1.90)
Marital Adjustment (DAS) (married subsample of N=258)	254	111.41 (17.23)
Chronic Stress (CSS – standardized score)	283	-.010 (.54)
Perceived Stress (PSS)	348	18.35 (6.30)
Depressive Symptoms (BDI)	348	3.98 (3.95)
Extraversion (NEO-FFI)	348	41.97 (6.53)
Agreeableness (NEO-FFI)	348	46.59 (5.35)
CRP at baseline (mg/L)	322	2.26 (2.05)
CRP at 3-year (mg/L)	327	1.97 (1.92)
CRP at 6-year (mg/L)	285	1.66 (1.66)

IL-6 at baseline (pg/mL)	322	1.80 (1.48)
IL-6 at 3-year (pg/mL)	327	1.97 (1.47)
IL-6 at 6-year (pg/mL)	285	2.72 (2.15)

Note: The original sample included 349 participants out of which 258 reported being married and 254 reported marital quality data. A smaller sample size for CSS is due to study protocol that allowed for the administration of this measure at a later point than the other baseline measures. Smaller sample sizes for inflammatory biomarkers are due to data missing at random and the exclusion of individuals suffering from acute infection at the time of study participation as indicated by CRP levels $\geq$ 10 mg/L.

Missing data patterns were examined to rule out any systematic contributors to missingness in data pertaining to demographic variables (age, sex, race, education), main social relationship and chronic stress predictors (social integration, perceived support, marital quality, chronic stress), and inflammatory biomarkers (valid IL-6 and CRP values at all 3 time points). Table 2 below shows missing data patterns (where x signifies available data) and their frequencies. The table illustrates that 204 out of the total 349 cases show complete data on all variables of main interest as listed above. A total of 47 cases show missing data pattern 9, where the chronic stress measure is missing. This is due to study protocol that administered this questionnaire later in the study timeline and is therefore missing by design and not a systematic contributor to missingness in data. A total of 44 cases show the missing data pattern 2, where valid data for CRP and IL-6 are missing at the 6-year time point. This is due to attrition but is not of significant concern given that covariance coverage showed that 82% of the total cases include valid data for both IL-6 and CRP at the 6-year follow-up, indicating high retention of participants over time. A further analysis of missingness in biomarker data at the 6-year follow up showed that, with the exception of age ($r = -.16$, $p = .003$), demographic, psychosocial or biological characteristics (i.e. sex, race, education, perceived stress, body mass index) were not related to missingness in these values (and therefore, attrition) ($r = -.08$, $p = .14$ for sex; $r = .10$, $p = .06$ for race; $r = -.01$, $p = .85$ for education; $r = .07$, $p = .19$ for perceived stress, $r = .05$, $p = .35$ for body-

mass index). The significant correlation with age was addressed by its inclusion as a demographic covariate in all subsequent analyses.

Table 2. Missing data patterns in full sample used for growth curve modeling (N=349).

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Age	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Race	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Education	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CSS	X	X	X	X	X	X	X	X									X	X	
ISEL	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X
SNI	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X
CRP T1	X	X	X	X				X	X	X	X	X				X	X	X	X
CRP T2	X	X			X	X		X	X	X			X	X		X	X	X	X
CRP T3	X		X		X		X	X	X		X		X		X		X		X
IL-6 T1	X	X	X	X				X	X	X	X	X				X	X	X	X
IL-6 T2	X	X			X	X		X	X	X			X	X		X	X	X	X
IL-6 T3	X		X		X		X	X	X		X		X		X		X		X

Note: Columns show missing data patterns where x=available data; CSS = Chronic Stress Scale; ISEL= Interpersonal Support Evaluation List; SNI = Social Network Inventory; T1 = Baseline; T2 = 3-year time point; T3 = 6-year time point.

Missing data pattern frequencies (N = 349)

Pattern Number	Frequency
1	**204**
2	**44**
3	7
4	3
5	10
6	3
7	3
8	1
9	**47**
10	9
11	1
12	1
13	2
14	2
15	2
16	1
17	2
18	1
19	1

Given these particular data patterns, the high % of available and valid data, and the high retention rate of participants over time, it was deemed that any missing data were missing at random (MAR). Under this assumption, full-information maximum likelihood (FIML) is an appropriate estimation method to handle missing data. The MAR assumption posits that any missingness in the data is not due to any unobserved variables. FIML is an estimation method that, under conditions of data MAR, creates a likelihood function and selects a set of values of the model parameters to maximize the likelihood function. It is considered a more effective approach to handle missing data over list-wise deletion due to its ability to include a greater number of observations under the likelihood function and maximize power. Further, under the assumption of MAR, it has been argued that FIML is a more suitable method for handling missing data than multiple imputation for reasons including: 1) its greater efficiency, 2) its ability to produce reliable and replicable results, 3) a lack of discrepancy between an imputation model and an analysis model, given that the analysis model is used to address missing data, and

4) its compatibility with multiple software packages (Allison, 2012). In the analyses below, the FIML estimation method was used its default format to estimate missing dependent variables in the analyses that were conducted in Mplus 7.4 (i.e. in growth curve analyses in Aim 1) and both independent and dependent variables in multiple regression models used to test screening criteria prior to mediation using SAS 9.4 under the PROC CALIS command. Given the limited number of cases with missing data on independent variables in the whole sample, FIML was not deemed as necessary to apply to these variables in Mplus 7.4 but its application to both independent and dependent variable was a default setting in the PROC CALIS command of SAS. Therefore, in growth curve analyses, sample sizes may slightly differ due to missing data on predictor variables and these changes are noted.

In the growth curve analyses described below, each social relationship characteristic (i.e. perceived support, social integration, and marital quality), as well as chronic stress, was tested as a predictor of initial status and the rate of change in IL-6 and CRP over a 6-year period using latent growth curve modeling. In baseline models, IL-6 and CRP values were regressed on the latent growth factors (i.e. intercept and slope terms) where the inflammatory markers measured at 3 time points were indicators of these latent growth factors, serving as the exogenous variables. A second set of models added demographic characteristics—age, sex, race, and education—as exogenous predictors of the growth factors for IL-6 and CRP to examine how these demographic characteristics predicted initial level and the rate of change in both inflammatory biomarkers. And a third set of predictor models examined social relationship characteristics (i.e. social integration, perceived social support, and marital quality), as well as chronic stress, as exogenous predictors of the growth factors (in addition to the time-invarying demographic covariates) to test if each social relationship characteristic predicted initial level

and rate of change in inflammatory biomarkers after adjustment for the demographic covariates. These models were run separately for IL-6 and CRP. In the case of significant results, follow-up analyses were proposed to adjust for measures of perceived stress (i.e. measured by the PSS), depressive symptoms (i.e. measured by the BDI), and personality characteristics (i.e. agreeableness and extraversion measured by the Neo Five Factor Inventory).

3.2 AIM 1: SOCIAL RELATIONSHIP CHARACTERISTICS AND RATE OF CHANGE IN INFLAMMATION

3.2.1 Baseline model

A baseline model for IL-6 examined the initial status and rate of change in IL-6 level over time using a total of 349 observations, yielding good model fit based on CFI and SRMR indices, but poor fit based on RMSEA and TLI indices (RMSEA = .14, CFI = .96; TLI = .88; SRMR = .037). This suggests that IL-6 values in this sample may not estimate a truly linear trend. Based on Figure 5, it can be seen that IL-6 values increase more sharply from 3-year to 6-year than from baseline to 3-year.

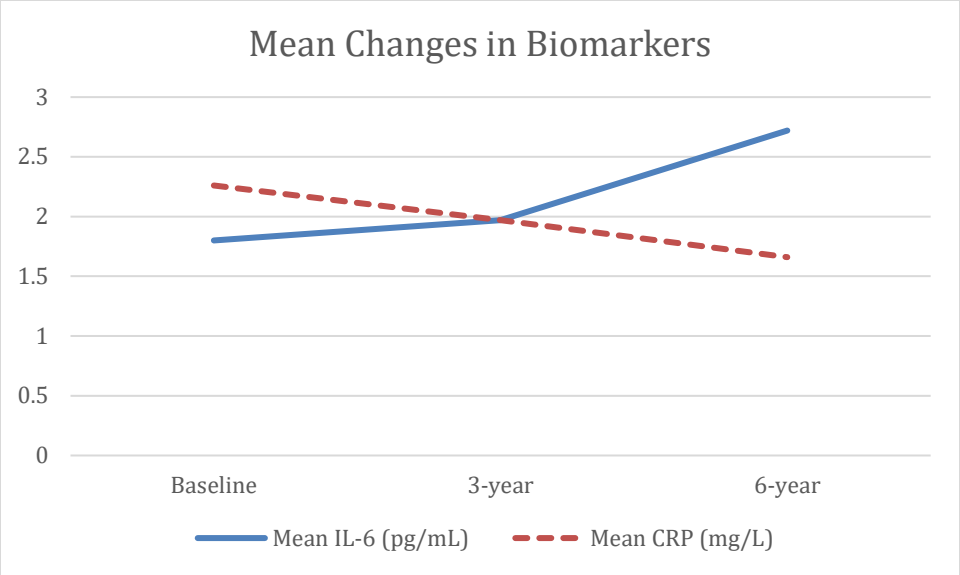

Figure 5. Mean Changes In IL-6 And CRP Level Over A 6-Year Period (N=349).

Given this steeper rise between the latter 2 time-points and the poor fit based on the RMSEA and TLI indices, the baseline model was modified by freeing the third parameter at the 6-year time point and allowing it to vary, essentially allowing the program to estimate the trend from data points rather than imposing a strictly linear trend. In this less restrictive baseline model for IL-6, model fit significantly improved as shown by all 4 indices (RMSEA = .00, CFI = 1.00, TLI = 1.00, SRMR = .00). Mean initial levels of log-transformed IL-6 level was .43 pg/mL and there was an increase in IL-6 level time at an average rate of .10 pg/mL. Both terms, intercept and slope, were significantly different from 0 (p= .00 for both terms). The covariance between the slope and intercept factors was not significant (r = .003, p=.73), suggesting that initial status of IL-6 level was not significantly related to the rate of increase in IL-6. Although there was significant variance around the intercept term (s^2_I = .122, p=.00), the variance surrounding rate of change in IL-6 was not significant (s^2_S = .009, p =.20), suggesting that individuals differed significantly from each other in their initial levels of IL-6 but not in their rate of increase over the 6-year period.

Given that the variance surrounding the rate of increase in IL-6 was not significant, each residual variance was subsequently fixed to be equivalent to each other in the model in order to 1) allow for better model fit and 2) allow the model to accommodate for the residual variance. This ultimately served to be a more parsimonious model by allowing for greater degrees of freedom. When each residual variance was fixed to be equivalent, model indices showed good fit (RMSEA = .00; CFI = 1.00; TLI = 1.013; SRMR = .015) and the variance around the intercept term remained significant (s^2_I = .124, p=.00). However, importantly, fixing each residual variance allowed for marginally significant variance around the slope term (s^2s = .012, p=.055), allowing for enough variability to be predicted by demographic and social predictors in the subsequent models. Therefore, the final IL-6 model used 2 model specifications: freeing the 3rd parameter of the IL-6 values at the 6-year follow-up (to allow for less constraint in estimating the linear model) and fixing each residual variance to be equivalent (to allow for marginally significant variance around the slope factor).

In regard to the baseline CRP model, the same 349 observations were included in analysis. The model showed good fit (RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .005), suggesting that CRP values do in fact show a linear trend over the 6-year period. Mean initial status of log transformed CRP level was .46 mg/L and interestingly, there was a decline in CRP level over time at a rate of -.17 mg/L. Both of these values were significantly different from 0 (p= .00 for both terms). There was also significant variance around both the intercept (s^2_I= .734, p=.000) and slope factors (s^2_S =.087, p=.02), suggesting that individuals significantly differed from each other in their initial levels of CRP, as well as their rate of decline. There was a significant covariance term between the intercept and slope factors (r = -.125, p=.009),

suggesting that individuals with higher initial levels of CRP showed a steeper decline over time. See Figure 6.

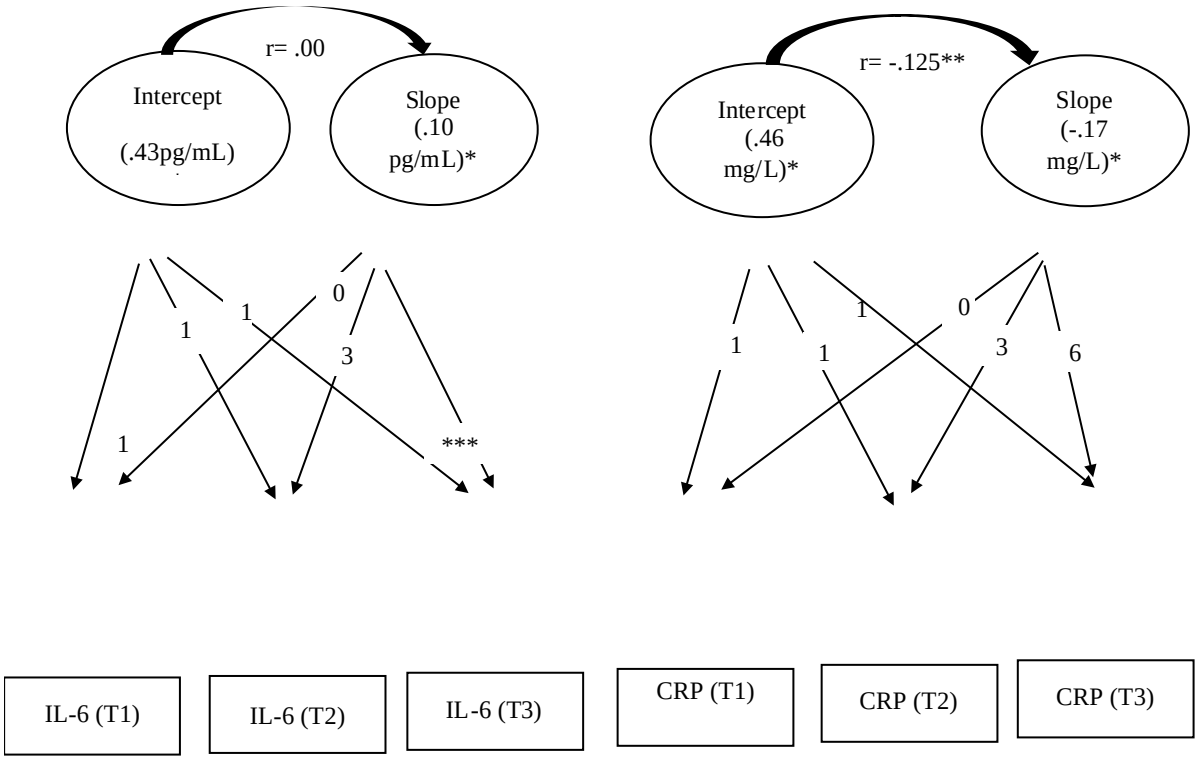

Figure 6. Baseline Model of Intercept and Slope Factors of IL-6 and CRP (N= 349). Note: *p<.05; **p<.01;***constraint free to vary; T1 = Baseline; T2 = 3-year follow-up; T3 = 6-year follow-up; IL-6 and CRP values are log-transformed. Model adjustments in the IL-6 model include allowing the third parameter at the 6-year time point to vary and fixing each residual variance to be equivalent to ultimately allow for marginally significant variance around the slope term.

3.2.2 Demographic model

Next, the results from the demographics model pertaining to IL-6 and CRP are presented. These models regressed IL-6 and CRP values at each time point on the intercept and the slope factors (as in the previous base model) and regressed the slope and intercept factors on demographic variables as predictors, namely age, sex, race, and education. The slope factor was regressed on

the intercept factor in each of the models, in order to control for possible effects of baseline inflammation on rate of change. In these analyses, age and education were treated as continuous variables, while sex and race were treated as categorical variables. Age and education were centered at the mean to ease interpretation, and categorical variables were coded such that sex = 0 indicated male, sex = 1 indicated female, race = 0 indicated White, and race = 1 indicated non-White.

Out of 349 observations, 345 observations were included in this model given that 4 observations contained missing data on predictor variables. The demographic model pertaining to IL-6 showed good model fit based on all indices (RMSEA = .00, CFI = 1.00, TLI = 1.01, SRMR = .02), indicating that these set of predictors accurately capture variation in outcome biomarker data. None of the demographic variables were associated with IL-6 intercept (all p's > .10) or IL-6 slope (all p's > .21). The same 345 observations were used to predict whether demographic variables predicted CRP growth factors in a model with good fit (RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .011). While age and race were not associated with CRP intercept (all p's > .17), sex and education were significant predictors of CRP intercept. Specifically, females showed a higher CRP intercept than males (b= .347, p=.001) and years of education was negatively associated with CRP intercept (b= -.046, p= .008). In the case of slope, age, race, and education were not associated with the rate of decline in CRP over time (all p's > .47), but females showed a greater rate of decline than males (b= -.099, p= .048). See Table 3.

Table 3. Unstandardized estimates from the growth curve analyses of the demographic model – the association of age, sex, race, education with IL-6 and CRP growth factors (N=345).

Demographic Characteristic	**IL-6 intercept**	**IL-6 slope**	**CRP intercept**	**CRP slope**
	b	**b**	**b**	**b**
Age	.001	.001	-.013	-.004
Sex	-.039	-.027	.347**	-.099**
Race	.097	.024	.204	-.009
Education	-.014	-.004	-.046**	-.004

R^2	2.5%	3.1%	9.7%**	26.9%**

Note: *p<.05; **p<.01; ***p<.001; For the IL-6 model RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .018; For the CRP model RMSEA = .00; CFI = .00; TLI = 1.00; SRMR = .011.

3.2.3 Social integration and biomarker trajectory

Predictor models were used in all subsequent analyses below to examine social relationship characteristics associated with biomarker growth factors after adjusting for time-invarying demographic covariates. A model based upon a set of 343 observations (6 observations were excluded due to missing data on x-variables) showed good fit (RMSEA = .01, CFI = 1.00, TLI = 1.00, SRMR = .02) Results of this model suggested that social integration was associated neither with initial level of IL-6 (b= -.009, p= .52) nor with the rate of increase in IL-6 (b= .003, p=.56). When the same model was run with CRP (RMSEA = .00, CFI = 1.00, TLI = 1.02, SRMR = .01) the data suggested that social integration was associated neither with CRP intercept (b= .037, p=.18) nor with CRP slope (b= .007, p=.57).

Further analyses tested whether the association of social integration with IL-6 and CRP growth factors was moderated by gender. Therefore, an interaction term was added to the model with social integration and demographic covariates in predicting IL-6 and CRP latent factors. A model with 343 observations with good fit (RMSEA = .02, CFI = 1.00, TLI = 1.00, SRMR = .02) showed a non-significant interaction between gender and social integration in association with IL-6 intercept (b= -.010, p= .72) and IL-6 slope (b= -.001, p=. 89). In a separate model (RMSEA = .00, CFI = 1.00, TLI = 1.02, SRMR = .01), the interaction term showed a non-significant association with CRP intercept (b= .072, p=.19) and CRP slope (b= -.026, p= .28).

3.2.4 Perceived social support and biomarker trajectory

The same set of 343 observations as above were used to test the association of perceived social support with the IL-6 and CRP growth factors. The model, which included demographic covariates, as well as the sum measure of ISEL, showed good fit (RMSEA = .00, CFI = 1.00, TLI = 1.01, SRMR = .02), and yielded a non-significant association with IL-6 intercept (b= .002, p= .25) and IL-6 slope (b= .00, p=.78). In a separate model, (RMSEA = .03, CFI = .99, TLI = .98, SRMR = .02) there were no significant associations shown between perceived support and either CRP intercept (b= .002, p=.65) or CRP slope (b= .002, p= .30). The same 343 observations were used to examine the moderating effect of gender on the association of perceived social support and growth factors of IL-6. After adding the interaction term to the well-fitted model (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .02), results did not show a significant association between the interaction term and IL-6 intercept (b= .00, p= .89) or IL-6 slope (b= .001, p= .48). Similarly, the moderating role of gender was not significant in a well-fitted model (RMSEA = .03; CFI = 1.00, TLI = .99, SRMR = .01) examining social support as a predictor of CRP intercept (b= -.005, p=.46) or CRP slope (b= .006, p= .06).

3.2.5 Stress buffering pathway

Although perceived social support did not independently associate with IL-6 or CRP growth factors, the stress-buffering role of perceived social support was explored, given prior literature supporting the moderating role of perceived social support in the association of chronic stress with various physical and mental health outcomes. Therefore, first, a main effect of chronic stress was examined in relation to IL-6 and CRP growth factors. Next, an interaction term was

created to indicate the buffering role of perceived social support on the association of chronic stress with inflammatory outcomes. And lastly, to be consistent with previous models, a 3-way interaction term was created using gender to test whether the buffering role of perceived social support was further moderated by gender, after adjusting for the lower-order 2-way interaction terms in the model between stress, support, and gender.

3.2.6 Stress buffering pathway and IL-6

To test the main effect of chronic stress on IL-6 growth factors, a model including 280 cases was used (given that 69 cases were excluded due to missing data, in large part, on the chronic stress measure due to study protocol). The model showed good fit (RMSEA = .02; CFI = .99, TLI = .99; SRMR = .02) and results showed that chronic stress was not associated with initial level of IL-6 (b= .006, p=.91) or with the rate of increase in IL-6 over time (b= .002, p=.92). The two-way interaction term of stress and support was added to the model and a set of 279 observations (70 observations were excluded due to missing data, again in large part, in the chronic stress measure due to study protocol) in a model with good fit (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .02) showed a non-significant association between the interaction term and IL-6 intercept (b= -.003; p=.36) and IL-6 slope (b= -.001; p= .42), suggesting that there is no stress-buffering effect of perceived social support on IL-6 growth factors. Next, the model was modified to test whether the stress-buffering role of perceived social support emerged when examined by sex. Therefore, a 3-way interaction term was added to the model above (with age, sex, race, education, chronic stress, perceived social support, and the lower order 2-way interaction between chronic stress, perceived social support, and gender as covariates). The same 279 observations were included in this model and the model showed good fit (RMSEA = .00;

CFI = 1.00; TLI = 1.08; SRMR = .01). Results showed that the stress-buffering role of perceived social support did not differ by gender as indicated by a non-significant 3-way interaction term in association with the IL-6 intercept (b= .005, p=. 47) and IL-6 slope (b= .002, p= .50).

3.2.7 Stress buffering pathway and CRP

All analyses above concerning the main effect of chronic stress, the stress-buffering role of perceived social support, and a potential difference in the stress-buffering role of perceived support based on gender, were repeated using CRP growth factors as the outcomes of interest. A model including demographic characteristics and chronic stress included 280 observations with good fit (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .01). Chronic stress did not show a significant main effect with CRP intercept (b= .159, p=.15) or CRP slope (b= -.016, p= .76). The stress-buffering role of perceived social support was tested in relation to CRP growth factors. The model included 279 observations with showed good fit (RMSEA = .03; CFI = 1.00; TLI = .99; SRMR = .01) and showed no stress-buffering effect of perceived social support as indicated by a non-significant interaction term in relation to CRP intercept (b= .009, p=.23) and slope (b= -.003, p=.37). The 3-way interaction term of stress, support, and gender (along with the lower-order 2-way interaction terms) were added to this well-fitted model of 279 observations (RMSEA = .02; CFI = 1.00; TLI = .99; SRMR = .01), which also did not show a significant association between the 3-way interaction term and CRP intercept (b= -.023, p= .06) or slope (b= -.002, p= .78).

3.2.8 Marital quality and biomarker trajectory

The next set of analyses tested whether marital quality, assessed by the Dyadic Adjustment Scale in a subsample of married individuals (N= 258), is associated with lower initial levels and a smaller rate of increase in IL-6 or a larger decline in CRP. This hypothesis is predicated on prior evidence suggesting that marital quality is inversely associated with circulating inflammatory markers, particularly IL-6, in cross-sectional studies.

3.2.9 Marital quality and IL-6

The model included a sample of 253 observations, given that 5 observations were excluded due to missing data on predictor variables (out of which 4 had missing data on marital quality), and showed good fit (RMSEA = .00; CFI = 1.00; TLI = 1.08; SRMR = .02). Notably, marital quality was not associated with IL-6 intercept (b= -.001, p=. 58) or IL-6 slope (b= .001, p= .39). To test whether the association of marital quality with IL-6 growth factors may be moderated by gender, the 2-way interaction term was added to the model with good model fit (RMSEA = .00; CFI = 1.00; TLI = 1.10; SRMR = .02). Results showed no significant interaction between marital quality and gender in predicting IL-6 intercept (b= -.001, p= .79) or slope (b= .001, p=.70).

3.2.10 Marital quality and CRP

The same set of 253 observations were used to test the association of marital quality with CRP growth factors. The model showed good fit (RMSEA = .04; CFI = .99; TLI = .97; SRMR = .02) and results showed a non-significant association or marital quality with CRP intercept (b= .002,

p= .61) and slope (b= .002, p= .27). Similarly, the 2-way interaction term also did not significantly associate with CRP intercept (b= -.004, p=.52) or CRP slope (b= .00, p=.90) in this model with 253 observations and good fit (RMSEA = .03; CFI = .99; TLI = .98; SRMR = .02).

3.2.11 Aim 1: Summary of results

In sum, baseline models of IL-6 and CRP showed that there was a somewhat linear increase in mean IL-6, and a relatively clearer linear decrease in mean CRP values over a 6-year period in this sample of older adults. In the case of IL-6, there was a steeper increase between 3-year and 6-year than from baseline to 3-year. There were significant individual differences in the initial level of IL-6 and marginally significant individual differences in the rate of increase over time. In the case of CRP, individuals significantly differed from each other in their initial levels, as well as their rate of decline over time. While initial levels of IL-6 were not related to the rate of increase in IL-6 over time, greater initial levels of CRP were associated with a steeper decline in CRP over the 6-year period.

Demographic characteristics were differentially associated with IL-6 and CRP growth factors. Age, sex, race, and education were not associated with IL-6 growth factors but females showed a higher CRP intercept and a greater decline in CRP over time than males. Years of education were inversely associated with CRP intercept. Social integration, perceived social support, marital quality (in a subsample of married individuals), and chronic stress did not significantly associate with initial level of IL-6 and CRP nor with the rate of change in these biomarkers over a 6-year period. None of these associations showed any moderation by gender, nor was there a stress-buffering effect of perceived support on biomarker growth factors. See Table 4.

Table 4. Unstandardized estimates of growth curve model results examining the association of baseline social relationship characteristics and chronic stress with 6-year IL-6 and CRP growth factors.

Variable	IL-6 intercept	IL-6 slope	CRP intercept	CRP slope
	b	b	b	b
Age	.002	.001	-.010	-.003
Sex	-.036	-.022	.361**	-.102*
Race	.089	.020	.183	-.002
Education	-.014	-.004	-.044*	-.006
SNI	-.009	.003	.037	.007
R^2 (N=343)	2.5%	3.1%	10.0%**	27.0%**
Age	.002	.001	-.011	-.003
Sex	-.036	-.022	.360**	-.102*
Race	.091	.021	.168	.008
Education	-.014	-.004	-.045**	-.005
SNI	-.004	.003	.001	.020
SNI x gender	-.010	-.001	.072	-.026
R^2 (N=343)	2.6%	3.0%	10.6%**	27.8%**
Age	.002	.001	-.012	-.004
Sex	-.041	-.023	.344**	-.110*
Race	.092	.020	.196	.005
Education	-.014	-.004	-.044*	-.005
ISEL	.002	.000	.002	.002
R^2 (N=343)	2.8%	2.9%	9.5%**	27.4**
Age	.002	.001	-.013	-.003
Sex	-.041	-.023	.346**	-.111**
Race	.093	.022	.187	-.014
Education	-.014	-.004	-.043*	-.006
ISEL	.002	-.001	.004	-.001
ISEL x gender	.000	.001	-.005	.006
R^2 (N=343)	2.8%	3.3%	9.6%**	29.4%**
Age	.002	.001	-.013	-.007
Sex	-.007	-.018	.367**	-.105
Race	.064	.032	.020	-.010
Education	-.011	-.001	-.045*	.001
CSS	.006	.002	.159	-.016
R^2 (N=280)	1.6%	1.8%	10.4%*	24.3%*
Age	.003	.001	-.014	-.005
Sex	-.011	-.018	.358**	-.111**

Race	.059	.033	.027	-.012
Education	-.010	-.001	-.047*	.003
CSS	.023	-.004	.192	-.018
ISEL	.004	.000	.002	.001
CSS x ISEL	-.003	-.001	.009	-.003
R^2 (N=279)	3.9%	2.7%	11.2%**	23.9%*
Age	.001	.001	-.014	-.005
Sex	-.016	-.016	.307**	-.109+
Race	.061	.037	.045	.002
Education	-.010	-.001	-.049*	.007
CSS	.012	-.040	.079	-.017
ISEL	.004	-.001	-.001	-.001
CSS x ISEL	-.005	-.002	.017*	-.001
ISEL x gender	.000	.002	.003	.007+
CSS x gender	.027	.071	.233	.012
CSS x ISEL x gender	.005	.002	-.023	-.002
R^2 (N=279)	4.3%	6.1%	13.5%**	26.6%**
Age	.002	.001	-.017	-.008
Sex	-.099	-.014	.363**	-.104
Race	.006	.012	.000	-.045
Education	-.016	-.002	-.066**	-.002
DAS	-.001	.001	.002	.002
R^2 (N=253)	3.7%	2.0%	13.4%**	28.5%**
Age	.002	.001	-.017	-.008
Sex	-.099	-.015	.364**	-.104
Race	.007	.012	.000	-.045
Education	-.016	-.002	-.065**	-.002
DAS	.000	.000	.004	.002
DAS x gender	-.001	.001	-.004	.000
R^2 (N=253)	3.7%	2.1%	13.6%**	28.4%**

Note: *p<.05; **p<.01; ***p<.001, +p=.05; SNI = Social Network Inventory; ISEL = Interpersonal Support Evaluation List; CSS = Chronic Stress Scale; DAS = Dyadic Adjustment Scale.

3.3 AIM 2: HEALTH BEHAVIORAL PATHWAY

Growth curve models in the previous section tested for a main effect between social relationship characteristics and the trajectory of change in biomarkers. The remainder of this project proposed to use a cross-lagged panel approach to test longitudinal mediation (by health behavior, affect, and daily social interaction) in the case of a 1) significant prospective main effect of social integration, perceived support, and marital quality with residualized change in biomarkers using multiple regression models (after adjustment for demographic covariates and baseline levels of biomarkers) and 2) significant correlation of mediator with both predictor at baseline and with change in biomarker. The first screening criterion examines change in a similar but slightly different manner compared to the growth curve analyses. While the growth curve analyses examine the rate of change as the outcome of interest using 3 time points, multiple regression models here examine residualized change after adjustment for baseline biomarker data. Given the additional time-point in the growth curve analyses (i.e. T2 at the 3-year follow-up), more weight should be placed in those findings. Nevertheless, the prospective association of baseline social relationship characteristics with residualized change in biomarkers was proposed as one of the required screening conditions prior to testing longitudinal mediation. For these reasons, these findings are presented next.

To this end, the PROC CALIS statement in SAS 9.4 was used to examine these longitudinal associations, given the procedure's ability to use FIML methods to inform estimates based on missing data on both the independent and dependent variables in multiple regression models (Allison, 2012). The second screening measure tested the significance of partial correlations between the mediator of interest (i.e. change in BMI and smoking from baseline to 3-year, and change in sleep duration from baseline to 6-year) with both predictor at baseline (i.e.

social integration, perceived support, and marital quality) and outcome variable (i.e. 6-year biomarker data after adjusting for biomarker levels at the previous time-point concurrent with the predictor, indicating change in these biomarkers). If both preliminary analyses yielded significant results (i.e. a significant direct effect with residualized change and a significant correlation of the mediator with both predictor and change in outcome), then cross-lagged panel analyses were pursued to test longitudinal mediation via health behaviors.

Using SAS 9.4 for analyses with social integration and perceived social support, a total of 349 observations were used. For analyses using marital quality, a smaller subsample of 254 married individuals with marital quality data was used. Sample characteristics of the whole sample are presented in Table 5. This table presents the same characteristics of predictor and biomarker outcome variables as in Table 1 but presents additional descriptive information regarding potential mediators.

Table 5. Sample characteristics for sample used to test prospective association of baseline social relationship characteristics with residualized change in IL-6 and CRP.

Characteristic	Sample size	Mean (SD) or % (n)
Mean age (SD)	349	60.49 (4.78)
% male (n)	349	49 (171)
% non-White (n)	349	16 (55)
% Bachelor's degree or higher (n)	349	51 (178)
ISEL score	347	137.65 (14.05)
SNI score	347	6.64 (1.90)
DAS score in married subsample (N=258)	254	111.41 (17.23)
Baseline % current smokers (n)	349	6.5 (23)
3-year % smokers (n)	341	6.7 (23)
6-year % smokers (n)	295	4.07 (14)
Baseline BMI (SD)	349	27.81 (4.62)
3-year BMI (SD)	340	27.94 (4.64)
6-year BMI (SD)	340	27.94 (4.64)
Sleep duration at baseline	349	6.87 (1.11)
Sleep duration at 6-year	281	6.86 (1.18)
Mean Positive Affect Baseline	342	5.95 (1.12)
Mean Negative Affect Baseline	342	2.08 (1.09)
Mean Positive Affect 6-year	262	6.70 (1.35)

Mean Negative Affect 6-year		262	0.87 (1.00)
Mean Positivity Baseline	Overall	342	6.57 (.91)
	Close Others	342	6.74 (91)
	Spouse	252	6.66 (.94)
Mean Negativity Baseline	Overall	342	1.39 (.98)
	Close Others	342	1.38 (.98)
	Spouse	252	1.45 (1.01)
Proportion of total interactions at baseline		342	.61 (.17)
Frequency of + Interactions at Baseline	Overall	342	.82 (.20)
	Close Others	341	.86 (.18)
	Spouse	252	.84 (.20)
Frequency of – Interactions at Baseline	Overall	342	.01 (.02)
	Close Others	341	.01 (.03)
	Spouse	252	.01 (.04)
Mean positivity at 6-year	Overall	262	7.63 (1.04)
	Close others	260	7.70 (1.07)
	Spouse	185	7.59 (1.19)
Mean negativity at 6-year	Overall	262	.38 (.51)
	Close others	260	.38 (.60)
	Spouse	185	.39 (.64)
Frequency of total interactions at 6-year		262	.56 (.21)
Frequency of + interactions at 6-year	Overall	261	.95 (.08)
	Close others	259	.95 (.11)
	Spouse	184	.94 (.15)
Frequency of – interactions at 6-year	Overall	261	.01 (.03)
	Close others	259	.01 (.07)
	Spouse	184	.01 (.08)
Baseline CRP (mg/L)		322	2.26 (2.05
3-year CRP (mg/L)		327	1.97 (1.92)
6-year CRP (mg/L)		285	1.66 (1.66)
Baseline IL-6 (pg/mL)		322	1.80 (1.48)
3-year IL-6 (pg/mL)		327	1.97 (1.47)
6-year IL-6 (pg/mL)		285	2.72 (2.15)

Note: Mean positivity and negativity in social interactions and mean positive and negative affect were scored on a transformed Likert scale of 0-9. Frequency of positive and negative interactions are proportion scores ranging from 0-100%. Mean and frequency measures of interactions with spouses were conducted in a subsample of married individuals.

Table 5 shows that Likert ratings of mean positive affect increased from baseline to 6-year (5.95 to 6.70), while mean negative affect declined from baseline to 6-year (2.08 to .87).

Similarly, mean positivity in social interactions from baseline to 6-year (6.57 to 7.63), while mean negativity in social interactions declined from baseline to 6-year (1.39 to .38). Proportion of negative interactions was remarkably low at both baseline and 6-year. That is, only 1% of total interactions were endorsed as negative, irrespective of partner type, both at baseline and 6-year. In contrast, the proportion of positive interactions was quite high at baseline and it rose substantially at 6-year. Approximately 82% of total interactions were endorsed as positive at baseline compared to 95% at 6-year.

Given this increase, a closer examination of this data showed that individuals spent less time, overall, in social interactions at 6-year than they did at baseline (i.e. 61% of the time at baseline vs. 56% at 6-year) and that this decrease was significant (i.e. $t(255) = 3.39$, $p = .0008$). Relatedly, it was seen that the number of valid interactions at 6-year (i.e. those that were current at the time of ED interview or in the 10 prior to the ED interview) were lower at 6-year than at baseline, allowing for a smaller denominator in the proportion ratio, and that a large majority of these valid interactions were positive, allowing for a larger numerator value in the ratio. It is possible that as participants aged, they became less socially active and with fewer interactions, each interaction may have been perceived as more positive or valued. Overall, fewer total social interactions at 6-year and the greater endorsement of these interactions as positive accounted for the increase in frequency positive interactions from baseline to 6-year.

Multiple regression models testing the prospective association of baseline social relationship characteristics with residualized change included 3 models where Model 1 adjusted for demographic characteristics (age, sex, race, education), Model 2 adjusted for baseline measure of inflammatory biomarkers, and in the case of any significant effects in Models 1 and 2, an additional Model 3 further adjusted for the alternative social relationship characteristics for

interpretive purposes. Results concerning perceived social support and social integration used a total of 349 observations under the estimation of FIML in the PROC CALIS command. Multiple regression results below report standardized regression estimates.

3.3.1 Social integration and residualized change

Results showed that social integration was not associated with residualized change in 6-year IL-6 level in Model 1 (B= -.004, p=.94) or in Model 2 (B= .01, p=.91). Similarly, social integration was not associated with residualized change in 6-year CRP in Model 1 (B= .07, p=.26) or in Model 2 (B= .03, p=.57).

3.3.2 Perceived social support and residualized change

Using the same sample of 349 observations, results showed that perceived social support was not associated with residualized change in IL-6 at the 6-year point in Model 1 (B= .024, p=.68) or in Model 2 (B= .003, p=.96). Perceived support was also not associated with residualized change in CRP at 6-year in Model 1 (B= .007, p=.91) or in Model 2 (B= .019, p=.71).

3.3.3 Marital quality and residualized change

Results of multiple regression analyses showed that marital quality in married individuals was not associated with residualized change in 6-year IL-6 level in Model 1 (B= .050, p=.46) or in Model 2 (B= .061, p=.34). Similarly, marital quality was not associated with residualized change in 6-year CRP in Model 1 (B= .062, p=.36) or in Model 2 (B= .050, p=.40).

In sum, none of the social relationship characteristics, including social integration, perceived social support, and marital quality, showed an independent, prospective association with residualized changes in inflammatory markers using multiple regression models. See Table 6.

Table 6. Standardized estimates from multiple regression models examining the prospective association of baseline social integration, perceived support, and marital quality with residualized change in IL-6 and CRP.

	6 year IL-6		6-year CRP	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Age	.052	.045	-.046	-.0
Sex	-.083	-.085	.005	-.080
Race	.115	.076	.014	-.004
Education	-.134*	-.111*	-.132*	-.054
Baseline biomarker	--	.377***	--	.530***
Social Integration (N=349)	-.004	.006	.065	.029
R^2	3.5%	17.6%	2.6%	28.9%
Age	.055	.045	-.059	-.033
Sex	-.086	-.087	.002	-.083
Race	.118	.077	.014	-.004
Education	-.134*	-.111*	-.135*	-.055
Baseline Biomarker	--	.377***	--	.532***
Perceived Social Support (N=349)	.024	.003	.007	.019
R^2	3.5%	17.6%	2.3%	29.0%
Age	.022	.022	-.127	-.093
Sex	-.122	-.101	.013	-.086
Race	.035	.034	-.060	-.031
Education	-.084	-.077	-.148*	-.057
Baseline Biomarker	--	.361***	--	.518***
Marital Quality (N=258)	.050	.061	.062	.049
R^2	2.1%	15.3%	4.7%	29.3%

Note: *p<.05, **p<.01, ***p<.001; Model 1 adjusts for age, sex, race, and education; Model 2 additionally adjusts for baseline measures of biomarker, allowing for a measure of residualized change.

A second screening criterion assessed partial correlations between social relationship predictors at baseline (i.e. social integration, social support, marital quality) with change in mediators of interest (i.e. BMI and smoking status at the 3-year mark while adjusting for baseline, and sleep duration at the 6-year mark while adjusting for baseline) and between

mediators with 6-year biomarkers (i.e. IL-6 and CRP at the 6-year time point after adjusting for biomarkers at the previous time-point). Note that in each case, the variables in columns are treated as independent variables and variables in rows indicate the adjusted change in outcome, except in the case of any cross-sectional correlations. See Table 7.

Table 7. Partial correlations (with sample sizes) between baseline measures of social relationship characteristics, change in behavioral mediators, and change in 6-year inflammatory outcomes.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. ISEL	.00 347																
2. SNI	.26*** 347	.00 347															
3. DAS (N=258)	42*** 254	.25*** 254	.00 254														
4. Baseline BMI	.11* 347	.14** 347	.03 254	.00 349													
5. 3-year BMI	.01 339	.06 339	.11 249	.93*** 340	.00 340												
6. 6-year BMI	.01 338	.03 339	.11 249	.92*** .340	.98*** 339	.00 340											
7. Baseline smoking status	.02 347	.04 347	.00 254	.04 349	.07 340	.07 340	.00 295										
8. 3-year smoking status	.03 340	.07 340	.04 250	.10 341	.14** 340	.14** 340	71*** 341	.00 341									

9. 6-year smoking status	.02 294	.03 294	.02 219	.03 295	.02 287	.09 287	76*** 295	72*** 288	.00 .295								
10. Baseline sleep duration	.04 347	.09 347	.00 254	.01 349	.00 340	.00 340	.12* 349	.12* 341	.13* 295	.00 349							
11. 6-year sleep duration	.06 280	.00 280	.08 207	.01 281	.03 273	.04 273	.07 281	.12* 274	.11 281	.52** 281	.00 281						
12. Baseline IL-6	.01 320	.03 320	.04 236	.15** 322	.17** 320	.14** 320	.14* 322	.13* 321	.13* 272	.09 322	.05 259	.00 322					
13. 3-year IL-6	.02 308	.03 308	.05 230	.21** 310	.24*** 325	.24*** 325	.16** 310	.15** 326	.16** 275	.03 310	.00 261	.39*** 310	.00 327				
14. 6-year IL-6	.02 262	.06 262	.12 194	.19** 263	.17** 266	23*** 277	.02 263	.06 267	.04 285	.01 263	.07 271	.22*** 263	.35*** 267	.00 285			
15. Baseline CRP	.01 320	.06 320	.01 236	.27*** 322	.25*** 320	.25*** 320	.23*** 322	.19*** 321	.19** 272	.01 322	.02 259	.23*** 322	.16*** 310	.01 263	.00 322		
16. 3-year CRP	.11 308	.06 308	.03 230	.07 310	.29*** 325	.28*** 325	.08 310	.16* 326*	.06 275	.02 310	.04 261	.08 310	22** 327	.07 267	.54*** 310	.00 327	
17. 6-year CRP	.07 262	.11 262	.07 194	.20*** 263	.18** 266	.32*** 277	.04 263	.01 267	.11 285	.02 263	05 271	.05 263	.02 267	.36*** 285	.33*** 263	.45*** 267	.00 285

Note: *p<.05, **p<.01, ***p<.001; ISEL = Interpersonal Support Evaluation List; SNI = Social Network Inventory; DAS = Dyadic Adjustment Scale. Correlations with IL-6 and CRP values use raw values, rather than log-transformed values, for ease of interpretation. Correlations concerning marital quality use a subsample of married individuals with data on marital quality (N=254). Prospective correlations partial out covariance for outcome (variables in rows) at concurrent time-point as the predictor, to indicate a measure of change (e.g. correlation of baseline social integration with 6-year IL-6 controls for baseline IL-6; correlation of 3-year smoking status with 6-year IL-6 controls for 3-year IL-6). There were no covariates in 1) cross-sectional associations, 2) retrospective correlations, and 3) in cases where the predictor and outcome were the same variable measured at different times, in which case correlations indicate unadjusted stability of measure over time.

The table above shows that none of the baseline social relationship characteristics were significantly correlated with change in health behavior mediators. For example, social integration was not significantly correlated with change in BMI from baseline to 3-year, with smoking status from baseline to 3-year, or with sleep duration from baseline to 6-year. Social support and marital quality were also not correlated with change in BMI from baseline to 3-year, with change in smoking status from baseline to 3-year, or with sleep duration change from baseline to 6-year. These results fail to meet the second proposed criterion of testing longitudinal mediation, which is a significant correlation between social constructs with change in behavioral mediators.

3.3.4 Aim 2: Summary of results

Overall, results showed that perceived social support, social integration, and marital quality did not show a significant direct, longitudinal effect with residualized change in inflammatory markers at the 6-year mark in multiple regression models, which fails to meet one of the proposed required criteria to pursue longitudinal mediation. Secondly, baseline social relationship constructs did not significantly correlate with changes in health behavior mediators, which fails to meet the second proposed required criterion to pursue mediation. Therefore, longitudinal analyses to test the mediating role of health behaviors were not pursued.

3.4 AIM 3: AFFECTIVE PATHWAY

The third aim of the project proposed to examine the potentially mediating role of positive and negative affect in daily life in the case of any significant direct longitudinal effects between

baseline measures of social relationship characteristics and residualized change in 6-year inflammatory outcomes. Given that there was no significant prospective association between social variables and these residualized biomarker change measures, these mediation analyses were not pursued. Nevertheless, partial correlations of positive and negative affect (measured through EMA interview at baseline and 6-year) with both baseline predictors (i.e. social integration, perceived social support, and marital quality) and inflammatory outcomes (i.e. change in biomarker data) are presented below in Table 8.

Table 8. Partial correlations (with sample sizes) between baseline measures of social relationship characteristics, change in mean positive and negative affect from baseline to 6-year, and change in inflammatory outcomes.

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. ISEL	1.00 347												
2. SNI	.26*** 347	.00 347											
3. DAS (N=258)	.42*** 254	.25*** 254	1.00 254										
4. Mean PA baseline	.29*** 341	.10* 341	.19** 249	1.00 342									
5. Mean NA baseline	-.20*** 341	.03 341	-.36*** 249	-.40*** 342	.00 342								
6. Mean PA 6 year	.14* 255	.08 255	.21** 188	.58*** 256	.13* 256	1.00 262							
7. Mean NA 6 year	-.00 255	.03 255	-.05 188	-.08 256	.39*** 256	-.51*** 262	1.00 262						
8. Baseline IL-6	..01 320	.03 320	-.04 236	-.04 317	.02 317	..01 242	-.03 242	.00 322					
9. 3-year IL-6	.02 308	.03 308	.05 230	.06 305	.09 305	.06 245	-.11 245	.39*** 310	.00 327				

10. 6-year IL-6	.02 262	.06 262	.12 194	.10 259	.07 259	.10 253	.16* 253	.22*** 263	.35*** 267	.00 285			
11. Baseline CRP	.01 320	.06 320	.01 236	-.04 317	.03 317	.05 242	-.08 242	.23*** 322	.16** 310	.01 263	.00 322		
12. 3-year CRP	.11 308	.06 308	03 230	.02 305	.06 305	-.04 245	.01 245	.08 310	.22*** 327	.06 267	.54*** 310	.00 327	
13. 6-year CRP	.07 262	.11 262	.07 194	.00 259	.01 259	-.01 253	.01 253	.05 263	.02 267	.36*** 285	.33*** 263	.45*** 267	.00 285

Note: p<.05, **p<.01, ***p<.001; ISEL = Interpersonal Support Evaluation List; SNI = Social Network Inventory; DAS = Dyadic Adjustment Scale. Correlations with IL-6 and CRP values use raw values, rather than log-transformed values, for ease of interpretation. Mean positive and negative affect at baseline and 6-year use transformed Likert scale scores ranging from 0-9. Correlations concerning marital quality use a subsample of married individuals with data on marital quality (N=254). Prospective correlations partial out covariance for outcome (variables in rows) at concurrent time-point as the predictor, to indicate a correlation with measure of change (e.g. correlation of baseline social integration with 6-year IL-6 controls for baseline IL-6, correlation of 3-year CRP with 6-year IL-6 controls for 3-year IL-6). There were no covariates in 1) cross-sectional associations, 2) retrospective correlations, and 3) in cases where the predictor and outcome were the same variable measured at different times, in which case correlations indicate unadjusted stability of measure over time.

Results from the table show that social integration at baseline was not correlated with change in mean positive affect from baseline to 6-year. Although social support and marital quality were both significantly correlated with an increase in mean positive affect from baseline to 6-year, mean positive affect at baseline was not correlated with 6-year change in IL-6 or 6-year change in CRP. This lack of correlation between mediator and change in biomarker outcome fails to meet the second proposed screening criterion to test for mediation. Additionally, the table above shows that social integration, social support, and marital quality were not significantly correlated with change in mean negative affect from baseline to 6-year, and that mean negative affect at baseline is not correlated with change in IL-6 and CRP from baseline to 6-year, precluding mediation analyses pertaining to negative affect.

3.4.1 Aim 3: Summary of results

Given that previous findings showed no significant prospective association of baseline social integration with residualized change in IL-6 or CRP and partial correlations showed no instances where baseline social constructs were related to change in mediator and that mediator was related to change in biomarker outcomes, longitudinal mediation analyses assessing EMA measures of positive and negative affect as mediators were not pursued.

3.5 AIM 4: SOCIAL INTERACTION PATHWAY

The fourth leg of the project proposed to examine the potentially mediating role of social interaction characteristics in daily life in the case of any significant direct longitudinal effects

between baseline measures of social relationship characteristics and residualized change in 6-year inflammatory outcomes. However, given that previous findings in this paper showed no significant, prospective effect between baseline measures of social relationship constructs and residualized change in IL-6 and CRP, longitudinal mediation analyses were not pursued.

Nevertheless, as in the case of health behaviors and affect, partial correlations between predictor (i.e. social integration, perceived social support, and marital quality at baseline), social interaction characteristics (i.e. frequency and quality of social interactions overall, with close others, and with spouses), and inflammatory outcomes are presented in tables below. Table 9a shows the prospective correlations between baseline social relationship measures with change in EMA social interactions from baseline to 6-year (see columns 1-3). Table 10 shows the correlation of baseline EMA social interaction characteristics with change in IL-6 and CRP (see rows 14-15).

Table 9. Partial correlations (with sample sizes) between baseline measures of social relationship characteristics with 6-year changes in EMA social interaction characteristics.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. ISEL	1 347															
2. SNI	.26*** 347	1 347														
3. DAS	.42*** 254	.25*** 254	1 254													
4. Frequency of social interactions – 6yr	.04 255	.18** 255	.12 188	1 262												
5. Frequency of + interactions – 6yr	.10 254	.10 254	.20** 188	.02 261	1 261											
6. Frequency of – interactions – 6yr	.04 254	.09 254	.04 188	.13* 261	.33*** 255	1 261										
7. Frequency of + int – close others- 6yr	.03 251	.05 251	.20** 188	.04 259	.68*** 252	.40*** 259	- 1 259									
8. Frequency of – int – close others – 6 yr	.02 251	.06 251	.10 188	.02 259	.18** 252	.68*** 259	-.64*** 259	1 259								
9. Frequency of + spousal interactions – 6 yr	.03 179	.03 179	.15* 177	.03 184	.69*** 184	-.54*** 184	.93*** 184	.61*** 184	1 184							

10. Frequency of – spousal interactions – 6 yr	.03 179	.05 179	.10 177	.06 184	.30*** 184	.81*** 184	-.76*** 184	.98*** 184	.68*** 184	1 184						
11. Mean + overall – 6 yr	.13* 255	.01 255	.18* 188	.02 262	.57*** 261	-.12* 261	.41*** 259	.10 259	.42*** 184	.17* 184	1 262					
12. Mean – overall – 6 yr	.09 255	.01 255	.01 188	.05 262	.42*** 255	.38*** 261	-.29*** 259	.27*** 259	.29*** 184	.29*** 184	-.44*** 262	1 262				
13. Mean + close others – 6 yr	.09 253	.02 253	.19** 188	.00 260	.48*** 253	-.15* 259	.54*** 259	.24*** 259	.55*** 184	.39*** 180	.96*** 260	-.43*** 260	1 260			
14. Mean – close others – 6 yr	.05 253	.02 253	.06 188	.02 260	.54*** 253	.45*** 259	-.51*** 259	.59*** 259	.54*** 184	.65*** 184	-.39*** 260	.90*** 260	-.39*** 260	1 196		
15. Mean + spousal interactions – 6 yr	.16* 180	.01 180	.17* 178	.00 185	.60*** 185	-.26*** 185	.57*** 185	.29*** 185	.64*** 184	.34*** 184	.92*** 185	-.43*** 185	.96*** 185	.50*** 185	1 185	
16. Mean – spousal interactions – 6 yr	.03 180	.06 180	.04 178	.01 185	.41*** 185	.54*** 185	-.63*** 185	64*** 185	.63*** 184	66*** 184	-.42*** 185	.84*** 185	-.53*** 185	.96*** 185	.55*** 185	1 185

Note: p<.05, **p<.01, ***p<.001; ISEL = Interpersonal Support Evaluation List; SNI = Social Network Inventory; DAS = Dyadic Adjustment Scale. Correlations with IL-6 and CRP values use raw values, rather than log-transformed values, for ease of interpretation. Mean social interaction characteristics use transformed Likert scale scores ranging from 0-9. Correlations concerning marital quality and characteristics of spousal interactions use a subsample of married individuals with data on marital quality (N=254). Columns 1-3 present prospective correlations between baseline social predictors and 6-year social interaction data that partial out covariance for social interaction variable at baseline to indicate a correlation with measure of change in social interaction variable from baseline to 6-year (e.g. correlation of baseline social integration with 6-year mean positivity in interactions controls for baseline mean positivity in interactions). Information in columns 4-16 can be considered as supplementary material that indicates cross-sectional, unadjusted correlations between social interaction variables at 6-year.

Table 10. Partial correlations (with sample sizes) between baseline measures of EMA social interaction characteristics with 6-year changes in IL-6 and CRP.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Frequency of social interactions – baseline	1 342														
2. Frequency of + interactions – baseline	.03 342	1 342													
3. Frequency of – interactions – baseline	.03 342	.35*** 342	1 342												
4. Frequency of + int – close others-baseline	.02 341	.91*** 341	.40*** 341	1 341											
5. Frequency of – int – close others – baseline	.02 341	.28*** 341	.80*** 341	.37*** 341	1 341										
6. Frequency of + spousal interactions – baseline	.01 252	.83*** 252	.38*** 252	.90*** 252	.37*** 252	1 252									
7. Frequency of – spousal interactions – baseline	.04 252	.15* 252	.62*** 252	.20** 252	82*** 252	.31*** 252	1 252								
8. Mean + overall – baseline	.02 342	.73*** 342	.30*** 342	.65*** 341	.25*** 341	.58*** 252	-.14* 252	1 342							

9. Mean – overall – baseline	.08 342	.30*** 342	.40*** 342	.33*** 341	.31*** 341	-.32*** 252	.20** 252	.45*** 342	1 342						
10. Mean + close others – baseline	.03 342	.65*** 342	.32*** 342	.67*** 341	.32*** 341	.61*** 252	-.19** 252	.94*** 342	.50*** 342	1 342					
11. Mean – close others – baseline	.08 342	.28*** 342	.39*** 342	.31*** 341	.37*** 341	-.32*** 252	.24*** 252	.45*** 342	.97*** 342	.52*** 342	1 342				
12. Mean + spousal interactions – baseline	.02 252	.62*** 252	.33*** 252	.65*** 252	.34*** 252	.71*** 252	-.31*** 252	.89*** 252	.50*** 252	.94*** 252	-.52*** 252	1 252			
13. Mean – spousal interactions – baseline	.08 252	.33*** 252	.41*** 252	.36*** 252	.37*** 252	-.36*** 252	.33*** 252	.52*** 252	.97*** 252	.57*** 252	.98*** 252	-.55*** 252	1 252		
14. 6-year IL-6	.07 259	.01 259	.01 259	.00 259	.05 259	.06 194	-.13 194	.13* 259	.06 259	.14* 259	-.10 259	.20** 194	-.17* 194	1 285	
15. 6-year CRP	.06 259	.01 259	.02 259	.03 259	.01 259	.07 194	-.02 194	.04 259	.08 259	.05 259	-.08 259	.07 194	-.10 94	.36*** 285	1 285

Note: p<.05, **p<.01, ***p<.001; ISEL = Interpersonal Support Evaluation List; SNI = Social Network Inventory; DAS = Dyadic Adjustment Scale. Correlations with IL-6 and CRP values use raw values, rather than log-transformed values, for ease of interpretation. Mean social interaction characteristics use transformed Likert scale scores ranging from 0-9. Correlations concerning characteristics of spousal interactions use a subsample of married individuals with data on marital quality (N=254). Rows 14 and 15 indicate prospective correlations between baseline EMA social interaction characteristics and 6-year IL-6 and CRP while partialing out covariance for baseline IL-6 and CRP, respectively, to indicate correlation with change in biomarkers. Information presented in rows 1-13 can be considered supplementary as it presents unadjusted, cross-sectional correlations between all EMA measures of social interaction characteristics at baseline.

Table 9a presents the correlations between baseline social relationship characteristics with 6-year change in EMA social interactions in columns 1-3. Table 10 presents the partial correlations between baseline EMA social interaction characteristics with 6-year change in IL-6 and CRP in rows 14-15. Results from table 9a show that higher social support and marital quality at baseline are correlated with a larger increase in mean positivity in all interactions and in interactions with spouses, whereas marital quality at baseline is correlated with a larger increase in mean positivity in interactions with close others. Table 10 shows that these social interaction characteristics (i.e. mean positivity in all interactions, with close others, and with spouse) at baseline are all, unexpectedly, correlated with a larger IL-6 increase from baseline to 6-year and mean negativity in spousal interactions at baseline is correlated with a smaller IL-6 increase from baseline to 6-year. These correlations should be interpreted with caution, given their unexpected direction and the limited variability in the positive and negative interactions in this sample. Specifically, only 1% of all social interactions were reported as negative and 82% were reported as positive at baseline (see Table 5).

For the purpose of mediation analyses, since there was no main effect between baseline social relationship constructs with 6-year changes in IL-6 and CRP using residualized change models, these EMA social interaction characteristics were not tested as mediators. However, given the unexpected direction of the correlations between baseline EMA social interaction characteristics and 6-year change in IL-6, exploratory analyses presented next explore the main effect of EMA social interaction characteristics with rate of change in biomarkers using growth curve modeling, as a more rigorous analysis of this association by using an additional time-point at the 3-year mark to model the trajectory of change.

3.5.1 Exploratory analyses with social interactions as predictors

Exploratory analyses (not initially proposed in this project) aimed to test a main effect between baseline measures of social interaction characteristics (collected through EMA monitoring) with initial levels and the rate of change in 6-year inflammatory biomarkers, treating the social interaction variables as predictors rather than mediators. Although this exploratory aim was not initially proposed in this project, it was later included due to its potential to follow-up on previous findings from this sample, reporting an inverse, cross-sectional association of frequency of positive interactions (overall and with close others) with circulating IL-6 levels baseline (Bajaj et al., 2016). This exploratory leg extends this previous paper by 1) examining the longitudinal association between baseline measures of social interactions and 6-year inflammatory biomarkers through growth curve modeling, and 2) using mean ratings of positivity and negativity, in addition to the frequency measure, as another assessment of the nature of social interactions. To maintain uniformity with the results previously presented, the subsequent analyses tested the association of EMA social interaction characteristics with initial levels and slope of change in IL-6 and CRP after adjustment for demographic covariates.

3.5.2 Frequency of total positive and negative social interactions and biomarker trajectory

First, frequency of total, positive, and negative social interactions at baseline were examined in relation to initial levels and the rate of change of IL-6 over the 6-year period. Out of the original 349 observations, 342 observations were used in this model (given that 7 cases were missing data on x-variables) with demographic covariates (i.e. age, sex, race, and education). The model

showed good fit (RMSEA = .00; CFI = .00; TLI = 1.02; SRMR = .02) and results showed that frequency of total interactions was not associated with IL-6 intercept (b= -.27, p= .08) or IL-6 slope (b= -.04, p= .47). A model with the same 342 observations with good fit (RMSEA = 00; CFI = 1.00; TLI = 1.03; SRMR = .01) showed that frequency of total interactions did not associate with CRP intercept (b= -.30, p= .34) or CRP slope (b= -.01, p=.95). Next, proportion scores of positive and negative social interactions overall were examined in relation to growth factors. The same model, with 342 observations with good fit (RMSEA = 00; CFI = 1.00; TLI = 1.01; SRMR = .02) showed that frequency of positive interactions, overall, did not significantly associate with IL-6 intercept (b= -.11, p= .39) or IL-6 slope (b= .00, p= .95). Similarly, the model (RMSEA = .02; CFI = .998; TLI = .993; SRMR = .013) showed that the frequency of positive interactions did not significantly associate with CRP intercept (b= .48, p= .07) or with CRP slope (b= .03, p=.81). Next, the same set of observations were used to examine the association of frequency of negative interactions and biomarker growth factors. Results of the model (RMSEA = .03, CFI = .99; TLI = .98; SRMR = .02) showed that the frequency of negative interactions, overall, did not significantly associate with IL-6 intercept (b= 1.89, p= .06) nor with IL-6 slope (b= -.06, p= .86). Similarly, frequency of negative interactions did not significantly associate with CRP intercept (b= 2.13, p= .29) or with CRP slope (b= .06, p= .95; RMSEA = .03; CFI = 996; TLI = .987; SRMR = .013). In sum, frequency of interactions and positive and negative interactions, overall, were not related to initial levels or the rate of change in IL-6 or CRP.

Next, frequency of positive and negative interactions with close others (i.e. spouse, friends, and family) were examined in relation to IL-6 and CRP growth factors. Out of the original 349, 341 observations were used in this model (8 were excluded due to missing data on x-variables) with good fit (RMSEA = .00; CFI = 1.00; TLI = 1.00; SRMR = .02). Results of the

model showed that frequency of positive interactions with close others did not significantly associate with IL-6 intercept (b= .02, p= .89) or with IL-6 slope (b= -.03, p= .64). Similarly, the model with the same 341 observations (RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .01) showed that frequency of positive interactions with close others did not associate with CRP intercept (b= .30, p= .29) or with CRP slope (b= .02, p= .85). The same 341 observations were used to examine the association of frequency of negative interactions with close others and IL-6 growth factors (RMSEA = .03, CFI = .99; TLI = .97; SRMR = .02). Results showed that there was no association of frequency of negative interactions with close others with IL-6 intercept (b= 1.40, p= .13) or with IL-6 slope (b= -.29, p= .40). Similarly, the same set of observations (RMSEA = .00; CFI = .00; TLI = 1.02; SRMR = .01) showed no significant association of frequency of negative interactions with close others and CRP intercept (b = .31, p= .87) or CRP slope (b = .13, p= .87).

Next, characteristics of spousal interactions within a married subsample were examined in relation to biomarker growth factors. Out of 254 married individuals with marital quality data, the model included 252 observations, given that 2 cases contained missing data on demographic covariates. The model showed good fit (RMSEA = .00; CFI = .00; TLI = 1.06; SRMR = .02). Frequency of positive spousal interactions were not associated with IL-6 intercept (b= -.03, p= .85) or with IL-6 slope (b= .02, p= .79). Similarly, the same model (RMSEA = .01; CFI = .00; TLI = .99; SRMR = .01) showed no significant association of frequency of positive spousal interactions with CRP intercept (b= .14, p= .65) or with CRP slope (b= .19, p= .21). To examine the association of negative spousal interactions, a model with the same set of observations showed good fit based on RMSEA, CFI, and SRMR indices (RMSEA = .04; CFI = .97; SRMR = .03) but moderate fit based on the TLI index (TLI = .93). Results showed that higher frequency

of negative spousal interaction was associated with greater, mean initial levels of IL-6 (b= 1.59, p= .04) after adjustment for demographic covariates but no association with IL-6 slope (b= -.76, p=.07). A model with the same set of observations with good fit (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .01) showed that frequency of negative spousal interactions was not associated with CRP intercept (b= -.24, p=.88) or with CRP slope (b = -.43, p= .55). In sum, frequency characteristics of social interactions overall, with close others, and with spouses generally did not associate with IL-6 or CRP growth factors, except for a positive association of negative spousal interaction frequency with IL-6 intercept. However, this finding should be interpreted with caution, given that only 1% of all spousal interactions were endorsed as negative among married individuals. Additionally, it is an isolated finding among a large number of analyses, rather than a part of consistent pattern of results.

3.5.3 Mean quality of social interactions and biomarker trajectory

In addition to the frequency characteristics of social interaction, mean measures of positivity and negativity within social interactions were examined in relation to biomarker factors. Out of the original 349 observations, the same 342 observations (as in the frequency analyses) were used to examine the association of mean positivity in all social interaction with IL-6 growth factors. The model showed good fit (RMSEA = .00; CFI = 1.00; TLI = 1.00; SRMR = .02). Results showed no association of mean positivity in all interactions with IL-6 intercept (b= -.03, p= .37) or with IL-6 slope (b= .02, p= .13). Similarly, a model with the same set of observations with good fit (RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .01) showed no association of mean positivity in all interactions with CRP intercept (b= .03, p= .60) or with CRP slope (b= .01, p= .63). The same model (RMSEA = .00; CFI = 1.00; TLI = 1.03; SRMR = .02) showed no association of

mean negativity in all social interactions with IL-6 intercept (b= -.01, p= .70) or with IL-6 slope (b=.01, p= .52), nor with CRP intercept (b=.06, p= .24) or CRP slope (b= -.02, p= .34) (RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .01).

Next, mean positivity and negativity in interactions with close others was examined. A model with the same set of 342 observations (RMSEA = .02; CFI = .997; TLI = 992; SRMR = .02) showed no significant association of mean positivity with spouse, friends, and family with IL-6 intercept (b=.00, p= .90) or with IL-6 slope (b=.01, p= .22). Similarly, mean positivity in interactions within close relationships was not associated with CRP intercept (b= .01, p= .81) or with CRP slope (b=.01, p= .60) using a model with the same set of observations (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .01). Mean negativity in interactions within close relationships was also unrelated to IL-6 intercept (b=-.01, p= .80) and with IL-6 slope (b=.00, p= .94) (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .017). It was also unrelated to CRP intercept (b=.06, p= .24) and with CRP slope (b= -.03, p= .30) (RMSEA = .00; CFI = 1.00; TLI = 1.01; SRMR = .011).

Lastly, mean quality of spousal interactions was examined in relation to biomarker growth factors. The same set of 252 observations (as in the frequency analyses) were used with good model fit (RMSEA = .00; CFI = 1.00; TLI = 1.065; SRMR = .018) in the IL-6 model. Mean positivity in spousal interactions, in married individuals, was not associated with IL-6 intercept (b=.01, p= .82) or with IL-6 slope (b= .02, p= .15), nor was it associated with CRP intercept (b= .02, p= .76) or with CRP slope (b=.03, p= .36) (RMSEA = .00; CFI = 1.00; TLI = 1.02; SRMR = .01). A model with the same 252 observations (RMSEA = .00; CFI = 1.00; TLI = .06; SRMR = .02) showed no association of mean negativity in spousal interactions with IL-6 intercept (b= .00, p=.95) or IL-6 slope (b= -.01, p=.37), nor with CRP intercept (b= .03, p= 57)

or CRP slope (b= -.04, p=.21). In sum, none of the mean ratings of positivity and negativity were associated with IL-6 or CRP growth factors irrespective of partner type. See Table 11.

Table 11. Unstandardized estimates of growth curve model results examining the association of baseline social interaction characteristics with 6-year IL-6 and CRP growth factors.

Variable	IL-6 intercept	IL-6 slope	CRP intercept	CRP slope
	b	b	b	b
Age	.002	.001	-.014	-.002
Sex	-.037	-.027	.309**	-.091
Race	.103	.018	.182	-.008
Education	-.035	-.012	-.141**	-.002
Proportion of total interactions	-.274	-.042	-.297	-.010
R^2 (N=342)	3.8%	3.6%	9.7%**	27.7%**
Age	.003	.001	-.014	-.002
Sex	-.042	-.028	.323**	-.092
Race	.099	.019	.204	-.009
Education	-.030	-.011	-.139**	-.001
Proportion of positive interactions	-.111	.003	.475	.031
R^2 (N=342)	2.5%	3.3%	10.6%**	27.2%**
Age	.004	.001	-.011	-.002
Sex	-.038	-.028	.306**	-.090
Race	.110	.019	.188	-.007
Education	-.033	-.011	-.139**	-.002
Proportion of negative interactions	1.891	-.064	2.133	.061
R^2 (N=342)	3.9%	3.2%	9.6%**	28.0%**
Age	.003	.001	-.013	-.002
Sex	-.037	-.029	.320**	-.089
Race	.105	.017	.192	-.009
Education	-.031	-.011	-.137**	-.001
Proportion of positive interactions – close others	.019	-.025	.296	.024
R^2 (N=341)	2.1%	3.3%	9.9%**	27.6%**

Age	.004	.001	-.013	-.002
Sex	-.044	-.026	.309**	-.090
Race	.112	.016	.182	-.008
Education	-.033	-.011	-.136**	-.001
Proportion of negative interactions – close others	1.37	-.287	.308	.128
R^2 (N=341)	3.3%	3.6%	9.4%**	27.9%**
Age	.003	.00	-.016	-.008
Sex	-.105	-.026	.317**	-.108
Race	-.013	.011	-.086	-.015
Education	-.033	-.006	-.190**	-.005
Proportion of positive spousal interactions	-.026	.018	.136	.185
R^2 (N=252)	3.0%	1.8%	13.2%**	31.8%**
Age	.004	.00	-.016	-.008
Sex	-.133*	-.015	.313*	-.112
Race	-.005	.009	-.092	-.022
Education	-.044	-.002	-.188**	-.002
Proportion of negative spousal interactions	1.590*	-.760	-.237	-.433
R^2 (N=252)	6.3%	6.2%	13.0%**	30.4%**
Age	.004	.001	-.014	-.002
Sex	-.044	-.023	.313**	-.089
Race	.101	.020	.184	-.007
Education	-.032	-.010	-.135**	-.001
Mean positivity in all interactions	-.025	.016	.029	.013
R^2 (N=342)	2.5%	5.3%	9.5%**	27.8%**
Age	.003	.001	-.010	-.003
Sex	-.039	-.027	.316**	-.093
Race	.105	.017	.177	-.005
Education	-.031	-.011	-.131**	-.004
Mean negativity in all interactions	-.010	.006	.062	.023
R^2 (N=342)	2.2%	3.6%	9.8%**	28.4%**

Age	.003	.001	-.013	-.002
Sex	-.038	-.024	.309**	-.088
Race	.103	.019	.183	-.007
Education	-.031	-.010	-.136**	-.001
Mean positivity in interactions with close others	.004	.013	.013	.014
R^2 (N=342)	2.2%	4.4%	9.4%**	27.8%**
Age	.003	.001	-.010	-.003
Sex	-.039	-.028	.316**	-.094
Race	.104	.018	.183	-.008
Education	-.031	-.011	-.132**	-.003
Mean negativity in interactions with close others	-.006	.001	.061	-.025
R^2 (N=342)	2.2%	3.2%	9.8%**	28.5%**
Age	.002	.00	-.016	-.008
Sex	-.101	-.019	.317*	-.107
Race	-.011	.011	-.089	-.020
Education	-.033	-.005	-.188**	-.003
Mean positivity in spousal interactions	.007	.021	.019	.028
R^2 (N=252)	3.0%	4.3%	13.0%**	31.0%**
Age	.002	.00	-.014	-.009
Sex	-.103	-.026	.307*	-.116+
Race	-.011	.014	-.099	-.012
Education	-.033	-.007	-.188**	-.006
Mean negativity in spousal interactions	-.002	-.012	.034	-.035
R^2 (N=252)	3.0%	2.6%	13.1%**	31.2%**

Note: *p<.05; **p<.01; ***p<.001; + p=.05; Frequency measures are scored as proportion measures ranging from 0-100%; Mean intensity ratings are scored on a Likert Scale of 0-9. Close others are defined as spouse, friends, and family members. Characteristics of spousal interactions were only studied in a subsample of married individuals.

3.5.4 Aim 4: Summary of results

In sum, exploratory analyses of the longitudinal association of EMA-based social interaction characteristics at baseline with biomarker trajectory showed that higher frequency of negative spousal interactions was associated with greater mean initial levels of IL-6 (indicated by the intercept factor), while no other social interaction characteristics were associated either biomarker growth factors. In contrast with the less sophisticated correlational findings in Table 9b, mean positivity in social interactions (overall, with close others, and with spouse) was not associated with the rate of change in IL-6. Therefore, these correlational findings should be interpreted with caution, given that greater weight is assigned to the results based on growth curve models based on its ability to incorporate an additional time-point. Further, the significant positive association between frequency of negative spousal interactions and IL-6 intercept should also be interpreted with caution, given that it was an isolated finding and that there were a small number of interactions with spouses that were endorsed as negative among married individuals.

4.0 DISCUSSION

The current study uniquely tested the role of social relationship characteristics in the longitudinal change in two pro-inflammatory biomarkers, IL-6 and CRP, which are implicated in the progression of CVD over time. The 3 global social relationship characteristics of interest were social integration, perceived social support, and marital quality. The study also conducted a series of exploratory analyses to test the predictive value of EMA-based social interactions in association with longitudinal change in pro-inflammatory biomarkers. This community sample consisted of healthy older adults, age 50-70 years, and examined a period of 6-years.

Firstly, this sample showed an average increase (mean slope = .10 pg/mL) in IL-6 levels, which was somewhat steeper than the average slope reported in the control group of another community sample over a 6-year period (i.e. mean slope = .004 pg/mL reported in Kiecolt-Glaser et al., 2003). In contrast to IL-6, the current sample of older adults showed a decline in CRP over a period of 6 years, which is inconsistent with the bulk of previous literature and conceptual schools of thought positing normative increases in pro-inflammatory cytokines and acute phase proteins in aging. In fact, given the increase in IL-6 in this sample and that IL-6 is one of the primary catalysts of the hepatic production of CRP, the decrease in CRP is all the more puzzling. The observed decline is most consistent with alterations in assay standards from year to year rather than a real decline (which is implausible and not supported by previous evidence) or due to random error. Therefore, changes in measurement standards may have contributed to the systematic shifts in mean values of CRP, affecting absolute degree of change but not the rank ordering of individuals nor the validity of the CRP data at each time-point.

None of the demographic characteristics in this sample predicted initial levels or the rate of increase in IL-6, suggesting that differences in age, gender, race, or education do not account for individual differences in IL-6 trajectory. Previous reports pertaining to gender and ethnic differences in IL-6 have been mixed. Excluding the conflicting findings from studies that examine stimulated measures of IL-6 (O'Connor et al., 2007; Aulock et al., 2006), previous literature shows no gender differences in circulating IL-6 in a sample of young adults (Yang et al., 2007) but some evidence of higher IL-6 levels in older women (Grunewald et al., 2006). While some studies report higher levels of IL-6 in African American women over the age of 65 (Allison et al., 2006; Walston et al., 2005), others show no such differences in older African American women ranging in age from 70-79 years old (Yaffe et al., 2003). One particular study examined circulating IL-6 levels in a community sample of 107 adults and reported that women and ethnic minorities had significantly higher circulating levels of IL-6 (Chapman et al., 2009). However, it should be noted that this particular study included samples of a lower mean age compared to the current study (i.e. 52 years old compared to approximately 61 years of the current study) and had significantly greater representation of females and of minorities in their urban sample (i.e. 77% were female; 57% were of ethnic minority with almost all of these participants identifying as of the African American race). Therefore, the lack of association of age, gender, and race with IL-6 initial levels and trajectory in the current study is consistent with the bulk of the cross-sectional evidence reporting a null association in samples with similar demographic characteristics.

In contrast, however, there are documented gender and ethnic differences in CRP levels. A multiethnic sample of 2,749 adults showed, aged 30-65, showed higher levels of CRP in African American individuals compared to Caucasians and in women compared to men (Khera

et al., 2005). These findings were replicated in the MESA cohort (i.e. Multiethnic Study of Atherosclerosis) of men and women, aged 45-84 years, where findings showed that women had higher levels of median CRP compared to men across all ethnic subgroups (Lakoski et al., 2006). Both of these samples had a significantly higher proportion of African Americans than the current study (i.e. 64% of the sample was African American in the former study; 61% of the sample was of ethnic minority in the latter study). The current study replicated these gender-specific findings by showing higher initial levels of CRP in women and the study extended previous findings by reporting a larger decline in CRP in women longitudinally compared to men. However, the low proportion of ethnic minority in the current sample may, in part, explain the non-significant association of race with CRP growth factors.

One of the most important questions examined in this project relate to the potential longitudinal link between social relationship characteristics and pro-inflammatory biomarkers. Specifically, this is the first study to test whether global social constructs that have been previously linked with mortality risk (i.e. social integration, perceived social support, and marital quality) predict the trajectory of change in circulating IL-6 and CRP using growth curve modeling and using a healthy sample. One of the most important implications of this prospective design is to establish directionality of effects to eliminate reverse causality as a possibility in the cross-sectional literature and address methodological limitations in the extant prospective literature. This is particularly important for IL-6, given that it has shown to induce feelings of social disconnection (Eisenberger, 2010) and the increasing understanding of the coregulatory processes between social behavior and pro-inflammatory cytokines (Eisenberger et al., 2017). The prospective analyses in this study showed no significant associations of social integration, social support, and marital quality at baseline with the trajectory of change in biomarkers over a

period of 6 years, suggesting that these particular social constructs do not play a role in the longitudinal change in IL-6 or CRP. It is important to interpret these findings in the specific contexts of the literature examining social integration, perceived support, and marital quality, as these segments of literature show disparate findings.

Firstly, the literature testing the link between social integration and circulating IL-6 and CRP is examined. While there are some cross-sectional studies that show no association between social integration and IL-6 or CRP (Bajaj et al., 2016, Cho et al., 2015), the vast majority of studies report a significant, inverse association of social integration with these pro-inflammatory biomarkers (Loucks et al., 2006a; Loucks et al., 2006b; Ford et al., 2006; Heffner et al., 2011; Hafner et al., 2011; Shankar & McMunn, 2011; Kamiya et al. 2010), suggesting that more socially integrated individuals have lower levels of circulating IL-6 and CRP. These findings are more consistent for CRP than for IL-6 (Loucks et al., 2006b; Ford et al., 2006; Heffner et al., 2011; Glei et al., 2012; Shankar & McMunn, 2011; Kamiya et al. 2010) and approximately half of the studies show a gender effect, such that the inverse association is present in men but not women (Loucks et al., 2006a; Loucks et al., 2006b; Ford et al., 2006; Hafner et al., 2011). However, given that the sample in the current study did not previously show a significant cross-sectional association of social integration with CRP or IL-6 (Bajaj et al., 2016), it is perhaps not surprising that this sample also does not yield a significant longitudinal association with the rate of change in these markers.

The contribution of the current study to the extant literature on social integration and inflammation has important implications. While the cross-sectional link between social integration and IL-6 and CRP has been replicated in many studies, the cross-sectional design of these studies does not eliminate reverse causality as a confound. It may be that acute or chronic

increases in IL-6 or CRP may affect the quantity of one's social participation, resulting in limited or irregular social contact and less diversity in one's social roles. Using a prospective design, the current study uniquely tested the directionality of this effect in a sample of healthy adults and drew the conclusion that social integration does not relate to long-term changes in these pro-inflammatory biomarkers. It may be, then, that previous cross-sectional observations linking social integration and inflammation are due to the effects of inflammation on social integration rather than vice versa.

The non-significant association of social integration with longitudinal changes in IL-6 and CRP deserves more attention and interpretation. In some ways, the null association reported here is inconsistent with the robust association reported between social integration with mortality (Holt-Lunstad et al., 2010) and with pro-inflammatory cytokines (Uchino et al., 2018). However, prospective evidence included in the latter meta-analysis uses a clinical population (Yang et al., 2014b) or examines social integration as a moderator rather than a predictor (Cho et al., 2015). Only one study, to our knowledge, reported a significant inverse association of social integration with CRP prospectively (Yang et al., 2016); however, this study did not adequately measure longitudinal changes in CRP as the study lacked repeated assessments of this biomarker. Further, the reported inverse association between social integration and CRP was present in every age group of the human lifespan except in the middle-aged MIDUS sample, which included 1) individuals aged 25-64, and 2) a homogenous mix of mostly White respondents with high levels of household income, high educational attainment, and high levels of social connectedness with little variability in this measure (all characteristics similar to those of the PHHP sample). In fact, Yang and colleagues (2016) also used another middle-aged sample (NHANES, aged 34-74) to test the association of social integration with CRP but found no such link. Therefore, the null

finding in this report may, in part, be attributed to the characteristics of this specific sample for the same reasons described above (i.e. relatively high levels of social integration), as well as good physical and mental health, and a healthy range of both IL-6 and CRP biomarkers. It is also possible that social integration is not associated with much variance in this age group because members of this age group tend to be highly embedded in their social networks due to demands of work, community, parenting, caregiving, etc. These demands may also carry with them significant stress and challenge, which may be another reason that this structural measure is not particularly beneficial for inflammatory outcomes, as argued by Yang and colleagues (2016). Overall, this literature can benefit from a replication of these findings in other samples of various age groups, with heterogeneous health characteristics, using a prospective design and methods of analysis, and using a similarly well-validated and complex measure of social integration.

In contrast with the literature pertaining to social integration, cross-sectional research examining the association of perceived support with IL-6 and CRP shows mixed findings as results vary in significance and in direction. Many studies, using a healthy sample, do not observe a significant, inverse association between global social support and IL-6 (Bajaj et al., 2016; Hemingway et al., 2003) or CRP (Bajaj et al. 2016; McDade et al., 2006; Kamiya et al., 2010; Hemingway et al., 2003; Glei et al., 2012). Limited prospective evidence either reports no longitudinal association between global social support and CRP in this age range (Yang et al., 2016) or reports a significant association of global social support with IL-6 (Hughes et al., 2014); however, these studies are limited by their study of clinical populations (Hughes et al., 2014) and inadequate operationalization and measure of longitudinal change (Yang et al., 2014; Yang et al., 2016). Given that previous work using this sample did not show a significant cross-sectional

association (Bajaj et al., 2016), again, it is perhaps not surprising that perceived social support also does not show a longitudinal main effect with IL-6 or CRP.

Rather than global social support, cross-sectional evidence suggests that it may be that specific types of support (i.e. emotional support) hold a main or buffering effect with inflammation (Mezuk et al., 2010). Prospective evidence, using healthy samples, also shows that source-specific support (e.g. from spouse, friends or family) (Yang et al., 2014; Eguchi et al., 2016) and social strain may associate with inflammatory outcomes, particularly with IL-6 and CRP (Yang et al., 2016 in MIDUS; Yang et al., 2014). Exploring subtypes of support, sources of support, and sources of social strain may elucidate whether there is a consistent, prospective main effect with circulating IL-6 or CRP in healthy samples of this age group.

In addition to all the reasons described above that may explain null prospective associations of social integration and support with inflammation (e.g. sample characteristics, potential of reverse causality, etc.), another important explanation may be due to the limited power of the current study. Given that we now know that social integration and perceived support both show an inverse association with pro-inflammatory biomarkers with a small effect size (Zr = -.07 for social integration and Zr = -.05 for perceived social support from Uchino et al. 2018), it is likely that the current study is underpowered to detect an association of a similar effect size. In fact, to detect a significant association of an effect size of .07 (in the case of social integration) and a power of .80, a study would need approximately 1,599 participants. This is a significantly larger sample size than N=349 in the whole sample of the current study. We now have more complete information about the effect sizes of these associations, based on estimates provided by Uchino and colleagues (2018), than we did while planning the current study and the statistical power required to detect these associations must be factored in while interpreting these

findings. Therefore, there may actually be a significant, prospective effect between these two social relationship constructs and change in IL-6 and CRP, and a study with a larger sample size would be better equipped to detect such associations.

In contrast to social integration, social support has long been viewed as an important moderator in the link between stress and disease as supported by much empirical evidence pertaining to both mental and physical health outcomes (Cohen & Wills, 1985; Olstad et al., 2001). While this is certainly the case with the physical and mental health outcomes mentioned above, there is only one study that reported this stress-buffering effect and that was specific to emotional support and was only found in women (Mezuk et el. 2010). A potential reason for the null buffering effect of social support found in the present study could be due to our measure of chronic stress. The Chronic Stress Scale (CSS) was developed to measure persistent stress in a sample of hurricane survivors to measure the effect of acute life events on psychological stress over time, positing chronic stress as a potential mediator of this effect (Norris & Uhl, 1993), which is perhaps not ideally suited for the characteristics of this healthy sample. Nevertheless, the bulk of the cross-sectional and prospective evidence does not point to a consistent buffering effect of social support in determining circulating levels of IL-6 or CRP in healthy samples and results of the current study are consistent with those findings.

Unlike the literature examining social integration and social support, research examining the association of marital quality with IL-6 and CRP is still emerging and yields preliminary findings. There are only 2 studies that examine a cross-sectional association of marital quality, measured as partner support and strain, with IL-6 and CRP and both studies use the same sample (i.e. the MIDUS cohort) and the same measure of marital quality (Whisman & Sbarra, 2012; Donoho et al., 2013). Both studies provided evidence for an inverse association of partner

support with IL-6 in women, while Donoho and colleagues further reported an inverse association with CRP. Given the cross-sectional nature of these findings, reverse causality emerges as a significant concern that is, in part, addressed by the prospective design of the current study. Results of the current study show that the inverse, cross-sectional association of marital quality with these biomarkers does not extend to a longitudinal setting. Specifically, marital quality does not significantly predict initial levels or the rate of change in these biomarkers over time.

One possible reason for this null prospective association is that any link between marital quality and inflammation may be limited to partner support, as shown in the cross-sectional evidence, rather than partner strain or global marital adjustment. In fact, both cross-sectional studies examining the link between marital quality and inflammation have used 6 items to assess partner support (e.g. "How much does your spouse really understand the way you feel about things?") and 6 items to assess partner strain (e.g. "How much does your spouse criticize you?") (Whisman & Sbarra, 2012; Donoho et al., 2013). It may be that positive, supportive aspects of marriage may be particularly important for women, rather than men. In contrast to marital quality, it may be that marital status is protective in men, given previous evidence that unmarried men tend to engage in higher risk behaviors after leaving an unhappy marriage (Waite et al., 2009) and tend to have a higher risk of mortality (House et al., 1982; Orth-Gomer et al., 1987). Additionally, both cross-sectional studies reported an inverse association with IL-6 but care must be taken in assuming the source of production of IL-6, given that it has multiple sources of production, can vary in function, and is implicated in causing feelings of social disconnection (Hansel et al., 2010; Eisenberger et al., 2012). And as mentioned previously, the effect of changes in IL-6 and CRP on marital adjustment, cross-sectionally and longitudinally, remain

unknown. More work examining the cross-sectional and longitudinal association of overall marital quality, partner support, and partner strain with pro-inflammatory biomarkers would elucidate whether there is a consistent main effect, whether the effects are bidirectional in nature, whether any observed effects are limited to support or strain, and whether there are demographic or psychological moderators of this association.

Exploratory analyses further examined social interaction characteristics as predictors of initial levels and rate of change in biomarkers through growth curve analyses. These analyses were conducted as follow-up to previous findings using this sample showing an inverse, cross-sectional association of the frequency of positive interactions overall and with close others with circulating IL-6 (Bajaj et al., 2016) and interpreted in the context of a larger body of work showing that the quality of social interactions relate to systemic inflammation (Fuligni et al., 2009; Chiang et al., 2012). Therefore, this portion of the study aimed to test whether frequency of interactions and mean quality of interactions longitudinally associated with circulating biomarkers.

Generally, there was a non-significant prospective association between baseline EMA measures of social interaction characteristics and the intercept and slope factors of IL-6 and CRP. Only one finding emerged pertaining to spousal interactions and in relation to initial levels of IL-6. Specifically, greater frequency of negative spousal interactions associated with higher initial levels of IL-6 in a sample of married individuals, but not with the rate of change in IL-6. This finding adds to the existing body of literature reporting cross-sectional, inverse associations between questionnaire-measures of marital quality and IL-6. It also adds to extant literature assessing the role of marital quality through EMA-based marital interactions. For example, a recent study reported an inverse, cross-sectional association between mean positive marital

interactions and an index of cardiovascular disease, intima-media thickness (IMT), and a positive association between mean negative marital interactions and IMT (Joseph et al., 2014). However, it should be acknowledged that the current finding was exploratory in nature and therefore, further replication of this finding in samples with more variability in reported positivity and negativity in marital interactions would add more confidence in these results.

Relatedly, it should be noted that the inverse, cross-sectional association between frequency of positive interactions and circulating IL-6 reported in Bajaj et al. (2016) was not found in the longitudinal setting of the current study as frequency of positive interactions, overall or with close others, did not predict the rate of change in IL-6 (or CRP). Two important differences in the previous and current study may account for the discrepancy in these findings. The first difference relates to the scoring of the social interaction data. In scoring positive interactions, the previously published study considered an interaction as positive if it met the criteria on one of the three positive interaction items. So, for example, if an interaction was rated as agreeable but not necessarily friendly or pleasant, the interaction was considered as a positive interaction. In contrast, the current study employed a more conservative approach and required that positive interactions be rated as agreeable, pleasant, and friendly. This approach operationalized positive interactions as those containing all 3 positive emotions and led to a reduced frequency of positive interactions in the sample. The same difference in scoring criteria also holds true in the case of negative interactions. The second difference relates to the handling of missing data. The previous study used list-wise deletion as a missing data strategy as it only included individuals who showed complete data for all variables of interest (e.g. social integration, social support, social interaction variables, and biomarker data). In contrast, the current study used the FIML method under the condition of data missing at random, which

allowed for the inclusion of a greater number of observations and maximized power. So, while the social interaction scoring strategy favors the previous study by including a greater number of and variability within positive and negative interactions, the second strategy pertaining to missing data favors the current study for its greater power to detect findings. These two differences, taken together, may have contributed to the difference in findings observed in the association of the frequency of positive interactions and the rate of change in biomarkers.

On the other hand, perhaps it is the case that the frequency of positive interactions, in fact, do not actually relate to longitudinal changes in these particular biomarkers. This would suggest that in fact, the association is not causal, such that reverse causality accounts for any observed effects. It could also suggest that the benefits of positive social engagement, if any, may be short-lasting and contribute to decreased levels of biomarkers during an acute time frame, which is certainly a conceivable explanation for a pleiotropic and multi-functional cytokine like IL-6. This particular cytokine is often considered a messenger cytokine as it is upstream in the acute phase response and has shown to have pro- and anti-inflammatory properties. Overall, the lack of findings in a longitudinal setting would indicate perhaps an effect of reverse causality and/or an ephemeral benefit of positive social interactions within one's larger social network and/or within close relationships as it pertains to changes in pro-inflammatory biomarkers.

In addition to the main findings discussed above, there were some ancillary findings reported in the correlational tables above. Firstly, Table 8 shows that perceived support and marital quality at baseline were positively correlated with 6-year positive affect after adjusting for baseline positive affect (assessed by EMA at both time points), indicating that those with higher perceptions of support and higher marital quality at baseline showed an increase in

positive affect from baseline to 6-year. This finding suggests a link between social relationships and positive affect, specifically as measured by EMA, but it should be further replicated and strengthened through more rigorous methods to study longitudinal change in positive affect. Secondly, Table 9b suggests that higher mean positivity in social interactions at baseline is unexpectedly correlated with a larger increase in IL-6 from baseline to 6-year, and lower mean negativity in spousal interactions at baseline is correlated with a smaller increase in IL-6 from baseline to 6-year. However, again, interpretation should be cautionary, given 1) that this finding is unexpected in direction, 2) the limited variability in the measure of positive and negative social interactions, and 3) that this finding was not replicated in the growth curve analyses.

4.1 SUMMARY

In sum, this study provides no evidence for a longitudinal association of social support, social integration, and marital quality with the rate of change in IL-6 or CRP over a period of 6 years in a community sample of healthy, older adults. The overall non-significant association is perhaps of little surprise, given that this particular sample did not previously report a significant cross-sectional association (Bajaj et al., 2016) and given the small effect size of the link between social support and integration with inflammation (Uchino et al., 2018). The small effect size indicates that systemic inflammation may only be one pathway linking social relationships to cardiovascular risk and there may be other more upstream biological pathways, activated by the autonomic and endocrine systems, that are more closely related to social relationship characteristics. Further, non-significant findings may be also attributed to the healthy characteristics of this sample and to the smaller sample size included in the current study, as

compared to other cross-sectional and prospective studies examining aspects of social relationships in relation to inflammation (Uchino et al., 2018). A brief power analysis shows that a much larger sample size would be necessary (over N=1500) to detect an association of a similar effect as reported by Uchino and colleagues (2018). The findings of the current study should be interpreted within these contextual parameters.

Exploratory findings provided support for a link between daily social behavior in marriage and IL-6. Namely, frequency of negative spousal interactions associated with a higher IL-6 intercept in growth curve analyses. The association of negative spousal interaction with greater initial levels of IL-6 are consistent with previous literature and extend the literature on marital quality and inflammation, as well as the literature using EMA to study daily marital exchanges.

4.2 STRENGTHS AND LIMITATIONS

This study comes with its set of limitations. Firstly, as mentioned previously, a limitation of this study is its inclusion of a remarkably healthy sample, which may partly account for the non-significant findings and may limit generalizeability. Secondly, this sample showed an unexpected decrease in CRP over time and a steeper rise in IL-6 from 3-year to 6-year, which may be due to differences in measurement standards. This issue highlights the importance of running inflammatory assays from different time-points at the same time to ensure that there is no systematic shift in the mean values of these biomarkers due to changes in measurement standards. Thirdly, recently published estimates of the effect sizes in the association of social integration and perceived support with biomarkers of inflammation showed that the current study

lacks adequate statistical power to detect an association between social integration and perceived support with inflammation. This data was not available during the planning phases of the current study but should now be considered in future studies that aim to examine the prospective association between these two social relationship constructs and inflammation.

However, major strengths of this study include using 1) a relatively large sample compared to EMA research standards, 2) novel, ambulatory methodology to measure daily social behavior, 3) a prospective design and analysis of change, and 4) growth curve analyses to examine biomarker trajectory. This study makes a unique contribution to the literature through these methodological strengths and provides new avenues of investigation.

4.3 FUTURE RESEARCH

There are a number of ways that future research can consider extending the literature on the prospective association between social relationships and health. First, future research may consider replication of these findings by testing the prospective association of social relationship constructs with changes in biomarkers of systemic inflammation in other samples with 1) more heterogeneous health characteristics, 2) more variability in chronic stress, 3) greater representation of racial and ethnic minorities, and 4) adequate power. This will allow for greater detection of main or stress-buffering effects of social relationships and increase generalizeability of findings.

Regarding perceived support, future research may consider whether sources of support or subtypes of support (e.g. emotional support) either directly associate with inflammatory outcome or moderate the effects of stress on pro-inflammatory cytokines. This is especially important,

given previous evidence that sources of support differentially predict mortality risk. Relatedly, future research may consider measuring perceived support from various support providers using both global measures (e.g. ISEL) and EMA measures and assess the utility of each instrument in any differences they play in findings.

Thirdly, future work may consider testing prospective association of social relationship characteristics during a shorter period of time, given that previous work has shown an association between social support and change in inflammation over 1 year (although in a clinical sample) (Hughes et al., 2014). Such effect sizes may also be larger and more readily detected in smaller samples. It is possible that measures of social relationships fluctuate, during this age range and in healthy samples, and using a shorter time-period would allow for greater detectability for any associations. Relatedly, the use of a shorter time-period may also allow for examination of a bidirectional relationship between pro-inflammatory biomarkers with longitudinal change in social support, social integration, and marital quality. This is particularly important due to increasing attention being devoted to the coregulation of social behavior and inflammation, leading to changes in sensitivity to positive and negative social cues (Eisenberger et al., 2017). Changes in both social behavior and inflammation may influence each other dynamically over time.

Measuring these dynamic changes in both social behavior and inflammation relates to the issue of repeated assessments and methodology. Future studies may continue to consider the utility of comparing global assessments of social relationship characteristics with EMA measures, not only in their assessment of perceived support from various support providers, but also in their assessment of daily social behaviors in association with biological processes implicated in cardiovascular risk. Similarly, future study designs may also utilize repeated

assessments of inflammatory biomarkers. Using samples with adequate variability in both positive and negative aspects of daily social exchanges may also allow for better detection of any bidirectional link between daily social behavior and inflammation.

And lastly, future research may continue to explore the longitudinal role of social relationship characteristics with inflammatory activity using other measures of social relationships (e.g. loss, defeat, rejection as discussed in Eisenberger et al., 2017), and with other pro-inflammatory biomarkers (e.g. TNF-alpha, IL-1, fibrinogen) that also play a significant role in cardiovascular risk.

APPENDIX A

SOCIAL NETWORK INVENTORY (SNI)

Instructions: This questionnaire is concerned with how many people you see or talk to on a regular basis including family, friends, workmates, neighbors, etc. Please read and answer each question carefully. Answer follow-up questions where appropriate.

1. Which of the following best describes your marital status?
____ (1) currently married & living together, or living with someone in marital-like relationship
____ (2) never married & never lived with someone in a marital-like relationship
____ (3) separated
____ (4) divorced or formerly lived with someone in a marital-like relationship
____ (5) widowed

2. How many children do you have? (If you don't have any children, check '0' and skip to question 3.)
____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

2a. How many of your children do you see or talk to on the phone at least once every 2 weeks?
____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

3. Are either of your parents living? (If neither is living, check '0' and skip to question 4.)
____ (0) neither ____ (1) mother only ____ (2) father only ____ (3) both

3a. Do you see or talk on the phone to either of your parents at least once every 2 weeks?
____ (0) neither ____ (1) mother only ____ (2) father only ____ (3) both

4. Are either of your in-laws (or partner's parents) living? (If you have none, check the appropriate space and skip to question 5.)
____ (0) neither ____ (1) mother only ____ (2) father only ____ (3) both ____ (4) not applicable

4a. Do you see or talk on the phone to either of your partner's parents at least once every 2 weeks?

_____ (0) neither _____ (1) mother only _____ (2) father only ____ (3) both

5. How many other relatives (other than your spouse, parents & children) do you feel close to? (If '0', check that space and skip to question 6.)

____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

5a. How many of these relatives do you see or talk to on the phone at least once every 2 weeks?

____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

6. How many close friends do you have? (meaning people that you feel at ease with, can talk to about private matters, and can call on for help)

____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

6a. How many of these friends do you see or talk to at least once every 2 weeks?

____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

7. Do you belong to a church, temple, or other religious group? (If not, check 'no' and skip to question 8.)

_____ no _____ yes

7a. How many members of your church or religious group do you talk to at least once every 2 weeks? (This includes at group meetings and services.)

____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

8. Do you attend any classes (school, university, technical training, or adult education) on a regular basis? (If not, check 'no' and skip to question 9.)

_____ no _____ yes

8a. How many fellow students or teachers do you talk to at least once every 2 weeks? (This includes at class meetings.)

____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

9. Are you currently employed either full or part-time? (If not, check 'no' and skip to question 10.)

____ (0) no _____ (1) yes, self-employed _____ (2) yes, employed by others

9a. How many people do you supervise?
____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

9b. How many people at work (other than those you supervise) do you talk to at least once every 2 weeks?
____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

10. How many of your neighbors do you visit or talk to at least once every 2 weeks?
_____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

11. Are you currently involved in regular volunteer work? (If not, check 'no' and skip to question 12.)
_____ no _____ yes

11a. How many people involved in this volunteer work do you talk to about volunteering-related issues at least once every 2 weeks?
____0 ____1 ____2 ____3 ____4 ____5 ____6 ____7 or more

12. Do you belong to any groups in which you talk to one or more members of the group about group-related issues at least once every 2 weeks? Examples include social clubs, recreational groups, trade unions, commercial groups, professional organizations, groups concerned with children like the PTA or Boy Scouts, groups concerned with community service, etc. (If you don't belong to any such groups, check 'no' and skip the section below.)
_____ no _____ yes

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APPENDIX B

INTERPERSONAL SUPPORT EVALUATION LIST (ISEL)

This scale is made up of a list of statements each of which may or may not be true about you. For each statement check "definitely true" if you are sure it is true about you and "probably true" if you think it is true but are not absolutely certain. Similarly, you should check "definitely false" if you are sure the statement is false and "probably false" is you think it is false but are not absolutely certain.

1. There are several people that I trust to help solve my problems.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

2. If I needed help fixing an appliance or repairing my car, there is someone who would help me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

3. Most of my friends are more interesting than I am.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

4. There is someone who takes pride in my accomplishments.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

5. When I feel lonely, there are several people I can talk to.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

6. There is no one that I feel comfortable to talking about intimate personal problems.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

7. I often meet or talk with family or friends.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

8. Most people I know think highly of me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

9. If I needed a ride to the airport very early in the morning, I would have a hard time finding someone to take me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

10. I feel like I'm not always included by my circle of friends.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

11. There really is no one who can give me an objective view of how I'm handling my problems.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

12. There are several different people I enjoy spending time with.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

13. I think that my friends feel that I'm not very good at helping them solve their problems.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

14. If I were sick and needed someone (friend, family member, or acquaintance) to take me to the doctor, I would have trouble finding someone.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

15. If I wanted to go on a trip for a day (e.g., to the mountains, beach, or country), I would have a hard time finding someone to go with me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

16. If I needed a place to stay for a week because of an emergency (for example, water or electricity out in my apartment or house), I could easily find someone who would put me up.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

17. I feel that there is no one I can share my most private worries and fears with.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

18. If I were sick, I could easily find someone to help me with my daily chores.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

19. There is someone I can turn to for advice about handling problems with my family.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

20. I am as good at doing things as most other people are.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

21. If I decide one afternoon that I would like to go to a movie that evening, I could easily find someone to go with me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

22. When I need suggestions on how to deal with a personal problem, I know someone I can turn to.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

23. If I needed an emergency loan of $100, there is someone (friend, relative, or acquaintance) I could get it from.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

24. In general, people do not have much confidence in me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

25. Most people I know do not enjoy the same things that I do.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

26. There is someone I could turn to for advice about making career plans or changing my job.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

27. I don't often get invited to do things with others.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

28. Most of my friends are more successful at making changes in their lives than I am.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

29. If I had to go out of town for a few weeks, it would be difficult to find someone who would look after my house or apartment (the plants, pets, garden, etc.).
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

30. There really is no one I can trust to give me good financial advice.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

31. If I wanted to have lunch with someone, I could easily find someone to join me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

32. I am more satisfied with my life than most people are with theirs.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

33. If I was stranded 10 miles from home, there is someone I could call who would come and get me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

34. No one I know would throw a birthday party for me.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

35. It would me difficult to find someone who would lend me their car for a few hours.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

36. If a family crisis arose, it would be difficult to find someone who could give me good advice about how to handle it.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

37. I am closer to my friends than most other people are to theirs.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

38. There is at least one person I know whose advice I really trust.
____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

39. If I needed some help in moving to a new house or apartment, I would have a hard time finding someone to help me.

____definitely true (3) ____definitely false (0)
____probably true (2) ____probably false (1)

40. I have a hard time keeping pace with my friends.

____definitely true (3) ____definitely false (0)

____probably true (2) ____probably false (1) .

APPENDIX C

DYADIC ADJUSTMENT SCALE (DAS)

Most persons have disagreements in their relationships. Please indicate below the approximate extent of agreement or disagreement between you and your partner for each item on the following list.

	Always Agree	**Almost Always Agree**	**Occasionally Disagree**	**Frequently Disagree**	**Almost Always Disagree**	**Always Disagree**
Handling Family Finances						
Matters of recreation						
Religious matters						
Demonstrations of affection						
Friends						
Sex Relations						
Conventionality (Correct or proper behavior)						
Philosophy of life						
Ways of dealing with parents or in-laws						
Aims, goals, and things believed important						
Amount of time spent together						

Making major decisions						
Household tasks						
Leisure time interests and activities						
Career decisions						
	All the time	**Most of the time**	**More often than not**	**Occasionally**	**Rarely**	**Never**
How often do you discuss or have you considered divorce, separation or terminating your relationship?						
How often do you or your mate leave the house after a fight?						
In general, how often do you think that things between you and your partner are going well?						
Do you confide in your mate?						
Do you ever regret that you married? (or lived together)						
How often do you and your partner quarrel?						
How often do you and your mate “get on each other’s nerves?”						

	Everyday	Almost everyday	Occasionally	Rarely	Never	
Do you kiss your mate?						
	All of them	**Most of them**	**Some of them**	**Very few of them**	**None of them**	
Do you and your mate engage in outside interests together?						

How often would you say the following events occur between you and your mate?

	Never	Less than once a month	Once or twice a month	Once of twice a week	Once a day	More often
Have a stimulating exchange of ideas						
Laugh together						
Calmly discuss something						
Work together on a project						

There are some things about which couples sometimes agree and sometimes disagree. Indicate if either item below caused differences of opinions or were problems in your relationship during the past few weeks (Check yes or no).

Yes	No	
		Being too tired for sex
		Not showing love

The circles on the following line represent different degrees of happiness in your relationship. The middle point, "happy," represents the degree of happiness of most

relationships. Please fill in the circle which best describes the degree of happiness, all things considered, of your relationship.

Extremely Unhappy	**Fairly Unhappy**	**A Little Unhappy**	**Happy**	**Very Happy**	**Extremely Happy**	**Perfect**

Which of the following statements best describes how you feel about the future of your relationship?

I want desperately for my relationship to succeed, and *would go to almost any length* to see that it does
I want very much for my relationship to succeed, and *will do all I can* to see that it does
I want very much for my relationship to succeed, and *will do my fair share* to see that it does
It would be nice if my relationship succeeded but *I can't do much more than I am doing now* help it succeed
It would be nice if it succeeded but *I refuse to do any more than I am doing now* to keep the relationship going
My relationship can never succeed and *there is no more that I can do* to keep the relationship going

APPENDIX D

CHRONIC STRESS SCALE (CSS)

SUBSCALE ITEMS

Marital Stress

In the past 6 months, how often …

…did your spouse expect more from you than he or she was willing to give back?

…did your spouse spend money in ways you thought unwise?

… did problems experienced by your spouse place an extra burden on you?

Parental Stress

In the past 6 months, how often…

…did your wonder if your children were trying hard enough to prepare for the life ahead of them?

…did you have to give attention to your children failing to get along with others?

…did your children seem to ignore your guidance and advice?

…did problems placed by your children place an extra burden on you?

Filial Stress

In the past 6 months, how often…

…was one of your parents or some other older relative complaining or critical of you?

…did you feel responsible for the care and well-being of a parent or any older relative?

…did you worry that a parent or some other older relative was declining in mental capacity?

…did problems experienced by a parent or another older relative place an extra burden on you?

Financial Stress

In the past 6 months, how often…

…did you not have enough money to afford the kind of clothing or food you or your family should have?

…did you have trouble meeting the monthly payments on bills?

…were you confident that your source of income was secure?

…did financial problems place an extra burden on you?

Occupational Stress

In the past 6 months, how often …

… did you feel our work was too dirty, noisy or dangerous?

…did you have more work than you could handle?

…were you treated unfairly by others on the job?

… did problems experienced by co-workers place an extra burden on you?

Ecological Stress

In the past 6 months, how often …

…did you feel crowded in your present housing situation?

…did you worry about crime in your neighborhood?

…did you worry about drugs in your neighborhood?

…was your neighborhood excessively noisy?

…did problems experienced by your neighbors place an extra burden on you?

Physical Stress

In the past 6 months, how often …

…did you have trouble getting around? I mean things like climbing stairs or getting outdoors

…did your health prevent you from doing things you wanted to do?

…did any physical disabilities place an extra burden on you?

Note: Response options to all questions were Never (0), Almost Never, Sometimes, Fairly Often, and Very Often (4) except for the third financial stress item, which was reverse-scored.

APPENDIX E

BASELINE EMA INTERVIEW ASSESSING SOCIAL INTERACTIONS

At time of BP -	Currently in a social interaction?	No, Yes

(If Yes, skip to "Think about this most recent interaction…" prompt.)

Most Recent Interaction -	When was your most recent interaction?	0-10 min before BP, 11-45 min Before BP, 45+ min before BP

PROMPT SCREEN: ***Think about this most recent interaction…***

Most Recent Interaction -	Length of Interaction	Less than 1 min, 1-10 Min, 10-20 min, 20-45 min, 45+ min
Most Recent Interaction-	Type of Interaction	In person, telephone, Email
Most Recent Interaction-	With how many people?	1 other, 2 others, 3 others, 4 or more
Most Recent Interaction-	Interacting with Whom?	Spouse/Partner, other Family or relative(s), Other friend(s), Coworker(s), other

(If <u>just</u> "Spouse/Partner," then skop to "Pleasant Interaction?" question. If any other response is chosen, with or without "Spouse/Partner," then NEXT.)

Most Recent Interaction -	Interacting with a "confidant"?	No, Yes

TERESA **Pleasant Interaction Subscale**

Most recent interaction-	Pleasant Interaction?	**NO** 1 2 3 4 5 6 7 8 9 10 11 **YES**

Most recent interaction- Agreeable Interaction? **NO** 1 2 3 4 5 6 7 8 9 10 11 **YES**

Most recent interaction- Friendly interaction? **NO** 1 2 3 4 5 6 7 8 9 10 11 **YES**

[Intimacy Interaction Subscale Questions- Not Used in this Study]
[Instrumental Support Subscale- Not Used in this Study]
[Emotional Support Subscale – Not Used in this Study]
[Support Provision item – Not Used in this Study]

Social Conflict Subscale

During Recent interaction- Someone treated you badly? **NO** 1 2 3 4 5 6 7 8 9 10 11 **YES**

During Recent interaction- Someone interfered with your efforts? **NO** 1 2 3 4 5 6 7 8 9 10 11 **YES**

During Recent interaction- Someone in conflict with you? **NO** 1 2 3 4 5 6 7 8 9 10 11 **YES**

PROMPT SCREEN: ***Think about time since last BP interview…***

Since Last BP interview- Any food, drink, or drug? No, Yes

(***If YES selected, then NEXT. If NO select ed, then END).***

Since last BP interview- Type(s) of consumption? Meal, Snack, Alcohol, Caffeine, Drug

END OF BP INTERVIEW.

APPENDIX F

6-YEAR EMA INTERVIEW ASSESSING SOCIAL INTERACTIONS

At time of BP -	Currently in a social interaction?	No, Yes

(If Yes, skip to "Think about this most recent interaction…" prompt.)

Most Recent Interaction -	When was your most recent interaction?	0-10 min before BP, 11-45 min Before BP, 45+ min before BP

(If no and most recent interaction ended 0-45 minutes ago, skip to "Think about this most recent interaction prompt)

(If no and most recent interaction ended 45+ minutes before BP… then following questions will appear)

PROMPT SCREEN: Think about this most recent interaction…

Most recent interaction -	With how many people?	1 other, 2 others, 3 others, 4 or more
Most recent interaction-	Interacting with Whom?	Spouse/Partner, Co-worker, other friend, other family or relative(s), other acquaintance(s), stranger
Most recent interaction-	Pleasant interaction?	**NO** 1 2 3 4 5 6 7 8 9 10 **YES**
Most recent interaction-	Agreeable interaction?	**NO** 1 2 3 4 5 6 7 8 9 10 **YES**
Most recent interaction-	Friendly interaction?	**NO** 1 2 3 4 5 6 7 8 9 10 **YES**

Most recent interaction-	Someone treated you badly?	**NO** 1 2 3 4 5 6 7 8 9 10 **YES**
Most recent interaction-	~~Someone interfered with your efforts?~~	**NO** 1 2 3 4 5 6 7 8 9 10 **YES**
Most recent interaction-	Someone in conflict with you?	**NO** 1 2 3 4 5 6 7 8 9 10 **YES**

[Other social interaction items- Not used in this study]

PROMPT SCREEN: Since last BP interview – Think about time since last BP interview

Since last BP interview: Type(s) of consumption — meal, snack, alcohol, caffeine Drug, none of the above

(If drug is selected, the following screen will appear)

PROMPT SCREEN: Since last BP interview – Please take a moment to fill out the accompanying form with the drug(s) you have consumed.

INTERVIEW COMPLETE: You have completed the interview.

BIBLIOGRAPHY

Allison, M. A., Criqui, M. H., McClelland, R. L., Scott, J. M., McDermott, M. M., Liu, K., ... & Kori, S. (2006). The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of the American College of Cardiology*, *48*(6), 1190-1197.

Allison, P.D. (2012, April). Handling missing data by maximum likelihood. In *SAS global forum (Vol. 23).*

Anisi, J., Majdiyan, M., Joshanloo, M., & Ghoharikamel, Z. (2011). Validity and reliability of NEO Five-Factor Inventory (NEO-FFI) on university students. International Journal of Behavioral Sciences, 5(4), 351-355.

Au, B., Smith, K. J., Gariépy, G., & Schmitz, N. (2015). The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA). *International journal of geriatric psychiatry*, *30*(9), 976-984.

Aulock, S. V., Deininger, S., Draing, C., Gueinzius, K., Dehus, O., & Hermann, C. (2006). Gender difference in cytokine secretion on immune stimulation with LPS and LTA. *Journal of interferon & cytokine research*, *26*(12), 887-892.

Bachman, J., O'Malley, P., Schulenber, J., Johnson, K., Bryant, A., Merline, A. (2002). The decline of substance use in young adulthood: Changes in social activities, roles, and beliefs. *Mahwah, NJ: Lawrence Erlbaum*

Bajaj, A., John-Henderson, N. A., Cundiff, J. M., Marsland, A. L., Manuck, S. B., & Kamarck, T. W. (2016). Daily Social Interactions, Close Relationships, and Systemic Inflammation in Two Samples: Healthy Middle-Aged and Older Adults. *Brain, Behavior, and Immunity*.

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents.*American journal of Epidemiology*, *109*(2), 186-204.

Black, P. H., & Garbutt, L. D. (2002). Stress, inflammation and cardiovascular disease. *Journal of psychosomatic research*, *52*(1), 1-23.

Blackburn, P., Després, J. P., Lamarche, B., Tremblay, A., Bergeron, J., Lemieux, I., & Couillard, C. (2006). Postprandial variations of plasma inflammatory markers in abdominally obese men. *Obesity*, *14*(10), 1747-1754.

Bolger, N., DeLongis, A., Kessler, R. C., & Schilling, E. A. (1989). Effects of daily stress on negative mood. *Journal of personality and social psychology*,*57*(5), 808.

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*, *33*(5), 585.

Carey, M. P., Spector, I. P., Lantinga, L. J., & Krauss, D. J. (1993). Reliability of the dyadic adjustment scale. *Psychological Assessment*, *5*(2), 238.

Cartier, A., Lemieux, I., Alméras, N., Tremblay, A., Bergeron, J., & Després, J. P. (2008). Visceral obesity and plasma glucose-insulin homeostasis: contributions of interleukin-6 and tumor necrosis factor-α in men. *The Journal of Clinical Endocrinology & Metabolism*, *93*(5), 1931-1938.

Chapman, B. P., Khan, A., Harper, M., Stockman, D., Fiscella, K., Walton, J., ... & Moynihan, J. (2009). Gender, race/ethnicity, personality, and interleukin-6 in urban primary care patients. *Brain, behavior, and immunity*, *23*(5), 636-642.

Chiang, J. J., Eisenberger, N. I., Seeman, T. E., & Taylor, S. E. (2012). Negative and competitive social interactions are related to heightened proinflammatory cytokine activity. *Proceedings of the National Academy of Sciences*, *109*(6), 1878-1882.

Chilcoat, H.D., Breslau, N. (1996). Alcohol disorders in young adulthood: effects of transitions into adult roles. *J. Health Soc. Behav.,* 37: 3339-49.

Cho, H. J., Seeman, T. E., Kiefe, C. I., Lauderdale, D. S., & Irwin, M. R. (2015). Sleep disturbance and longitudinal risk of inflammation: Moderating influences of social integration and social isolation in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Brain, behavior, and immunity, 46, 319-326.

Cohen, S. (2004). Social relationships and health. *American psychologist*,*59*(8), 676.

Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. *Health psychology*, *7*(3), 269.

Cohen, S., & Janicki-Deverts, D. (2009). Can we improve our physical health by altering our social networks?. *Perspectives on Psychological Science*,*4*(4), 375-378.

Cohen, S., Kamarck, T., & Mermelstein, R. (1994). Perceived stress scale. Measuring stress: A guide for health and social scientists.

Cohen, S., & Lemay, E. P. (2007). Why would social networks be linked to affect and health practices?. *Health Psychology*, *26*(4), 410.

Cohen, S., Mermelstein, R., Kamarck, T., & Hoberman, H. M. (1985). Measuring the functional components of social support. In *Social support: Theory, research and applications* (pp. 73-94). Springer Netherlands.

Cohen, S., & Williamson, G. (1988). Perceived stress in a probability sample of the US In S. Spacapam & S. Oskamp (Eds.), The social psychology of health: Claremont symposium on applied social psychology (pp. 31-67).

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychological bulletin*, *98*(2), 310.

Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M. (1997). Social Ties and Susceptibility to the Common Cold-Reply. JAMA, 278(15), 1232-1232.

Cole, D. A., & Maxwell, S. E. (2003). Testing mediational models with longitudinal data: questions and tips in the use of structural equation modeling. *Journal of abnormal psychology*, *112*(4), 558.

Costa, P. T., & McCrae, R. R. (1988). Personality in adulthood: a six-year longitudinal study of self-reports and spouse ratings on the NEO Personality Inventory. Journal of personality and social psychology, 54(5), 853.

Costa, P. T., & McCrae, R. R. (1992). Normal personality assessment in clinical practice: The NEO Personality Inventory. Psychological assessment, 4(1), 5.

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M., ... & Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Archives of pediatrics & adolescent medicine, 163(12), 1135-1143.

Davis, M. C., & Swan, P. D. (1999). Association of negative and positive social ties with fibrinogen levels in young women. *Health Psychology*, *18*(2), 131.

de Heredia, F. P., Gómez-Martínez, S., & Marcos, A. (2012). Obesity, inflammation and the immune system. Proceedings of the Nutrition Society, 71(2), 332-338.

Després, J. P. (2003). Inflammation and cardiovascular disease: is abdominal obesity the missing link?. *International journal of obesity. Supplement*, *27*(3), S22-S24.

Deverts, D. J., Cohen, S., DiLillo, V. G., Lewis, C. E., Kiefe, C., Whooley, M., & Matthews, K. A. (2010). Depressive symptoms, race, and circulating C-reactive protein: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychosomatic medicine*, *72*(8), 734.

Donoho, C. J., Crimmins, E. M., & Seeman, T. E. (2013). Marital quality, gender, and markers of inflammation in the MIDUS cohort. *Journal of Marriage and Family*, *75*(1), 127-141.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression.*Biological psychiatry*, *67*(5), 446-457.

Duncan, G.J., Wilkerson, B., England, P. (2006). Cleaning up their act: the effects of marriage and cohabitation on licit and illicit drug use. *Demography,* 43: 691-710

Eguchi, H., Shimazu, A., Kawakami, N., Inoue, A., & Tsutsumi, A. (2016). Source-specific workplace social support and high-sensitivity C-reactive protein levels among Japanese workers: A 1-year prospective cohort study. American journal of industrial medicine, 59(8), 676-684.

Eisenberger, N. I., Inagaki, T. K., Mashal, N. M., & Irwin, M. R. (2010). Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain, behavior, and immunity*, *24*(4), 558-563.

Eisenberger, N. I. (2012). The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. Nature Reviews Neuroscience, 13(6), 421.

Eisenberger, N. I., Moieni, M., Inagaki, T. K., Muscatell, K. A., & Irwin, M. R. (2017). In sickness and in health: the co-regulation of inflammation and social behavior. Neuropsychopharmacology, 42(1), 242.

Emerging Risk Factors Collaboration. (2012). C-reactive protein, fibrinogen, and cardiovascular disease prediction. *The New England journal of medicine*,*367*(14), 1310.

Feeney, B. C., & Collins, N. L. (2014). A new look at social support A theoretical perspective on thriving through relationships. *Personality and Social Psychology Review*, 1088868314544222.

Ford, E. S., Loucks, E. B., & Berkman, L. F. (2006). Social integration and concentrations of C-reactive protein among US adults. *Annals of epidemiology*, *16*(2), 78-84.

Fuligni, A. J., Telzer, E. H., Bower, J., Cole, S. W., Kiang, L., & Irwin, M. R. (2009). A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. *Psychosomatic Medicine*, *71*(3), 329.

Friedman, E. M., Hayney, M., Love, G. D., Singer, B. H., & Ryff, C. D. (2007). Plasma interleukin-6 and soluble IL-6 receptors are associated with psychological well-being in aging women. *Health Psychology*, *26*(3), 305.

Friedman, E. M., Hayney, M. S., Love, G. D., Urry, H. L., Rosenkranz, M. A., Davidson, R. J., ... & Ryff, C. D. (2005). Social relationships, sleep quality, and interleukin-6 in aging women. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(51), 18757-18762.

Gallo, L. C., Ghaed, S. G., & Bracken, W. S. (2004). Emotions and cognitions in coronary heart disease: Risk, resilience, and social context. *Cognitive Therapy and Research*, *28*(5), 669-694.

Gardner, K. A., & Cutrona, C. E. (2004). Social support communication in families. *Handbook of family communication*, 495-512.

Glei, D. A., Goldman, N., Ryff, C. D., Lin, Y. H., & Weinstein, M. (2012). Social relationships and inflammatory markers: An analysis of Taiwan and the US. *Social science & medicine*, *74*(12), 1891-1899.

Golden, J., Conroy, R. M., & Lawlor, B. A. (2009). Social support network structure in older people: underlying dimensions and association with psychological and physical health. *Psychology, Health & Medicine*, *14*(3), 280-290.

Gottman, J. M., & Notarius, C. I. (2000). Decade review: Observing marital interaction. *Journal of Marriage and Family*, *62*(4), 927-947.

Gouin, J. P., Hantsoo, L. V., & Kiecolt-Glaser, J. K. (2011). Stress, negative emotions, and inflammation.

Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A. S., & Singer, B. H. (2006). Combinations of biomarkers predictive of later life mortality. *Proceedings of the National Academy of Sciences*, *103*(38), 14158-14163.

Häfner, S., Emeny, R. T., Lacruz, M. E., Baumert, J., Herder, C., Koenig, W., ... & KORA Study Investigators. (2011). Association between social isolation and inflammatory markers in depressed and non-depressed individuals: results from the MONICA/KORA study. *Brain, behavior, and immunity*, *25*(8), 1701-1707.

Hänsel, A., Hong, S., Cámara, R. J., & Von Kaenel, R. (2010). Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neuroscience & Biobehavioral Reviews, 35(1), 115-121.

Hanson, B. S., Isacsson, S. O., Janzon, L., & Lindell, S. E. (1990). Social support and quitting smoking for good. Is there an association? Results from the population study,"Men born in 1914," Malmö, Sweden. *Addictive behaviors*, *15*(3), 221-233.

Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine*, *352*(16), 1685-1695.

Harrison, N. A., Brydon, L., Walker, C., Gray, M. A., Steptoe, A., & Critchley, H. D. (2009). Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biological psychiatry*, *66*(5), 407-414.

Heffner, K. L., Waring, M. E., Roberts, M. B., Eaton, C. B., & Gramling, R. (2011). Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. *Social Science & Medicine*,*72*(9), 1482-1488.

Helminen, A., Halonen, P., Rankinen, T., Nissinen, A., & Rauramaa, R. (1995). Validity assessment of a social support index. *Scandinavian Journal of Public Health*, *23*(1), 66-74.

Hemingway, H., Shipley, M., Mullen, M. J., Kumari, M., Brunner, E., Taylor, M., ... & Marmot, M. (2003). Social and psychosocial influences on inflammatory markers and vascular

function in civil servants (the Whitehall II study). *The American journal of cardiology*, *92*(8), 984-987.

Hong, S., Mills, P. J., Loredo, J. S., Adler, K. A., & Dimsdale, J. E. (2005). The association between interleukin-6, sleep, and demographic characteristics. *Brain, behavior, and immunity*, *19*(2), 165-172.

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS Med*, *7*(7), e1000316.

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspectives on Psychological Science, 10(2), 227-237.

House, J. S., Robbins, C., & Metzner, H. L. (1982). The association of social relationships and activities with mortality: prospective evidence from the Tecumseh Community Health Study. American journal of epidemiology, 116(1), 123-140.

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science*, *241*(4865), 540-545.

Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural equation modeling: a multidisciplinary journal*, *6*(1), 1-55.

Inagaki, T. K., Muscatell, K. A., Irwin, M. R., Cole, S. W., & Eisenberger, N. I. (2012). Inflammation selectively enhances amygdala activity to socially threatening images. Neuroimage, 59(4), 3222-3226.

Inagaki, T. K., Muscatell, K. A., Irwin, M. R., Moieni, M., Dutcher, J. M., Jevtic, I., ... & Eisenberger, N. I. (2015). The role of the ventral striatum in inflammatory-induced approach toward support figures. Brain, behavior, and immunity, 44, 247-252.

Gouin, J. P., Scarcello, S., da Estrela, C., Paquin, C., & Barker, E. T. (2016). Dyadic coping and inflammation in the context of chronic stress. Health Psychology, 35(10), 1081.

Hughes, S., Jaremka, L. M., Alfano, C. M., Glaser, R., Povoski, S. P., Lipari, A. M., ... & Malarkey, W. B. (2014). Social support predicts inflammation, pain, and depressive symptoms: Longitudinal relationships among breast cancer survivors. Psychoneuroendocrinology, 42, 38-44.

Iwata, M., Ota, K. T., & Duman, R. S. (2013). The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. *Brain, behavior, and immunity*, *31*, 105-114.

Janicki, D. L., Kamarck, T. W., Shiffman, S., Sutton-Tyrrell, K., & Gwaltney, C. J. (2005). Frequency of spousal interaction and 3-year progression of carotid artery intima medial thickness: the Pittsburgh Healthy Heart Project.*Psychosomatic Medicine*, *67*(6), 889-896.

Janicki, D. L., Kamarck, T. W., Shiffman, S., & Gwaltney, C. J. (2006). Application of ecological momentary assessment to the study of marital adjustment and social interactions during daily life. *Journal of Family Psychology*, *20*(1), 168.

Janicki, D.L. (2006) *CHRONIC STRESS, INFLAMMATION, AND PROGRESSION OF CAROTID ARTERY ATHEROSCLEROSIS: A MEDIATION MODEL* (Doctoral dissertation, University of Pittsburgh).

Jaremka, L. M., Lindgren, M. E., & Kiecolt-Glaser, J. K. (2013). Synergistic relationships among stress, depression, and troubled relationships: insights from psychoneuroimmunology. *Depression and anxiety*, *30*(4), 288-296.

Jones, K. G., Brull, D. J., Brown, L. C., Sian, M., Greenhalgh, R. M., Humphries, S. E., & Powell, J. T. (2001). Interleukin-6 (IL-6) and the prognosis of abdominal aortic aneurysms. *Circulation*, *103*(18), 2260-2265.

Joseph, N. T., Kamarck, T. W., Muldoon, M. F., & Manuck, S. B. (2014). Daily Marital Interaction Quality and Carotid Artery Intima Medial Thickness in Healthy Middle Aged Adults. *Psychosomatic medicine*, *76*(5), 347.

Kamarck, T. (2012). Psychosocial stress and cardiovascular disease: An exposure science perspective. *Psychological Science Agenda*.

Kamarck, T. W., Shiffman, S., Sutton-Tyrrell, K., Muldoon, M. F., & Tepper, P. (2012). Daily psychological demands are associated with six-year progression of carotid artery atherosclerosis: The Pittsburgh Healthy Heart Project. *Psychosomatic medicine*, *74*(4), 432.

Kamiya, Y., Whelan, B., Timonen, V., & Kenny, R. (2010). The differential impact of subjective and objective aspects of social engagement on cardiovascular risk factors. *BMC geriatrics*, *10*(1), 1.

Khera, A., McGuire, D. K., Murphy, S. A., Stanek, H. G., Das, S. R., Vongpatanasin, W., ... & de Lemos, J. A. (2005). Race and gender differences in C-reactive protein levels. *Journal of the American college of cardiology*, *46*(3), 464-469.

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annual review of psychology*, *53*(1), 83-107.

Kiecolt-Glaser, J. K., Loving, T. J., Stowell, J. R., Malarkey, W. B., Lemeshow, S., Dickinson, S. L., & Glaser, R. (2005). Hostile marital interactions, proinflammatory cytokine production, and wound healing.*Archives of general psychiatry*, *62*(12), 1377-1384.

Kiecolt-Glaser, J. K., Preacher, K. J., MacCallum, R. C., Atkinson, C., Malarkey, W. B., & Glaser, R. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the national Academy of Sciences*, *100*(15), 9090-9095.

Lacey, R. E., Kumari, M., & Bartley, M. (2014). Social isolation in childhood and adult inflammation: Evidence from the National Child Development Study. *Psychoneuroendocrinology*, *50*, 85-94.

Lakoski, S. G., Cushman, M., Criqui, M., Rundek, T., Blumenthal, R. S., D'agostino, R. B., & Herrington, D. M. (2006). Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal*, *152*(3), 593-598.

Libby, P., Ridker, P. M., & Maseri, A. (2002). Inflammation and atherosclerosis. *Circulation*, *105*(9), 1135-1143.

Lin, N., Ye, X., & Ensel, W. M. (1999). Social support and depressed mood: A structural analysis. *Journal of Health and Social behavior*, 344-359.

Locke, H. J., & Wallace, K. M. (1959). Short marital-adjustment and prediction tests: Their reliability and validity. *Marriage and family living*,*21*(3), 251-255.

Loucks, E. B., Berkman, L. F., Gruenewald, T. L., & Seeman, T. E. (2005). Social integration is associated with fibrinogen concentration in elderly men. Psychosomatic Medicine, 67(3), 353-358.

Loucks, E. B., Sullivan, L. M., D'AGOSTINO Sr, R. B., Larson, M. G., Berkman, L. F., & Benjamin, E. J. (2006). Social networks and inflammatory markers in the Framingham Heart Study. *Journal of biosocial science*,*38*(06), 835-842.

Loucks, E. B., Berkman, L. F., Gruenewald, T. L., & Seeman, T. E. (2006). Relation of social integration to inflammatory marker concentrations in men and women 70 to 79 years. *The American journal of cardiology*, *97*(7), 1010-1016.

Maier, S. F., & Watkins, L. R. (1998). Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological review*, *105*(1), 83.

Marucha, P. T., Crespin, T. R., Shelby, R. A., & Andersen, B. L. (2005). TNF-α levels in cancer patients relate to social variables. Brain, behavior, and immunity, 19(6), 521-525.

Matthews, K. A., Schott, L. L., Bromberger, J. T., Cyranowski, J. M., Everson-Rose, S. A., & Sowers, M. (2010). Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women?. *Brain, behavior, and immunity*, *24*(1), 96-101.

Mathieu, P., Lemieux, I., & Després, J. P. (2010). Obesity, inflammation, and cardiovascular risk. *Clinical pharmacology & therapeutics*, *87*(4), 407-416.

Mayne, T. J. (1999). Negative affect and health: The importance of being earnest. *Cognition & Emotion*, *13*(5), 601-635.

McDade, T. W., Hawkley, L. C., & Cacioppo, J. T. (2006). Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. *Psychosomatic medicine,68*(3), 376-381.

Messay, B., Lim, A., & Marsland, A. L. (2012). Current understanding of the bi-directional relationship of major depression with inflammation. *Biology of mood & anxiety disorders*, *2*(1), 1.

Mezuk, B., Roux, A. V. D., & Seeman, T. (2010). Evaluating the buffering vs. direct effects hypotheses of emotional social support on inflammatory markers: The multi-ethnic study of atherosclerosis. *Brain, behavior, and immunity*, *24*(8), 1294-1300.

Miller, M. A., Kandala, N. B., Kivimaki, M., Kumari, M., Brunner, E. J., Lowe, G. D., ... & Cappuccio, F. P. (2009). Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep*, *32*(7), 857-864.

Mullington, J. M., Haack, M., Toth, M., Serrador, J. M., & Meier-Ewert, H. K. (2009). Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Progress in cardiovascular diseases*, *51*(4), 294-302.

Murray, R. P., Johnston, J. J., Dolce, J. J., Lee, W. W., & O'Hara, P. (1995). Social support for smoking cessation and abstinence: The Lung Health Study. *Addictive behaviors*, *20*(2), 159-170.

Muscatell, K. A., Eisenberger, N. I., Dutcher, J. M., Cole, S. W., & Bower, J. E. (2016). Links between inflammation, amygdala reactivity, and social support in breast cancer survivors. Brain, behavior, and immunity, 53, 34-38.

Muscatell, K. A., Dedovic, K., Slavich, G. M., Jarcho, M. R., Breen, E. C., Bower, J. E., ... & Eisenberger, N. I. (2016). Neural mechanisms linking social status and inflammatory responses to social stress. Social cognitive and affective neuroscience, 11(6), 915-922.

Norris, F. H., & Uhl, G. A. (1993). Chronic stress as a mediator of acute stress: The case of Hurricane Hugo. Journal of Applied Social Psychology, 23(16), 1263-1284.

Nowakowski, A. C., & Sumerau, J. E. (2015). Swell foundations: Fundamental social causes and chronic inflammation. Sociological Spectrum, 35(2), 161-178.

O'Connor, M. F., Motivala, S. J., Valladares, E. M., Olmstead, R., & Irwin, M. R. (2007). Sex differences in monocyte expression of IL-6: role of autonomic mechanisms. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *293*(1), R145-R151.

O'Donovan, A., Hughes, B. M., Slavich, G. M., Lynch, L., Cronin, M. T., O'Farrelly, C., & Malone, K. M. (2010). Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion–biology relationships. *Brain, behavior, and immunity*, *24*(7), 1074-1077.

O'Farrell, T. J., Hooley, J., Fals-Stewart, W., & Cutter, H. S. (1998). Expressed emotion and relapse in alcoholic patients. *Journal of Consulting and Clinical Psychology*, *66*(5), 744.

Olstad, R., Sexton, H., & Søgaard, A. J. (2001). The Finnmark Study. A prospective population study of the social support buffer hypothesis, specific stressors and mental distress. *Social Psychiatry and Psychiatric Epidemiology*, *36*(12), 582-589.

Orth-Gomer, K., & Johnson, J. V. (1987). Social network interaction and mortality: a six year follow-up study of a random sample of the Swedish population. Journal of chronic diseases, 40(10), 949-957.

Pandey, R., & Choubey, A. K. (2010). Emotion and health: An overview.*Journal of Projective Psychology and Mental Health*, *17*(2), 135-152.

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., ... & Rifai, N. (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation, 107(3), 499-511.

Pressman, S. D., Cohen, S., Miller, G. E., Barkin, A., Rabin, B. S., & Treanor, J. J. (2005). Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology*, *24*(3), 297.

Pressman, S. D., & Cohen, S. (2012). Positive emotion word use and longevity in famous deceased psychologists. *Health Psychology*, *31*(3), 297.

Reynolds, W. M., & Gould, J. W. (1981). A psychometric investigation of the standard and short form Beck Depression Inventory. Journal of Consulting and Clinical Psychology, 49(2), 306.

Robles, T. F., Slatcher, R. B., Trombello, J. M., & McGinn, M. M. (2014). Marital quality and health: A meta-analytic review. *Psychological Bulletin*,*140*(1), 140.

Runsten, S., Korkeila, K., Koskenvuo, M., Rautava, P., Vainio, O., & Korkeila, J. (2014). Can social support alleviate inflammation associated with childhood adversities?. Nordic Journal of Psychiatry, 68(2), 137-144.

Santini, Z. I., Koyanagi, A., Tyrovolas, S., Mason, C., & Haro, J. M. (2015). The association between social relationships and depression: A systematic review. *Journal of affective disorders*, *175*, 53-65.

Schultze-Florey, C. R., Martínez-Maza, O., Magpantay, L., Breen, E. C., Irwin, M. R., Gündel, H., & O'Connor, M. F. (2012). When grief makes you sick: Bereavement induced systemic inflammation is a question of genotype. Brain, behavior, and immunity, 26(7), 1066-1071.

Seeman, T. E., Gruenewald, T. L., Cohen, S., Williams, D. R., & Matthews, K. A. (2014). Social relationships and their biological correlates: Coronary Artery Risk Development in Young Adults (CARDIA) study. Psychoneuroendocrinology, 43, 126-138.

Shaffer, J. A., Edmondson, D., Chaplin, W. F., Schwartz, J. E., Shimbo, D., Burg, M. M., ... & Davidson, K. W. (2011). Directionality of the relationship between depressive symptom dimensions and C-reactive protein in patients with acute coronary syndromes. *Psychosomatic medicine*, *73*(5), 370.

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology*, *30*(4), 377.

Shiels, M. S., Katki, H. A., Freedman, N. D., Purdue, M. P., Wentzensen, N., Trabert, B., ... & Goedert, J. J. (2014). Cigarette smoking and variations in systemic immune and inflammation markers. *Journal of the National Cancer Institute*, *106*(11), dju294.

Shor, E., Roelfs, D. J., & Yogev, T. (2013). The strength of family ties: A meta-analysis and meta-regression of self-reported social support and mortality. *Social Networks*, *35*(4), 626-638.

Sirois, B. C., & Burg, M. M. (2003). Negative emotion and coronary heart disease a review. *Behavior modification*, *27*(1), 83-102.

Slopen, N., Kubzansky, L. D., McLaughlin, K. A., & Koenen, K. C. (2013). Childhood adversity and inflammatory processes in youth: a prospective study. Psychoneuroendocrinology, 38(2), 188-200.

Smith, D. A., Breiding, M. J., & Papp, L. M. (2012). Depressive moods and marital happiness: within-person synchrony, moderators, and meaning.*Journal of Family Psychology*, *26*(3), 338.

Smith, K. P., & Christakis, N. A. (2008). Social networks and health. *Annu. Rev. Sociol*, *34*, 405-429.

Solarz, D. E., Mullington, J. M., & Meier-Ewert, H. K. (2011). Sleep, inflammation and cardiovascular disease. *Frontiers in bioscience (Elite edition)*, *4*, 2490-2501.

Spanier, G. B. (1976). Measuring dyadic adjustment: New scales for assessing the quality of marriage and similar dyads. *Journal of Marriage and the Family*, 15-28.

Stellar, J. E., John-Henderson, N., Anderson, C. L., Gordon, A. M., McNeil, G. D., & Keltner, D. (2015). Positive affect and markers of inflammation: Discrete positive emotions predict lower levels of inflammatory cytokines.*Emotion*, *15*(2), 129.

Steptoe, A., O'Donnell, K., Badrick, E., Kumari, M., & Marmot, M. (2008). Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women the Whitehall II Study. *American Journal of Epidemiology*, *167*(1), 96-102.

Steptoe, A., Wardle, J., Pollard, T. M., Canaan, L., & Davies, G. J. (1996). Stress, social support and health-related behavior: a study of smoking, alcohol consumption and physical exercise. *Journal of psychosomatic research*, *41*(2), 171-180.

Steptoe, A., Kunz-Ebrecht, S., Owen, N., Feldman, P. J., Rumley, A., Lowe, G. D., & Marmot, M. (2003). Influence of socioeconomic status and job control on plasma fibrinogen responses to acute mental stress. Psychosomatic Medicine, 65(1), 137-144.

Stewart, J. C., Rand, K. L., Muldoon, M. F., & Kamarck, T. W. (2009). A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain, behavior, and immunity*, *23*(7), 936-944.

Tracey, K. J. (2002). The inflammatory reflex. *Nature*, *420*(6917), 853-859.

Treiber, F. A., Baranowski, T., Braden, D. S., Strong, W. B., Levy, M., & Knox, W. (1991). Social support for exercise: relationship to physical activity in young adults. *Preventive medicine*, *20*(6), 737-750.

Trevino, D. B., Young, E. H., Groff, J., & Jono, R. T. (1990). The association between marital adjustment and compliance with antihypertension regimens.*The Journal of the American Board of Family Practice*, *3*(1), 17-25.

Uchino, B. N., Ruiz, J. M., Smith, T. W., Smyth, J. M., Taylor, D. J., Allison, M., & Ahn, C. (2016). Ethnic/racial differences in the association between social support and levels of C-reactive proteins in the North Texas Heart Study. Psychophysiology, 53(1), 64-70.

Uchino, B. N., Trettevik, R., Kent de Grey, R. G., Cronan, S., Hogan, J., & Baucom, B. R. (2018). Social support, social integration, and inflammatory cytokines: A meta-analysis. Health Psychology, 37(5), 462.

Umberson, D. (1987). Family status and health behaviors: Social control as a dimension of social integration. *Journal of health and social behavior*, 306-319.

Umberson, D. (1992). Gender, marital status and the social control of health behavior. *Social science & medicine*, *34*(8), 907-917.

Umberson, D., Williams, K., Powers, D. A., Liu, H., & Needham, B. (2006). You make me sick: Marital quality and health over the life course. *Journal of Health and Social Behavior*, *47*(1), 1-16.

Van Gaal, L. F., Mertens, I. L., & Christophe, E. (2006). Mechanisms linking obesity with cardiovascular disease. *Nature*, *444*(7121), 875-880.

Vella, E. J., Kamarck, T. W., & Shiffman, S. (2008). Hostility moderates the effects of social support and intimacy on blood pressure in daily social interactions. *Health Psychology*, *27*(2S), S155.

Waite, L. J., Luo, Y., & Lewin, A. C. (2009). Marital happiness and marital stability: Consequences for psychological well-being. Social Science Research, 38(1), 201-212.

Walston, J., Arking, D. E., Fallin, D., Li, T., Beamer, B., Xue, Q., ... & Chakravarti, A. (2005). IL-6 gene variation is not associated with increased serum levels of IL-6, muscle, weakness, or frailty in older women. *Experimental gerontology*, *40*(4), 344-352.

Whisman, M. A., & Sbarra, D. A. (2012). Marital adjustment and interleukin-6 (IL-6). *Journal of Family Psychology*, *26*(2), 290.

Wickrama, K. A. S., Conger, R. D., & Lorenz, F. O. (1995). Work, marriage, lifestyle, and changes in men's physical health. *Journal of behavioral medicine*, *18*(2), 97-111.

Wium-Andersen, M. K., Ørsted, D. D., Nielsen, S. F., & Nordestgaard, B. G. (2013). Elevated C-reactive protein levels, psychological distress, and depression in 73 131 individuals. *JAMA psychiatry*, *70*(2), 176-184.

Yaffe, K., Lindquist, K., Penninx, B. W., Simonsick, E. M., Pahor, M., Kritchevsky, S., ... & Harris, T. (2003). Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology*, *61*(1), 76-80.

Yang, K., Xie, G., Zhang, Z., Wang, C., Li, W., Zhou, W., & Tang, Y. (2007). Levels of serum interleukin (IL)-6, IL-1β, tumour necrosis factor-α and leptin and their correlation in depression. *Australian & New Zealand Journal of Psychiatry*, *41*(3), 266-273.

Yang, Y. C., McClintock, M. K., Kozloski, M., & Li, T. (2013). Social Isolation and Adult Mortality The Role of Chronic Inflammation and Sex Differences. *Journal of health and social behavior*, 0022146513485244.

Yang, Y. C., Schorpp, K., & Harris, K. M. (2014). Social support, social strain and inflammation: Evidence from a national longitudinal study of US adults. Social Science & Medicine, 107, 124-135.

Yang, Y. C., Li, T., & Frenk, S. M. (2014b). Social network ties and inflammation in US adults with cancer. Biodemography and social biology, 60(1), 21-37.

Yang, Y. C., Boen, C., Gerken, K., Li, T., Schorpp, K., & Harris, K. M. (2016). Social relationships and physiological determinants of longevity across the human life span. Proceedings of the National Academy of Sciences, 113(3), 578-583.