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Gender differences in longitudinal relationships between depression and anxiety symptoms and inflammation in the health and retirement study

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Abstract

Depression and anxiety have been linked to elevated inflammation in cross-sectional and longitudinal studies. Yet, in terms of longitudinal studies, findings are inconsistent regarding whether depression predicts worsening inflammation or vice versa, and anxiety has been infrequently examined. Further, we know little about longitudinal relationships between inflammation and specific symptom profiles of depression and anxiety. The current study examined longitudinal associations between depression and anxiety symptoms and inflammation in 13,775 people (59% women, average age = 67) participating in the Health and Retirement Study - a population-based study focused on older adults. High sensitivity C-reactive protein and depression and anxiety symptoms were measured at two time-points separated by four years. We used cross-lagged panel models to examine bidirectional relationships, and tested interactions with gender. We found that depressive symptoms predicted increasing inflammation for men, but not for women, and inflammation predicted worsening depression for women, but not for men. These gender differences were driven by somatic symptoms. Specifically, somatic symptoms predicted increasing inflammation for men only and were predicted by inflammation for women only. Regardless of gender, inflammation predicted worsening dysphoric symptoms of depression, and lack of positive affect predicted increasing inflammation over time. Anxiety was not associated with inflammation longitudinally. These findings indicate bidirectional relationships between depressive symptoms and inflammation, but not between anxiety symptoms and inflammation, and that the direction of these effects may differ by gender and type of depressive symptom.

Keywords

Inflammation; Depression; Anxiety; C-Reactive protein; Gender differences; Longitudinal; Sex differences

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Declarations of interest

None.

1. Introduction

Depression and anxiety disorders affect approximately 30% of the population at some point during the lifespan (Kessler et al., 2005). As reviewed below, a large body of research now links depression and anxiety symptoms (although anxiety has been less commonly studied) with elevated inflammation, which may be one mechanism that explains the higher prevalence of medical illnesses in people with these symptoms. Moreover, inflammation may actually evoke symptoms of depression and anxiety (Dantzer et al., 2008; Miller and Raison, 2016; Slavich and Irwin, 2014). Many studies examining associations of depression and anxiety symptoms with inflammatory markers have used cross-sectional samples, precluding examination of directionality. Thus, additional analyses using longitudinal samples, although unable to demonstrate causality, can add to existing knowledge on whether inflammation precedes onset of depression and anxiety symptoms or vice versa. Tests of directionality can further our understanding of bidirectional associations between depression and anxiety with inflammation, and inform research on potential treatment targets for co-occurring as well as independent diagnoses of depression, anxiety, and inflammation-associated medical conditions. Despite the large literature linking depression and anxiety with inflammation, little is known about associations of specific depression and anxiety symptoms with inflammation. Some symptoms may be more strongly associated with inflammation than others, and some symptoms may be a consequence of inflammation whereas others predict increases in inflammation. The current study examined associations of depression and anxiety symptoms with inflammation in a population-based longitudinal sample of older adults. We used cross-lagged analyses to assess directionality of relationships, and examined symptom clusters to pinpoint which symptoms show stronger associations with inflammation over time.

In cross-sectional samples, depression has been repeatedly linked with elevated inflammation (Bremmer et al., 2008; Capuron et al., 2008; Elovainio et al., 2009; Köhler-Forsberg et al., 2017; Ladwig et al., 2003; Penninx et al., 2003; Tayefi et al., 2017; Toker et al., 2005; Vogelzangs et al., 2012) and only a few published studies have reported no association between depression and inflammation (Duivis et al., 2013; Liukkonen et al., 2011; O'Donovan et al., 2010; Vogelzangs et al., 2013). Studies examining links between anxiety and inflammation appear less frequently in the literature, but anxiety has been associated with elevated inflammation cross-sectionally in many (Liukkonen et al., 2011; O'Donovan et al., 2010; Tayefi et al., 2017; Vogelzangs et al., 2013), but not all (Duivis et al., 2013; Toker et al., 2005) studies. Thus, while there is more evidence for a cross-sectional link between depressive symptoms and inflammation, fewer published studies have examined anxiety, making it difficult to assess whether anxiety is less strongly associated (and thus not reported due to publication bias) or simply less frequently studied.

There are plausible pathways by which inflammation can promote psychiatric symptoms *and* by which depression and anxiety can promote inflammation (Miller and Raison, 2016; O'Donovan et al., 2013; Slavich and Irwin, 2014) and a few studies have tested longitudinal relationships of depression and anxiety with inflammatory markers. Depression has been shown to predict increasing inflammation over 1, 5, and 6 year time periods (Copeland et al., 2012; Deverts et al., 2010; Stewart et al., 2009), with no evidence in these studies for

inflammation predicting worsening depression. However, a meta-analysis of eight papers (Valkanova et al., 2013), and three more recent studies (Khandaker et al., 2017, 2014; Zalli et al., 2016) indicate that earlier levels of inflammation do predict subsequent depression. To our knowledge, only one study has assessed the association between anxiety (specifically generalized anxiety disorder) and inflammation longitudinally (Copeland et al., 2012), finding that anxiety was associated with increasing inflammation over time in a sample of 1,420 young adults. This relationship was no longer statistically significant after covarying body mass index (BMI) and medication use, and inflammation did not longitudinally predict increases in anxiety. These findings suggest bidirectional associations between depression and inflammation and possibly between anxiety and inflammation. Large-scale longitudinal studies including measures of both depression and anxiety can add to the growing body of literature linking these symptoms with inflammatory markers.

Across studies, it is clear that some but not all individuals with depressive and anxiety disorders show elevated inflammation, and it is possible that inflammation produces specific symptom profiles. For example, a number of studies have suggested that the somatic symptoms of depression in particular may be associated with inflammatory markers, with support for this hypothesis emerging in both cross-sectional (Elovainio et al., 2009; Jokela et al., 2016; Low et al., 2009; White et al., 2017), and longitudinal samples (Deverts et al., 2010; Stewart et al., 2009). In addition, cognitive symptoms (Gimeno et al., 2009; Köhler-Forsberg et al., 2017) and depressed mood (Capuron et al., 2008; White et al., 2017) have also been linked with inflammation. In terms of directionality examined in longitudinal studies, somatic depressive symptoms (Deverts et al., 2010; Stewart et al., 2009) and low positive affect (Deverts et al., 2010) predicted later elevated inflammation, but inflammation did not predict worsening somatic symptoms (Stewart et al., 2009). One cross-sectional study examining anxiety subscales found that somatic anxiety symptoms were associated with multiple markers of inflammation whereas cognitive symptoms were only associated with elevated C-reactive protein in men (Duivis et al., 2013). However, to our knowledge, no prior studies have examined anxiety subscales and inflammation in longitudinal studies. Understanding if specific symptom profiles are characteristic of elevated inflammation can shed light on potential biological pathways that underlie the association, and research in large longitudinal samples is needed to examine the interplay between specific depressive and anxiety symptoms and inflammation over time.

In the present study, we used data from the Health and Retirement Study (HRS), a large population-based sample of older Americans, to examine bidirectional relationships of depression and anxiety with the inflammatory marker high sensitivity C-reactive protein (hsCRP) at two time points separated by four years. Because prior studies have found gender differences in the link between depression and anxiety symptoms and inflammation with men typically showing a stronger link than women (Elovainio et al., 2009; Ladwig et al., 2003; Liukkonen et al., 2011; Toker et al., 2005; Vogelzangs et al., 2012, 2013), we also examined interactions with gender. Data were analyzed using a cross-lagged panel analysis, which allows simultaneous modeling of associations between inflammation and depression and anxiety symptoms over time. We hypothesized that inflammation would be associated with increasing levels of depression and anxiety, and that depression and anxiety would predict increasing levels of inflammation over time. Further, for depression, we examined

whether different facets of depression including low positive affect, dysphoria, and somatic symptoms were differentially associated with levels of hsCRP.

2. Method

2.1. Participants

Participants were drawn from HRS, a longitudinal study of a population-based sample of more than 20,000 Americans over the age of 50 (although partners and spouses of primary participants could also participate even if they were under the age of 50). HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. The target population for the original HRS cohort includes all adults in the contiguous United States born during the years 1931–1941 who reside in households, with a 2:1 oversample of African-American and Hispanic populations. The original sample has been refreshed with new birth cohorts over the years. In 2006, the study implemented a psychosocial questionnaire (Clarke et al., 2008) and biomarker assessment (Crimmins et al., 2013). Depression symptoms were assessed in 2006, 2008, 2010, and 2012 (as well as other years not used in the present analysis). Anxiety and hsCRP were assessed in one cohort of participants in 2006, which was followed up in 2010, and in another cohort of participants in 2008, which was followed up in 2012. We combined data from the two cohorts and thus treated data from 2006 and 2008 as Time 1, and data from 2010 and 2012 as Time 2. Cohort was included as a covariate in analyses. All participants who had at least one available biomarker data point were included in analyses (N = 13,775). Participant demographic and clinical characteristics are reported in Table 1.

2.2. Measures

2.2.1. Demographics—Self-report questionnaires were administered to all participants to gather information on demographics and health behaviors. Race was categorized as Caucasian, African-American, or Other using dummy codes. Education was categorized as high school education or greater (1) or less than high school education (0).

2.2.2. Health behaviors and indices—Smoking was categorized as those who currently smoke cigarettes (1) or those who do not (0). BMI was assessed using self-reported weight in pounds and self-reported height in inches and calculated using the equation $(\text{weight}/\text{height}^2) * 703$. Alcohol use was assessed by asking participants the number of days per week they drank alcohol and the average number of drinks they would have on days they drank. These values were multiplied to determine the number of average drinks per week. A dichotomous heavy alcohol use score was calculated such that participants who drank more than the suggested healthy amount (7 drinks per week for women and 14 for men (Department of Health and Human Services and U.S. Department of Agriculture, 2015) were categorized as heavy drinkers (1) and everyone else was categorized as a non-heavy drinker (0). Physical activity was evaluated by asking participants whether or not they participated in vigorous activity more than once per week. Medical illness was calculated as the sum of the number of current or prior diagnoses of the following health conditions: hypertension, diabetes mellitus, cancer (excluding skin cancer), chronic lung disease (excluding asthma), heart conditions (heart attack, coronary heart disease, angina, congestive

heart failure, or other heart problems), stroke, and arthritis. Covariates were assessed in 2006 for the first cohort and 2008 for the second cohort.

2.2.3. Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977)—Depression was assessed using a modified nine-item version of the CES-D. Participants answered yes or no to items assessing whether, for much of the past week, they felt: (1) depressed; (2) everything was an effort; (3) sleep was restless; (4) happy; (5) lonely; (6) enjoyed life; (7) sad; (8) that they could not get going; and (9) that they had a lot of energy. A previous study (Yang and Jones, 2008), which used exploratory and confirmatory factor analysis, found that a three-factor solution resulted in the best model fit for the CES-D in HRS. Based on these results, the authors identified three subscales for this measure: somatic (items 2, 3, 8, and 9), lack of positive affect (items 4 and 6 reverse coded), and dysphoria (items 1, 5, and 7). Further, the full scale has been evaluated within HRS to have good internal consistency (α = 0.80 to 0.83) for a brief measure (Wallace et al., 2000). Alphas for the data analyzed in the current study were 0.80–0.81.

2.2.4. Beck Anxiety Inventory (BAI; Beck et al., 1988)—Anxiety symptoms were assessed with a five-item version of the BAI.

Respondents were asked how often during the past week they: 1) had fear of the worst happening; 2) were nervous; 3) felt their hands trembling; 4) had a fear of dying; and 5) felt faint. Respondents rated the frequency of these symptoms from “never” = 1 to “most of the time” = 4. This measure has good internal consistency (α = 0.81) (Clarke et al., 2008), and alphas in the current data were 0.81–0.82.

2.2.5. High Sensitivity C-reactive Protein (hsCRP)—Blood samples were obtained from participants by cleaning a finger with an alcohol prep pad and pricking the finger with a lancet. Samples were collected on a blood spot card, air-dried for 10 to 15 min, and placed in foil pouches. The samples were then mailed to the University of Vermont and assayed for hsCRP using a standard enzyme-linked immunosorbent assay (ELISA) (Crimmins et al., 2013). The hsCRP assay had a lower limit of detection of 0.04 mg/L, with an intra-assay imprecision of 8% and an inter-assay imprecision of 11%.

2.3. Statistical analyses

We used structural equation modeling to test cross-lagged panel models (path model only) with hsCRP, and CES-D or BAI at Time 1 predicting hsCRP, CES-D or BAI at Time 2. CES-D and BAI were tested in separate models as follows. We first examined main effects of hsCRP and CES-D or BAI at Time 1 on hsCRP and CES-D or BAI at Time 2. We then tested interactions between hsCRP at Time 1 and gender and between CES-D or BAI at Time 1 and gender, including the hsCRP × gender and CES-D or BAI × gender effects as well as main effects of hsCRP, CES-D or BAI, and gender. If the interaction was significant, we examined associations separately by gender. We used clustered standard errors to account for the clustering of observations within households, which relaxes the assumption of independence of errors, replacing it with the assumption of independence between clusters and allowing errors to be correlated within clusters. Initial models were adjusted for

age, cohort, and education, and then additionally for health covariates including number of medical conditions, exercise, smoking, alcohol use, and BMI (gender was tested as a moderator as described above). For depression, we also examined longitudinal associations between each subscale and hsCRP over and above all covariates including health covariates. The models were estimated using full information maximum likelihood, which includes all participants regardless of missing data, and has advantages over multiple imputation (Allison, 2012). Consistent with prior studies, raw hsCRP values were log transformed. Outliers, defined as values of hsCRP greater than 10 mg/l (N = 1155; 5.6%), were excluded because they may represent individuals with acute inflammation due to infection or injury. Data were analyzed using Stata 14.

3. Results

Bivariate correlations are displayed in Table 2. For men, higher hsCRP was weakly associated with worse depressive and anxiety symptoms, and with smoking, lack of exercise, higher BMI and the presence of medical conditions. For women, higher hsCRP was weakly associated with worse depressive but not anxiety symptoms, and with lack of exercise, higher BMI and the presence of medical conditions. Higher hsCRP was also associated with older age and lower levels of education for both men and women. Depression and anxiety were strongly correlated with each other and were associated with smoking, lack of exercise, higher BMI, the presence of more medical conditions, and lower levels of education for both men and women.

3.1. Depressive symptoms total scale

Prior to inclusion of health behavior covariates, hsCRP scores at T1 significantly predicted CES-D scores at T2 ($\beta = .04$, CI = 0.02, 0.06, $p < .001$) and CES-D scores at T1 significantly predicted hsCRP scores at T2 ($\beta = 0.02$, CI = 0.01, 0.04, $p = .009$). After adjustment for health behavior covariates, hsCRP scores at T1 significantly predicted CES-D scores at T2 ($\beta = 0.03$, CI = 0.01, 0.06, $p = .006$), but CES-D scores at T1 no longer significantly predicted hsCRP scores at T2 ($p = .789$).

3.1.1. Interactions with gender—Prior to inclusion of health behavior covariates, hsCRP scores at T1 significantly interacted with gender to predict CES-D scores at T2 ($\beta = -0.02$, CI = −0.04, −0.00, $p = .043$), whereas CES-D scores at T1 did not significantly interact with gender to predict hsCRP at T2 ($p = .073$). Because one direction of effects was significantly moderated by gender, we examined the bidirectional associations between CES-D and hsCRP separately by gender. Higher hsCRP at T1 significantly predicted worse CES-D scores at T2 for women ($\beta = .05$, CI = .03–0.07, $p < .001$) but not for men ($p = .059$). On the other hand, higher CES-D scores at T1 predicted increasing hsCRP over time for men ($\beta = 0.05$; CI = .02–0.08; $p = .001$), but not for women ($p = .283$). After adjustment for health behavior covariates, interactions with gender became statistically significant for both directions of effects (see Fig. 1). Higher hsCRP at T1 significantly interacted with gender to predict worse CES-D scores at T2 ($\beta = -0.03$; CI −0.05 to −0.00; $p = .023$). Moreover, worse CES-D scores at T1 significantly interacted with gender to predict higher hsCRP at T2 ($\beta = 0.03$, CI = .00–.05, $p = .034$). Examining effects separately for men and women, as

shown in Fig. 1a and Table 3, higher hsCRP at T1 significantly predicted worsening CES-D scores over time for women (β = 0.03, CI = 0.01–0.06, p = .006), but not for men (p = .746). As shown in Fig. 1b and Table 3, higher CES-D scores at T1 predicted increasing hsCRP over time for men (β = 0.03; CI = 0.00–.06; p = .034), but not for women (p = .789).

3.2. Depressive symptom subscales

For subscales of the CES-D, over and above health behavior covariates, hsCRP at T1 did not significantly predict somatic symptoms at T2 (p = .154), and somatic symptoms at T1 did not significantly predict hsCRP at T2 (p = .748). For dysphoria symptoms, higher hsCRP at T1 was significantly associated with increasing dysphoria over time (β = .03, CI = .01, 0.05, p = .001), but worse dysphoria at T1 was not significantly associated with increasing hsCRP over time (p = .390). Finally, hsCRP at T1 was not significantly associated with lack of positive affect at T2 (p = .064), whereas lack of positive affect at T1 was significantly associated with increasing hsCRP over time (β = 0.02, CI = 0.00, 0.03, p = .043).

3.2.1. Interactions with gender—Because gender interactions emerged for total CES-D scores, we also examined interactions for CES-D subscales. Over and above health behavior covariates, worse somatic symptoms significantly interacted with gender at T1 to predict increases in hsCRP over time (β = 0.03; CI = .01–0.06; p = .009), and higher hsCRP at T1 significantly interacted with gender to predict worsening somatic symptoms over time (β = −0.03; CI = −0.05 to −0.01; p = .009). Model results are shown separately by gender in Table 4. For men, worse somatic symptoms at T1 significantly predicted increasing hsCRP over time (β = 0.04; CI = 0.01–0.07; p = .006), but the association was not significant for women (p = .390). For women, higher hsCRP at T1 significantly predicted worsening somatic symptoms over time (β = 0.03; CI = 0.00–0.05; p = .027), but the association was not significant for men (p = .410).

Neither dysphoria nor positive affect subscales scores at T1 significantly interacted with gender to predict hsCRP at T2 (ps = .163), and hsCRP at T1 did not significantly interact with gender to predict dysphoria or positive affect scores at T2 (ps > .141).

3.3. Anxiety symptoms total scale

For unadjusted models, BAI scores at T1 did not significantly predict hsCRP at T2 (p = .078) and hsCRP at T1 did not significantly predict BAI scores at T2 (p = .180).[2] Associations remained non-significant after controlling for health behaviors (ps > .220).

3.3.1. Interactions with gender—Prior to inclusion of health behaviors as covariates, BAI scores at T1 did not interact with gender to predict hsCRP at T2 (p = .569) and hsCRP at T1 did not interact with gender to predict BAI scores at T2 (p = .135). Associations remained non-significant after controlling for health behaviors (ps > .381).

[2]In models without health behavior covariates, when outliers for hsCRP were included, higher hsCRP predicted worsening anxiety symptoms over time (B = .03, p = .003) and worse anxiety symptoms predicted increasing hsCRP over time (B = .02, p = .033). When health behaviors were included, effects became non-significant in both directions.

3.4. Anxiety symptoms subscales

For anxiety subscales, neither somatic nor neurophysiological symptoms significantly predicted or were predicted by inflammation in adjusted models (ps > .081). Because no interactions with gender were found for the full BAI scale, we did not examine gender interactions for the BAI subscales.

3.5. Clinical cutoffs

Given the availability of clinical cutoffs for both hsCRP and the CESD measure used in HRS, we examined frequencies of individuals falling above the cutoffs for both measures. Specifically, for hsCRP, we used the American Heart Association and Centers for Disease Control and Prevention cut-off recommendations of low (< 1 mg/L), medium (1–3 mg/L) and high (> 3 mg/L) CRP levels (Pearson et al., 2003), and for CES-D, we used the cut off of ≥3 indicating possible depression (Wallace et al., 2000). We examined frequencies for high CES-D scores at T1 predicting categories of hsCRP at T2, and categories of hsCRP at T1 predicting high CES-D scores at T2. Results are shown in Table 5.

4. Discussion

The present study aimed to test longitudinal bidirectional relationships of depression and anxiety symptoms with the inflammatory marker hsCRP in a population-based sample of 13,775 older adults. Interestingly, over a four-year period, depressive symptoms predicted increasing inflammation for men, but not for women, and inflammation predicted worsening depression for women, but not for men. These gender differences appeared to be driven primarily by somatic depressive symptoms, which predicted increasing inflammation for men only and were predicted by inflammation for women only. Regardless of gender, inflammation predicted worsening dysphoric symptoms of depression, and lack of positive affect predicted increasing inflammation over time. Anxiety was not associated with inflammation long-itudinally. Taken together, and consistent with prior work (Copeland et al., 2012; Deverts et al., 2010; Stewart et al., 2009; Wium-Andersen et al., 2013), these findings indicate bidirectional relationships between depressive symptoms and inflammation such that depressive symptoms lead to worsening inflammation and high levels of inflammation increase depressive symptoms. Interestingly, the direction of these effects may differ by gender and type of depressive symptom.

The observed gender difference in the association between depression and inflammation is consistent with a number of prior studies (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlinger, 2004; Vetter et al., 2013). However, whereas prior researchers have shown stronger associations between depression and inflammation in men than in women, we found something slightly different - that the direction of the relationship (hsCRP predicting worsening depression for women and depression predicting worsening hsCRP for men) differed by gender. One possible explanation is that most prior studies testing gender differences have used cross-sectional samples, which would not allow gender comparisons for different directions of effects. However, even if the direction of effects differed by gender, one would still expect relationships for both genders in cross-sectional analyses. Another possible explanation has to do with the age of our sample. One theory for why

women do not show as strong a relationship between depression and inflammation as men is that female hormones may serve as a protective factor against the inflammatory processes resulting from depression (Elovainio et al., 2009). In support of this theory, hormone replacement therapy can improve mood in menopausal women (Onalan et al., 2005), and menopause and ovariectomy have been linked to low-grade systemic inflammation (Abu-Taha et al., 2009). Thus, because our sample consisted primarily of older adults, a large portion of the women may have been post-menopausal meaning that lower levels of female sex hormones may explain why significant associations were observed for both women and men.

Consistent with prior work, we showed bidirectional effects (albeit different directions for men and women) for the association between somatic depressive symptoms and hsCRP. The current measure of somatic symptoms included items related to low energy and motivation and restless sleep. The link to somatic symptoms in particular is consistent with research showing a causal link between inflammation (induced via administration of high dose cytokines) with neurovegetative symptoms termed “sickness behaviors” (Dantzer, 2004), and our findings suggest that this causal pathway may be particularly strong for women. The fact that inflammation predicted increasing dysphoric symptoms (e.g. feeling sad, depressed, lonely) over time, but not the reverse, is also consistent with a sickness behavior model because inflammation has been shown to induce feelings of sadness and social withdrawal (Dantzer, 2004). Finally, we showed that low positive affect (reverse coded for happy, enjoyed life, had a lot of energy) predicted increasing inflammation over time, but not the reverse (although the reverse association reached marginal significance). This suggests that, whereas some symptoms may be more strongly induced by inflammation, others, such as feeling unhappy and not enjoying life, may perpetuate it. One possibility is that low positive affect is a proxy for greater perceived life stress, which can increase circulation of proinflammatory cytokines via dysregulation of the sympathetic nervous system and the hypoththalamtic-pituitary-adrenal axis (Brydon et al., 2005; Esler et al., 1982; Veith et al., 1994; von Känel et al., 2006).

Contrary to some prior studies (Liukkonen et al., 2011; O’Donovan et al., 2010; Tayefi et al., 2017; Vogelzangs et al., 2013), we found no evidence in the current sample for a link between anxiety symptoms and hsCRP. Studies far more commonly test the association between inflammation and depressive symptoms than anxiety symptoms, and one possibility is that null findings have generally gone unpublished for anxiety. Of those studies that have shown a link between anxiety and inflammation over and above covariates, all were cross-sectional. Further, one showed an association between anxiety and IL-6, but not hsCRP (O’Donovan et al., 2010), and, to our knowledge, none excluded participants with very high hsCRP levels, which could be, but are not always, indicative of acute infection (Liukkonen et al., 2011; O’Donovan et al., 2010; Tayefi et al., 2017; Vogelzangs et al., 2013). It should be noted that in our data, prior to exclusion of participants with hsCRP greater than 10 mg/L, we did find significant associations of higher hsCRP with anxiety symptoms. Thus, the different findings may be attributed to the exclusion of outliers on our outcome measure. Furthermore, we saw significant correlations between anxiety and inflammation for men when examining preliminary zero-order correlations (Table 2), meaning that the analytic approach and adjustment for covariates can impact whether this association is detected. A

systematic review or meta-analysis that examines study design, type of sample, statistical approach, covariates, and handling of outliers may help clarify factors that affect the association between anxiety and inflammation. It also should be noted that, despite mixed findings in the literature for the association between anxiety and inflammation, anxiety has been robustly and independently associated with medical illness in cross-sectional and longitudinal studies (Janszky et al., 2010; Kawachi et al., 1994a,b; Kawachi et al., 1994a,b; Niles et al., 2015; Scott et al., 2007). Thus, biological pathways other than inflammation (e.g. prolonged autonomic nervous system activation) may explain this relationship.

Although the current study had key strengths including a large population-based sample and longitudinal assessment with two time points, there are also limitations. A longitudinal design allows testing of how a predictor affects the *change* in an outcome over time, which provides a more stringent test of directionality than a cross-sectional design, but without random assignment, inference of causality is not possible. Thus, this study does not allow us to determine whether depression causes inflammation or inflammation causes depression, but only that depressive symptoms are a risk factor for increasing inflammation over time and vice versa. Another limitation of the current study is that we only examined two timepoints, which does not allow us to test the trajectory of depressive and anxiety symptoms and inflammation over multiple timepoints. It is possible that the interrelationship between these factors is more complex than what can be captured with an assessment of just two time points. Another limitation is the reliance on self-report and the brevity of the measures of depression and anxiety symptoms. Due to the large number of measures and assessments included in HRS, the depression and anxiety symptom scales, although well validated, are brief. Further, the subscales considered in our analyses were based on prior work using exploratory and confirmatory factor analyses. There are other possible subscales that could be considered, but analysis of additional subscales was beyond the scope of the present manuscript. Finally, hsCRP is only one possible marker of inflammation. Although it provides an index of systemic inflammation, no single measure can entirely represent the complex nature of inflammation.

In conclusion, our findings have a number of implications for better understanding the relationship of depressive and anxiety symptoms with inflammation as indexed by hsCRP. First, we demonstrated bidirectional relationships between depressive symptoms and inflammation over time, suggesting that treating depressive symptoms may lessen disease risk via reduced inflammation *and* treating chronic inflammation or associated medical illness may improve symptoms of depression. Second, our findings indicate that the moderating effect of gender on the association between depressive symptoms and inflammation, which in previous studies has been described simply as a stronger effect for men than for women, may be more complex and may depend on which direction (depression proceeding inflammation or inflammation proceeding depression) is being assessed. Third, we showed that the direction of the association between depressive symptoms and inflammation over time differed depending on the type of depressive symptom assessed (somatic, dysphoric, positive affect), alluding to potentially different biological pathways underlying the association depending on the direction of the effect. Finally, we were unable to detect an association between inflammation and anxiety despite adequate power, suggesting that anxiety may not be as strongly linked to inflammation as depression.

Overall, these findings add to a growing body of literature examining the interplay between biological and psychological processes with potential implications for reducing both the risk of medical illness and the onset of depressive symptoms.

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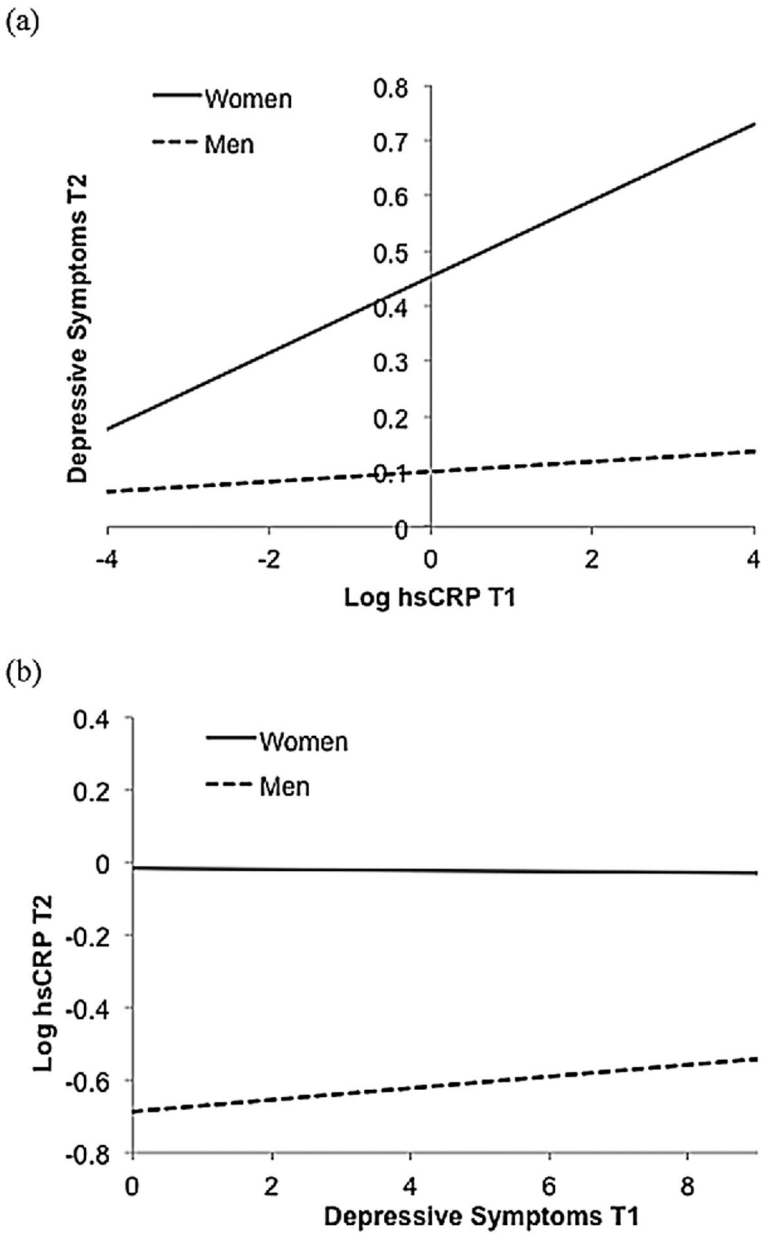

Fig. 1.

Bidirectional longitudinal relationships from time 1 (T1) to time 2 (T2) between hsCRP and depressive symptoms moderated by gender.

Table 1

Demographic and clinical characteristics of the sample.

	2006 Cohort (Mean, SD, Range)				**2008 Cohort (Mean, SD, Range)**			
	Men (N = 3000)		***Women (N = 4338)***		***Men (N = 2718)***		***Women (N = 4047)***	
Age	67.4 (9.9)		66.7 (10.8)		69.2 (9.7)		68.3 (10.5)	
	31–96		30–97		26–97		28–100	
White, N (%)	2523 (84.1)		3481 (80.2)		2245 (82.6)		3261 (80.6)	
Smoker, N (%)	431 (21.3)		577 (27.9)		384 (20.1)		549 (27.7)	
Heavy Alcohol Use, N (%)	209 (7.0)		242 (5.6)		188 (6.9)		225 (5.6)	
No Vigorous Exercise, N (%)	2116 (70.7)		3497 (80.7)		1947 (71.7)		3238 (80.0)	
Body Mass Index	28.3 (4.8)		28.6 (6.2)		28.2 (4.8)		28.6 (6.2)	
	14.8–51.9		12.9–61.9		10.7–55.3		13.3–68.6	
Number of Medical Conditions, N (%)								
0	488 (16.3)		649 (15.0)		369 (13.6)		491 (12.1)	
1	818 (27.3)		1124 (25.9)		628 (23.1)		988 (24.4)	
2	776 (25.9)		1229 (28.3)		719 (26.5)		1203 (29.7)	
3 or more	918 (30.5)		1336 (30.8)		1002 (36.8)		1365 (33.8)	
	Year 1	*Year 4*	*Year 1*	*Year 4*	*Year 1*	*Year 4*	*Year 1*	*Year 4*
CES-D Score	1.6 (2.0)	1.6 (2.0)	2.1 (2.4)	2.0 (2.3)	1.6 (2.0) 0–9	1.6 (2.0)	2.0 (2.3)	2.0 (2.3)
	0–9	0–9	0–9	0–9		0–9	0–9	0–9
Somatic	(1.2)	(1.2)	(1.3)	1.2 (1.3)	1.1 (1.2) 0–4	(1.2)	(1.3)	(1.3)
	0–4	0–4	0–4	0–4		0–4	0–4	0–4
Positive Affect	0.2 (0.5)	0.2 (0.5)	0.2 (0.6)	0.2 (0.6)	0.2 (0.5) 0–2	0.2 (0.5)	0.2 (0.6)	0.2 (0.6)
	0–2	0–2	0–2	0–2		0–2	0–2	0–2
Dysphoria	0.4 (0.8)	0.3 (0.8)	0.6 (1.0)	0.5 (0.9)	0.3 (0.8) 0–3	0.3 (0.8)	0.5 (1.0)	0.5 (0.9)
	0–3	0–3	0–3	0–3		0–3	0–3	0–3
BAI Score	7.5 (2.7)	7.6 (2.8)	8.0 (3.0)	7.9 (2.9) 5–20	7.7 (2.9) 5–20	7.6 (2.8)	8.1 (3.0)	7.9 (3.0)
	5–20	5–20	5–20			5–19	5–20	5–20
hs C-Reactive Protein	1.9 (3.5)	3.8 (8.9)	2.4 (4.0)	3.9 (7.6)	2.3 (5.3)	4.4 (10.3)	2.4 (4.0)	4.7 (10.2)
	0.0–81.1	0.1–154.8	0.0–101.6	0.1–185.4	0.0–112.1	0.1–244.7	0.0–83.6	0.1–221.8

Note:

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CES-D = Center for Epidemiological Studies Depression scale; BAI = Beck Anxiety Inventory scale; hs = high sensitivity.

Table 2

Bivariate correlations separate by gender.

	hsCRPl	hsCRP2	Depl	Dep2	Anxl	Anx2	Smoke	Ale	Exercise	BMI	Age	HS
Men												
hsCRP2	.55**											
Depl	.15**	.12**										
Dep2	.10*	.14**	.56**									
Anxl	.08**	.07**	.41**	.35**								
Anx2	.07**	.08**	.36**	.43**	.57**							
Smoke	.11**	.08**	.13**	.14**	.12**	.13**						
Ale	−.02	.01	.01	.02	.00	.01	.12**					
Exercise	−.12**	−.11**	−.17**	−.13**	−.10**	−.07**	−.09**	.01				
BMI	.22**	.18**	.05**	.04**	.03	.01	−.18**	−.05**	−.08**			
Age	.05**	.06**	−.01	.01	−.03*	−.03	−.28**	−.11**	−.07**	−.16**		
HS	−.09**	−.06**	−.17**	−.14**	−.15**	−.14**	−.09**	.00	.09**	.01	−.11**	
Med	.16**	.15**	.22**	.20**	.16**	.15**	−.13**	−.06**	−.15**	.15**	.33**	−.11**
	hsCRPl	hsCRP2	Depl	Dep2	Anxl	Anx2	Smoke	Ale	Exercise	BMI	Age	HS
Women												
hsCRP2	.64**											
Depl	.08**	.08**										
Dep2	.10**	.09**	.57**									
Anxl	.04**	.06**	.48**	.42**								
Anx2	.05**	.02*	.38**	.48**	.56**							
Smoke	0.03	.04*	.13**	.13**	.12**	.09**						
Ale	−.02*	−.03**	−.03**	−.03*	−.02*	−.04**	.08**					
Exercise	−.10**	−.10**	−.18**	−.16**	−.11**	−.10**	−.10**	.07**				
BMI	.38**	.33**	.12**	.12**	.04**	.04**	−.13**	−.09**	−.09**			
Age	−.07**	−.07**	.00	.03**	.00	.05**	−.26**	−.08**	−.12**	−.20**		

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HS	−.09**	−.09**	−.20**	−.20**	−.19**	−.16**	−.10**	.06**	.12**	−.07**	−.08**	
Med	.12**	.13**	.25**	.25**	.22**	.20**	−.05**	−.06**	−.18**	.19**	.31**	−.17**

Note:

*$p < .05$,

**$p < .01$; For column and row labels, 1 and 2 refer to Time 1 and Time 2; hsCRP = high sensitivity C-Reactive Protein; Dep = Depression measured by the Center for Epidemiologic Studies Depression Scale; Anx = Anxiety measured by the Beck Anxiety Inventory; Smoke = current smoker; Alc = Current heavy alcohol user; BMI = body mass index; HS = completed high school or greater education; Med = Number of medical conditions.

Table 3

Longitudinal Associations Between Depression (Total CES-D), Inflammation (C-Reactive Protein), and Covariates by Gender for Fully Adjusted Models.

Tl Variable Predicting Total CES-D Score at T2										
	Men					*Women*				
Tl Variable	β	Lower CI	Upper CI	Robust SE	*p*	β	Lower CI	Upper CI	Robust SE	*p*
CES-D	0.53	0.50	0.56	0.02	< .001	0.51	0.48	0.53	0.01	< .001
hs C-Reactive Protein	0.00	−0.02	0.03	0.01	.746	0.03	0.01	0.06	0.01	.006
Cohort	0.01	−0.02	0.03	0.01	.621	0.00	−0.02	0.02	0.01	.856
Age	0.02	−0.01	0.06	0.02	.155	0.03	0.00	0.05	0.01	.032
HS Education	−0.05	−0.08	−0.02	0.01	< .001	−0.07	−0.10	−0.05	0.01	< .001
Medical Conditions	0.09	0.06	0.12	0.02	< .001	0.10	0.08	0.13	0.01	< .001
Vigorous Exercise	−0.01	−0.04	0.01	0.01	.346	−0.03	−0.05	−0.01	0.01	.001
Smoke	0.07	0.04	0.11	0.02	< .001	0.06	0.03	0.09	0.02	< .001
Heavy Alcohol Use	0.01	−0.02	0.03	0.01	.447	−0.01	−0.03	0.01	0.01	.386
Body Mass Index	0.02	−0.01	0.05	0.02	.263	0.01	−0.02	0.04	0.01	.476
Intercept	0.05	−0.29	0.39	0.18	.773	0.20	−0.04	0.44	0.12	.104
Tl Variable Predicting hs C-Reactive Protein at T2										
	Men					*Women*				
Tl Variable	*β*	Lower CI	Upper CI	Robust SE	*p*	*β*	Lower CI	Upper CI	Robust SE	*p*
CES-D	0.03	0.00	0.06	0.02	.034	0.00	−0.03	0.02	0.01	.789
hs C-Reactive Protein	0.53	0.50	0.56	0.02	< .001	0.60	0.58	0.63	0.01	< .001
Cohort	0.07	0.05	0.10	0.01	< .001	0.07	0.05	0.10	0.01	< .001
Age	0.06	0.02	0.09	0.02	.001	−0.02	−0.05	0.01	0.01	.159
HS Education	0.00	−0.03	0.03	0.01	.794	−0.02	−0.04	0.01	0.01	.130
Medical Conditions	0.04	0.01	0.07	0.02	.018	0.01	−0.02	0.03	0.01	.586
Vigorous Exercise	−0.02	−0.05	0.01	0.01	.238	−0.01	−0.03	0.01	0.01	.482
Smoke	0.04	0.00	0.08	0.02	.046	0.03	−0.01	0.06	0.02	.137
Heavy Alcohol Use	0.01	−0.02	0.04	0.01	.432	0.00	−0.02	0.02	0.01	.904
Body Mass Index	0.08	0.05	0.12	0.02	< .001	0.09	0.06	0.12	0.01	< .001
Intercept	−0.70	−1.08	−0.32	0.19	< .001	−0.02	−0.28	0.25	0.14	.906

Note:

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CES-D = Center for Epidemiologic Studies Depression Scale; T1 = Time 1; T2 = Time 2; hs = high sensitivity; HS Education = completed high school or greater education; β = Standardized Beta; CI = 95% Confidence Interval; SE = Standard Error.

Table 4

Longitudinal Associations Between Somatic Depressive Symptoms, Inflammation (C-Reactive Protein), and Covariates by Gender for Fully Adjusted Models.

Tl Variable Predicting CES-D Somatic Subscale Score at T2										
	Men					*Women*				
Tl Variable	®	Lower CI	Upper CI	Robust SE	*p*	®	Lower CI	Upper CI	Robust SE	*p*
CES-D Somatic	0.51	0.48	0.54	0.01	< .001	0.47	0.45	0.49	0.01	< .001
hs C-Reactive Protein	−0.01	−0.03	0.02	0.01	.712	0.03	0.00	0.05	0.01	.031
Cohort	0.00	−0.02	0.03	0.01	.907	0.00	−0.02	0.02	0.01	.848
Age	0.03	0.00	0.06	0.02	.064	0.04	0.02	0.07	0.01	.001
HS Education	−0.06	−0.09	−0.03	0.01	< .001	−0.05	−0.08	−0.03	0.01	< .001
Medical Conditions	0.11	0.08	0.14	0.02	< .001	0.12	0.09	0.14	0.01	< .001
Vigorous Exercise	−0.02	−0.05	0.00	0.01	0.084	−0.04	−0.06	−0.02	0.01	< .001
Smoke	0.07	0.03	0.10	0.02	< .001	0.08	0.05	0.11	0.02	< .001
Heavy Alcohol Use	0.01	−0.01	0.04	0.01	0.378	−0.02	−0.04	0.00	0.01	.071
Body Mass Index	0.02	−0.01	0.05	0.02	0.275	0.03	0.01	0.06	0.01	.014
Intercept	0.10	−0.23	0.43	0.17	0.565	0.02	−0.22	0.26	0.12	.866
Tl Variable Predicting hs C-Reactive Protein at T2										
	Men					*Women*				
Tl Variable	®	Lower CI	Upper CI	Robust SE	*p*	®	Lower CI	Upper CI	Robust SE	*p*
CES-D Somatic	0.03	0.00	0.07	0.02	.026	−0.01	−0.03	0.01	0.01	.356
hs C-Reactive Protein	0.53	0.50	0.56	0.02	< .001	0.60	0.58	0.63	0.01	< .001
Cohort	0.07	0.05	0.10	0.01	< .001	0.07	0.05	0.09	0.01	< .001
Age	0.06	0.02	0.09	0.02	.001	−0.02	−0.05	0.01	0.01	.158
HS Education	0.00	−0.03	0.03	0.01	.793	−0.02	−0.04	0.00	0.01	.116
Medical Conditions	0.04	0.00	0.07	0.02	.026	0.01	−0.02	0.03	0.01	.499
Vigorous Exercise	−0.02	−0.04	0.01	0.01	.258	−0.01	−0.03	0.01	0.01	.434
Smoke	0.04	0.00	0.08	0.02	.039	0.03	−0.01	0.06	0.02	.107
Heavy Alcohol Use	0.01	−0.02	0.04	0.01	.425	0.00	−0.02	0.02	0.01	.916
Body Mass Index	0.08	0.05	0.12	0.02	< .001	0.09	0.07	0.12	0.01	< .001
Intercept	−0.71	−1.08	−0.33	0.19	< .001	−0.01	−0.28	0.25	0.14	.912

Note:

CES-D = Center for Epidemiologic Studies Depression Scale; T1 = Time 1; T2 = Time 2; hs = high sensitivity; HS Education = completed high school or greater education; β = Standardized Beta; CI = 95% Confidence Interval; SE = Standard Error.

Table 5

Frequency statistics of high CES-D scores (≥3) by hsCRP categories by gender.

	Tl hsCRP by T2 High CES-D N (%)		
	Low hsCRP	*Medium hsCRP*	*High hsCRP*
Men	408 (19.3)	268 (23.2)	105 (28.0)
Women	684 (26.3)	603 (29.9)	341 (36.7)
	Tl High CES-D by T2 hsCRP N (%)		
	Low hsCRP	*Medium hsCRP*	*High hsCRP*
Men	208 (16.6)	191 (17.4)	636 (27.0)
Women	402 (26.0)	419 (26.3)	1230 (33.1)

Note:

CES-D = Center for Epidemiologic Studies Depression Scale; T1 = Time 1; T2 = Time 2; hsCRP = high sensitivity c-reactive protein.