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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.

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.,

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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 (weight/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