Title

How is inflammation biology truly associated with depression in patients with stable coronary heart disease?: Insights from the heart and Soul study.

Authors

Lee, Chiyoung
Whooley, Mary
Yang, Qing
et al.

Publication Date

2024-05-01

DOI

10.1016/j.bbih.2024.100747

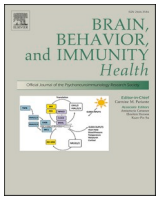
Peer reviewed

Brain, Behavior, & Immunity - Health 37 (2024) 100747

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



How is inflammation biology truly associated with depression in patients with stable coronary heart disease?: Insights from the heart and Soul study

Chiyoung Lee [a,*], Mary Whooley [b,c], Qing Yang [d], Daniel P. Moriarity [e]

[a] University of Arizona College of Nursing, Tucson, AZ, USA
[b] Department of Medicine, University of California San Francisco School of Medicine, San Francisco, CA, USA
[c] San Francisco Veterans Affairs Health Care System, San Francisco, CA, USA
[d] School of Nursing, Duke University, Durham, NC, USA
[e] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Coronary heart disease
Depression
Inflammation
Moderated non-linear factor analysis

ABSTRACT

Depression is known to be associated with inflammation among patients with established coronary heart disease (CHD), but it is unclear whether this is due to individual depression symptoms or to the broader construct of depression. We addressed this gap by using moderated non-linear factor analysis (MNLFA) to determine the extent that inflammation is associated with latent depression and/or individual symptoms in this patient group. We evaluated 1,024 outpatients with stable CHD from the baseline cross-sectional data of the Heart and Soul Study. Depression was assessed using the 9-item Patient Health Questionnaire, while inflammation was evaluated via C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) levels. MNLFA is based on the concept of model parameter moderation with regard to individual characteristics. Using the MNLFA approach, we simultaneously tested for differences in (1) latent depression, (2) individual depression items, and (3) the factor loading of the item on latent depression as a function of inflammatory markers, with and without covariate adjustment. Higher TNF-α levels were associated with both higher levels of a latent depression factor and greater endorsement of an individual symptom (appetite changes). Increased CRP levels were significantly associated with greater appetite changes, lower concentration difficulty, and greater fatigue. Elevated IL-6 levels were only related to greater fatigue, while increased MCP-1 levels were linked to greater sleep disturbance. After adjusting for covariates, some associations became insignificant. Inflammatory markers were not consistent predictors of factor loadings. This study represents the initial step to discussing how inflammation biology is truly related to depression among patients with established CHD.

1. Introduction

Depression is a well-known risk factor for incident coronary heart disease (CHD) and for cardiovascular morbidity and mortality among patients with established CHD (Carney and Freedland, 2017; Goldston and Baillie, 2008; Shimbo et al., 2005). Stress hormones such as catecholamines and cortisol, inflammation, and increased sympathetic nervous activity have been proposed as factors explaining the association between depression and CHD events (Davidson, 2012). Of those, inflammation has received much focus as a potentially modifiable risk factor for CHD events in patients with depression (Bankier et al., 2009; Howren et al., 2009; Janszky et al., 2005; Lespérance et al., 2004; Nikkheslat et al., 2015).

Studies on the association between inflammation and depression have predominantly used sum scores to measure depression, likely because of the ease of use and, perhaps, a field-wide acceptance of assessments using sum scores as long as the measure of internal consistency (i.e., Cronbach's alpha) is deemed "good enough". However, the sum of scores method weighs all symptoms equally, which is a psychometric and clinical concern, recognized by researchers and clinicians, that can affect the precision of clinical decision-making (Bauer and Curran, 2015; Campbell, 1960; McNeish and Wolf, 2020). The recognition of this concern resulted in symptom-level studies, which thus far demonstrated that atypical forms of depression, such as somatic and neurovegetative symptoms, are likely the factors driving associations of depression with inflammatory markers (Lee and Whooley, 2023;

* Corresponding author.
E-mail address: clee33@arizona.edu (C. Lee).

https://doi.org/10.1016/j.bbih.2024.100747
Received 12 November 2023; Received in revised form 1 February 2024; Accepted 26 February 2024
Available online 12 March 2024

Smolderen et al., 2012). Such studies that leveraged more granular information on individual symptoms have not only helped explain the inconsistencies in the literature concerning the inflammation–depression association in patients with established CHD but have also provided insights for devising targeted anti-inflammatory interventions for depression.

However, empirical studies have nevertheless reported on significant associations between inflammation and the continuous summary indices of depression severity (e.g., sum scores, mean scores) in patients with established CHD (Sforzini et al., 2019; Whooley et al., 2007). This poses a question on the true association between inflammation and depression among this patient population. That is, the level of measurement at which level of depression is truly associated with inflammation—the symptom level or also with the broader depression construct. Indeed, only testing symptom-level associations presumes the independence of symptoms from their associations with an underlying (latent) disease construct (Moriarity et al., 2023). Such an approach precludes the possibility of conclusively determining whether inflammation is associated with depression or more intrinsically with individual symptoms when controlling for one or the other (Moriarity et al., 2023). Researchers must account for the possibility that inflammation might have concomitant associations with depression at the symptom level and at a broader disease construct level in a hierarchical inflammatory phenotype (Moriarity et al., 2022, 2023). Evaluating the associations of inflammatory markers with individual symptoms versus sum scores using separate statistical models may overlook the possibility of both scenarios being true.

1.1. Moderated non-linear factor analysis

Moderated non-linear factor analysis (MNLFA), a measurement technique originally developed to assess measurement invariance (Bauer and Hussong, 2009), provides a unique method to investigate both the broader depression construct and individual symptoms in the same model and how they all vary as a function of the inflammatory process. MNLFA is based on the concept of model parameter moderation regarding individual characteristics (i.e., predictors) (Bauer, 2017). Specifically, it *simultaneously* tests whether a measure is invariant across a set of categorical and/or continuous predictors (or their interactions), with respect to factor means and variances (referred to as "impact") and item intercepts/thresholds and factor loadings (referred to as "differential item functioning [DIF]"). In our case, we evaluate this moderation along the continuum of inflammation markers. Put simply, MNLFA allows tests of inflammatory markers as simultaneous predictors of (1) latent depression, (2) individual symptoms, and (3) symptom factor loadings. Fig. 1 presents a simplified schematic of an MNLFA within the context of our study.

Fig. 1 presents a simplified illustration of MNLFA. MNLFA is a highly flexible, non-linear latent factor model which clarifies the associations among the latent construct, observed items/indicators, and predictors (Bauer and Hussong, 2009; Curran et al., 2014). MNLFA hypothesizes that all the indicators (i.e., individual depression items in Fig. 1) measure the same construct. All the indicators are linked to the latent variable via factor loadings, which indicate the predicted change in items associated with a one-unit shift in the latent variable. Fig. 1 shows the impact path whereby predictor(s) affect the latent variable (mean impact, variance impact) and the DIF paths whereby predictor(s) affect the measurement of the items (intercept DIF, loading DIF). In the current study, only mean impact, intercept IDF, and loading DIF were tested.

As shown in Fig. 1, MNLFA can directly test whether a continuously distributed characteristic, such as C-reactive protein (CRP) level, is systematically associated with higher levels of depression (factor mean) and greater variability of depression (factor variance). MNLFA also can test whether specific items on a depression scale are differentially endorsed (item intercepts/thresholds) or more strongly indicative (factor loadings) of underlying depression, when CRP is assessed on a continuum. Such tests are not possible with a traditional item response theory, DIF, or multi-group confirmatory factor analysis (CFA) approach, where measurement invariance is examined across categorical grouping variables (Curran et al., 2014; Gottfredson et al., 2019). These approaches can be problematic, primarily because of the possible loss of information on individual differences within groups (MacCallum et al., 2002; Hildebrandt et al., 2009, 2016). Furthermore, in the absence of clinically or theoretically meaningful cutoffs for biological variables of interest, using MNLFA is more suitable (Moriarity et al., 2022). While we only provide a brief overview here, more details of MNLFA can be found elsewhere (Bauer, 2017; Bauer and Hussong, 2009; Curran et al., 2014).

Moriarity et al. (2023) first used the MNLFA approach to investigate how both the broader depression construct and individual symptoms are associated with CRP levels across multiple waves of the National Health and Nutrition Examination Survey. The authors found that both the latent depression and individual symptoms (appetite change and fatigue) were consistently associated with CRP levels among the representative U.S. population. However, no studies have used MNLFA to elucidate such inflammation–depression associations among patients with established CHD, which we address in this study.

1.2. Aim of the study

We aimed to determine the extent that inflammation is associated with latent depression and/or individual symptoms in patients with

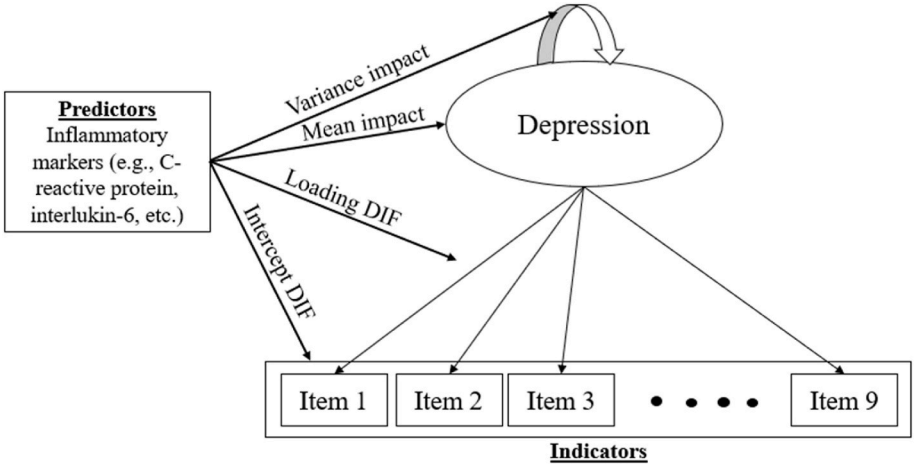


Fig. 1. A simplified illustration of moderated non-linear factor analysis (MNLFA).

established CHD. To realize this aim, we examined the extent to which critical parameters in the depression measurement model are moderated by inflammatory markers using the MNLFA approach. In particular, we simultaneously tested inflammatory markers as predictors of (1) latent depression (factor means), (2) individual depression symptom items (item intercepts), and (3) the factor loading of the item on latent depression.

2. Methods

2.1. Dataset and study population

We evaluated patients with stable CHD who were recruited for the Heart and Soul Study from 2000 to 2002. The Heart and Soul Study is a prospective cohort study investigating the effect of psychosocial factors on the prognosis of stable CHD. The enrollment process has been previously described (Ruo et al., 2003).

Briefly, participants were recruited from two departments of Veterans Affairs (VA) medical centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System), one university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Eligibility criteria included: (1) history of myocardial infarction (MI), (2) history of coronary revascularization, (3) $\geq$ 50% angiographic stenosis in at least 1 coronary artery, or (4) exercise-induced ischemia on treadmill electrocardiogram or nuclear perfusion imaging. Exclusion criteria were: (1) history of myocardial infarction within the past 6 months, (2) inability to walk a block, or (3) intention to move out of the local area within 3 years. All participants underwent a baseline examination, which consisted of an interview and a physical examination including blood pressure measurement using sphygmomanometer, a fasting venous blood sample collection, a standardized medical history questionnaire, echocardiography, and exercise treadmill testing. Between September 2000 and December 2002, a total of 1,024 participants completed the baseline examination whose data are used in this study.

2.2. Measurement

2.2.1. Depression criteria

The 9-item self-reported Patient Health Questionnaire (PHQ-9) was used to measure the symptoms of depression as outlined in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Kroenke et al., 2001). As a concise questionnaire with excellent reliability and validity (Kendrick et al., 2009; Kroenke et al., 2001; Mitchell et al., 2016), PHQ-9 has been widely used for cardiovascular patients (Lichtman et al., 2008). It is also recommended by the American Heart Association for screening depression in patients with CHD (Lichtman et al., 2008), making it an increasingly important tool in both clinical and research settings. The PHQ-9 assesses the following nine symptoms: (1) loss of interest, (2) appetite changes, (3) concentration difficulty, (4) suicidal ideation, (5) fatigue, (6) feelings of worthlessness, (7) psychomotor problems, (8) feelings of sadness, and (9) sleep disturbance. The questionnaire assesses the presence of these symptoms in the preceding 2 weeks, with each item scored as 0 (not at all), 1 (several days), 2 (more than half of the days), or 3 (nearly every day). The total score is computed by summing the individual item scores.

2.2.2. Inflammatory markers

In this study, we incorporated proinflammatory cytokines, including CRP, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1). Participants were instructed to fast for 12 h (except for medication consumable with water), avoid consuming aspirin for 1 week, and avoid smoking for 5 h before their appointment. Venous blood samples were obtained, and plasma and serum samples were stored at −70 °C. The laboratory technicians performing the inflammatory marker assays were blinded to the results of the depression interview. High-sensitivity CRP was measured by the Roche Integra assay or the Beckman Extended Range assay. Results from these 2 assays were highly correlated ($r = 0.99$). The Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc, St Charles, MO – subsequently acquired by Millipore) was used to measure IL-6, TNF-α and MCP-1 levels.

2.2.3. Covariates

We chose variables previously identified as crucial contributors to the inflammation–depression association or found to generally affect either inflammation or depression in CHD patients as relevant covariates (Fried et al., 2020; Moriarity et al., 2021; O'Connor et al., 2009; Smith et al., 2018). These included age (continuous), sex (male or female), race (Latinx, Asian or Pacific Islander, African American, White, Other), income level (less than $10,000, $10,000-$19,999, $20,000-$29,000, $30,000-$39,999, $40,000-$50,000, greater than $50,000), body mass index (BMI; kg/m^2), the number of chronic medical conditions, and the use of antidepressants including selective serotonin reuptake inhibitors, tricyclics, or other classes of antidepressants (yes or no). The number of chronic medical conditions was assessed by the question "has a medical doctor ever told you that you have [condition]?" Responses include 13 conditions: hypertension; heart attack; angina; congestive heart failure; stroke; diabetes; peripheral vascular disease; emphysema, asthma, or chronic obstructive pulmonary disease; kidney disease; liver disease, hepatitis or cirrhosis; arthritis, gout, or chronic joint problems, thyroid disease; elevated cholesterol. The total number of chronic medical conditions was calculated, thereby resulting in a continuous scale ranging from 0 to 13. The descriptions of the patients based on these covariates are presented in Supplementary Table 1.

2.3. Statistical analysis

Analyses used M*plus* 8.8 (Muthén and Muthén, 2018), supplemented by R version 4.0.3 (R Core Team), with M*plus*Automation as an add-on package. RStudio was used as an integrated development environment for R.

We first tested the unidimensionality of PHQ-9 by implementing a one-factor CFA model with weighted least squares means and variance adjusted (WLSMV) estimation (Flora and Curran, 2004). Model fit was assessed using standard indices as operationalized in M*plus* in conjunction with the WLSMV estimator, such as the root mean square error of approximation (RMSEA) (Steiger, 1990) and the comparative fit index (CFI) (Bentler, 1990). The criteria for excellent (or acceptable) model fit were based on conventional standards: CFI $>$ 0.95 (0.90) and RMSEA $<$ 0.05 (0.10). We also reported the Chi-square goodness-of-fit ($\chi 2$) statistic for completeness. However, as this metric is known to be sensitive to sample size (Bollen, 1989), only the CFI and RMSEA were considered for assessment of fit. Next, we automated a series of MNLFA models with a separate model for each predictor (i.e., inflammatory marker). The latent variable (i.e., the latent factor reflected by the PHQ-9 items), an individual indicator variable (i.e., the PHQ-9 item), and the factor loading of the item onto the latent variable (i.e., from the latent factor to the PHQ-9 item) were regressed on each inflammatory marker in a single group model. MNLFA models were estimated both with and without covariates. Inflammatory markers and covariates were mean-centered for use in analyses. Missing data were handled with the full-information-maximum-likelihood procedure available in M*plus* assuming their random occurrence. All parameters were estimated at $\alpha = 0.05$.

3. Results

3.1. Confirmatory factor analyses

A CFA model with the PHQ-9 items loading onto a single latent depression factor demonstrated acceptable to excellent model fit (CFI =

0.985, RMSEA = 0.082 [90% CI: 0.072, 0.092]). The $\chi 2$ test was significant ($\chi 2$ (27) = 211.83, $p < 0.001$).

3.2. Moderated non-linear factor analyses

The results for the MNLFA model without covariates are presented in Table 1. Among the broad panel of inflammatory markers, only higher TNF-α levels were associated with higher latent depression (average range of $rs = 0.091–0.148$, $ps = < 0.001–0.005$). Three of the nine items varied as a function of CRP; specifically, higher CRP levels were associated with greater appetite changes ($r = 0.103$, $p = 0.001$), lower concentration difficulty ($r = -0.067$, $p = 0.038$), and greater fatigue ($r = 0.072$, $p = 0.024$). Higher IL-6 levels were associated with greater fatigue ($r = 0.063$, $p = 0.048$). While significantly associated with latent depression, higher TNF-α levels were also associated with greater appetite changes ($r = 0.066$, $p = 0.039$). Higher levels of MCP-1 were only linked to greater increased sleep disturbance ($r = 0.081$, $p = 0.012$).

After adjusting for covariates (as detailed in Table 2), TNF-α levels were no longer associated with latent depression. However, higher CRP levels still were found to be linked to greater appetite changes ($r = 0.116$, $p = 0.003$) and lower concentration difficulties ($r = -0.080$, $p = 0.042$). Additionally, higher levels of MCP-1 also remained significantly linked to greater sleep disturbance ($r = 0.095$, $p = 0.016$). Supplementary Table 2 shows that inflammatory markers were not consistent predictors of factor loadings.

4. Discussion

This study elucidated novel perspectives on the relationship between inflammation and depression among patients with stable CHD, employing a MNLFA approach to simultaneously examine both the broader depression construct and individual symptoms in the same model. Importantly, before adjusting for covariates, we found that higher TNF-α levels were associated with higher levels of a latent depression factor as well as greater endorsement of the individual symptom (appetite changes) beyond the influences of a latent depression factor. These observations align with previous characterizations of a hierarchical inflammatory phenotype of depression (Moriarity et al., 2023). Whereas, CRP, IL-6, and MCP-1 appeared to specifically correlate with individual depression symptoms, but not with a latent depression factor as a whole, supporting the view that many inflammatory processes may not all be equally related to all symptoms of depression (Felger and Miller, 2020; Fried et al., 2020).

The findings of this study corroborate prior research, which demonstrates that heart failure patients with depression exhibit a higher expression of TNF-α as compared to healthy individuals (Moorman et al., 2007). Additionally, studies employing symptom-level analyses have established a correlation between alterations in appetite and inflammation, particularly with regard to TNF-α (Lamers et al., 2018; Lekander et al., 2005). Our research confirmed that both these scenarios (TNF-α–latent depression and TNF-α–symptom correlations) are true among patients with stable CHD. This indicates that patients exhibiting higher TNF-α levels are likely to demonstrate depression scores biased towards increased instances of appetite changes relative to those with lower TNF-α levels with the same depression scores. That is, identical depression scores may not accurately represent differences in the depression construct between groups. Therefore, conducting mean comparisons of unidimensional depression sum scores and TNF-α, without considering symptom-specific associations, may be methodologically flawed (Putnick and Bornstein, 2016). Yet, this observed bias was confined to a single symptom among the nine examined, exhibiting a relatively small effect size, thus implying that it may not constitute a substantive issue for TNF-α. However, the link between inflammation and depression seems to operate in a positive feedback loop, and these small effects may accrue over time (Moriarity et al., 2020).

Furthermore, the findings led us to contemplate the distinct modes of association between TNF-α and depression symptomatology. The mechanistic underpinnings linking TNF-α to individual symptoms could diverge from those associated with the broader depression construct. It has been argued that TNF-α not only precipitates symptoms of sickness behavior, such as changes in appetite, but also true major depressive disorders (Himmerich et al., 2008; Tizard, 2008).

In this study, we found CRP and the IL-6, its upstream stimulator, to be associated with individual symptoms but not with the latent depression among patients with CHD. This finding again underscores the need to discern the level at which depression measurement best correlates with inflammation biology. Notably, elevated CRP levels were correlated with greater appetite changes and fatigue, while increased IL-6 levels corresponded to higher fatigue. These associations are in line with previous studies utilizing network analysis techniques to examine the comprehensive perspective on inflammation-symptom correlations (further details on network analysis can be found in Borsboom et al., 2021); particularly, CRP levels have been found to specifically characterize these two sickness behavior symptoms compared to other depression criteria (Fried et al., 2020; Moriarity et al., 2021; Lee et al., 2023; Lee and Whooley, 2023). Concurrently, substantial evidence have established a significant correlation between IL-6 and fatigue across varied clinical samples, including women with CHD (Janszky et al., 2005), hemodialysis patients (Bossola et al., 2015), and HIV-positive individuals (Pala et al., 2016). In a case-control study by Pedraz-Petrozzi et al. (2020), of all proinflammatory cytokines, only IL-6 predicted fatigue. This was further supported by the Mendelian randomization analyses from the study by Milaneschi et al. (2021), which indicated a potential causal relationship between the IL-6/IL-6 receptor pathway and fatigue problems among the population cohort.

Interestingly, our results also showed an inverse correlation between

Table 1
Latent + symptom-level relations with inflammatory markers.

	Latent Dep[a]	Lost_int	App	Conc	Suic	Fati	Worth	Motor	Sad	Slp
CRP	$r = 0.032$	$r = -0.016$	$r = 0.103$	$r = -0.067$	$r = 0.022$	$r = 0.072$	$r = -0.041$	$r = 0.031$	$r = -0.010$	$r = -0.011$
	$p = 0.325$	$p = 0.627$	$p = 0.001$*	$p = 0.038$*	$p = 0.489$	$p = 0.024$*	$p = 0.207$	$p = 0.335$	$p = 0.760$	$p = 0.736$
IL-6	$r = 0.005$	$r = 0.018$	$r = 0.021$	$r = -0.040$	$r = 0.022$	$r = 0.063$	$r = -0.046$	$r = 0.018$	$r = -0.013$	$r = -0.024$
	$p = 0.889$	$p = 0.568$	$p = 0.519$	$p = 0.209$	$p = 0.492$	$p = 0.048$*	$p = 0.152$	$p = 0.568$	$p = 0.676$	$p = 0.452$
TNF-α	$r = 0.111$	$r = 0.040$	$r = 0.066$	$r = -0.009$	$r = 0.024$	$r = 0.023$	$r = -0.044$	$r = -0.014$	$r = -0.016$	$r = -0.063$
	$p = 0.001$*	$p = 0.213$	$p = 0.039$*	$p = 0.784$	$p = 0.462$	$p = 0.474$	$p = 0.171$	$p = 0.658$	$p = 0.625$	$p = 0.051$
MCP-1	$r = 0.028$	$r = 0.022$	$r = -0.056$	$r = -0.032$	$r = 0.045$	$r = -0.037$	$r = -0.036$	$r = -0.053$	$r = 0.049$	$r = 0.081$
	$p = 0.395$	$p = 0.501$	$p = 0.082$	$p = 0.324$	$p = 0.159$	$p = 0.246$	$p = 0.257$	$p = 0.102$	$p = 0.126$	$p = 0.012$*

Note.
r = converted correlation coefficient, p = p-value.
Dep, depression; Lost_int, loss of interest; App, appetite changes; Conc, concentration difficulty; Suic, suicidal ideation; Fati, fatigue; Worth, feelings of worthlessness; Motor, psychomotor problems; Sad, feelings of sadness; Slp, sleep disturbance.
*Indicates significant results.
[a] Statistics for "Latent Dep" represent mean results across all 9 item-level models.

Table 2
Latent + symptom-level relations with inflammatory markers including covariates.[a]

	Latent Dep[b]	Lost_int	App	Conc	Suic	Fati	Worth	Motor	Sad	Slp
CRP	$r = 0.007$	$r = -0.017$	$r = 0.116$	$r = -0.080$	$r = 0.005$	$r = 0.036$	$r = -0.048$	$r = 0.043$	$r = 0\text{-}0.001$	$r = -0.012$
	$p = 0.863$	$p = 0.673$	$p = 0.003$*	$p = 0.042$*	$p = 0.908$	$p = 0.361$	$p = 0.221$	$p = 0.278$	$p = 0.976$	$p = 0.762$
IL-6	$r = 0.005$	$r = 0.018$	$r = 0.036$	$r = -0.050$	$r = 0.026$	$r = 0.040$	$r = -0.057$	$r = 0.033$	$r = 0.015$	$r = -0.037$
	$p = 0.904$	$p = 0.657$	$p = 0.367$	$p = 0.200$	$p = 0.504$	$p = 0.312$	$p = 0.150$	$p = 0.398$	$p = 0.700$	$p = 0.342$
TNF-α	$r = 0.076$	$r = 0.029$	$r = 0.074$	$r = -0.013$	$r = 0.057$	$r = 0.037$	$r = -0.056$	$r = -0.031$	$r = -0.012$	$r = -0.062$
	$p = 0.061$	$p = 0.464$	$p = 0.059$	$p = 0.733$	$p = 0.149$	$p = 0.343$	$p = 0.158$	$p = 0.437$	$p = 0.767$	$p = 0.116$
MCP-1	$r = 0.012$	$r = 0.013$	$r = -0.067$	$r = -0.034$	$r = 0.027$	$r = -0.038$	$r = -0.057$	$r = -0.055$	$r = 0.054$	$r = 0.095$
	$p = 0.770$	$p = 0.737$	$p = 0.089$	$p = 0.395$	$p = 0.488$	$p = 0.336$	$p = 0.147$	$p = 0.165$	$p = 0.171$	$p = 0.016$*

Note.
r = converted correlation coefficient, p = p-value.
Dep, depression; Lost_int, loss of interest; App, appetite changes; Conc, concentration difficulty; Suic, suicidal ideation; Fati, fatigue; Worth, feelings of worthlessness; Motor, psychomotor problems; Sad, feelings of sadness; Slp, sleep disturbance.
*Indicates significant results.
[a] Adjustd for age, sex, race, income level, BMI, the number of chronic medical conditions, and the use of antidepressants.
[b] Statistics for "Latent Dep" represent mean results across all 9 item-level models.

CRP levels and concentration difficulty, contrary to the prevailing literature. Studies have suggested that chronic systemic inflammation and oxidative stress, which are characteristics of cardiovascular diseases, may cause neuroinflammation and neurodegeneration, thereby increasing the risk of cognitive impairment (McDonagh et al., 2021; Rusanen et al., 2014). Generally, individuals with pre-existing CHD show a greater likelihood of experiencing cognitive impairment than the general population (Muller et al., 2007; Singh-Manoux et al., 2008) possibly because of the presence of chronic systemic inflammation related to the underlying atherosclerotic process (Casserly and Topol, 2004). Individuals with mild cognitive impairment and dementia also have an increased level of inflammatory markers, including CRP (Vuorinen et al., 2015; Komen et al., 2022). However, these findings should be carefully interpreted because our study does not conclusively establish whether concentration difficulty associated with depression indicates an independent dysfunction related to cognitive impairment in patients with stable CHD. In addition, concentration difficulty is only one example of many types of cognitive deficits. Additional evidence is needed to expand this interpretation.

It is worth noting that several inflammation–latent depression and inflammation–symptom relations involving TNF-α, CRP, and IL-6 disappeared after adjusting for covariates, indicating that some covariates contribute to these associations. Specifically, BMI is acknowledged as a significant confounding factor in the correlation between inflammation and depression, with adipose tissue acting as a proactive endocrine organ and producing a multitude of proinflammatory cytokines (Coppack, 2001). Additionally, not all individuals with depression display elevated levels of inflammatory markers. The correlation between inflammation and depression could be influenced by variables such as sex or race (Beydoun et al., 2020; Morris et al., 2011). Although drawing any causal or mediating inferences regarding these covariates in the inflammation–depression association remains a challenge due to cross-sectional nature of the current analytic approach, this issue can be addressed as an extension of the current work.

Finally, higher MCP-1 levels only showed a robust association with sleep disturbance, regardless of covariate adjustment. MCP-1 is recognized as a key cytokine, instrumental in activating monocytes and other immune cells, which play a pivotal role in inflammation (Imani et al., 2022). Previous studies suggest a potential involvement of MCP-1 in the pathophysiology of major depressive disorder (Grassi-Oliveira et al., 2012; Lehto et al., 2010; Myung et al., 2016); however, the precise mechanism underpinning the relationship between MCP-1 concentrations and depression remains to be elucidated. Prior to the present study, no study had demonstrated that MCP-1 is related to specific symptoms of depression such as sleep disturbance, except Goldsmith et al. (2016, 2020) who found that the inflammatory cytokine MCP-1 exhibits a consistent association with psychomotor problems. Analogous findings have been reported in research focused on obstructive sleep apnea (OSA), primarily demonstrating that adults with OSA have increased MCP-1 levels (Ohga et al., 2003; Imani et al., 2022). The hypoxic stress induced by OSA could elevate circulating MCP-1, thus providing a potential biological plausibility for the connection between OSA and cardiovascular disease (Kim et al., 2010). A recent study by Kazmi et al. (2022) revealed associations between MCP-1 and poor sleep quality in individuals with alcohol use disorder. Further research is necessary to deepen our understanding of this association.

4.1. Limitations

This study presents several limitations. First, the cross-sectional design hampers our capacity to ascertain whether inflammation precedes depression (either as a latent factor or individual symptom), or if depression precedes inflammation. It also potentially hinders us from determining whether antidepressant therapy modifies cytokine levels. Second, the PHQ-9 fails to provide information regarding symptom directionality (e.g., increased versus decreased appetite), which could have obscured potential associations in the analyses. Future research should employ measures that disaggregate symptoms, fostering a more comprehensive understanding of how the inflammatory process correlates with nuanced depression symptoms among patients with stable CHD. Third, although our MNLFA model accounts for key covariates, its high computational demands, particularly its need for large sample sizes, limited our ability to include other vital covariates in the analyses. Specifically, in addition to antidepressant use, crucial clinical or treatment-related covariates, such as the use of anti-inflammatory medications (including NSAIDs or aspirin) or substance use (e.g., smoking or alcohol consumption), could not be considered because further including them posed model convergence issues. These factors, which can influence inflammation, should be carefully studied as potential covariates in future research with sufficient power. Lastly, although this exploratory investigation focused on well-studied inflammatory markers in the field, future research should explore a broader range of critical inflammatory markers, such as interleukin-1, particularly for cardiovascular patients.

5. Conclusion

This study, which was based on MNLFA, represents the initial step to discussing how inflammation biology is truly related to depression among patients with established CHD. Our insights substantiate the need for further research to test for measurement noninvariance of depression measures as a function of inflammatory processes to pinpoint areas where this poses a significant issue warranting attention.

Funding

None.

Ethics statement

For the present secondary data analysis, the first author received the data from the principal investigator of the Heart and Soul Study after receiving approval from University of Washington (approval no. STUDY00015032). All methods and procedures were conducted in accordance with the relevant guidelines and regulations. The Heart and Soul Study was approved by the following institutional review boards: the Committee on Human Research at the University of California, San Francisco; the Research and Development Committee at the San Francisco Veterans Affairs Medical Center; the Medical Human Subjects Committee at Stanford University; the Human Subjects Committee at the Veterans Affairs Palo Alto Health Care System; and the Data Governance Board of the Community Health Network of San Francisco.

Consent to participate

All participants provided written informed consent.

CRediT authorship contribution statement

Chiyoung Lee: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Mary Whooley:** Data curation, Investigation, Supervision, Writing – review & editing. **Qing Yang:** Conceptualization, Formal analysis, Supervision, Writing – review & editing. **Daniel P. Moriarity:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no competing interests.

Data availability

Data will be made available on request.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100747.

References

Bankier, B., Barajas, J., Martinez-Rumayor, A., Januzzi, J.L., 2009. Association between major depressive disorder and C-reactive protein levels in stable coronary heart disease patients. J. Psychosom. Res. 66 (3), 189–194. https://doi.org/10.1016/j.jpsychores.2008.09.010.

Bauer, D.J., 2017. A more general model for testing measurement invariance and differential item functioning. Psychol. Methods 22 (3), 507–526. https://doi.org/10.1037/met0000077.

Bauer, D.J., Hussong, A.M., 2009. Psychometric approaches for developing commensurate measures across independent studies: traditional and new models. Psychol. Methods 14 (2), 101–125. https://doi.org/10.1037/a0015583.

Bauer, D., Curran, P., 2015. The discrepancy between measurement and modeling in longitudinal data analysis. In: Harring, J.R., Stapleton, L.M., Beretvas, S.N. (Eds.), Advances in Multilevel Modeling for Educational Research: Addressing Practical Issues Found in Real-World Applications. Information Age Publishing, pp. 3–38.

Bentler, P.M., 1990. Comparative fit indexes in structural models. Psychol. Bull. 107 (2), 238–246. https://doi.org/10.1037/0033-2909.107.2.238.

Beydoun, M.A., Obhi, H.K., Weiss, J., Canas, J.A., Beydoun, H.A., Evans, M.K., Zonderman, A.B., 2020. Systemic inflammation is associated with depressive symptoms differentially by sex and race: a longitudinal study of urban adults. Mol. Psychiatry. 25 (6), 1286–1300.

Bollen, K.A., 1989. Structural Equations with Latent Variables, vol. 210. John Wiley & Sons.

Borsboom, D., Deserno, M.K., Rhemtulla, M., Epskamp, S., Fried, E.I., McNally, R.J., et al., 2021. Network analysis of multivariate data in psychological science. Nat Rev Methods Primers 1 (1), 58.

Bossola, M., Di Stasio, E., Giungi, S., Rosa, F., Tazza, L., 2015. Fatigue is associated with serum interleukin-6 levels and symptoms of depression in patients on chronic hemodialysis. J. Pain Manag. 49 (3), 578–585. https://doi.org/10.1016/j.jpainsymman.2014.07.009.

Campbell, D.T., 1960. Recommendations for APA test standards regarding construct, trait, or discriminant validity. Am. Psychol. 15 (8), 546–553. https://doi.org/10.1037/h0048255.

Carney, R.M., Freedland, K.E., 2017. Depression and coronary heart disease. Nat. Rev. Cardiol. 14 (3), 145–155.

Casserly, I., Topol, E.J., 2004. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 363 (9415), 1139–1146. https://doi.org/10.1016/S0140-6736(04)15900-X.

Coppack, S.W., 2001. Pro-inflammatory cytokines and adipose tissue. Proc. Nutr. Soc. 60 (3), 349–356. https://doi.org/10.1079/PNS200111.

Curran, P.J., McGinley, J.S., Bauer, D.J., Hussong, A.M., Burns, A., Chassin, L., Sher, K., Zucker, R., 2014. A moderated non-linear factor model for the development of commensurate measures in integrative data analysis. Multivariate Behav. Res. 49, 214–231. https://doi.org/10.1080/00273171.2014.889594.

Davidson, K.W., 2012. Depression and coronary heart disease. Int. Sch. Res. Notices, 743813.

Felger, J.C., Miller, A.H., 2020. Identifying immunophenotypes of inflammation in depression: dismantling the monolith. Biol. Psychiatr. 88 (2), 136–138. https://doi.org/10.1016/j.biopsych.2020.04.024.

Flora, D.B., Curran, P.J., 2004. An empirical evaluation of alternative methods of estimation for confirmatory factor analysis with ordinal data. Psychol. Methods 9 (4), 466–491. https://doi.org/10.1037/1082-989X.9.4.466.

Fried, E.I., Von Stockert, S., Haslbeck, J.M.B., Lamers, F., Schoevers, R.A., Penninx, B.W. J.H., 2020. Using network analysis to examine links between individual depressive symptoms, inflammatory markers, and covariates. Psychol. Med. 50 (16), 2682–2690. https://doi.org/10.1017/S0033291719002770.

Goldsmith, D.R., Haroon, E., Woolwine, B.J., Jung, M.Y., Wommack, E.C., Harvey, P.D., et al., 2016. Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. Brain Behav. Immun. 56, 281–288. https://doi.org/10.1016/j.bbi.2016.03.025.

Goldsmith, D.R., Massa, N., Pearce, B.D., Wommack, E.C., Alrohaibani, A., Goel, N., et al., 2020. Inflammatory markers are associated with psychomotor slowing in patients with schizophrenia compared to healthy controls. NPJ Schizophr 6 (1), 8.

Goldston, K., Baillie, A.J., 2008. Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. Clin. Psychol. Rev. 28 (2), 288–306. https://doi.org/10.1016/j.cpr.2007.05.005.

Gottfredson, N.C., Cole, V.T., Giordano, M.L., Bauer, D.J., Hussong, A.M., Ennett, S.T., 2019. Simplifying the implantation of modern scale scoring methods with an automated r package: automated moderated nonlinear factor analysis (aMNLFA). Addict. Beyond Behav. 94, 65–73. https://doi.org/10.1016/j.addbeh.2018.10.031.

Grassi-Oliveira, R., Brieztke, E., Teixeira, A., Pezzi, J.C., Zanini, M., Lopes, R.P., Bauer, M.E., 2012. Peripheral chemokine levels in women with recurrent major depression with suicidal ideation. Br. J. Psychiatry 34, 71–75. https://doi.org/10.1590/S1516-44462012000100013.

Hildebrandt, A., Lüdtke, O., Robitzsch, A., Sommer, C., Wilhelm, O., 2016. Exploring factor model parameters across continuous variables with local structural equation models. Multivariate Behav. Res. 51 (2–3), 257–258. https://doi.org/10.1080/00273171.2016.1142856.

Himmerich, H., Fulda, S., Linseisen, J., Seiler, H., Wolfram, G., Himmerich, S., et al., 2008. Depression, comorbidities and the TNF-α system. Eur. Psychiatr. 23 (6), 421–429. https://doi.org/10.1016/j.eurpsy.2008.03.013.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71 (2), 171–186. https://doi.org/10.1097/PSY.0b013e3181907c1b.

Imani, M.M., Sadeghi, M., Mohammadi, M., Brühl, A.B., Sadeghi-Bahmani, D., Brand, S., 2022. Association of blood MCP-1 levels with risk of obstructive sleep apnea: a systematic review and meta-analysis. Medicina 58 (9), 1266. https://doi.org/10.3390/medicina58091266.

Janszky, I., Lekander, M., Blom, M., Georgiades, A., Ahnve, S., 2005. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. Brain Behav. Immun. 19 (6), 555–563. https://doi.org/10.1016/j.bbi.2005.01.001.

Kazmi, N., Wallen, G.R., Yang, L., Alkhatib, J., Schwandt, M.L., Feng, D., et al., 2022. An exploratory study of pro-inflammatory cytokines in individuals with alcohol use disorder: MCP-1 and IL-8 associated with alcohol consumption, sleep quality, anxiety, depression, and liver biomarkers. Front. Psychiatr. 13, 931280 https://doi.org/10.3389/fpsyt.2022.931280.

Kendrick, T., Dowrick, C., McBride, A., Howe, A., Clarke, P., Maisey, S., et al., 2009. Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data. Bmj 338. https://doi.org/10.1136/bmj.b750.

Kim, J., Lee, C.H., Park, C.S., Kim, B.G., Kim, S.W., Cho, J.H., 2010. Plasma levels of MCP-1 and adiponectin in obstructive sleep apnea syndrome. Arch. Otolaryngol. Head Neck Surg. 136 (9), 896–899. https://doi.org/10.1001/archoto.2010.142.

Komen, J.J., Pottegård, A., Mantel-Teeuwisse, A.K., Forslund, T., Hjemdahl, P., Wettermark, B., Klungel, O.H., 2022. Oral anticoagulants in patients with atrial fibrillation at low stroke risk: a multicentre observational study. Eur. Heart J. 43 (37), 3528–3538. https://doi.org/10.1093/eurheartj/ehac111.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Lamers, F., Milaneschi, Y., De Jonge, P., Giltay, E.J., Penninx, B.W.J.H., 2018. Metabolic and inflammatory markers: associations with individual depressive symptoms. Psychol. Med. 48 (7), 1102–1110. https://doi.org/10.1017/S0033291717002483.

Lee, C., Min, S.H., Niitsu, K., 2023. C-Reactive protein and specific depression symptoms among older adults: an exploratory investigation of multi-plane networks using cross-sectional data from NHANES (2017–2020). Biol. Res. Nurs. 25 (1), 14–23. https://doi.org/10.1177/10998004221110602.

Lee, C., Whooley, M.A., 2023. Networks of C-reactive protein and depression symptoms in patients with stable coronary heart disease: findings from the Heart and Soul Study. Int. J. Methods Psychiatr. Res., e1968 https://doi.org/10.1002/mpr.1968.

Lehto, S.M., Niskanen, L., Herzig, K.H., Tolmunen, T., Huotari, A., Viinamäki, H., et al., 2010. Serum chemokine levels in major depressive disorder. Psychoneuroendocrinology 35 (2), 226–232. https://doi.org/10.1016/j.psyneuen.2009.06.007.

Lekander, M., AndrÈasson, A., Elofsson, S., UndÈn, A.L., 2005. # 85 Cytokines, symptoms of sickness and self-rated health. Brain Behav. Immun. 4 (19), e45. https://doi.org/10.1016/j.bbi.2005.10.092.

Lespérance, F., Frasure-Smith, N., Théroux, P., Irwin, M., 2004. The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. Am. J. Psychiatr. 161 (2), 271–277. https://doi.org/10.1176/appi.ajp.161.2.271.

Lichtman, J.H., Bigger Jr., J.T., Blumenthal, J.A., Frasure-Smith, N., Kaufmann, P.G., Lespérance, F., et al., 2008. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American heart association Prevention Committee of the Council on cardiovascular Nursing, Council on clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on quality of care and Outcomes research: endorsed by the American Psychiatric association. Circulation 118 (17), 1768–1775. https://doi.org/10.1161/CIRCULATIONAHA.108.190769.

MacCallum, R.C., Zhang, S., Preacher, K.J., Rucker, D.D., 2002. On the practice of dichotomization of quantitative variables. Psychol. Methods 7 (1), 19–40. https://doi.org/10.1037/1082-989X.7.1.19.

McDonagh, T.A., Metra, M., Adamo, M., Gardner, R.S., Baumbach, A., Böhm, M., et al., 2021. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. Heart J. 42 (36), 3599–3726. https://doi.org/10.1093/eurheartj/ehab368.

McNeish, D., Wolf, M.G., 2020. Thinking twice about sum scores. Behav. Res. Methods 52 (6), 2287–2305. https://doi.org/10.3758/s13428-020-01398-0.

Milaneschi, Y., Kappelmann, N., Ye, Z., Lamers, F., Moser, S., Jones, P.B., et al., 2021. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. Mol. Psychiatry. 26 (12), 7393–7402.

Mitchell, A.J., Yadegarfar, M., Gill, J., Stubbs, B., 2016. Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: a diagnostic meta-analysis of 40 studies. BJPsych Open 2 (2), 127–138. https://doi.org/10.1192/bjpo.bp.115.001685.

Moorman, A.J., Mozaffarian, D., Wilkinson, C.W., Lawler, R.L., McDonald, G.B., Crane, B.A., et al., 2007. In patients with heart failure elevated soluble TNF-receptor 1 is associated with higher risk of depression. J. Card. Fail. 13 (9), 738–743. https://doi.org/10.1016/j.cardfail.2007.06.301.

Moriarity, D.P., Joyner, K.J., Slavich, G.M., Alloy, L.B., 2022. Unconsidered issues of measurement noninvariance in biological psychiatry: a focus on biological phenotypes of psychopathology. Mol. Psychiatr. 27 (3), 1281–1285.

Moriarity, D.P., Kautz, M.M., Mac Giollabhui, N., Klugman, J., Coe, C.L., Ellman, L.M., et al., 2020. Bidirectional associations between inflammatory biomarkers and depressive symptoms in adolescents: potential causal relationships. Clin. Psychol. Sci. 8 (4), 690–703. https://doi.org/10.1177/2167702620917458.

Moriarity, D.P., Slavich, G.M., Alloy, L.B., Olino, T.M., 2023. Hierarchical inflammatory phenotypes of depression: a novel approach across five independent samples and 27,730 adults. Biol. Psychiatr. 93 (3), 253–259. https://doi.org/10.1016/j.biopsych.2022.08.017.

Moriarity, D.P., Horn, S.R., Kautz, M.M., Haslbeck, J.M., Alloy, L.B., 2021. How handling extreme C-reactive protein (CRP) values and regularization influences CRP and depression criteria associations in network analyses. Brain Behav. Immun. 91, 393–403. https://doi.org/10.1016/j.bbi.2020.10.02.

Morris, A., Zhao, L., Ahmed, Y., Stoyanova, N., Hooper, W.C., Gibbons, G., et al., 2011. Association between depression and inflammation–differences by race and sex: the META-Health study. Psychosom. Med. 73 (6), 462. https://doi.org/10.1097/PSY.0b013e318222379c.

Muller, M., Grobbee, D.E., Aleman, A., Bots, M., van der Schouw, Y.T., 2007. Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis 190 (1), 143–149. https://doi.org/10.1016/j.atherosclerosis.2006.

Muthén, L.K., Muthén, B., 2018. Mplus. In: The Comprehensive Modelling Program for Applied Researchers, vol. 5. User's Guide.

Myung, W., Lim, S.W., Woo, H.I., Park, J.H., Shim, S., Lee, S.Y., Kim, D.K., 2016. Serum cytokine levels in major depressive disorder and its role in antidepressant response. Psychiatry Investig 13 (6), 644–651. https://doi.org/10.4306/pi.2016.13.6.644.

Nikkheslat, N., Zunszain, P.A., Horowitz, M.A., Barbosa, I.G., Parker, J.A., Myint, A.M., et al., 2015. Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. Brain Behav. Immun. 48, 8–18. https://doi.org/10.1016/j.bbi.2015.02.002.

O'Connor, M.F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav. Immun. 23 (7), 887–897. https://doi.org/10.1016/j.bbi.2009.04.005.

Ohga, E., Tomita, T., Wada, H., Yamamoto, H., Nagase, T., Ouchi, Y., 2003. Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. J. Appl. Physiol. 94 (1), 179–184. https://doi.org/10.1152/japplphysiol.00177.2002.

Pala, A.N., Steca, P., Bagrodia, R., Helpman, L., Colangeli, V., Viale, P., Wainberg, M.L., 2016. Subtypes of depressive symptoms and inflammatory biomarkers: an exploratory study on a sample of HIV-positive patients. Brain Behav. Immun. 56, 105–113. https://doi.org/10.1016/j.bbi.2016.02.013.

Pedraz-Petrozzi, B., Neumann, E., Sammer, G., 2020. Pro-inflammatory markers and fatigue in patients with depression: a case-control study. Sci. Rep. 10 (1), 9494. https://doi.org/10.1038/s41598-020-66532-6, 494.

Putnick, D.L., Bornstein, M.H., 2016. Measurement invariance conventions and reporting: the state of the art and future directions for psychological research. Dev. Rev. 41, 71–90. https://doi.org/10.1016/j.dr.2016.06.004.

Ruo, B., Rumsfeld, J.S., Hlatky, M.A., Liu, H., Browner, W.S., Whooley, M.A., 2003. Depressive symptoms and health-related quality of life: the Heart and Soul Study. JAMA 290 (2), 215–221. https://doi.org/10.1001/jama.290.2.215.

Rusanen, M., Kivipelto, M., Levälahti, E., Laatikainen, T., Tuomilehto, J., Soininen, H., Ngandu, T., 2014. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. J. Alzheim. Dis. 42 (1), 183–191. https://doi.org/10.3233/JAD-132363.

Sforzini, L., Pariante, C.M., Palacios, J.E., Tylee, A., Carvalho, L.A., Viganò, C.A., Nikkheslat, N., 2019. Inflammation associated with coronary heart disease predicts onset of depression in a three-year prospective follow-up: a preliminary study. Brain Behav. Immun. 81, 659–664. https://doi.org/10.1016/j.bbi.2019.07.023.

Shimbo, D., Chaplin, W., Crossman, D., Haas, D., Davidson, K.W., 2005. Role of depression and inflammation in incident coronary heart disease events. Am. J. Cardiol. 96 (7), 1016–1021. https://doi.org/10.1016/j.amjcard.2005.05.064.

Singh-Manoux, A., Sabia, S., Lajnef, M., Ferrie, J.E., Nabi, H., Britton, A.R., Marmot, M. G., Shipley, M.J., 2008. History of coronary heart disease and cognitive performance in midlife: the Whitehall II study. Eur. Heart J. 29 (17), 2100–2107. https://doi.org/10.1093/eurheartj/ehn298.

Smith, K.J., Au, B., Ollis, L., Schmitz, N., 2018. The association between C-reactive protein, interleukin-6 and depression among older adults in the community: a systematic review and meta-analysis. Exp. Gerontol. 102, 109–132. https://doi.org/10.1016/j.exger.2017.12.005.

Smolderen, K.G., Spertus, J.A., Reid, K.J., Buchanan, D.M., Vaccarino, V., Lichtman, J.H., et al., 2012. Association of somatic and cognitive depressive symptoms and biomarkers in acute myocardial infarction: insights from the translational research investigating underlying disparities in acute myocardial infarction patients' health status registry. Biol. Psychiatr. 71 (1), 22–29. https://doi.org/10.1016/j.biopsych.2011.07.029.

Steiger, J.H., 1990. Structural model evaluation and modification: an interval estimation approach. Multivariate Behav. Res. 25 (2), 173–180. https://doi.org/10.1207/s15327906mbr2502_4.

Tizard, I., 2008. Sickness behavior, its mechanisms and significance. Anim. Health Res. Rev. 9 (1), 87–99.

Vuorinen, M., Spulber, G., Damangir, S., Niskanen, E., Ngandu, T., Soininen, H., et al., 2015. Midlife CAIDE dementia risk score and dementia-related brain changes up to 30 years later on magnetic resonance imaging. J. Alzheim. Dis. 44 (1), 93–101. https://doi.org/10.3233/JAD-140924.

Whooley, M.A., Caska, C.M., Hendrickson, B.E., Rourke, M.A., Ho, J., Ali, S., 2007. Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. Biol. Psychiatr. 62 (4), 314–320. https://doi.org/10.1016/j.biopsych.2006.10.016.