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Hierarchical Inflammatory Phenotypes of Depression: A Novel Approach Across Five Independent Samples and 27,730 Adults

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ABSTRACT

BACKGROUND: Although characterizing associations between inflammation and depression may prove critical for informing theory, research, and treatment decisions, extant research has been limited by ignoring the possibility that inflammation may be simultaneously associated with depression broadly and with a subset of symptoms. This lack of direct comparison has hampered attempts to understand inflammatory phenotypes of depression and critically fails to consider that inflammation might be uniquely associated with both depression broadly and individual symptoms.

METHODS: We used moderated nonlinear factor analysis in 5 NHANES (National Health and Nutrition Examination Survey) cohorts (N = 27,730, 51% female, mean age = 46 years).

RESULTS: C-reactive protein (CRP) is simultaneously associated with latent depression, appetite, and fatigue. Specifically, CRP was associated with latent depression in all 5 samples (rs: 0.044–0.089; ps: $<$ .001–.002) and was associated with both appetite (significant rs: 0.031–0.049, significant ps: .001–.007) and fatigue (significant rs: 0.030–0.054, significant ps: $<$ .001–.029) in 4 samples. These results were largely robust to covariates.

CONCLUSIONS: Methodologically, these models indicate that the Patient Health Questionnaire-9 is scalar non-invariant as a function of CRP (i.e., identical Patient Health Questionnaire-9 scores may represent different constructs in those with high vs. low CRP levels). Therefore, mean comparisons of depression total scores and CRP might be misleading without accounting for symptom-specific associations. Conceptually, these findings indicate that studies investigating inflammatory phenotypes of depression should examine how inflammation is simultaneously related both to depression broadly and to specific symptoms, and whether these relations function via different mechanisms. This has the potential to yield new theoretical insights and may lead to the development of novel therapies for reducing inflammation-related symptoms of depression.

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Contemporary theories of psychopathology generally acknowledge that depression is a heterogeneous disorder in terms of both pathogenesis and phenotypic expression. Moreover, research suggests that certain biological processes, such as inflammation (1,2), gray matter volume (3), and genetic profiles (4), may be associated with particular depressive phenotypes. Characterization of biological phenotypes of depression may refine etiologic theory, advance precision medicine, and increase the replicability of future research; however, extant biological phenotyping studies are restricted by analytic limitations.

To illustrate, consider the growing body of research showing that some inflammatory proteins, such as C-reactive protein (CRP), are related to depression symptom severity (5) and depression diagnoses (6). However, several symptom-level studies have found that inflammation is uniquely associated with neurovegetative symptoms, such as changes in appetite and fatigue [(7–11); of note, (7) and (10) used different subsamples of the NESDA (Netherlands Study of Depression and Anxiety) dataset], suggesting that these relations may be driven by symptom-specific associations. Both diagnosis/sum score and individual symptom–focused approaches include implicit assumptions that weaken their ability to generate knowledge about how inflammatory biology is truly related to depression. Specifically, whereas testing the association between inflammation and depression total scores or diagnoses assumes equal associations between inflammation and all symptoms of depression, testing solely symptom-level associations assumes an independence of symptoms divorced from their associations with an underlying (latent) disease construct.

Studies investigating inflammatory proteins as predictors of both summary scores and individual symptoms of depression have found mixed support for an association between proteins and depression summary scores. Specifically, whereas some studies have found associations only between inflammation and individual symptoms (10,12), others also found associations between proteins and depression sum scores (7). Critically, however, depression sum scores and individual symptoms have always been tested as outcomes of

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inflammatory proteins in separate models. This precludes falsifiability of whether inflammation is associated with depression or individual symptoms when accounting for the other. Furthermore, it does not account for the possibility that inflammation might be simultaneously and uniquely associated with depression generally as well as individual symptoms in a hierarchical inflammatory phenotype.

Thus, there are 2 related levels for which inflammation may be associated with depression. Understanding at which level inflammation–depression associations exist has numerous applied implications for immunopsychiatry. First, it is critical to inform treatment planning and determine whether adjunctive anti-inflammatory treatments might improve depression broadly or are likely to be symptom specific (13). Second, understanding the level at which inflammation is associated with behavior is critical to guide etiological theory (e.g., different mechanisms might explain why inflammation is associated with depression generally vs. individual symptoms such as appetite change). Third, it could guide research methodology (e.g., selection of measures including key symptoms and analytic strategies).

To address these issues, we used an applied measurement technique—namely, moderated nonlinear factor analysis (MNLFA) (14)—to simultaneously examine how CRP was related to both latent depression and individual depression symptoms. These models can also test the extent to which the association between the latent depression score and manifestation of specific symptoms (i.e., factor loadings) differed as a function of CRP. Unlike prior studies, this technique directly tests whether CRP is associated with individual symptoms and/or latent depression when accounting for one another. Based on prior symptom-level research using CRP and the depression measure used in this study (Patient Health Questionnaire [PHQ]-9) (8), we hypothesized that CRP would be specifically associated with levels of reported appetite and fatigue but no other individual symptoms. Additionally, we explored whether CRP would be associated with latent depression or how symptoms reflect the latent depression construct (i.e., the factor loadings) above and beyond the CRP and individual symptom relations.

METHODS AND MATERIALS

Participants and Procedures

This study used data from 5 NHANES (National Health and Nutrition Examination Survey) samples (NHANES 2005–2006, 2007–2008, 2009–2010, 2015–2016, 2017–2020). These cohorts were selected because they all included CRP and the PHQ-9. The NHANES samples are nationally representative community samples of the United States and are designed by the National Center of Health Statistics at the Centers for Disease Control and Prevention to examine a wide variety of physical and mental health constructs in the United States. The National Center of Health Statistics oversaw all data collection and approved the NHANES study protocol [for details about the survey designs and methodologies, see (15–17)]. CRP and depression measurements were completed on the same day. Participants who either did not have a CRP sample taken or had >50% item missingness on the PHQ-9 were removed. Of the 27,739 participants with CRP and PHQ-9 data, only 9 had >50% item missingness on the PHQ-9. Thus, the analytic sample size across all 5 cohorts was 27,730 adults. Descriptive statistics are reported in Table 1. Cohorts were analyzed separately because 1) they did not need to be aggregated to improve power given their large sizes, 2) this allowed for internal replication, and 3) it facilitated investigation of whether cohort effects/changes in CRP collection/assay methodology (detailed below) might have influenced results.

Measures

Depression Criteria. The PHQ-9 (18) is a 9-item self-report measure that was administered to assess the frequency of 9 DSM-IV diagnostic criteria during the past 2 weeks, including 1 additional item to assess impairment due to symptoms. The 9 items measuring symptoms were used in analyses (see Table 2 for wording). Participants were asked to rate each item using a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). Diagnostic interview data were not available, but meta-analyses suggest a clinical cutoff of 8 to 11 (19). The proportion of cases exceeding these scores, and those reporting impairment due to depression symptoms, is presented in Table 1.

C-Reactive Protein. Blood was drawn via venipuncture and assayed for CRP. Specimens were frozen at −70 °C until the day of the assay. Some methodological details differed between cohorts. NHANES 2005–2006, 2007–2008, and 2009–2010 quantified CRP by latex-enhanced nephelometry using a Behring Nephelometer. Samples were diluted and quantities were calculated using a calibration curve. The lower limit of detection (LLOD) was 0.02 mg/dL (lower values were set at 0.01 mg/dL). CRP samples in NHANES 2015–2016 were assayed using the SYNCHRON System(s) High Sensitivity C-Reactive Protein reagent (Beckman Coulter). The system portioned out 1-part sample to 26-parts reagent into a cuvette and monitored change in absorbance at 940 nm. This change is proportional to the concentration of CRP and is used to calculate the concentration based on a single-point–adjusted, predetermined calibration curve. There was a change in laboratory equipment during the 2015–2016 survey cycle from the Beckman Coulter UniCel DxC 600 Synchron chemistry analyzer to the Beckman Coulter UniCel DxC 600i Synchron chemistry analyzer. An internal comparison study by NHANES staff indicated no statistical adjustment was required to correct this change. Samples were estimated singly as part of a Multi-analyte Biochemistry Panel. LLOD for CRP was 0.11 mg/L. Values lower than this were set to 0.08 mg/L (determined by the formula LLOD/sqrt [2]). Samples in the 2017–2020 cohort were analyzed with the Roche Cobas 6000 chemistry analyzer. LLOD was 0.15 mg/L, with levels below this value set to 0.11 mg/L per the same calculation as the 2015–2016 cohort. More detailed information can be found in the CRP-specific PDF on the laboratory methods section of the NHANES website.

Covariates. In sensitivity analyses, we covaried for demographic characteristics that are related to differences in both CRP and depression [i.e., potential confounders, specifically gender (20,21), age (22,23), disease burden (23,24), race

Table 1. Summary of Characteristics From NHANES Samples

Variable	2005–2006, *n* = 4629	2007–2008, *n* = 5180	2009–2010, *n* = 5351	2015–2016, *n* = 4876	2017–2020, *n* = 7694
Depression Score	2.75 (3.78) [0–27]	3.31 (4.30) [0–27]	3.36 (4.36) [0–27]	3.30 (4.28) [0–27]	3.30 (4.27) [0–27]
% Above Clinical Cutoffs	237–464 (5%–10%)	301–716 (8%–14%)	427–740 (8%–14%)	330–625 (7%–13%)	563–1081 (7%–14%)
Impairment From Depression	807 (17%)	977 (19%)	1062 (20%)	784 (16%)	1349 (18%)
Age, Years	44.33 (19.17) [18–84]	47.27 (17.31) [18–79]	46.02 (17.18) [18–79]	46.52 (17.15) [18–79]	47.44 (17.07) [18–79]
Gender, Female	2391 (52%)	2603 (50%)	2683 (50%)	2486 (51%)	3913 (51%)
Race/Ethnicity					
Mexican American	987 (21%)	928 (18%)	1016 (19%)	900 (19%)	948 (12%)
Non-Hispanic Black	1076 (23%)	1004 (19%)	914 (17%)	1003 (21%)	1927 (25%)
Non-Hispanic White	2258 (49%)	2466 (48%)	2612 (49%)	1642 (34%)	2786 (36%)
Other Hispanic	138 (3%)	594 (12%)	545 (10%)	631 (13%)	794 (10%)
Other[a]	170 (4%)	188 (4%)	264 (5%)	700 (14%)	1239 (16%)

Values are presented as mean (SD) [range] for continuous variables or *n* (%) for categorical variables. Apparent discrepancies between the analytic *n* and the percentage associated with these frequencies is due to missing data at the variable level.

NHANES, National Health and Nutrition Examination Survey.

[a]"Other" includes participants of other races and multiracial participants.

(21,25), and socioeconomic status (26,27)]. Female gender was the reference group. Due to concerns about confidentiality, participants ages ≥85 years are coded as "85" in NHANES 2005–2006. This threshold was changed to "80" in the other cohorts. Cases at these thresholds were retained in the dataset, but the value for age was deleted because it is impossible to determine participants' true age. Disease burden (Table S1) was operationalized as the sum of chronic illnesses and major medical events. History of disease was asked for all diagnoses except for current asthma, liver condition, thyroid condition, or anemia treatment in the past 3 months. Race/ethnicity categories were "Non-Hispanic White" (reference group), "Mexican American," "Other Hispanic," "Non-Hispanic Black," and "Other Race-Including Multiracial." Socioeconomic status was measured by the ratio of family income to the poverty threshold (poverty income ratio). Poverty income ratio values > 5 in the NHANES are set to 5 to protect confidentiality. Some common control variables in immunopsychiatry studies were not included because of the cross-sectional data (resulting in an inability to model temporal, directed effects) and evidence that one of the focal variables (i.e., CRP or depression) might mediate the effects of the potential covariate [e.g., body mass index (28)] on the other focal variable, which would reduce estimate precision for the effects of interest (29).

Table 2. Item Descriptions

Term	Description
Sad	"Feeling down, depressed or hopeless"
Anhedonia	"Have little interest in doing things"
Sleep Problems	"Trouble sleeping or sleeping too much"
Fatigue	"Feeling tired or having little energy"
Appetite Changes	"Poor appetite or overeating"
Psychomotor Changes	"Moving or speaking slowly or too fast"
Difficulty Concentrating	"Trouble concentrating on things"
Feels Bad About Self	"Feeling bad about oneself"
Thoughts of Death	"Thought you would be better off dead"

Statistical Analyses

Models were estimated in Mplus 8 (30), and model execution and result summaries were facilitated using the MplusAutomation package (31) in R 3.6.2 (32). Initial models fit single factor confirmatory factor analyses to the PHQ-9 using the robust weighted least squares mean and variance adjusted estimator (WLSMV) (33). The comparative fit index (CFI) (34) and root-mean-square error of approximation (RMSEA) (35) were used to evaluate model fit. We report χ^2 values for completeness, but this metric is typically oversensitive at the sample sizes used here (36). According to conventional standards, excellent fit is indicated by CFI ≥ 0.95 and RMSEA values ≤ 0.05; acceptable fit is indicated by CFI > 0.90 and RMSEA = 0.05–0.10. MNLFA were estimated using maximum likelihood with robust standard errors (MLR). Data were not imputed because it was unnecessary from a power perspective, and the MLR estimator is capable of handling missing data. Symptom-specific MNLFA models simultaneously tested CRP as a predictor of 1) an individual symptom, 2) the factor loading of that symptom onto latent depression, and 3) latent depression. Our in-text reported MNLFAs were estimated without covariates (models with covariates are described in the tables in the Supplement). CRP and covariates were mean centered. All parameters were estimated at $\alpha = 0.05$. Code, data, and output can be found at https://osf.io/zm92u/.

RESULTS

Confirmatory Factor Analyses

Confirmatory factor analyses with the 9 depression items loading onto a single latent depression factor had acceptable-to-excellent fit across all samples according to the CFI and RMSEA (Table 3).

Moderated Nonlinear Factor Analyses

Results are listed in Table 4. Higher CRP levels were associated with higher latent depression in all models (range of average *r*s = 0.044–0.089, *p*s = .002–<.001). Higher CRP levels

Table 3. Fit Statistics of Different Models

NHANES Sample	*n*	χ^2 (*df*)	*p*	CFI	RMSEA	90% CI RMSEA
2017–2020	7694	810.480 (27)	<.001	0.979	0.061	0.058–0.065
2015–2016	4876	475.951 (27)	<.001	0.979	0.058	0.054–0.063
2009–2010	5351	548.060 (27)	<.001	0.980	0.060	0.056–0.064
2007–2008	5180	417.667 (27)	<.001	0.983	0.056	0.052–0.061
2005–2006	4629	406.621 (27)	<.001	0.980	0.055	0.050–0.060

CFI, comparative fit index; NHANES, National Health and Nutrition Examination Survey; RMSEA, root-mean-square error of approximation.

were associated with greater untypical appetite in 4 of the 5 cohorts (*r*s = 0.031–0.049, *p*s = .007–.001 in significant models). In the same 4 cohorts, higher CRP levels also were associated with greater fatigue (*r*s = 0.030–0.054, *p*s = .029–< .001 in significant models). The next most consistent item-level association was psychomotor changes; however, this was only found in 2 cohorts, and the *p* values were never <.01 (unlike the appetite and fatigue findings). Thus, the evidence that CRP is uniquely associated with psychomotor changes is not strong. These findings were largely consistent with covariates included (Table S2). CRP was not a consistent predictor of factor loadings (Table S3).

DISCUSSION

In recent years, researchers have questioned the extent to which inflammation is associated with specific symptoms of depression versus depression more broadly (37,38). Studies investigating this question have examined how inflammatory proteins are related to individual symptoms versus broad depression composites/diagnoses in separate models. However, this fails to consider that both possibilities might be true. Furthermore, failing to simultaneously model inflammation–depression and inflammation–symptom associations precludes falsification of theories that inflammation is specifically associated with individual symptoms. To address these critical issues, we tested both conceptualizations in the same model. We found that higher CRP levels were consistently and uniquely associated with higher levels of a latent depression factor, greater endorsement of untypical appetite, and more fatigue across most cohorts in a hierarchical phenotype. Therefore, it appears as though CRP is associated with depression broadly, inasmuch as depression is reflected by each of the 9 symptoms. At the same time, however, CRP appears to be specifically associated with fatigue and appetite independent of its relation to depression as a whole. Moreover, these results were largely robust while adjusting for gender, age, disease burden, race, and socioeconomic status. In addition to the substantive and methodological implications of these results described below, finding that CRP is simultaneously related to both latent depression and individual symptoms underscores the importance of simultaneously testing multiple levels of measurement in phenotyping research to facilitate the falsifiability of hypotheses regarding the granularity of associations.

It is important to highlight that because these CRP–latent depression and CRP–symptom associations were robust to one another, they reflect unique ways that CRP is associated with psychopathology. It is important to consider that the mechanisms underlying the CRP–latent depression and CRP–symptom relations might differ in nature and directionality. For example, depression is associated with impairment across a variety of life domains [e.g., interpersonal dysfunction, impaired academic and work performance (39)] and lifestyle characteristics [e.g., increased substance use (39), poor diet (40)]. Increases in impairment/distress or immune-modulating lifestyle changes could mediate the association between latent depression and inflammatory biology. Furthermore, individuals with depression have shown a decreased ability to regulate inflammatory stress reactivity (41). Consequently, this depression-associated acute dysregulation might contribute to abnormalities in inflammatory profiles.

Research linking inflammatory activity to changes in appetite and fatigue suggests different mechanistic pathways. Both symptoms are well-established sickness behaviors in animal models of depression (42) and are believed to conserve

Table 4. Latent + Symptom-Level Relations With CRP

NHANES Sample	*n*	Latent Dep.[a]	Anhedonia	Appetite	Conc.	Death	Fatigue	Feels Bad	Motor	Sad	Sleep
2017–2020	7694	*r* = 0.065 *p* < .001[b]	*r* = 0.004 *p* = .731	*r* = 0.031 *p* = .007 [b]	*r* = −0.006 *p* = .600	*r* = −0.015 *p* = .187	*r* = 0.051 *p* < .001[b]	*r* = −0.026 *p* = .022[b]	*r* = −0.009 *p* = .419	*r* = −0.023 *p* = .042[b]	*r* = 0.011 *p* = .356
2015–2016	4876	*r* = 0.089 *p* <.001[b]	*r* = −0.024 *p* = .092	*r* = 0.049 *p* = .001[b]	*r* = −0.033 *p* = .023[b]	*r* = −0.011 *p* = .425	*r* = 0.054 *p* < .001[b]	*r* = −0.006 *p* = .680	*r* = 0.010 *p* = .488	*r* = −0.002 *p* = .889	*r* = −0.004 *p* = .762
2009–2010	5351	*r* = 0.044 *p* = .002[b]	*r* = 0.011 *p* = .432	*r* = 0.045 *p* = .001[b]	*r* = −0.029 *p* = .034[b]	*r* = −0.008 *p* = .536	*r* = 0.030 *p* = .029[b]	*r* = −0.005 *p* = .734	*r* = −0.034 *p*= .014[b]	*r* = −0.023 *p* = .095	*r* = −0.008 *p* = .567
2007–2008	5180	*r* = 0.066 *p* < .001[b]	*r* = 0.034 *p* = .015[b]	*r* = 0.040 *p* = .004[b]	*r* = −0.009 *p* = .519	*r* = 0.012 *p* = .391	*r* = 0.033 *p* = .016[b]	*r* = −0.019 *p* = .169	*r* = −0.014 *p* = .302	*r* = −0.022 *p* = .110	*r* = 0.000 *p* = .976
2005–2006	4629	*r* = 0.067 *p* < .001[b]	*r* = −0.006 *p* = .668	*r* = 0.011 *p* = .438	*r* = −0.010 *p* = .482	*r* = −0.008 *p* = .596	*r* = 0.022 *p* = .130	*r* = −0.021 *p* = .162	*r* = 0.032 *p*= .032[b]	*r* = −0.028 *p* = .057	*r* = 0.036 *p* = .015[b]

CRP, C-reactive protein; Conc., difficulties concentrating; Dep, depression; NHANES, National Health and Nutrition Examination Survey; *r*, converted correlation coefficient.

[a]Statistics for "Latent Dep." represent mean results across all 9 item-level models.

[b]Indicates significant results.

physical resources to help promote recovery from illness or injury. Consistent with these models, experimental administration of an inflammatory challenge by lipopolysaccharide injection has been shown to cause fatigue in mice (43). Additionally, inflammation has been associated with both increases (10,44–46) and decreases (47,48) in appetite, although most research suggests that inflammation is associated with greater appetite in the context of depression. Future research should consider potential moderators that might influence whether inflammation is associated with increased or decreased appetite. For example, it has been posited that hypothalamic-pituitary-adrenal axis and corticotropin-releasing factor abnormalities might moderate the inflammation-appetite association in depression (49). To maximize the clinical relevance of this work, it is imperative that future research explores whether the unique associations between inflammatory biology and 1) latent depression and 2) individual symptoms are attributable to the same mechanisms.

In addition to these etiological and clinical implications, the finding that CRP is consistently and robustly associated with specific symptoms beyond the influences of the latent depression factors has implications for research methodology. Specifically, given higher levels of CRP, there are higher expected values of fatigue and appetite problems, holding depression levels equal. In other words, individuals with higher CRP levels are likely to have depression scores biased toward elevated levels of untypical appetite or fatigue relative to those with lower CRP levels but identical depression scores. Therefore, there are possible systematic biases in depression severity and observed scores for depression in what is described as scalar noninvariance [for a more thorough overview of measurement noninvariance as a function of biological phenotypes of psychopathology, see (50); for an overview on adjusting analytic models to account for noninvariance, see (51)]. Consequently, standard analytic approaches involving mean comparison (but not rank-order comparison) in immunopsychiatry may not be ideal. However, given that this bias was seen in only 2 of the 9 symptoms and that effect sizes were small, this is likely not a hugely influential issue for CRP and the PHQ-9. It is worth noting that while small, the effect sizes observed in this study are larger than the average effect sizes found in a recent meta-analysis (52), highlighting the possibility that structural equation modeling's ability to correct for measurement error might deattenuate downward-biased effect sizes resulting from unreliable measures (53,54). Furthermore, if CRP is truly a unique predictor of both latent depression (i.e., the variance shared among depression symptoms) and individual symptoms, larger effect sizes might be the result of selecting a model that more closely matches the naturally occurring relations (resulting in less error). Moreover, small effect sizes could be clinically meaningful over time given the bidirectional, cumulative effects between inflammatory biology and depression (55).

This study also highlights that future immunopsychiatric research should test multiple levels of depression (e.g., sum scores, subscales, individual symptoms) to fully characterize the relations between the immune system and psychopathology (56). Ideally, this would involve models that simultaneously test the associations between immune biology and psychopathology at multiple levels of measurement to facilitate falsifiability of theories about what levels of depression are associated with immune processes.

One critical consideration is whether physicians and researchers should consider whether these symptom-level biases may be particularly important to account for in depression diagnosis in medical populations characterized by high CRP levels (e.g., potentially reflective of an immunometabolic subtype that might be particularly responsive to adjunctive anti-inflammatory treatments). Specifically, it is plausible that individuals with immunometabolic depression might report fewer total symptoms but have notably elevated neurovegetative, relative to other, symptoms.

This study has several strengths. First, this study used a novel and sophisticated analytic approach that is well suited to comprehensive phenotyping research that provides substantive and methodological insights. Second, the data consisted of 5 large, independent cohorts. In addition to high statistical power for individual models, this feature facilitated repeated internal replication. Furthermore, given that data collection for these cohorts spanned 15 years, this internal replication was able to rule out potential cohort effects. Additionally, consistent results despite equipment change for CRP measurement highlight that the primary findings were not sensitive to technological updates. Finally, despite its limitations (described below), the popularity of the PHQ-9 in epidemiological research and clinical work increases the relevance of this work.

Several limitations also should be noted. Most importantly, the PHQ-9 includes items assessing both extremes of a given symptom (i.e., double-barreled), including increased or decreased appetite and both psychomotor agitation and retardation; therefore, it is unclear from this study if CRP is only related to one extreme of these symptoms. Of note, the items measuring psychomotor difficulties (which were significantly associated with CRP in 4 of 10 models [including supplementary analyses] and replicated across 2 cohorts) were double barreled. If CRP is specifically associated with psychomotor agitation or slowing, the discrepancies between cohorts for this item might be attributable to different participants endorsing this item for different reasons. Relatedly, many depression symptoms are multifaceted and not thoroughly assessed using the PHQ-9. A more thorough depression measure might capture additional nuance of the associations between the immune system and depression. Some NHANES cohorts use the Composite International Diagnostic Interview (CIDI), which does not include some of the weaknesses described above, to measure depression; however, these data were determined unsuitable for this project for several key reasons. Importantly, the CIDI uses skip-logic to only ask about "B-Criterion" if participants endorse "A-Criterion." Thus, use of the CIDI would no longer test CRP–symptom associations; rather, it would test the association between CRP and B-Criterion conditional on the presence of A-Criterion. Furthermore, this would substantially reduce sample size to the point that these analyses would be underpowered (e.g., of 778 participants who completed the CIDI in 1999–2000, only 109 had data on change in appetite). Finally, unlike the PHQ-9 (which asks about symptoms over the past 2 weeks), the CIDI asked about symptoms at any point in the past year, not current depression at the time of the blood draw.

Therefore, although the interview was administered at the same time as the blood draw, there could be substantial differences in the time between the endorsed symptoms and CRP measurement. This would be a severe limitation given the temporal specificity [the degree to which the association between variables changes across time (53)] in the relation between immune measurement and depression (20,57). Finally, although CRP is arguably the most widely used inflammatory protein in depression research, a dataset with additional inflammatory proteins is needed to facilitate the comparison of these results to those involving other proteins. Furthermore, given the plethora of proteins involved in inflammation, it is plausible that the small effect sizes observed in this study might underestimate the relation between inflammation and depression more broadly.

Some might consider the population-based samples (instead of clinical samples) in this study as a weakness. However, individuals with subthreshold depression still report impairment (58) and can benefit from treatment (59), underscoring the clinical value of work in this population. Additionally, prior research suggests that attempts to characterize inflammatory phenotypes of depression replicate well between clinically enriched samples [e.g., NESDA (7)] and population-based samples [e.g., NHANES (8)], suggesting that these relations are not moderated by clinical status. Finally, each cohort had hundreds of (and one had more than 1000) cases above meta-analytic clinical cutoffs on the PHQ-9, suggesting that individuals with clinically diagnosable depression were well represented in these datasets.

Conclusions

In conclusion, this study advances research on inflammation and depression by demonstrating that CRP has small but robust associations with latent depression as well as untypical appetite and fatigue across 5 cohorts and 27,730 participants. Moreover, these results persisted while adjusting for covariates. These findings suggest that inflammatory biology is associated both with depression as a latent construct and with untypical appetite and fatigue in what we describe as a hierarchical inflammatory phenotype of depression. In addition to these etiological and theoretical contributions, these results also indicate that the PHQ-9, a commonly used measure of depression, may have biased scores in individuals with higher levels of CRP. Diagnostically, results suggest that depression in medical populations with elevated CRP levels might be biased toward neurovegetative symptoms (even if other symptoms are less strongly/frequently endorsed) and might be particularly responsive to targeting inflammation.

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