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Systemic low-grade inflammation associated with specific depressive symptoms: insights from network analyses of five independent NHANES samples

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To the editor:

Major depressive disorder (MDD) is a heterogeneous disorder with varying symptom presentations and underlying biological mechanisms.[1] The mainstream neurobiological hypotheses of depression involve monoamine neurotransmitters, hypothalamic–pituitary–adrenal axis, immune-inflammation and the glutamate system.[1] Numerous meta-analyses have reported that patients with MDD have a higher level of peripheral and cerebrospinal inflammatory markers, including C- reactive protein (CRP), interleukin 1beta (IL-1β), IL-6 and tumour necrosis factor-alpha (TNF-α).[2 3] CRP, as an acute marker of reactant, is the most well-studied biomarker of MDD; numerous investigations revealed that elevated CRP was linked to core symptoms of MDD, including increased depressive mood[4] and greater anhedonia.[5] Several studies also have discovered links between CRP and cognitive symptoms (eg, difficulty concentrating)[6] and suicidal behaviours.[7] Moreover, CRP is more commonly reported in association with neurovegetative symptoms, including fatigue or loss of energy, changes in appetite and sleep problems.[6] The association between CRP and specific symptoms remains unknown; uncovering specific symptoms driven by CRP could help identify the possible inflammatory subtypes of depression to pave the way for more specific anti-inflammatory treatments.

PARTICIPANTS

The data for this secondary analysis was derived from five National Health and Nutrition Examination Survey (NHANES) samples (2005–2006, 2007–2008, 2009–2010, 2015–2016 and 2017–2020). NHANES encompasses nationally representative community samples within the USA, and the surveys are designed to examine the nutritional status and physical and mental health. NHANES has been conducting ongoing 2-year cycles of surveys of a representative, stratified, multistage probability sample of the US population since 1999. Each wave of surveys recruits a different set of participants. Those who were chosen and consented to participate completed a computer-assisted interview done in their homes by trained staff. Following the home interview, all tests (including the blood draw) and additional interviews (including the assessment of depressive symptoms) were carried out at mobile examination centres.

The five NHANES samples had 56 565 subjects; those with incomplete CRP measurement, CRP levels ≥10 mg/L and incomplete Patient Health Questionnaire-9 (PHQ-9) assessment were excluded (see online supplemental figure 1). Finally, the sample size of this study across the five independent samples was 24 932 subjects.

DEPRESSIVE SYMPTOMS ASSESSMENT

The well-validated PHQ-9 is a self-report questionnaire with nine items and has a total score range of 0–27, with higher scores indicating more depressive symptoms.[8] The PHQ-9 was used to assess the frequency of nine Diagnostic and Statistical Manual of Mental Disorders-fourth edition depression diagnostic criteria over the past 2 weeks, each item using a 4-point Likert scale ranging from 0 (not at

all) to 3 (nearly every day). Specific information on the above nine symptoms is presented in the online supplemental table 1.

CRP MEASUREMENT

The CRP measurement and PHQ-9 assessment were finished on the same day. The serum levels of CRP in the NHANES 2005–2006, 2007–2008 and 2009–2010 samples were measured via latex-enhanced nephelometry using a Behring Nephelometer. The NHANES 2015–2016 sample detected CRP levels using the SYNCHRON System (s) High Sensitivity C-Reactive Protein reagent (Beckman Coulter). The CRP level of the NHANES 2017–2020 sample was detected with the Roche Cobas 6000 chemistry analyser. More details of the CRP measurements are presented in the online supplemental materials.

DATA ANALYSIS

This study used principal component analysis as a visual tool to detect the batch effect using a global normalisation and dimension reduction method. The relationship between depressive symptoms and CRP was examined by Spearman correlation using the R-package *ggcor*. To assess the robust relationship between CRP and specific depressive symptoms across the five NHANES samples, network analyses were used to estimate these unique relations. We performed network analyses with Gaussian graphical models using the R-package *mgm*. More details of the batch effect and network analysis are presented in the online supplemental materials.

SAMPLE CHARACTERISTICS

The final samples of five NHANES independent data sets included 24 932 participants (table 1); 49.2% were women and the mean age of the total samples was 48.0 (18.8) years, the mean (standard deviation (SD)) body mass index (BMI) was 28.6 (6.4), 42.0% of participants had not worked in the week before enrolment. Only 2.2% of participants were in poor general health. The race/ethnicity distribution of total samples was 42.7% non-Hispanic, 20.7% non-Hispanic black, 17.1% Mexican American, 9.8% other Hispanic and 9.6% other race. Moreover, the median total score of PHQ-9 in five samples was 2.

THE BATCH EFFECT

Given that the data of the five data sets were well clustered together, and none of the data sets was found to deviate from the others (see online supplemental figure 2A), we did not find the presence of the batch effect. Therefore, we could combine data from different years for further correlation and network analyses.

CORRELATION ANALYSES

The CRP level was positively related to all nine depressive symptoms of PHQ-9 (r=0.02–0.08, all p<0.05), especially for fatigue (r=0.08, p<0.001) and appetite changes (r=0.08, p<0.001) (see online supplemental figure 2B). Among nine symptoms, depressive mood and low self-esteem had the strongest correlation (r=0.56, p<0.001), followed by the correlation between fatigue and sleep problems (r=0.47, p<0.001).

NETWORK ANALYSES

Figure 1 displays the network between nine depressive symptoms and CRP with gender, age and race as covariates across five independent samples and total samples (figure 1A–F). The CRP showed a weak but consistent edge with fatigue even after adjusting covariates (figure 1G). We found CRP shared edges with anhedonia, sleep problems and appetite changes in some samples but not all five. Moreover, we found that CRP was consistently associated with age and gender across different samples but not for race (figure 1G). Furthermore, among the nine symptoms, depressive mood, low self-esteem and thoughts of death still had the strongest association with each other.

However, the highest predictability estimates of nodes in different networks were not depressive mood or fatigue. The highest predictability estimates for other networks were sleep problems (including NHANES total samples, 2007–2008, 2009–2010, 2017–2020) and anhedonia (including NHANES 2005–2006, 2015–2016). The predictability of CRP was increased (3.4%–5.9%) in the adjusted networks but still shared a slight variance with other variables.

CONCLUSION

This study proposes that CRP level was associated with specific depressive symptoms, and our findings indicate a consistent and significant relationship between CRP and fatigue across five independent samples as well as the total samples. However, the evidence does not support a similar association between CRP and anhedonia, sleep problems or appetite changes. This study provides insights into the possible inflammation-related depressive phenotype and may guide the identification of the inflammatory subtypes of depression, which would enhance individualised treatment.

This study highlights that CRP was consistently and robustly associated with a particular neurovegetative symptom: fatigue rather than broad emotional or neurocognitive symptoms. The result was consistent with previous studies, showing a stable relationship between CRP and fatigue. The pooled analysis of 15 population-based cohorts with 56 351 adults demonstrated that a higher level of CRP was reliably associated with the loss of energy.[9] Furthermore, a longitudinal study illustrated that baseline CRP levels could predict fatigue 5 years later;

Table 1 Summary of characteristics from five National Health and Nutrition Examination Survey samples

	All five samples	2017–2020	2015–2016	2009–2010	2007–2008	2005–2006
	n=24 932	n=7053	n=4388	n=4814	n=4620	n=4057
Gender, female	12 264 (49.2)	3488 (49.5)	2163 (49.3)	2349 (48.8)	2255 (48.8)	2009 (49.5)
Age (years)	48.0 (18.8)	49.2 (18.4)	48.4 (18.5)	47.7 (18.5)	48.9 (18.6)	44.8 (19.9)
Age (stratification)						
18 ≤age < 40	9230 (37.0)	2394 (33.9)	1589 (36.2)	1766 (36.7)	1654 (35.8)	1827 (45.0)
40 ≤age < 60	7678 (30.8)	2225 (31.5)	1362 (31.0)	1562 (32.4)	1405 (30.4)	1124 (27.7)
Age ≥60	8024 (32.2)	2434 (34.5)	1437 (32.7)	1486 (30.9)	1561 (33.8)	1106 (27.3)
BMI (kg/m^2)	28.6 (6.4)	29.4 (6.9)	28.9 (6.5)	28.5 (6.2)	28.3 (6.1)	28.0 (6.1)
Occupation						
Working in last week*	14 443 (57.9)	4154 (58.9)	2571 (58.6)	2679 (55.7)	2606 (56.4)	2433 (60.0)
Not working in last week†	10 475 (42.0)	2897 (41.1)	1807 (41.2)	2134 (44.3)	2013 (43.6)	1624 (40.0)
Missing	14 (0.1)	2 (<0.1)	10 (0.2)	1 (<0.1)	1 (<0.1)	0
General health condition						
Excellent	1772 (7.1)	0 (0.0)	394 (9.0)	477 (9.9)	466 (10.1)	435 (10.7)
Very good	5052 (20.3)	0 (0.0)	1149 (26.2)	1332 (27.7)	1309 (28.3)	1262 (31.1)
Good	7174 (28.8)	0 (0.0)	1830 (41.7)	1899 (39.4)	1849 (40.0)	1596 (39.3)
Fair	3336 (13.4)	0 (0.0)	882 (20.1)	933 (19.4)	840 (18.2)	681 (16.8)
Poor	544 (2.2)	0 (0.0)	133 (3.0)	172 (3.6)	156 (3.4)	83 (2.0)
Missing	7054 (28.3)	7053 (100.0)	0 (0.0)	1 (< 0.1)	0 (0.0)	0 (0.0)
Race/ethnicity						
Mexican American	4273 (17.1)	870 (12.3)	816 (18.6)	910 (18.9)	820 (17.7)	857 (21.1)
Other Hispanic	2450 (9.8)	736 (10.4)	566 (12.9)	487 (10.1)	530 (11.5)	131 (3.2)
Non-Hispanic white	10 646 (42.7)	2555 (36.2)	1498 (34.1)	2373 (49.3)	2228 (48.2)	1992 (49.1)
Non-Hispanic black	5159 (20.7)	1719 (24.4)	852 (19.4)	796 (16.5)	870 (18.8)	922 (22.7)
Other race	2404 (9.6)	1173 (16.6)	656 (14.9)	248 (5.2)	172 (3.7)	155 (3.8)
CRP (mg/L)‡	1.7 (0.7–3.5)	1.7 (0.8–3.6)	1.6 (0.6–3.5)	1.6 (0.6–3.3)	1.7 (0.7–3.4)	1.7 (0.7–3.8)
PHQ-9 total score‡	2 (0–4)	2 (0–5)	2 (0–4)	2 (0–5)	2 (0–4)	2 (1–4)

Values of other variables except CRP and PHQ-9 were presented as a number (n) with percentage (%) or mean (standard deviation, SD).
*Working in last week: including two situations: (1) working at a job or business; (2) with a job or business but not at work.
†Not working in last week: including two situations: (1) looking for work; (2) not working at a job or business.
‡Values were presented as median (interquartile range).
BMI, body mass index; CRP, C-reactive protein; PHQ-9, Patient Health Questionnaire-9.

the association remained even after adjusting for a series of known risk factors.[10] This study also indicated that the relationship between CRP and fatigue was bidirectional: baseline fatigue can predict CRP at a 5-year follow-up.[10]

In this study, CRP was not consistently associated with anhedonia, sleep problems and appetite changes across five samples. We speculate that fatigue is the core symptom mediating the relationship between CRP and the inflammatory phenotype rather than sleep problems and appetite changes. Moreover, we consistently found that anhedonia, sleep problems and appetite changes were more closely associated with fatigue than other symptoms, especially for sleep problems. Our findings confirm the sickness behaviour theory, which proposes that peripheral inflammation can trigger a cascade of initially adaptive behaviours, such as anhedonia, fatigue, sleep problems and appetite changes. Further research is needed to dissect the interplay among sickness behaviours, which may underlie the inflammation-specific phenotypes.

This study has several strengths. First, this study has a large sample size with five independent samples to maximise generalisability, which offers higher statistical power for network analyses. Second, the data collection involved five time periods spanning 15 years; this study design could allow internal replication in different samples and periods, further confirming the robust relationship between CRP and fatigue. Third, we used a novel and intuitive statistical method to visualise the interactive relationship between the inflammatory marker and depressive

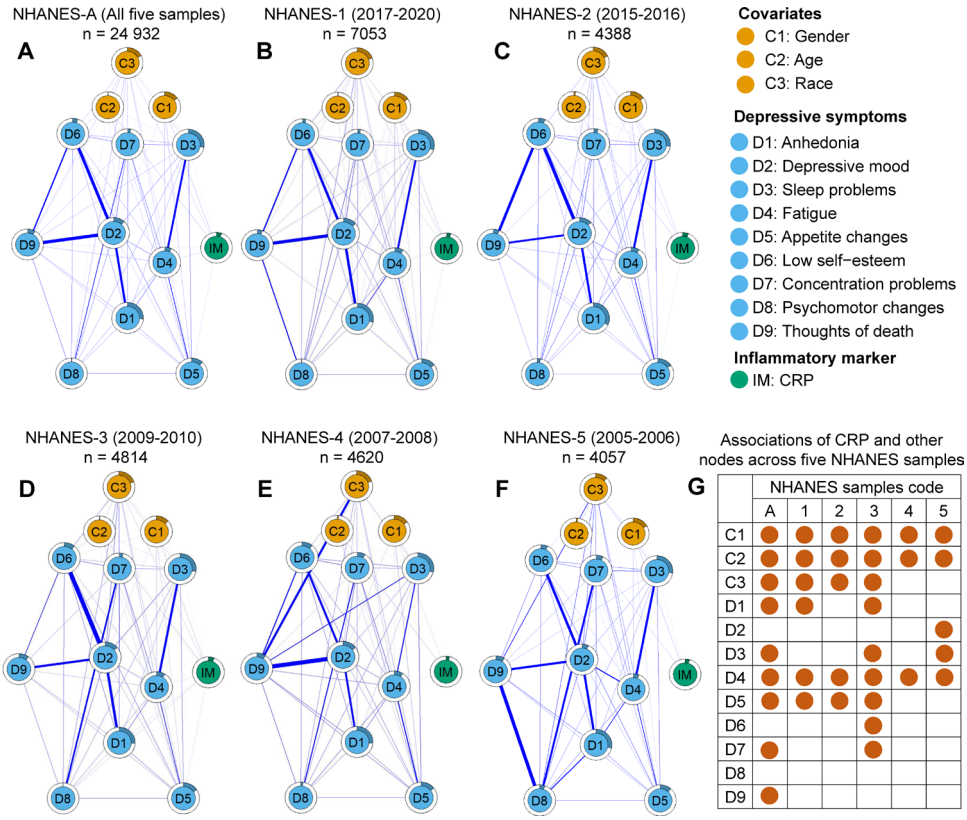

Figure 1 (A–F) Adjusted network analyses of nine depressive symptoms and CRP with covariates, including age, gender and race. (G) CRP shared an edge with other nodes across five NHANES samples. Orange circles represent a significant association of CRP with that symptom or covariate. Blue edges indicate positive partial correlations between nodes, and the darkened portions of the rings surrounding nodes show the portion of each node's variance that is explained by the nodes that connect with it. Additionally, thicker and more saturated edges represent stronger associations. CRP, C-reactive protein; NHANES, National Health and Nutrition Examination Survey.

symptoms. However, this study should be viewed in light of its limitations. First, it is impossible to identify the causal relationship between CRP and fatigue due to the nature of the cross-sectional design. Second, this study only used one item of PHQ-9 to measure fatigue, which does not adequately capture the nature of fatigue. Further studies need to adopt more comprehensive tools, such as the Multidimensional Fatigue Inventory,[11] to assess fatigue to reflect the specific domains related to inflammation. Third, we only used an inflammatory marker to reflect systemic inflammation. Although CRP is a reliable indicator of central and peripheral inflammation, not entirely representative of the complex immune-inflammation system, certain inflammatory markers may be associated with specific depressive symptoms. A large sample study observed a fascinating separation among inflammatory markers regarding their links with appetite; higher CRP levels were associated with an increased appetite while higher IL-6 levels decreased it.[12] Moreover, IL-1α and IL-1β are involved in the innate immune system, and a previous review article emphasised the vital role of IL-1α and IL-1β in the development of central fatigue.[13] Additionally, evidence from both human and animal studies indicates that TNF-α plays a crucial role in regulating the sleep and wakefulness system.[14] Fourth, the current study could not account for potential confounding factors due to missing data, such as BMI, smoking, chronic medical conditions and medications; these factors may mediate the relationship between CRP and fatigue.[15] Fifth, because the participants were derived from a nationally representative community without a clinical diagnosis of MDD, the generalisability of the findings for patients with MDD was hampered. The pattern of results needs to be confirmed in patients with MDD.

In summary, this study highlights that systematic inflammation is robustly associated with fatigue in five large and independent samples. Our findings confirm the sickness behaviour theory and reveal a specific rather than a generalised effect of inflammation on depressive symptoms. This study may help identify potential inflammatory subtypes of depression. More research is needed to determine if patients manifesting these subtypes are more responsive to anti-inflammatory treatments for depression.

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Contributors JL and HH conceived and coordinated the study, performed analyses and wrote the paper. Y-AS, JC, LC and TS revised the paper. All authors reviewed the results and approved the final version of the manuscript.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The NHANES study protocols were approved by the National Center for Health Statistics Research Ethics Review Board in accordance with the revised Declaration of Helsinki. Written informed consent was acquired by each subject. NCHS Ethics Review Board (ERB) Approval for NHANES 2017-2020 , 2015-2016 , 2009-2010 , 2007-2008 , 2005-2006 were Protocol #2018-01, Protocol #2011-17 and Protocol #2005-06. All participants gave informed consent before taking part.

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