

# Letters

## RESEARCH LETTER

### Inflammation and Specific Symptoms of Depression

Elevated levels of inflammatory markers, such as C-reactive protein, are well-documented in people with depression.<sup>1,2</sup> Raison and Miller<sup>3</sup> suggested that this association may, in fact, be symptom-specific. Higher levels of inflammation are particularly likely to underlie depression symptoms that characterize sickness behavior, including fatigue, reduced appetite, withdrawal, and inhibited motivation. From an evolutionary perspective, such symptoms have the beneficial effect of preserving energy resources for use in fighting infection and promoting healing processes.<sup>4,5</sup> Here, we tested the hypothesis that the association between C-reactive protein and depression is symptom-specific.

**Methods** | Data were collected from 3 cross-sectional studies: the US National Health and Nutrition Surveys of 2005-2006 (n = 4593), 2007-2008 (n = 5151), and 2009-2010 (n = 5327) that underwent National Center for Health Statistics institutional research ethics review board approval.<sup>6</sup> Written informed consent was obtained from all participants. We included all 15 071 participants with relevant data (mean age, 47.5 years; 50.1% female) whether or not they had specific symptoms of depression. C-reactive protein was measured using standard procedures (median, 2 mg/L; interquartile range, 0.8-4.7 mg/L; to convert to nanomoles per liter, multiply by 9.524).<sup>6</sup> C-reactive protein values were log-transformed and standardized (SD = 1). Depressive symptoms were assessed using the Depression Screener Questionnaire as part of computer-assisted personal interviews.<sup>6</sup> The 9 items of the

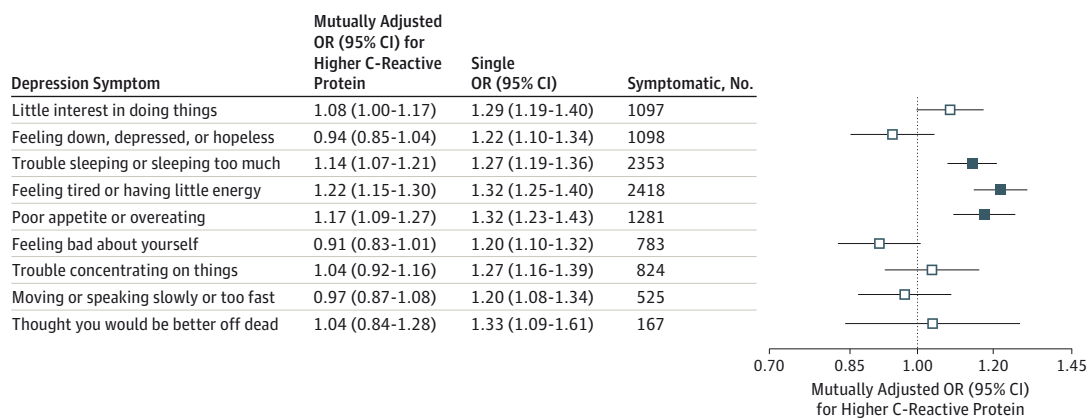
questionnaire are used to quantify how often the participant had been bothered by specific symptoms during the last 2 weeks, each self-rated on a 4-point scale (Figure). We coded the items as dichotomous variables with responses “More than half the days” and “Nearly every day” indicating the presence of the symptom.

This current cross-sectional survey study did not require institutional review board approval because the analysis involved existing and publicly available data without participant identifiers.

First, we examined associations between C-reactive protein and all depression items in separate models, adjusting for sex, age, and race/ethnicity (single associations). To assess independent associations with specific symptoms—which took into account the overlap between different depressive symptoms—we additionally adjusted these models for the sum of the remaining depression items (mutually adjusted associations). Across the 9 depression symptoms, the average Pearson correlation coefficient between individual symptoms and the sum of all the other depression symptoms was  $r = 0.60$  (range, 0.36-0.71). All analyses were first fitted separately in the 3 cohort studies using logistic regression analysis with appropriate sampling weights and then pooled together using fixed-effect meta-analysis.

**Results** | When not adjusted for the other depression symptoms, C-reactive protein was associated with all the specific depression symptoms (Figure). When these associations were adjusted for the other depression symptoms, independent associations were apparent only with sleep problems (odds ratio [OR], 1.14; 95% CI, 1.07-1.21), tiredness or lack of energy (OR,

Figure. Associations Between C-Reactive Protein and Depression Symptoms Pooled With Meta-analysis Across 3 US National Health and Nutrition Surveys Cohort Studies (N = 15 071)



Values are odds ratios (ORs) and their 95% CIs per 1-SD increase in log-transformed C-reactive protein. Filled squares denote statistically significant ORs ( $P < .05$ ) and empty squares statistically nonsignificant ORs. Single associations with depression symptoms are adjusted for age, sex, and race/ethnicity. Mutually adjusted associations are further adjusted for the sum of all the other depression symptoms besides the outcome symptom.

1.22; 95% CI, 1.15-1.30), and changes in appetite (OR, 1.17; 95% CI, 1.09-1.27) (Figure). The independent association with anhedonia was close to statistical significance ( $P = .06$ ). When C-reactive protein was categorized into quartiles, independent dose-response patterns were observed for sleeping problems (ORs of 1.29, 1.33, and 1.51 for the second, third, and fourth C-reactive protein quartiles, respectively, compared with the first;  $P < .001$ ), tiredness or lack of energy (ORs of 1.02, 1.32, and 1.68 for the second, third, and fourth quartiles, respectively;  $P < .001$ ), and changes in appetite (ORs of 1.18, 1.23, and 1.65 for the second, third, and fourth quartiles, respectively;  $P < .001$ ).

**Discussion** | Inflammation was associated with a range of depression symptoms, particularly with tiredness, lack of energy, sleep problems, and changes in appetite. These symptoms characterize sickness behaviors that are observed in people who are physically ill.<sup>4</sup> Inflammation was also associated with the cognitive and emotional symptoms of depression (eg, anhedonia, depressed mood, feelings of self-worth, concentration, and suicidal ideation); however, these associations were not independent of the other depression symptoms. This pattern of results is consistent with the evolutionary view linking inflammation and depression with pathogen host defense<sup>2</sup> because tiredness, lack of energy, and reduced appetite are primary characteristics of sickness behavior. Further research is needed to determine whether changes in inflammation predict changes in specific symptoms and to identify metabolic pathways that mediate such changes.

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*Study concept and design:* Jokela, Kivimäki.

*Acquisition, analysis, or interpretation of data:* All authors.

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1. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimäki M. Cumulative meta-analysis of interleukins 6 and 1 $\beta$ , tumour necrosis factor  $\alpha$  and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun*. 2015; 49:206-215.
2. Raison CL, Miller AH. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Mol Psychiatry*. 2013;18(1):15-37.
3. Miller AH, Raison CL. Are anti-inflammatory therapies viable treatments for psychiatric disorders? where the rubber meets the road. *JAMA Psychiatry*. 2015; 72(6):527-528.
4. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.
5. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*. 2012;37(1):137-162.
6. Centers for Disease Control and Prevention; National Center for Health Statistics. National Health and Nutrition Examination Survey. <http://www.cdc.gov/nchs/nhanes.htm>. Accessed July 1, 2015.

## COMMENT & RESPONSE

### Disseminating Justified, Well-Designed, and Well-Executed Studies Despite Nonsignificant Tests

**To the Editor** In her editorial<sup>1</sup> published in *JAMA Psychiatry*, Dr Kraemer gives important insights into using covariates, thereby adding to her large body of highly valuable publications.

Notably, she also stated, "Tests that are not statistically significant should be regarded as indicative of poorly justified, designed, or executed hypothesis-testing studies...."<sup>1</sup> This statement may trigger undesirable recommendations to scientists, reviewers, and editors. Most importantly, those deciding on dissemination of study results may be reluctant to report a statistically nonsignificant test if it is perceived as indicative of poorly justified, designed, or executed (PJDE) methodology, which would impair scientific dissemination and the validity of meta-analytic findings. Therefore, and in line with recent recommendations to reduce dissemination bias,<sup>2</sup> we would like to reflect on this statement.

Dr Kraemer's statement questions current research conventions. Most importantly, considering nonsignificance as a logical consequence of PJDE methods rather than a credible result would disestablish the classic hypothesis-testing approach. Moreover, the statement challenges, for example, the usefulness of noninferiority or equivalence trials<sup>3</sup> that aim to provide evidence for noninferiority or similarity by statistically nonsignificant results if sufficiently precise.

We agree with Dr Kraemer that statistically nonsignificant tests cannot be regarded as proof of the null hypothesis and share further positions proposing that inferential frameworks other than null hypothesis testing have advantages<sup>3,4</sup>; however, as yet, available data do not support the view that statistical nonsignificance would be related per se to lower study quality.<sup>5</sup> Further, whether nonsignificance is a useful indicator for PJDE studies may be questioned, depending on the definition of *indicative* and *PJDE*. First, nonsignificance would be a highly specific indicator of PJDE studies only if nearly all well justified, designed, and executed studies led to significant results. Second, PJDE methods may increase systematic