Association Between Systemic Inflammation and Individual Symptoms of Depression: A Pooled Analysis of 15 Population-Based Cohort Studies

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Objective: Evidence from anti-inflammatory drug trials for the treatment of depression has been inconsistent. This may be ascribed to the differing symptom-specific effects of inflammation. Accordingly, the authors explored the associations between systemic inflammation and an array of individual symptoms of depression across multiple studies.

Methods: This random-effects pooled analysis included 15 population-based cohorts and 56,351 individuals age 18 years and older. Serum or plasma concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6) were measured at baseline. Using validated self-report measures, 24 depressive symptoms were ascertained in 15 cross-sectional studies, and, in seven cohorts, were also assessed at follow-up (mean follow-up period, 3.2 years).

Results: The prevalence of depressive symptoms ranged from 1.1% (suicidal ideation) to 21.5% (sleep problems). In cross-sectional analyses, higher concentrations of CRP were robustly associated with an increased risk of experiencing four physical symptoms (changes in appetite, felt everything was an effort, loss of energy, sleep problems) and one cognitive symptom (little interest in doing things). These associations remained after adjustment for sociodemographic variables, behavioral factors, and chronic conditions; in sex- and age-stratified analyses; in longitudinal analyses; when using IL-6 as the inflammatory marker of interest; in depressed individuals; and after excluding chronically ill individuals. For four exclusively emotional symptoms (bothered by things, hopelessness about the future, felt fearful, life had been a failure), the overall evidence was strongly against an association with inflammation.

Conclusions: These findings suggest symptom-specific rather than generalized effects of systemic inflammation on depression. Future trials exploring anti-inflammatory treatment regimens for depression may benefit from targeting individuals presenting with symptom profiles characterized by distinct inflammation-related physical and cognitive symptoms.

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It is well documented that depression is a growing public health concern and a major cause of disability worldwide (1), leading to a significant reduction in quality of life (2) and impaired psychosocial functioning (3). In addition to being an important condition in its own right, depression has been associated with an elevated risk of morbidity (4), cognitive decline (5), and mortality (6). However, the pathophysiology of depression is not fully understood. Approximately one-third of patients with depression fail to respond to conventional antidepressant therapies, and less than 40% obtain remission after initial treatment (7). Furthermore, there have been no clinically reliable predictors of treatment response to existing antidepressant treatment regimens (8).

Following the extensive search for biomarkers linked to depression, there has been emerging interest in the role of immune system disturbances, in particular systemic inflammation, in depression etiology. This view is supported by findings on shared genetic variants between the immune system and depression (9). In addition, proinflammatory systemic cytokines have been found to be capable of affecting depression-related endocrine functioning and neurotransmitter metabolism by traversing the blood-brain barrier or inducing activation of afferent fibers of the vagus nerve (10, 11), including the central synthesis and reuptake of amine transmitters (12, 13). To date, however, the collective evidence from population-based cohort studies and clinical

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trials on the association between systemic inflammation and depression has been inconsistent (14–18). Since depression is a multifaceted mental disorder with varying types of symptom expressions (19), this discordance may be ascribed to symptom-specific effects of inflammation that are lost when a single aggregate measure of depression is used (20). According to the two most widely used classificatory diagnostic systems of mental disorders—ICD-11 (21) and DSM-5 (22)—depression can be broadly classified into emotional (e.g., depressed mood, anhedonia), cognitive (e.g., difficulties concentrating), and physical (e.g., sleep problems, fatigue, changes in appetite) symptoms. Different symptoms may have distinct underlying etiological pathways, but few studies to date have examined the associations between systemic inflammation and individual symptoms of depression (3, 23–27). Further limitations in this field of research include the reliance on small sample sizes, insufficient control for potential confounding factors, and a lack of evaluation of temporality and consistency of potential symptom-specific associations across different subgroups and inflammatory markers.

In this multicohort study of 15 population-based cohorts comprising up to 56,351 individuals, we sought to address these limitations by exploring the cross-sectional and longitudinal associations of two systemic inflammatory markers—C-reactive protein (CRP) and interleukin-6 (IL-6)—with 24 individual symptoms of depression, including physical, emotional, and cognitive symptom domains, and biased perceptions of self. To evaluate the robustness of evidence for or against an association with individual symptoms of depression, we explored these associations in subgroups of men and women, subgroups of younger and older adults, among individuals with depression, and after excluding those with high levels of inflammation or chronic illnesses.

METHODS

Study Population

We identified eligible large-scale cohort studies on inflammation and depressive symptoms by searching the collections of the UK Data Service (https://ukdataservice.ac.uk), the Inter-University Consortium for Political and Social Research (http://www.icpsr.umich.edu/icpsrweb/ICPSR/), and the Individual-Participant Data Meta-Analysis in Working Populations (IPD-Work) consortium (28). Study selection was based on three quality assessment criteria: first, studies provided individual-level data for adults; second, studies used validated assessment methods to measure circulating inflammatory biomarkers, depressive symptoms, and covariates; and third, studies adopted either a cross-sectional or a longitudinal (i.e., at least two waves of data collection) design.

As shown in Figure S1 in the online supplement, we identified 15 independent population-based cohort studies, which were initiated between 1985 and 2018. These were from the United Kingdom (Whitehall II, the English Longitudinal Study of Ageing [ELSA], and Understanding Society [UKHLS]), the United States (the Health and Retirement Study [HRS], the National Health and Nutrition Examination Survey [NHANES], Midlife in the United States [MIDUS], and the National Social Life, Health, and Aging Project [NSHAP]), Ireland (the Irish Longitudinal Study on Ageing [TILDA]), Mexico (the Mexican Health and Aging Study [MHAS]), Taiwan (the Social and Biomarkers of Aging Study [SEBAS]), and Costa Rica (the Costa Rican Longevity and Healthy Aging Study [CRELES]). Participants under age 18 and those with missing data on depressive symptoms, inflammatory markers, and/or covariates were excluded from the present analyses.

Ethical approval for the included studies was granted by the relevant local or institutional ethical review boards. All participants provided written informed consent prior to their participation in these studies. The downloaded data were anonymous. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Assessment of Systemic Inflammation and Baseline Covariates

Plasma or serum blood samples were used to assess baseline levels of CRP and IL-6 using standard operating protocols as detailed in appendix 1 in the online supplement. The selection of demographic, socioeconomic, behavioral, and chronic illness–related covariates was based on previous research (29). Demographic variables included age and sex. Educational qualification was used as a single indicator of socioeconomic position. Behavioral factors included self-reported smoking status (never smoker, ex-smoker, current smoker), alcohol consumption (frequency of drinking alcohol), physical activity (physically active or not active), and body mass index (BMI). Chronic illness–related covariates comprised self-reported indications of coronary heart disease, stroke, diabetes, and cancer (yes or no). In addition, we included systolic and diastolic blood pressure.

In sensitivity analyses of cohort studies with relevant data, additional covariates included adverse childhood experiences (a standardized sum score) and the time interval between blood collection and measurement of depressive symptoms at baseline (see appendix 1 in the online supplement) (30, 31).

Assessment of Depressive Symptoms

Overall depression status (i.e., elevated versus nonelevated levels of depressive symptoms) and a total of 24 individual symptoms of depression were ascertained from a variety of validated self-report measures of depressive symptoms, including the Center for Epidemiological Studies Depression Scale (32) (cohorts ELSA, TILDA, Whitehall II, NSHAP, MIDUS, SEBAS, MHAS, HRS), the Depression Screening Questionnaire, based on the Patient Health Questionnaire (33) (NHANES), the General Health Questionnaire (34) (UKHLS), and the Geriatric Depression Scale (35) (CRELES). Standard (most commonly) or distribution-based threshold values were used to classify individuals with high overall depressive symptoms in each cohort (see Table S1 in

the online supplement). The questionnaires assessed how often participants had experienced specific depressive symptoms during the past 7–14 days. Accordingly, respondents were asked whether they had experienced crying spells, changes in appetite, little interest in doing things, effort doing things, low energy levels, low mood, feelings of sadness, feelings of loneliness, sleep problems, trouble concentrating, hopelessness about the future, moving or speaking slowly or too fast, talking less than usual, were bothered by things, felt fearful, felt life had been a failure, felt bad about themselves, felt people disliked them, felt people were unfriendly, did not enjoy life, felt they would be better off dead, and could not shake off the blues. Response scales varied by measure and study and were therefore harmonized by coding items as dichotomous variables (coded 1 if the symptom was present and 0 if it was absent). Our domain classification of symptoms was informed by ICD-11 (21), DSM-5 (22), and a previous mixed-methods investigation on depression outcome domains that matter to patients, caregivers, and health care professionals (19). Symptoms were categorized as detailed in Table 1. In seven cohorts, depressive symptoms were measured repeatedly, at baseline when inflammatory markers were assessed, and 1 to 5 years later (mean follow-up period, 3.2 years) (see Table S4 in the online supplement).

Statistical Analysis

CRP and IL-6 values were log-transformed because of their skewed distribution. Our primary analyses were based on CRP, as this indicator of systemic inflammation was available in all studies (N=15). A total of three cohorts had data on IL-6 (see Table S4 in the online supplement). We used a two-step individual-participant-data meta-analysis. Analyses were first conducted separately in each study cohort; study-specific estimates and standard errors were subsequently combined in a meta-analytical framework. Analyses were based on individuals with no missing data on the exposure, outcome, and covariates.

Study-specific cross-sectional associations between inflammatory markers and individual symptoms of depression were estimated using multivariate logistic regression analyses. Odds ratios and their 95% confidence intervals were computed. In addition to an unadjusted model (crude model), we generated five multivariable-adjusted effect estimates in a serial manner. In model 1, effect estimates were adjusted for age and sex (basic model); in model 2, estimates were adjusted as in model 1, additionally controlling for the influence of education; in model 3, estimates were adjusted as in model 1 with the addition of illness-related variables; and in model 4, estimates were adjusted as in model 1 and for behavioral factors. In model 5, analyses were adjusted for all of the above-mentioned potential confounders and mediators. Variables in each covariate group were entered simultaneously into the models. To examine whether robust associations were largely driven by high levels of inflammation, we repeated these analyses after excluding participants with CRP levels ≥10 mg/L. This exclusion threshold has previously been used in studies on systemic low-grade inflammation (36).

Study-specific effect estimates were pooled using random-effects meta-analyses. In comparison to fixed-effects models, random-effects models provide a more conservative estimate. Heterogeneity was examined by computing I^2 and τ^2 statistics. The first refers to the total proportion of variation in effect sizes that is not due to sampling error, and the latter indicates intercohort variance (37). To investigate whether systemic inflammation preceded individual depressive symptoms, analyses were repeated longitudinally, with individual symptoms of depression at follow-up as the outcome of interest, additionally adjusting the effect estimates for the respective depression symptom at baseline.

The strength of evidence for each inflammation-depressive symptom association was evaluated on the basis of the following criteria: magnitude of the effect ("large" was denoted by an odds ratio in the basic model ≥1.20 and $p<0.05$; "moderate" by an odds ratio between 1.10 and 1.19 and $p<0.05$; and "small" by an odds ratio <1.10, but $p<0.05$; "no association" was denoted by $p>0.05$); robustness to multivariable adjustments ("yes," a significant effect estimate after adjustment for all covariates in the analysis of CRP and depressive symptoms, and a comparable point estimate for the same symptom in the smaller IL-6 data set; otherwise "no"); temporality ("yes," a significant association in the longitudinal analysis; otherwise "no"); consistency across inflammatory markers ("yes," a statistically significant association of both CRP and IL-6 with depressive symptoms in the basic model; otherwise "no"); heterogeneity in study-specific estimates ("low," $I^2<25\%$; "moderate," I^2 between 25% and 50%; and "high," $I^2>50\%$); and generalizability across subgroups (men, women, age groups 18–60 years and >60 years, and a subgroup of depressed people, that is, the potential target group for anti-inflammatory treatment trials for depression).

We also performed a number of additional sensitivity analyses. To explore whether adjustment for adverse childhood experiences affected the strength of the age- and sex-adjusted cross-sectional association between CRP and the symptoms that were robustly associated with inflammation in our main analysis, we computed a standardized adverse childhood experience sum score in each cohort with relevant data (mean=0, SD=1). To test whether the time interval between blood collection and measurement of depressive symptoms during baseline data collection influenced the robustness of the identified associations, analyses were stratified by dividing studies according to the timing of exposure and outcome ascertainment (i.e., blood collection and depression measured on the same day versus time interval ≥1 day). To examine whether the association between inflammation and depressive symptoms was independent of comorbid medical illnesses, we repeated the analysis in a subgroup of individuals without chronic illnesses.

Finally, we conducted a post hoc analysis to examine whether individuals with both high levels of CRP and high levels of the identified symptoms were a distinct

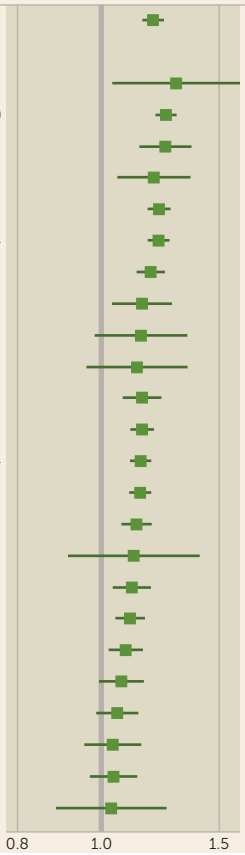
TABLE 1. Summary of overall evidence for the association between systemic inflammation and 24 individual symptoms of depression

Depressive Symptom	Prevalence (%)	Symptom Domain	Strength of Overall Evidence	Effect Size[a]	Robust to Multivariable Adjustment	Support for Temporality	Consistent Across Inflammatory Markers	Heterogeneity (I^2, τ^2)[b]	Generalizable Across Subgroups
Support for an association									
1. Changes in appetite	7.4	Physical symptom	Strong	Large	Yes	Yes	Yes	Low (0%, 0.0003)	Yes
2. Felt everything was an effort	16.0	Physical symptom	Strong	Large	Yes	Yes	Yes	High (79%, 0.0142)	Yes
3. Could not get going/loss of energy	19.6	Physical symptom	Strong	Large	Yes	Yes	Yes	Low (21%, 0.0023)	Yes
4. Little interest in doing things/ unmotivated	11.2	Cognitive symptom	Moderate	Large	Yes	Yes[c]	Missing data	Low (22%, 0.0010)	Yes
5. Sleep was restless	21.5	Physical symptom	Moderate	Moderate	Yes	Yes	Yes	High (67%, 0.0031)	Yes
Evidence against an association									
6. Bothered by things	6.7	Emotional symptom	Strong	No association	No	No	Yes	Low (14%, 0.0027)	N/A
7. Felt hopeless about the future	18.2	Emotional symptom	Strong	No association	No	No	Yes	Low (0%, 0.0016)	N/A
8. Felt fearful	3.8	Emotional symptom	Moderate	No association	No	No	Yes	High (61%, 0.0131)	N/A
9. Life had been a failure	3.5	Emotional symptom	Moderate	No association	No	No	Yes	High (62%, 0.0160)	N/A
Uncertain evidence									
10. Difficulties concentrating	8.7	Cognitive symptom	Moderate	Moderate	Yes	Yes	Yes	Moderate (47%, 0.0031)	No
11. Could not shake off the blues	4.3	Perception of self	Mixed	Moderate	No	No	No	Low (0%, 0.0016)	N/A
12. Felt worse than others	13.6	Perception of self	Mixed	No association	No	Yes	No	Low (0%, 0.0016)	N/A
13. Felt depressed	10.2	Emotional symptom	Mixed	Moderate	Yes	Yes	No	Moderate (43%, 0.0026)	N/A
14. Felt unhappy	12.5	Emotional symptom	Mixed	Moderate	No	Yes	Yes	Moderate (49%, 0.0068)	N/A
15. Talked less than usual	7.0	Physical symptom	Mixed	No association	No	Yes	No	Low (0%, <0.0001)	N/A
16. Felt lonely	11.5	Emotional symptom	Mixed	Moderate	No	Yes	No	Low (0%, 0.0002)	N/A
17. People were unfriendly	3.1	Cognitive symptom	Mixed	No association	No	No	Yes	Moderate (36%, 0.0189)	N/A
18. Did not enjoy life	10.6	Emotional symptom	Mixed	Moderate	No	No	No	Moderate (29%, 0.0028)	N/A
19. Had crying spells	2.5	Physical symptom	Mixed	Large	No	No	No	Moderate (36%, 0.0180)	N/A
20. Felt sad	14.1	Emotional symptom	Mixed	Small	No	No	No	Low (21%, 0.0017)	N/A
21. People dislike me	2.4	Perception of self	Mixed	No association	No	No	No	High (57%, 0.0326)	N/A
22. Feeling bad about yourself	5.3	Perception of self	Mixed and lacking	Moderate	No	Missing data	Missing data	Low (0%, 0.0002)	N/A
23. Moving or speaking slowly/too fast	3.6	Physical symptom	Mixed and lacking	Moderate	No	Missing data	Missing data	Low (0%, 0.0015)	N/A
24. Thought you would be better off dead	1.1	Self-harm symptom	Mixed and lacking	Large	No	Missing data	Missing data	Low (19%, 0.0095)	N/A

[a] Large: odds ratio ≥1.20 and $p<0.05$; moderate: odds ratio between 1.10 and 1.19 and $p<0.05$; small: odds ratio <1.10 and $p<0.05$; no association, $p>0.05$.
[b] Low: $I^2<25\%$; moderate: I^2 between 25% and 50%; high: $I^2>50\%$.
[c] Results are limited to the Health and Retirement Study.

FIGURE 1. Unadjusted and serially adjusted cross-sectional association between C-reactive protein (CRP) and 24 symptoms of depression (random-effects meta-analysis)

Outcome	N (participants)/ N (studies)	Crude Odds Ratio and 95% CI	Odds Ratio (95% CI) per 1 SD Higher CRP[a] Model 1	Model 2	Model 3	Model 4	Model 5
Depression	56,220 / 15		1.18 (1.14–1.22)	1.15 (1.11–1.18)	1.16 (1.12–1.20)	1.06 (1.03–1.10)	1.05 (1.02–1.09)
Depressive symptoms							
Had crying spells	9,786 / 3		1.24 (1.00–1.53)	1.22 (0.98–1.51)	1.22 (0.99–1.51)	1.12 (0.92–1.36)	1.10 (0.94–1.30)
Changes in appetite[b]	34,615 / 10		1.23 (1.18–1.27)	1.20 (1.16–1.24)	1.21 (1.17–1.26)	1.12 (1.07–1.18)	1.14 (1.09–1.19)
Felt everything was an effort[b]	27,130 / 8		1.23 (1.12–1.36)	1.21 (1.11–1.32)	1.21 (1.10–1.34)	1.11 (1.04–1.19)	1.12 (1.04–1.21)
Thought you would be better off dead	22,420 / 5		1.22 (1.06–1.39)	1.18 (1.03–1.36)	1.18 (1.03–1.34)	1.10 (0.95–1.27)	1.07 (0.93–1.24)
Little interest in doing things[b]	31,000 / 6		1.21 (1.16–1.26)	1.18 (1.13–1.23)	1.19 (1.14–1.24)	1.10 (1.05–1.15)	1.09 (1.04–1.14)
Could not get going/loss of energy[b]	50,736 / 14		1.20 (1.16–1.24)	1.18 (1.14–1.23)	1.19 (1.14–1.23)	1.09 (1.06–1.13)	1.08 (1.05–1.12)
Feeling bad about yourself	22,420 / 5		1.18 (1.12–1.24)	1.15 (1.09–1.21)	1.15 (1.09–1.20)	1.05 (0.99–1.11)	1.03 (0.97–1.09)
Could not shake off the blues	9,786 / 3		1.16 (1.04–1.29)	1.14 (1.04–1.26)	1.16 (1.04–1.29)	1.03 (0.91–1.16)	1.03 (0.91–1.15)
People were unfriendly	12,195 / 5		1.15 (0.97–1.36)	1.11 (0.95–1.31)	1.14 (0.96–1.35)	1.07 (0.90–1.27)	1.03 (0.85–1.24)
Life had been a failure	9,786 / 3		1.15 (0.95–1.38)	1.14 (0.95–1.35)	1.15 (0.96–1.39)	1.06 (0.91–1.25)	1.07 (0.92–1.23)
Moving or speaking slowly or too fast	22,420 / 5		1.14 (1.07–1.22)	1.11 (1.04–1.19)	1.11 (1.04–1.20)	1.06 (0.98–1.13)	1.04 (0.97–1.11)
Felt lonely	27,130 / 8		1.13 (1.09–1.17)	1.10 (1.06–1.14)	1.12 (1.08–1.16)	1.05 (0.99–1.11)	1.04 (0.99–1.09)
Sleep problems[b]	55,165 / 14		1.13 (1.09–1.17)	1.11 (1.07–1.15)	1.11 (1.08–1.15)	1.06 (1.02–1.10)	1.05 (1.01–1.09)
Felt depressed	54,563 / 13		1.13 (1.09–1.18)	1.10 (1.06–1.14)	1.11 (1.06–1.16)	1.03 (1.00–1.07)	1.02 (0.98–1.06)
Trouble concentrating[b]	37,821 / 9		1.12 (1.07–1.18)	1.11 (1.05–1.16)	1.11 (1.06–1.16)	1.07 (1.02–1.11)	1.07 (1.01–1.13)
People dislike me	11,593 / 4		1.12 (0.90–1.39)	1.09 (0.88–1.35)	1.11 (0.90–1.35)	0.99 (0.78–1.25)	0.98 (0.78–1.22)
Felt unhappy	33,329 / 9		1.11 (1.04–1.18)	1.09 (1.03–1.17)	1.10 (1.02–1.18)	1.05 (0.97–1.13)	1.04 (0.96–1.12)
Did not enjoy life	33,329 / 9		1.10 (1.04–1.15)	1.08 (1.02–1.14)	1.08 (1.03–1.14)	1.03 (0.97–1.09)	1.02 (0.97–1.08)
Felt sad	26,528 / 7		1.07 (1.01–1.12)	1.05 (1.01–1.10)	1.05 (1.01–1.10)	0.99 (0.94–1.05)	1.00 (0.95–1.04)
Talked less than usual	9,786 / 3		1.06 (0.99–1.15)	1.05 (0.98–1.14)	1.06 (0.98–1.15)	1.00 (0.92–1.09)	1.00 (0.92–1.09)
Felt worse than others	9,786 / 3		1.05 (0.97–1.13)	1.02 (0.96–1.10)	1.05 (0.96–1.15)	1.03 (0.95–1.12)	1.02 (0.95–1.10)
Bothered by things	9,786 / 3		1.05 (0.94–1.16)	1.04 (0.95–1.15)	1.05 (0.95–1.16)	0.96 (0.85–1.09)	0.96 (0.86–1.08)
Felt hopeless about the future	10,972 / 4		1.04 (0.97–1.11)	1.02 (0.95–1.10)	1.04 (0.98–1.10)	1.00 (0.92–1.09)	1.00 (0.92–1.09)
Felt fearful	9,786 / 3		1.03 (0.87–1.23)	1.03 (0.86–1.22)	1.02 (0.84–1.25)	0.97 (0.77–1.22)	0.97 (0.76–1.23)



[a] Model 1 was adjusted for age and sex; model 2 was adjusted as in model 1 and additionally adjusted for education; model 3 was adjusted as in model 1 and additionally adjusted for health-related factors; model 4 was adjusted as in model 1 and additionally adjusted for behavioral factors; and model 5 was adjusted for all of the above-listed covariates.
[b] Statistically significant after all adjustments.

subpopulation. In doing so, participants were divided into four groups: high CRP (≥3 mg/L) and high symptom level (top tertile); high CRP–low symptom level; low CRP–high symptom level; and low CRP–low symptom level. To assign values for missing data on individual symptoms of depression across the 15 cohort studies, we performed a multiple imputation analysis with 52 imputed data sets. Next, we computed the expected frequencies of belonging to each group, based on the assumption that the two dichotomous variables (high versus low CRP and high versus low levels of depressive symptoms) were independent. We then compared the observed frequencies (O) to the expected frequencies (E) within each group by calculating the observed-to-expected ratio (O/E), and we computed chi-square statistics to test the difference in the distributions across observed and expected counts. In addition, we explored how individuals with both high CRP and high levels of the identified symptoms may differ from other study members. Differences in means and proportions in sociodemographic, behavioral, and illness-related factors were tested using two-sided t tests and chi-square tests of independence (see Table S5 in the online supplement). These analyses were repeated in the subgroup of depressed individuals (Table S6 in the online supplement).

All study-specific analyses were conducted in Stata, version 14.1, and random-effects meta-analyses were performed using the *metafor* package (38) in RStudio, version 4.0.2. Statistical code is provided in appendix 5 in the online supplement.

RESULTS

The pooled data from 15 cohort studies comprised 56,351 participants with a mean age of 57.8 years (SD=12.0). Of these, 27,125 (48.5%) were men and 29,226 (51.5%) women. The geometric mean was 0.89 mg/L for CRP (95% CI=0.85, 0.94) and 0.74 pg/mL for IL-6 (95% CI=0.70, 0.78). The number of cohorts included in the symptom-specific

TABLE 2. Serially adjusted cross-sectional association between interleukin-6 (IL-6) and five depressive symptoms (random-effects meta-analysis)

		Odds Ratio per 1 SD Higher IL-6[a]									
		Model 1		Model 2		Model 3		Model 4		Model 5	
Depression Status and Depressive Symptom (Outcome)[b]	N Sample / N Studies	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Depression	5,373 / 3	1.22	1.09, 1.38	1.22	1.08, 1.37	1.19	1.06, 1.35	1.10	0.97, 1.25	1.08	0.95, 1.23
Felt everything was an effort[c]	5,374 / 3	1.47	1.21, 1.78	1.43	1.17, 1.75	1.41	1.15, 1.72	1.39	1.13, 1.72	1.31	1.12, 1.54
Changes in appetite[c]	5,375 / 3	1.46	1.27, 1.68	1.45	1.26, 1.67	1.41	1.22, 1.63	1.35	1.16, 1.58	1.31	1.06, 1.63
Could not get going/ loss of energy	5,376 / 3	1.31	1.03, 1.67	1.30	1.02, 1.66	1.25	0.98, 1.60	1.16	0.97, 1.38	1.12	0.92, 1.35
Sleep problems	5,376 / 3	1.16	1.03, 1.31	1.16	1.02, 1.31	1.13	1.01, 1.26	1.13	1.00, 1.28	1.09	0.97, 1.22
Trouble concentrating	4,773 / 2	1.20	1.01, 1.43	1.21	1.01, 1.43	1.16	0.99, 1.36	1.17	0.99, 1.38	1.13	0.98, 1.30

[a] Model 1 was adjusted for age and sex; model 2 was adjusted as in model 1 and additionally adjusted for education; model 3 was adjusted as in model 1 and additionally adjusted for health-related factors; model 4 was adjusted as in model 1 and additionally adjusted for behavioral factors; and model 5 was adjusted for all of the above-listed covariates.
[b] The symptoms listed are the individual symptoms of depression that were robustly associated with CRP in the main analysis, excluding "little interest in doing things," for which no data were available.
[c] Statistically significant in all adjustments.

meta-analyses ranged from 2 to 14, depending on the depressive symptom. Across all cohorts, the weighted mean prevalence of depressive symptoms varied from 1.1% (suicidal ideation) to 21.5% (sleep problems) (see Table 1). The mean prevalence for overall elevated symptoms of depression was 14.0% (see Table S1 in the online supplement).

Figure 1 shows the pooled effect estimates of the cross-sectional associations between CRP, depression status, and 24 individual depressive symptoms. In analyses adjusted for age and sex, the odds ratio per one-standard-deviation-higher CRP level for depression was 1.18 (95% CI=1.14, 1.22), but it was attenuated to 1.05 (95% CI=1.02, 1.09) after additional adjustment for sociodemographic, illness-related, and behavioral factors. In symptom-specific analyses adjusted for age and sex, higher CRP concentrations were associated with increased odds of reporting six of seven physical symptoms, two of three cognitive symptoms, five of nine emotional symptoms, two of four biased self-perceptions, and one of one self-harm-related symptom. After further adjustment for socioeconomic, chronic illness–related, and behavioral risk factors, CRP remained robustly associated with four physical symptoms (changes in appetite, felt everything was an effort, could not get going or loss of energy, sleep problems), two cognitive symptoms (trouble concentrating, little interest in doing things/unmotivated), and one emotional symptom (felt depressed). A similar pattern of associations emerged in the sensitivity analysis excluding participants with CRP concentrations ≥10 mg/L, although the association with "felt everything was an effort" was weakened after additional adjustment for behavioral factors (see Figure S6 in the online supplement). In domain-specific analyses (basic model), CRP was most strongly associated with physical and cognitive symptoms and least associated with emotional symptoms (see Figure S9 in the online supplement).

Table 2 depicts the pooled effect estimates from cross-sectional analyses for IL-6 and depression status, as well as the individual symptoms of depression that were robustly associated with CRP in our main analysis. Higher IL-6 levels were associated with an increased risk of depression (age- and sex-adjusted odds ratio=1.22, 95% CI=1.09, 1.38), although statistical significance at conventional levels was lost after adjustment for all available covariates (odds ratio=1.08; 95% CI=0.95, 1.23). In symptom-specific analyses (basic model), higher IL-6 levels were associated with increased odds of experiencing five of the seven symptoms previously identified to be robustly associated with CRP in our main analysis (no association was observed with the symptom "felt depressed," and no data were available to test the symptom "little interest in doing things"). In multivariable-adjusted analyses, point estimates for the association between IL-6 and these five symptoms (odds ratios ranged from 1.09 to 1.31) were similar to or higher than the corresponding point estimates observed in the larger analysis of CRP (odds ratios ranged from 1.05 to 1.14).

To examine generalizability, we assessed heterogeneity (I^2 and τ^2) in study-specific estimates for symptoms that were consistently associated with systemic inflammation in our main analyses (Table 1). Heterogeneity in study-specific estimates was small or moderate for "changes in appetite" (I^2=0%, τ^2=0.0003), "could not get going/loss of energy" (I^2=21%, τ^2=0.0023), "trouble concentrating" (I^2=22%, τ^2=0.0031), and "little interest in doing things/unmotivated" (I^2=47%, τ^2=0.0010), but high for "sleep problems" (I^2=67%, τ^2=0.0031) and "felt everything was an effort" (I^2=79%, τ^2=0.0142). Of the 14 studies with data on "sleep problems," 13 supported excess risk (odds ratios >1), and

one study favored a protective effect (odds ratio <1). For the symptom "felt everything was an effort," seven of eight studies supported excess risk in relation to higher CRP concentrations, although the magnitude of the effect estimates varied between cohorts.

Overlapping point estimates and accompanying 95% confidence intervals in analyses stratified by age, sex, and timing of exposure and outcome measurement at baseline suggest that the inflammation–depressive symptom associations varied little between subgroups (Figure 2; see also Table S7 in the online supplement). In depressed individuals, higher levels of CRP were significantly associated with increased odds of reporting "changes in appetite," "could not get going/loss of energy levels," "little interest in doing things/unmotivated," and "sleep problems." The effect estimate for "felt everything was an effort" was of similar magnitude but with wider 95% confidence intervals. These five robust cross-sectional associations were replicated in analyses excluding chronically ill individuals and in longitudinal analyses (Figure 2). Additionally, the previously identified longitudinal associations largely remained after multivariable adjustments (see Figure S8 in the online supplement). In contrast, the association with "trouble concentrating" was attenuated after adjustment for adverse childhood experiences, and no association with this particular symptom was observed in the age- and sex-adjusted analyses among depressed individuals (Figure 2).

The overall evidence on the symptom-specific associations with systemic inflammation is summarized in Table 1. In terms of the effect size, robustness to multivariable adjustments, evidence on temporality, consistency across inflammatory markers, and consistency of associations across cohorts and subgroups, strong evidence for an association with systemic inflammation was obtained for three physical symptoms (changes in appetite: age- and sex-adjusted odds ratio=1.23, 95% CI=1.18, 1.27; felt everything was an effort: odds ratio=1.23, 95% CI=1.12, 1.36; could not get going/loss of energy: odds ratio=1.20, 95% CI=1.16, 1.24). Moderate evidence was found for one further physical symptom (sleep problems: odds ratio=1.13, 95% CI=1.09, 1.17) and one cognitive symptom (little interest in doing things/unmotivated: odds ratio=1.21, 95% CI=1.16, 1.26). Moreover, the overall evidence was strongly against an association with four emotional symptoms (bothered by things: odds ratio=1.05, 95% CI=0.94, 1.16; felt hopeless about the future: odds ratio=1.04, 95% CI=0.97, 1.11; felt fearful: odds ratio=1.03, 95% CI=0.87, 1.23; life had been a failure: odds ratio=1.15, 95% CI=0.95, 1.38), while for the remaining 14 symptoms the evidence was mixed (see also Figure S10 in the online supplement).

Post Hoc Analysis

Further analyses confirmed that individuals with both elevated levels of CRP and high levels of the five inflammation-related symptoms represented a distinct subpopulation. The number of individuals with high CRP concentrations and high symptom levels was 1.3 times higher than expected (O/E=1.31, χ^2=472.5, df=3, N=56,351, p<0.001). They differed from other participants in terms of sociodemographic, behavioral, and illness-related profiles, the most observable differences being their lower educational qualifications, lower physical activity levels, higher BMI, and higher prevalence of diabetes, coronary heart disease, stroke, and cancer, but lower alcohol consumption (all p<0.001) (see Table S5 in the online supplement). Among depressed people, a similar pattern emerged: elevated levels of CRP and high inflammation-related symptom levels also appeared to denote a specific subpopulation (O/E=1.11, χ^2=108.1, df=3, N=6,814, p<0.001) with a specific risk factor profile (see Table S6 in the online supplement).

DISCUSSION

Our findings from up to 15 cohort studies comprising 56,351 adults across multiple countries suggest that systemic inflammation is robustly associated with a distinct set of symptoms, both physical (changes in appetite, felt everything was an effort, could not get going/loss of energy, sleep problems) and cognitive (little interest in doing things/unmotivated). These associations were evident across subgroups and two inflammatory biomarkers, in analyses excluding participants with CRP values ≥10 mg/L, after adjustment for socioeconomic, behavioral, and disease-related factors, and in analyses additionally controlling for adverse childhood experiences. In contrast, we found strong evidence against an association with a number of exclusively emotional symptoms, including fearfulness, feeling bothered by things, hopelessness about the future, and feeling life had been a failure.

These results confirm the findings of previous cross-sectional studies showing differential associations between systemic inflammation and changes in appetite (3, 23, 27), lower energy levels (3, 23, 24), and sleep problems (3, 23, 24). Furthermore, in a recent report using NHANES data on 15,071 U.S. adults (23), a weak association was reported between CRP and little interest in doing things.

In individuals with depression, inflammation was associated with "changes in appetite," "could not get going/loss of energy," "little interest in doing things/unmotivated," and "sleep problems." The effect estimate for "felt everything was an effort" was comparable to or higher than those for the other four symptoms, but less precisely estimated. In contrast, although we found a robust association with the symptom "difficulties concentrating" in our main analysis, this relationship was absent in the subgroup of depressed individuals. Thus, our findings support the notion that in depressed individuals, systemic inflammation is primarily associated with physical symptoms and the anhedonia-related symptom "little interest in doing things." If causality is confirmed in future studies, the identified symptom profile could be used to define a subpopulation of depressed people most likely to benefit from anti-inflammatory therapies.

FIGURE 2. Association between C-reactive protein (CRP) and six depressive symptoms in subgroups, after additional adjustments and longitudinally (random-effects meta-analysis)

[a] Adjusted for age and sex as appropriate.
[b] Adjusted for age, sex, and adverse childhood experiences (ACE).
[c] These analyses excluded individuals with a self-reported history of coronary heart disease, stroke, cancer, hypertension, or diabetes.
[d] Adjusted for age, sex, and depressive symptom at baseline.

Findings from our longitudinal analyses are partially consistent with two previously published smaller-scale studies. For example, a longitudinal investigation of 2,731 children found that higher IL-6 levels, but not CRP levels, were linked to an increased risk of experiencing concentration difficulties at follow-up, in addition to diurnal mood variation, sleep problems, and fatigue (26). In an analysis of 2,872 Dutch adults, a higher basal inflammation index, as indicated by increased mean levels of CRP, IL-6, and tumor necrosis factor–alpha, was associated with subsequent physical symptoms (e.g., changes in appetite, sleep problems, and lower energy levels) (39). However, the latter findings should be interpreted with caution, given the study's relatively small sample size, an overrepresentation of women, and the limited set of covariates controlled for in the analyses. Moreover, collapsing biologically distinct inflammatory markers into a single mean index of basal inflammation may mask biomarker-specific effects on depressive symptomatology. Sources of heterogeneity in previous studies include differences in study design, sample size, methodology, sample characteristics, and varying statistical adjustments used to control for the influence of potential confounding factors. In the present study, we attempted to move beyond these differences by harmonizing the data from 15 population-based cohort studies, employing a rigorous statistical approach, and adjusting for the effects of a wide range of covariates.

Our results lend support to the sickness behavior theory (40), which posits that peripherally localized inflammatory activity can initiate a cascade of initially adaptive depressive-like symptoms in a subset of people, collectively known as sickness behavior. These include a lack of energy (lethargy), changes in appetite, sleepiness, reduced social exploration, and, at times, confusion. Sickness behavior is also characterized by depressed mood and increased sensitivity to pain (hyperalgesia). In the present study, evidence on the association between inflammation and depressed mood was mixed, and no data were available on hyperalgesia. In addition, we found strong evidence against an association between inflammation and four exclusively emotional symptoms: "bothered by things," "felt hopeless about the future," "felt fearful," and "life had been a failure," most of which have previously been classified as non–sickness behaviors (39).

Our multivariable-adjusted findings highlight the potential contributions of lifestyle factors to the CRP-depression association because adjustment for lifestyle covariates led to substantial attenuation, an observation that accords with findings from a recent large-scale case-control study (41). The latter investigation found that the association between CRP and overall depression was strongly attenuated but remained statistically significant at conventional levels after controlling for the effects of age, sex, early-life trauma, self-reported health status, alcohol intake, smoking, and BMI. Of these, smoking and BMI appeared to be the most influential factors. Similarly, BMI exerted the greatest attenuating effect in our analyses. This suggests that a high BMI may contribute to both inflammation and depressive symptoms, lie on the causal pathway between inflammation and depressive symptoms, or both (3, 18, 24, 27, 42). IL-6 and CRP are synthesized in response to adipocytes within adipose tissue (43), and higher levels of body fat, in particular visceral fat, are related to metabolic inflammation and depression (44, 45). Moreover, we found that adjustment for BMI particularly reduced the strength of the relationships between inflammation and physical or energy-conserving symptoms, including "changes in appetite," "lower energy levels," and "sleep problems"—a finding supported elsewhere (46). The precise drivers and mechanisms by which increased levels of circulating inflammatory markers exert an influence on depressive symptoms remain unclear. Further research is needed to dissect the interplay between metabolic conditions, inflammation, and individual symptoms of depression and to examine whether other sources, such as genetic susceptibility to systemic inflammation or stress-related responses of the body, may underlie the inflammation–depressive symptom association (47).

Our results may have important implications for future research by suggesting a more targeted, symptom-focused approach to exploring the link between systemic inflammation and depression, particularly in anti-inflammatory drug trials. Current evidence from early-stage clinical trials on the effect of anti-inflammatory drug therapies on depression is sparse, and interpretation of findings is hampered by methodological heterogeneity across studies (48, 49). First results indicate modest antidepressant effects of cytokine inhibitors and celecoxib add-on therapy to conventional antidepressants in depressed patients with prior elevated levels of systemic inflammation (50). However, clinical studies on possible symptom-specific effects of anti-inflammatory therapies are still missing.

The present study has a number of strengths, including its large sample size, which offers higher statistical precision than extant studies; the use of more than one inflammatory marker to assess systemic inflammation; ascertainment of the robustness of associations in multivariable-adjusted analyses; confirmation of the generalizability of the findings across multiple cohorts and subgroups; and the use of longitudinal data to assess temporality. However, our results need to be interpreted in light of some limitations. Causal inference is limited by the use of observational data. Our exposure variable, systemic inflammation, was measured only once at baseline; repeated measurement of inflammatory markers would have enabled us to better capture the time-varying nature of inflammation. Measurement error due to diurnal changes in IL-6, fasting status, and analytical methods may have biased the estimates of our secondary exposure. The primary analysis was based on CRP—a largely stable biomarker which is unaffected by diurnal variations (51). However, IL-6 is less stable and fluctuates throughout the day. In this study, measurement of IL-6 was based on serum blood samples collected in the morning after overnight fasting in all cohorts. Hence, confounding due to

variability in the time of blood collection, analytical method, and fasting status is likely to be limited in our sample. A further limitation is that the assessment of depressive symptoms was based on self-report rather than clinical interviews, which are considered to be the gold-standard method in psychiatric research. In addition, although we included a wide range of covariates, we were not able to control for the influence of anti-inflammatory, antidepressant, or anticoagulation drugs, which may have modified the association between systemic inflammation and depressive symptoms.

In summary, we found that circulating inflammatory markers were robustly associated with a defined set of physical and cognitive symptoms. There was equally strong evidence against an association with exclusively emotional symptoms characterized by fearfulness and negative feelings about life and the future. These findings are largely consistent with the sickness behavior theory of depression. The scientifically reliable identification of symptom-specific associations with inflammation is valuable, as it demonstrates a differential rather than a generalized effect of inflammation on depression. Hence, our findings may pave the way toward a new inflammatory depression phenotype and can guide systematic efforts to develop novel inflammation-targeted treatments. Patient recruitment to future anti-inflammatory drug trials should be based on symptom profiles characterized by the inflammation-related depressive symptoms observed in this study.

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Examination Questions: Frank et al.

1. **There has been emerging interest in the role of immune system disturbances, in particular systemic inflammation, in depression etiology; based on the present findings, which of the following describes this association best?**
   A. Systemic inflammation is associated with overall depression.
   B. Systemic inflammation is not associated with overall depression.
   C. Systemic inflammation is primarily associated with emotional symptoms, such as depressed mood, hopelessness about the future, and fearfulness.
   D. Systemic inflammation is primarily associated with physical symptoms, such as sleep problems, lower energy levels, and changes in appetite.
2. **The present study also looked at the influence of socio-demographic, illness-related, and lifestyle factors on the association between systemic inflammation and individual symptoms of depression. Which of the following factors exerted the greatest attenuating effect on the link between inflammation and physical or energy-conserving symptoms and may therefore contribute to both inflammation and depressive symptoms, lie on the causal pathway between inflammation and these symptoms, or both?**
   A. Cardiovascular disease
   B. Body mass index
   C. Education
   D. Cancer
3. **The current findings on systemic inflammation and depressive symptoms inform future anti-inflammatory treatment trials. In light of this evidence, which of the following hypotheses would be the most relevant to be tested?**
   A. Antidepressant drug therapies may be particularity effective in reducing physical symptoms in people with both depression and elevated levels of systemic inflammation.
   B. Anti-inflammatory therapies may be particularly effective in reducing emotional symptoms in people with both depression and elevated levels of systemic inflammation.
   C. Anti-inflammatory therapies may be particularity effective in reducing physical symptoms of depression and anhedonia in people with both depression and elevated levels of systemic inflammation.
   D. Anti-inflammatory therapies may be effective in reducing physical symptoms and anhedonia in people with both depression and elevated symptoms of systemic inflammation, particularly in women.