



Inflammation and specific symptoms of depression: cross-sectional sex-specific associations between C-reactive protein and symptoms of depression in the lifelines cohort study[☆]

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ABSTRACT

Increasing evidence suggests that systemic inflammation may be associated with specific depressive symptoms, though potential sex differences remain unclear. This study investigated whether elevated levels of systemic inflammation were associated with the endorsement of specific depressive symptoms among depressed individuals and whether these associations differed by sex. Participants ($n = 52,781$; 59.14% female) aged 44.42 years ($SD = 12.15$) who completed the Mini International Neuropsychiatric Interview (MINI) and who had systemic inflammation indexed via circulating C-reactive protein (CRP) at the baseline assessment of the population-based Lifelines Cohort Study were examined. Those who screened into the depression module of the MINI ($n = 2,799$) were included in analyses examining whether the likelihood of endorsing specific symptoms of depression differed for those with higher ($CRP \geq 2$ mg/L) and lower levels of CRP ($CRP < 2$ mg/L) using logistic regression. Moderation analyses tested whether associations between CRP and depressive symptoms differed by sex. Individuals with elevated CRP were more likely to endorse specific depressive symptoms, including anhedonia ($OR = 1.31$, $p = 0.002$), sleep disturbances ($OR = 1.26$, $p = 0.003$), and fatigue ($OR = 1.37$, $p < 0.0001$) compared to those with low levels of inflammation. The only sex-based difference observed was that men with elevated inflammation were more likely to endorse suicidal ideation/behavior (SIB) than women with elevated inflammation ($OR = 1.82$, $p = 0.02$). No associations between inflammation and depression symptoms were observed among women. These findings support an inflammatory phenotype of depression characterized by anhedonia, fatigue, and sleep disturbance. It also provides preliminary evidence to suggest that men who exhibit high levels of inflammation may be at increased risk for SIB, highlighting a need for additional research on this clinically important subject.

1. Introduction

Depression affects millions of people worldwide and accounts for 40% of total days lost due to poor mental health and is associated with increased risks for diabetes, stroke, heart failure, and cognitive decline (Martin et al. 2016, Qiao, Liu et al. 2021). By 2030, depression is expected to become the leading contributor to the global disease burden (Zhang et al. 2024). In light of its high prevalence, impact on daily

functioning, and associated health risks, it is concerning that more than 30% of people with depression do not respond to anti-depressant treatments (Al-Harbi, 2012). A better mechanistic understanding of depression is needed to guide the development of new treatment options.

There is convergent evidence that inflammation may play a causal role in depression. Approximately 30% of depressed individuals exhibit elevated inflammation (Orsolini et al. 2022, Sforzini et al. 2023) and

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depressed individuals exhibiting this inflammatory phenotype respond to anti-inflammatory treatments (Mac Giollabhui, Madison et al. 2026). Further, experimental induction of an inflammatory response via administration of endotoxins is associated with an increase in depressive symptoms (Yirmiya et al. 2000, Eisenberger et al. 2009) and Mendelian randomization studies also have found that inflammatory mediators demonstrate a causal effect on depression (Kelly et al. 2021, Mac Giollabhui et al. 2025). Higher levels of inflammation are associated with more severe depressive severity (Tabatabaeizadeh et al., 2018) and a clinical profile characterized by higher reports of depression-associated somatic symptoms, such as low energy, poor sleep, changes in appetite, fatigue, anhedonia and cognitive dysfunction (Foley et al. 2021, Milaneschi et al. 2021, Moriarity et al. 2021, Moriarity et al. 2023). There is also emerging evidence linking elevated inflammation to suicidality (suicidal ideation, suicidal attempts, and suicidal completions) (O'Donovan et al. 2013, Baldini et al. 2025), though the association has not consistently been established (Foley et al. 2021).

Mechanistic studies outline why dysregulated immune function may lead to a specific presentation of clinical symptoms. Inflammatory cytokines, such as interleukin-6 (IL-6) and IL-1 β , can activate 2,3-dioxygenase and the production of downstream metabolites including kynurenic acid and quinolinic acid (Brundin et al. 2017) that are associated with specific symptoms of depression, such as anhedonia (Chen et al. 2021) and suicidality (Steiner et al. 2011, Erhardt et al. 2013). There is accumulating evidence linking inflammation with anhedonia via impaired dopamine synthesis (Felger et al. 2015, Lucido et al. 2021). Similarly, inflammatory cytokines have been shown to disrupt leptin and insulin signaling (Shoelson et al., 2006, Cui et al., 2017) which are hypothesized to contribute to a higher prevalence of fatigue and sleep disturbances in depressed individuals with higher levels of inflammation (Milaneschi et al. 2020). Indeed, there are multiple potential mechanisms linking inflammatory depression with a specific symptom presentation characterized by anhedonia, fatigue, sleep disturbance, psychomotor slowing, and suicidality.

Not only might an inflammatory subtype of depression be associated with a specific clinical presentation, but there is reason to believe that this relationship may differ based on sex. Women are twice as likely to experience depression as men (Bijl et al., 1998; Kessler et al., 1994), and are more likely to present with depression-associated somatic symptoms such as fatigue, dysregulated appetite and sleep disturbances (Silverstein, 1999, Marcus et al. 2008, Kim et al. 2015). Depressed men, in contrast, are more likely to die by suicide (Hedegaard, 2021, World Health 2021, Wu et al. 2021). Sex differences are also evident in immune function: approximately 80% of autoimmune disorders occur in women (Beeson, 1994, Whitacre, 2001) and women are more likely to exhibit chronic, low-grade inflammation (Mac Giollabhui et al. 2021) as well as an increased pro-inflammatory response to vaccines/pathogens (Cook, 2008, Klein et al. 2015, Klein and Flanagan, 2016). It is possible that heightened inflammatory activity confers risk for depression and indeed, there is evidence that women show greater increases of depressive symptoms than men in response to immune challenges (Eisenberger et al. 2009, Moieni et al. 2015). Alternatively, rather than women demonstrating hyper-reactivity in immune activation as compared to men, immune challenges may activate different signaling pathways in men and women (Eisenberger et al. 2009, Moieni et al. 2015), which in turn lead to differing behavioral expressions. Some studies have shown that IL-6, IL-1 β , IL-8, interferon- γ (IFN- γ), and leptin levels are significantly elevated only in depressed women, whereas interleukin-17 (IL-17) levels are elevated only in depressed men (Birur et al. 2017, Kim et al. 2021, Jarkas et al. 2024), with IL-17 linked with anhedonia in men alone (Jha et al. 2018). Thus, there is a strong rationale for investigating whether higher levels of inflammatory activation lead to different symptoms of depression in men and women.

Few studies have tested this hypothesis empirically and results across these studies have been mixed. Higher levels of circulating inflammatory markers (C-reactive protein [CRP], IL-1 β , and tumor necrosis factor-

α [TNF- α]) were associated with specific symptoms (e.g., anhedonia, fatigue, suicidality) only among female participants with depression in two clinical samples ($n \approx 200$) (Birur et al. 2017, Köhler-Forsberg et al. 2017) whereas a study of 1,236 inpatients who met criteria for a depressive episode based on their electronic health records reported an association between CRP and specific symptoms in males (hopelessness, sluggishness, and cognitive dysfunction) but not in females, in whom CRP was associated with cognitive dysfunction alone (Chen et al. 2024). It is unclear whether mixed results reflect differences in the measurement of psychiatric symptoms/immune function or in the clinical characteristics of the samples (e.g., depression, severity/recurrence, comorbid conditions). This lack of empirical studies and mixed results highlight the need for further research to replicate prior findings and to help clarify how inflammation may contribute to distinct depressive symptom profiles in a sex-specific manner.

The current study investigated whether inflammation is associated with specific depressive symptoms and further whether these associations differ by sex using data from 2,799 individuals taking part in the baseline assessment of the Lifelines Study who screened into the depression module of a structured psychiatric interview and had a marker of systemic inflammation – CRP – assessed via venous blood draw. Specifically, we hypothesized that depressed individuals, and in particular women, with higher levels of CRP (CRP ≥ 2 mg/L) would be more likely to endorse specific depressive symptoms (anhedonia, fatigue, sleep and appetite dysregulation) that are reliably associated with higher levels of inflammation. CRP ≥ 2 mg/L was selected as it is considered to represent clinically significant levels of inflammation (Orsolini et al. 2022, Sforzini et al. 2023) and the rationale for the use of 2 mg/L is discussed in further detail in the ‘Analyses’ section.

2. Methods

2.1. Participants

The current study drew on data from Lifelines. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Participants were enrolled between 2006 and 2013 and recruited from their general practitioner (49%), participating family members (38%), and self-registration on the Lifelines website (13%). Recruitment via general practitioner excluded individuals with a limited Dutch language proficiency, serious psychiatric or physical illness, or a life expectancy under five years. Follow-up assessments occurred approximately 3.9 years after baseline (SD = 1.23). Both visits included two parts: diagnostic interviews and cognitive tasks in the first, followed by biological sample collection two weeks later. All participants included in the study gave written informed consent, and the study was approved by the University Medical Center Groningen's ethics committee (document number METC UMCG METc 2007/152). Further information about this cohort and its study design has been published elsewhere (Scholtens et al. 2015).

Of the 167,729 individuals aged 0 to 93 years who were enrolled at the Baseline visit (Scholtens et al. 2015), the present study focuses on sub-sets of individuals who (i) had CRP measured in circulating blood ($n = 52,781$) and (ii) who screened into the Mini International Neuropsychiatric Interview depression module by endorsing the initial depression item, the initial anhedonia item, or both ($n = 2,799$).

2.2. Measures

Depressive Disorder: The Mini International Neuropsychiatric Interview (MINI) is a reliable, valid, and brief structured interview that was

designed to screen for psychiatric disorders. Lifelines used an adapted version (administering a limited range of anxiety and mood modules) of a Dutch translation of the MINI that was administered by trained interviewers at baseline and self-administered on location at follow-up – details on the version used in Lifelines have previously been published (Wanders et al., 2016).

CRP: Blood samples were obtained before 10 AM via venipuncture following an overnight fast. Complete details on blood specimen data collection have previously been reported (Scholtens et al. 2015, Mac Giollabhui et al. 2021). CRP was quantified using three separate methods for baseline assessment (Method 1: 12.90% of total CRP values assessed in serum; CardioPhase hsCRP; Method 2: 84.58% of total CRP values, assessed in plasma; CardioPhase high sensitivity hsCRP, Siemens Healthcare Diagnostics, Marburg, Germany; Method 3: 2.52% of total CRP values; assessed in plasma; CRPL3, Roche Diagnostics, Mannheim, Germany). Assay methods 2 and 3 were identical and only differed in terms of the manufacturer. A conversion formula ($\text{new} = 0.92 \times \text{old} - 0.01$) was derived from an internal validation using 39 samples, according to the AMC (alternative method comparison, Deming Regression) protocol, in order that Method 1 could be compared with Method 2 and 3 (Mac Giollabhui et al. 2021). For CardioPhase hsCRP, the intra-assay coefficient of variability was 3.45% and the inter-assay coefficient of variability was 3.15%. For CRPL3, the intra-assay coefficient of variability was 4.15% and the inter-assay coefficient of variability was 5.8%.

Sociodemographic, psychological and biomedical variables: Sex, age and educational attainment were self-reported by participants. Educational attainment was classified by Lifelines into three categories: low [no education, primary education, lower/preparatory vocational education, lower general secondary education (leaving secondary school aged > 16 years)], moderate (intermediate vocational education/apprenticeship, higher secondary education), and high (higher vocational education, university). BMI was derived from measured height and weight obtained during the physical examination, with height recorded to the nearest 0.1 cm and weight measured without shoes to the nearest 0.1 kg. Inflammatory medical conditions were assessed based on self-reported physician diagnoses of arthritis, asthma, Crohn's disease, coeliac disease, multiple sclerosis, psoriasis, rheumatoid arthritis, and diabetes. The number of stressful life events experienced in the prior year was assessed using the Dutch version of a 12-item self-report questionnaire – for more details, see validation paper in Lifelines (Rosmalen et al. 2012). Smoking status was assessed using a self-report item asking whether the participant currently smokes or has smoked within the prior month and alcohol use was assessed using a self-report question asking how frequently they consumed alcohol in the prior month, with responses including: 'not this month', '1 day a month', '2–3 days a month', '1 day a week', '2–3 days a week', '4–5 days a week', and '6–7 days a week'. Medication use was recorded and classified according to the Anatomical Therapeutic Chemical (ATC) coding scheme; antidepressant use was operationalized as any medication recorded beginning with "N06A..." and anti-inflammatory use was operationalized as any medication recorded beginning with "L04..." or "H02AB..." or "M01A...".

2.3. Analyses

Analyses were conducted in R 4.4.0. Logistic regression models were estimated with the 'stats' package and graphed with 'ggplot'. CRP was dichotomized using a cut-off of 2 mg/L as it fulfills the criterion of representing clinically significant inflammation, as indicated as a 'risk-enhancing factor' in updated American Heart Association guidelines (Arnett et al. 2019) and increasingly widespread use of 2 mg/L as a threshold in clinical studies of inflammation in depression, psychosis and cardiovascular disease (Ridker et al. 2017, Bekhbat et al. 2025, Goldsmith et al. 2025). Logistic regression analyses investigated the association between CRP $\geq$ 2 mg/L and depression and endorsement of specific depressive symptoms assessed on the MINI. Next, sex-based

differences in the association of CRP with depression and specific depressive symptoms were investigated using moderation analysis.

3. Results

3.1. Participant characteristics

Participants from the baseline assessment of the Lifelines Cohort ($n = 52,781$) were aged 44.42 years on average ($SD = 12.15$). The majority of participants were female (59.14%) and 3.5% met criteria for a depressive disorder. Educational attainment was distributed across low (30.62%), moderate (39.14%), and high (28.95%) levels, with data missing for 676 participants. The average CRP level was 2.59 ($SD = 4.69$; median = 1.2) and approximately one-third of the cohort had a CRP $\geq$ 2 mg/L. The average BMI was 26.19 kg/m^2 ($SD = 4.30$), and 14.87% of participants reported a diagnosis of an inflammatory medical condition. A sub-group of 2,799 individuals screened into and completed the MINI depression module. The mean age of this group was 44.18 ($SD = 11.95$) and 63.69% were female. Approximately 48% of individuals screening into the MINI depression module met criteria for a depressive disorder and the average CRP level was 3.22 ($SD = 5.04$), with nearly 40% having a CRP $\geq$ 2 mg/L. Within this subgroup, 21.93% reported a diagnosis of an inflammatory medical condition, and the mean BMI was 27.17 kg/m^2 ($SD = 5.27$). Approximately 32% of men and 45% of women exhibited CRP $\geq$ 2 mg/L, resulting in women being 1.74 times more likely to exhibit CRP $\geq$ 2 mg/L. Additional information is reported on smoking status, alcohol use, life stress, and medication use – see Table 1 for details. Further sex-stratified baseline characteristics, together with statistical comparisons between males and females in both the complete sample and the sub-group who screened into the MINI, are reported in Supplementary Table 1.

3.2. CRP status and specific depressive symptoms

Individuals who exhibited CRP $\geq$ 2 mg/L were 1.47 times ($p < 0.0001$) more likely to meet criteria for a depressive disorder. Among the 2,799 participants who completed the MINI Depression Module,

Table 1
Lifelines cohort sample characteristics at baseline assessment.

	Baseline Cohort ($n = 52,781$)	Completed MINI Depression Module ($n = 2,799$)
Age [Mean (SD)]	44.42 (12.15)	44.18 (11.95)
Sex (% Female)	59.14%	63.69%
Education Attainment ^a		
-Low	30.62%	
-Moderate	39.14%	
-High	28.95%	
Any Depressive Disorder (Current Major Depression or Dysthymia)	3.48%	47.62%
C-reactive protein level (mg/L), Mean (SD)	2.59 (4.69)	3.22 (5.04)
% $\geq$ 2mg/L	32.79%	39.73%
% $\geq$ 3mg/L	24.06%	30.33%
BMI	26.19 (4.30)	27.17 (5.27)
Number of Stressful Life Events (Past year) ^b	1.04 (1.29)	1.92 (1.83)
Number of Drinking Occasions (Past month)	4.78 (2.03)	4.33 (2.08)
Current Smoker (Yes/No)	21.94%	34.44%
Inflammatory Condition Diagnosis	14.87%	21.93%
Anti-Inflammatory Medication Use	5.27%	9.18%
Anti-Depressant Medication Use	5.35%	18.08%

^a = missing educational attainment in 676 cases in baseline cohort, therefore % does not add to 100%; ^b = missing data in 989 cases and 4 cases were removed in which every item was endorsed.

individuals with higher inflammation (CRP ≥ 2 mg/L) demonstrated an increased likelihood of endorsing anhedonia (OR = 1.31, $p = 0.002$), sleep disturbances (OR = 1.26, $p = 0.003$), and fatigue (OR = 1.37, $p < 0.0001$) compared to those with low inflammation (CRP < 2 mg/L). No other significant associations between participants' CRP levels and depression symptoms were found. See Table 2 for details.

3.3. CRP status and specific depressive Symptoms: Sex-Specific associations

The likelihood of meeting criteria for depression based on CRP ≥ 2 mg/L did not differ between men and women (OR = 0.97, $p = 0.78$). The likelihood of endorsing suicidal ideation/behavior (SIB) based on CRP ≥ 2 mg/L, however, was significantly greater in men (OR = 1.82, $p = 0.02$). The association of other depressive symptoms and inflammation did not significantly differ by sex. See Table 3 for details.

3.4. Sensitivity analyses of alternative CRP Operationalizations: Sex-Specific associations

When we replicated analyses using a cut-off of CRP ≥ 3 mg/L, higher CRP (compared to lower CRP) was associated with a greater likelihood of endorsing both anhedonia and fatigue, but not dysregulated sleep. When examining whether the association of CRP ≥ 3 mg/L and specific symptoms of depression differed for men and women, women were more likely to endorse cognitive problems and anhedonia (trend-level association) and an association between suicidality and inflammation was no longer observed to differ in men. These results are now reported in Supplementary Table 2. When we examined whether the likelihood of endorsing a symptom of depression was associated with a continuous log-transformed operationalization of CRP, an association was observed with anhedonia, sleep, and fatigue such that higher CRP was associated with a greater likelihood of endorsing these symptoms. Using a continuous measure of CRP in sex-based analyses, a stronger association between CRP and cognitive problems was observed for women and no other statistically significant results were observed.

4. Discussion

The current study investigated whether inflammation, as indexed using CRP, is associated with depression and specific depressive symptoms and, further, whether these associations differ by sex. Within a population-based sample, CRP was associated with an increased prevalence of depression and amongst individuals screening into the

Table 2

Likelihood of endorsing specific symptoms of depression as well as descriptive statistics based on CRP ≥ 2 mg/L versus CRP < 2 mg/L.

Depressive Sx.		CRP < 2 mg/L	CRP ≥ 2 mg/L	Odds Ratio
Sadness	No	611 (59%)	1066 (60%)	0.97, $p = 0.69$
	Yes	417 (41%)	705 (40%)	
Anhedonia	No	483 (65%)	1194 (58%)	1.31, $p = 0.002$
	Yes	265 (35%)	857 (42%)	
Appetite	No	1098 (61%)	579 (58%)	1.17, $p = 0.051$
	Yes	694 (39%)	428 (42%)	
Sleep	No	779 (63%)	898 (57%)	1.26, $p = 0.003$
	Yes	458 (37%)	664 (43%)	
Psychomotor Disturbance	No	841 (61%)	836 (59%)	1.07, $p = 0.41$
	Yes	545 (39%)	577 (41%)	
Fatigue	No	606 (65%)	1071 (57%)	1.37, $p < 0.0001$
	Yes	328 (35%)	794 (43%)	
Guilt	No	1222 (61%)	455 (58%)	1.13, $p = 0.16$
	Yes	790 (39%)	332 (42%)	
Concentration	No	831 (60%)	846 (60%)	1.00, $p = 0.99$
	Yes	556 (40%)	566 (40%)	
Suicidality	No	1512 (60%)	165 (56%)	1.19, $p = 0.16$
	Yes	993 (40%)	129 (44%)	

Table 3

Likelihood of endorsing specific symptoms of depression as well as descriptive statistics based on CRP ≥ 2 mg/L versus CRP < 2 mg/L and sex.

Depressive Sx.	Sex		CRP < 2 mg/L	CRP ≥ 2 mg/L	Odds Ratio: CRP*Sex ^a
Sadness	Male	No	303 (43.2%)	147 (44.8%)	0.95, $p = 0.78$
		Yes	398 (56.8%)	181 (55.2%)	
	Female	No	308 (31.6%)	270 (34.0%)	
		Yes	668 (68.4%)	524 (66.0%)	
Anhedonia	Male	No	184 (26.2%)	77 (23.5%)	1.23, $p = 0.28$
		Yes	517 (73.8%)	251 (76.5%)	
	Female	No	299 (30.6%)	188 (23.7%)	
		Yes	677 (69.4%)	606 (76.3%)	
Appetite	Male	No	493 (70.3%)	231 (70.4%)	1.17, $p = 0.37$
		Yes	208 (29.7%)	97 (29.6%)	
	Female	No	605 (62.0%)	463 (58.3%)	
		Yes	371 (38.0%)	331 (41.7%)	
Sleep	Male	No	380 (54.2%)	168 (51.2%)	1.07, $p = 0.70$
		Yes	321 (45.8%)	160 (48.8%)	
	Female	No	399 (40.9%)	290 (36.5%)	
		Yes	577 (59.1%)	504 (63.5%)	
Psychomotor Disturbance	Male	No	391 (55.8%)	180 (54.9%)	0.97, $p = 0.85$
		Yes	310 (44.2%)	148 (45.1%)	
	Female	No	450 (46.1%)	365 (46.0%)	
		Yes	526 (53.9%)	429 (54.0%)	
Fatigue	Male	No	294 (41.9%)	128 (39.0%)	1.24, $p = 0.22$
		Yes	407 (58.1%)	200 (61.0%)	
	Female	No	312 (32.0%)	200 (25.2%)	
		Yes	664 (68.0%)	594 (74.8%)	
Guilt	Male	No	539 (76.9%)	248 (75.6%)	1.01, $p = 0.96$
		Yes	162 (23.1%)	80 (24.4%)	
	Female	No	683 (70.0%)	542 (68.3%)	
		Yes	293 (30.0%)	252 (31.7%)	
Concentration	Male	No	358 (51.1%)	171 (52.1%)	1.04, $p = 0.80$
		Yes	343 (48.9%)	157 (47.9%)	
	Female	No	473 (48.5%)	385 (48.5%)	
		Yes	503 (51.5%)	409 (51.5%)	
Suicidality	Male	No	640 (91.3%)	281 (85.7%)	0.55, $p = 0.02$
		Yes	61 (8.7%)	47 (14.3%)	
	Female	No	872 (89.3%)	712 (89.7%)	
		Yes	104 (10.7%)	82 (10.3%)	

^a = Odds ratio with female as reference category; CRP = C-reactive protein

depression module of a structured diagnostic assessment ($n = 2,799$), individuals with higher levels of inflammation ($\text{CRP} \geq 2 \text{ mg/L}$) were more likely to endorse specific depression symptoms – anhedonia, sleep disturbances, and fatigue – than individuals with lower levels of inflammation ($\text{CRP} < 2 \text{ mg/L}$). When investigating potential sex-based differences in the association of inflammatory status ($\text{CRP} \geq 2 \text{ mg/L}$) and specific depressive symptoms in those who screened into a diagnostic assessment of depression, the only difference observed was that men with higher levels of inflammation were more likely to endorse SIB than women with higher levels of inflammation or individuals with lower levels of inflammation.

Our findings show that individuals with high inflammation were more likely to endorse anhedonia than individuals with low inflammation. These results are aligned with a substantial body of research linking increased immune activation with anhedonia (Felger and Treadway, 2017, Lucido et al. 2021). A recent systematic review and meta-analysis by Mac Giollabhui, Madison, Lydston, Miller, Quang and Liu has demonstrated that anti-inflammatory treatment reduces anhedonia in depressed individuals with high levels of inflammation and convergent experimental research has also shown that individuals with higher levels of inflammation are more likely to report increased anhedonia in response to a lipopolysaccharide inflammatory challenge (Savitz et al. 2025, Mac Giollabhui et al., 2026). Inflammation has been shown to affect reward circuitry associated with anhedonia (Harrison et al. 2009, Eisenberger et al. 2010, Miller and Raison, 2016), potentially via changes in dopamine and glutamate transmission (Felger et al., 2013, Lucido et al. 2021). It should be noted, however, that null results are also observed in the relationship between inflammation and anhedonia (Foley et al., 2021) and, similarly, an analysis of data from the US National Health and Nutrition Surveys did not find higher levels of CRP associated with anhedonia (Jokela, Virtanen et al. 2016). Differing results may reflect differences in how anhedonia and inflammation are operationalized and assessed; for example, there has generally been a reliance on anhedonia measures assessing consummatory anhedonia (i.e., the capacity to experience pleasure in the moment of a rewarding activity) whereas studies suggest that inflammation may be specifically associated with motivational anhedonia (i.e., the drive/interest in pursuing rewarding experiences) (Treadway and Zald, 2011, Pizzagalli, 2022, Treadway, 2025). These results are aligned with a growing body of evidence indicating that dysregulated inflammatory physiology is causally linked with anhedonia.

Individuals with $\text{CRP} \geq 2 \text{ mg/L}$ were more likely to endorse sleep disturbances than those with low inflammation. This result is consistent with prior research. A systematic review of 72 studies found that sleep disturbances were associated with higher levels of CRP and IL-6, but not TNF- α (Irwin et al., 2016). Similarly, in patients diagnosed with inflammatory bowel disease, high CRP was associated with poor sleep quality (Wilson et al., 2015). Studies examining data from the UK Biobank (UKB), the National Health and Nutrition Examination Survey and the Netherlands Study of Depression and Anxiety (NESDA) consistently found that CRP was associated with poorer sleep (Prather et al., 2015, Jokela et al., 2016, Milaneschi et al., 2021, Yin et al., 2023). It should be noted that two of these studies found that inflammatory biomarkers were only consistently observed with hypersomnia, rather than loss of sleep (Prather et al., 2015, Milaneschi et al. 2021); sleep disturbance in this study assessed either hypersomnia or loss of sleep and so we cannot exclude the possibility that the reported association of sleep disturbance and CRP masks a stronger specific association with hypersomnia. The precise causal relationship between sleep, inflammation, and depression, however, is unclear. Insomnia may be independently associated with alterations to the reward-related regions of the brain implicated in depression (Irwin, 2025), which may or may not be mediated by inflammatory physiology. Further work is needed to determine whether inflammation plays a mechanistic role.

The association of high inflammation and fatigue aligns with results from multiple cohort studies. NESDA, UKB and the Coronary Artery Risk

Development in Young Adults have all observed a link between inflammatory biomarkers (e.g., CRP, IL-6, and TNF- α) and fatigue (Cho et al. 2009, Milaneschi, Kappelmann et al. 2021, Norton, Blaydon et al. 2024). This finding is not surprising given that fatigue is a critical component of the coordinated set of behavioral and psychological changes that accompany inflammation (i.e., sickness behavior) (Karshikoff, Sundelin et al. 2017, Lee and Giuliani 2019). Indeed, patients receiving interferon- α – a treatment inducing a potent inflammatory response – report high levels of fatigue (Dipasquale, Cooper et al. 2016, Dowell, Cooper et al. 2016). Chronic low-grade inflammation may be associated with fatigue via multiple mechanisms, including: capacity of circulating immune cells to access the central nervous system via circumventricular organs, compromised mitochondrial function reducing energy at a cellular level (Lopez-Armada, Riveiro-Naveira et al. 2013, Lacourt, Vichaya et al. 2018), and via disruptions to insulin and leptin signaling, which could alter the energy allocation systems in the hypothalamus and insula (Milaneschi, Lamers et al. 2020).

Contrary to study hypotheses, women with high CRP were not more likely to endorse specific symptoms of depression reliably associated with inflammation, such as anhedonia, fatigue, sleep/appetite dysregulation, when compared to men. This suggests that, although inflammation is associated with specific symptoms of depression, this relationship does not differ in men and women. Our results contribute to an inconsistent literature that have separately reported sex-specific associations between inflammation and depressive symptoms (e.g., pessimism, cognitive dysfunction, lassitude, suicidality) in women (Birur, Amrock et al. 2017, Köhler-Forsberg, Buttenschön et al. 2017) or in men (Chen, Dong et al. 2024). Divergent results may be due to clinical characteristics of the analyzed sample (e.g., comorbidities, prevalence of inflammation-related risk factors, such as adiposity) or differences in how immune function/depression were assessed. Further research is needed to determine the conditions (if any) under which the relationship between inflammation and depression differs based on sex. It is worth noting that, in this study, women who screened into the diagnostic assessment of depression were 1.74 times more likely to exhibit elevated inflammation than men; thus, inflammation may still represent a sex-specific risk factor for depression. Further, sensitivity analyses did point to potential sex-specific relationships linking CRP and cognitive function in women, further highlighting the need for more research to replicate and extend findings.

The only sex-based difference we observed in our primary analyses was that men with elevated inflammation were 1.82 times more likely to endorse SIB than women with elevated inflammation. Previous work has shown that several inflammatory markers (CRP, IL-6, IL-10, and TNF- α) are related to increased suicidal ideation and suicide attempts (Brundin, Erhardt et al. 2015), with alterations in the kynurenine pathway and in blood-brain-barrier permeability hypothesized to play mechanistic roles (Vasupanrajit, Jirakran et al. 2022). Studies examining whether the relationship between inflammation and suicidality differ based on sex, however, have been inconsistent. Some studies have found inflammation to be associated with suicidality only in depressed women (Birur, Amrock et al. 2017) and some in depressed men only (Jha, Minhajuddin et al. 2019). Once more, it is possible that differences in the literature could be the result of differences in how suicidality or inflammation is measured or clinical characteristics (e.g., symptom severity, trauma history, etc.) and we cannot exclude the possibility that this association was observed by chance, particularly as this finding would not be statistically significant if a conservative adjustment for the 18 statistical tests performed and presented in Tables 2 and 3 – a possibility that is further suggested by the failure to consistently observe this association in sensitivity analyses. Similarly, the use of a dichotomous measure of depression prevents us exploring whether potential sex-specific relationships exist at varying levels of depressive symptom severity; this is particularly important given that women tend to report more severe overall depressive symptom severity as well as a greater range of symptoms. More research is needed to determine how

inflammation is associated with suicidality in men and women.

These results should be considered in the context of the limitations of this research. Although these data are based on a relatively large number of individuals from a population-based cohort study completing a structured diagnostic assessment of depression, data were cross-sectional and the number of individuals endorsing SIB (the most rarely endorsed symptom) was relatively small (108 men and 186 women) for sex-stratified analyses. Furthermore, although CRP is a well-established marker of inflammation, the lack of additional inflammatory measures that have been used in previous literature (e.g., IL-1 β , TNF- α) limits complete comparability with previous findings. In addition, acute illness and injury was not assessed at the time of the blood draw and we cannot exclude the possibility that, for some depressed individuals, elevated CRP reflected an acute, time-limited increase in inflammatory activity rather than the chronic activation that was the focus of these analyses. Further, we were unable to assess in this manuscript the degree to which clinical factors, such as the use of anti-inflammatory and anti-depressant medications, may have influenced the presentation of depression and circulating levels of CRP. This is especially true considering evidence suggesting that there may be sex differences in inflammatory responses in depression and what biomarkers are expressed (Birur et al. 2017, Kim, Kim et al. 2021, Jarkas et al. 2024). In addition, it should be noted that all depressive symptoms assessed were binary in nature and may not capture what is likely a linear relationship between inflammation and the severity of symptoms. Similarly, the lack of a continuous measure of depression severity limits interpretation of the findings. Data suggest that SIB is associated with greater overall symptom severity and that women tend to report greater symptom severity and a wider range of symptoms. This study was unable to assess whether sex-specific or symptom-specific association could be observed at varying levels of depressive symptom severity. Sleep disturbance, as assessed via the MINI in the current study, is operationalized as either sleeping too much or not enough; similarly appetite dysregulation comprised either increased or decreased appetite. As distinct clinical manifestations, such as insomnia or hypersomnia, likely have unique independent associations with inflammation, the gross measure of sleep disturbance may not fully capture a unique relationship between inflammation and hypersomnia. Finally, the SIB question on the MINI also was crude in nature and assessed both passive and active suicidal ideation and behavior using a single item; there are known sex-based differences in suicidal ideation and behavior that this measure was not able to disaggregate.

These data support a growing literature characterizing an inflammatory phenotype of depression characterized by higher rates of fatigue, poor sleep and anhedonia. These data also provide preliminary evidence to suggest that men who exhibit high levels of inflammation may be at increased risk for SIB, highlighting a need for additional research on this clinically important subject.

CRedit authorship contribution statement

Naoise Mac Giollabhui: Writing – review & editing, Software, Investigation, Formal analysis. **Ravi J. Kingan:** Writing – original draft, Investigation. **Sara R. McLain:** Writing – original draft, Investigation. **Catharina A. Hartman:** Writing – review & editing, Supervision, Methodology. **Richard T. Liu:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

Richard T. Liu is a consultant for Relmada Therapeutics, and Naoise Mac Giollabhui is a consultant for Boehringer Ingelheim and Jimini Health. Given their his role as Guest Editor, Naoise Mac Giollabhui had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another editor.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2026.107040>. Supplementary material includes tables describing cohort characteristics by sex and associations between CRP ≥ 3 mg/L and depressive symptoms by sex.

Data availability

Data are maintained by the Lifelines Cohort Study and questions about data access should be directed to the Lifelines Cohort Study.

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