

Systemic Inflammatory Biomarkers in DSM-5–Defined Disorders and COVID-19: Evidence From Published Meta-analyses

Angela Duong, Hyunjin Jeong, Dana El Soufi El Sabbagh, and Ana C. Andreazza

ABSTRACT

On March 11, 2020, the World Health Organization declared the outbreak of the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) as a global pandemic. At the center of SARS-CoV-2 is the activation of inflammatory markers; remarkably, interleukin 6 and C-reactive protein seem to be consistently elevated in patients with SARS-CoV-2. Here, we showed that increased systemic C-reactive protein and interleukin 6 are common biomarkers of both severe COVID-19 and DSM-5–defined disorders. However, it is not known whether patients with psychiatric disorders with preexisting increased interleukin 6 and C-reactive protein are more vulnerable to severe complications of COVID-19 because of the additive inflammatory processes.

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On March 11, 2020, the World Health Organization declared the outbreak of the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) as a global pandemic. The impact of COVID-19 is drastic, infecting more than 250 million people worldwide, killing more than 5 million people (as of November 11, 2021), and causing a significant halt to business and education. With the magnitude of this global crisis, we are also observing increased frequency and extent of mental disorders. The first clue behind the relationship between COVID-19 and neuropsychiatric manifestations was from a case study involving a woman in her late 50s (1). In this study, the woman with a positive test result for SARS-CoV-2 presented with altered mental status, including confusion, lethargy, and disorientation. Building on this finding, several observational studies reported that more than one third of patients with COVID-19 presented with neuropsychiatric manifestations, including dizziness, headache, impaired consciousness, seizure, hallucinations, psychosis, and delirium (2), raising a crucial question of whether the psychiatric patient population exposed to SARS-CoV-2 may be more vulnerable to having a severe COVID-19 phenotype. Indeed, patients with preexisting mood disorders were found to have more severe COVID-19 symptoms and were more likely to be hospitalized and have a higher mortality rate, indicating that they should be viewed as an at-risk cohort (3). While these findings highlight the vulnerability of the psychiatric population to COVID-19, no studies have yet evaluated the biological basis that could potentially explain these clinical observations.

One potential biological process that supports these clinical observations is the preexisting increased systemic inflammation frequently observed in patients with mental disorders. Inflammatory biomarkers are crucial for evaluating systemic inflammation and are well documented to be associated with

the severity or rapid progression of COVID-19. Several biomarkers of systemic inflammation, such as C-reactive protein (CRP) and inflammatory cytokines, including interleukins (ILs), interferons, and tumor necrosis factors, are widely studied in COVID-19 and mental disorders. However, studies evaluating the relationship between inflammation, COVID-19, and mental disorders are limited. Here, we aimed to review and gather evidence from previously published systematic reviews and meta-analyses examining CRP and cytokine levels in patients with COVID-19 or patients with mental disorders.

Over the course of the COVID-19 pandemic, five systematic reviews and meta-analyses were published examining cytokine levels in patients with COVID-19. The following search terms on PubMed were used to identify the systematic reviews and meta-analyses: (SARS-CoV-2 OR COVID-19) AND (CRP OR C-reactive protein OR inflammatory cytokines OR cytokines) (Table 1 and Figure 1). We chose to gather evidence from meta-analysis studies because of the unique ability of meta-analyses to combine datasets across multiple independent studies to compute a more reliable statistical significance and effect size. One study reported that IL-6 is significantly elevated in patients with COVID-19 who show adverse clinical presentations (4). Another meta-analysis found elevated levels of CRP, ferritin, and other cytokines such as IL-6, tumor necrosis factor α , interferon γ , IL-8, IL-2, and IL-10 in patients with COVID-19 (5). Another team examining inflammatory markers in nonsevere, severe, and nonsurvivor patients with COVID-19 found increased levels of IL-6, CRP, IL-10, IL-2 receptor, and serum amyloid A in the severe and nonsurvivor patient groups (6). Similarly, in two other meta-analyses, patients with severe disease states showed elevated white blood cell counts, CRP, IL-6, and IL-10, and the nonsurvivor groups expressed even higher levels of these markers (7,8). The

Table 1. Meta-analysis Study Results on the Inflammatory Biomarkers in Patients With COVID-19

Meta-analyses		Results on Inflammatory Biomarkers								
Study	PMID	CRP	IL-6	TNF- α	IFN- γ	IL-1 β	IL-8	IL-2	IL-10	sIL-2R
Coomes and Haghbayan, 2020 (4)	32845568	–	↑	–	–	–	–	–	–	–
Akbari <i>et al.</i> , 2020 (5)	32735885	↑	↑	↑	↑	→	↑	↑	↑	–
Mahat <i>et al.</i> , 2021 (6)	33778183	↑	↑	→	–	–	–	–	↑	↑
Ji <i>et al.</i> , 2020 (7)	33217868	↑	↑	→	–	–	–	–	↑	–
Henry <i>et al.</i> , 2020 (8)	32286245	↑	↑	–	–	–	↑	–	↑	↑

↑, increase; ↓, decrease; →, no change; –, not reported.

CRP, C-reactive protein; IFN- γ , interferon γ ; IL, interleukin; PMID, PubMed identifier; sIL-2R, soluble IL-2 receptor; TNF- α , tumor necrosis factor α .

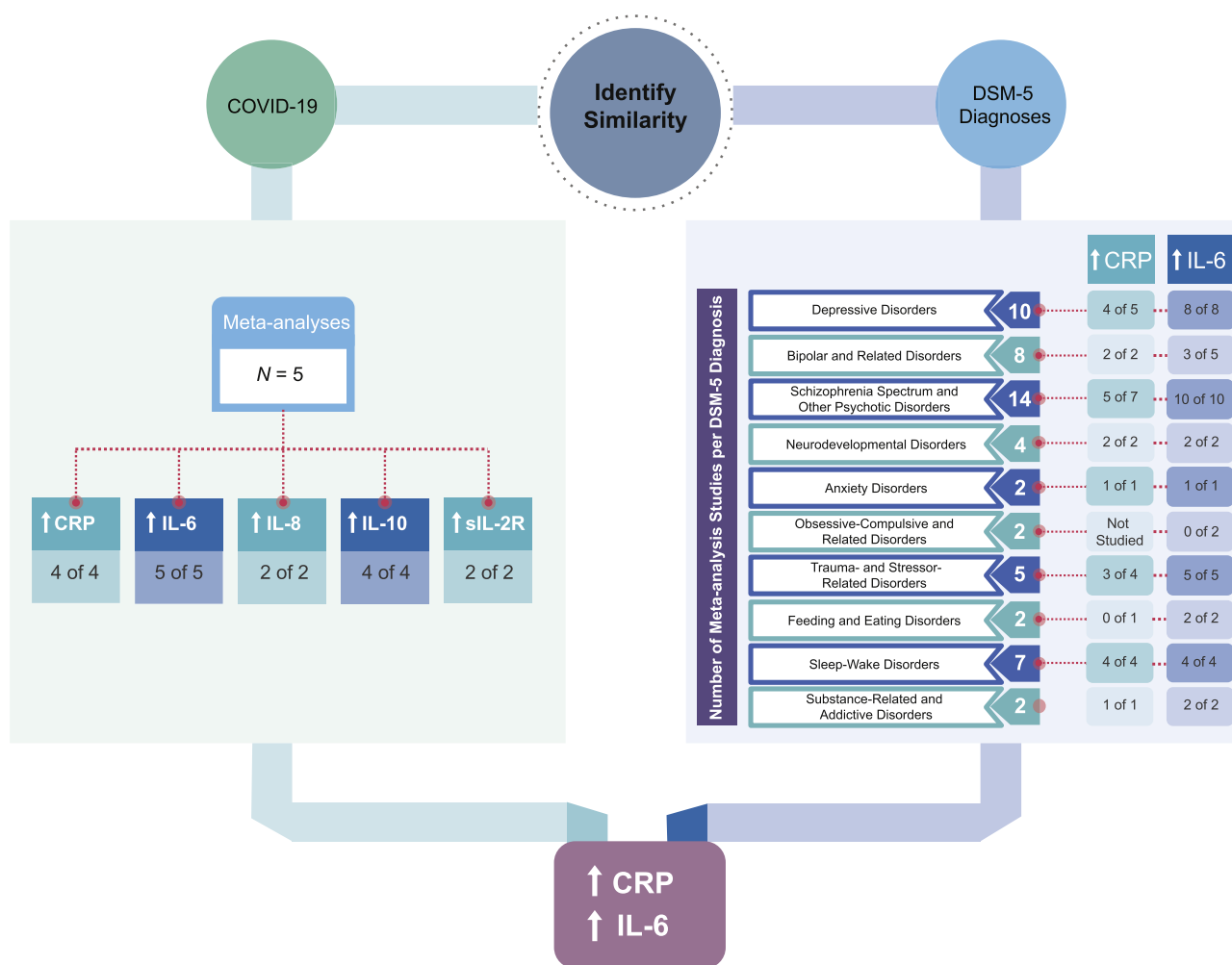


Figure 1. Study workflow on the identification of similarity between severe COVID-19 and DSM-5 diagnoses. The left panel shows the identification of meta-analyses evaluating inflammatory markers in patients with COVID-19 and the number of studies showing increased levels of inflammatory cytokines of the total number of meta-analyses for each cytokine. The right panel shows the number of meta-analysis studies identified across DSM-5–defined psychiatric disorders, along with the number of studies showing an increase in CRP and IL-6 among the total number of studies identified for each DSM-5 diagnosis. Inflammatory markers were compared between severe COVID-19 and DSM-5 diagnoses, leading to the identification of increased CRP and IL-6. CRP, C-reactive protein; IL, interleukin; PMID, PubMed identifier; sIL-2R, soluble IL-2 receptor.

common inflammatory biomarkers found among all these meta-analyses published to date are CRP, IL-6, IL-8, IL-10, and soluble IL-2 receptor. These studies suggest that

tracking these inflammatory markers can allow for prediction of COVID-19 severity. However, none of the meta-analyses stratified the COVID-19 patient population by diagnoses of

Table 2. Meta-analysis Study Results on the Inflammatory Biomarkers Across DSM-5 Diagnoses

DSM-5 Classification	Patient Group	Meta-analyses		Results on Inflammatory Biomarkers								
		Study	PMID	CRP	IL-6	TNF- α	IFN- γ	IL-1 β	IL-8	IL-2	IL-10	sIL-2R
Depressive Disorders	MDD (youth and adolescents)	Colasanto <i>et al.</i> , 2020 (11)	33065836	↑	↑	→	-	-	-	-	-	-
	MDD	Osimo <i>et al.</i> , 2020 (12)	32113908	↑	↑	↑	→	↑	↑	↑	↑	↑
	Drug-naïve first-episode MDD	Çakici <i>et al.</i> , 2020 (13)	32330592	↑	↑	↑	↑	↑	↓	↑	→	-
	MDD	Osimo <i>et al.</i> , 2019 (14)	31258105	↑	-	-	-	-	-	-	-	-
	MDD (elderly)	Ng <i>et al.</i> , 2018 (15)	30104698	→	↑	→	-	↑	-	-	-	-
	MDD	Köhler <i>et al.</i> , 2017 (16)	28122130	-	↑	↑	↓	→	→	-	↑	↑
	MDD (acutely ill)	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	↑	↓	→	-	→	↑	↑
	MDD (chronically ill)	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	→	-	→	→	↓	→	→
	MDD	Dowlati <i>et al.</i> , 2010 (18)	20015486	-	↑	↑	→	→	→	→	→	-
MDD	Howren <i>et al.</i> , 2009 (19)	19188531	↑	↑	-	-	-	-	-	-	-	
Bipolar and Related Disorders	BD	Solmi <i>et al.</i> , 2021 (20)	34332041	↑	↑	↑	-	→	-	-	-	-
	BD	Fernandes <i>et al.</i> , 2016 (21)	27838212	↑	-	-	-	-	-	-	-	-
	BD mania	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	↑	-	-	-	-	→	↑
	BD euthymic (chronically ill)	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	→	→	↑	-	→	↑	↑
	BD depression (chronically ill)	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	→	→	-	-	-	-	→	-
	BD	Dargél <i>et al.</i> , 2016 (22)	25742201	↑	-	-	-	-	-	-	-	-
	BD	Munkholm <i>et al.</i> , 2013 (23)	23768870	-	→	↑	→	→	→	→	→	↑
	BD	Modabbernia <i>et al.</i> , 2013 (24)	23419545	-	↑	↑	→	↑	→	→	↑	↑
Schizophrenia Spectrum and Other Psychotic Disorders	Drug-naïve first-episode SCZ	Çakici <i>et al.</i> , 2020 (13)	32330592	↑	↑	↑	↑	→	↑	→	→	-
	High-risk psychosis	Park and Miller, 2019 (25)	30967316	→	↑	→	→	↓	→	-	→	-
	First-episode psychosis	Fraguas <i>et al.</i> , 2019 (26)	30169868	→	↑	↑	→	→	→	→	→	→
	SCZ spectrum disorders	Bora, 2019 (27)	31284882	↑	-	-	-	-	-	-	-	-
	SCZ	Wang <i>et al.</i> , 2017 (28)	29088880	↑	-	-	-	-	-	-	-	-
	SCZ	Fernandes <i>et al.</i> , 2016 (29)	26169974	↑	-	-	-	-	-	-	-	-
	First-episode psychosis	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	↑	↑	↑	↑	→	↑	↑
	SCZ (acutely ill)	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	↑	↑	↑	↑	→	↓	↑
	SCZ (chronically ill)	Goldsmith <i>et al.</i> , 2016 (17)	26903267	-	↑	↑	↓	↑	-	→	→	↑
	SCZ	Miller <i>et al.</i> , 2014 (30)	23428789	↑	-	-	-	-	-	-	-	-
	Medication-naïve first-episode psychosis	Uptegrove <i>et al.</i> , 2014 (31)	24704219	-	↑	↑	→	↑	-	→	-	↑
	SCZ (acutely relapsed)	Miller <i>et al.</i> , 2011 (32)	21641581	-	↑	↑	↑	↑	-	↑	→	↓
	First-episode psychosis	Miller <i>et al.</i> , 2011 (32)	21641581	-	↑	↑	↑	↑	↑	-	→	-
SCZ	Potvin <i>et al.</i> , 2008 (33)	18005941	-	↑	→	-	→	-	→	-	↑	
Neurodevelopmental Disorders	ASD	Yin <i>et al.</i> , 2020 (34)	32272227	↑	-	-	-	-	-	-	-	-
	ASD	Nadeem <i>et al.</i> , 2020 (35)	32448119	↑	-	-	-	-	-	-	-	-
	ASD	Saghazadeh <i>et al.</i> , 2019 (36)	31125917	-	↑	↑	↑	↑	→	→	-	→
	ASD	Masi <i>et al.</i> , 2015 (37)	24934179	-	↑	→	↑	↑	↑	-	→	-

Table 2. Continued

DSM-5 Classification	Patient Group	Meta-analyses		Results on Inflammatory Biomarkers								
		Study	PMID	CRP	IL-6	TNF- α	IFN- γ	IL-1 β	IL-8	IL-2	IL-10	sIL-2R
Anxiety Disorders	GAD	Costello <i>et al.</i> , 2019 (38)	31326932	↑	–	↑	↑	–	–	–	–	–
	Anxiety	Renna <i>et al.</i> , 2018 (39)	30199144	–	↑	↑	→	↑	→	→	→	–
Obsessive-Compulsive and Related Disorders	OCD	Cosco <i>et al.</i> , 2018 (40)	30382535	–	→	→	→	→	–	–	→	–
	OCD	Gray and Bloch, 2012 (41)	22477442	–	→	→	–	↓	–	–	–	–
Trauma- and Stressor-Related Disorders	PTSD	Yang and Jiang, 2020 (42)	32158005	↑	↑	↑	↑	↑	→	↑	→	–
	Childhood sexual abuse	D'Elia <i>et al.</i> , 2018 (43)	30127754	↑	↑	↑	–	–	–	–	–	–
	PTSD	Renna <i>et al.</i> , 2018 (39)	30199144	–	↑	↑	→	↑	→	→	→	–
	Childhood trauma	Baumeister <i>et al.</i> , 2016 (44)	26033244	↑	↑	↑	–	–	–	–	–	–
Feeding and Eating Disorders	Anorexia and bulimia nervosa	Dalton <i>et al.</i> , 2018 (46)	29906710	–	↑	↑	–	→	–	–	–	–
	Anorexia nervosa	Solmi <i>et al.</i> , 2015 (47)	25462897	↓	↑	↑	–	↑	–	–	–	–
Sleep-Wake Disorders	Narcolepsy	Mohammadi <i>et al.</i> , 2020 (48)	32315956	–	↑	↑	–	–	→	–	→	–
	OSA	Van der Touw <i>et al.</i> , 2019 (49)	30908094	↑	–	–	–	–	–	–	–	–
	OSA	Li and Zheng, 2017 (50)	28187003	–	–	↑	–	–	–	–	–	–
	OSA	Li <i>et al.</i> , 2017 (51)	28489776	↑	–	–	–	–	–	–	–	–
	OSA	Zhong <i>et al.</i> , 2016 (52)	26564171	–	↑	–	–	–	–	–	–	–
	Sleep disturbance	Irwin <i>et al.</i> , 2016 (53)	26140821	↑	↑	→	–	–	–	–	–	–
	OSA	Nadeem <i>et al.</i> , 2013 (54)	24127144	↑	↑	↑	–	–	↑	–	–	–
Substance-Related and Addictive Disorders	Alcohol use disorders	Adams <i>et al.</i> , 2020 (55)	32805393	–	↑	↑	→	→	↑	→	→	→
	Substance use disorders	Wei <i>et al.</i> , 2020 (56)	32533781	↑	↑	↑	→	→	↑	→	↑	–

↑, increase; ↓, decrease; →, no change; –, not reported.

ASD, autism spectrum disorder; BD, bipolar disorder; CRP, C-reactive protein; GAD, generalized anxiety disorder; IFN- γ , interferon γ ; IL, interleukin; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; OSA, obstructive sleep apnea; PMID, PubMed identifier; PTSD, posttraumatic stress disorder; SCZ, schizophrenia; sIL-2R, soluble IL-2 receptor; TNF- α , tumor necrosis factor α .

mental disorders or reported the prevalence of mental disorders, although some individual studies did attempt this analysis. One research group evaluated CRP levels in COVID-19 survivors with a previous diagnosis of mental disorders and did not find a difference compared with those without a diagnosis of mental disorders (9). However, CRP measurements were collected from the patients at a 1-month follow-up, which may not reflect the active disease state of COVID-19. Preliminary findings from a cross-sectional survey study identified no changes in IL-6, IL-8, IL-10, tumor necrosis factor α , and CRP in patients with COVID-19 stratified by with or without psychiatric symptoms (10). However, higher levels of IL-1 β were significantly associated with a higher score of depression, anxiety, and insomnia. Even then, the authors did not comment on whether these patients had a prior diagnosis of mental disorders before contracting SARS-CoV-2. It remains unclear which inflammatory biomarkers are associated with a dual diagnosis of COVID-19 and mental disorders.

To understand whether inflammatory biomarkers associated with the severity of COVID-19 are also reported in patients with mental disorders, we compared the COVID-19 meta-analysis findings with previously published meta-analyses of inflammatory biomarkers for all disorders defined by the DSM-5. The following search terms on PubMed were used to identify the systematic reviews and meta-analyses for DSM-5–defined disorders: (CRP OR C-Reactive Protein OR inflammatory cytokines OR cytokines) and (bipolar disorder OR major depressive disorder OR depression OR schizophrenia OR psychosis OR psychotic disorders OR neurodevelopmental disorders OR anxiety disorders OR obsessive-compulsive disorder OR OCD OR post-traumatic stress disorder OR PTSD OR anorexia OR bulimia OR sleep disorder OR obstructive sleep apnea OR substance use disorder OR addictive disorder OR addiction). We identified a total of 56 meta-analysis studies of systemic inflammatory biomarkers across 10 DSM-5 classifications (10 for depressive disorders, 8 for bipolar and related disorders, 14 for schizophrenia spectrum and other psychotic disorders, 4 for neurodevelopmental disorders, 2 for anxiety disorders, 2 for obsessive-compulsive and related disorders, 5 for trauma- and stressor-related disorders, 2 for feeding and eating disorders, 7 for sleep-wake disorders, and 2 for substance-related and addictive disorders) (Figure 1). We included all meta-analysis studies for reproducibility purposes. While each DSM-5 classification displayed a unique inflammatory profile, IL-6 and CRP were observed to be consistently shared across all DSM-5 disorders except for obsessive-compulsive disorders and feeding and eating disorders for CRP (Table 2) (11–56). Our observation of increased IL-6 and CRP from this parallel comparison of meta-analyses would need to be further investigated in future comparative cross-sectional and longitudinal studies using patient samples to better understand whether IL-6 and CRP are commonly elevated in COVID-19 and mental disorders. Examining whether these inflammatory markers are associated with symptom severity of COVID-19 and mental disorders would also be crucial to understand whether high inflammation may be a potential mechanism for the severe outcomes seen in patients with mental disorders infected by COVID-19.

Chronic inflammation, a state of persistent low-grade inflammation in the absence of acute infection, is commonly

associated with mental disorders. Several studies have shown that high levels of inflammatory molecules in the blood can induce significant permeability to the blood-brain barrier (57). When this occurs, these inflammatory molecules can enter the brain through the blood-brain barrier, potentially disrupting the neural circuits that control mood and behavior, leading to symptoms of mental disorders. The causal link between cytokines and psychiatric symptoms has already been demonstrated in human and animal studies showing that administration of interferon alpha leads to sickness behaviors and depressive-like symptoms (58). Based on these previous findings, it is plausible that synergistic interactions between chronic inflammation and acute inflammation caused by SARS-CoV-2 infection could potentially exacerbate the severity of COVID-19 within the psychiatric patient population. So far, analyses of the cerebrospinal fluid have shown increased levels of IL-6 in patients with COVID-19, major depressive disorder, and schizophrenia, suggesting potential effects on the brain. While studies have shown that peripheral inflammation can induce effects on the brain, it remains unclear whether this is the underlying biological mechanism that contributes to the vulnerability of psychiatric patients to severe COVID-19 or vulnerability of patients with COVID-19 to psychiatric manifestations. Future longitudinal studies and validation studies using animal models of COVID-19 and mental disorders are needed to establish this causal relationship.

COVID-19 is a heterogeneous disease with a variety of effects and manifestations on the immune system's inflammatory response. By examining evidence from meta-analyses, most of the studies reviewed happened to conclude that IL-6 and CRP are increased in mental disorders and COVID-19 independently. It remains unknown whether mental disorders with preexisting increased IL-6 and CRP may be more vulnerable to severe complications of COVID-19 because of the additive inflammatory processes. In addition, patients with mental disorders often have clinical comorbidities such as obesity, which might also increase the inflammation levels and contribute to more severe COVID-19–related complications. Needless to say, there is a need to evaluate patients with COVID-19 with a clinically confirmed mental disorder, at high risk for a mental disorder, and those experiencing psychosis and mood changes. Inflammatory indicators could help identify critical patients with COVID-19 and facilitate the initiation of a treatment plan. Perhaps this would be through monitoring inflammatory markers such as IL-6 and CRP. Early identification of potential hyperinflammation in the psychiatric patient population with COVID-19 may be crucial in alleviating the mental health conditions associated with the COVID-19 pandemic.

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ARTICLE INFORMATION

From the Department of Pharmacology and Toxicology (AD, HJ, DESES, ACA) and Department of Psychiatry (ACA), University of Toronto; and the

Centre for Addiction and Mental Health (HJ, ACA), Toronto, Ontario, Canada.

Address correspondence to Ana C. Andreazza, Ph.D., at ana.andreazza@utoronto.ca.

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REFERENCES

- Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B (2020): COVID-19-associated acute hemorrhagic necrotizing encephalopathy: Imaging features. *Radiology* 296:E119–E120.
- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* (2020): Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 77:683–690.
- Ceban F, Nogo D, Carvalho IP, Lee Y, Nasri F, Xiong J, *et al.* (2021): Association between mood disorders and risk of COVID-19 infection, hospitalization, and death: A systematic review and meta-analysis. *JAMA Psychiatry* 78:1079–1091.
- Coomes EA, Haghbayan H (2020): Interleukin-6 in Covid-19: A systematic review and meta-analysis. *Rev Med Virol* 30:1–9.
- Akbari H, Tabrizi R, Lankarani KB, Aria H, Vakili S, Asadian F, *et al.* (2020): The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Life Sci* 258:118167.
- Mahat RK, Panda S, Rathore V, Swain S, Yadav L, Sah SP (2021): The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: A systematic review and meta-analysis. *Clin Epidemiol Glob Health* 11:100727.
- Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, Zhang J (2020): Association of elevated inflammatory markers and severe COVID-19: A meta-analysis. *Medicine (Baltimore)* 99:e23315.
- Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G (2020): Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin Chem Lab Med* 58:1021–1028.
- Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, *et al.* (2020): Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav Immun* 89:594–600.
- Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, *et al.* (2020): Factors related to mental health of inpatients with COVID-19 in Wuhan, China. *Brain Behav Immun* 89:587–593.
- Colasanto M, Madigan S, Korczak DJ (2020): Depression and inflammation among children and adolescents: A meta-analysis. *J Affect Disord* 277:940–948.
- Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD (2020): Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain Behav Immun* 87:901–909.
- Çakici N, Sutherland AL, Penninx BWJH, Dalm VA, de Haan L, van Beveren NJM (2020): Altered peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: A meta-analysis. *Brain Behav Immun* 88:547–558.
- Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM (2019): Prevalence of low-grade inflammation in depression: A systematic review and meta-analysis of CRP levels. *Psychol Med* 49:1958–1970.
- Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, Ho RC (2018): IL-1 β , IL-6, TNF- α and CRP in elderly patients with depression or Alzheimer's disease: Systematic review and meta-analysis. *Sci Rep* 8:12050.
- Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, *et al.* (2017): Peripheral cytokine and chemokine alterations in depression: A meta-analysis of 82 studies. *Acta Psychiatr Scand* 135:373–387.
- Goldsmith DR, Rapaport MH, Miller BJ (2016): A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry* 21:1696–1709.
- Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL (2010): A meta-analysis of cytokines in major depression. *Biol Psychiatry* 67:446–457.
- Howren MB, Lamkin DM, Suls J (2009): Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom Med* 71:171–186.
- Solmi M, Suresh Sharma M, Osimo EF, Fornaro M, Bortolato B, Croatto G, *et al.* (2021): Peripheral levels of C-reactive protein, tumor necrosis factor- α , interleukin-6, and interleukin-1 β across the mood spectrum in bipolar disorder: A meta-analysis of mean differences and variability. *Brain Behav Immun* 97:193–203.
- Fernandes BS, Steiner J, Molendijk ML, Dodd S, Nardin P, Gonçalves CA, *et al.* (2016): C-reactive protein concentrations across the mood spectrum in bipolar disorder: A systematic review and meta-analysis. *Lancet Psychiatry* 3:1147–1156.
- Dargél AA, Godin O, Kapczynski F, Kupfer DJ, Leboyer M (2015): C-reactive protein alterations in bipolar disorder: A meta-analysis. *J Clin Psychiatry* 76:142–150.
- Munkholm K, Braüner JV, Kessing LV, Vinberg M (2013): Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. *J Psychiatr Res* 47:1119–1133.
- Modabbernia A, Taslimi S, Brietzke E, Ashrafi M (2013): Cytokine alterations in bipolar disorder: A meta-analysis of 30 studies. *Biol Psychiatry* 74:15–25.
- Park S, Miller BJ (2020): Meta-analysis of cytokine and C-reactive protein levels in high-risk psychosis. *Schizophr Res* 226:5–12.
- Fraguas D, Díaz-Caneja CM, Ayora M, Hernández-Álvarez F, Rodríguez-Quiroga A, Recio S, *et al.* (2019): Oxidative stress and inflammation in first-episode psychosis: A systematic review and meta-analysis. *Schizophr Bull* 45:742–751.
- Bora E (2019): Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: A meta-analysis [published correction appears in *Psychol Med* 2021; 51:1589]. *Psychol Med* 49:1971–1979.
- Wang Z, Li P, Chi D, Wu T, Mei Z, Cui G (2017): Association between C-reactive protein and risk of schizophrenia: An updated meta-analysis. *Oncotarget* 8:75445–75454.
- Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, *et al.* (2016): C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: Meta-analysis and implications. *Mol Psychiatry* 21:554–564.
- Miller BJ, Culppepper N, Rapaport MH (2014): C-reactive protein levels in schizophrenia: A review and meta-analysis. *Clin Schizophr Relat Psychoses* 7:223–230.
- Upthegrove R, Manzanares-Teson N, Barnes NM (2014): Cytokine function in medication-naïve first episode psychosis: A systematic review and meta-analysis. *Schizophr Res* 155:101–108.
- Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B (2011): Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biol Psychiatry* 70:663–671.
- Potvin S, Stip E, Seppehy AA, Gendron A, Bah R, Kouassi E (2008): Inflammatory cytokine alterations in schizophrenia: A systematic quantitative review. *Biol Psychiatry* 63:801–808.
- Yin F, Wang H, Liu Z, Gao J (2020): Association between peripheral blood levels of C-reactive protein and autism spectrum disorder in children: A systematic review and meta-analysis. *Brain Behav Immun* 88:432–441.
- Nadeem R, Hussain T, Sajid H (2020): C reactive protein elevation among children or among mothers' of children with autism during pregnancy, a review and meta-analysis. *BMC Psychiatry* 20:251.
- Saghazadeh A, Ataeinia B, Keynejad K, Abdolalizadeh A, Hirbod-Mobarakeh A, Rezaei N (2019): A meta-analysis of pro-inflammatory cytokines in autism spectrum disorders: Effects of age, gender, and latitude. *J Psychiatr Res* 115:90–102.
- Masi A, Quintana DS, Glozier N, Lloyd AR, Hickie IB, Guastella AJ (2015): Cytokine aberrations in autism spectrum disorder: A systematic review and meta-analysis. *Mol Psychiatry* 20:440–446.
- Costello H, Gould RL, Abrol E, Howard R (2019): Systematic review and meta-analysis of the association between peripheral

- inflammatory cytokines and generalised anxiety disorder. *BMJ Open* 9:e027925.
39. Renna ME, O'Toole MS, Spaeth PE, Lekander M, Mennin DS (2018): The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: A systematic review and meta-analysis. *Depress Anxiety* 35:1081–1094.
 40. Cosco TD, Pillinger T, Emam H, Solmi M, Budhdeo S, Prina AM, *et al.* (2019): Immune aberrations in obsessive-compulsive disorder: A systematic review and meta-analysis. *Mol Neurobiol* 56:4751–4759.
 41. Gray SM, Bloch MH (2012): Systematic review of proinflammatory cytokines in obsessive-compulsive disorder. *Curr Psychiatry Rep* 14:220–228.
 42. Yang JJ, Jiang W (2020): Immune biomarkers alterations in post-traumatic stress disorder: A systematic review and meta-analysis. *J Affect Disord* 268:39–46.
 43. D'Elia ATD, Matsuzaka CT, Neto JBB, Mello MF, Juruena MF, Mello AF (2018): Childhood sexual abuse and indicators of immune activity: A systematic review. *Front Psychiatry* 9:354.
 44. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V (2016): Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- α . *Mol Psychiatry* 21:642–649.
 45. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, *et al.* (2015): Inflammatory markers in post-traumatic stress disorder: A systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry* 2:1002–1012.
 46. Dalton B, Bartholdy S, Robinson L, Solmi M, Ibrahim MAA, Breen G, *et al.* (2018): A meta-analysis of cytokine concentrations in eating disorders. *J Psychiatr Res* 103:252–264.
 47. Solmi M, Veronese N, Favaro A, Santonastaso P, Manzato E, Sergi G, Correll CU (2015): Inflammatory cytokines and anorexia nervosa: A meta-analysis of cross-sectional and longitudinal studies. *Psychoneuroendocrinology* 51:237–252.
 48. Mohammadi S, Mayeli M, Saghazadeh A, Rezaei N (2020): Cytokines in narcolepsy: A systematic review and meta-analysis. *Cytokine* 131:155103.
 49. Van der Touw T, Andronicos NM, Smart N (2019): Is C-reactive protein elevated in obstructive sleep apnea? A systematic review and meta-analysis. *Biomarkers* 24:429–435.
 50. Li Q, Zheng X (2017): Tumor necrosis factor alpha is a promising circulating biomarker for the development of obstructive sleep apnea syndrome: A meta-analysis. *Oncotarget* 8:27616–27626.
 51. Li K, Wei P, Qin Y, Wei Y (2017): Is C-reactive protein a marker of obstructive sleep apnea?: A meta-analysis. *Medicine (Baltimore)* 96:e6850.
 52. Zhong A, Xiong X, Shi M, Xu H (2016): Roles of interleukin (IL)-6 gene polymorphisms, serum IL-6 levels, and treatment in obstructive sleep apnea: A meta-analysis. *Sleep Breath* 20:719–731.
 53. Irwin MR, Olmstead R, Carroll JE (2016): Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 80:40–52.
 54. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, *et al.* (2013): Serum inflammatory markers in obstructive sleep apnea: A meta-analysis. *J Clin Sleep Med* 9:1003–1012.
 55. Adams C, Conigrave JH, Lewohl J, Haber P, Morley KC (2020): Alcohol use disorder and circulating cytokines: A systematic review and meta-analysis. *Brain Behav Immun* 89:501–512.
 56. Wei ZX, Chen L, Zhang JJ, Cheng Y (2020): Aberrations in peripheral inflammatory cytokine levels in substance use disorders: A meta-analysis of 74 studies. *Addiction* 115:2257–2267.
 57. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008): From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci* 9:46–56.
 58. Capuron L, Miller AH (2004): Cytokines and psychopathology: Lessons from interferon-alpha. *Biol Psychiatry* 56:819–824.