Education

ROYAL COLLEGE of PHYSICIANS of EDINBURGH

Journal of the Royal College of Physicians of Edinburgh
1–6

DOI: 10.1177/14782715221115776
journals.sagepub.com/home/rcp
SAGE

Investigating inflammation in depression in the chronically ill: Theoretical model and perspectives

Christophe Clesse[1,2], Muhammad Magdi Yaqoob[3], Kamaldeep Bhui[4,5,6] and Livia A Carvalho[1]

Abstract

Background: Inflammation is a risk factor for chronic physical illnesses. Evidence is building that inflammation is also a risk factor for mental illnesses making inflammation a common mechanism which could explain the high comorbidity between mental and physical illnesses.

Method: Based on a systematic search, a review on factors associated with inflammation in the depressed chronically ill has been conducted. Relevant articles have been selected according to the methodological considerations (scope, sample size, type of analysis and bias).

Results: Five categories of factors mediate the association between chronic physical and mental illnesses: (1) social–demographic factors, (2) social–economic background, (3) adverse health behaviours, (4) psychological stress and (5) genetics. Psychological therapies and medication also moderate this association. A theoretical model of the interplay between inflammation, depression and chronic physical illness is then presented.

Discussion: Inflammation contribute to both chronic physical and mental illnesses. These conclusions support future advances in clinical and research practice, as well as training and education.

Keywords

inflammation, chronic illness, depression, mental health, risk factors

Introduction

Inflammation is a well-known risk factor for chronic physical illnesses. Evidence is building that inflammation is also a risk for mental illnesses making inflammation a common, modifiable mechanism which could potentially explain why mental and physical illnesses are highly comorbid. Low-grade chronic inflammation affects around a third of patients with depression potentially characterising a particular subset of the disease.[1] Evidence for a key role of activated immune cells – such as monocytes and T cells – in depression now exists.[2] Peripheral inflammation impacts brain function[3] and predisposes the brain in such a way that genetic and environmental influences – such as stress or trauma – can precipitate the symptoms of depression.[4] There is also evidence – albeit preliminary – that the association between inflammation and depression might be causal. Inflammation, when chronic, predicts the development of depressive symptoms in previously healthy individuals[5] while anti-inflammatory drugs reduce depressive symptoms in people with or without classic inflammatory diseases.[6] Mendelian randomisation studies also suggest that pro-inflammatory cytokines such interleukin-6 (IL-6) are likely causal to the development of depression.[7]

Peripheral inflammation is even more prevalent in those with more complex depression such as those with comorbid physical illnesses.[8,9] This results in higher morbidities and a lower life expectancy than the physically healthy depressed individual or the chronically ill without mental illness. The detection of chronic low-grade inflammation in the periphery may then guide the clinician to better evaluate patients' risks factors for depression and physical chronic illness and evaluate the need of an add-on

[1]Department of Clinical Pharmacology, William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK
[2]Center for Psychiatry and Mental Health, Wolfson Institute of Population Health, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK
[3]Translational Medicine and Therapeutics, William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK
[4]Department of Psychiatry and Nuffield Department of Primary Care Health Sciences, University of Oxford, London, UK
[5]5East London NHS Foundation Trust, London, UK
[6]Oxford Health NHS Foundation Trust, Oxford, UK

Corresponding author:
Christophe Clesse, William Harvey Research Institute, Barts & The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK.
Email: christophe.clesse@hotmail.fr; c.clesse@qmul.ac.uk

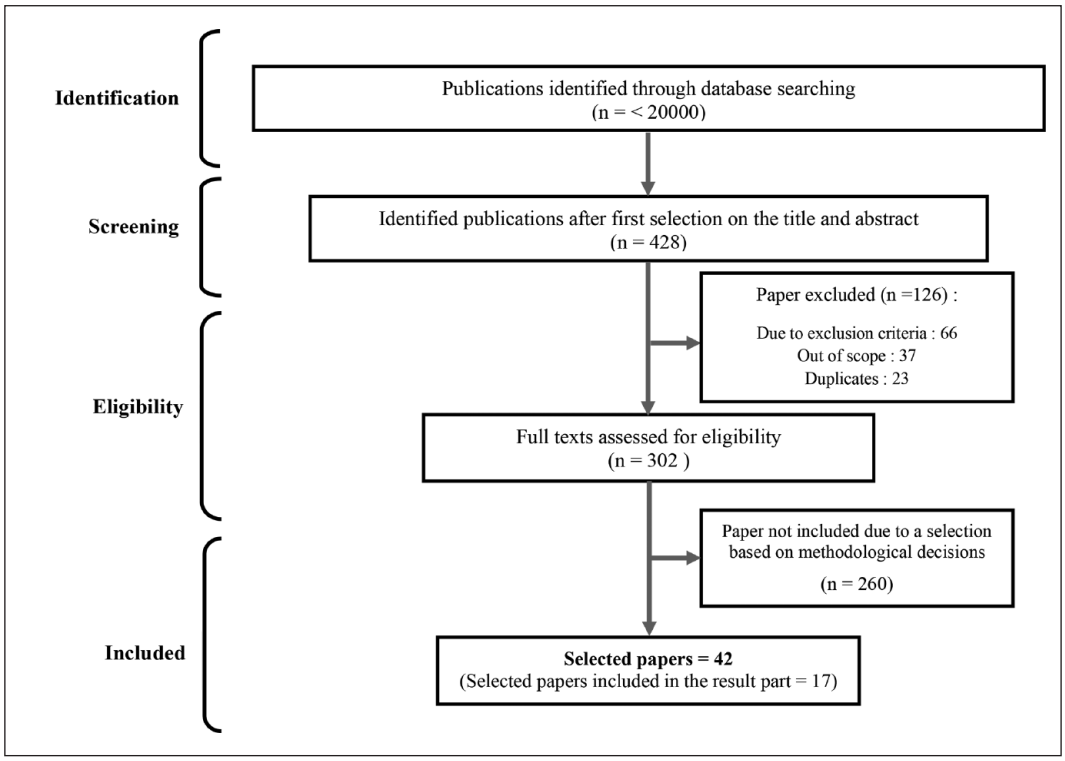

Figure 1. Selection process of relevant papers.

anti-inflammatory treatment to potentiate the effect of traditional monoaminergic antidepressants.[6]

To guide today's science, and clinical practice for the implementation of a better detection, diagnosis and treatment of depression in the chronically ill, we conducted a comprehensive assessment of factors associated with inflammation in the depressed chronically ill. We then produced a theoretical model of the interplay between inflammation, depression and chronic physical illness that could guide future advances in research and clinical practice in the medical field.

Method

Based on a systematic search strategy,[10] we conducted a review which aim to gather the factors associated with inflammation in the depressed chronically ill. This led to the creation of a theoretical model presenting the interplay between inflammation, depression and chronic physical illness.

Search strategy

Relevant studies published between 2000 and December 2021 have been selected from 'Pubmed', 'Web of Science', 'Science direct', 'PsychInfo and Psycarticle', 'Cochrane', 'Biomed' and 'Google Scholar' databases. A combination of keywords was used by matching the three following lists: 'Non-Communicable Disease', 'NCD', 'Chronic disease', 'Chronic illness' with 'Inflammation'; 'Low-grade Inflammation' with 'Depression', 'Depressive symptoms', 'MDD'. The scope of this research includes publications focusing on the interplay between chronic physical illness, inflammation and depression and notably papers focusing on the main non-communicable diseases such as cardiovascular diseases, cancers, diabetes, chronic kidney disease and chronic obstructive pulmonary disease.[11]

Inclusion criteria rely on the scope of the review and the type of article (meta-analysis, systematic reviews, literature reviews, quantitative and qualitative articles). We excluded opinion articles, editorials and short comments. Identification of the studies was carried out by the title and abstract content.

Study selection

A study selection was performed after a full-text assessment. For every relevant factor mentioned by scientific literature, we first selected studies based on the design of the study. More precisely, we considered studies providing information about potential associated factors in the interplay between inflammation and depression in chronically ill patients. Then we retain studies presenting critical consideration regarding the factor's type of association (causality, association and mediation). Then, in line with the new evidence-based pyramid,[12] we only selected one to two studies per relevant factor, based on the methodological criteria (type of study, sample size, implementation of potential cofounders, type of analysis, potential bias and quality of the review).

Presentation of the results

The conducted selection process then led to group 17 selected publications with the help of a thematic categorisation (Figure 1). We considered five categories of factors

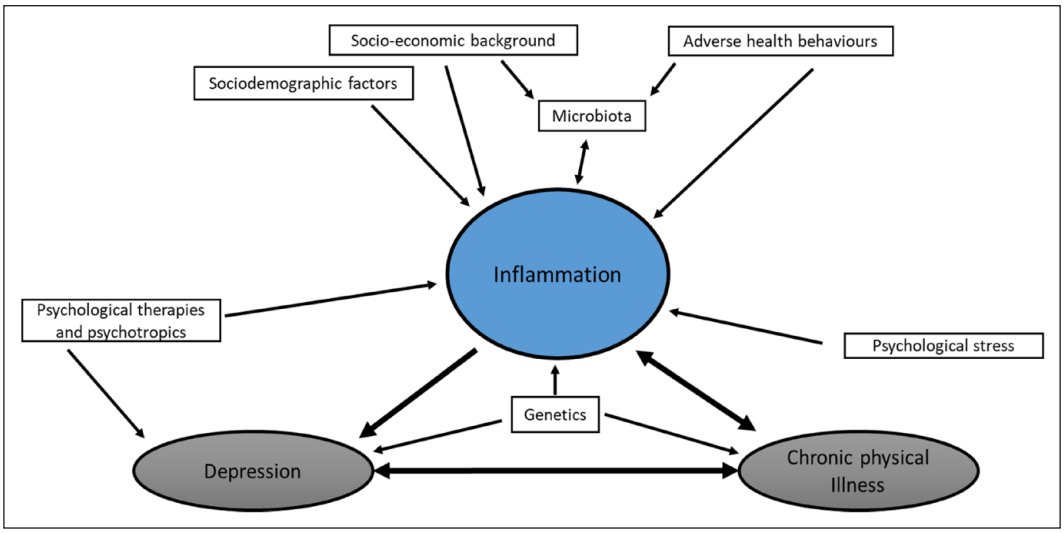

Figure 2. Theoretical model representing the association between depression, chronic physical illness, inflammation and their interrelated mechanisms.

which impact depression and chronic physical illness through inflammation, and one category that moderates this association. A model representing the interrelation between depression, chronic physical illness and inflammation is then presented (Figure 2). We finally present a discussion about the clinical and theoretical implications of these results, considering its perspectives for the medical profession.

Results

Five categories of factors have an impact on chronic physical illness and depression through inflammation: (1) social–demographic factors (e.g. age, gender, marital status); (2) social–economic background (e.g. education level, profession, income or wealth); (3) adverse health behaviours (e.g. smoking, alcohol or drug abuse, poor diet, obesity); (4) psychological stress (e.g. childhood maltreatment, social isolation/lack of social support, domestic violence, psychological trauma) and (5) genetics. One category of factors moderates the association between physical and mental illnesses such as depression: psychological therapies and medications. Each category and their influential relations on inflammation, depression and chronic physical illness have been gathered in a theoretical model (Figure 2).

First, social–demographic factors play a significant role in the physical and mental illness comorbidity by being particularly associated with worse comorbid depression symptoms in woman,[13] in the elderly[13] and in ethnical minorities.[14] Research in this area is still ongoing, but there is initial evidence to suggest that women and the elderly respond to psychological stress laboratory tests with higher levels of peripheral inflammation.[15] Inconclusive results may also be a factor of different authors screening different inflammatory biomarkers.[1]

Second, inflammation is impacted by a range of social–economic factors.[16] A multi-cohort study identifies that a disadvantaged socioeconomic position at each life stage is independently associated with systemic inflammation.[17] Recent meta-analysis shows childhood socioeconomic status is linked to inflammation.[18] Other socioeconomic disadvantages may contribute to depression by increasing psychological stress related to, for example, job uncertainty, lack of enough food or lack of nutritional value, potable water, decreased access to care and medical treatment.

Increased inflammation due to adverse health behaviours including sleep quality, cigarette consumption, drug abuse and a poor diet may contribute to the development of depression.[19,20] Mendelian randomisation and meta-analysis studies show a likely causal association of inflammation and obesity,[21] with nonetheless inconsistent conclusions about its detailed pathway. Studies also suggest the link between adverse health behaviours and inflammation to be partly due to decreased antioxidants molecules and decreased anti-inflammatory molecules by lack of exercise.[22]

Recently, low socioeconomic factors and adverse health behaviours have also been associated with inflammation due to an unhealthy change in the microbiota.[23] Microbiota influence on inflammation occurs through its connection with the central nervous system and immune system in a bidirectional causal way.[23] Through is afferent fibres, the vagus nerve can stimulate cholinergic anti-inflammatory pathway and anti-inflammatory hypothalamic–pituitary–adrenal (HPA) axis pathway to regulate inflammation.[24,25] Through internal dysbiosis or a leaky gut, microbiome can also impact the level of inflammation and contribute or aggravate chronic illness and depression.[23] Studies suggest that healthier, anti-inflammatory diet may be beneficial to patients by reducing depression symptomatology.[26]

Individuals who are genetically determined to have higher inflammation have increased risk of chronic physical illness and depression levels.[27] Polymorphism in the IL-10 promoter –1082 gene shows that (A/A) individuals (lower IL-10 producers) report higher depressive levels than (A/G) allele carriers.[27] In addition to cytokines, chronic stress may also increase inflammation via epigenetic changes and predict higher rates of depressive symptoms.[28]

Finally, there is some evidence to suggest that factors that improve depressive symptoms such as psychological therapies and psychotropic anti-inflammatory medication can also decrease inflammation levels. Meta-analysis confirmed that antidepressant therapy[29] and anti-inflammatory therapy[6] decreased depression and inflammation.

Discussion

The higher prevalence of depression commonly observed in the chronically physically ill may be partly explained by the impact of low-grade chronic inflammation.[9] In the physically ill, unabated activation of the immune system may occur due to systemic infection, cancer, auto-immune diseases and other inflammation-related illnesses.[30] As a response, innate immune cells produce pro-inflammatory cytokines which impair brain function and cause sickness behaviours such as depression.[4,31]

Peripheral inflammation as shown by increased cytokines and acute phase proteins such as C-reactive protein (CRP), tumour necrosis factor, IL-6 and IL-1B protein levels can lead to neuroinflammation. Transduction pathway from peripheral immune signals to the brain includes (a) neural pathway where peripherally produced pathogen-associated molecular patterns (PAMPs) and cytokines activate afferent nerves, which, in turn, project to several other brain areas related to mood; and (b) humoral pathway where PAMPs at the choroid plexus and circumventricular organs PAMPs induce the production and release of cytokines via mechanisms still not exactly known.[30] Once in the brain, pro-inflammatory cytokines may influence mood via different pathways. First, cytokines can induce the kynurenine pathway by metabolising tryptophan into kynurenine, and then to neurotoxic metabolites. Decreased tryptophan will also impair its availability for serotoninergic and melatonin production.[32] Second, pro-inflammatory cytokines also induce HPA axis hyperactivity and subsequently induce glucocorticoid resistance.[33] Third, pro-inflammatory cytokines can lead to an increase in cell death, apoptosis and impairments in neuroplasticity and neurogenesis that can precipitate the symptoms of depression.[34,35]

The causal impact of depression on inflammation is still under investigation. Longitudinal studies that explored causal impact of depression on inflammation suggested that depression is a predictor for future increased levels of inflammatory markers such as CRP and IL-6.[36,37] These studies are subjected to bias due to reverse causation and confounders. In a recent mendelian randomisation study, there was no evidence of a direct causal association of depression in inflammation levels.[38] These results should be regarded with caution as preliminary genetic instruments for depression used in mendelian randomisation analysis are still relatively weak, and only account for 1.5–3.2% of explanation of depression.[39]

Today, understanding and assessing the interrelation between chronic physical illnesses, inflammation and depression as the main mental health comorbidity appears to be one of the next main focal points in the medical field. The existing interplay between inflammation and depression implies that chronic physical illnesses generate higher inflammation levels, that can induce depression.[4,7] In parallel, depression and its related psychosocial stress are associated with future higher levels of inflammation and, subsequently, can induce worse clinical outcomes among these patients.[8,9,37]

In the years to come, targeting inflammation levels to hinder the onset of depressive symptoms and aggravation of chronic physical illnesses could be one of the primary objectives of clinical support. To do so, medical field will have to implement prevention strategies that decrease inflammation levels. First, providing a better evaluation of the inflammatory profile of patients could be used to assess potential depression prognostics,[40] while evaluating the potential risk of developing chronic physical illnesses from high inflammation levels. Second, using the theoretical model of this present article, prevention strategies could target causal risks factors for inflammation (social–demographic factors, social–economic background, adverse health behaviours, psychological stress and genetics). Future prevention strategies could also favour protective behaviours to hinder the impact of high inflammation levels. Adjusted clinical guidance, such as exercising,[41] endorse an adaptative diet,[42] targeting an adjusted BMI or using an anti-inflammatory add-on such as omega 3,[43] could therefore protect patients from the morbid consequences of constant high inflammation levels. Finally, alongside with the anti-inflammatory effect of psychological interventions[44] and antidepressants therapy,[29] future potential treatments such as anticytokine treatments[45] and anti-inflammatory therapy[13] could be used to target morbid consequences of low-grade inflammation. Implementation of these prevention strategies could help reduce/stabilise the synergetic impact from the interplay between inflammation, depression and chronic physical illnesses.

Conclusion

Our model points to inflammation as a common, shared mechanism contributing to both chronic physical and mental illnesses. This was partly explained by inflammation-related poor social–economic and demographic background, chronic psychological stress and poor health behaviours. Future prevention strategies in the medical field should address these risk factors categories to better support physical and mental health.

Author contributions

Christophe Clesse undertook searches, screening, selection of articles, built the model and wrote the paper with Livia A Carvalho (PI). Livia A Carvalho and Christophe Clesse were responsible for the conception and design of the review. All authors contributed to the commenting, interpretation of the results and revisions of the manuscript. Livia A Carvalho and Kamaldeep Bhui were responsible for the conception and design and funding application of the original larger programme. All authors have approved the final version.

Author statement

All author had full access to the full data in the study and accept responsibility to submit for publication.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Barts Charity grant to Professor K Bhui (PI), Livia A Carvalho (CI), Muhammad Magdi Yaqoob (CI) Karl Marlowe (CI), Raj Thuraisingham, Fiona Loud (PPI partner), Brian Gracey (PPI partner).

References

1. Osimo EF, Baxter LJ, Lewis G et al. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med* 2019; 49: 1958–70.
2. Carvalho LA, Bergink V, Sumaski L et al. Inflammatory activation is associated with a reduced glucocorticoid receptor alpha/beta expression ratio in monocytes of inpatients with melancholic major depressive disorder. *Transl Psychiatry* 2014; 4: e344.
3. Banks WA. From blood–brain barrier to blood–brain interface: new opportunities for CNS drug delivery. *Nat Rev Drug Discov* 2016; 15: 275–92.
4. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016; 16: 22–34.
5. Zalli A, Jovanova O, Hoogendijk WJG et al. Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology* 2016; 233: 1669–78.
6. Köhler-Forsberg O, Lydholm CN, Hjorthøj C et al. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr Scand* 2019; 139: 404–19.
7. Khandaker GM, Zuber V, Rees JM et al. Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. *Mol Psychiatry* 2020; 25: 1477–86.
8. Prins Bram P, Abbasi A, Wong A et al. Investigating the causal relationship of C-reactive protein with 32 complex somatic and psychiatric outcomes: a large-scale cross-consortium Mendelian randomization study. *PLoS Med* 2016; 13: e1001976.
9. Mulugeta A, Zhou A, King C et al. Association between major depressive disorder and multiple disease outcomes: a phenome-wide Mendelian randomisation study in the UK Biobank. *Mol Psychiatry* 2020; 25: 1469–76.
10. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J* 2009; 26: 91–108.
11. World Health Organization. Global Status Report on noncommunicable diseases 2014, https://apps.who.int/iris/bitstream/handle/10665/148114/9789241564854_eng.pdf (2014, accessed 30 June 2021).
12. Murad MH, Asi N, Alsawas M et al. New evidence pyramid. *Evid Based Med* 2016; 21: 125–7.
13. Lotfaliany M, Bowe SJ, Kowal P et al. Depression and chronic diseases: co-occurrence and communality of risk factors. *J Affect Disord* 2018; 241: 461–8.
14. Beydoun MA, Obhi HK, Weiss J et al. Systemic inflammation is associated with depressive symptoms differentially by sex and race: a longitudinal study of urban adults. *Mol Psychiatry* 2020; 25: 1286–300.
15. Ronaldson A, Gazali AM, Zalli A et al. Increased percentages of regulatory T cells are associated with inflammatory and neuroendocrine responses to acute psychological stress and poorer health status in older men and women. *Psychopharmacology* 2016; 233: 1661–8.
16. Muscatell KA, Brosso SN, Humphreys KL. Socioeconomic status and inflammation: a meta-analysis. *Mol Psychiatry* 2020; 25: 2189–99.
17. Berger E, Castagné R, Chadeau-Hyam M et al. Multi-cohort study identifies social determinants of systemic inflammation over the life course. *Nat Commun* 2019; 10: 773.
18. Milaniak I, Jaffee SR. Childhood socioeconomic status and inflammation: a systematic review and meta-analysis. *Brain Behav Immun* 2019; 78: 161–76.
19. Weinberger JF, Raison CL, Rye DB et al. Inhibition of tumor necrosis factor improves sleep continuity in patients with treatment resistant depression and high inflammation. *Brain Behav Immun* 2015; 47: 193–200.
20. Gialluisi A, Bonaccio M, Di Castelnuovo A et al. Lifestyle and biological factors influence the relationship between mental health and low-grade inflammation. *Brain Behav Immun* 2020; 85: 4–13.
21. Tyrrell J, Mulugeta A, Wood AR et al. Using genetics to understand the causal influence of higher BMI on depression. *Int J Epidemiol* 2019; 48: 834–48.
22. Paolucci EM, Loukov D, Bowdish DME et al. Exercise reduces depression and inflammation but intensity matters. *Biol Psychol* 2018; 133: 79–84.
23. Peirce JM, Alviña K. The role of inflammation and the gut microbiome in depression and anxiety. *J Neurosci Res* 2019; 97: 1223–41.
24. Pavlov VA, Parrish WR, Rosas-Ballina M et al. Brain acetylcholinesterase activity controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. *Brain Behav Immun* 2009; 23: 41–5.
25. Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J Physiol* 2016; 594: 5781–90.
26. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: a systematic review and meta-analysis. *Clin Nutr* 2019; 38: 2045–52.
27. Holtzman S, Abbey SE, Chan C et al. A genetic predisposition to produce low levels of IL-10 is related to depressive symptoms: a pilot study of patients with end stage renal disease. *Psychosomatics* 2012; 53: 155–61.
28. Tozzi L, Farrell C, Booij L et al. Epigenetic changes of FKBP5 as a link connecting genetic and environmental risk factors with structural and functional brain changes in major depression. *Neuropsychopharmacology* 2018; 43: 1138–45.
29. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* 2011; 36: 2452–9.
30. Dantzer R, O'Connor JC, Freund GG et al. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008; 9: 46–56.
31. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. *Neuron* 2020; 107: 234–56.
32. Hunt C, Macedo E, Cordeiro T, Suchting R et al. Effect of immune activation on the kynurenine pathway and depression symptoms – a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2020; 118: 514–23.

33. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosom Med* 2011; 73: 114–26.
34. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev* 2012; 36: 764–85.
35. Borsini A, Cattaneo A, Malpighi C et al. Interferon-alpha reduces human hippocampal neurogenesis and increases apoptosis via activation of distinct STAT1-dependent mechanisms. *Int J Neuropsychopharmacol* 2018; 21: 187–200.
36. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: a meta-analysis. *J Affect Disord* 2020; 277: 940–8.
37. Mac Giollabhui N, Ng TH, Ellman LM et al. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. *Mol Psychiatry* 2021; 26: 3302–14.
38. Perry BI, Upthegrove R, Kappelmann N et al. Associations of immunological proteins/traits with schizophrenia, major depression and bipolar disorder: a bi-directional two-sample mendelian randomization study. *Brain Behav Immun* 2021; 97: 176–85.
39. Howard DM, Adams MJ, Clarke TK et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci* 2019; 22: 343–52.
40. Strawbridge R, Arnone D, Danese A et al. Inflammation and clinical response to treatment in depression: a meta-analysis. *Eur Neuropsychopharmacol* 2015; 25: 1532–43.
41. Gleeson M, Bishop NC, Stensel DJ et al. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 2011; 11: 607–15.
42. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis* 2014; 24: 929–39.
43. Bae J-H, Kim G. Systematic review and meta-analysis of omega-3-fatty acids in elderly patients with depression. *Nutr Res* 2018; 50: 1–9.
44. O'Toole MS, Bovbjerg DH, Renna ME et al. Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: a systematic review and meta-analysis. *Brain Behav Immun* 2018; 74: 68–78.
45. Kappelmann N, Lewis G, Dantzer R et al. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry* 2018; 23: 335–43.