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Inflammation and Depression: A Public Health Perspective

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- Figure 1. Target populations for primary and secondary prevention of inflammation-related depression

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Abstract

The multifaceted role of low-grade systemic inflammation in depression and physical illnesses like cardiovascular disease highlights complex interactions between the body, brain and mind. While current research on inflammation and depression has largely focused on exploring possible disease mechanisms and therapeutic potential, we seek to broaden the current discussion by introducing a public health perspective. In this Viewpoint, we propose that inflammation and its contributing sources could represent important targets for public health strategies aimed at improving both mental and physical health. We discuss potential universal, selective and indicated primary prevention strategies for inflammation-related depression. We consider potential approaches to secondary prevention, including scope for anti-inflammatory treatment and CRP testing for guiding treatment allocation and prognosis. Preventive strategies discussed here could also be relevant for other inflammation-mediated mental health conditions.

Inflammation as a public health target for chronic physical and mental illnesses

Low-grade systemic inflammation (hereinafter referred to as inflammation), characterised by persistent sub-acute elevated levels of inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) (Danesh, 2000), is implicated in the pathogenesis of many chronic physical and mental conditions, including coronary heart disease, diabetes mellitus, depression and schizophrenia (Berk et al., 2013). Current research has predominantly focused on understanding possible pathophysiological roles of inflammation and its therapeutic potential. In this Viewpoint, we propose that inflammation and its modifiable sources represent important targets for public health interventions for improving physical and mental health. We focus on depression as an exemplar for inflammation-mediated mental disorders given its significant burden and strong link with inflammation. However, we acknowledge that our discussion is also relevant for other inflammation-mediated conditions, and that other mechanisms like hypothalamic-pituitary-adrenal axis dysfunction can work in conjunction with or independently of inflammation in depression.

Multiple lines of evidence support a causal role for inflammation in depression (Khandaker et al., 2017). These include animal studies reporting that inflammation-induced sickness behaviour resembles somatic/neurovegetative symptoms of depression in rodents and primates (Dantzer et al., 2008), case-control studies reporting elevated CRP and other inflammatory mediator levels in depressed patients (Osimo et al., 2020) and randomised controlled trials (RCTs) reporting antidepressant effect for anti-inflammatory drugs (Kappelmann et al., 2018). Causal inferential techniques like Mendelian randomisation also show that genetic variants regulating levels/activities of CRP and IL-6 are associated with depression (Khandaker et al., 2020).

Recent evidence showing linear trends of increasing depression risk with increasing CRP levels in the population suggests that inflammation and depression could share a similar relationship like blood pressure and stroke (Ye et al., 2021). This makes inflammation a potential candidate for public health interventions. Using conservative estimates for prevalence of inflammation (CRP=3-10mg/L) in depression (16%) and corresponding risk ratio (1.76), we estimate the population attributable fraction of inflammation for depression to be about 7%. This means roughly 1 in 15 depression cases may be attributed to inflammation, which equates to millions of people globally, given the 10-20% estimated lifetime prevalence for depression (Lim et al., 2018).

Primary preventive strategies for inflammation-related depression

Universal, selective and indicated preventive strategies directed towards general, at-risk and high-risk populations, respectively, could be a useful framework for thinking about the primary prevention of inflammation-related depression (Figure 1).

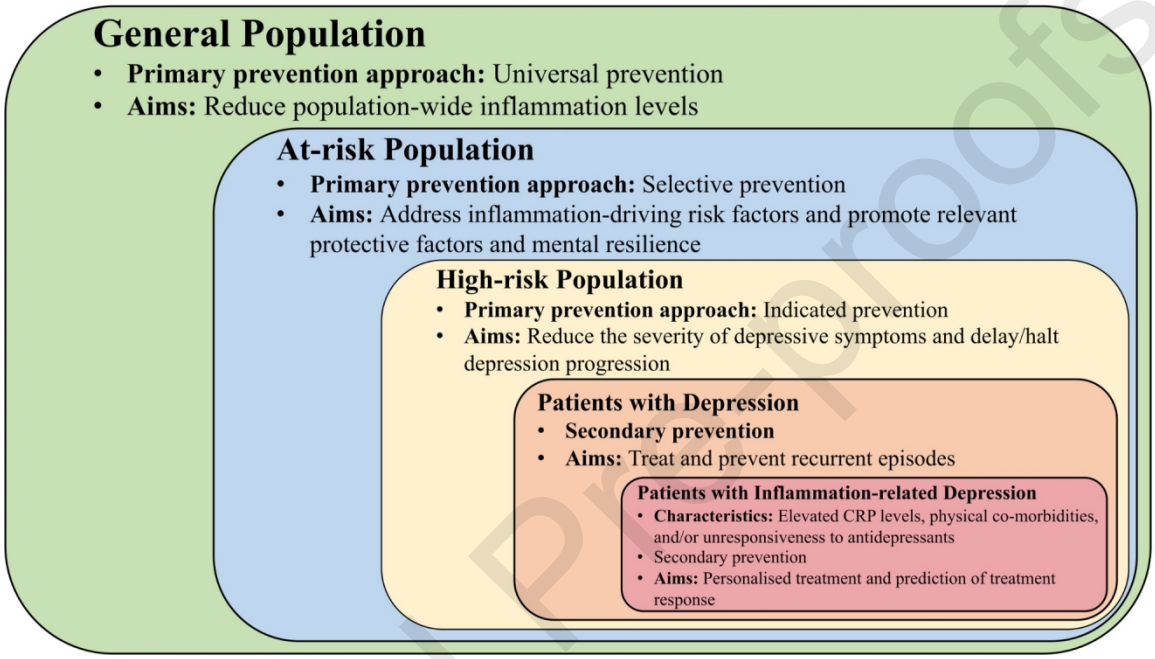

Figure 1. Target populations for primary and secondary prevention of inflammation-related depression

Note: Relative size of each box is not representative of the true size for each respective population group.

The main goal of universal preventive strategies would be to reduce inflammation levels in the general population. Such strategies could involve interventions aimed at achieving regular physical activity, weight reduction and diets with a low dietary inflammatory index. While universal preventive strategies possess the greatest potential in reducing incidence of depression, no RCT, to our knowledge, has investigated the impact of universal preventive interventions targeting inflammation on depression risk. We now require large-scale studies

that examine: a) the impact of weight reduction, dietary and other interventions on inflammation levels in the general population; b) the impact of such interventions on inflammation-related depression incidence.

Selective preventive strategies target at-risk individuals whose depression risk is higher than the general population and seek to reduce inflammation by addressing underlying pro-inflammatory risk factors and promoting relevant protective factors. Typical examples may include promoting sustained physical activity among patients with chronic diseases and stress management programmes in high-intensity occupational settings. Key issues to consider include determining the appropriate at-risk group and choice of intervention. Because depression risk is higher in at-risk groups compared to the general population, assessing the impact of selective preventive interventions on inflammation levels and subsequent depression risk may be a more feasible first step.

Indicated preventive strategies target "high-risk" individuals, i.e., those exhibiting depressive symptoms but are below the threshold for a depression diagnosis. One important goal for indicated preventive strategies is improving detection of high-risk individuals for clinical monitoring, management and/or referral. Whether evidence of inflammation in symptomatic individuals increases risk of progressing to clinical depression requires further evaluation. Adapting existing clinical models like collaborative care could be useful for delivering preventive interventions for symptomatic, help-seeking individuals. Further integration of physical and mental healthcare, including increased mental health input from primary to tertiary care settings, could improve monitoring of depressive symptoms and use of self-help interventions. This approach could be particularly useful for individuals with chronic inflammatory physical illnesses. However, it is worth noting that increasing detection and

monitoring of mildly symptomatic individuals could contribute to the over-medicalisation of depression.

Secondary preventive strategies for inflammation-related depression

Inflammation is associated with poor response to conventional antidepressants and psychotherapies, and it has been proposed that depressed patients with evidence of inflammation may be suitable candidates for anti-inflammatory treatment. Targeting inflammation may also be a useful approach for secondary prevention of depression, which aims to effectively treat and prevent recurrence (Figure 1). Specifically, inflammation could be a useful means for guiding treatment decision and predicting/monitoring response.

Meta-analyses of RCTs have showed that adjunct anti-inflammatory drugs provide greater benefit than antidepressants alone (effect size ~0.35) (Köhler et al., 2014) and that anti-inflammatory drugs improve depressive symptoms in individuals with chronic inflammatory diseases independently of improvements in physical illness (effect size ~0.40) (Kappelmann et al., 2018). Emerging evidence from RCTs suggest that anti-inflammatory treatment could be useful for depressed individuals with evidence of inflammation (CRP >3 mg/L) (Nettis et al., 2021). Future large-scale clinical trials are needed to test efficacy of anti-inflammatory drugs as monotherapy or adjunct therapy for depression. Studies are also needed to examine whether assessing inflammatory markers and identifying a subset of newly diagnosed patients with inflammation-related depression could be a cost-effective way of predicting treatment response, finding more suitable, personalised treatment regimens and improving treatment outcomes.

Conclusion

As our understanding of the complex interactions between the body, brain and mind improves, this understanding needs to be matched with a concerted effort to develop not only

new treatments but also public health strategies that recognise the broad-spectrum impact of targeting inflammation and its modifiable sources. By offering an initial primary and secondary prevention framework for inflammation-related depression, we call to attention the need for more interdisciplinary research that will drive integration between physical and mental healthcare and other innovative public health approaches.

Declaration of Interests

All authors do not have any conflicts of interest to report regarding this specific work. MH reports receiving personal fees from MSD Gilead. PBJ is a scientific advisory board chair for Ricordati and a scientific advisory board member for Janssen.

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