

A comprehensive matrix of factors contributing to depression

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A study drawing on the expansive UK Biobank dataset to explore the lifestyle, genetic and biological underpinnings of mental health highlights the influence of lifestyle on depression risk and suggests that detailed investigations into lifestyle factors, in conjunction with psychological aspects and advanced analysis methods, may reveal a deeper understanding of the complexities of mental health.

In this issue of *Nature Mental Health*, Zhao et al.¹ offer a complex yet insightful exploration of the psychological, genetic and biological mechanisms underpinning mental health. The authors used the UK Biobank, a robust longitudinal dataset providing a range of demographic, behavioral, imaging and biomarker data, to elucidate the intricate relationships between genetics, lifestyle factors, brain structure, immunometabolic function and depression.

The study drew on data about participants' adherence to the following behaviors, which we refer to collectively as 'lifestyle': (1) moderate alcohol consumption; (2) a healthy diet; (3) regular physical activity; (4) healthy sleep patterns; (5) non-smoking; (6) low-to-moderate sedentary behavior; and (7) frequent social contact. Participants in the study were grouped into three lifestyle categories based on a score of 0 to 7 derived from these seven key behavioral factors. Favorable lifestyle was classified as adhering to 5 to 7 healthy factors, intermediate lifestyle involved adhering to 3 to 4 healthy factors, and unfavorable lifestyle meant adhering to 0 to 2 healthy factors, with guidelines for each factor such as never smoking, moderate alcohol consumption and regular physical activity shaping the categorizations. The risk of depression decreased in more favorable classes compared with less favorable classes, showing the protective influence of a healthy lifestyle. A Mendelian randomization analysis provided evidence of a causal relationship between lifestyle factors and depression, showing that even a genetic vulnerability to depression could be mitigated by lifestyle changes.

In their sophisticated examination of the underlying mechanisms of depression, Zhao et al.¹ applied a structural equation model, unravelling complex associations between lifestyle, polygenic risk score, brain structure, immunometabolic function and depression. Using confirmatory factor analysis, they identified the left lateral orbitofrontal cortex in cortical volume and the left thalamus proper in subcortical volume as the most substantial predictors for the latent variable of brain structure. Similarly, increased levels of markers such as C reactive protein, triglycerides, glycated hemoglobin (HbA1c) and glucose

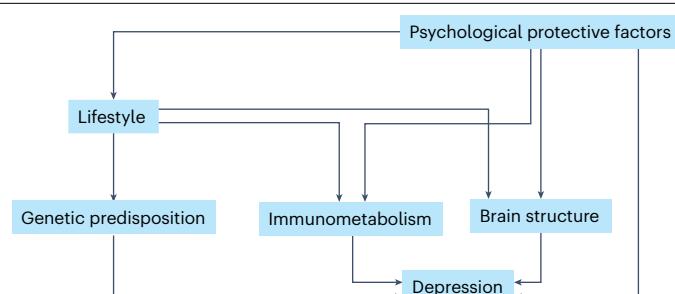


Fig. 1 | A modified model of depression including psychological protective factors. Psychological protective factors include self-esteem, mindfulness, effective coping strategies, positive traits and social support.

influenced immunometabolic function, which involves the interaction between the body's defense system and its energy usage. The authors then demonstrated that lifestyle – or daily habits – significantly predicted depression, immunometabolic function and brain structure. Lifestyle also had a potent effect in overriding the impact of polygenic risk score, a genetic score forecasting predisposition to certain conditions – such as depression. Together, these findings emphasize how lifestyle adjustments can potentially reduce the onset of depression, especially in individuals who are genetically inclined towards it, and present a comprehensive perspective on the condition, weaving in genetic, structural, metabolic and lifestyle considerations.

The exploration of the link between a healthy lifestyle and a reduced depression risk, including relationships with genetics and brain structures, is not in itself novel. Previous evidence has indicated that adherence to healthy lifestyles can lower the risk of depression regardless of genetic risk². Depression has been associated with regional variations in the volume of grey matter, with specific lifestyle factors contributing to this, although these alterations are possibly long-term consequences and not dynamically related to the trajectory of depression³. Further, multi-component lifestyle-modification interventions have shown promise in mitigating depressive symptoms, particularly in patients diagnosed with major depression, although the clinical effect size is small, indicating the need for more comprehensive and individualized lifestyle interventions⁴. The study by Zhao et al. stood out for its rigorous nine-year longitudinal design, exploring the protective roles of seven healthy lifestyle factors on depression and illustrating how genetic vulnerability to depression can be offset by lifestyle changes. Supported by Mendelian randomization analysis and structural equation modeling, their findings reinforce the understanding that adherence to a healthy lifestyle substantially diminishes the risk of depression, thus making a noteworthy contribution to the field. However, more nuanced analyses are necessary. Here, we comment on aspects related to the analyses of the effects of lifestyle factors.

The work presented by Zhao et al.¹ highlights opportunities for further research to scrutinize the role of critical psychological protective factors. Notably, a range of such factors, including self-esteem, mindfulness, effective coping strategies, positive traits and strong social support systems, have been shown to be pivotal in building resilience and combatting depression⁵. Incorporating mindfulness and acceptance, specifically, could provide essential insights into how individuals can effectively manage negative thoughts and emotions, reducing the risk of depression, particularly when used as a preventive strategy aligned with a public health perspective^{6,7}. Including these additional variables as more detailed lifestyle factors or as separate psychological protective factors into their model would offer a broader and more holistic perspective on the complex dynamics at play in depression, thereby potentially informing more effective prevention and treatment strategies. Figure 1 shows a modified model of depression, illustrating that lifestyle has a protective influence through its effects on immunometabolism and brain structure. This influence mitigates the effects of genetic predisposition¹. Meanwhile, psychological protective factors can influence lifestyle, immunometabolism and brain structure, potentially providing further protection against depression⁵⁻⁷.

Moreover, the statistical approach taken by Zhao et al.¹, although rigorous, could be further enhanced by employing network analysis techniques⁸. In particular, the use of Bayesian inference in Gaussian graphical models could provide a more sophisticated exploration of the interactive relationships between the diverse factors at play⁹. Such analysis can generate a comprehensive matrix of lifestyle, biological and psychological factors associated with depression, providing more nuanced insights into the complex interplay of these variables. The assessment by Zhao et al. of the effects of the seven lifestyle factors into a single three-point ordinal scale is a severe reduction in detail, which precluded any ability to test for any interactions between the individual factors. Future studies should estimate unique protective contributions of specific lifestyle factors using more precise estimates.

Furthermore, the use of directional graphical models in network analysis could provide valuable insights into the causal dynamics between these variables¹⁰. Directional graphical models, in the context of network analysis, refer to statistical diagrams that visually

represent relationships and the flow of causality among variables, enabling researchers to understand how changes in one variable may directly influence others. Such models could help establish potential causal pathways, elucidating how changes in one variable might propagate through the network and impact depression. This could enhance our understanding of the intricate mechanisms underlying depression and guide the development of more targeted, effective interventions.

In conclusion, the work by Zhao et al.¹ contributes to our understanding of the multifaceted nature of depression and further extends the framework outlined by previous research. Building on this work, the exploration of the role of more detailed lifestyle factors and the addition of psychological factors would yield richer insights, particularly when combined with analytic methods such as network analysis. These approaches have the potential to reveal a more nuanced view of the complexities of mental health and foster the development of more effective intervention strategies.

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Competing interest

The authors declare no competing interests.