

Integrated lifestyle factors mitigate depression risk across varied genetic susceptibility

A large-scale prospective cohort study with 287,282 participants revealed that the integration of multiple healthy lifestyle factors (a favorable lifestyle) was associated with a lower risk of depression. Categorizing participants on the basis of their polygenic risk scores for depression demonstrated that the effect of this favorable lifestyle persisted even among participants with high genetic susceptibility.

This is a summary of:

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The problem

The multifaceted etiology of depression¹ – which encompasses genetic predisposition, immunometabolic dysregulation and brain-structure atrophy – has produced challenges for the development of effective treatment. The escalating global prevalence of depression has imparted a substantial public health burden², so the need to devise effective preventive measures against depression has become increasingly evident. Risk factors for depression are mainly environmental; thus, modulating lifestyle in a positive, preventative direction, such as implementing a healthier diet or engaging in more social support, might outweigh the risk of genetic predisposition.

Prior investigations have revealed the beneficial impact of individual favorable lifestyle changes on depression prevention^{3,4}, but potential synergistic effects arising from the integration of multiple healthy lifestyle factors, their capacity to outweigh depression risk factors, and the underlying mechanisms remain comparatively less explored⁵. A thorough exploration of these uncharted territories might identify promising and comprehensive prevention strategies tailored to at-risk people and might thereby address a pressing need in depression prevention⁶.

The solution

We selected 287,282 participants with over 9 years of follow-up from the UK Biobank to investigate the integrated influence of seven healthy lifestyle factors – moderate alcohol consumption, a nourishing diet, regular physical activity, optimal sleep patterns, non-smoking status, limited-to-moderate sedentary behavior, and frequent social interactions – on depression risk. Participants were assigned a score of 1 point for each lifestyle factor they practiced (on the basis of national recommendations), and the resulting lifestyle score was subsequently categorized as a favorable (five to seven lifestyle factors), intermediate (two to four lifestyle factors) or unfavorable (zero to one lifestyle factors) lifestyle class. Next, Mendelian randomization assessed whether causal associations existed between a favorable lifestyle and depression. We stratified 197,344 participants into low, intermediate and high genetic risk subgroups on the basis of their polygenic risk scores for depression (calculated from the UK Biobank genotype data in conjunction with a genome-wide association result for depression) to explore whether heterogeneity in the impact of healthy lifestyle factors existed across participants with varying genetic susceptibility.

Finally, we used structural equation models on 18,244 participants to model the interplay of favorable lifestyle, genetic susceptibility, immunometabolism, brain structure and depression.

Our investigation revealed a monotonically decreasing risk of depression for participants who integrated the practice of more lifestyle factors across the three lifestyle classes. The seven lifestyle factors were each individually associated with decreased depression risk (<25%), but the adoption of an intermediate lifestyle or favorable lifestyle was associated with a 41% or 57% lower risk of depression, respectively, compared with an unfavorable lifestyle (Fig. 1a). Furthermore, Mendelian randomization confirmed a causal relationship between lifestyle score and depression risk. Another monotonically decreasing trend in depression risk existed across increasingly favorable lifestyle classes, and this persisted across all three genetic risk subgroups. In sum, our findings demonstrate synergistic protective effects that stem from the integration of multiple healthy lifestyle factors in mitigating depression risk. This collective impact seems to surpass the influence of genetic disposition, as indicated by the diverse underlying mediating mechanisms of brain structure and immunometabolic function.

The implications

Our study revealed a robust and consistent dose–response relationship between an increasing number of favorable lifestyle factors and a reduction in depression risk that was independent of genetic susceptibility. This finding strongly suggests that integrated lifestyle interventions hold promise as effective preventive strategies for people at high risk of depression. Thus, combined lifestyle modifications could potentially serve as personalized and tailored approaches to mitigating depression risk, particularly in people with a genetic predisposition to the condition.

The assessment of lifestyle factors relied on subjective self-report questionnaires and thereby potentially introduced measurement error and subjectivity into the data. Compared with the general UK population, the UK Biobank has a ‘healthy volunteer’ selection bias. As depression frequently has its onset in adolescence, in our future research studies we intend to determine whether the integration of healthy lifestyle factors can also reduce the risk of depression in adolescents.

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EXPERT OPINION

“The categorization of individuals into three classes based on the degree of lifestyle engagement provides a useful and practical way to understand the relationship between lifestyle and depression. Overall, the reported results provide strong evidence

for the protective role of a healthy lifestyle in reducing the risk of incident depression and highlight potential mechanisms linking lifestyle factors with depression.”

Oleg Medvedev, University of Waikato, Hamilton, New Zealand.

FIGURE

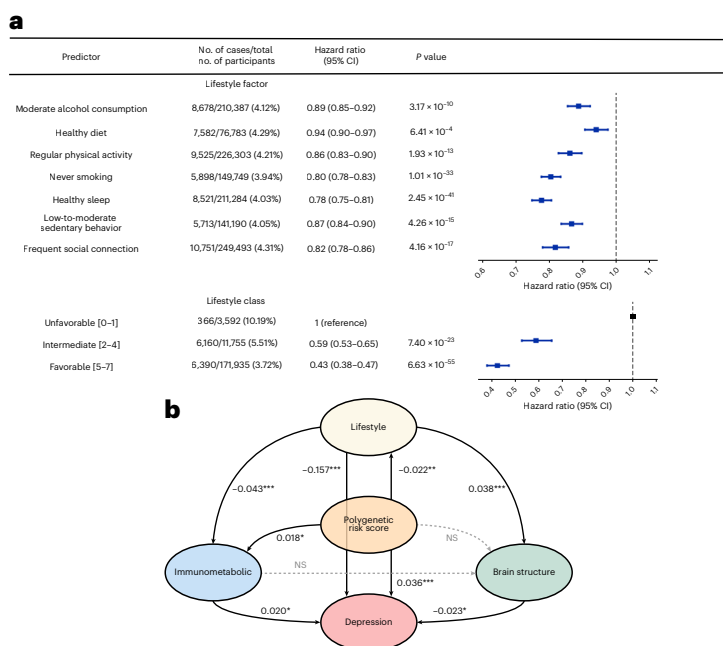


Fig. 1 | Depression risk according to lifestyle factors and underlying mechanisms. a, The association of lifestyle factors and classes with depression risk in 287,282 UK Biobank participants. Lifestyle class was assigned by allocating participants 1 point for each lifestyle factor they practiced (on the basis of national recommendations). Lifestyle score was reclassified into three classes: favorable (5–7), intermediate (2–4) and unfavorable (0–1). The results were adjusted for age, sex, Townsend deprivation index, body mass index and education level. CI, confidence interval. **b**, Structural equation model of 18,244 participants, showing that brain structure and immunometabolic function are the latent variables that mediate the effect of lifestyle on depression. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$; NS, not significant. © 2023, Zhao, Y. et al.

BEHIND THE PAPER

The study was conducted by a team of researchers belonging to the Feng and Cheng lab, from the Institute of Science and Technology for Brain-Inspired Intelligence at Fudan University, in conjunction with the Department of Neurology and the Institute of Neurology at Huashan Hospital, China. We also have close academic collaboration with the University of Cambridge and the University of Warwick. The study’s most challenging and crucial aspects entailed

first identifying credible criteria to define what constitutes a favorable lifestyle and then effectively handling and analyzing the big data obtained from UK Biobank. To tackle the latter, members of the Feng and Cheng lab dedicated their expertise to adeptly managing big data and developing algorithms, while our collaborating neurologists provided invaluable insights to define favorable lifestyle parameters on the basis of reliable guidelines. **J.F.**

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FROM THE EDITOR

“Zhao et al. used UK Biobank data to examine the role of lifestyle factors in depression. They conducted multiple analyses and estimated underlying mechanisms related to brain structure, immunometabolism and genetics.”

Ioannis Bakoyiannis, Associate Editor, Nature Mental Health.