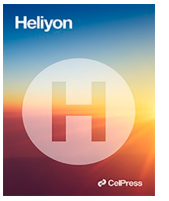
Heliyon 10 (2024) e30718

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Causal relationships between serum albumin, neuroticism and suicidal ideation in depressed patients: A Mendelian randomization study

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ARTICLE INFO

Keywords:
Depression
Mendelian randomization
Neuroticism
Serum albumin
Suicidal ideation

ABSTRACT

Although serum albumin and neuroticism have revealed a strong association with suicidal ideation in individuals with depression, the causal relationship between them is uncertain. This study analyzed the causal association of serum albumin, neuroticism and suicidal ideation using large-scale GWAS data and Univariable Mendelian Randomization (UVMR) methods. The Multivariable MR (MVMR) analysis was used to explore the causal pathways. UVMR analysis revealed that genetically determined serum albumin is causally associated with neuroticism ($\beta = -0.006$ $_{S.D.}$; 95 % *CI*: 0.009, −0.002; $p = 0.003$) and suicidal ideation ($\beta = 0.009$ $_{S.D.}$; 95 % *CI*: 0.001, 0.016; $p = 0.037$); and that neuroticism mediates 100 % of the causal association between serum albumin and suicidal ideation in individuals with depression. These findings suggest genetic evidence for the causal effect of serum albumin on suicidal ideation in depressed patients and the significant mediation effect of neuroticism on this causal association. This study proves the protective role of serum albumin for neuroticism and the riskiness of personality traits for suicidal ideation in individuals with depression.

1. Introduction

Suicide is the fourth leading cause of death worldwide and becoming a significant issue of public mental health [1]. Several studies proposed a continuous sequence of suicide severity from suicidal ideation (SI), suicide attempts, then to suicide [2,3]. SI is an important indicator for assessing suicide risk, including whether suicidal thoughts or threats will be followed by suicide action [4]. Moreover, SI is strongly linked to psychiatric disorders, particularly, depression [5]. It has been demonstrated that lifetime SI in depressed patients is 53.1 % [6], and sixty percent of deaths from suicide is associated with depressive disorders [7]. Meanwhile, SI is a common and major crucial symptom of depressive disorder [8]. However, the risk factors of SI in individuals with depression are still unclear.

To date, the stress-diathesis model is a most common and useful model to explain why one person commits suicide during a depressive episode and another does not. This model proposes that SI and suicidal behavior are the results of interactions between

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https://doi.org/10.1016/j.heliyon.2024.e30718
Received 5 March 2023; Received in revised form 28 April 2024; Accepted 2 May 2024
Available online 4 May 2024

environmental stressors and predispositions [9,10]. Typical environmental stressors refer to various stressful events in the daily life, while predisposition is mainly caused by both biological and psychological factors. Family studies have shown a significant genetic predisposition with SI and behaviors with heritability ranging from 30 % to 55 % [11]. Meanwhile, physiological cause of suicide can result from gene-environment interactions, such as decreased levels of serum albumin [9].

Albumin is a most abundant protein and a multifaceted factor in physiological processes, including its involvement in the pathophysiology of depression, particularly, its strong association with SI. Matsunaga study [12] found that increased positive emotions are accompanied by elevated serum albumin level, whereas negative emotions are negatively associated with serum albumin levels. Moreover, decreased levels of serum albumin are negatively related to severe depressive symptoms only in depressed patients with SI [13,14]. Collectively, serum albumin is able to serving as a "barometer" for SI in depressed patients and play an important role in depressive symptoms and SI.

In terms of the predisposition of psychological qualities, personality traits, such as neuroticism, are the most critical factors on the development of SI and suicidal behavior [15,16]. Neuroticism is one of the major traits describing human personality and manifests in the emotional regulation and stability of individuals [17]. According to the personality structure theory of Eysenck, individuals with high neuroticism prone to be emotionally unstable and to experience negative emotions in response to stress [18]. Adams et al. found that depression and neuroticism share numerous genetic risk factors [19]. Furthermore, in persons with a history of depression, neuroticism additionally increases the risk of recurrence by facilitating reactivation of SI [20]. A meta-analysis study suggests that neuroticism could be a stable personality trait and vulnerable to SI [21]. Another study also suggests that neuroticism-correlated copings, such as the emotion-oriented coping, are predictive to SI [22]. It is acknowledged that personality traits might have biological origins [23]. Individuals being high in neuroticism exhibit high levels of inflammatory cytokines, such as interleukin-6 [24]. A large body of studies have revealed that serum albumin is decreased with increased inflammation suggesting an involvement in inflammatory system. Moreover, elevated serum albumin could improve brain circulation and protect structure and function of brain [25]. Individuals with high neuroticism often manifest abnormalities in serum albumin [23,26]. These findings imply that serum albumin plays a role in neuroticism. However, the effect of albumin in neuroticism is rarely reported.

Although the accumulated evidence from observational studies suggests that serum albumin is associated with both the neuroticism and SI in depressed patients, traditional observational studies are often influenced by confounding factors and potential reverse causal associations [27]. Thus, it is still unclear whether the relationships between serum albumins, neuroticism and SI are causal in depression and what is the causal pathways. Mendelian Randomization (MR) analyses applies genetic variants as instruments to estimate the causality between exposure and outcome which is a widely used with large-scale genome-wide association studies (GWASs) [28]. Multivariable MR (MVMR) is an extension of MR and used to estimate the effect of each genetic variants associated exposure on a single outcome. MVMR can equivalently analyses the mediation effects within the MR framework [29]. Thus, MVMR allows estimation of the different effects required for mediation analyses and keeps the benefits of causal inference when genetic tools were used, such as avoiding bias due to confounding [29]. Thus, a Univariable Mendelian Randomization (UVMR) analysis was used to explore the separate causation between serum albumin, neuroticism, and SI using GWAS data as well as the potential mediation effect. Univariable

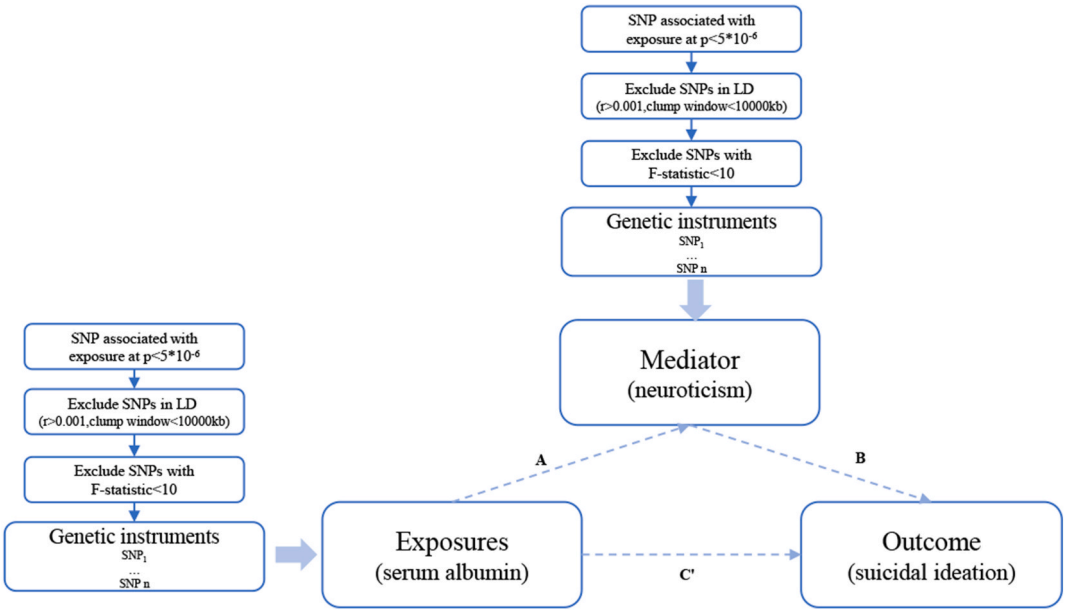

Fig. 1. Flowchart of the mediated MR design. The mediated MR is performed in two steps. The first step is to calculate the effect of exposure on the mediating variable A. The second step is to calculate the effect of mediation on outcome B. Then the two coefficients are multiplied to obtain the mediating effect. C′ is the effect of exposure on the outcome after adjusting for the mediating variable. SNP, single nucleotide polymorphism. LD, linkage disequilibrium.

Findings in this study may provide an instruction on etiological diagnosis, early-stage prevention, and treatments of SI.

2. Materials and methods

2.1. Study design

The single nucleotide polymorphism (SNP) loci for serum albumin, neuroticism and SI in depressed patients were screened and collated from three GWAS databases (all three databases were European populations). The potential causal relationship between serum albumin, neuroticism, and SI was investigated in depressed patients using Mendelian randomization analysis. The design is shown in Fig. 1.

2.2. GWAS summary data

The SNP–phenotype of serum albumin, neuroticism, and SI were obtained from the MR-Base (http://www.mrbase.org/). Specifically, the genetic associations of serum albumin were obtained from Prins et al. study [30], which include 9824 European participants. Genetic associations of neuroticism were obtained from a GWAS data including 168,105 European individuals [31]. The genetic associations of SI were obtained from a GWAS data including 32,630 Europeans with depression and 30,018 healthy Europeans.

2.3. Genetic instruments selection and data harmonization

Genetic instruments of exposures (serum albumin or neuroticism) were selected based on independent SNPs ($r^2 < 0.001$ & distance >10,000 kb) and at a genome-wide significance ($P < 5 \times 10^{-6}$). Furthermore, the instrument strength was assessed using *F*-statistic of each exposure. Instruments with $F > 10$ were considered valid [29].

2.4. MR analysis

The mediated MR analysis was performed using the two-sample MR, MRPRESSO, and the R packages of MR. The UVMR was performed to estimate the total causal effects of serum albumin on SI, and neuroticism on SI. MVMR was used for mediation analysis to decompose the effects of exposure on outcomes through mediating variables. While the MVMR analysis [32] was used to evaluate the direct effects of serum albumin and neuroticism on SI, the indirect effects of the mediating variables were assessed by the difference method. The main MR analysis was conducted with an inverse-variance weighted method (IVW). A bilateral $p < 0.05$ was considered significant difference. The thresholds were further adjusted by Bonferroni correction for the number of exposed phenotypes. Thus, the threshold of statistical significance for the 2 exposures was set at $p < 0.05/2 = 0.025$.

2.5. Sensitivity analysis

Sensitivity analysis is used to assess the robustness of the results and widely used in MR studies. Specifically, the heterogeneity was evaluated with IVW and MR Egger approaches. MR-PRESSO was used to estimate the directional pleiotropy [33] while the MR-Egger regression was used to obtain intercept [34]. The leave-one-out analysis was performed to evaluate whether MR estimates were biased or driven by a single SNP. The p value with more than 0.05 was considered acceptable. Moreover, the weak instrument bias and the

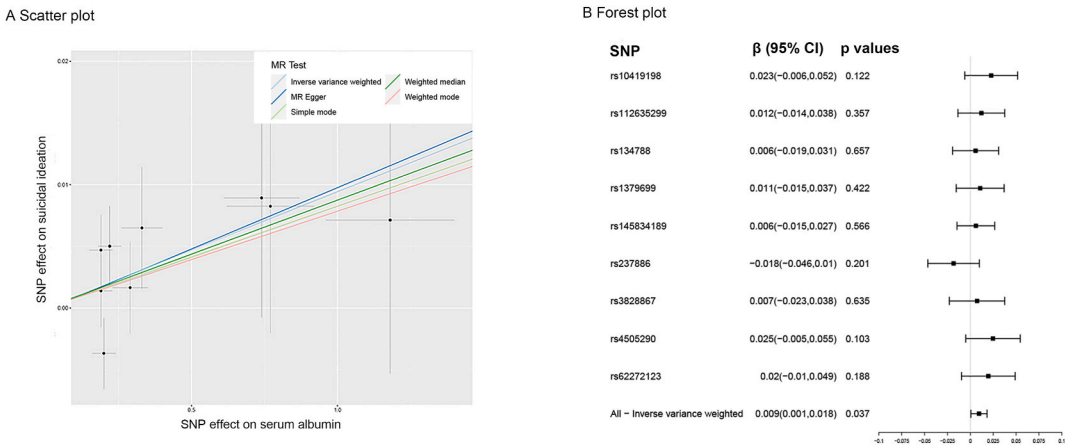

Fig. 2. Mendelian Randomization (MR) Plots for Relationship of serum albumin vs. suicidal ideation. A, Scatterplot of single-nucleotide polymorphism (SNP) potential effects on serum albumin vs. suicidal ideation, with the slope of each line corresponding to estimated MR effect per method. **B,** Forest plot of individual and combined SNP MR-estimated effects sizes. Data are expressed as raw β values with 95 % CI.

bias of IVW utilizing GWAS were further analyzed using the robust adjusted profile score (MR.RAPS) [35].

3. Results

3.1. Genetic instrumental variables

Totally, 13 independent SNPs were identified as genetic instruments for serum albumin levels while 77 independent SNPs were identified for neuroticism (Appendix S1) with valid F-statistic value for each individual SNP (F = 16–64), and a mean of 25.09 and 29.64 for serum albumin levels and neuroticism, respectively. Moreover, the conditional F-statistic value of MVMR was 15.19 for serum albumin and neuroticism, which were over the limiting value (F > 10) and suggesting a strong power of selected genetic instruments.

3.2. Univariable and multivariable Mendelian randomization

UVMR indicated a protective effect of genetically predicted serum albumin levels on neuroticism in the main IVW analyses ($\beta = -0.006$ S.D.; 95 % *CI*: 0.009, −0.002; $p = 0.003$, Fig. 2). Meanwhile, a direct causal association of serum albumin level with neuroticism ($\beta = 0.009$ S.D.; 95 % *CI*: 0.001, 0.016; $p = 0.037$, Fig. 3) and SI ($\beta = 0.120$ S.D.; 95 % *CI*: 0.059, 0.0180; $p < 0.001$, Fig. 4 and Fig. 5) was also observed using the IVW method. Similar results were gotten from the mr.raps, the simple mode, the weighted median, and weighted mode analyses (Table 1 and Appendix S2).

In addition, the MVMR analysis was conducted to examine the mediation effect of neuroticism on the causal association of serum albumin with SI. Results showed a significant direct causal effect of neuroticism on SI after adjusting the serum albumin ($\beta = 0.120$ SD.; 95 % *CI*: 0.053, 0.187; $p < 0.001$). There was no significant direct effect of serum albumin on SI after adjusting neuroticism ($\beta = 0.007$ S.D.; 95 % *CI*: 0.001, 0.014; $p = 0.080$), which suggested that neuroticism had complete mediating effect on the causal relationship between serum albumin levels and SI (Fig. 6).

3.3. Sensitivity analysis

In this study, sensitivity analysis approaches, such as the IVW, the mr.raps, MR Egger, leave-one-out analysis, and MR-PRESSO, were used to assess biases (Table 2). The results of the IVW and the mr.raps were concordant, i.e. , the difference test between these two estimates is not significant (Appendix S3). The MR-Egger intercept, Cochran's Q test, and MR-PRESSO analysis did not show horizontal pleiotropy (Appendix S4-S6). The leave-one-out analysis showed that the overall error line was not significantly changed after removing each SNP (all error lines are to the right of 0 or to the left of 0) (Appendix S7). The CI of MR-Egger included 0, which suggested a possible violation for the assumption of no measurement error [36].

4. Discussion

Growing evidence suggests significant effects of serum albumin and neuroticism on suicide in depressed patients with uncertain causal relationships. In this study, the causal association of serum albumin with neuroticism and SI was explored within an MR framework using large-scale GWAS data, while the mediation effect of neuroticism on the association of serum albumin with SI was investigated in depressive patients. Our results provided strong genetic evidence for a causal effect of serum albumin on SI and a complete mediation of neuroticism on this causal association in patients with depression.

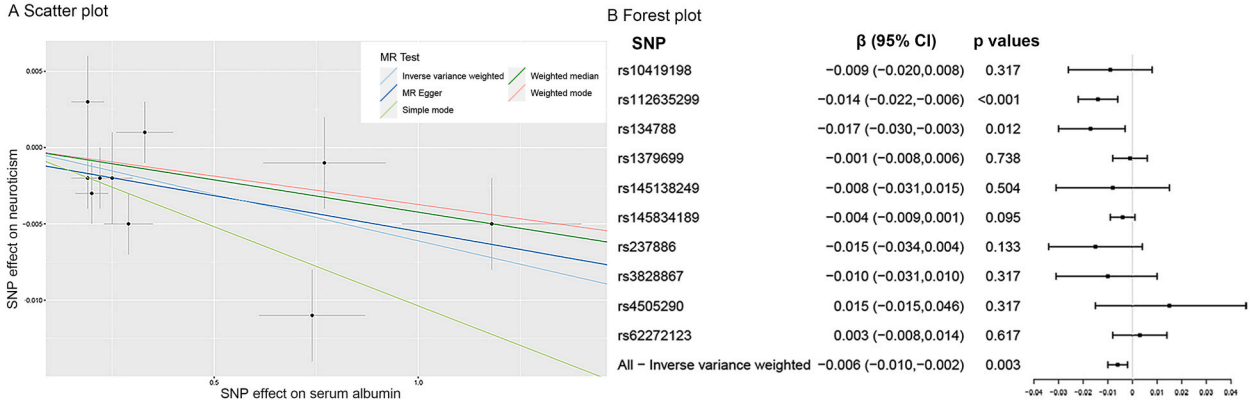

Fig. 3. Mendelian Randomization (MR) Plots for Relationship of serum albumin vs. neuroticism. A, Scatter plot of single-nucleotide polymorphism (SNP) potential effects on serum albumin vs. neuroticism, with the slope of each line corresponding to estimated MR effect per method. **B,** Forest plot of individual and combined SNPMR-estimated effects sizes. Data are expressed as raw β values with 95 % CI.

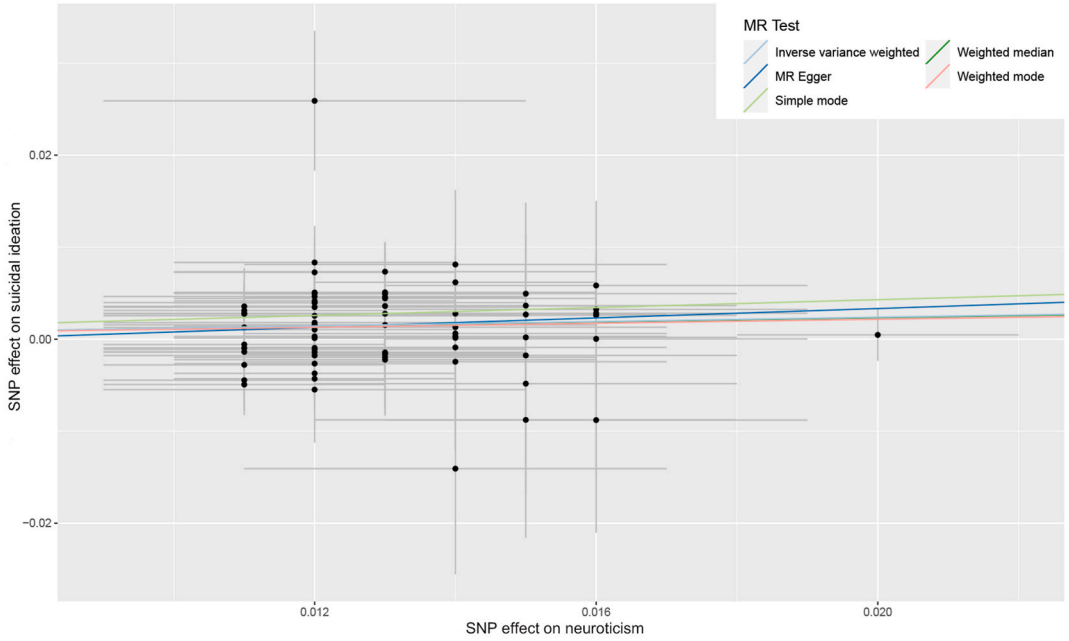

Fig. 4. Scatter plot. Scatter plot of single-nucleotide polymorphism (SNP) potential effects on neuroticism vs. suicidal ideation, with the slope of each line corresponding to estimated MR effect per method.

This study observed a casual association of serum albumin with SI in patients with depression. This finding is consistent with previous reports [13,37]. For example, a previous study has observed a lowered serum albumin level in patients with major depressive disorder, but it is increased after antidepressant treatment [37]. Another study in depressive patients has observed an inverse association between the level of serum albumin and the severity of depressive symptoms only in these patients ever having suicide attempt [13]. In contrast, some studies found no significant relationship between serum albumin and suicide [38,39]. The reason for these controversial findings might include that observational studies are unable to fully account for confounding factors and mediators, such as personality trait. Our findings from a genetic perspective clarified the causal relationship between serum albumin and SI. We hypotheses that the causal relationship may be associated with changes of serum albumin on brain structures. For example, serum albumin has been proven to improve brain circulation and exert a protective effect on neurons and glia [25]. An increased density of microglia has been observed in the thalamus, anterior cingulate cortex, and dorsolateral prefrontal cortexof the depressed suicidal patients compared to health controls [40]. Another study has observed an increased density of microglia in the white matter of the PFC in depressed suicidal patients compared to non-suicidal subjects [41]. Moreover, the role of microglia in suicide is considered as a new therapeutic target for suicide prevention [42]. Thus, the effects of serum albumin on SI in depressed patients may be mediated via its effects on microglia.

Neuroticism is a stable personality trait and individuals with high neuroticism are prone to distortions in thinking and cognition, presence of loneliness, impulsive behavior, and negative emotional, which are also important components of suicidal susceptibility [43]. In the present study, we found a direct causal association between neuroticism and SI in individuals with depression. Namely, neurotic personality directly increased the risk of suicide. This is similar to findings in a previous study that higher in neuroticism scores is associated with stronger SI [44]. The Suicide Schema Assessment Model [45] considers that neurotic individual has a selective processing bias for negative information, which causes itself sustaining negative emotional states and has a disposition to suicide-related information. This in turn inhibits adaptive cognitions and behaviors, and activates suicidal schemas, and subsequently results in hopelessness and distress. To escape from unbearable hopelessness and distress, individuals tend to develop SI. Overall, the established theories and published studies have evidenced that individuals with higher neuroticism preferably focus on the negative components of events, have less ability to regulate emotions and caught up in negative emotions, followed by increasing stress susceptibility and risk of SI [46]. This suggests that personality traits, especially the high neuroticism, should be vigorously emphasized in the clinical assessment, prevention, and treatment of suicidal ideation in patients with depression.

In addition, we also found a casual effect of genetically predicted serum albumin levels on neuroticism, and neuroticism mediated of the causal association between serum albumin and SI. Although it lacks observational studies on the causal association between serum albumin and neuroticism, previous studies have suggested that individuals with high neuroticism tend to be more emotionally unstable and have a higher stress susceptibility [47]. Moreover, serum albumin is extremely sensitive to environmental stressors and can reflect emotional states [12]. These findings suggest that albumin may also be a potential biomarker for stress response in individuals with high level neuroticism. From the molecular level, albumin is an extracellular molecule to maintain the plasma redox state, and lower albumin level predisposes to elevate the levels of free radicals [48], which are detected in individuals with a history of

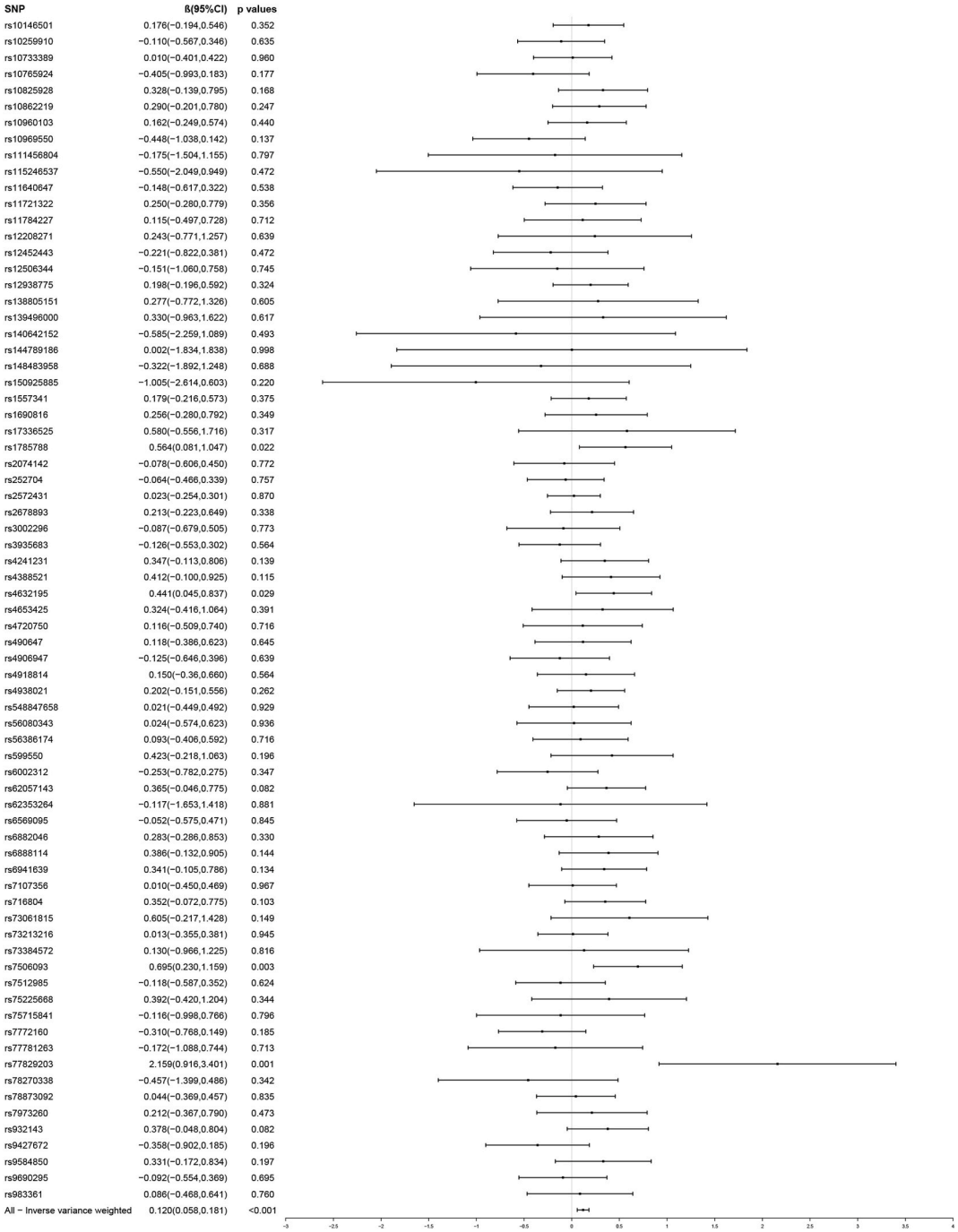

Fig. 5. Forest plot. Forest plot of individual and combined SNP MR-estimated effects sizes on neuroticism vs. suicidal ideation. Data are expressed as raw β values with 95 % CI.

SI over the last three months [49] and neuroticism [50]. Simultaneously, serum albumin is also a transporter and storage protein for fatty acids. Several studies have found that the deficiency of omega-3 polyunsaturated fatty acids is associated with depression symptom, neuroticism, and suicide [51,52]. In addition, serum albumin has been revealed to involve in the inflammation [53], such as that abnormal levels of some inflammatory factors are strongly associated with SI in patients with depression [54,55]. Individuals with high neuroticism also show elevated levels of inflammatory cytokines [24]. Collectively, these previous findings provide potential molecular evidence to support our findings directly or indirectly. However, experimental studies are still necessary to further conform the causality, mechanisms, and treatment potential for serum albumin involving in SI in depressed patients.

Table 1
MR results for the relationship among serum albumin, neuroticism and suicidal ideation.

Mendelian randomization (MR)	Exposure vs. Outcome	IVM β (95 % CI)	MR.raps β (95 % CI)	*P* (IVW)	*P* (mr.raps)	SNPs
UVMR (total effect)						
	SA vs. Ne	−0.006 (−0.009, −0.002)	−0.005 (−0.007, −0.003)	0.003	0.001	10
	SA vs. SI	0.009 (0.001, 0.016)	0.010 (0.006, 0.018)	0.037	0.036	9
	Ne vs. SI	0.119 (0.058, 0.179)	0.118 (0.055, 0.181)	<0.001	<0.001	73
MVMR (direct effect)	SA vs. SI	0.007 (−0.001, 0.014)	/	0.08	/	9
	Ne vs. SI	0.120 (0.053, 0.187)	/	<0.001	/	9

Note: UVMR, Univariate MR; MVMR, Multivariate MR; SA, serum albumin; Ne, neuroticism; SI, suicidal ideation; IVW, the inverse-variance weighted method. The same below.

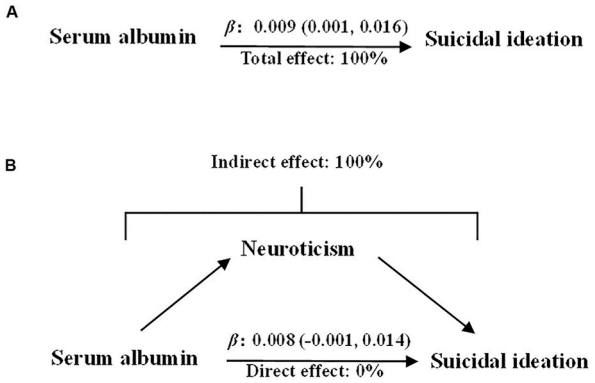

Fig. 6. Mediation Model Diagram. A diagram illustrating the breakdown of (A) the total effect of serum albumin on suicidal ideation into (B) a direct effect and an indirect effect via neuroticism.

Table 2
Sensitivity analysis for the relationship among serum albumin, neuroticism and suicidal ideation.

Exposure vs. Outcome	Method	Test of heterogeneity		Test of pleiotropy	
		Q	*P* values	Egger intercept	*P* values
SA vs. SI	MR Egger	6.301	0.505	−0.001	0.950
	IVW	6.305	0.613		
SA vs. Ne	MR Egger	14.214	0.076	−0.001	0.640
	IVW	14.633	0.101		
Ne vs. SI	MR Egger	69.642	0.523	−0.001	0.560
	IVW	69.983	0.545		

5. Conclusion

This study provided strong genetic evidence for the causal association between serum albumin and SI, and a mediating effect of neuroticism on this causal association. Our findings will contribute to better prediction and intervention of SI in patients with depression with the serum albumin and personality traits.

6. Limitations and implications

There are some limitations in this study. First, although the genetic variance is less affected by behavioral, social, and psychological confounders, Mendelian randomization analysis is inherently an epidemiological approach. Other factors such as the influence of individual childhood trauma or acute stressful events are also important and need attention in future studies. Second, this study used pooled GWAS data, which could not assess the non-linear relationship between exposure and outcome. It also could not be stratified by factors such as sex and age because of the lack of individual data. Third, the genetic sample was onlyfrom European ancestry in this study, which limits the extrapolation of findings. The reliability of findings in this study should be verified in other ethnic groups. Next but not last, although this study conducted a pleiotropy test through the MR-Egger intercept and MR-PRESSO, pleiotropy could cause the assumptions of independence and exclusivity to be invalid, which in turn affects the robustness of Mendelian randomization. Therefore, future studies should adopt more methods of pleiotropy tests to take into account the effect of gene pleiotropy and sample structure [56].

Data availability statement

All data are publicly available and can free download from the MR-Base (http://www.mrbase.org/). Further inquiries can be directed to the corresponding authors.

Ethics approval statement

Not applicable.

CRediT authorship contribution statement

Dongling Yuan: Writing – review & editing, Writing – original draft, Validation, Software, Data curation, Conceptualization. **Jialing Wu:** Writing – original draft, Software, Data curation. **Shansi Li:** Software, Data curation. **Xiao Zhou:** Software, Data curation. **Ruoyi Zhang:** Methodology, Data curation. **Yi Zhang:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by National Natural Science Foundation of China (No. 81701333), Natural Science Foundation of Hunan Province (No. 2022JJ70146) and Hunan Province Traditional Chinese Medicine Research Program (No. E2022038).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30718.

References

[1] Suicide Worldwide in, 2019. https://www.who.int/publications-detail-redirect/9789240026643. (Accessed 3 November 2022).
[2] E. Ropaj, Hope and suicidal ideation and behaviour, Curr. Opin. Psychol. 49 (2023) 101491, https://doi.org/10.1016/j.copsyc.2022.101491.
[3] N. Perroud, R. Uher, J. Hauser, M. Rietschel, N. Henigsberg, A. Placentino, D. Kozel, W. Maier, O. Mors, D. Souery, M. Dmitrzak-Weglarz, L. Jorgensen, Z. Kovacic, C. Giovannini, J. Mendlewicz, A. Zobel, J. Strohmaier, P. McGuffin, K.J. Aitchison, A. Farmer, History of suicide attempts among patients with depression in the GENDEP project, J. Affect. Disord. 123 (2010) 131–137, https://doi.org/10.1016/j.jad.2009.09.001.
[4] A.B. Miller, M.J. Prinstein, Adolescent suicide as a Failure of acute stress-response systems, Annu. Rev. Clin. Psychol. 15 (2019) 425–450, https://doi.org/10.1146/annurev-clinpsy-050718-095625.
[5] N.A. Jackson, M.M. Jabbi, Integrating biobehavioral information to predict mood disorder suicide risk, Brain Behav. Immun. - Health. 24 (2022) 100495, https://doi.org/10.1016/j.bbih.2022.100495.
[6] M. Dong, S.-B. Wang, Y. Li, D.-D. Xu, G.S. Ungvari, C.H. Ng, I.H.I. Chow, Y.-T. Xiang, Prevalence of suicidal behaviors in patients with major depressive disorder in China: a comprehensive meta-analysis, J. Affect. Disord. 225 (2018) 32–39, https://doi.org/10.1016/j.jad.2017.07.043.
[7] G. Turecki, D.A. Brent, D. Gunnell, R.C. O'Connor, M.A. Oquendo, J. Pirkis, B.H. Stanley, Suicide and suicide risk, Nat. Rev. Dis. Prim. 5 (2019) 1–22, https://doi.org/10.1038/s41572-019-0121-0.
[8] P.E. Croarkin, P.A. Nakonezny, Z.-D. Deng, M. Romanowicz, J.L.V. Voort, D.D. Camsari, K.M. Schak, J.D. Port, C.P. Lewis, High-frequency repetitive TMS for suicidal ideation in adolescents with depression, J. Affect. Disord. 239 (2018) 282–290, https://doi.org/10.1016/j.jad.2018.06.048.
[9] K. van Heeringen, J.J. Mann, The neurobiology of suicide, Lancet Psychiatr. 1 (2014) 63–72, https://doi.org/10.1016/S2215-0366(14)70220-2.
[10] D.B. O'Connor, N. Gartland, R.C. O'Connor, Stress, cortisol and suicide risk, Int. Rev. Neurobiol. 152 (2020) 101–130, https://doi.org/10.1016/bs.irn.2019.11.006.
[11] M. Voracek, L.M. Loibl, Genetics of suicide: a systematic review of twin studies, Wien Klin. Wochenschr. 119 (2007) 463–475, https://doi.org/10.1007/s00508-007-0823-2.
[12] M. Matsunaga, S. Sato, T. Isowa, H. Tsuboi, T. Konagaya, H. Kaneko, H. Ohira, Profiling of serum proteins influenced by warm partner contact in healthy couples, Neuroendocrinol. Lett. 30 (2009) 227–236.
[13] L. Ambrus, S. Westling, Inverse association between serum albumin and depressive symptoms among drug-free individuals with a recent suicide attempt, Nord. J. Psychiatr. 73 (2019) 229–232, https://doi.org/10.1080/08039488.2019.1610056.
[14] N. Ruljancic, M. Mihanovic, I. Cepelak, A. Bakliza, K.D. Curkovic, Platelet serotonin and magnesium concentrations in suicidal and non-suicidal depressed patients, Magnes. Res. 26 (2013) 9–17, https://doi.org/10.1684/mrh.2013.0332.
[15] C. Doihara, C. Kawanishi, N. Ohyama, T. Yamada, M. Nakagawa, Y. Iwamoto, T. Odawara, Y. Hirayasu, Trait impulsivity in suicide attempters: preliminary study, Psychiatr. Clin. Neurosci. 66 (2012) 529–532, https://doi.org/10.1111/j.1440-1819.2012.02379.x.
[16] J. Ormel, B.F. Jeronimus, R. Kotov, H. Riese, E.H. Bos, B. Hankin, J.G.M. Rosmalen, A.J. Oldehinkel, Neuroticism and common mental disorders: meaning and utility of a complex relationship, Clin. Psychol. Rev. 33 (2013) 686–697, https://doi.org/10.1016/j.cpr.2013.04.003.
[17] J.M. Digman, Higher-order factors of the Big five, J. Pers. Soc. Psychol. 73 (1997) 1246–1256, https://doi.org/10.1037//0022-3514.73.6.1246.
[18] J.L. Ireland, C.A. Ireland, Personality structure among prisoners: how valid is the five-factor model, and can it offer support for Eysenck's theory of criminality? Crim. Behav. Ment. Health CBMH. 21 (2011) 35–50, https://doi.org/10.1002/cbm.770.

[19] M.J. Adams, D.M. Howard, M. Luciano, T.-K. Clarke, G. Davies, W.D. Hill, , 23andMe Research Team, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, D. Smith, I.J. Deary, D.J. Porteous, A.M. McIntosh, Genetic stratification of depression by neuroticism: revisiting a diagnostic tradition, Psychol. Med. 50 (2020) 2526–2535, https://doi.org/10.1017/S0033291719002629.

[20] T. Barnhofer, T. Chittka, Cognitive reactivity mediates the relationship between neuroticism and depression, Behav. Res. Ther. 48 (2010) 275–281, https://doi.org/10.1016/j.brat.2009.12.005.

[21] A.M. García Herrero, J. Sánchez-Meca, F.J. Álvarez Muñoz, M. Rubio-Aparicio, F. Navarro-Mateu, [Neuroticism and suicidal thoughts: a meta-analytic study], Rev. Esp. Salud Publica 92 (2018) e201808049.

[22] J.D. Hafferty, L.B. Navrady, M.J. Adams, D.M. Howard, A.I. Campbell, H.C. Whalley, S.M. Lawrie, K.K. Nicodemus, D.J. Porteous, I.J. Deary, A.M. McIntosh, The role of neuroticism in self-harm and suicidal ideation: results from two UK population-based cohorts, Soc. Psychiatr. Psychiatr. Epidemiol. 54 (2019) 1505–1518, https://doi.org/10.1007/s00127-019-01725-7.

[23] D.H. Barlow, K.K. Ellard, S. Sauer-Zavala, J.R. Bullis, J.R. Carl, The origins of neuroticism, Perspect. Psychol. Sci. J. Assoc. Psychol. Sci. 9 (2014) 481–496, https://doi.org/10.1177/1745691614544528.

[24] A.R. Sutin, A. Terracciano, B. Deiana, S. Naitza, L. Ferrucci, M. Uda, D. Schlessinger, P.T. Costa, High neuroticism and low conscientiousness are associated with interleukin-6, Psychol. Med. 40 (2010) 1485–1493, https://doi.org/10.1017/S0033291709992029.

[25] K.D. Prajapati, S.S. Sharma, N. Roy, Current perspectives on potential role of albumin in neuroprotection, Rev. Neurosci. 22 (2011) 355–363, https://doi.org/10.1515/RNS.2011.028.

[26] E. Bondy, D.A.A. Baranger, J. Balbona, K. Sputo, S.E. Paul, T.F. Oltmanns, R. Bogdan, Neuroticism and reward-related ventral striatum activity: Probing vulnerability to stress-related depression, J. Abnorm. Psychol. 130 (2021) 223–235, https://doi.org/10.1037/abn0000618.

[27] Z. Zhuang, M. Gao, R. Yang, N. Li, Z. Liu, W. Cao, T. Huang, Association of physical activity, sedentary behaviours and sleep duration with cardiovascular diseases and lipid profiles: a Mendelian randomization analysis, Lipids Health Dis. 19 (2020) 86, https://doi.org/10.1186/s12944-020-01257-z.

[28] C.A. Emdin, A.V. Khera, S. Kathiresan, Mendelian randomization, JAMA 318 (2017) 1925–1926, https://doi.org/10.1001/jama.2017.17219.

[29] E. Sanderson, Multivariable Mendelian randomization and mediation, Cold Spring Harb. Perspect. Med. 11 (2021) a038984, https://doi.org/10.1101/cshperspect.a038984.

[30] B.P. Prins, K.B. Kuchenbaecker, Y. Bao, M. Smart, D. Zabaneh, G. Fatemifar, J. Luan, N.J. Wareham, R.A. Scott, J.R.B. Perry, C. Langenberg, M. Benzeval, M. Kumari, E. Zeggini, Genome-wide analysis of health-related biomarkers in the UK Household Longitudinal Study reveals novel associations, Sci. Rep. 7 (2017) 11008, https://doi.org/10.1038/s41598-017-10812-1.

[31] P. Turley, R.K. Walters, O. Maghzian, A. Okbay, J.J. Lee, M.A. Fontana, T.A. Nguyen-Viet, R. Wedow, M. Zacher, N.A. Furlotte, , 23andMe Research Team, Social Science Genetic Association Consortium, P. Magnusson, S. Oskarsson, M. Johannesson, P.M. Visscher, D. Laibson, D. Cesarini, B.M. Neale, D.J. Benjamin, Multi-trait analysis of genome-wide association summary statistics using MTAG, Nat. Genet. 50 (2018) 229–237, https://doi.org/10.1038/s41588-017-0009-4.

[32] S. Burgess, R.M. Daniel, A.S. Butterworth, S.G. Thompson, EPIC-InterAct Consortium, Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways, Int. J. Epidemiol. 44 (2015) 484–495, https://doi.org/10.1093/ije/dyu176.

[33] M. Verbanck, C.-Y. Chen, B. Neale, R. Do, Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases, Nat. Genet. 50 (2018) 693–698, https://doi.org/10.1038/s41588-018-0099-7.

[34] J. Bowden, G. Davey Smith, S. Burgess, Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression, Int. J. Epidemiol. 44 (2015) 512–525, https://doi.org/10.1093/ije/dyv080.

[35] S. Wang, H. Kang, Weak-instrument robust tests in two-sample summary-data Mendelian randomization, Biometrics 78 (2022) 1699–1713, https://doi.org/10.1111/biom.13524.

[36] W. Zhou, G. Liu, R.J. Hung, P.C. Haycock, M.C. Aldrich, A.S. Andrew, S.M. Arnold, H. Bickeböller, S.E. Bojesen, P. Brennan, H. Brunnström, O. Melander, N. E. Caporaso, M.T. Landi, C. Chen, G.E. Goodman, D.C. Christiani, A. Cox, J.K. Field, M. Johansson, L.A. Kiemeney, S. Lam, P. Lazarus, L. Le Marchand, G. Rennert, A. Risch, M.B. Schabath, S.S. Shete, A. Tardón, S. Zienolddiny, H. Shen, C.I. Amos, Causal relationships between body mass index, smoking and lung cancer: univariable and multivariable Mendelian randomization, Int. J. Cancer 148 (2021) 1077–1086, https://doi.org/10.1002/ijc.33292.

[37] T. Liu, S. Zhong, X. Liao, J. Chen, T. He, S. Lai, Y. Jia, A meta-analysis of oxidative stress Markers in depression, PLoS One 10 (2015) e0138904, https://doi.org/10.1371/journal.pone.0138904.

[38] J.H. Baek, E.-S. Kang, M. Fava, D. Mischoulon, A.A. Nierenberg, B.-H. Yu, D. Lee, H.J. Jeon, Serum lipids, recent suicide attempt and recent suicide status in patients with major depressive disorder, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 51 (2014) 113–118, https://doi.org/10.1016/j.pnpbp.2014.01.018.

[39] T.-L. Huang, Decreased serum albumin levels in Taiwanese patients with schizophrenia, Psychiatr. Clin. Neurosci. 56 (2002) 627–630, https://doi.org/10.1046/j.1440-1819.2002.01066.x.

[40] H. Wang, Y. He, Z. Sun, S. Ren, M. Liu, G. Wang, J. Yang, Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression, J. Neuroinflammation 19 (2022) 132, https://doi.org/10.1186/s12974-022-02492-0.

[41] T.P. Schnieder, I. Trencevska, G. Rosoklija, A. Stankov, J.J. Mann, J. Smiley, A.J. Dwork, Microglia of prefrontal white matter in suicide, J. Neuropathol. Exp. Neurol. 73 (2014) 880–890, https://doi.org/10.1097/NEN.0000000000000107.

[42] R. Brisch, S. Wojtylak, A. Saniotis, J. Steiner, T. Gos, J. Kumaratilake, M. Henneberg, R. Wolf, The role of microglia in neuropsychiatric disorders and suicide, Eur. Arch. Psychiatry Clin. Neurosci. 272 (2022) 929–945, https://doi.org/10.1007/s00406-021-01334-z.

[43] B. Bi, W. Liu, D. Zhou, X. Fu, X. Qin, J. Wu, Personality traits and suicide attempts with and without psychiatric disorders: analysis of impulsivity and neuroticism, BMC Psychiatr. 17 (2017) 294, https://doi.org/10.1186/s12888-017-1453-5.

[44] V. Vidal-Arenas, A.J. Bravo, J. Ortet-Walker, G. Ortet, L. Mezquita, M.I. Ibáñez, Null Cross-Cultural Addictions Study Team, Neuroticism, rumination, depression and suicidal ideation: a moderated serial mediation model across four countries, Int. J. Clin. Health Psychol. IJCHP. 22 (2022) 100325, https://doi.org/10.1016/j.ijchp.2022.100325.

[45] J. Johnson, P. Gooding, N. Tarrier, Suicide risk in schizophrenia: explanatory models and clinical implications, the Schematic Appraisal Model of Suicide (SAMS), Psychol. Psychother. 81 (2008) 55–77, https://doi.org/10.1348/147608307X244996.

[46] A. Liao, R. Walker, T.J. Carmody, C. Cooper, M.A. Shaw, B.D. Grannemann, P. Adams, G.E. Bruder, M.G. McInnis, C.A. Webb, D.G. Dillon, D.A. Pizzagalli, M. L. Phillips, B.T. Kurian, M. Fava, R.V. Parsey, P.J. McGrath, M.M. Weissman, M.H. Trivedi, Anxiety and anhedonia in depression: associations with neuroticism and cognitive control, J. Affect. Disord. 245 (2019) 1070–1078, https://doi.org/10.1016/j.jad.2018.11.072.

[47] X. Wang, J. Lin, Q. Liu, X. Lv, G. Wang, J. Wei, G. Zhu, Q. Chen, H. Tian, K. Zhang, X. Wang, N. Zhang, X. Yu, Y.-A. Su, T. Si, Major depressive disorder comorbid with general anxiety disorder: associations among neuroticism, adult stress, and the inflammatory index, J. Psychiatr. Res. 148 (2022) 307–314, https://doi.org/10.1016/j.jpsychires.2022.02.013.

[48] S. Chen, H.S. Xia, F. Zhu, G.Z. Yin, Z.K. Qian, C.X. Jiang, X.C. Gu, X.Y. Yin, W.J. Tang, T.H. Zhang, J.J. Wang, Q.F. Jia, L. Hui, Association between decreased serum albumin levels and depressive symptoms in patients with schizophrenia in a Chinese Han population: a pilot study, Psychiatr. Res. 270 (2018) 438–442, https://doi.org/10.1016/j.psychres.2018.10.012.

[49] T. Koweszko, J. Gierus, A. Zalewska, M. Maciejczyk, N. Waszkiewicz, A. Szulc, The relationship between suicide and oxidative stress in a Group of psychiatric Inpatients, J. Clin. Med. 9 (2020) 3462, https://doi.org/10.3390/jcm9113462.

[50] M. Matsushita, T. Kumano-Go, N. Suganuma, H. Adachi, S. Yamamura, H. Morishima, Y. Shigedo, A. Mikami, M. Takeda, Y. Sugita, Anxiety, neuroticism and oxidative stress: cross-sectional study in non-smoking college students, Psychiatr. Clin. Neurosci. 64 (2010) 435–441, https://doi.org/10.1111/j.1440-1819.2010.02109.x.

[51] S. Fujiwara, T. Amisaki, Fatty acid binding to serum albumin: molecular simulation approaches, Biochim. Biophys. Acta 1830 (2013) 5427–5434, https://doi.org/10.1016/j.bbagen.2013.03.032.

[52] M. Pompili, L. Longo, G. Dominici, G. Serafini, D.A. Lamis, J. Sarris, M. Amore, P. Girardi, Polyunsaturated fatty acids and suicide risk in mood disorders: a systematic review, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 74 (2017) 43–56, https://doi.org/10.1016/j.pnpbp.2016.11.007.

[53] D. Lindqvist, F.S. Dhabhar, S.J. James, C.M. Hough, F.A. Jain, F.S. Bersani, V.I. Reus, J.E. Verhoeven, E.S. Epel, L. Mahan, R. Rosser, O.M. Wolkowitz, S. H. Mellon, Oxidative stress, inflammation and treatment response in major depression, Psychoneuroendocrinology 76 (2017) 197–205, https://doi.org/10.1016/j.psyneuen.2016.11.031.
[54] O. Ekinci, A. Ekinci, The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio, Nord. J. Psychiatr. 71 (2017) 574–580, https://doi.org/10.1080/08039488.2017.1363285.
[55] Y. Xu, J. Liang, W. Gao, Y. Sun, Y. Zhang, F. Shan, J. Ge, Q. Xia, Peripheral blood cytokines as potential diagnostic biomarkers of suicidal ideation in patients with first-episode drug-naïve major depressive disorder, Front. Public Health 10 (2022) 1021309, https://doi.org/10.3389/fpubh.2022.1021309.
[56] X. Hu, J. Zhao, Z. Lin, Y. Wang, H. Peng, H. Zhao, X. Wan, C. Yang, Mendelian randomization for causal inference accounting for pleiotropy and sample structure using genome-wide summary statistics, Proc. Natl. Acad. Sci. U.S.A. 119 (2022) e2106858119, https://doi.org/10.1073/pnas.2106858119.