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ORIGINAL RESEARCH

Association of Emotional Stress and Adaptive Behavior with Stroke Risk: A Mendelian Randomization Study

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Abstract

Although emotional stress and adaptive behavior are known to influence cardiovascular health, direct evidence linking them to stroke remains limited. This study aims to clarify the associations between emotional stress, adaptive behaviors, and the risk of stroke. We conducted a two-sample Mendelian randomization analysis using data from the UK Biobank, the European Bioinformatics Institute, the Integrative Epidemiology Unit, and the FinnGen project. Indirect effects were estimated using the product of coefficients method. Low satisfaction with family relationships was associated with increased risks of all stroke and ischemic stroke. Mood swings were linked to higher risks of all stroke, ischemic stroke, and large-artery stroke, while feelings of tension were associated with large-artery stroke and small vessel stroke. Interestingly, nervousness was inversely associated with intracerebral hemorrhage risk. Participation in group leisure activities was associated with reduced risks of all stroke, ischemic stroke, and small vessel stroke. In contrast, several adaptive behaviors were linked to increased stroke risk, including vigorous physical activity (all stroke), summer outdoor activities (all stroke and ischemic stroke), winter outdoor activities (all stroke), and prolonged television watching (all stroke, ischemic stroke, and large-artery stroke). Mediation analyses suggested that hypertension, type 2 diabetes, atherosclerotic heart disease, and chronic ischemic heart disease may partially mediate these associations. The study provides genetic evidence supporting a potential causal relationship between emotional stress, adaptive behaviors, and stroke subtypes. Individuals can easily modify adaptive behaviors and manage emotional stress in their daily routines. Understanding these associations may inform future strategies for stroke prevention; however, due to limitations inherent in the current study design, our findings require further validation in large-scale prospective cohort studies.

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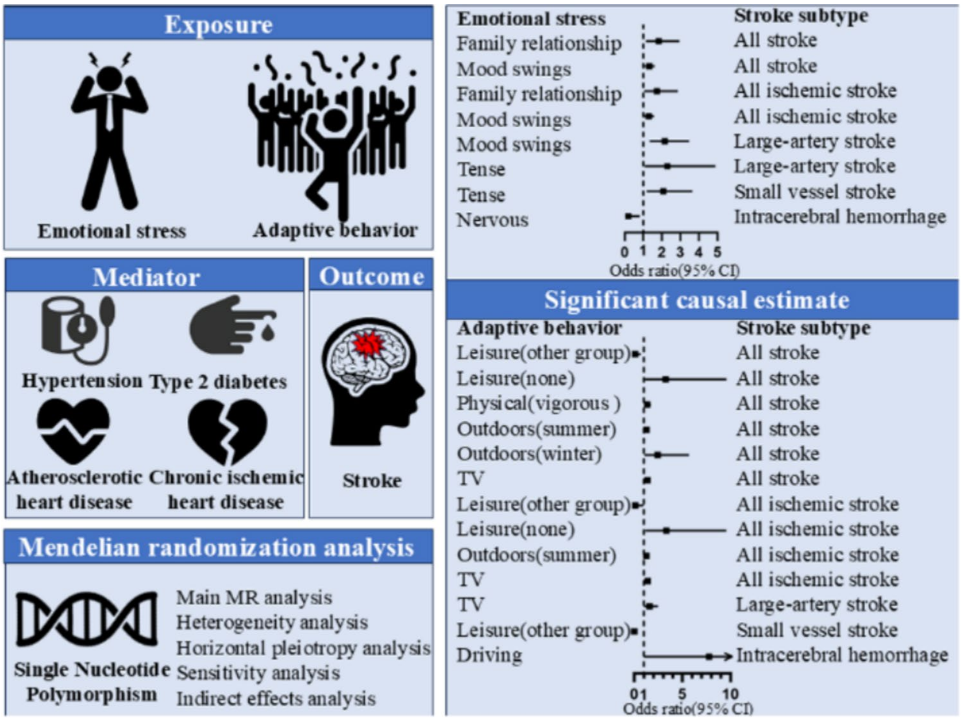
Graphical Abstract

Emotional Stress, Adaptive behavior, and Stroke Risk. This study examined the genetic associations between emotional stress, adaptive behavior, and stroke risk, as well as the mediating effects of traditional stroke risk factors in these relationships.



Keywords Emotional stress · Adaptive behavior · Stroke · Modifiable risk factor · Mendelian randomization

Background

Stroke ranks as the second leading cause of death globally and the third in terms of combined mortality and disability (Collaborators 2021; Tsao et al. 2023). The burden is particularly pronounced in certain countries; for example, in China, stroke remains the leading cause of death (Ma et al. 2021). Stroke risk factors are typically categorized as modifiable or non-modifiable, with emotional stress being a key modifiable factor (Kotlega et al. 2016).

Numerous studies have explored the relationship between emotional stress and cardiovascular disease, particularly heart disease, which is a major contributor to stroke (Edmondson et al. 2013; Frerich et al. 2022). Emotional stress can trigger sympathetic nervous system activation (Mittleman et al. 1995), catecholamine release (Mittleman and Mostofsky 2011), systemic vasoconstriction (Boltwood et al. 1993), and increases in heart rate and blood pressure (Verrier et al. 1987; Muller et al. 1997, 1989). These physiological changes alter myocardial oxygen demand and may precipitate plaque rupture in vulnerable atherosclerotic lesions (Braunwald 1998). In contrast to conditions like traumatic cervical artery dissection, stroke triggers are often less obvious. Although some studies suggest that physical or emotional triggers may initiate stroke events, comparable to myocardial infarction, robust causal evidence remains limited (Guiraud et al. 2010; Wegener 2022).

A series of studies have established a significant correlation between positive emotions and a reduced risk of stroke, with INTERSTROKE providing compelling evidence for this association (Ostir et al. 2001; Lambiase et al. 2015; Berges et al. 2011; Smyth et al. 2022). The findings of this extensive multinational cohort study demonstrate that acute anger or emotional distress is significantly linked to the onset of all stroke subtypes, including ischemic stroke and intracerebral hemorrhage (ICH), whereas acute intense physical exertion is specifically associated with ICH (Smyth et al. 2022). Moreover, there is evidence that suggests a correlation between mood swings and an increased vulnerability to intracranial aneurysms as well as aneurysm-related subarachnoid hemorrhage (Peng et al. 2023). Although previous literature has reported an association between emotional stress and stroke risk, the causal relationship remains unclear (O'Donnell et al. 2010; Smyth et al. 2022). Simultaneously, there remains a lack of consensus regarding the potential efficacy of certain adaptive behaviors commonly employed to cope with emotional stress in mitigating stroke risk (Wegener 2022). Furthermore, the assessment of emotional stress as a risk factor for disease necessitates meticulous selection of measurement tools, their integration with disease outcomes, and identification of appropriate mediators. Additionally, there is a need for further studies that manipulate both emotional stresses and positive affect/adaptive behavior (Pressman et al. 2019).

With the increasing accumulation of genome-wide association studies (GWAS) data, Mendelian randomization (MR) has become a reliable tool for analyzing risk factors. It utilizes single nucleotide polymorphisms (SNPs) as instrumental variables to evaluate causal connections between potential risk factors and outcome variables (Burgess et al. 2018). We utilized MR method to examine the causal involvement of emotional stress and its adaptive behaviors in relation to stroke subtypes. Additionally, we utilized a series of established risk factors as mediating variables to explore the potential impact of emotional stress and its associated adaptive behaviors on stroke through these conventional risk factors.

Methods

Research Framework and Data Origins

We utilized a two-sample MR approach to assess the causal association between emotional stress, adaptive behaviors, and stroke subtypes (Sanderson et al. 2022). We applied the Pleiotropic Genetic Variants in Multivariable MR to estimate causal effects. The "Product of coefficients" method was used to evaluate indirect effects (Burgess and Thompson 2015). A detailed visual illustration of the research plan can be observed in Fig. 1.

Data set acquired from openly accessible GWAS regarding sixteen emotional stresses, fourteen adaptive behaviors, seven stroke subtypes, and eight mediators (Table 1). The range of participants included in the studies varied from 105,358 to 655,666 individuals with European heritage. Additional information regarding characteristics and associated research can be found in Supplementary Table 1. Stroke cases were defined according to the criteria set by the World Health Organization, which encompassed sudden onset neurological changes presumed to be of vascular

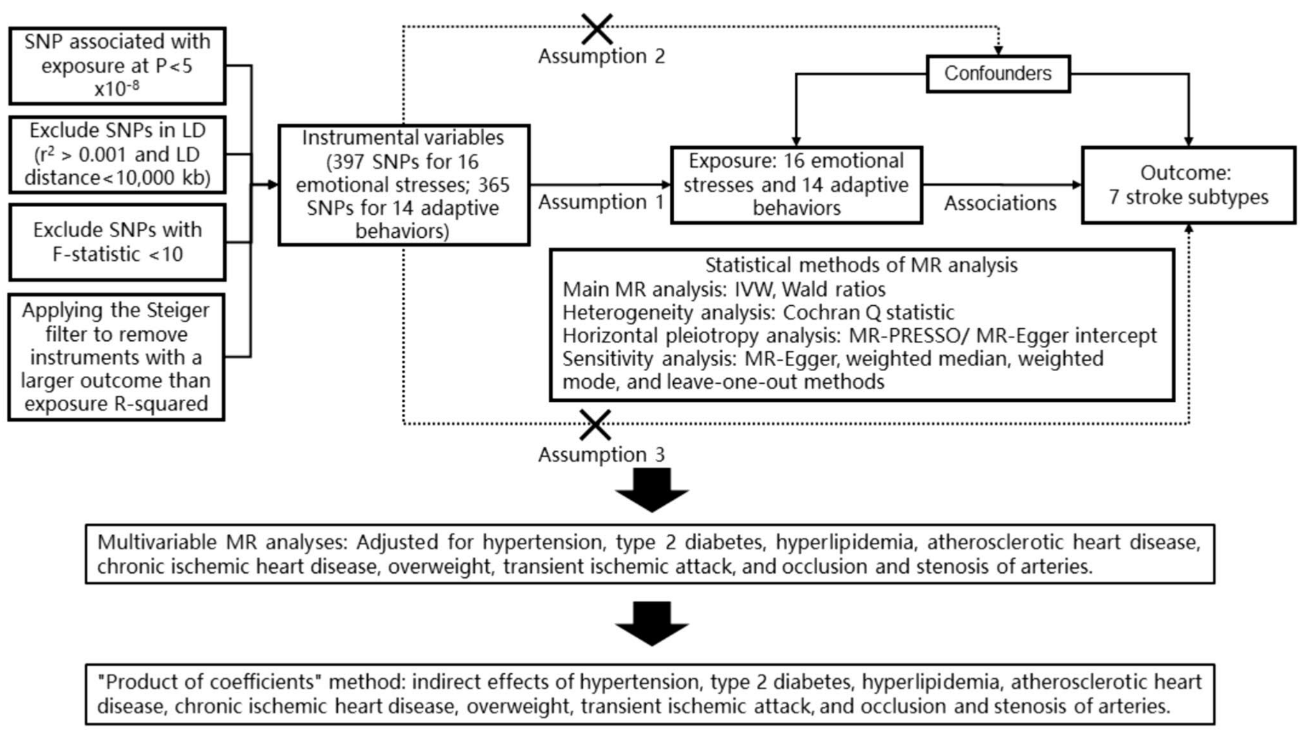


Fig. 1 Schematic layout and flow of MR analysis. This figure illustrates the research question, analytical process, and data sources employed. Utilizing comprehensive GWAS summary statistics, we performed MR analysis to explore the causal links between 16 emotional stressors/14 adaptive behaviors and 7 stroke subtypes. Sensitivity analyses were applied to ensure the robustness of MR results. The analysis was grounded in the following assumptions: (1) The genetic variant is strongly related to the exposure; (2) It is independent of any confounders affecting the exposure-outcome relationship; (3) Its influence on the outcome is exclusively attributed to the exposure, barring potential horizontal pleiotropy

Table 1 Summary of data entries used in the study

Data entry	Abbreviation	Data entry	Abbreviation
Health satisfaction	Health S	Moderate physical activity	Physical(moderate)
Financial situation satisfaction	Financial S	Vigorous physical activity	Physical(vigorous)
Family relationship satisfaction	Family S	Time spent driving	Driving
Friendships satisfaction	Friendships S	Time spent outdoors in summer	Outdoors(summer)
Work/job satisfaction	Work S	Time spent outdoors in winter	Outdoors(winter)
Experiencing mood swings	Mood swings	Time spent using computer	Computer
Suffer from 'nerves'	Nerves	Time spent watching television (TV)	TV
Ever suffered mental distress preventing usual activities	Mental distress	All stroke	AS
Fed-up feelings	Fed-up	All ischemic stroke	AIS
Worrier/anxious feelings	Worrier/anxious	Large-artery stroke	LAS
Guilty feelings	Guilty	Small vessel stroke	SVS
Nervous feelings	Nervous	Cardioembolic stroke	CES
Sensitivity/hurt feelings	Sensitivity/hurt	Intracerebral hemorrhage	ICH
Feeling lonely	Lonely	Subarachnoid hemorrhage	SAH
Feeling miserable	Miserable	Hypertension	/
Feeling tense	Tense	Type 2 diabetes	/
Adult education class	Adult education	Hyperlipidemia	/
Pub/social club	Pub/club	Atherosclerotic heart disease	/
Religious group	Religious group	Chronic ischemic heart disease	/
Sports club/gym	Sports/gym	Overweight	/
Other group activity	Leisure (other group)	Transient ischemic attack	/
None Leisure/social activities	Leisure (none)	Occlusion and stenosis of arteries	/
Light physical activity	Physical(light)		

origin and lasting for a minimum duration of 24 h. Reclassifying stroke subtypes was done using the TOAST criteria (Adams et al. 1993). Further information can be found in the supplementary.

Instrumental Variable Selection

In this study, genetic instruments were chosen for each exposure, based on their statistical significance ($P < 5 \times 10^{-8}$) in the relevant GWAS data, which were publicly available. The linkage disequilibrium (LD) clumping was subsequently performed to ensure the independence of the selected instruments, by selecting only the SNP with the highest significance among those exhibiting LD $r^2 \geq 0.001$. To mitigate weak instrument bias and enhance causal inference, all F-statistic values exceeded 10. Moreover, we employed the Steiger filter to eliminate SNPs exhibiting a higher R-Squared value in stroke subtypes compared to those associated with emotional stress or adaptive behavior. Details on the SNP selection process are provided in Supplementary Table 2 and in the instrumental variable selection and exposure definition section of the Supplementary Materials.

Statistical Analyses

In this study, we conducted sequential two-sample MR analyses using the inverse variance-weighted (IVW) random-effects method, the two-sample design allows the use of independent datasets for exposure and outcome, which helps reduce potential confounding and improves the robustness and reliability of causal inference (Smith and Ebrahim 2003). To strengthen the dependability of our results, we incorporated MR-Egger, weighted median, and weighted mode methodologies as supplementary measures (Sanderson et al. 2022). Heterogeneity was assessed by conducting Cochran's Q test, with a significance level established at $p < 0.05$ (Burgess et al. 2013). In addition, we evaluated the presence of horizontal pleiotropy using MR pleiotropy residual sum and outlier (MR-PRSSO) analysis or the MR-Egger intercept test, with a significance level below 0.05 indicating its existence (Verbanck et al. 2018; Bowden et al. 2015). MR analyses were conducted using the TwoSampleMR (version 0.6.0), MendelianRandomization (version 0.8.0), and MRPRESSO (version 1.0) packages within R Software 4.3.3 (https://www.R-project.org). Indirect effects were estimated using an online tool available at http://quantpsy.org/sobel/sobel.htm.

Results

The Influence of Emotional Stress and Adaptive Behavior on Stroke Subtypes

We conducted an analysis of fourteen adaptive behaviors and sixteen emotional stresses to investigate their associations with stroke subtypes, employing the random-effects IVW method. Figure 2 presents a comprehensive summary of the direction and strength of association estimates for each adaptive behavior and emotional stress in relation to each stroke subtype. MR analysis identified 21 causal relationships between genetically predicted emotional stresses/adaptive behaviors and 7 stroke subtypes. Among emotional stresses, we identified 2 causal relationships in AS, 2 in AIS, 2 in LAS, 1 in SVS, and 1 in ICH. In terms of adaptive behaviors, we identified 6 causal relationships in AS, 4 in AIS, 1 in LAS, 1 in SVS, and 1 in ICH (Fig. 2 and Supplementary Table 3).

The forest plots in Figs. 3 and 4 illustrate the specific details regarding significant ($p < 0.05$) causal estimations of associations between emotional stresses/adaptive behaviors and each stroke subtype. In terms of the relationship between emotional stresses and stroke subtypes, our results indicated that low satisfaction in family relationships is linked to an elevated likelihood of AS (odds ratio [OR] = 1.830, 95% confidence interval [CI] 1.139–2.941;

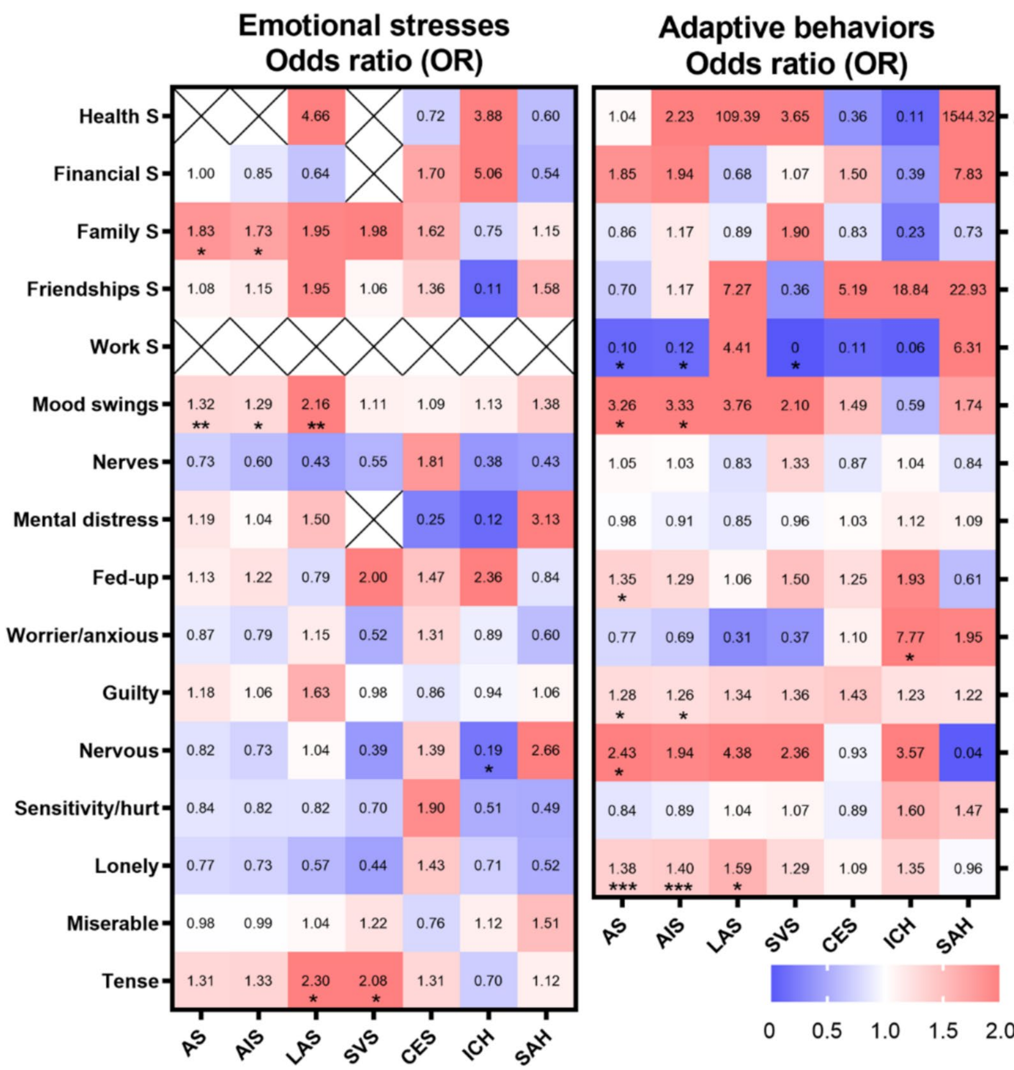


Fig. 2 The influence of emotional stresses and adaptive behaviors on stroke subtypes. The colors represent the magnitude and orientation of the odds ratio (limited to 2) for estimating causal effects using the IVW MR approach. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The satisfaction assigned values are as follows: extremely happy (1), very happy (2), moderately happy (3), moderately unhappy (4), very unhappy (5), and extremely unhappy (6). The severity of other emotional stress is positively associated with their assignment. Comprehensive definitions of exposure can be found in the supplementary materials

$P = 0.013$) and AIS (OR = 1.729, 95% CI 1.046–2.858; $P = 0.033$). Mood swings are linked to an elevated risk of AS (OR = 1.318, 95% CI 1.071–1.621; $P = 0.009$), AIS (OR = 1.292, 95% CI 1.054–1.585; $P = 0.014$), and LAS (OR = 2.157, 95% CI 1.343–3.466; $P = 0.001$), while tension increases the likelihood of LAS (OR = 2.295, 95% CI 1.080–4.877; $P = 0.031$) and SVS (OR = 2.077, 95% CI 1.184–3.644; $P = 0.011$). Surprisingly, nervousness appears to decrease the risk of ICH (OR = 0.186, 95% CI 0.043–0.809; $P = 0.025$).

Regarding adaptive behaviors, participating in group leisure activities may decrease the risk of AS (OR = 0.098, 95% CI 0.014–0.672; $P = 0.018$), AIS (OR = 0.115, 95% CI 0.014–0.962; $P = 0.046$), and SVS (OR = 0.003, 95% CI 0.000–0.298; $P = 0.013$). The absence of group leisure activities may heighten the susceptibility to AS (OR = 3.257, 95% CI 1.110–9.563; $P = 0.032$) and AIS (OR = 3.325, 95% CI 1.159–9.545; $P = 0.030$). The noteworthy point is that inappropriate adaptive behaviors can potentially elevate the risk of stroke, with vigorous physical activity increasing the susceptibility to AS (OR = 1.349, 95% CI 1.055–1.727; $P = 0.017$), summer outdoor activities raising the likelihood of AS (OR = 1.280, 95% CI 1.041–1.574; $P = 0.019$) and AIS (OR = 1.256, 95% CI 1.006–1.568; $P = 0.044$),

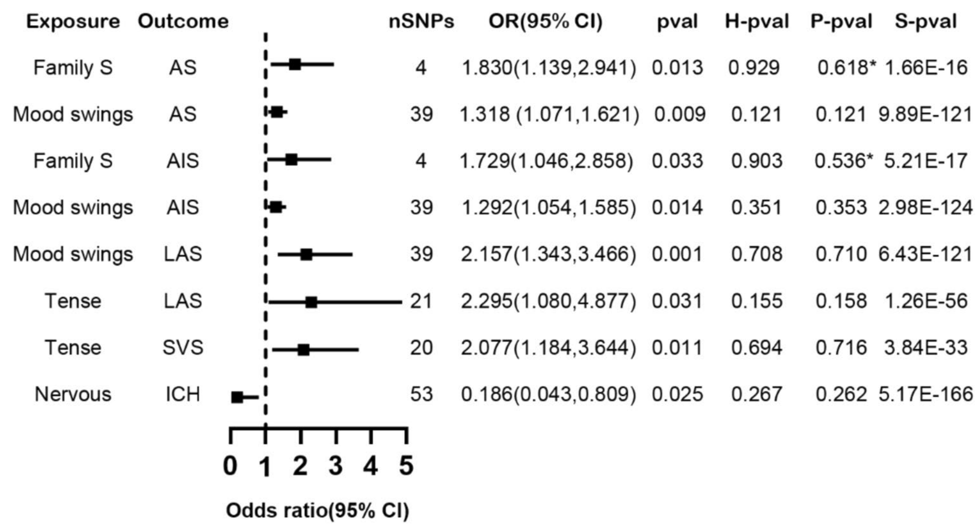


Fig. 3 Associations between genetically inferred emotional stresses and stroke subtypes using MR. Findings were obtained from IVW analyses. *The *p*-value for horizontal pleiotropy was estimated using the MR-Egger intercept, while the remaining *p*-values for horizontal pleiotropy were computed using MR-PRESSO. H-pval, *p*-value for heterogeneity; P-pval, p-value for horizontal pleiotropy; S-pval, *p*-value for Steiger test

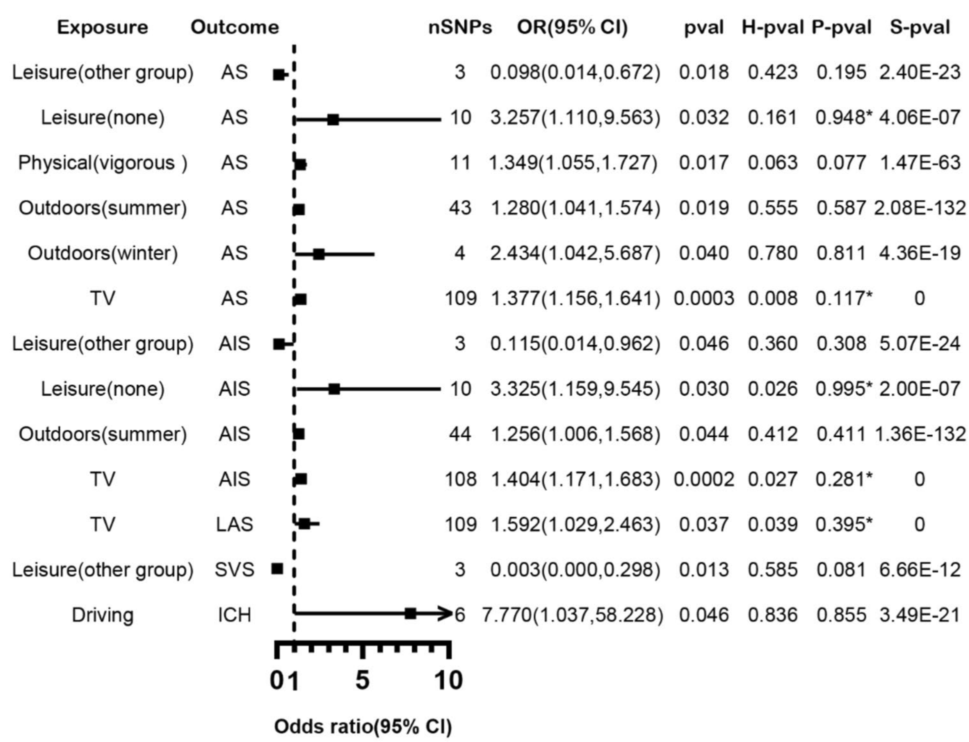


Fig. 4 Associations between genetically inferred adaptive behaviors and stroke subtypes using MR. Findings were obtained from IVW analyses. *The *p*-value for horizontal pleiotropy was estimated using the MR-Egger intercept, while the remaining *p*-values for horizontal pleiotropy were computed using MR-PRESSO. H-pval, *p*-value for heterogeneity; P-pval, p-value for horizontal pleiotropy; S-pval, *p*-value for Steiger test

winter outdoor activities amplifying the vulnerability to AS (OR = 2.434, 95% CI 1.042–5.687; $P = 0.040$), prolonged driving duration poses a potential risk for exacerbating ICH (OR = 7.770, 95% CI 1.037,58.228; $P = 0.046$), and excessive TV watching heightening the risks of AS (OR = 1.377, 95% CI 1.156–1.641; $P = 0.0003$), AIS (OR = 1.404, 95% CI 1.171–1.683; $P = 0.0002$), and LAS (OR = 1.592, 95% CI 1.029–2.463; $P = 0.013$).

The scatterplots in Figs. 5 and 6 illustrate the relationships between each genetic variant and their respective outcomes for all emotional stresses/adaptive behaviors with significant associations ($p < 0.05$). The comprehensive findings are meticulously compiled in Supplementary Table 3. The findings were further corroborated by conducting a leave-one-out sensitivity analysis (Supplementary Table 4). The sensitivity tests revealed no evidence of heterogeneity. Furthermore, there was no detection of horizontal pleiotropy (Figs. 3, 4, Supplementary Tables 5, and 6).

Assessment of the Mediators for the Association Between Emotional Stresses/Adaptive Behaviors and Stroke Subtypes

After obtaining a series of emotional stresses and adaptive behaviors significantly associated with stroke subtypes, we performed a multivariate analysis by integrating these traits with eight common stroke risk factors: hypertension, type 2 diabetes, hyperlipidemia, atherosclerotic heart disease, chronic ischemic heart disease, overweight, transient ischemic attack, and occlusion and stenosis of arteries (Xu et al. 2022; Tondel et al. 2022). The results revealed that there was no significant correlation among the relevant traits after adjusting for multiple factors, suggesting their dependence on these 8 risk factors (Table 2). Consequently, a mediation effect analysis was conducted. Our findings suggest that Hypertension, Type 2 diabetes, Atherosclerotic heart disease, and Chronic ischemic heart disease may act as mediators linking emotional stresses/adaptive behaviors to stroke subtypes (Table 3 and Supplementary Table 7).

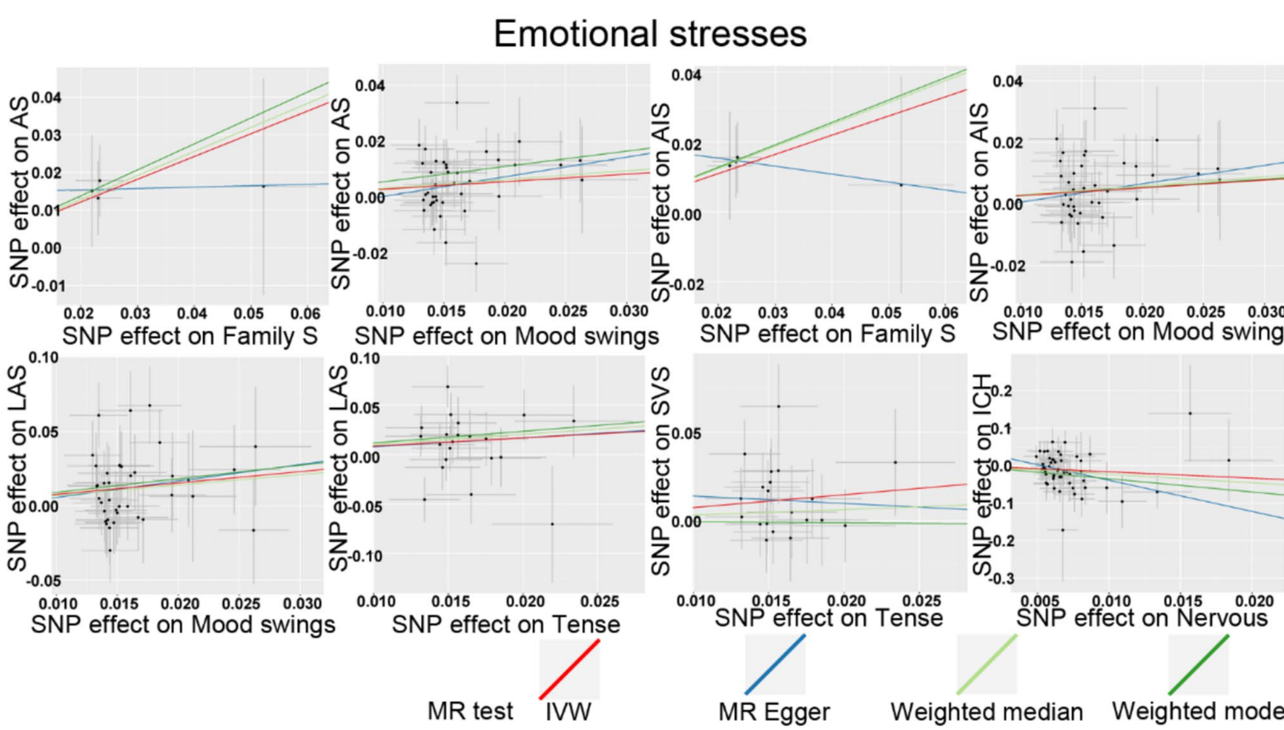


Fig. 5 Significant causal estimates of genetic links between emotional stresses and stroke subtypes. The genetic variants that show significant associations with causal estimates at a significance level of $p < 0.05$ are graphed in relation to their corresponding outcome associations. Each variant is represented by a circle, indicating the alteration in trait levels and the associated increased risk. The 95% confidence intervals for the genetic associations are shown as horizontal and vertical lines intersecting each circle. The effect allele of each trait was used to align the associations. Different MR approaches are represented by colored lines, depicting the slope (causal estimate) obtained

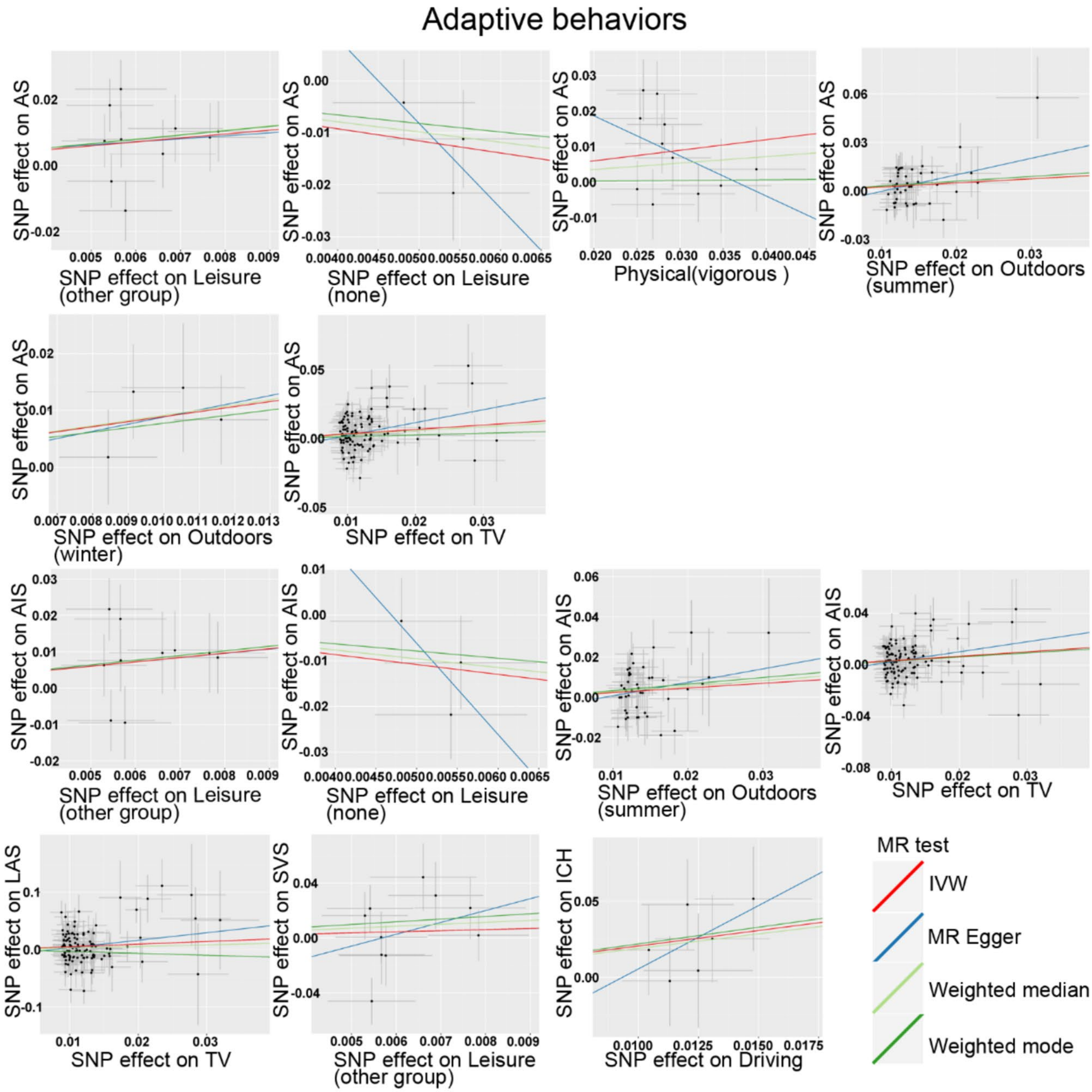


Fig. 6 Significant causal estimates of genetic links between emotional stresses and stroke subtypes. The genetic variants that show significant associations with causal estimates at a significance level of $p < 0.05$ are graphed in relation to their corresponding outcome associations. Each variant is represented by a circle, indicating the alteration in trait levels and the associated increased risk. The 95% confidence intervals for the genetic associations are shown as horizontal and vertical lines intersecting each circle. The effect allele of each trait was used to align the associations. Different MR approaches are represented by colored lines, depicting the slope (causal estimate) obtained

Discussion

Regarding the association between emotional stressors and stroke subtypes, our findings reveal that low satisfaction in family relationships correlates with an elevated risk of AS and AIS Furthermore, mood swings are linked to increased risks of AS, AIS, and LAS, while tension is associated with a heightened likelihood of LAS and SVS. Interestingly, feelings of nervousness appear to decrease the risk of ICH. In terms of adaptive behaviors, the absence of group leisure activities may elevate the risk of AS, AIS,

Table 2 Multivariable MR analyses for significant causal estimates

Exposure	Outcome	nSNPs	OR (95% CI)	*p*-value
Family S	AS	97	0.994 (0.961, 1.029)	0.739
Mood swings	AS	102	1.007 (0.974, 1.041)	0.666
Family S	AIS	95	0.998 (0.963, 1.035)	0.931
Mood swings	AIS	100	1.003 (0.969, 1.039)	0.854
Mood swings	LAS	101	1.022 (0.952, 1.097)	0.549
Tense	LAS	98	1.022 (0.950, 1.099)	0.561
Tense	SVS	96	1.018 (0.961, 1.079)	0.538
Nervous	ICH	99	0.981 (0.923, 1.042)	0.530
Leisure (other group)	AS	101	0.994 (0.961, 1.028)	0.727
Leisure(none)	AS	98	0.994 (0.960, 1.029)	0.726
Physical(vigorous)	AS	98	1.008 (0.974, 1.042)	0.659
Outdoors(summer)	AS	102	0.993 (0.960, 1.028)	0.703
Outdoors(winter)	AS	97	0.994 (0.961, 1.029)	0.739
TV	AS	112	0.996 (0.963, 1.030)	0.803
Leisure (other group)	AIS	99	0.998 (0.963, 1.034)	0.919
Leisure(none)	AIS	96	0.998 (0.963, 1.035)	0.920
Outdoors(summer)	AIS	101	0.998 (0.963, 1.034)	0.891
TV	AIS	110	1.000 (0.965, 1.036)	0.990
TV	LAS	111	0.975 (0.907, 1.049)	0.497
Leisure (other group)	SVS	98	0.983 (0.926, 1.043)	0.570
Driving	ICH	98	0.982 (0.922, 1.045)	0.558

Adjusted for hypertension, type 2 diabetes, hyperlipidemia, atherosclerotic heart disease, chronic ischemic heart disease, overweight, transient ischemic attack, and occlusion and stenosis of arteries

and SVS. Our study identifies adaptive behaviors that heighten the risk of stroke, including engaging in vigorous physical activity (AS), participating in summer outdoor activities (AS and AIS), engaging in winter outdoor activities (AS), and spending prolonged periods watching TV (AS, AIS, and LAS). Hypertension, type 2 diabetes, atherosclerotic heart disease, and chronic ischemic heart disease may serve as mediators linking emotional stresses and adaptive behaviors to specific stroke subtypes.

According to the findings of this study, active engagement in social activities has been shown to be associated with a decreased risk of stroke. This finding aligns with our intuitive perception that leisure and social activities can effectively alleviate emotional stress, while also providing new evidence for the causal relationship between these activities and stroke, which is consistent with previous investigations (Chida and Steptoe 2008; Zhang and Han 2016; Boehm and Kubzansky 2012). Moreover, there exist several physiological theories that substantiate the correlation between social engagements and human well-being. Multiple research studies have provided evidence indicating a connection between feelings of solitude and lack of social interaction with the stimulation of the hypothalamic–pituitary–adrenal axis. As a result, this leads to an enhanced response in the sympathetic nervous system, a higher secretion of inflammatory cytokines, and elevated levels of oxidative stress (Li and Xia 2020; Hackett et al. 2019). These factors collectively exert significant influences on the occurrence of stroke; however, a comprehensive understanding of their underlying

Table 3 Assessment of the mediators for the association between emotional stresses/adaptive behaviors and stroke subtypes for significant causal estimates

Exposure	Outcome	Mediator	IE div TE (95% CI)	*p*-value
Family S	AS	Hypertension	0.149 (0.145, 0.181)	0.008
Mood swings	AS	Type 2 diabetes	0.149 (0.141, 0.209)	0.002
Family S	AIS	Hypertension	0.171 (0.155, 0.538)	0.008
Mood swings	AIS	Type 2 diabetes	0.174 (0.160, 0.295)	0.002
Mood swings	LAS	Type 2 diabetes	0.110 (0.075, 0.118)	0.007
Mood swings	LAS	Atherosclerotic heart disease	0.148 (0.016, 0.179)	0.036
Mood swings	LAS	Chronic ischemic heart disease	0.193 (0.094, 0.217)	0.014
Tense	LAS	Atherosclerotic heart disease	0.192 (0.105, 0.196)	0.034
Tense	LAS	Chronic ischemic heart disease	0.186 (0.124, 0.189)	0.032
Tense	SVS	Atherosclerotic heart disease	0.119 (0.065, 0.126)	0.022
TV	AS	Hypertension	0.277 (0.256, 0.351)	4.32E−06
TV	AS	Type 2 diabetes	0.132 (0.127, 0.134)	4.62E−04
TV	AIS	Hypertension	0.272 (0.254, 0.333)	4.60E−06
TV	AIS	Type 2 diabetes	0.135 (0.127, 0.138)	4.44E−04
TV	LAS	Hypertension	0.265 (0.200, 2.333)	1.89E−05
TV	LAS	Type 2 diabetes	0.186 (0.159, 1.041)	0.003
TV	LAS	Atherosclerotic heart disease	0.333 (0.314, 0.924)	0.016
TV	LAS	Chronic ischemic heart disease	0.314 (0.284, 1.268)	0.008

The "Product of coefficients" method was employed to assess indirect effects. IE div TE, The intermediary effect accounts for a proportion of the total effect mechanisms necessitates extensive basic experiments and clinical cohorts.

In a recent investigation, Song et al. identified a correlation between the occurrence rate of type 2 diabetes and factors such as social isolation and feelings of loneliness (Song et al. 2023). Our study also analyzed datasets on social isolation and loneliness, specifically examining "Leisure/social activities" and "Feeling lonely". Additionally, given that type 2 diabetes is a prevalent risk factor for stroke, we have employed it as a mediator variable in our study. Consistent with Song's research findings, engaging in leisure or social activities can alleviate emotional stress and minimize the risk of stroke subtypes; however, these effects are not mediated by regulating type 2 diabetes as an intermediate variable. Feeling lonely did not influence susceptibility to any specific stroke subtype. Furthermore, our study revealed that mood swings, vigorous physical activity, and excessive television viewing impact stroke occurrence through their relationship with type 2 diabetes, this suggests that these factors may also be linked to type 2 diabetes, as they were not the primary focus of this study and were not extensively examined.

In our results, we identified several findings that diverge from conventional expectations. Specifically, feelings of nervousness were associated with a reduced risk of ICH, while participation in outdoor activities correlated with an increased risk of stroke. The apparent protective effect of nervousness may reflect heightened health awareness among individuals experiencing such emotions, potentially leading to more cautious behaviors that lower stroke risk. This interpretation aligns with previous research indicating that certain anxiety-related states can promote proactive health management (Gross and Hen 2004; Craske et al. 2009). Conversely, the association between outdoor activities and elevated stroke risk might be attributable to environmental stressors, including exposure to extreme seasonal temperatures, which can trigger spikes in blood pressure and activate the sympathetic nervous system, thereby increasing stroke susceptibility (Analitis et al. 2008; Schifano et al. 2009). These unexpected findings underscore the complexity of stroke risk profiles and may also reflect inherent limitations of our analytical methods, warranting further investigation.

In this study, to capture various nuances of emotional stress as accurately as possible, certain traits related to emotional stress may exhibit similarities, such as "Suffer from nerves", "Worrier/anxiety feelings", and "Nervous feelings". However, through meticulous examination, we have identified a significant association between "Nervous feelings" and ICH while the other two factors did not show a substantial correlation with stroke incidence. This discrepancy might arise due to the distinct questionnaire items used for classification purposes, which are elaborated upon in the supplementary materials. The inquiries pertaining to the three characteristics are as follows: "Do you suffer from nerves", "Are you a worrier", and "Would you call yourself a nervous person". The formulation of different questions within these three categories could potentially lead to varying relationships with stroke even when considering similar emotional stress indicators. Nevertheless, additional investigation is necessary to clarify the underlying processes by which "Nervous feelings" may mitigate the risk of ICH.

Emotional stress represents a modifiable risk factor for stroke, and its adaptive behavior can be subconsciously regulated in daily life. Revealing the correlation between adaptive behavior and emotional stress with stroke risk could fundamentally alter the likelihood of stroke occurrence. This, in turn, could promote the development of cost-effective and actionable stroke prevention strategies. However, it should be noted that our findings are currently confined to individuals with European heritage. Further investigation is warranted to ascertain the generalizability of these results across diverse ancestral populations.

Conclusions

In summary, we conducted a two-sample MR analysis to assess the prospective relationship between sixteen emotional stresses, fourteen adaptive behaviors, and seven stroke subtypes. The results obtained from this study suggest the existence of a possible genetic inclination connecting adaptive behavior and emotional stress to stroke subtypes. As these behavioral traits are modifiable in daily life, understanding their links to stroke risk may inform future prevention strategies. Nevertheless, these results should be interpreted with caution and require further validation in large-scale prospective cohort studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10571-025-01577-7.

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Data Availability The data utilized in this investigation were readily available to the public (https://gwas.mrcieu.ac.uk/) and can be retrieved through the materials and methods section as well as the supplementary.

Declarations

Competing Interests The authors declare no competing interests.

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