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ORIGINAL RESEARCH

A Mendelian Randomization Study of the Association Between Loud Music Exposure Frequency and Anxiety Disorders in European Populations

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Objective: This study aimed to examine whether loud music is causally associated with anxiety disorder.

Methods: Two-sample Mendelian randomization (MR) analyses were conducted using inverse variance weighting (IVW), weighted median, MR-EGGER regression methods, simple mood and weighted mood. This study utilized publicly available pooled statistical datasets from genome-wide association studies (GWAS) of loud music exposure in European populations as the exposure factor. Various subtypes of anxiety disorders were used as outcomes, with GWAS data for generalized anxiety disorder being sourced from the IEU Open and GWAS data for panic disorder, agoraphobia, and social phobia being sourced from the Finnish database.

Results: The IVW method demonstrated evidence supporting a causal relationship between loud music and generalized anxiety (OR = 1.050, 95% CI: 1.015–1.086, P = 0.004). The weighted median method revealed evidence of a causal relationship between loud music and agoraphobia (OR = 0.263, 95% CI: 0.070–0.985, P = 0.047). None of the methods revealed evidence of a causal relationship between loud music and panic disorder or social anxiety disorder. Cochran's Q test and funnel plot did not reveal evidence of heterogeneity or asymmetry, thus suggesting that there were no directional multi-effects.

Conclusion: The results suggest that loud music may be a risk factor for generalized anxiety. While the IVW method did not show a significant causal relationship between loud music exposure and agoraphobia, the WM method indicated an inverse association. Therefore, a potential causal relationship between loud music exposure and agoraphobia cannot be readily dismissed. Whether loud music serves as a protective factor for agoraphobia requires further clarification through clinical and epidemiological investigations.

Keywords: music, anxiety disorder, generalized anxiety, agoraphobia, panic disorder, social phobias, Mendelian randomisation

Introduction

Music can influence human physiological responses through various aspects such as pitch, dynamics, timbre, and intervals.[1] Consequently, these properties of music can be utilized for interventions and treatments of psychological disorders such as anxiety disorders and depression. Music therapy typically employs soft music with moderate or low volume. When music volume increases, it often leads to hearing damage. Existing studies have reported that among adolescents frequently exposed to loud music, the incidence of hearing loss reaches 8.6%, while tinnitus occurrence is 5.8%.[2] A recent study indicated that exposure to loud favorite music increases salivary cortisol concentrations.[3] However, it remains unreported whether loud music exerts negative effects on mental disorders similar to noise pollution, or whether it enhances the efficacy of music therapy.

Anxiety disorders represent a category of mental conditions characterized by excessive fear, worry, and accompanying avoidance behaviors, having become one of the most prevalent mental health issues worldwide.[4] The clinical manifestations of anxiety disorders demonstrate high heterogeneity. According to the Diagnostic and Statistical

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Manual of Mental Disorders (Fifth Edition, DSM-5) classification, they primarily include subtypes such as generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobia, and agoraphobia.[5] Approximately 4.05% of the global population is affected by anxiety disorders.[6] These disorders significantly impair patients' concentration, leading to markedly reduced work or academic efficiency. In social contexts, patients often avoid social situations due to fear of panic attacks, gradually resulting in social isolation and broken relationships.[7] Current research indicates that the pathogenesis of anxiety disorders involves genetic susceptibility, dysfunction in neurotransmitter systems (eg, 5-HT, GABA, NE), abnormalities in the amygdala-prefrontal cortex neural circuitry, and interactions with environmental stress factors (eg, childhood trauma, chronic stress).[8] Nevertheless, the pathological mechanisms of anxiety disorders remain incompletely elucidated, and clinical practice still faces challenges such as low early identification rates and poor treatment adherence.

Mendelian randomization (MR) has been a commonly used method in epidemiological analysis and research in recent years. This analytical approach employs the instrumental variable method to strengthen causal inference in nonexperimental settings and utilizes genetic variation as an instrumental variable to investigate the causal association between exposure and outcomes (rather than environmentally modifiable exposures).[9] According to Mendelian inheritance laws, alleles are randomly distributed from parents to offspring, which is analogous to the randomization process occurring in randomized controlled trials. Additionally, MR is unaffected by traditional confounding factors such as environmental exposure, socioeconomic status, or disease status, thereby satisfying the temporal order requirement. Therefore, MR effectively eliminates confounding factors and reverse causality, thereby yielding evidence with a quality that is comparable to that of randomized controlled trials.

However, there are currently no published studies that have focused on the association between loud music and anxiety disorders. Therefore, this two-sample MR analysis examined pooled data on music and anxiety disorders to explore the genetic causal relationship between music and agoraphobia. The findings of this study will facilitate the development of effective prevention and treatment strategies for clinical practice. To our knowledge, this is the first study to explore the effects of loud music on anxiety disorders.

Methods

Mendelian Randomization Analysis Data Sources

The GWAS data that were used in this study were obtained from the IEU open GWAS website (https://gwas.mrcieu.ac.uk/) and the Finnish Consortium. The GWAS data that were used in this study were derived from European populations including both males and females. Detailed information on the data is provided in Supplementary Table 1. The definition of loud music exposure frequency in the GWAS database is derived from the UK Biobank questionnaire (ID: 4836), which defines loud music as: "ever listened to music for more than 3 hours per week at a volume which you would need to shout to be heard or if wearing headphones, someone else would need to shout for you to hear them". Since these data were obtained from public databases, no additional ethical review was required for this study.

Mendelian Randomization Study Design

This Mendelian randomization analysis aimed to elucidate the causal relationship between music and agoraphobia. Music was the instrumental variable, and agoraphobia was the outcome variable. The instrumental variable was selected based on the following three criteria: a. the instrumental variable was strongly correlated with the exposure factor (the correlation assumption); b. the instrumental variable was independent of the confounding factors (the independence assumption); and c. the effect of the instrumental variable on the outcome was fully mediated through the exposure and not through other pathways (the exclusivity assumption). First, highly correlated SNP loci ($P < 1\times10^{-5}$) were screened from the GWAS dataset for left thyroid hormone. To eliminate the influence of linkage disequilibrium on the analysis results, the clump parameters were established according to the following standards: R^2= 0.001 and KB = 10,000. To ensure a strong association between the instrumental variable and the exposure factor, this study calculated the F statistic for weak instrumental variable effects. Therefore, the F statistics for all of the included SNPs in the MR analysis were greater than 10 to exclude the influence of weak instrumental variables. To ensure the reproducibility of the MR analysis

and the robustness of the results, this study utilized effect allele frequency (EAF) and strand orientation information to align SNPs between the exposure and outcome GWAS datasets, ensuring the alignment of effect alleles; palindromic SNPs with EAF close to 0.5 (range 0.45–0.55) were excluded to reduce potential bias caused by such SNPs; MR-Egger intercept test was employed to assess potential bias arising from sample overlap. After screening, a total of 34 SNPs met the inclusion criteria.

Mendelian Randomization Analysis

This study employed five methods (inverse-variance weighted [IVW], weighted median [WM], MR-Egger, simple mode, and weighted mode methods) to investigate the causal relationship between loud music exposure and anxiety disorders. Among these, the inverse-variance weighted (IVW) method served as the primary analytical method, whose results carry the highest evidence level.[10] The weighted median (WM) method can provide statistically valid results even when up to 50% of the genetic instrumental variables are invalid.[11] MR-Egger regression was used to verify the robustness of the primary results.[12] The simple mode and weighted mode methods were used as auxiliary validation methods to provide supplementary evidence. Since the outcome of this study was a binary variable, the MR analysis used odds ratios (OR) as the effect measures, with 95% confidence intervals (CIs) also being utilized. A p value less than 0.05 was considered to be statistically significant. For P-values at the borderline significance level (0.04–0.05), this study applied the False Discovery Rate (FDR) correction. If the P-value remained below 0.05 after FDR correction, it was considered statistically significant.

To further validate the stability and reliability of the study results, quality control assessments, including heterogeneity tests, horizontal pleiotropy tests, and sensitivity analyses, were performed. The Cochran Q statistic was calculated using both the IVW method and MR-Egger regression. Moreover, $P > 0.05$, indicated no significant heterogeneity. This study used the MR-Egger intercept term and the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) to assess pleiotropy at the SNP level. Sensitivity analysis was conducted using the leave-one-out method to sequentially exclude each of the included SNPs, and the causal effect was re-estimated by calculating the results of the remaining SNPs. If the overall error line demonstrated little change after each SNP was excluded, the results were considered to be reliable.

Results

Identification of Instrumental Variables

This study identified 34 independent SNPs from music as the instrumental variables, all of which were strongly correlated with music ($F > 10$). However, these SNPs may have exhibited linkage disequilibrium. To eliminate the interference of linkage disequilibrium on the results, linkage disequilibrium was removed, and a total of 34 SNPs were obtained.

Results of Mendelian Randomization

Loud Music and Generalized Anxiety

Ultimately, 34 SNPs were identified in the GWAS data for loud music and subjected to MR analysis. The IVW results indicated a significant causal relationship between loud music and the risk of generalized anxiety (OR = 1.050, 95% CI: 1.015–1.086, P = 0.004). However, the other four methods did not reveal a causal relationship between loud music and generalized anxiety (Table 1 and Figure 1A). When considering the greater precision advantage of the IVW method compared to the weighted median method and MR-Egger analysis, the results of the MR analysis may support a potential causal relationship between loud music and generalized anxiety. This MR analysis did not identify significant heterogeneity or horizontal pleiotropy (Supplementary Tables 2 and 3). The scatter points on the funnel plot were roughly symmetrically distributed on both sides of the IVW line, thereby indicating that there was no risk of bias (Figure 1B). Figure 1C is a forest plot depicting the causal effect of single nucleotide polymorphisms related to loud music on generalized anxiety. Moreover, the leave-one-out method did not reveal any significant differences after sequentially excluding the SNPs. The leave-one-out sensitivity analysis plot is shown in Figure 1D. The results of this study suggest

Table 1 Two-Sample Mendelian Randomization Analysis Between Loud Music Exposure Frequency and Anxiety Disorder

Outcome	Method	b	SE	P value	OR (95% Two-Side CI)
Generalized anxiety	MR Egger	0.054	0.036	0.147	1.055(0.983–1.133)
	Weighted median	0.038	0.025	0.123	1.039(0.990–1.091)
	Inverse variance weighted	0.049	0.017	0.004	1.050(1.015–1.086)
	Simple mode	0.008	0.051	0.884	1.008(0.911–1.114)
	Weighted mode	0.005	0.051	0.928	1.005(0.910–1.110)
Agoraphobia	MR Egger	−1.795	0.969	0.074	0.166(0.025–1.110)
	Weighted median	−1.334	0.673	0.047	0.263(0.070–0.985)
	Inverse variance weighted	−0.785	0.517	0.129	0.456(0.166–1.256)
	Simple mode	−1.495	1.246	0.239	0.224(0.019–2.579)
	Weighted mode	−1.650	1.052	0.127	0.192(0.024–1.510)
Panic disorder	MR Egger	−0.095	0.377	0.803	0.910(0.435–1.903)
	Weighted median	−0.038	0.281	0.893	0.963(0.555–1.671)
	Inverse variance weighted	0.013	0.201	0.947	1.014(0.684–1.502)
	Simple mode	0.033	0.516	0.950	1.033(0.375–2.483)
	Weighted mode	0.049	0.427	0.909	1.051(0.455–2.425)
Social phobias	MR Egger	−1.221	0.613	0.055	0.295(0.089–0.980)
	Weighted median	−0.576	0.408	0.158	0.562(0.252–1.251)
	Inverse variance weighted	−0.449	0.332	0.176	0.638(0.333–1.224)
	Simple mode	0.349	0.914	0.705	1.418(0.237–8.500)
	Weighted mode	−1.287	0.746	0.094	0.276(0.064–1.192)

that loud music may be a risk factor for generalized anxiety. Although the inverse-variance weighted (IVW) method showed a significant causal association between loud music preference and generalized anxiety (OR = 1.050, 95% CI: 1.015–1.086, P = 0.004), it should be noted that the effect size is small, suggesting that its clinical significance needs to be comprehensively evaluated in conjunction with other factors.

Loud Music and Agoraphobia

The IVW method (OR = 0.456, 95% CI: 0.166–1.256, P = 0.123) and MR-Egger regression method (OR = 0.166, 95% CI: 0.025–1.110, P = 0.073) did not reveal a significant causal relationship between loud music and the risk of agoraphobia. However, the weighted median method (OR = 0.263, 95% CI: 0.070–0.985, after FDR correction, P = 0.047) indicated a significant causal relationship between loud music and the risk of developing agoraphobia, with loud music being identified as a protective factor against agoraphobia (Table 1 and Figure 2A). Although the IVW method represents the primary reference standard, the weighted median method still demonstrates a certain degree of reliability, with a higher precision being observed compared to the MR-Egger regression method. Therefore, a causal relationship between loud music and agoraphobia could not be ruled out. Additionally, this MR analysis did not identify significant heterogeneity or horizontal pleiotropy (Supplementary Tables 2 and 3). The scatter points on the funnel plot were roughly symmetrically distributed on both sides of the IVW line, thereby indicating that there was no risk of bias (Figure 2B). Figure 2C is a forest plot depicting the causal effect of single nucleotide polymorphisms related to loud music on agoraphobia. The leave-one-out method indicated that the statistical results remained unchanged after sequentially excluding the included SNPs. The leave-one-out sensitivity analysis plot is shown in Figure 2D.

Loud Music and Panic Disorder

None of the five methods revealed a significant causal relationship between loud music and panic disorder (Table 1 and Figure 3A). This MR analysis did not identify significant heterogeneity or horizontal pleiotropy (Supplementary Tables 2 and 3). The scatter points on the funnel plot were roughly symmetrically distributed on both sides of the IVW line, thereby indicating that there was no risk of bias (Figure 3B). Figure 3C is a forest plot depicting the causal effect of

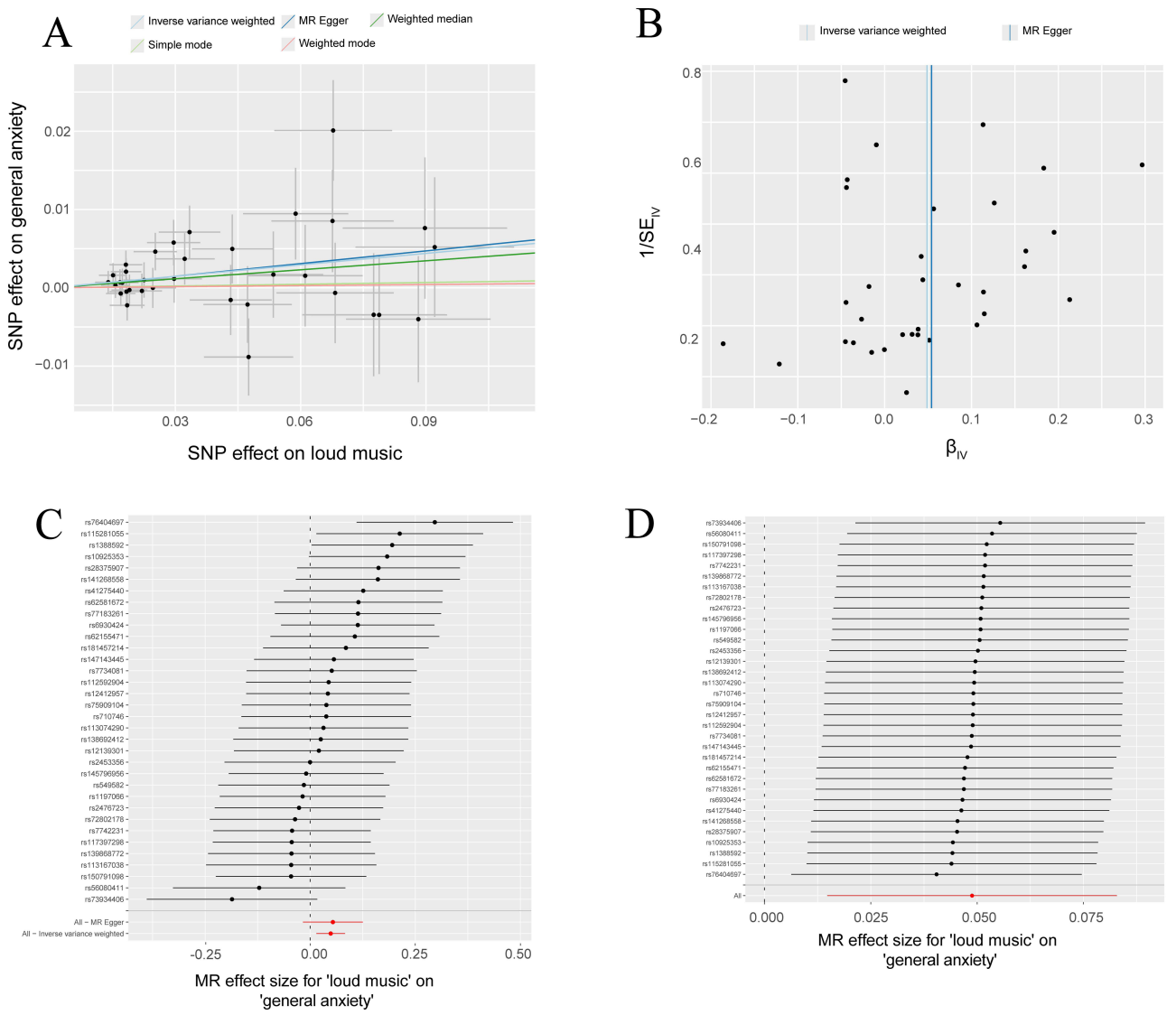

Figure 1 Two-sample Mendelian randomization analysis between loud music exposure frequency and generalized anxiety. (**A**) Scatter plot of causality between loud music and generalized anxiety. (**B**) Funnel plot for loud music on generalized anxiety. (**C**) Forest plot of SNPs associated loud music and generalized anxiety. (**D**) Leave-one-out of SNPs associated loud music and generalized anxiety.

single nucleotide polymorphisms related to loud music on panic disorder. The leave-one-out method indicated no significant differences in the statistical results after sequentially excluding the included SNPs (Figure 3D).

Loud Music and Social Phobias

None of the five methods revealed a significant causal relationship between loud music and social phobias (Table 1 and Figure 4A). This MR analysis did not identify significant heterogeneity or horizontal pleiotropy (Supplementary Tables 2 and 3). The scatter points on the funnel plot were roughly symmetrically distributed on both sides of the IVW line, thereby indicating that there was no risk of bias (Figure 4B). Figure 4C is a forest plot depicting the causal effect of single nucleotide polymorphisms related to loud music on social phobias. The leave-one-out method indicated no significant differences in the statistical results after sequentially excluding the included SNPs (Figure 4D).

Reverse Two-Sample MR Analysis

To investigate the reverse causal relationship between loud music and anxiety disorders, this study conducted a reverse MR analysis. In the reverse two-sample MR, various types of anxiety disorders were the exposure factors, while loud

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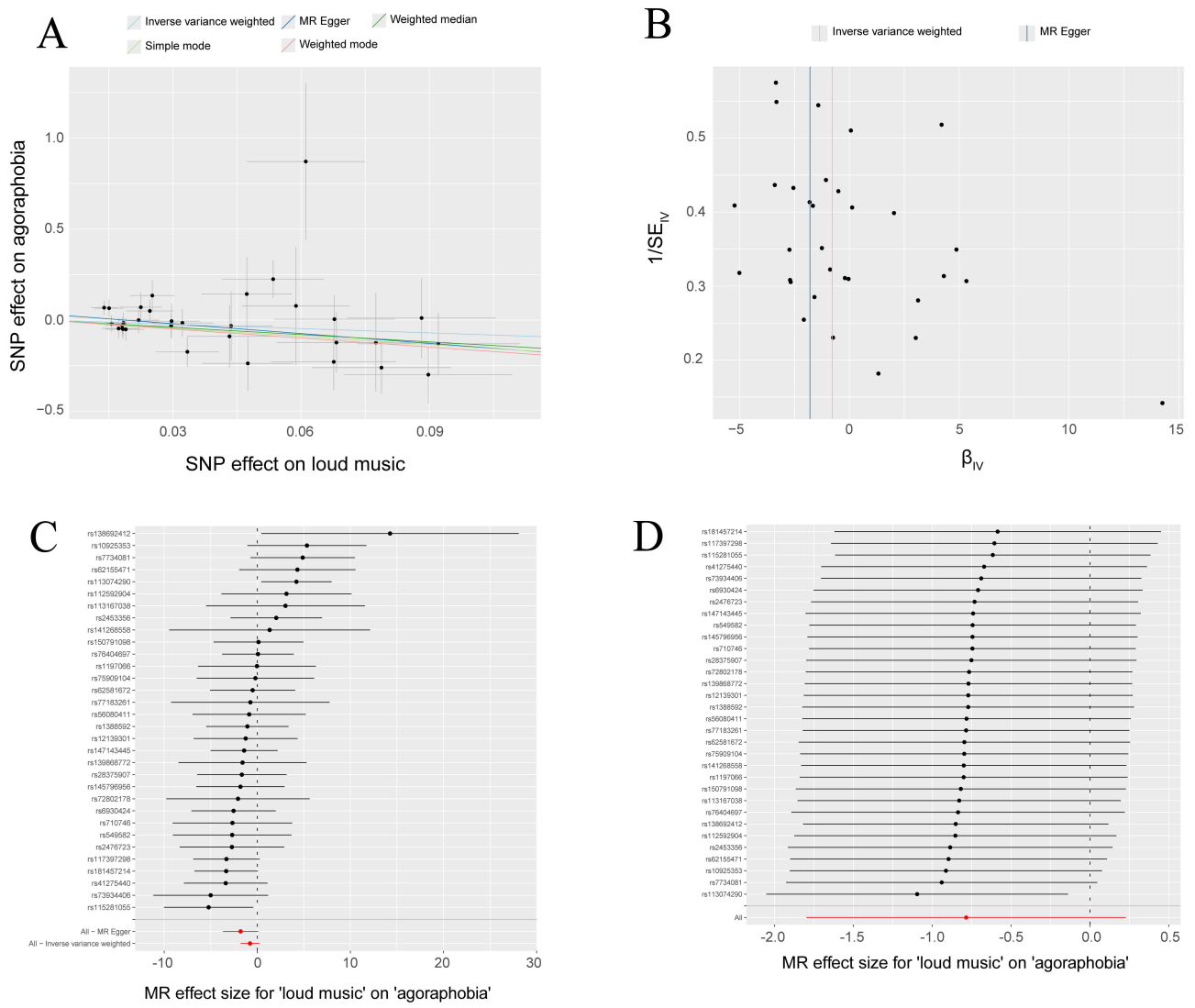

Figure 2 Two-sample Mendelian randomization analysis between loud music exposure frequency and agoraphobia. (**A**) Scatter plot of causality between loud music and agoraphobia. (**B**) Funnel plot for loud music on agoraphobia. (**C**) Forest plot of SNPs associated loud music and agoraphobia. (**D**) Leave-one-out of SNPs associated loud music and agoraphobia.

music was the outcome factor. We set the p value to less than 1×10^{-5}. The threshold for removing linkage disequilibrium is $R^2 < 0.001$ and KB > 10,000. All SNPs exhibited F values greater than 10. The results of the Mendelian randomization analysis did not indicate a causal relationship between anxiety disorders and loud music. (Supplementary Table 4). Cochran Q test, MR-Egger intercept test, and MR-PRESSO test did not reveal any heterogeneity (Supplementary Tables 5 and 6). The scatter plot illustrating the causal relationship between generalized anxiety and loud music is shown in Supplementary Figure 1A, the funnel plot in Supplementary Figure 1B, the forest plot for single nucleotide polymorphisms causal effects in Supplementary Figure 1C, and the results of leave-one-out in Supplementary Figure 1D. The scatter plot illustrating the causal relationship between agoraphobia and loud music is shown in Supplementary Figure 2A, the funnel plot in Supplementary Figure 2B, the forest plot for single nucleotide polymorphisms causal effects in Supplementary Figure 2C, and the results of leave-one-out in Supplementary Figure 2D. The scatter plot illustrating the causal relationship between panic disorder and loud music is shown in Supplementary Figure 3A, the funnel plot in Supplementary Figure 3B, the forest plot for single nucleotide polymorphisms causal effects in Supplementary Figure 3C, and the results of leave-one-out in Supplementary Figure 3D. The scatter plot illustrating the causal relationship between social phobias and loud music is shown in Supplementary Figure 4A, the funnel plot in

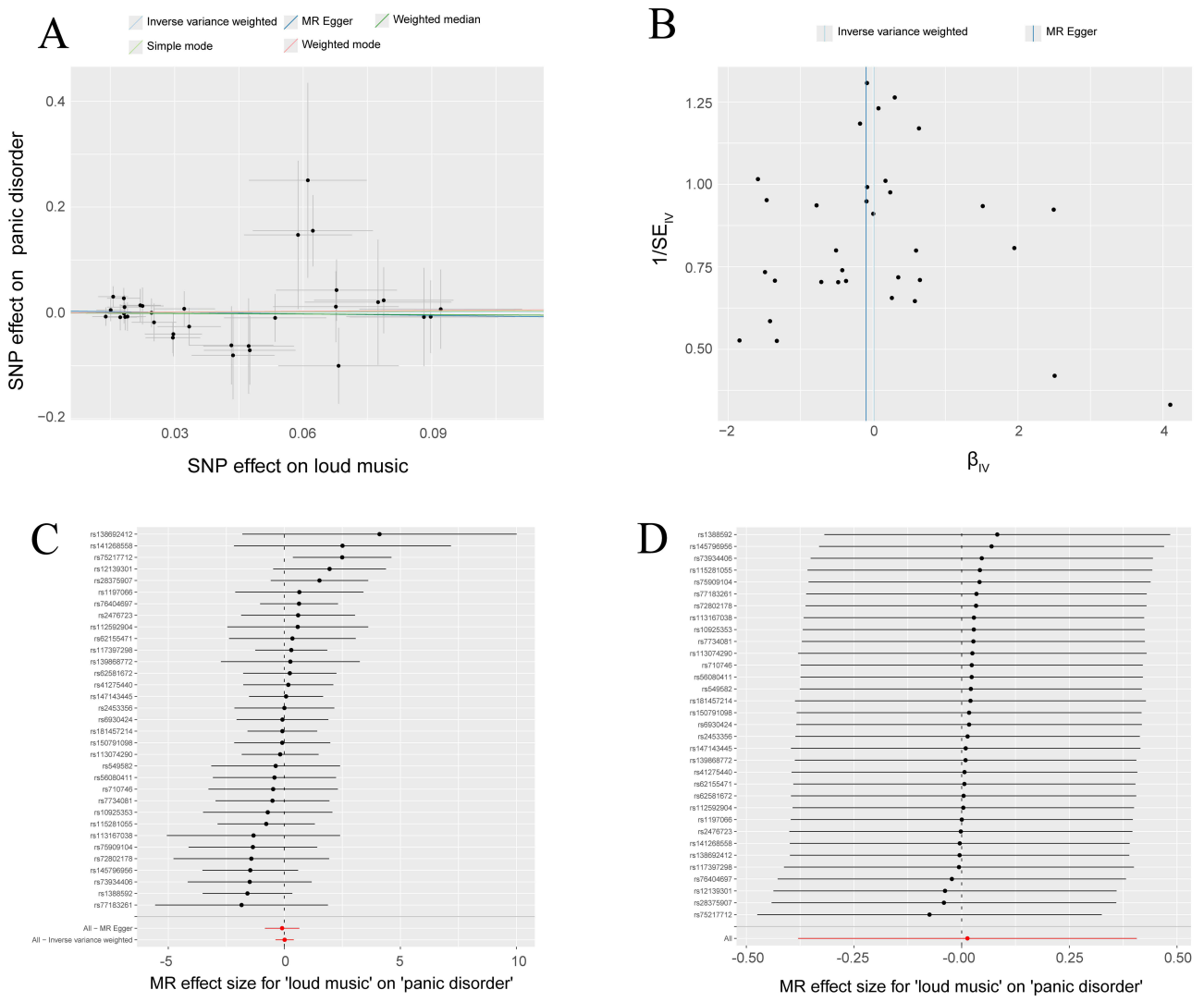

Figure 3 Two-sample Mendelian randomization analysis between loud music exposure frequency and panic disorder. (**A**) Scatter plot of causality between loud music and panic disorder. (**B**) Funnel plot for loud music on panic disorder. (**C**) Forest plot of SNPs associated loud music and panic disorder. (**D**) Leave-one-out of SNPs associated loud music and panic disorder.

Supplementary Figure 4B, the forest plot for single nucleotide polymorphisms causal effects in Supplementary Figure 4C, and the results of leave-one-out in Supplementary Figure 4D.

Discussion

This study utilized large-sample GWAS public data and a two-sample MR study to investigate the genetic causal relationship between music and anxiety disorders. To our knowledge, this is the first study to explore the associations between music and different subtypes of anxiety disorders.

γ-aminobutyric acid (GABA) plays a crucial role in the development of generalized anxiety. Basic research has confirmed significant GABA dysfunction in animal models of generalized anxiety.[13] A study on the Piperaceae plant (Piper amalago) revealed that its extract can produce anxiolytic effects similar to those of diazepam by activating GABA-A receptors.[14] Another study on medicinal plants revealed that 20-hydroxyecdysone obtained from Rhaponticum uniflorum and Serratula centauroides exhibits anxiolytic effects, which are mediated through GABA.[15] Additionally, another study demonstrated that tetrahydrocarbazoles exhibit dose-dependent anxiolytic effects, which can be abolished by the GABA receptor antagonist bicuculline.[16] Moreover, in the clinical treatment of anxiety disorders, benzodiazepines

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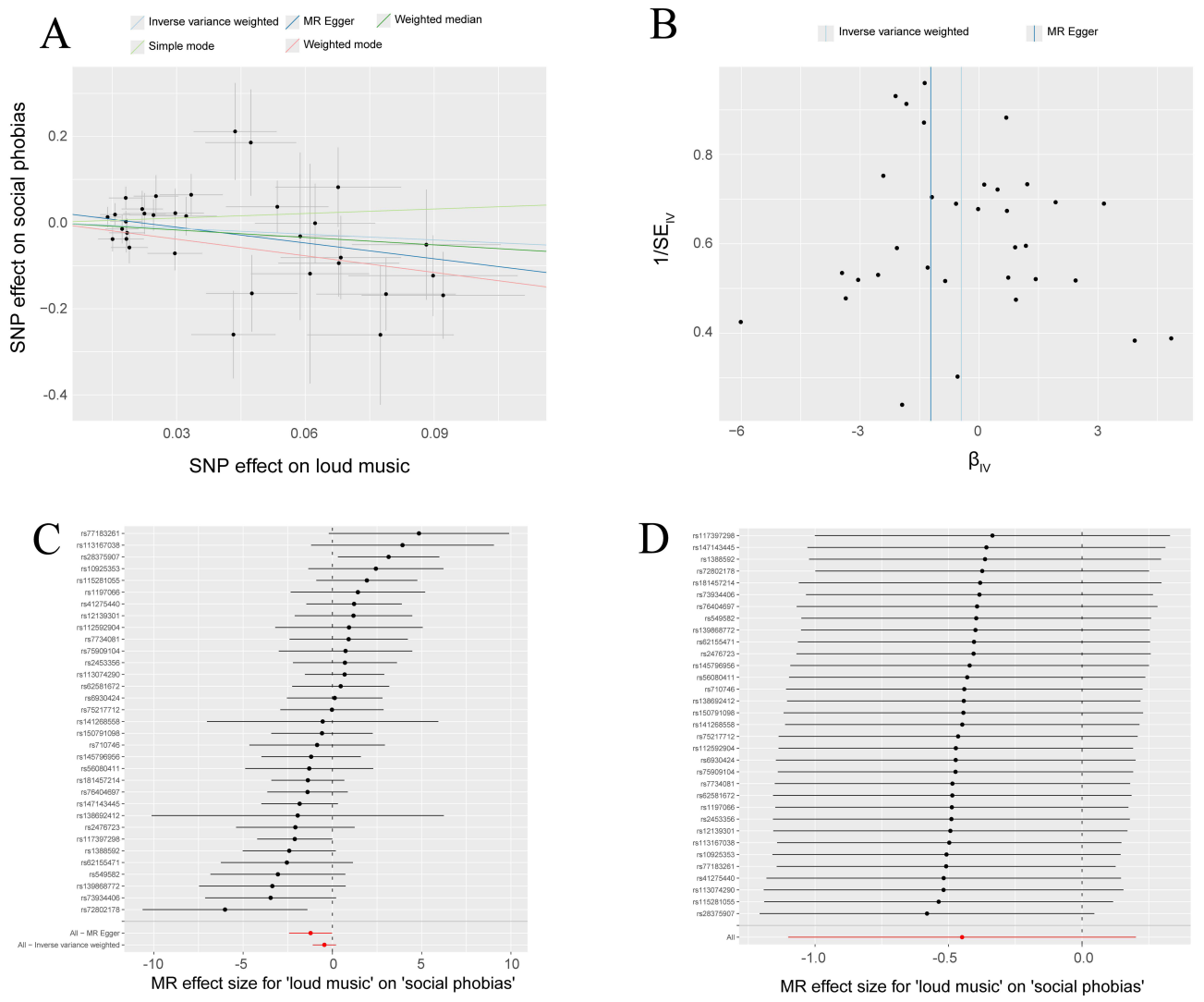

Figure 4 Two-sample Mendelian randomization analysis between loud music exposure frequency and social phobias. (**A**) Scatter plot of causality between loud music and social phobias. (**B**) Funnel plot for loud music on social phobias. (**C**) Forest plot of SNPs associated loud music and social phobias. (**D**) Leave-one-out of SNPs associated loud music and social phobias.

exhibit rapid onset of action in alleviating anxiety.[17] These findings suggest that impaired GABA function in the brain is an important cause of anxiety.

The results of this study indicate a positive causal relationship between loud music and anxiety, thereby suggesting that loud music may lead to the onset of anxiety. Although music therapy has demonstrated therapeutic effects for various mental and psychological disorders, the type of music that is used in music therapy is typically moderate to low in volume and has a slow rhythm. Prolonged exposure to loud music may demonstrate effects that are similar to those of noise. Multiple studies have confirmed that noise can lead to a decrease in GABA function. Specifically, compared to rats living in quiet environments, chronic exposure to noise can cause a 15% decrease in GABA levels in the striatum of rats.[18] Additionally, prolonged exposure to bright light and loud noise in mice can lead to a decrease in GABA levels in the brain, thereby inducing sleep-wake disorders.[19] In mice with Alzheimer's disease, chronic noise exposure also causes GABA dysfunction.[20] Therefore, we speculate that prolonged exposure to loud music may weaken GABA function in the brain, thus potentially leading to the development of anxiety disorders.

The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in regulating anxiety.[21] In animal models of anxiety disorders, lithium salts have been found to exert an inhibitory effect on the HPA axis by suppressing the activity

of nitric oxide synthase in the prefrontal cortex and hippocampus and downregulating the expression of IL-1β, which significantly improves anxiety in animals.[22] Another study revealed that cortisol levels in the brains of rats with anxiety disorders were significantly elevated. N-acetylcysteine can reduce cortisol levels in the brains of rats with anxiety disorders, thereby effectively improving their anxiety symptoms.[23] A study using the virtual Trier Social Stress Test (TSST) demonstrated that oxytocin could significantly reduce plasma cortisol levels, thereby improving patients' anxiety symptoms.[24] The translocator protein (TSPO) plays a crucial role in regulating HPA axis function.[25] Additionally, studies have demonstrated that the TSPO agonist GD-23 can improve anxiety-like symptoms in rats and that this effect could be reversed by the TSPO antagonist PK11195.[26] The abovementioned studies confirm the role of the HPA axis in anxiety. Furthermore, increased HPA axis function can lead to the development of anxiety.

Although music can exert a certain regulatory effect on the HPA axis, existing research has specifically focused on music therapy.[27] The type of music that is used in music therapy is characterized by a slow rhythm and low volume;[28] moreover, there are currently no studies that have investigated the relationship between loud music and the HPA axis. Long-term exposure to loud music exerts effects that are similar to those of noise on the human body. Furthermore, the impact of noise on the HPA axis has been confirmed by multiple studies. For example, a study on industrial chronic noise demonstrated that workers exposed to industrial noise for extended periods of time exhibited significantly elevated cortisol levels in their saliva.[29] Additionally, prolonged exposure to low-intensity noise was observed to lead to a significant increase in corticotropin levels in mouse plasma.[30] Acute noise exposure also activates the HPA axis. A study conducted on volunteers revealed that exposure to 90 decibels of noise for 20 minutes caused the salivary cortisol levels of these participants to increase from 3.25 ng/mL to 3.25 ng/mL, which represented a statistically significant difference.[31] Previous studies have demonstrated that both acute and chronic noise exposure can upregulate the transcription of corticotropin-releasing hormone (CRH) mRNA in the hypothalamus, thereby increasing HPA axis excitability.[32] Therefore, the positive causal relationship between loud music and anxiety is likely closely related to the upregulation of HPA axis excitability caused by loud music.

In the MR analysis results, the IVW method demonstrated a significant positive causal relationship between loud music exposure and generalized anxiety, with no heterogeneity or horizontal pleiotropy detected. Furthermore, all five methods consistently showed effect estimates in the same direction. Thus, the Mendelian randomization results provide strong evidence supporting a causal relationship between loud music exposure and generalized anxiety, indicating that loud music is highly likely to be a risk factor for generalized anxiety. However, it is important to note that although a significant causal association was observed between loud music exposure and generalized anxiety (OR = 1.050, 95% CI: 1.015–1.086, P = 0.004), the odds ratio of 1.05 corresponds to only a 5% increase in the risk of anxiety disorders. From a clinical perspective, a 5% increase in risk indeed constitutes a "small effect size". Nevertheless, MR primarily focuses on establishing the direction of causality rather than the magnitude of the effect size. More importantly, the significant result from the IVW method (P = 0.004), along with the absence of heterogeneity and horizontal pleiotropy, supports the conclusion that loud music exposure may increase the risk of generalized anxiety. From a public health standpoint, even a 5% increase in risk could have significant implications at the population level. This study provides a novel starting point for future mechanistic research. Larger sample sizes will be required in future studies to precisely estimate the effect size and its clinical significance.

The core features of agoraphobia are intense fear and avoidance of specific places or situations. The neurobiological mechanisms of agoraphobia involve abnormalities in multiple neurotransmitter systems, primarily including imbalances in 5-HT, norepinephrine, DA, GABA, and glutamate.[33] Among these neurotransmitters, 5-HT plays a crucial role in agoraphobia. Previous studies have demonstrated that the reduced expression of 5-HT1A receptors in the amygdala and prefrontal cortex can lead to impaired fear regulation.[34,35] Moreover, the activation of 5-HT_{1A} receptors in the amygdala can weaken the response to fear stimuli.[36] Patients with agoraphobia often exhibit abnormal amygdala-prefrontal cortex (PFC) connectivity, thereby leading to an exaggerated threat assessment of open/crowded environments. Serotonin deficiency enhances amygdala-dependent fear memory consolidation, which causes patients to develop persistent fear in specific scenarios.[37,38] Animal models have demonstrated that mice with knockouts of the 5-HT_{1A} receptor are more prone to forming irreversible fear memories.[39] Currently, selective serotonin reuptake inhibitors (SSRIs) are the most effective medications for treating agoraphobia. SSRIs block 5-HT reuptake, thereby enhancing inhibitory control over the amygdala-PFC pathway and reducing the frequency of agoraphobic episodes.[40,41]

The effects of music on serotonin (5-HT) levels have been confirmed by multiple studies. Tryptophan in the human body primarily follows two metabolic pathways: metabolism via the kynurenine pathway to cortisol and metabolism via the serotonin pathway to 5-HT.[42] Music can reduce the diversion of tryptophan to the kynurenine pathway, thereby allowing for more tryptophan to be converted into 5-HT.[43] Music can also reduce cortisol levels, thus alleviating its inhibition of tryptophan hydroxylase (TPH) and promoting 5-HT synthesis.[44,45] Moreover, music stimulates serotonergic neuronal activity in the dorsal raphe nucleus (DRN) through pleasurable responses in the limbic system, including the amygdala and hippocampus, thereby increasing 5-HT release.[46] Therefore, the enhancement of 5-HT function is likely one of the potential mechanisms by which music improves agoraphobia.

The role of dopamine (DA) in agoraphobia is complex and involves multiple aspects, such as motivation and behavioral inhibition. Although the core symptoms of agoraphobia (such as fear of open/crowded spaces) are typically more directly associated with the 5-HT system, the DA system indirectly influences the development and maintenance of agoraphobia by regulating reward prediction, risk assessment, and motor behavior.[47] DA neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), and they typically promote exploratory behavior and approach motivation.[48] Reduced DA function can lead to enhanced avoidance behaviors, with patients being more likely to choose "safe behaviors" (such as staying at home) rather than exploring the outside world.[49] Due to reduced DA function, patients may also experience a lack of positive incentives, thereby leading to a more negative expectation of "going out".[50] Functional magnetic resonance imaging (fMRI) studies conducted in agoraphobia patients have demonstrated reduced NAc responses to potential reward stimuli (such as social interaction).[51] Experimental results from basic research indicate that mice with blocked dopamine D2 receptors exhibit stronger avoidance behaviors.[52] Furthermore, the activation of dopamine D2 receptors can improve fear.[53]

Previous research has indicated that music can directly or indirectly activate the dopaminergic pathway, thereby producing pleasure, enhancing motivation, and even alleviating certain neuropsychiatric symptoms. Music triggers DA release.[54] When listening to one's favorite music, the amount of DA released in the NAc is positively correlated with subjective pleasure.[55] Additionally, fMRI has demonstrated that during the climactic parts of music, VTA activity is significantly enhanced.[56] In Parkinson's disease patients, rhythmically strong music (such as drum beats) improves motor symptoms via the DA pathway.[57] These findings suggest that music can enhance DA function in the brain. The exposure factor utilized in this study was loud music. Loud music can produce effects that are similar to those of choir singing or live concerts; thus, the promotion of DA release is likely one of the mechanisms by which music improves agoraphobia.

It should be noted that as the primary method in Mendelian randomization analysis, the Inverse-Variance Weighted (IVW) method did not demonstrate a significant causal relationship between loud music exposure and agoraphobia ($P = 0.129$, $OR = 0.456$). However, the Weighted Median (WM) method indicated a causal association between loud music exposure and agoraphobia ($P = 0.047$). The IVW method offers the highest statistical power in MR analysis, but its validity relies on the strong assumption that all instrumental variables are valid.[10] In contrast, the WM method operates under more relaxed assumptions, allowing for up to 50% of the instrumental variables to be invalid, thereby providing greater robustness against outliers and invalid instruments.[11] In this study, the significant result obtained from the WM method ($P = 0.047$) suggests that after accounting for the potential influence of invalid instruments, a causal relationship may exist between loud music exposure and agoraphobia. Although P-values differed across methods, we observed complete consistency in the direction of effect estimates across all five MR methods employed, including IVW, WM, and MR-Egger. This high degree of consistency in effect direction provides important supporting evidence for a potential association between the exposure and outcome, reducing the likelihood that the results occurred by chance. The results of this study indicate no significant heterogeneity or horizontal pleiotropy in the MR analysis. This suggests a high probability that the instrumental variables satisfy the core assumptions of MR, indicating relatively robust findings. Therefore, the MR results provide a certain degree of evidence supporting a causal relationship between loud music exposure and agoraphobia. Consequently, the potential protective effect of loud music exposure on agoraphobia should not be readily dismissed. The relationship between loud music exposure and agoraphobia requires further validation through evidence-based medical research.

This study also has certain limitations. First, all of the data on music and various types of anxiety disorder originated from European populations; therefore, whether these data are applicable to other countries and regions remains to be further studied. Second, MRI results can only partially elucidate causal relationships at the genetic level, and the association between the two diseases requires further validation via additional epidemiological methods. Furthermore, the small odds ratio (OR = 1.05) observed for generalized anxiety in this study warrants cautious interpretation in practical applications. Future studies with larger sample sizes are needed to precisely estimate the effect size and its clinical significance. Additionally, the causal relationship between loud music exposure and agoraphobia requires further validation through evidence-based medical research. Finally, although Mendelian randomization mimics randomized trials by leveraging the random allocation of genetic variants, it cannot fully exclude the influence of gene-environment interactions. Future studies should incorporate socioeconomic variables as covariates or conduct cross-population validations to strengthen the robustness of causal inferences.

Conclusions

The results of the Mendelian randomization analysis indicate a positive causal relationship between loud music exposure and generalized anxiety. Although the IVW method did not show a significant causal relationship between loud music exposure and agoraphobia, the WM method indicated an inverse causal relationship, with no heterogeneity or horizontal pleiotropy detected. Therefore, a causal relationship between loud music exposure and agoraphobia cannot be readily dismissed. Whether loud music serves as a protective factor for agoraphobia requires further clarification through clinical and epidemiological investigations. No significant causal relationships were found between loud music exposure and panic disorder or social anxiety disorder. This study is the first to report associations between loud music exposure and major subtypes of anxiety disorders, potentially providing a new research direction for the treatment of anxiety disorders.

Abbreviations

5-HT, 5-Hydroxytryptamine; DA, dopamine; FDR, false discovery rate; Fmri, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; GWAS, genome-wide association; HPA, hypothalamic-pituitary-adrenal; IC, information component; IVW, inverse-variance weighted; MPGS, Multi-item Gamma Poisson Contraction-machine; MR, Mendelian randomisation; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; NAc, nucleus accumbens; OR, odds ratio; SNP, single-nucleotide polymorphism; SSRIs, selective serotonin reuptake inhibitors; TSPO, translocator protein; TSST, Trier Social Stress Test; VTA, ventral tegmental area; WM, weighted median.

Data Sharing Statement

All raw data and code are available upon request. For requests concerning the raw data, please contact the corresponding author.

Ethics Statement

All the data used in this study were obtained from public databases, so no additional ethical review was required according to item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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