

# Acute Exacerbation of Chronic Subjective Tinnitus: a Cross-sectional Study

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## Research

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# Abstract

**Background:** To analyze data from the tinnitus study that addresses the factors contributing to the acute exacerbation of chronic subjective tinnitus, and providing a comprehensive landscape of multiple factors action patterns on acute exacerbation of tinnitus.

**Methods:** It reports data from patients with chronic subjective tinnitus, enabling a direct comparison of results between the stable stage of chronic tinnitus and the acute exacerbation of chronic tinnitus samples. Participants had completed comprehensive audiometric testing and numerous questionnaires.

**Results:** Results are presented from n=602 participants across the two sites, including 204 patients in the stable stage of tinnitus and 398 patients in acute exacerbation of tinnitus. The data reveal that: ☒ Acute exacerbation of chronic tinnitus is affected by many factors, among them, aggravated hearing loss, fatigue, stress, disturbed sleep, negative emotion, upper respiratory tract infection, noise exposure, and abruptly changed barometric pressure may aggravate the tinnitus; ☒ Smoking, drink, and course of tinnitus are not risked factors for acute exacerbation of chronic tinnitus; ☒ Comparison of the importance of the four factors induce acute exacerbation of chronic tinnitus, fatigue and stress are the most important, then, in turn, negative emotions and sleep disorders.

**Conclusions:** ☒ There were many incentives for acute exacerbation of chronic tinnitus and multiple causes coexist under normal conditions. ☒ The prevention and prognosis management of acute exacerbation of chronic tinnitus should be approached from multiple dimensions, which includes biological, social support, patient psychology.

**Trial registration:** Not applicable

## Background

Tinnitus is under the impression of sounds in the absence of external sounds. Subjective tinnitus and hallucinations are phantom sounds but subjective tinnitus is different from hallucinations and objective tinnitus that is caused by sounds generated in the body and conducted to the ear. Tinnitus faces by 10–15% of adults, and, for about 20% of those, their tinnitus is “bothersome”<sup>1</sup>. The impact of tinnitus is well recognized both for the general population<sup>2</sup> and for military Veterans. For these patients it can reduce the quality of life by generating anxiety and concentration problems impairing the ability to do intellectual work, making it difficult to sleep; causing depression and tinnitus can ultimately lead to suicide<sup>3</sup>. Tinnitus-related research emerged from the study of the high prevalence of tinnitus in American Veterans. Tinnitus and hearing loss greatly impact Veterans following their military career, as well as the mounting evidence correlating hearing loss and tinnitus to anxiety, sleep disorders, and other troubling comorbidities related to a decreased quality of life<sup>4,5</sup>. As the population ages, the pace of life further accelerates, the noise exposure opportunities such as construction noise and entertainment noise increase, and the incidence of war and armed conflict in some areas, the incidence of tinnitus will continue to rise. A gap in the literature is the absence of studies concerning how to control the exacerbation of tinnitus. The present study reports Tinnitus aggravating data that address this gap to prevent the occurrence of tinnitus-related comorbidities, and improve the management of tinnitus.

## Methods

### Subjects and study design

Consecutive patients experiencing chronic subjective tinnitus were allocated for the study. They were assigned to one of two groups: Group I, the group in the stable stage of tinnitus; Group II, the group in acute exacerbation of chronic tinnitus. The patient was considered to be in acute exacerbation of chronic tinnitus whose Tinnitus Handicap Inventory (THI) score was increased by 6 points or more compared to the previous score. Conversely, in the stable stage of tinnitus. After taking patients' history, routine otolaryngologic examination and audiologic evaluation were performed to determine whether the patients were appropriate for the study. All subjects were drawn from the same population. The study was approved by the Ethical Committee of The Third Affiliated Hospital of Sun Yat-Sen University (ethics approval number: [2019]02-479-01).

The exclusion criteria: course of tinnitus  $\geq$  0.5 years, objective tinnitus, otosclerosis, chronic otitis media, vestibular schwannoma, Meniere disease, otorrhea, history of the previous ear and neurotologic surgery, history of temporal bone trauma, endocrinologic disease, psychiatric disorder, and history of ototoxicity. The cutoff of course was chosen because 0.5 year is the threshold for chronic tinnitus.

All patients underwent a detailed physical examination at their first visit, along with a history-taking that included demographic characteristics, occupation, smoking and drinking behavior, and duration of tinnitus, and accompanying symptoms. Tinnitus handicap inventory (THI) was used to assess the tinnitus severity. Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS) were used to assess the negative emotion level; patients whom SAS or SDS score was greater than 50 were considered to be in negative emotions<sup>6,7</sup>. That the score of the Pittsburgh Sleep Quality Index (PSQI) greater than 5 be considered that patients have sleep disorders<sup>8</sup>. That the score on Psychosomatic Tension Relaxation Inventory (PSTRI) greater than or equal to 65 indicates patients were relatively stressed<sup>9</sup>. Fatigue severity scale (FSS) was intended to measure fatigue severity of tinnitus; that the score greater than or equal to 36 means patients were relatively fatigued<sup>10</sup>. The average pure-tone threshold loss  $\geq$  10dB, which means that the hearing loss is aggravated. If after an abrupt change in barometric pressure tinnitus worse, we believe sudden change in barometric pressure is the culprit. Diving, by air and other behaviors, can reach the air pressure difference inside and outside the tympanic membrane.

## Analysis

The normality test was conducted by the Shapiro-Wilk W test. Chi-squared tests were used to compare categorical variables. SPSS 20.0 software was utilized to perform all statistical analyses, with a P-value  $<0.05$  considered statistically significant. Taking into account the high correlation between fatigue, stress, sleep disorders, and negative emotions, a decision tree was used to analyze the influence mode of these four factors on the acute exacerbation of tinnitus. Random forests were used to assess the importance of these four factors. The importance of each variable can be measured by the mean decrease of the accuracy or "Gini" index. The greater the mean decrease accuracy or the mean decrease "Gini", the more essential the factor is.

## Results

602 patients with chronic tinnitus were allocated for this study. The stable chronic subjective tinnitus group included 208 women (52.3%) and 190 men (47.7%), with a total of 398; the age range was between 15 and 85 years. The acute exacerbation of chronic subjective tinnitus group included 105 women (51.5%) and 99 men (48.5%) with a total of 204; the age range was between 17 and 84 years. There were no significant differences between the groups in sex, smoking and drinking behavior, and duration of tinnitus ( $P > 0.05$ , Table 1). The

proportion of young and middle-aged in acute exacerbation of chronic tinnitus group is higher than the stable chronic tinnitus group ( $P < 0.05$ , Table 1).

Table 1  
Risk factors of acute exacerbation of chronic tinnitus

Influencing factors		Acute exacerbation of tinnitus	stable stage of tinnitus	<i>P</i> -value
Smoking	Yes	55	98	0.533
	No	149	300	
Drinking	Yes	86	175	0.757
	No	118	223	
Sex	Female	105	208	0.854
	Male	99	190	
Age (ys)	15–39	70	92	0.001
	40–59	84	154	
	≥60	50	152	
Duration (ys)	0.5-1	112	201	0.400
	1–2	41	99	
	≥2	51	98	
N: no; Y: yes				

There were significant differences between the groups in aggravated hearing loss, fatigue, stress, negative emotions, sleep disorders, upper respiratory tract infections, noise exposure, and abrupt change in barometric pressure ( $P < 0.05$ , Table 2). That means these factors may induce acute exacerbation of chronic tinnitus. It shows that head and neck trauma, traditional Chinese medicine, electric injury, and secondary and above surgery can't worsen tinnitus ( $P > 0.05$ , Table 2).

Table 2  
inducement of acute aggravation of chronic tinnitus

inducement		stable stage of tinnitus	Acute exacerbation of tinnitus	P-value	inducement		stable stage of tinnitus	Acute exacerbation of tinnitu	P-value
Fatigue	N	335	51	P < 0.001	Head and neck trauma	N	389	198	P = 0.397
	Y	63	153			Y	9	6	
Stress	N	319	41	P < 0.001	Abrupt change in barometric pressure	N	385	172	P < 0.001
	Y	79	163			Y	13	32	
Sleep disorders	N	290	48	P < 0.001	Traditional Chinese medicine	N	368	196	P = 0.057
	Y	108	156			Y	30	8	
Negative emotions	N	273	19	P < 0.001	Electric injury	N	390	200	P = 0.616
	Y	125	185			Y	8	4	
Upper respiratory tract infections	N	388	185	P < 0.001	Secondary and above surgery	N	387	197	P = 0.410
	Y	10	19			Y	11	7	
Noise exposure	N	385	176	P < 0.001	Aggravated hearing loss	N	341	103	P < 0.001
	Y	13	28			Y	57	101	
N: no; Y: yes									

A decision tree was used to analyze the influence mode of these four factors on the acute exacerbation of tinnitus. As shown in Fig. 1, 99% of chronic subjective tinnitus patients with fatigue, stress and negative emotions have aggravated tinnitus; 84% of chronic subjective tinnitus patients with fatigue, negative emotions, sleep disorder, and no stress have aggravated tinnitus. 58% of chronic subjective tinnitus patients with fatigue, stress, and no negative emotion have aggravated tinnitus. Then, We evaluated the importance of four factors by model comparison, using random forest. Table 3 presents the results of the analysis of the random forest. According to the value of the mean decrease accuracy or the mean decrease "Gini", we can understand that fatigue and stress are the most important factors, followed by negative emotions and sleep disorder.

Table 3  
Random forest

inducements	the mean decrease accuracy	the mean decrease "Gini"
fatigue	0.08010	56.57149
stress	0.07609	58.53614
Sleep disorder	0.03675	17.08442
negative emotion	0.07591	46.17750
The mean decrease accuracy and the mean decrease "Gini" are indicators to assess the importance.		

## Discussion

There are many factors that can lead to the acute exacerbation of tinnitus and new factors are continuously being identified. At present, it is more well-recognized with diseases that can cause tinnitus such as migraine, OSAHS, allergic rhinitis, etc. Some newly discovered phenomena such as tinnitus patients suffer from nasal septum deviation and the tinnitus disappeared after surgery to correct the nasal septum deviation, and tinnitus patients also suffered from sinusitis and tinnitus disappeared after the cure of sinusitis. The intrinsic link between these comorbidities and tinnitus is still under research.

The relationship between hearing loss and tinnitus has always been a difficult problem for tinnitus researchers. Hearing loss is a risk factor for tinnitus and tinnitus is almost always accompanied by hearing loss, however, it is currently considered that tinnitus is not directly related to the degree of the hearing loss. Tinnitus may be the result of a combination of causes. In the past years, it has become evident that hearing impairments can indirectly influence the function of the central nervous system and promote expression of neural plasticity while hearing impairments may both be the result of a combination of deficits in the auditory periphery and the effect of changes in the central nervous system. In recent years, evidence has accumulated that plastic changes in the central auditory nervous system can cause tinnitus because symptoms such as tinnitus are likely to have components that originate in the central nervous system, causing deprivation and changed balance between inhibition and excitation<sup>11</sup>. Therefore, in addition to hearing loss, other factors that can affect neural plasticity may also cause tinnitus, and cochlear-related diseases that can cause hearing loss may indirectly cause tinnitus<sup>12</sup>. This study found that the aggravation of tinnitus is often accompanied by the aggravation of hearing loss, probably because the deterioration of hearing impairment breaks the rebalancing of nervous system inhibition and excitement and the aggravation of tinnitus. Therefore, factors that can cause deterioration of hearing impairment loss may also aggravate tinnitus, such as hypoperfusion of cochlea or a viral infection.

In general, people who present with tinnitus are more likely to have sleep disorders, depression, anxiety, stress, and suicidal ideation<sup>13</sup>. Concentration, emotional stability, alertness, and adequate sleep may all influence the ability of Service members to carry out their assigned tasks, especially military man. One might therefore speculate that bothersome tinnitus may complicate the efficiency of operational missions<sup>14</sup>.

Fatigue and stress are the two most important factors aggravating tinnitus. However, in the clinic, patients often complain of insomnia, short sleep time, easy to wake up, etc., causing doctors to misjudge the role of sleep disorders in the acute exacerbation of chronic tinnitus, and ignore the effects of fatigue and stress, while the objective sleep quality score of patients shows no serious sleep disorders and fatigue-stress assessment shows

patients with more severe fatigue stress. Stress events may cause a psychosocial stress response in patients, which may cause functional changes in the immune system, such as immune defense, immune homeostasis, and immune surveillance, and changes in the immune system may be related to the occurrence and aggravation of tinnitus<sup>15,16</sup>. Current research suggests that psychosocial stress is related to biological factors such as genetics, neuroendocrine system, and intestinal flora changes, and inheritance is the key factor determining the physiological response of stress. 5-hydroxytryptamine transporter (5HTT) gene polymorphism is an important factor determining the individual's difference in physiological stress response. IL-1 $\beta$  of testers carrying the SS gene without carrying the SL gene is significantly increased after the Trier Social Stress Test<sup>17</sup>; changes in the endocrine system are mainly associated with the activation of sympathetic-adrenal medulla (SAM) system and hypothalamic-pituitary-adrenal (HPA), which affects the balance of the autonomic nervous system, the secretion and synthesis of hormones, as well as related biological changes. The decline in the richness and diversity of intestinal microflora caused by stress response may be closely related to the brain-intestinal-microbial axis, with the fluctuation of adrenaline causing the deterioration of immune regulation<sup>18</sup>. In a word, fatigue stress may cause a physiological stress response in patients with tinnitus, resulting in changes in the neuroendocrine system and some biological factors like intestinal flora in susceptible populations. And then it will cause abnormal immune system responses such as the increased level of the pro-inflammatory cytokine IL-1 $\beta$  mRNA, central IL-6, and so on. The function of the immune system will change and the integrity of the blood-brain barrier will be altered and psychological abnormalities or diseases will be induced such as depression, anxiety, hypertension<sup>19-21</sup>, eventually aggravating tinnitus.

Sleep is a major concern for military personnel and can directly impact safety and performance<sup>22</sup>. Nearly half of the soldiers had a sleep disorder or sleep-related medical diagnosis in 2018<sup>23</sup>. Simultaneously, sleep is an essential physiological process. Sleep disorders affect performance in multiple domains of functioning including but not restricted to cognitive, emotional, metabolic, and immunologic. Sleep disorder is a major problem associated with tinnitus, especially in acute exacerbation. The more serious sleep-disturbed, the worse their tinnitus is. The prevalence of disturbed sleep in tinnitus persons varies from 25 to 60%<sup>24,25</sup>. Tinnitus patients with disturbed sleep often have a headache and appear memory deficits<sup>26</sup>, simultaneously migraine is currently thought to be closely related to the occurrence of tinnitus to aggravate sleep disorders<sup>27</sup>. Sleep disorders may cause central sensitization, reduced adaptability, and then the central nervous system is more sensitive to tinnitus stimulation, resulting in increased tinnitus. We detected coexistence and mutual interactions of fatigue, stress, sleep disorders, and negative emotions. As Fig. 1 shows the one key finding of this study, the coexistence of fatigue stress and negative emotions is the main model leading to worse tinnitus. Jastreboff<sup>28</sup> presented a tinnitus neurophysiological model based on the relationship between the auditory system and the limbic system and autonomic nervous system after tinnitus occurrence. Their relationship has also been verified clinically. Fatigue stress increased the negative emotions of patients, then negative emotions caused disturbed sleep by excessive autonomic nervous system excitement. If the limbic system and cerebral cortex are not adjusted in time, sleep disorders can cause negative emotions to further aggravate. Finally, tinnitus worsens. Insomnia and tinnitus in sleep-disturbed tinnitus patients can be treated with hypnotics or with insomnia-specific psychotherapy or cognitive behavior therapy.

Most patients with tinnitus have no serious emotional problems, and a part of them have negative emotions such as irritability, anxiety, and depression. Among them, anxiety (47%) is the main performance<sup>29</sup>. Anxiety patients are often characterized by some accentuated personality traits such as introversion, dysfunctional cognition. Many aspects of such dysfunctional cognitions are also frequently found in tinnitus patients. This cognition can come from the patient itself or outsiders or even doctors. For example, getting to realize that tinnitus beyond their control and fear that the tinnitus will get worse. According to De Ridder<sup>30</sup>, it is believed that the relationship between

tinnitus and emotion is mainly manifested in the central and autonomic nervous system. When tinnitus occurs, tinnitus and negative emotions jointly activate the marginal neuronal reflex to form a negative feedback pathway with tinnitus-negative emotions-aggravation of tinnitus that strengthens negative emotions, making tinnitus worse or decompensated. When the negative factors caused by tinnitus continue to affect the physiological and psychological changes in the body, these changes will adversely affect the tinnitus, thus forming a vicious feedback loop, causing serious consequences. However, due to the presence of the limbic system, it can suppress the tinnitus signal from reaching the auditory cortex to a certain extent to prevent the brain from consciously perceiving the tinnitus signal<sup>31</sup>. Thus it relieves the negative emotions of patients. For anxious or depressed tinnitus patients, treatment of concurrent anxiety or depression symptoms in tinnitus patients is essential. Treatment options include pharmacological, for example, antidepressants, and psychotherapeutic approaches.

Usually, we believe that peripheral damage caused by noise in the cochlea leads to abnormal neural activity in the brain and the false perception of tinnitus. Prolonged exposure to noisy environments causes neural degeneration in the central nervous system or changes in the balance of excitation and inhibition in auditory pathways. Tinnitus appeared afterward<sup>32,33</sup>. For such reason, Gilles, A<sup>34</sup> emphasizes the prevention of noise or loud sounds, reducing the probability of tinnitus from the source, as well as the maintenance of tinnitus prognosis. Besides, Shiming Yang proposed a brand new hypothesis named "bionic active noise reduction" by presenting the innate structures in the auditory system that may contribute to noise suppression. If this hypothesis can be verified, it may have significant implications for noise protection in social medical services, especially to prevent the occurrence and aggravation of tinnitus<sup>35</sup>. The study also found that abrupt changes in barometric pressure such as diving in water or during a flight are also the cause of acute exacerbation of chronic tinnitus. Barotrauma may have caused aggravated tinnitus because of the cochlear fluids has been further affected for an abrupt change in barometric pressure. Aggravated tinnitus may either be temporary or persistent.

Patients with tinnitus frequently have headaches but the relation between these two disorders is not always casual. More and more researcher believes that headaches and tinnitus may be symptoms of the same disease. they cause a high degree of disability, and both are often accompanied by psychiatric disorders<sup>36</sup>. Additionally, these two symptoms share some common mechanisms in their tendency to become chronic. However, in this study, it was regrettable that headaches were not included in the study to prove that the onset of headache can induce acute exacerbation of chronic tinnitus. In the face of exacerbation of chronic subjective tinnitus, we not only need to think about the problem from the perspective of hearing loss-tinnitus, but also understand the possible causes of the disease aggravation from the factors of social support, patient's work, and life, and social psychological stress, and analyze the intrinsic relationship between incentives and diseases, help patients rebuild good living habits, social interpersonal relationships, improve their ability to cope with stressors, and prevent tinnitus aggravation and prognosis maintenance.

## Conclusions

Fatigue, stress, negative emotions, and sleep disorders are considered important factors that trigger the acute exacerbation of chronic tinnitus and the four factors often coexist and affect each other. it is necessary to help patients rebuild good living habits, social interpersonal communication, and improve their ability to respond to stressors to prevent acute exacerbation of chronic tinnitus□

## Abbreviations

Tinnitus Handicap Inventory (THI)

Self-rating Anxiety Scale (SAS)

Self-rating Depression Scale(SDS)

Pittsburgh Sleep Quality Index (PSQI)

Psychosomatic Tension Relaxation Inventory (PSTRI)

Fatigue Severity Scale (FSS)

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS)

5-hydroxytryptamine transporter (5HTT)

sympathetic-adrenal medulla (SAM)

hypothalamic-pituitary-adrenal (HPA)

## **Declarations**

## **Ethics approval and consent to participate**

All participants were informed about the data involved in this study and agreed to the publication of the article. The present experimental protocol was reviewed and approved by the Ethical Committee of The Third Affiliated Hospital of Sun Yat-Sen University (ethics approval number: [2019]02-479-01).

## **Consent for publication**

Not applicable

## **Availability of data and materials**

All data generated or analysed during this study are included in this published article.

## **Competing interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Author contributors

BF and YL are considered first authors who performed the experiments, analyzes the data, and wrote the manuscript and contributed equally to this work. JG and ZZL analyzed the data and perfected the manuscript. JC, LY, KZ, DC participated in patient’s data collection. ZCLand XZ analyzed and diagnosed all 602 patients with tinnitus and discussed the results and commented on the manuscript at all stages.

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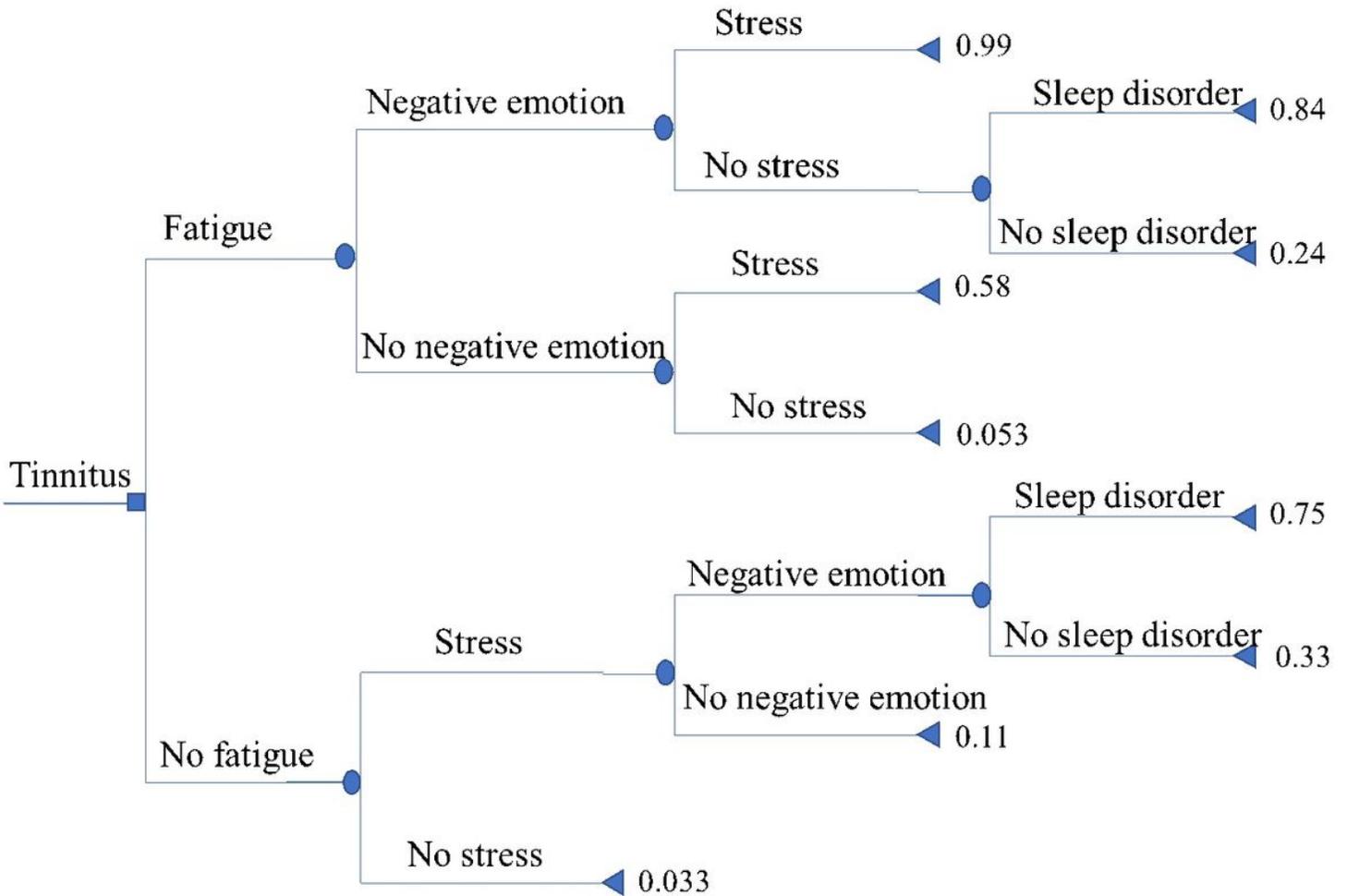
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## Figures



**Figure 1**

The decision analysis model shows the influence mode of these four factors on tinnitus. The square indicates a decision node; a circle indicates a chance node (events occurring or not); a triangle indicates an endpoint node.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CoverLetter.docx](#)