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Logistic Regression Analysis of the Influencing Factors Associated with Effectiveness of Intensive Sound Masking Therapy in Patients with Tinnitus

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Logistic Regression Analysis of the Influencing Factors Associated with Effectiveness of Intensive Sound Masking Therapy in Patients with Tinnitus

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Abstract

Objectives: Investigate influencing factors of intensive sound masking therapy on tinnitus using Logistic Regression Analysis, which would contribute to predict effectiveness of sound masking intervention for patients with tinnitus.

Design: The study used a retrospective cross-section analysis.

Participants: A total of 102 patients with tinnitus were recruited at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China.

Intervention: Intensive sound masking therapy was used as an intervention approach for patients with tinnitus.

Primary and secondary outcome measures: All participants underwent audiological investigations and tinnitus pitch and loudness matching measurements, follow by seven days sound masking intervention. The Tinnitus Handicap Inventory (THI) was used as the outcome measures before and after the sound marking intervention. Multivariate logistic regression models were performed to assess the independent association of socio-demographic and tinnitus relevant factors with effective therapy.

Results: According to the THI score changes *pre*-and *post*-sound masking intervention, fifty-one participants were entered in the effective group, whereas the remaining 51 participants were in the non-effective group. Student *t*-test showed that participants in the effective group were significantly younger than those in the non-effective group. In addition, significantly higher flat audiogram configurations were found in the effective group than in non-effective group. Further multivariable logistic regression analysis showed that age had negative influence on therapeutic effectiveness, while flat audiogram configurations and THI score before treatment were positively associated with therapeutic effectiveness.

Conclusion: Flat audiogram, younger age, and higher THI scores before treatment appear the predictive factors for having significant effective outcomes of sound masking treatment. However, gender, tinnitus laterality, duration and hearing threshold seem not to be related to the effectiveness of intensive sound masking treatment.

Key Words:

Sound Masking; Tinnitus; Audiometric Configuration; Prognostic Factors

ARTICLE SUMMARY

Article focus

1. Are there any influencing factors associated with short-term effectiveness after intensive sound masking therapy in patients with tinnitus?
2. If so, can these factors be used to predict effectiveness of sound masking intervention for patients with tinnitus?

Key Messages

1. Flat audiogram, younger age, and higher THI scores before treatment appear the predictive factors associated with significant effective outcomes of sound masking treatment.
2. Gender, tinnitus laterality, duration and hearing threshold seem not to be related to the effectiveness of intensive sound masking treatment.
3. Future prospective longitudinal research is needed to explore the long-term effectiveness of sound masking.

Strengths

- A relatively large sample of participants were included in the present study;
- A robust analytical method (i.e., Logistic regression) was employed to explore the predictive factors associated with significant effective outcomes of sound masking treatment.

Limitation

- Due to patient adherence in the context of Chinese culture and Healthcare system, only intensive sound masking intervention was provided, and the short-term effectiveness was subsequently assessed.

INTRODUCTION :

Tinnitus is the perception of noise in the absence of any external sound. It is considered as one of the most common and disturbing health problems[1]. Epidemiological studies indicate that one third of all adults report experiencing tinnitus at some time in their lives and 10 to 15% have prolonged tinnitus requiring medical interventions[2]. Although a number of interventions are available for tinnitus management within ENT/Audiology clinics, at present, no particular treatment for tinnitus has been found effective in all patients with tinnitus [3,4]. Moreover, there are large discrepancies in terms of effectiveness because of the complex mechanisms behind the symptoms and the severity of impact on sufferers, as well as many influencing factors such as age, tinnitus duration and degree of hearing loss[1,5].

A recent study by Theodoroffet al.[1] found that younger age, better self-reported hearing problem, shorter durations of tinnitus and better hearing threshold at low frequency were positive predictors of the effectiveness of tinnitus sound masking and Tinnitus Retraining Therapy (TRT). In addition, other factors have been suggested as being prognostic to outcome though these results are inconsistent. For example, Koizumi et al.[6] found better outcomes with TRT for patients with higher levels of tinnitus loudness, while Ariizumi et al.[7] reported lower tinnitus loudness to be predictive of better outcomes with TRT.

Using intervention with repetitive transcranial magnetic stimulation (rTMS), Kleinjung et al.[2] suggests that mild hearing loss and shorter duration of tinnitus are more likely to being beneficial. Graul et al.[8] reported that young in age and more severe depression contributed to a positive response with cognitive-behavioral therapy (CBT). Conrad et al.[9] suggests that dysfunctional cognition is associated with CBT outcome, i.e., more severe dysfunctional cognition results in a more negative emotional outcome after CBT intervention.

Tinnitus sound masking has been widely used as an intervention for patients with any characteristic of tinnitus[10]. According to the Cochrane reviewed by Hobson et al.[3,4], however, no significant difference was shown in the loudness of tinnitus or the overall severity of tinnitus following the use of sound masking therapy compared to other interventions.

To our best knowledge, there are few studies available on the factors that affect the effectiveness of sound masking therapy. Knowing the possible influencing factors on the effectiveness of sound masking intervention would be valuable to provide guidance for predicting outcomes and therapeutic strategy selection.

Evidence has shown that audiometric configuration is associated with ear pathologies. For example, noise induced hearing loss is related to the audiogram with a 3-6 kHz dip[11]. Understanding audiometric configurations may provide insights into the etiologic mechanism and prevalence of tinnitus[12-15]. For instance, in the study by Demeester et al.[15], prevalence of tinnitus was found to be significantly higher in individuals with a high-frequency steeply sloping audiogram than in those with a flat audiogram. However, it is still unclear as to the influence of audiometric configurations on the effectiveness of sound masking intervention for people with tinnitus. The purpose of this study was to identify the influencing factors on tinnitus sound masking using Logistic Regression Analysis, which would contribute to predict effectiveness of intensive sound masking intervention for patients with tinnitus.

MATERIALS AND METHODS

Participants

The present research was a retrospective study. A total of 102 patients with tinnitus who underwent audiological investigations and specific tinnitus examinations, follow by seven days sound masking intervention at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China were selected. This study was approved by the ethics committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

Routine Audiological Examinations

Routine audiological examination consisted of otoscopy, followed by pure-tone audiometry in which air conduction thresholds were measured for both ears at 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 4.0 kHz and 8.0 kHz, and bone conduction hearing thresholds were measured between 250 Hz and 4.0 kHz in a sound-proof booth. On the basis of the audiograms, the audiometric configurations were classified as either flat, high-frequency gently sloping (HFGS), high-frequency steeply sloping (HFSS), low-frequency ascending (LFA), mid-frequency U-curve (MFU) and mid-frequency reversed U-curve (MFRU) in accordance with the criteria used in the study by Hannula et al.(2011).

Tinnitus Specific Assessments

Tinnitus pitch and loudness matching measurements were performed in the ipsilateral ear to the tinnitus. During the tinnitus test, the tone was set successively to 9 audiometric frequencies between 125 Hz and 8.0 kHz (i.e., 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 3.0 kHz, 4.0 kHz, 6.0 kHz, and 8.0kHz). Firstly, the audiometric tones were used to roughly match the tinnitus pitch. Participants were then asked whether the tinnitus sounded like a pure-tone, such as the one that had just been perceived during audiometry. At the end of the pitch-matching test participants were asked to indicate which of the frequencies most closely matched the pitch of their tinnitus until a pure-tone was found. If there was no matching with a pure tone, narrow-band noise was used. When the matching frequency was found, the level was initially set to 5 dB above the measured audiometric threshold to find an approximate level, then the level was adjusted in 1 dB step until the subject indicated that the tone matched the loudness of their tinnitus.

The Sound Masking Intervention

Due to patient adherence in the context of Chinese culture and Healthcare system, only intensive sound marking intervention was provided, and the short-term effectiveness was subsequently assessed. The narrow-band noise at 10 dB above the tinnitus frequency was delivered to mask the tinnitus through headphones (Beyerdynamic DT880 pro) 4-6 times daily for 20-30 minutes, for a week[16,17].

Self-reported tinnitus issues and Tinnitus Handicap Inventory (THI) Questionnaire

Information on the tinnitus characteristics was collected. Patients were asked to describe the tinnitus duration and laterality, being in the right, left or bothears. The effectiveness of the sound masking intervention was evaluated using the Tinnitus Handicap Inventory (THI) before and after intervention. THI is a 25-item measurement for evaluating the self-perceived level of handicap caused by tinnitus, based on a 0-100 increasing handicap scale (with 100 being total handicap and 0 being no handicap)[18]. The significant effectiveness was defined as a minimum of 7 points improvement in overall THI score after the sound masking intervention[19,20].

Statistical Analysis

Continuous data were expressed as mean±standard deviation (SD) or median (interquartile range, IQR), as appropriate, and categorical data were shown as frequencies and percentages. Student's t-tests (for continuous variables), Wilcoxon Rank sum tests (for skewed distribution of continuous variables), and chi-square tests (for categorical variables) were used to assess differences in socio-demographic characteristics and tinnitus relevant factors by therapeutic efficacy (effectiveness versus non-effectiveness). A p level of less than 0.05 was considered statistically significant. Multivariate logistic regression models were performed to assess the independent association of socio-demographic and tinnitus relevant factors with effective therapy while controlling for each of the other factors. Odds ratio (OR) and its 95% confidence interval (CI) was estimated for each factor. $p<0.05$ (two-sided) was considered to be statistically significant. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

On the basis of the THI score changes *pre*-and *post*-sound masking intervention (i.e., equal or greater than7 points), fifty-one participants were entered in the effective group, whereas the remaining 51 participants were in the non-effective group. THI scores were significantly reduced in the effective group (t=-14.07, $p<0.001$), whereas no significant effect (t=-1.98, p>0.05) was found in the non-effective group when comparing THI score pre and post sound masking (Figure 1).

Please insert Figure 1 near here

Figure 2 shows the averaged pure tone hearing threshold across frequencies from 125 Hz to 8000 Hz on tinnitus ears and non-tinnitus ears in both effective and non-effective groups. The hearing threshold of each frequency from 125 Hz to 8000 Hz revealed no significant differences between the two groups in both tinnitus (p>0.05) and non tinnitus ears (p>0.05). Significantly higher hearing thresholds of each frequency in tinnitus ears were found in both effective (p<0.05) and non effective groups (p<0.05) when compared to hearing threshold in non tinnitus ears.

Please insert Figure 2 near here

As shown in Table1, statistical analysis was conducted to compare various factors between effective and non-effective groups. There was no significant difference in gender distribution between effective and non-effective groups (Chi-square analysis,x^2=2.53, p=0.163).

Please insert Table 1 near here

Student *t-test* showed that participants in the effective group were significantly younger than those in the non-effective group (t=-2.55, p=0.012). Further analysis showed that median scores of THI obtained from participants in the effective group before receiving the sound masking intervention were significantly higher than those in non-effective group (THI: 54.04 vs. 37.57,t=4.11,p<0.001).

According to audiometric configurations classification criteria, patients in the effective group had a flat audiogram (62.75%) , HFGS (17.65%) and HFSS (15.69%), whilst patients in non-effective group had flat audiogram (35.29%) , HFGS (23.53%) and HFSS (31.37%) audiometric configurations, respectively. Only 7 cases had LFA, MFU or MFRU audiometric configurations, which were classified as 'others' for the purpose of analysis. Further comparison analysis indicated that significantly higher flat audiogram configurations together with lower HFGS and HFSS audiograms were found in the effective group than in non-effective group (x^2=8.30, df=3; *p*=0.04).However, there were no significant differences in the tinnitus assessment results (i.e.,tinnitus loudness, tinnitus pitch, tinnitus laterality, duration, sound category) between effective and non-effective groups.

To identify predictive factors for effectiveness with sound masking intervention, a logistic regression analysis was performed. Results of the multivariable logistic regression analysis were presented in Table 2. It showed that age was negatively associated with effective treatment (OR=0.96, 95% CI: 0.93, 0.99, *p*=0.014), indicating that one year younger in age would be associated with 4% increase in effectiveness of sound masking intervention; while flat audiogram configurations (OR=7.06, 95% CI: 0.95, 52.20, *p*=0.056) and THI score before treatment (OR=1.08, 95%CI: 1.00, 1.16, *p*=0.045) were positively associated with successful treatment, indicating that participants with flat audiogram configurations were 7.06 time more likely to be successfully treated as compared to those with other audiogram configurations, and one unit increase in THI score before treatment was associated with 8% increase in therapeutic effectiveness.

Please insert Table 2 near here

Discussion

The data obtained from the present study demonstrate that certain factors can be prognostic for the effectiveness of intensive sound masking intervention. According to logistic regression analysis, age, audiogram configuration and THI scores prior to treatment were significantly related to the effectiveness of sound masking treatment, i.e., patients with flat audiogram, younger in age, as well as higher scores of THI were more likely to have positive outcomes. These findings explicit the importance of individual factors, which may provide useful indicators for predicting likelihood of the therapeutic effectiveness.

In the present study, participants with flat audiogram were more likely to respond positively to intensive sound masking intervention compared with those with a HFSS or HFGS audiogram but unrelated to average hearing threshold. Even though no previous study investigated the influence of audiometric configuration on the outcome of tinnitus intervention, the study by Chang et al. [21] showed that patients with a flat pattern audiogram benefited more from hearing aids compared to those with rising or decreasing audiogram in terms of improvement of psychological handicap and quality of life. Therefore, audiometric configuration appears an important factor rather than hearing thresholds when assessing people with hearing disorders.

Furthermore, higher THI scores before treatment were correlated with a better response to sound masking. These results are consistent with the findings of Koizumi et al.[6] and Theodoroff et al.[1], who found tinnitus retraining therapy (TRT) more effective in patients with higher THI scores. Koizumi et al.[6] further suggested that TRT should be introduced to tinnitus patients with THI score higher than 50 points. Because overall THI score may reflect the distress in tinnitus patients, these results suggested that sound masking may be regarded as a useful therapy to alleviate the distress cause by tinnitus, particularly in patients in severe distress[22]. Recent magnetoencephalography (MEG) data reported by Adjamianet al.,[23] support the efficacy of sound masking on psychological handicap (depression and anxiety), reflecting a reduction in delta band activity, which is considered a possible neuronal marker for the effect of masking[10].

In addition, younger age had a positive effect on the benefits of sound masking. Von Wedel et al. [24]suggested that younger tinnitus patients are more likely to report distress and tinnitus annoyance than older patients. Moreover, Seydel et al.[25] demonstrated that young tinnitus subjects suffered distress more severely than older tinnitus subjects. It indicates that young tinnitus subjects are more likely to have a greater need for alleviating the distress by using sound masking intervention.

It is noteworthy that influencing factors associated with only short-term effectiveness after intensive sound masking therapy was investigated due to patient adherence issue. Future prospective longitudinal research is needed to explore the long-term effectiveness of sound masking therapy, together with its associated influencing factors.

Conclusion

This retrospective study suggests that flat audiogram, younger age, and high scores for THI are predictive of beneficial treatment outcomes. Gender, tinnitus laterality, duration and hearing threshold seemed not to be related to the effectiveness of intensive sound masking treatment. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contributing to the effectiveness of tinnitus interventions.

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Contributors YXC and YQZ Contributed to the study design. HDY, JJJ, XYH and XYZ collected the data. QZ and HDY designed the plan of analysis. QZ, HX and SJC performed the final analyses. YXC, FZ, HJM and XTC drafted the manuscript and interpreted the results. All authors made substantive editorial contributions at all stages of manuscript preparation.

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Competing interest

None.

Data sharing statements

No additional data are available. However, the original data that support the findings derived from this study can be requested by emailing yiqingzheng@hotmail.com

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Captions of Figures

Figure 1. (Color online) Comparison of THI scores between *pre*-and *post*-sound masking intervention in effective and non-effective groups.

*Note:** there was a significant difference at p<0.05.

Figure 2. (Color online) The averaged pure tone hearing thresholds on tinnitus ears and non-tinnitus ears in both effective and non-effective groups.

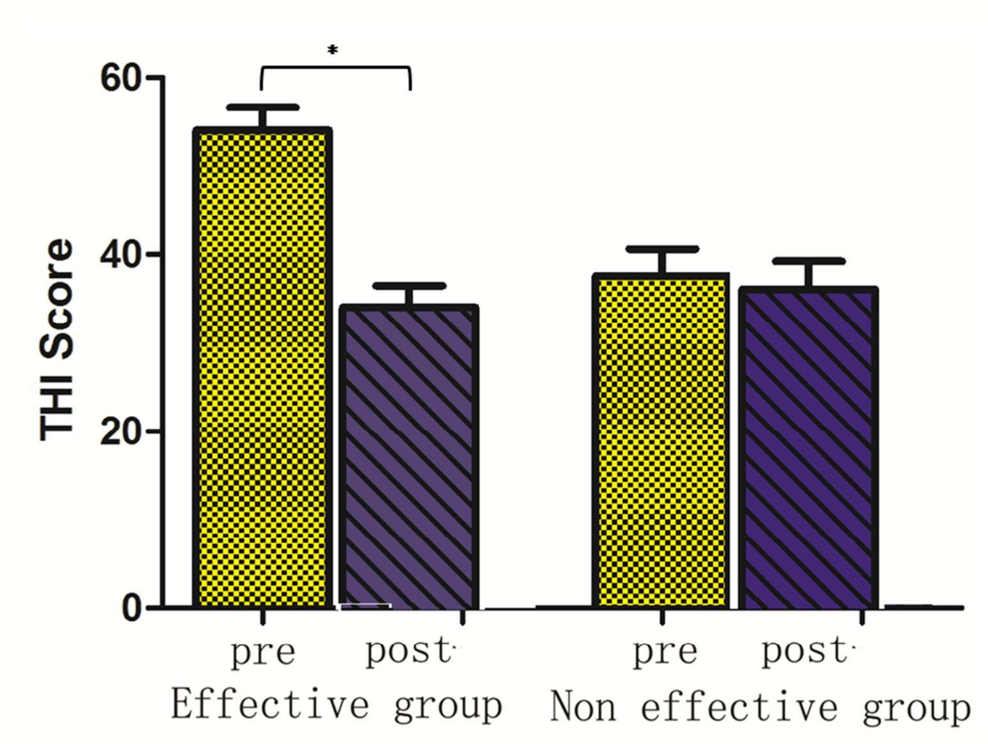

Figure 1. (Color online) Comparison of THI scores between pre-and post-sound masking intervention in effective and non-effective groups.

254x190mm (96 x 96 DPI)

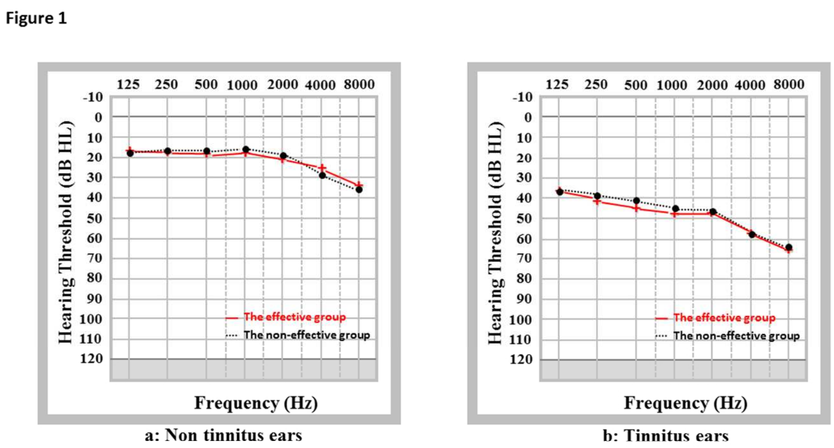

Figure 2. (Color online) The averaged pure tone hearing thresholds on tinnitus ears and non-tinnitus ears in both effective and non-effective groups.

338x190mm (96 x 96 DPI)

Table 1. Socio-demographic characteristics of patients by therapeutic outcome

Variables	Total (n=102)	Effectiveness (n=51)	Ineffectiveness (n=51)	Chi-square/ t	P value
Gender (n,%)				2.53	0.163
Male	46(45.1%)	19(37.3%)	27(52.9%)		
Female	56(54.9%)	32(62.7%)	24(47.1%)		
Age (years, mean±SD)	44.98 ± 15.41	41.20 ± 15.41	48.76 ± 14.58	-2.55	**0.012***
Tinnitus loudness	61.23 ± 23.42	61.10 ± 24.71	61.35 ± 22.30	-0.06	0.96
Tinnitus pitch (n,%)				4.29	0.12
[250-1000) Hz	17(16.67%)	6(11.76%)	11(21.57%)		
[1000-4000) Hz	24(23.53%)	16(31.37%)	8(15.69%)		
[4000-8000] Hz	61(59.80%)	29(56.87%)	32(62.74%)		
Laterality (n,%)				0.00	1.00
Left	54(52.94%)	27(52.94%)	27(52.94%)		
Right	36(35.29%)	18(35.29%)	18(35.29%)		
Binaural	12(11.77%)	6(11.77%)	6(11.77%)		
Duration (n,%)				0.82	0.66
Acute (<1 month)	68(66.66%)	32(62.75%)	36(70.59%)		
Subacute (1-3 month)	17(16.67%)	10(19.61%)	7(13.73%)		
Chronic (>1 month)	17(16.67%)	9(17.64%)	8(15.68%)		
Audiogram configurations (n,%)				8.30	**0.04***
Flat	50(49.02%)	32(62.75%)	18(35.29%)		
HFGS	21(20.59%)	9(17.65%)	12(23.53%)		
HFSS	24(23.63%)	8(15.69%)	16(31.37%)		
Others	7(6.76%)	2(3.91%)	5(9.81%)		
Sound category (n,%)				1.96	0.16
Pure tone	78(74.29%)	42(82.35%)	36(70.59%)		
Noise	24(25.71%)	9(17.65%)	15(29.41%)		
Hearing threshold	53.75 ± 27.66	52.51 ± 26.94	54.98 ± 28.57	-0.45	0.65
Prior treatment THI	45.80 ± 21.76	54.04 ± 18.45	37.57 ± 21.86	4.11	**<0.001***

Notes: *p<0.05; Continuous variables were expressed as Median ± SD. T tests, or chi-square tests were used to do group comparisons, as appropriate; THI: Tinnitus Handicap Inventory; HFGS: high-frequency gently sloping; HFSS: high-frequency steeply sloping.

Table 2. Association of socio-demographic factors and audiogram configurations with effective therapy: multivariate logistic regression analysis

Variables	*B*	*SE*	*Wald*	*P* value	*OR*	95% *CI*	
						Lower	Upper
Age (year)	-0.04	0.17	6.10	**0.014****	0.96	0.93	0.99
Audiogram configurations		9.82		**0.020****			
Flat	1.95	1.02	3.66	**0.056***	7.06	0.95	52.20
HFGS	0.99	1.08	0.86	0.35	2.71	0.33	22.30
HFSS	0.18	1.04	0.03	0.86	1.20	0.16	9.29
Others	reference				1.00		
Prior treatment THI	0.08	0.04	4.01	**0.045****	1.08	1.00	1.16
Hearing threshold	-0.01	0.01	0.42	0.52	0.99	0.98	1.01

Notes: *p<0.1, ** p<0.05; OR:Odds Ratio; 95%CI: 95% Confidence Interval.

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Logistic Regression Analysis of the Influencing Factors Associated with Effectiveness of Intensive Sound Masking Therapy in Patients with Tinnitus

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Abstract

Objectives: Investigate influencing factors of intensive sound masking therapy on tinnitus using Logistic Regression Analysis.

Design: The study used a retrospective cross-section analysis.

Participants: A total of 102 patients with tinnitus were recruited at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China.

Intervention: Intensive sound masking therapy was used as an intervention approach for patients with tinnitus.

Primary and secondary outcome measures: All participants underwent audiological investigations and tinnitus pitch and loudness matching measurements, follow by intensive sound masking intervention. The Tinnitus Handicap Inventory (THI) was used as the outcome measurement pre- and post-treatment. Multivariate logistic regression was performed to investigate association of demographic and audiological factors with effective therapy.

Results: According to the THI score changes *pre*-and *post*-sound masking intervention, fifty-one participants were entered in the effective group, whereas the remaining 51 participants were in the non-effective group. Participants in the effective group were significantly younger than those in the non-effective group. In addition, significantly more participants had flat audiogram configurations in the effective group than in non-effective group. Multivariable logistic regression analysis showed that age, audiometric configuration and THI score pre-treatment were significantly associated with therapeutic effectiveness. Further analysis showed that patients with flat audiometric configurations were 5.45 times more likely to be successfully intervention than those with high-frequency steeply sloping audiograms.

Conclusion: Audiometric configuration, age and THI scores before treatment appear the predictive factors for having significant effective outcomes of sound masking treatment, but gender, tinnitus characteristics and hearing threshold are not related to the effectiveness of intensive sound masking treatment. Future randomized control study is needed to provide further evidence for prognostic factors to the effectiveness of tinnitus interventions.

Key Words:

Sound Masking; Tinnitus; Audiometric Configuration; Prognostic Factors

ARTICLE SUMMARY

Article focus

1. Are there any influencing factors associated with short-term effectiveness after intensive sound masking therapy in patients with tinnitus?
2. If so, can these factors be used to predict effectiveness of sound masking intervention for patients with tinnitus?

Key Messages

1. Audiometric configuration, younger age, and higher THI scores before treatment appear the predictive factors associated with significant effective outcomes of sound masking treatment.
2. Gender, tinnitus laterality, duration and hearing threshold seem not to be related to the effectiveness of intensive sound masking treatment.
3. Future randomized control study is needed to provide further evidence for prognostic factors to the effectiveness of tinnitus interventions.

Strengths

- A relatively large sample of participants were included in the present study;
- A robust analytical method (i.e., Logistic regression) was employed to explore the predictive factors associated with significant effective outcomes of sound masking treatment.

Limitation

- Due to patient adherence in the context of Chinese culture and Healthcare system, only intensive sound masking intervention was provided, and the short-term effectiveness was subsequently assessed.

INTRODUCTION :

Tinnitus is the perception of noise in the absence of any external sound. It is considered as one of the most common and disturbing health problems[1]. It is widely accepted that tinnitus is a symptom caused by diverse pathologies as a result of not only peripheral hearing loss, but also the aberrant neural activity in central auditory nervous system[2-4]. Subsequently various theories have been proposed to elaborate underlying possible mechanisms, such as Discordant theory (i.e., the discordant dysfunction of damaged outer hair cells and intact inner hair cells)[5], and Auditory plasticity theory (damaged cochlea activates auditory plasticity by enhancing neural activity in the central auditory pathway, which results in abnormal input to the central auditory system)[4].

Epidemiological studies indicate that one third of all adults report experiencing tinnitus at some time in their lives and 10 to 15% have prolonged tinnitus requiring medical interventions[6]. At present, a number of interventions are available for tinnitus management within ENT/Audiology clinics, mainly including pharmacotherapy, cognitive behavioral therapy (CBT), habituation therapy (Tinnitus retraining therapy, TRT), electrical suppression (e.g., repetitive transcranial magnetic stimulation r-TMS) and sound therapy (e.g., sound masking). Of these, tinnitus sound masking therapy has been widely used as an intervention for patients with any characteristic of tinnitus[7]. According to the Cochrane reviewed by Hobson et al.[8, 9], however, no significant difference was shown in the loudness of tinnitus or the overall severity of tinnitus following the use of sound masking therapy compared to other interventions.

Furthermore, evidence has shown that no single treatment for tinnitus is found effective in all patients with tinnitus[8, 9]. These discrepancies in terms of effectiveness are largely due to the complex mechanisms behind the symptoms as indicated above and the severity of impact on sufferers. Previous studies suggest that there are many influencing factors such as age, tinnitus characteristics and hearing status, along with other demographic factors, which affect effeciveness of tinnitus management[1, 10]. However, the results appear inconsistent. For example, Koizumi et al.[11] found better outcomes with TRT for patients with higher levels of tinnitus loudness, while Ariizumi et al.[12] reported lower tinnitus loudness to be predictive of better outcomes with TRT.

In addition, Kleinjung et al.[6] suggests that mild hearing loss and shorter duration of tinnitus are more likely to being beneficial using rTMS. These results are generally in keeping with influencing factors obtained from using sound masking therapy[1]. It is also noteworthy that young in age and more severe depression contributed to a positive response with CBT[13]. Conrad et al.[14] further clarifies that dysfunctional cognition is associated with CBT outcome, i.e., more severe dysfunctional cognition results in a more negative emotional outcome after CBT intervention.

To our best knowledge, there are few studies available on the factors that affect the effectiveness of sound masking therapy. A recent study by Theodoroff et al.[1] appears the only report directly investigating the factors associated with effective tinnitus treatment using sound masking therapy[1]. Although they found several positive predictors, such as younger age, better self-reported hearing difficulty, shorter durations of tinnitus and better hearing threshold at low frequency region, these results were obtained by combining tinnitus treatment data of either using sound masking therapy or TRT. The separate analysis showed that participants with younger age perceived significantly better response to intervention only in TRT group (p<0.017), but age was not a significant factor in the group using sound masking therapy (p=0.143). Such bias indicated that further investigation is needed to clarify possible factors associated with effective sound masking therapy.

Evidence has shown that audiometric configuration is associated with ear pathologies. For example, noise induced hearing loss is related to the audiogram with a 3-6 kHz dip[15]. Understanding audiometric configurations may provide insights into the etiologic mechanism and prevalence of tinnitus[16-19]. For instance, in the study by Demeester et al.[19], prevalence of tinnitus was found to be significantly higher in individuals with a high-frequency steeply sloping audiogram than in those with a flat audiogram. However, it is still unclear as to the influence of audiometric configurations on the effectiveness of sound masking intervention for people with tinnitus.

The purpose of this study was to identify the influencing factors on tinnitus sound masking using Logistic Regression Analysis, which would contribute to predict effectiveness of intensive sound masking intervention for patients with tinnitus. The significant results would be valuable to provide guidance for predicting the effectiveness of sound masking intervention outcomes and thus therapeutic strategy selection.

MATERIALS AND METHODS

Participants

The present research was a retrospective study. A total of 102 patients with tinnitus who underwent audiological investigations and specific tinnitus examinations, follow by seven days sound masking intervention at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China were initially considered. The detailed selection criteria are as follows:

(1) They had sought clinical help for their tinnitus problem, which had lasted more than 2 weeks;

(2) They had no history of head trauma or central nervous system disorders;

(3) They had mild to severe sensorineural hearing loss. All tinnitus patients with either current conductive hearing loss or previous middle ear surgery (e.g., mastoidectomy) were excluded[17].

(4) The tinnitus patients with pulsatile tinnitus due to aberrant vascular malformation were also excluded.

The mean age of all participants was 44.98 years (SD: 15.41). There were 46 males and 56 females (Table 1). This study was approved by the ethics committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

Routine Audiological Examinations

Routine audiological examination consisted of otoscopy, followed by pure-tone audiometry in which air conduction thresholds were measured for both ears at 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 4.0 kHz and 8.0 kHz, and bone conduction hearing thresholds were measured between 250 Hz and 4.0 kHz in a sound-proof booth. The mean hearing threshold is the average of hearing sensitivity at the frequencies of 500, 1000, 2000 and 4000 Hz.

On the basis of the audiograms, the audiometric configurations were classified as either flat, high-frequency gently sloping (HFGS), high-frequency steeply sloping (HFSS), low-frequency ascending (LFA), mid-frequency U-curve (MFU) and mid-frequency reversed U-curve (MFRU) in accordance with the criteria used in the study by Hannula et al.[15].

Tinnitus Specific Assessments

Patients were asked to describe the tinnitus characteristics, including duration and laterality (i.e., being in the right, left or both ears, central in the head). Tinnitus pitch and loudness matching measurements were performed ipsilaterally to the ear with predominant or louder tinnitus if there was a difference between the two sides. However, if the tinnitus ear had severe hearing loss, the contralateral ear was tested instead[20]. When the tinnitus was equally loud on both sides or was localized in the head, the matching tones were given to the ear with the better hearing. Otherwise, the ear was chosen randomly if there was no difference between the acuity of the two ears.

During the tinnitus pitch matching tests, the 9 audiometric frequencies between 125 Hz and 8.0 kHz (i.e., 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 3.0 kHz, 4.0 kHz, 6.0 kHz, and 8.0kHz) were firstly used to roughly match the tinnitus pitch. Participants were initially asked to make a clear distinction between the tinnitus pitch perception and presented matching tones, and then they reported verbally whether the matching tone needed to go higher or lower until the exact matching tone or a close approximation to their tinnitus was obtained. The test tone was adjusted in a half-octave step. If there was no matching with a pure tone perceived by participants, narrow-band noise was used instead.

When the matching frequency was found, the level was initially set to 5 dB above the measured audiometric threshold to find an approximate tinnitus loudness level, then the level was adjusted in 1 dB step until the subject indicated that the tone matched the loudness of their tinnitus[20].

The Sound Masking Intervention

Due to patient adherence in the context of Chinese culture and Healthcare system, high drop-out rate was occurred when they were provided a longer duration of sound masking intervention. Considering the nature of (i.e., a retrospective study) and main purpose of the present study, current data was obtained only from intensive sound marking intervention, and the short-term effectiveness was subsequently assessed. The narrow-band noise at 10 dB above the tinnitus frequency was delivered to mask the tinnitus through headphones (Beyerdynamic DT880 pro) 4-6 times daily for 20-30 minutes, for a week[21, 22].

Self-reported tinnitus issues and Tinnitus Handicap Inventory (THI) Questionnaire

Information on the tinnitus characteristics was collected. Patients were asked to describe the tinnitus duration and laterality, being in the right, left or both ears. According to the tinnitus sound masking therapy protocol, the effectiveness of the sound masking intervention was evaluated using the Tinnitus Handicap Inventory (THI) pre and post intervention, i.e., THI questionnaire was provided to investigate their tinnitus issues before the treatment initially, and this procedure was conducted again seven days after sound masking therapy at tinnitus review clinics. THI is a 25-item measurement for evaluating the self-perceived level of handicap caused by tinnitus, based on a 0-100 increasing handicap scale (with 100 being total handicap and 0 being no handicap)[23]. The significant effectiveness was defined as a minimum of 7 points improvement in overall THI score after the sound masking intervention[24, 25].

Statistical Analysis

Continuous data were expressed as mean±standard deviation (SD) or median (interquartile range, IQR), as appropriate, and categorical data were shown as frequencies and percentages. Student's *t*-tests (for continuous variables), Wilcoxon Rank sum tests (for skewed distribution of continuous variables), and chi-square tests (for categorical variables) were used to assess differences in socio-demographic characteristics and tinnitus relevant factors by therapeutic efficacy (effectiveness versus non-effectiveness). Multivariate logistic regression models were performed to assess the independent association of demographic and tinnitus relevant factors with effective therapy. Odds ratio (OR) and its 95% confidence interval (CI) was estimated for each factor. A *p* level of less than <0.05 (two-sided) was considered to be statistically significant. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

On the basis of the THI score changes *pre*-and *post*-sound masking intervention (i.e., equal or greater than 7 points), fifty-one participants were entered in the effective group, whereas the remaining 51 participants were in the non-effective group. Table 1 shows comparisons of related factors between effective and ineffective groups, respectively. In the present study, age and gender factors were compared between the effective group and the non-effective group using Student *t*-test and Chi-square test, respectively. Student *t*-test showed that participants in the effective group were significantly younger than those in the non-effective group (t=-2.55, p=0.012). However, there was no significant difference in gender between these two groups (x^2=2.53, df=1, p=0.163).

Please insert Table 1 near here

For the purpose of understanding the basic hearing status, the averaged pure tone hearing thresholds across frequencies from 125 Hz to 8000 Hz on tinnitus ears and non-tinnitus ears were analyzed in both effective and non-effective groups. As shown in Figure 1, the hearing threshold of each frequency from 125 Hz to 8000 Hz revealed no significant differences between the two groups in both tinnitus (p>0.05) and non tinnitus ears (p>0.05). Significantly worse hearing threshold at each frequency in tinnitus ears were found in both effective (p<0.05) and non-effective groups (p<0.05) when compared to hearing threshold in non-tinnitus ears.

Please insert Figure 1 near here

According to audiometric configurations classification criteria, patients in the effective group had a flat audiogram (62.75%) , HFGS (17.65%) and HFSS (15.69%), whilst patients in non-effective group had flat audiogram (35.29%) , HFGS (23.53%) and HFSS (31.37%) audiometric configurations, respectively. Only 7 cases had LFA, MFU or MFRU audiometric configurations, which were classified as 'others' for the purpose of analysis. Further comparison analysis indicated that significantly higher flat audiogram configurations together with lower HFGS and HFSS audiograms were found in the effective group than in non-effective group (x^2=8.30, df=3; p=0.04) (Table 1). Further analysis of tinnitus characteristics in terms of tinnitus laterality, duration, together with tinnitus pitch and loudness, there were no significant differences in these factors between effective and non-effective groups.

Furthermore, as shown in Table 1, the THI score of pre-sound masking intervention was used as baseline measurement. The averaged THI scores of pre-sound masking intervention were 54.04 (SD=18.45) and 37.57 (SD=21.86) for the effective and non-effective groups, respectively. Significantly lower THI score of *pre*-sound masking intervention was found in the non-effective group than that in the effective group (t=4.11, p<0.001). However, there was no significant difference in the THI score of *post*-sound masking intervention between two groups. As a result, significant difference of the THI score changes between pre and post treatments was found when comparing two groups (19.10 vs. 0.98, t=12.54, p<0.001). Further analysis showed that THI scores were significantly reduced in the effective group (t=-14.07, p<0.001), whereas no significant reduction in the THI scores was found in the non-effective group in comparison of THI score between pre- and post- sound masking (t=-1.98, p=0.054).

To identify predictive factors for effectiveness with sound masking intervention, all factors that showed significantly between both effective and non-effective groups were used as variables for a logistic regression analysis. Because audiometric configuration variable was categorised as four sub-groups, estimates of pair comparisons were subsequently performed. Results of the multivariable logistic regression analysis were summarised in Table 2. Age factor was negatively associated with effective treatment (OR=0.96, 95% CI: 0.93, 0.99, p=0.007), indicating that one year older in age would be associated with 4% decrease in the effectiveness of sound masking intervention. Audiometric configuration factor was also found to be an independent factor associated with the effectiveness of the sound masking treatment (p=0.027). Further analysis showed that tinnitus patients with flat audiometric configuration was 5.45 times more likely to be successfully intervention when compared to those with HFSS configurations (OR=5.45, 95% CI: 1.67, 17.86, p=0.005). However, no significant results were found when conducting the pair comparisons of other audiometric configurations. In addition, THI score pre-treatment was positively associated with successful treatment (OR=1.04, 95%CI: 1.02, 1.07, p<0.001), indicating that one unit increase in THI score before treatment was associated with 4% increase in therapeutic effectiveness.

Please insert Table 2 near here

Discussion

The data obtained from the present study demonstrate that certain factors can be prognostic for the effectiveness of intensive sound masking intervention. According to logistic regression analysis, age, audiogram configuration and THI scores prior to treatment were significantly related to the effectiveness of sound masking therapy, i.e., patients with flat audiogram, younger in age, as well as higher scores of THI were more likely to have positive outcomes. These findings explicit the importance of individual factors, which may provide useful indicators for predicting likelihood of the therapeutic effectiveness.

In the present study, participants with flat audiogram were more likely to respond positively to intensive sound masking intervention compared with those with a HFSS audiogram but unrelated to average hearing threshold. To our best knowledge, no previous study investigated the influence of audiometric configuration on the outcome of tinnitus intervention, even though the study by Chang et al. [26] showed that patients with a flat pattern audiogram benefited more from hearing aids compared to those with rising or decreasing audiogram in terms of improvement of psychological handicap and quality of life. The present result is likely due to tinnitus characteristics together with their associated hearing status. By recording Transient Otoacoustic Emiisions (TEOAEs), Kim et al.[17] found that normal TEOAE rates were significantly higher in tinnitus patients with flat audiogram than those in the HFGS and HFSS groups. Moreover, tinnitus patients with HFSS had significantly lower response rates of TEOAEs at 3, 4 and 6 kHz than tinnitus patients with flat audiogram. Therefore, better hearing status in tinnitus patients with flat audiogram may be underlying factor, which is consistent with the previous finding reported by Theodoroff et al.[1]. However, this result should be interpreted with cautious due to the retrospective nature of this study. The further prospective research is needed using systematic approaches, such as randomized controlled trail[27].

Furthermore, higher THI scores before treatment were correlated with a better response to sound masking. These results are consistent with the findings of Koizumi et al.[11] and Theodoroff et al.[1], who found tinnitus retraining therapy (TRT) more effective in patients with higher THI scores. Koizumi et al.[11] further suggested that TRT should be introduced to tinnitus patients with THI score higher than 50 points. Because overall THI score may reflect the distress in tinnitus patients, these results suggested that sound masking may be regarded as a useful therapy to alleviate the distress cause by tinnitus, particularly in patients in severe distress[28].

There are several possible mechanisms behind sound masking therapy, but the exact mechanism is still unclear. Overall, it is generally accepted that there is a reduction of a response to a signal due to the presence of another. The neuro-physiological mechanism can be explained that the original neural activity caused by the first sound signal (tinnitus) is reduced by the neural activity of the other sound (e.g., masking noise). For example, recent magnetoencephalography (MEG) data reported by Adjamianet al.,[29] support the efficacy of sound masking on psychological handicap (depression and anxiety), reflecting a reduction in delta band activity, which is considered a possible neuronal marker for the effect of masking[7].

Various advanced neuroimaging techniques such as fMRI and PET appeared a valuable tool to explore the mechanism of tinnitus. For example, Lanting et al.[30] suggested that tinnitus may correspond to enhance neural activity across several areas of the central auditory system using fMRI and PET. In the meantime, they also found that neural activities in non-auditory areas (i.e., frontal areas, limbic system and cerebellum) seem also associated with the perception of tinnitus. Therefore, further studies on the comparison of the subjective perception of tinnitus and central neural activity changes between *pre*- and *post*-sound masking therapy are needed in order to clarify the neural marker as well as the mechanisms of the effective sound masking therapy.

In the present study, younger age had a positive effect on the benefits of sound masking therapy. Von Wedel et al.[31] suggested that younger tinnitus patients are more likely to report distress and tinnitus annoyance than older patients. Moreover, Seydel et al.[32] demonstrated that younger tinnitus subjects suffered distress more severely than older tinnitus subjects, which is due to higher levels of occupational and personal stress among younger subjects[32]. As a result, younger subjects are likely to be more beneficial of alleviating their high level distress provided by sound masking intervention[7]. In addition, the other explanation could be due to better coping capability in younger tinnitus suffers than older subjects [32]

It is noteworthy that influencing factors associated with only short-term effectiveness after intensive sound masking therapy was investigated due to patient adherence issue. Future prospective longitudinal research is needed to explore the long-term effectiveness of sound masking therapy, together with its associated influencing factors.

Conclusion

This retrospective study suggests that factors of audiometric configuration, age, and THI scores pre-treatment are predictive of beneficial sound masking outcomes. Further analysis indicates that tinnitus patients with flat audiogram configuration are more likely to achieve successfully intervention when compared to those with high-frequency steeply sloping audiograms. Gender, tinnitus laterality, duration and hearing threshold are not related to the effectiveness of intensive sound masking treatment. However, these results should be interpreted with caution due to the retrospective nature of this study. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contributing to the effectiveness of tinnitus interventions.

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Contributors YXC and YQZ Contributed to the study design. HDY, JJJ, XYH and XYZ collected the data. QZ and HDY designed the plan of analysis. QZ, HX and SJC performed the final analyses. YXC, FZ, HJM and XTC drafted the manuscript and interpreted the results. All authors made substantive editorial contributions at all stages of manuscript preparation.

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Competing interest

None.

Data sharing statements

No additional data are available. However, the original data that support the findings derived from this study can be requested by emailing yiqingzheng@hotmail.com

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Captions of Figures

Figure 1. (Color online) The averaged pure tone hearing thresholds on tinnitus ears and non-tinnitus ears in both effective and non-effective groups.

Table 1. Comparison of demographic and audiological characteristics between the effective and non-effective groups in tinnitus patients with sound masking intervention

Variable	Total (*n*=102)	Effective Group (*n*=51)	Non-effective Group (*n*=51)	Chi-square/ *t*-test	*p* value
Demographic characteristics					
Age (years, Mean±SD)	44.98 ± 15.41	41.20 ± 15.41	48.76 ± 14.58	-2.55	**0.012***
Gender (*n*, %)				2.53	0.163
Male	46 (45.1%)	19 (37.3%)	27 (52.9%)		
Female	56 (54.9%)	32 (62.7%)	24 (47.1%)		
Hearing status					
Hearing threshold in tinnitus ears (dB HL)	53.75 ± 27.66	52.51 ± 26.94	54.98 ± 28.57	-0.45	0.65
Audiogram configurations (*n*, %)				8.30	**0.04***
Flat	50 (49.02%)	32 (62.75%)	18 (35.29%)		
HFGS	21 (20.59%)	9 (17.65%)	12 (23.53%)		
HFSS	24 (23.63%)	8 (15.69%)	16 (31.37%)		
Others	7 (6.76%)	2 (3.91%)	5 (9.81%)		
Tinnitus characteristics					
Laterality (*n*, %)				0.00	1.00
Left	54 (52.94%)	27 (52.94%)	27 (52.94%)		
Right	36 (35.29%)	18 (35.29%)	18 (35.29%)		
Binaural	12 (11.77%)	6 (11.77%)	6 (11.77%)		
Duration (*n*, %)				0.82	0.66
Acute (<1 month)	68 (66.66%)	32 (62.75%)	36 (70.59%)		
Subacute (1-3 months)	17 (16.67%)	10 (19.61%)	7 (13.73%)		
Chronic (>3 months)	17 (16.67%)	9 (17.64%)	8 (15.68%)		
Tinnitus pitch (*n*, %)				4.29	0.12
Low (250-1000) Hz	17 (16.67%)	6 (11.76%)	11 (21.57%)		
Mid (1000-4000) Hz	24 (23.53%)	16 (31.37%)	8 (15.69%)		
High (4000-8000] Hz	61 (59.80%)	29 (56.87%)	32 (62.74%)		
Tinnitus loudness (dB)	61.23 ± 23.42	61.10 ± 24.71	61.35 ± 22.30	-0.06	0.96
Outcome measurement					
Pre-treatment THI	45.80 ± 21.76	54.04 ± 18.45	37.57 ± 21.86	4.11	**<0.001***
Post- treatment THI	35.76 ± 19.94	34.94 ± 17.39	36.59 ± 22.35	-0.42	0.679
THI change	10.04 ± 11.64	19.10 ± 9.69	0.98 ± 3.54	12.54	**<0.001***

Notes:
*: Statistical significance;
THI: Tinnitus Handicap Inventory;
HFGS: High-frequency gently sloping;
HFSS: High-frequency steeply sloping.

Table 2. Association of socio-demographic factors and audiogram configurations with effective therapy: multivariate logistic regression analysis

Variables	*B*	*SE*	*Wald*	*P* value	*OR*	95% *CI*	
						Lower	Upper
Age (year)	-0.04	0.17	7.34	**0.007***	0.96	0.93	0.99
Audiogram configurations		9.18		**0.027***			
Flat	1.70	0.61	7.85	**0.005***	5.45	1.67	17.86
HFGS	0.81	0.71	1.31	0.252	2.24	0.56	8.93
HFSS	reference				1.00		
Others	0.05	1.03	<0.01	0.960	1.05	0.14	7.89
Prior treatment THI	0.04	0.01	12.58	**<0.001***	1.04	1.02	1.07

Notes: *p<0.05; OR:Odds Ratio; 95%CI: 95% Confidence Interval.

Figure 1

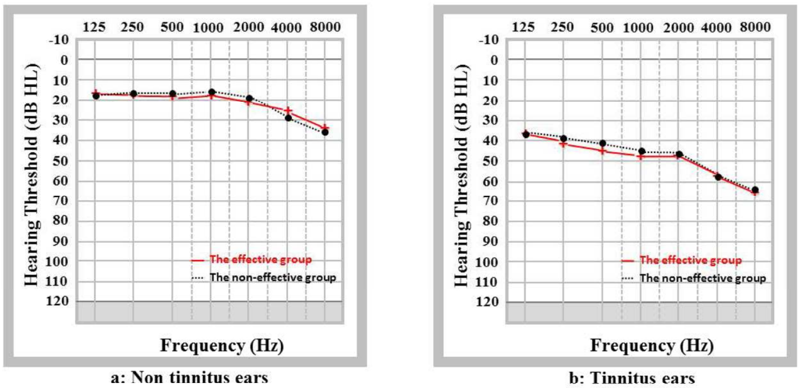

Figure 1. (Color online) The averaged pure tone hearing thresholds on tinnitus ears and non-tinnitus ears in both effective and non-effective groups.

190x107mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4-5	Explain the scientific background and rationale for the investigation being reported
Objectives	6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6,8	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7-8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6,8,14	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	9	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	9*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	9-11, table1*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	9-11, table1,2 *	Report numbers of outcome events or summary measures
Main results	9-11, table1,2	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	9-11, table1,2	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11-12	Summarise key results with reference to study objectives
Limitations	14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	11-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	11-13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	15	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Keywords:	Sound Masking, Tinnitus, Audiometric Configuration, Prognostic Factors

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Logistic Regression Analysis of Factors Influencing the Effectiveness of Intensive Sound Masking Therapy in Patients with Tinnitus

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Abstract

Objectives: To investigate factors influencing the effectiveness intensive sound masking therapy on tinnitus using Logistic Regression Analysis.

Design: The study used a retrospective cross-section analysis.

Participants: 102 patients with tinnitus were recruited at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China.

Intervention: Intensive sound masking therapy was used as an intervention approach for patients with tinnitus.

Primary and secondary outcome measures: participants underwent audiological investigations and tinnitus pitch and loudness matching measurements, followed by intensive sound masking therapy. The Tinnitus Handicap Inventory (THI) was used as the outcome measure pre- and post-treatment. Multivariate logistic regression was performed to investigate the association of demographic and audiological factors with effective therapy.

Results: According to the THI score changes *pre*-and *post*-sound masking intervention, fifty-one participants were categorised into an effective group, the remaining 51 participants were placed in a non-effective group. Those in the effective group were significantly younger than those in the non-effective group (p=0.012). Significantly more participants had flat audiogram configurations in the effective group (p=0.04). Multivariable logistic regression analysis showed that age (OR=0.96, 95% CI: 0.93, 0.99, p=0.007), audiometric configuration (p=0.027) and THI score pre-treatment (OR=1.04, 95% CI: 1.02, 1.07, p<0.001) were significantly associated with therapeutic effectiveness. Further analysis showed that patients with flat audiometric configurations were 5.45 times more likely to respond to intervention than those with high-frequency steeply sloping audiograms (OR=5.45, 95% CI: 1.67, 17.86, p=0.005).

Conclusion: Audiometric configuration, age and THI scores appear to be predictive for the effectiveness of sound masking treatment. Gender, tinnitus characteristics and hearing threshold measures seem not to be related to treatment effectiveness. Further randomized control study is needed to provide further evidence of the effectiveness of prognostic factors in tinnitus interventions.

Key Words:

Sound Masking; Tinnitus; Audiometric Configuration; Prognostic Factors

Strengths

- A relatively large sample of participants were included in the present study;
- A robust analytical method (i.e., Logistic regression) was employed to explore the predictive factors associated with significant effective outcomes of sound masking treatment.

Limitation

- Due to patient adherence in the context of Chinese culture and Healthcare system, only intensive sound masking intervention was provided, and the short-term effectiveness was subsequently assessed in present study.

INTRODUCTION :

Tinnitus is the perception of noise in the absence of any external sound. It is considered as one of the most common and disturbing health problems[1]. It is widely accepted that tinnitus is a symptom caused by diverse pathologies as a result of not only peripheral hearing loss, but also aberrant neural activity in the central auditory nervous system[2-4]. Various theories have been proposed to elaborate underlying possible mechanisms, such as; Discordant theory - the discordant dysfunction of damaged outer hair cells and intact inner hair cells[5], and Auditory plasticity theory - damaged cochlea activates auditory plasticity by enhancing neural activity in the central auditory pathway, which results in abnormal input to the central auditory system[4].

Epidemiological studies indicate that one third of all adults experience tinnitus at some time in their lives and 10 to 15% have prolonged tinnitus requiring medical intervention[6]. A number of interventions are available for tinnitus management within ENT/Audiology clinics, including; pharmacotherapy, cognitive behavioural therapy (CBT), habituation therapy (Tinnitus retraining therapy, TRT), electrical suppression (e.g., repetitive transcranial magnetic stimulation r-TMS) and sound therapy (e.g., sound masking). Of these, tinnitus sound masking therapy has been widely used in patients reporting any tinnitus characteristics[7]. According to the Cochrane review by Hobson et al.[8, 9], no significant difference was shown in the loudness of tinnitus or the overall severity of tinnitus following the use of sound masking therapy when compared to other interventions.

Furthermore, evidence has shown that no single treatment for tinnitus is found effective in all patients[8, 9]. These discrepancies in effectiveness are largely due to the complex mechanisms behind the symptoms as indicated above and the severity of impact on sufferers. Previous studies suggest that there are many influencing factors such as; age, tinnitus characteristics, hearing status and demographic factors, which affect the effectiveness of tinnitus management[1,10]. However, the results appear inconsistent. For example, Koizumi et al.[11] found better outcomes with TRT for patients with higher levels of tinnitus loudness, while Ariizumi et al.[12] reported lower tinnitus loudness to be predictive of better outcomes with TRT.

In addition, Kleinjung et al.[6] suggest that mild hearing loss and shorter tinnitus duration are more likely to be beneficial when using rTMS. These results are in keeping with the influencing factors seen when using sound masking therapy[1]. It is also noteworthy that younger age and severe depression contributed to a positive response with CBT[13]. Conrad et al.[14] further clarify that dysfunctional cognition is associated with CBT outcome, i.e., more severe dysfunctional cognition results in a more negative emotional outcome after CBT intervention.

To our best knowledge, there are few studies available on the factors that influence the effectiveness of sound masking therapy. A recent study by Theodoroff et al.[1] appears to be the only report directly investigating the factors associated with effective tinnitus treatment using sound masking therapy[1]. Although they found several positive predictors, such as younger age, better self-reported hearing difficulty, shorter durations of tinnitus and better hearing threshold at low frequency region, these results were obtained by combining tinnitus treatment data from sound masking therapy or TRT. The separate analysis showed that younger participants had significant improvement only in the TRT group (p<0.017) and that age was not a significant factor in the group using sound masking therapy (p=0.143). Such bias indicated that further investigation is needed to clarify possible factors associated with effective sound masking therapy.

Evidence has shown that audiometric configuration is associated with ear pathologies. For example, noise induced hearing loss is related to the audiogram with a 3-6 kHz dip[15]. Understanding audiometric configurations may provide insights into the etiologic mechanism and prevalence of tinnitus[16-19]. In the study by Demeester et al.[19], tinnitus was found to be significantly more prevalent in individuals with a high-frequency steeply sloping audiogram than those with a flat audiogram. However, it is still unclear as to how audiometric configuration affects sound masking intervention in tinnitus.

The purpose of this study was to use Logistic Regression Analysis to identify any factors that might influence on tinnitus sound masking, and which might predict the effectiveness of sound masking interventions in tinnitus sufferers. Significant result would offer valuable to practice in predicting the effectiveness of sound masking intervention and thus influence therapeutic strategy selection.

MATERIALS AND METHODS

Participants

The present research was a retrospective study of 102 patients with tinnitus who underwent audiological investigations and specific tinnitus examinations, followed by seven days sound masking intervention at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China. Detailed selection criteria for inclusion in this study are:-

(1) They had sought clinical help for their tinnitus problem, which had lasted more than 2 weeks;

(2) They had no history of head trauma or central nervous system disorders;

(3) They had mild to severe sensorineural hearing loss. All tinnitus patients with either current conductive hearing loss or previous middle ear surgery (e.g., mastoidectomy) were excluded[17].

(4) The tinnitus patients with pulsatile tinnitus due to aberrant vascular malformation were also excluded.

Mean age was 44.98 years (SD: 15.41). There were 46 males and 56 females (Table 1). This study was approved by the ethics committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

Routine Audiological Examinations

Routine audiological examination consisted of otoscopy, followed by pure-tone audiometry in which air conduction thresholds were measured for both ears at 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 4.0 kHz and 8.0 kHz, and bone conduction hearing thresholds were measured between 250 Hz and 4.0 kHz in a sound-proof booth. The mean hearing threshold is the average of hearing sensitivity at the frequencies of 500, 1000, 2000 and 4000 Hz.

On the basis of the audiograms, the audiometric configurations were classified as either flat, high-frequency gently sloping (HFGS), high-frequency steeply sloping (HFSS), low-frequency ascending (LFA), mid-frequency U-curve (MFU) and mid-frequency reversed U-curve (MFRU) in accordance with the criteria used in the study by Hannula et al.[15].

Tinnitus Specific Assessments

Patients were asked to describe their tinnitus characteristics, including duration and laterality (i.e., being in the right, left or both ears or central in the head). Tinnitus pitch and loudness matching measurements were performed ipsilaterally to the ear with predominant or louder tinnitus if there was a difference between the two sides. However, if the tinnitus ear had severe hearing loss, the contralateral ear was tested instead[20]. When the tinnitus was equally loud on both sides or was localized in the head, the matching tones were given to the ear with the better hearing. Otherwise, the ear was chosen randomly if there was no difference between the acuity of the two ears.

During the tinnitus pitch matching tests, the 9 audiometric frequencies between 125 Hz and 8.0 kHz (i.e., 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 3.0 kHz, 4.0 kHz, 6.0 kHz, and 8.0kHz) were firstly used to roughly match the tinnitus pitch. Participants were initially asked to make a clear distinction between the tinnitus pitch perception and presented matching tones, and then they reported verbally whether the matching tone needed to go higher or lower until the exact matching tone or a close approximation to their tinnitus was obtained. The test tone was adjusted in a half-octave step. If there was no matching with a pure tone perceived by participants, narrow-band noise was used instead.

When the matching frequency was found, the level was initially set to 5 dB above the measured audiometric threshold to find an approximate tinnitus loudness level, then the level was adjusted in 1 dB step until the subject indicated that the tone matched the loudness of their tinnitus[20].

The Sound Masking Intervention

Due to patient adherence in the context of Chinese culture and Healthcare system, a high drop-out rate occurred when patients received a longer duration of sound masking intervention. Considering the nature (i.e., a retrospective study) and main purpose of the present study, current data was obtained only from intensive sound masking intervention, and the short-term effectiveness was assessed. The narrow-band noise at 10 dB above the tinnitus frequency was delivered to mask the tinnitus through headphones (Beyerdynamic DT880 pro) 4-6 times daily for 20-30 minutes, for a week[21, 22].

Self-reported tinnitus issues and Tinnitus Handicap Inventory (THI) Questionnaire

Information on the tinnitus characteristics was collected. Patients were asked to describe the tinnitus duration and laterality (i.e., in the right, left or both ears). According to the tinnitus sound masking therapy protocol, the effectiveness of the sound masking intervention was evaluated using the Tinnitus Handicap Inventory (THI) pre and post intervention. The THI questionnaire was provided to the patient before initial treatment, and after seven days of sound masking therapy at tinnitus review clinics. The THI is a 25-item measure for evaluating the self-perceived level of handicap caused by tinnitus, based on a 0-100 increasing handicap scale (with 100 being total handicap and 0 being no handicap)[23]. Significant effectiveness was defined as a minimum of 7 points improvement in overall THI score after the sound masking intervention[24, 25].

Statistical Analysis

Continuous data are expressed as mean±standard deviation (SD) or median (interquartile range, IQR), as appropriate, and categorical data are shown as frequencies and percentages. Student's *t*-tests (for continuous variables), Wilcoxon Rank sum tests (for skewed distribution of continuous variables), and chi-square tests (for categorical variables) were used to assess differences in socio-demographic characteristics and tinnitus relevant factors by therapeutic efficacy (effectiveness versus non-effectiveness). Multivariate logistic regression models were performed to assess the independent association of demographic and tinnitus relevant factors with effective therapy. Odds ratio (OR) and its 95% confidence interval (CI) were estimated for each factor. A p level of less than <0.05 (two-sided) was considered to be statistically significant. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

On the basis of the THI score changes *pre*-and *post*-sound masking intervention (i.e., equal or greater than7 points), fifty-one participants were entered in the effective group, whereas the remaining 51 participants were placed in the non-effective group. Table 1 shows comparisons of related factors between effective and ineffective groups, respectively. In the present study, age and gender factors were compared between the effective group and the non-effective group using Student *t*-test and Chi-square test, respectively. The Student *t*-test showed that participants in the effective group were significantly younger than those in the non-effective group (t=-2.55, p=0.012). However, there was no significant difference in gender between these two groups (x^2=2.53, df=1, p=0.163).

Please insert Table 1 near here

For the purpose of understanding the basic hearing status, the averaged pure tone hearing thresholds across frequencies from 125 Hz to 8000 Hz on tinnitus ears and non-tinnitus ears were analyzed in both groups. As shown in Figure 1, the hearing threshold of each frequency from 125 Hz to 8000 Hz revealed no significant differences between the two groups (p>0.05). Significantly worse hearing thresholds at each frequency in tinnitus ears were found in both groups (p<0.05) when compared to hearing thresholds in non-tinnitus ears.

Please insert Figure 1 near here

Based on audiometric configuration classification criteria, patients in the effective group had; a flat audiogram (62.75%), HFGS (17.65%) and HFSS (15.69%). Patients in the non-effective group had flat audiogram (35.29%), HFGS (23.53%) and HFSS (31.37%) configurations, respectively. Only 7 cases had LFA, MFU or MFRU, which were classified as 'others' for the purpose of analysis. Further comparative analysis indicated that there were significantly more flat audiogram configurations together with lower HFGS and HFSS audiograms in the effective group than in the non-effective group (x^2=8.30, df=3; p=0.04) (Table 1). Laterality, duration, tinnitus pitch and loudness showed no significant differences between the two groups.

As shown in Table 1, the THI score of pre-sound masking intervention was used as a baseline measurement. The averaged THI scores pre intervention were 54.04 (SD=18.45) and 37.57 (SD=21.86) for effective and non-effective groups, respectively. Significantly lower THI scores were found *pre*- intervention in the non-effective group (t=4.11, p<0.001). However, there was no significant difference in the THI scores *post*-intervention between the two groups. As a result, significant differences were found in the *pre* and *post* THI score changes between the groups as a result of the intervention (19.10 vs. 0.98, t=12.54, p<0.001). Further analysis showed that THI scores were significantly reduced in the effective group (t=-14.07, p<0.001), whereas no significant reduction in the THI scores was found in the non-effective group in comparison of THI score between pre- and post- sound masking (t=-1.98, p=0.054).

To identify predictive factors for the effectiveness of sound masking intervention, all factors that showed significance between both effective and non-effective groups were used as variables for a logistic regression analysis. Because the audiometric configuration variable was categorised as four sub-groups, estimates of pair comparisons were subsequently performed. Results of the multivariable logistic regression analysis are summarised in Table 2. Age factor was negatively associated with effective treatment (OR=0.96, 95% CI: 0.93, 0.99, p=0.007), indicating that an increase in age of one year is associated with a 4% decrease in the effectiveness of the intervention. Audiometric configuration factor was also found to be an independent factor associated with intervention effectiveness (p=0.027). Further analysis showed that tinnitus patients with a flat audiometric configuration were 5.45 times more likely to have a successfully intervention when compared to those with HFSS configurations (OR=5.45, 95% CI: 1.67, 17.86, p=0.005). However, no significant results were found when comparing the other audiometric configurations. In addition, THI score pre-treatment was positively associated with successful treatment (OR=1.04, 95%CI: 1.02, 1.07, p<0.001), indicating that one unit increase in THI score before treatment was associated with 4% increase in therapeutic effectiveness.

Please insert Table 2 near here

Discussion

The present study demonstrates that certain factors can be prognostic for the effectiveness of intensive sound masking therapy. Logistic regression analysis indicates that age, audiogram configuration and THI scores prior to treatment were significantly related to the effectiveness of sound masking therapy. Patients with a flat audiogram, being younger in age and having higher THI scores were more likely to have positive outcomes. These findings show the importance of individual factors in predicting the likelihood of therapeutic effectiveness.

Participants with a flat audiogram were more likely to respond positively to intensive sound masking intervention than those with a HFSS audiogram but there was no relation to an average hearing threshold profile. To our best knowledge, no previous study has investigated the influence of audiometric configuration on the outcome of tinnitus intervention, even though the study by Chang et al.[26] showed that patients with a flat pattern audiogram benefited more from hearing aids compared to those with rising or decreasing audiogram in terms of improvement of psychological handicap and quality of life. The present result is likely to be due to tinnitus characteristics together with their associated hearing status. By recording Transient Otoacoustic Emiisions (TEOAEs), Kim et al.[17] found that normal TEOAE rates were significantly higher in tinnitus patients with flat audiogram than those in the HFGS and HFSS groups. Moreover, tinnitus patients with HFSS had significantly lower response rates of TEOAEs at 3, 4 and 6 kHz than tinnitus patients with flat audiogram. Therefore, better hearing status in tinnitus patients with a flat audiogram may be underlying factor, which is consistent with the previous finding reported by Theodoroff et al.[1]. However, this result should be interpreted with cautious due to the retrospective nature of this study. To resolve further prospective research is needed using systematic approaches, such as randomized controlled trials[27].

Higher THI scores before treatment were correlated with a better response to sound masking. These results are consistent with the findings of Koizumi et al.[11] and Theodoroff et al.[1], who found tinnitus retraining therapy (TRT) more effective in patients with higher THI scores. Koizumi et al.[11] further suggested that TRT should be introduced to tinnitus patients with THI score higher than 50 points. Because overall THI score may reflect the distress in tinnitus patients, these results suggested that sound masking may be regarded as a useful therapy to alleviate the distress cause by tinnitus, particularly in patients in severe distress[28].

There are several possible mechanisms behind sound masking therapy, but the exact mechanism is still unclear. Overall, it is generally accepted that there is a reduction in response to a signal due to the presence of another. The neuro-physiological mechanism can be explained through an understanding that the neural activity caused by the first sound signal (tinnitus) is reduced by the neural activity of the other sound (e.g., masking noise). For example, recent magnetoencephalography (MEG) data reported by Adjamianet al.,[29] support the efficacy of sound masking on psychological handicap (depression and anxiety), reflecting a reduction in delta band activity, which is considered a possible neuronal marker for the effect of masking[7].

Various advanced neuroimaging techniques such as fMRI and PET provide a valuable tool to explore the mechanism of tinnitus. For example, Lanting et al.[30] used fMRI and PET to identify enhanced neural activity across several areas of the central auditory system. They also found that neural activity in non-auditory areas (i.e., frontal areas, limbic system and cerebellum) seemed to associate with the perception of tinnitus. Further studies comparing the subjective perception of tinnitus and central neural activity changes between *pre*- and *post*-sound masking therapy are needed in order to clarify the neural marker as well as the mechanisms of the effective sound masking therapy.

In the present study, younger age had a positive effect on the benefits of sound masking therapy. Von Wedel et al.[31] suggested that younger tinnitus patients are more likely to report distress and tinnitus annoyance than older patients. Moreover, Seydel et al.[32] demonstrated that younger tinnitus subjects suffered distress more severely than older tinnitus subjects, due to higher levels of occupational and personal stress among younger subjects[32]. As a result, younger subjects are likely to gain more benefit in alleviating their high level distress by sound masking intervention[7]. Another explanation could be the better coping capability of younger tinnitus suffers than older subjects[32].

There are some limitations in the present study that need to be considered. Influencing factors associated with long-term effectiveness of sound masking therapy could not be investigated due to the patient adherence issue. Moreover, because of the retrospective design of the study, only THI is used to measure the effectiveness of sound masking therapy. Additional tinnitus measurements could be taken it into account, such as Visual Analogue Scale (VAS), and Tinnitus Functional Index (TFI) [33]. Therefore, future prospective longitudinal research is needed to explore the long-term effectiveness of sound masking therapy, together with its associated influencing factors.

Conclusion

This retrospective study suggests that audiometric configuration, age, and THI scores pre-treatment are predictive of beneficial sound masking outcomes. Further analysis indicates that tinnitus patients with a flat audiogram configuration are more likely to achieve a successful intervention when compared to those with high-frequency steeply sloping audiograms. Gender, tinnitus laterality, duration and hearing threshold are not related to the effectiveness of intensive sound masking treatment. However, these results should be interpreted with caution due to the retrospective nature of this study. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contribute to the effectiveness of tinnitus interventions.

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Contributors YXC and YQZ Contributed to the study design. HDY, JJJ, XYH and XYZ collected the data. QZ and HDY designed the plan of analysis. QZ, HX and SJC performed the final analyses. YXC, FZ, HJM and XTC drafted the manuscript and interpreted the results. All authors made substantive editorial contributions at all stages of manuscript preparation.

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Competing interests

None declared.

Data sharing statements

No additional data are available. However, the original data that support the findings derived from this study can be requested by emailing yiqingzheng@hotmail.com

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Captions of Figures

Figure 1. (Color online) The averaged pure tone hearing thresholds on tinnitus ears and non-tinnitus ears in both effective and non-effective groups.

Table 1. Comparison of demographic and audiological characteristics between the effective and non-effective groups in tinnitus patients with sound masking intervention

Variable	Total (*n*=102)	Effective Group (*n*=51)	Non-effective Group (*n*=51)	Chi-square/ *t*-test	*p* value
Demographic characteristics					
Age (years, Mean±SD)	44.98 ± 15.41	41.20 ± 15.41	48.76 ± 14.58	-2.55	**0.012***
Gender (*n*, %)				2.53	0.163
Male	46 (45.1%)	19 (37.3%)	27 (52.9%)		
Female	56 (54.9%)	32 (62.7%)	24 (47.1%)		
Hearing status					
Hearing threshold in tinnitus ears (dB HL)	53.75 ± 27.66	52.51 ± 26.94	54.98 ± 28.57	-0.45	0.65
Audiogram configurations (*n*, %)				8.30	**0.04***
Flat	50 (49.02%)	32 (62.75%)	18 (35.29%)		
HFGS	21 (20.59%)	9 (17.65%)	12 (23.53%)		
HFSS	24 (23.63%)	8 (15.69%)	16 (31.37%)		
Others	7 (6.76%)	2 (3.91%)	5 (9.81%)		
Tinnitus characteristics					
Laterality (*n*, %)				0.00	1.00
Left	54 (52.94%)	27 (52.94%)	27 (52.94%)		
Right	36 (35.29%)	18 (35.29%)	18 (35.29%)		
Binaural	12 (11.77%)	6 (11.77%)	6 (11.77%)		
Duration (*n*, %)				0.82	0.66
Acute (<1 month)	68 (66.66%)	32 (62.75%)	36 (70.59%)		
Subacute (1-3 months)	17 (16.67%)	10 (19.61%)	7 (13.73%)		
Chronic (>3 months)	17 (16.67%)	9 (17.64%)	8 (15.68%)		
Tinnitus pitch (*n*, %)				4.29	0.12
Low (250-1000) Hz	17 (16.67%)	6 (11.76%)	11 (21.57%)		
Mid (1000-4000) Hz	24 (23.53%)	16 (31.37%)	8 (15.69%)		
High (4000-8000] Hz	61 (59.80%)	29 (56.87%)	32 (62.74%)		
Tinnitus loudness (dB)	61.23 ± 23.42	61.10 ± 24.71	61.35 ± 22.30	-0.06	0.96
Outcome measurement					
Pre-treatment THI	45.80 ± 21.76	54.04 ± 18.45	37.57 ± 21.86	4.11	**<0.001***
Post- treatment THI	35.76 ± 19.94	34.94 ± 17.39	36.59 ± 22.35	-0.42	0.679
THI change	10.04 ± 11.64	19.10 ± 9.69	0.98 ± 3.54	12.54	**<0.001***

Notes: *: Statistical significance;
THI: Tinnitus Handicap Inventory;
HFGS: High-frequency gently sloping;
HFSS: High-frequency steeply sloping.

Table 2. Association of socio-demographic factors and audiogram configurations with effective therapy: multivariate logistic regression analysis

Variables	*B*	*SE*	*Wald*	*P* value	*OR*	95% *CI*	
						Lower	Upper
Age (year)	-0.04	0.17	7.34	**0.007***	0.96	0.93	0.99
Audiogram configurations		9.18		**0.027***			
Flat	1.70	0.61	7.85	**0.005***	5.45	1.67	17.86
HFGS	0.81	0.71	1.31	0.252	2.24	0.56	8.93
HFSS	reference				1.00		
Others	0.05	1.03	<0.01	0.960	1.05	0.14	7.89
Prior treatment THI	0.04	0.01	12.58	**<0.001***	1.04	1.02	1.07

Notes: *: Statistical significance;
OR: Odds Ratio;
95% CI: 95% Confidence Interval.

Figure 1

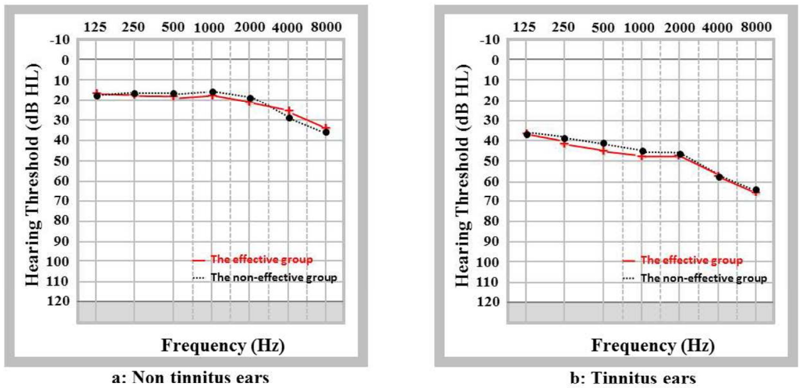

Figure 1. (Color online) The averaged pure tone hearing thresholds on tinnitus ears and non-tinnitus ears in both effective and non-effective groups.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4-5	Explain the scientific background and rationale for the investigation being reported
Objectives	6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6,8	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7-8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6,8,14	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	9	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	9*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	9-11, table1*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	9-11, table1,2 *	Report numbers of outcome events or summary measures
Main results	9-11, table1,2	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	9-11, table1,2	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11-12	Summarise key results with reference to study objectives
Limitations	14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	11-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	11-13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	15	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.