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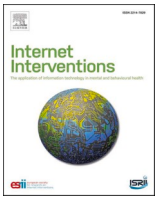

The Fudan Tinnitus Relieving System (FTRS): The initial results of a smartphone application for tinnitus management and treatment

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ABSTRACT

Objective: Tinnitus is highly prevalent in the population, but there are currently few effective therapeutic interventions. Mobile applications (apps) might be helpful in tinnitus diagnosis and treatment by offering sound or music tools as well as questionnaires. We assessed the efficacy of a free, publicly available smartphone app (Fudan Tinnitus Relieving System, FTRS) for self-management of tinnitus and related symptoms.

Methods: Among a total of 3564 participants recruited primarily online, 2744 patients had complete information at baseline and were an average of 37 years old and were 59.84 % male. Web-administered self-report measures THI, HADS, AIS, and other multi-dimensional scales were conducted at baseline and at 1 month and 2 months following treatment. Data from 54 participants who completed continuous follow-up were used for the final efficacy analysis and longitudinal analysis.

Results: Following the intent-to-treat principle, *t*-tests revealed that the distribution of patients and the tinnitus features of patients of different genders were heterogeneous. One-way ANOVA showed that after using the FTRS app, THI scores showed a decreasing trend ($p < 0.001$).

Conclusion: FTRS use resulted in significantly greater improvements in tinnitus and other outcomes relative to their baseline condition before treatment. Given the ubiquity of smartphones, FTRS may provide a wide-reaching and convenient public health intervention for individuals with tinnitus symptoms.

1. Introduction

Tinnitus is a condition in which sound can be perceived in the absence of a corresponding external stimulus, and it has an estimated prevalence of 10–15 % globally and 8–30 % in China (Baguley et al., 2013; Bauer, 2018; Zhang et al., 2021). In the United States, tinnitus results in an estimated prevalence of 10 % to 15 % in adults (Henry et al., 2005, Hoffman and G, 2004), and it has affected 50 million Americans in the last 30 years (Axelsson and Ringdahl, 1989; McCormack et al., 2016; Shargorodsky et al., 2010). Tinnitus is thought to be related to functional or physiological changes at different levels of the auditory pathway, and multiple causes are responsible for the onset of tinnitus, among which hearing loss is the most important (Nondahl et al., 2011; Roberts et al., 2010). Tinnitus disturbs daily life of people at all ages (Nondahl et al., 2012; Langguth et al., 2019), and 33 % of patients with bothersome tinnitus also suffer from depression, (Salazar et al., 2019), and most studies have focused on the widespread anxiety and depression accomplishing tinnitus patients (Trevis et al., 2018). Tinnitus also lays a huge financial burden on society; for example, the National Health Service of the UK spends about £750 million annually on treating tinnitus patients, at an average cost of £717 per patient (Stockdale et al., 2017). These physical and economic costs make tinnitus a significant public health problem.

Most current tinnitus management strategies involve large investments of time and energy. The evaluation of patients with newly diagnosed tinnitus depends on qualitative descriptions of their symptoms and their medical histories, comprehensive audiologic evaluations, and standard questionnaires, and evidence-based tinnitus treatments to reduce tinnitus-related symptoms include cognitive behavioral therapy, acoustic stimulation, and educational counseling. No medications, supplements, or herbal remedies have been shown to substantially reduce the severity of tinnitus. Cognitive behavioral treatment (CBT) and sound therapy are two alternative choices proven to be efficient in treating tinnitus (Fuller et al., 2020; McKenna et al., 2020; Landry et al., 2020). CBT seeks to rectify the patient's maladaptation of cognitive patterns, thus replacing irrational beliefs with reasonable ones to eliminate emotional problems (Fuller et al., 2020). Sound therapy has evolved from the initial masking therapy and tinnitus retraining therapy to the widely used tailor-made notched music training (TMNMT). The short-term efficacy of TMNMT has been demonstrated (Stein et al., 2016), and the use of methods such as TMNMT and CBT to treat tinnitus through smartphone apps has great prospects (Nagaraj and Prabhu,

Abbreviations: CBT, Cognitive behavioral treatment; TMNMT, tailor-made notched music training; FTRS, Fudan Tinnitus Relieving System; THI, Tinnitus index; HADS, Hospital Anxiety and Depression Scale; AIS, Athens Insomnia Scale; GIS, geographic information system.

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2020). Thus, population-level interventions seem feasible.

Smartphones are ideal for delivering such interventions because they are widely used by adults in China. Some previous studies have combined the developing technology of smart-phone applications (apps) with tinnitus diagnosis and therapy (Kim et al., 2017; Tyler et al., 2018; Mehdi et al., 2020b; Sereda et al., 2019; Schlee et al., 2016; Nagaraj and Prabhu, 2020; Probst et al., 2016; Kutyba et al., 2022; Mehdi et al., 2020a) and shown that such apps are helpful not only due to the variability of tinnitus, but also for treating tinnitus conveniently in large patient populations. Given our current understanding of tinnitus, the use of smart phone apps in the treatment of tinnitus is undoubtedly the most convenient and most acceptable way for patients, and a large number of users will be able to provide strong evidence for their efficacy. A review has summarized the efficacy of smartphone apps and concluded that the current smartphone apps have very promising clinical efficacy in tinnitus treatment and management. However, the review also noted that although many tinnitus management and treatment apps can be found online, few apps can verify their effectiveness through clinical research. Thus we are still at the very beginning stage of the development of tinnitus management apps, and evidence their effectiveness against tinnitus is very limited (Mehdi et al., 2020a).

In view of the lack of clinical efficacy research of smartphone apps for tinnitus management and treatment, we developed the app—Fudan Tinnitus Relieving System (FTRS)—and completed the management, treatment, data collection, and efficacy statistics of tinnitus patients through the app. We made a preliminary tinnitus diagnosis for all registered patients through the app and collected data on tinnitus frequency and intensity through the self-help frequency matching of the app and provided corresponding sound therapy. At the same time, we provided several questionnaires in the app and followed up with users to evaluate the efficacy of the app. We hypothesized that the FTRS app is helpful in reducing the severity of tinnitus and that the treatment effect is maintained for at least 2 months.

2. Methods

2.1. Participants

The participants were users of the FTRS app (Android or iOS version) from 18 May 2018 to 20 January 2021. They approved the user registration agreement and agreed their data being used for scientific purposes. The patients who completed the standardized questionnaires were recruited. Initially, 3564 patients qualified for the study, and 820 were excluded due to the lack of complete personal information or tinnitus features and were not suitable for analysis. 2690 were excluded due to discontinued use of the app before the end of the study, discontinued sound therapy, or loss of contact. Ultimately, 54 patients with consecutive evaluations of three months were included in the final analysis.

The sensitive information relevant to patient privacy was removed before analysis. All participants approved the collection and analysis of their data in the user registration agreement. The scientific research was approved by the ethical committee of Eye & ENT Hospital of Fudan University.

2.2. Multi-dimensional evaluation

Standardized questionnaires were used to evaluate the efficacy of the sound therapy of the app, including the Tinnitus Handicap Inventory (THI) (Newman et al., 1996), the Hospital Anxiety and Depression Scale (HADS) (Zöger et al., 2004), and the Athens Insomnia Scale (AIS) (Enomoto et al., 2018; Budd and Pugh, 1996; Cima et al., 2011). Besides tinnitus severity, data from the THI, HADS, and AIS were also used to analyze quality of life in tinnitus patients. The THI is a self-reported questionnaire on the impact of tinnitus on daily life. It was first developed in 1996, and it mainly focuses on functional, emotional, and catastrophic reactions scales (Newman et al., 1996). The maximum score is 100 points, and the tinnitus-related discomfort is more severe with a higher score. For each item the response of “yes” is 4 points, “sometimes” is 2 points, and “no” is 0 points, and scores of 0 to 16 points are considered slight disability, 18 to 36 points are considered mild disability, 38 to 56 points are considered moderate disability, and 58 to 100 points are considered severe disability. The 95 % confidence interval is 20 points, that is to say, there is a statistical difference of 20 points or more between the two tests. HADS is composed of the anxiety subscale (HADS-A, the first seven questions) and the depression subscale (HADS-D, the last seven questions) (Zöger et al., 2004). HADS-A, HADS-D, and AIS are scales commonly used in the clinic to assess anxiety, depression, and insomnia-related problems. Because anxiety and depression are common and considerable concomitant symptoms of tinnitus, we can use these scales to evaluate the impact of tinnitus on patients’ quality of life. We applied a tinnitus severity assessment scale modified and translated by Langguth et al. (2013) from Biesinger et al. (1998). The scale divides tinnitus patients into four grades, and patients with no annoying tinnitus are in grade I-no impairment. If tinnitus is sometimes annoying in defined conditions such as in a quiet environment, then patients are defined as grade II-slight impairment. When tinnitus is getting worse such that patients are permanently annoyed with disturbances in private and professional areas, it is grade III. Finally, when patients with severe impairment are unable to work and live normally, it is considered grade IV.

2.3. Acoustic therapy guidance and follow-up assignment

Patients are recommended to listen to tailor-made music through the app at any time of the day for a total time of no <2 h. It can be played with headphones or the patients can use speakers, and the latter is recommended. The volume should be slightly higher than the tinnitus volume for better desensitization. When using the headphones, the patient should rest for a few minutes every half hour as well as keep an appropriate volume. For patients with insomnia, it is proposed to listen to music for half an hour to 1 h at a fixed time before going to bed every night and combining the music with slow and deep breathing in order to relax and fall asleep. In addition, diverting attention and relaxing can help ease the phenomenon. Patients can fill in self-help questionnaires on the app at the beginning of treatment and every month thereafter to record its efficacy. We used the basic information and results of questionnaires at baseline, and after 1 month and 2 months of treatment.

2.4. Statistical analysis

Demographics and baseline characteristics such as age, THI, HADS-A, HADS-D, and AIS were summarized by gender. We summarized the descriptive statistics of continuous variables (mean, standard deviation) and summarized the number of patients in each category of categorical variables and proportions. Differences in characteristics between the groups were tested with chi-square/adjusted chi-square tests for categorical variables and *t*-tests for normally distributed continuous variables. We drew a GIS map to show the distribution of those patients. Box plots were used to identify changes in the main parameter value over 2 months, and one-way ANOVA was used for the continuous variable. Two-sided values of $p < 0.05$ were deemed statistically significant. All statistical analyses were performed using R software (version 4.0.5).

2.5. Longitudinal analysis

A total of 784 participants with completed records of personal information and four scales were included in several longitudinal models to explore the changes in scores over time. For each scale, random effect (individual level) and fixed effect (treatment time, sex, age, etc.) were added into the models in sequence that allowed the tinnitus scale scores to vary with individuals, time, demographic predictors (age, sex) and

tinnitus-specific predictors (frequency, location, influence, and duration).

The model fit of the models was assessed and compared with R^2. We refitted the final model with only significant predictors and compared the final model with the null model. The model fit of the models was assessed and compared with R^2. The results were based on the better models.

3. Results

3.1. The flowchart and geographic information system (GIS) analysis of the study

All registered app users were regarded as potential enrolled patients, among which 3564 users completed the tinnitus pitch matching and completed the baseline assessment with the multidimensional follow-up scales after registering with the app. Of these, 2744 users completed the key information such as age, gender, and profiles related to tinnitus. We used data from these 2744 users to analyze the overall effect of FTRS sound therapy on tinnitus symptoms. Furthermore, to examine the continuous efficacy of FTRS, we chose participants requesting monthly follow-up assessments, and ultimately 54 patients had complete questionnaires and basic information at baseline and at 1 month and 2 months after FTRS treatment. These data were used to analyze the improvement in patients' quality of life. The flowchart of data sorting is shown in Fig. 1.

In addition, to investigate the geographical distribution of patients with tinnitus we also conducted GIS analysis. As shown in Fig. 2, we demonstrated that the FTRS app was widely adopted throughout China except for few regions such as Hong Kong, Macao, Taiwan, and the South China Sea Islands. Most of the users were from the densely populated Yangtze River Delta of China followed by Shandong, Sichuan, Henan, and other densely populated provinces. The patients' good compliance and follow-up in these economically developed areas might increase the risk of false-positive bias, but the geographical distribution of the patients participating in the study is well representative of the patients in the whole country.

3.2. Descriptive analysis and tinnitus features

Results obtained from the 2744 patients were analyzed, including 1102 (40.2 %) females and 1642 (59.8 %) males (Table 1). The mean age of the participants was 37.19 ± 12.56 years for males and 36.78 ± 12.78 years for females. Patients of both sexes with high-frequency tinnitus accounted for the largest proportion at over 80 %, and 22.4 % of the males and 21.3 % of the females reported a frequency around 12,000 Hz. Interestingly, 23.5 % of the females complained about low-frequency tinnitus (120 Hz, 250 Hz, and 500 Hz), and nearly 50 % of them, 11 % of the total female patients, had tinnitus frequency around 125 Hz, while only 5.2 % of the male patients reported low-pitched tinnitus at 125 Hz. Notably, the duration of tinnitus was longer in males (32.50 ± 65.12 months) than in females (20.30 ± 39.05 months). The proportion of patients with grade IV tinnitus were strikingly similar and high in both males (38.3 %) and females (38.3 %), while only 29 % of male and 28.5 % of female patients had grade II, and 25.2 % of male and 24.2 % of female patients had grade III. Fewer than 10 % of the patients were undisturbed by their tinnitus.

Patients of both sexes showed an increase in number with the disability level according to the THI scale. Among male patients, 180 (11.0 %) had slight disability, and 396 (24.1 %) complained of mild disability, while the patients with moderate (472, 28.7 %) and severe disability (594, 36.2 %) made up nearly 65 % of the total male patients. Similarly, female patients mostly presented with severe (423, 38.4 %) or moderate (307, 27.9 %) disability, while patients with slight (112, 10.2 %) and mild (260, 23.6 %) disability were no >35 % of the total female patients. For the HADS scales, the total proportion of male patients suffering from anxiety (690, 42 %) significantly exceeded that in female patients (409, 37.1 %), and the proportion of male patients suffering from depression was 561 (34.2 %) compared to 324 (29.4 %) of female patients. The majority of both male patients (1047 (63.8 %)) and female patients (669 (60.7 %)) suffered from insomnia. Generally, anxiety, depression, and insomnia are common in patients with tinnitus, thus patients are troubled not only by the sound of the tinnitus, but also by various negative emotional states.

In addition to these analyses, we performed a correlation analysis of

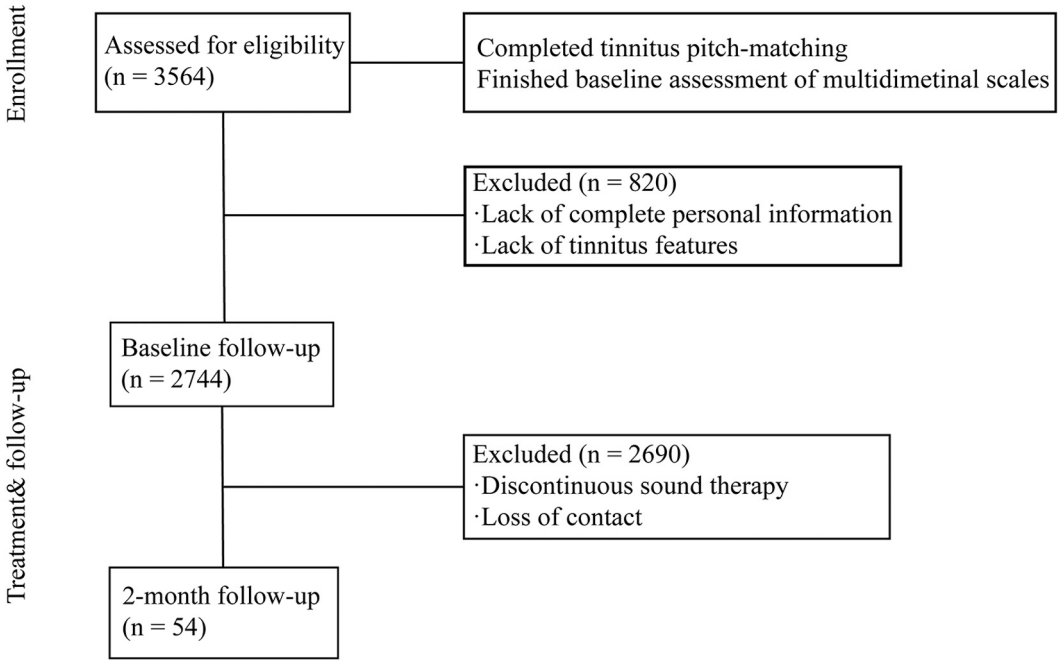


Fig. 1. Data sorting and analysis process of the FTRS app in this study. A total of 3564 patients completing all of the questionnaires were first recruited, and 2744 of them with full personal data remained for analysis of the efficacy of the app on tinnitus symptoms. Finally, 54 patients completed all required information at all follow-up timepoints, and their data were used to analyze the improvement in patients' quality of life.

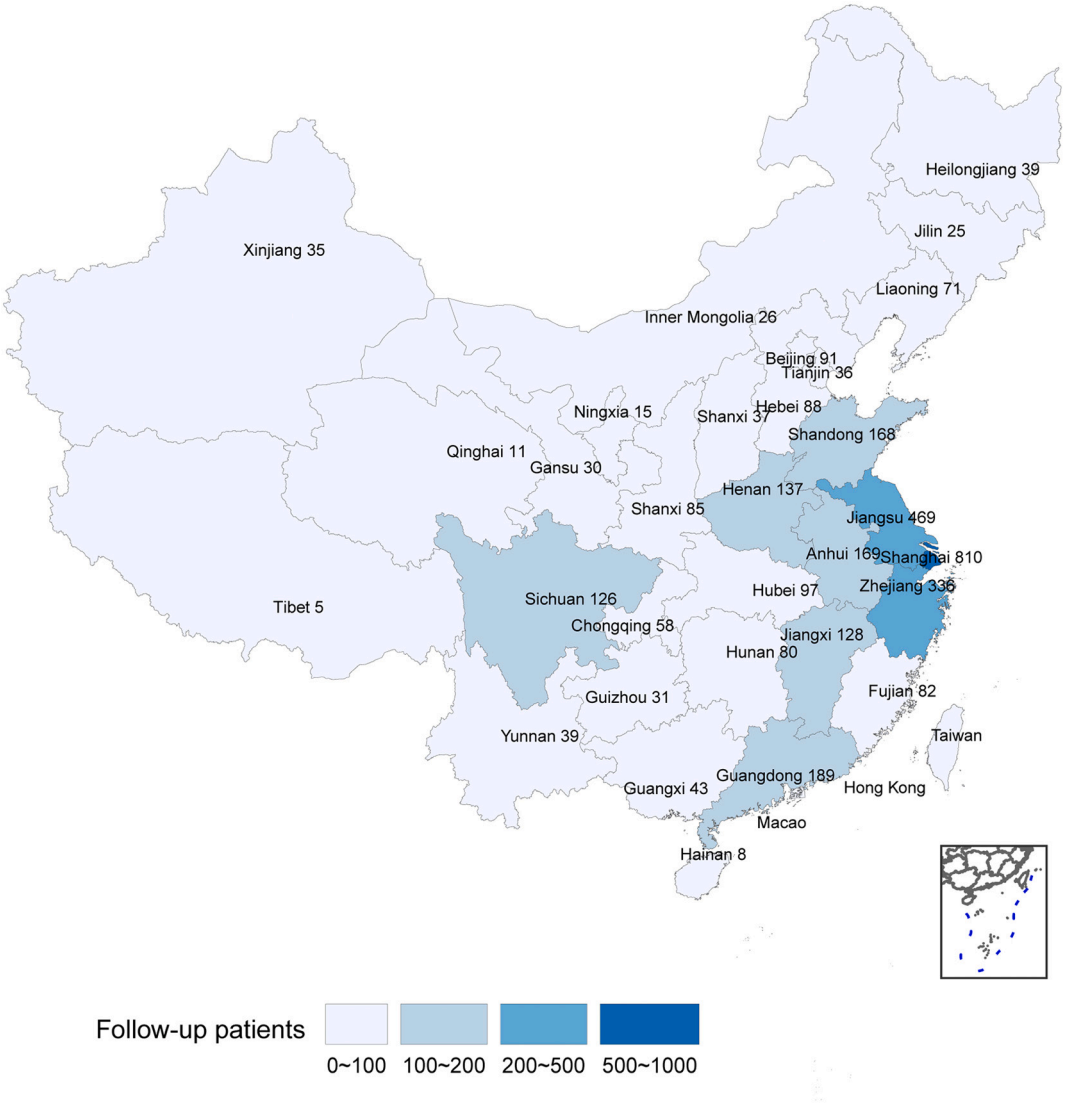


Fig. 2. GIS map of the distribution of tinnitus patients in China. There were >500 patients in Shanghai and over 200 patients living in Jiangsu and Zhejiang Province. Shandong, Henan, Anhui, Jiangxi, Guangdong, and Sichuan Province each had >100 patients. There were no >100 patients each scattered in the other provinces, and there were no patients from Hong Kong, Macao, Taiwan, or the South China Sea Islands.

grades sorted by tinnitus-related disability level divided by THI scores with general information and various scales, and these results indicated that patients with higher THI scores or more severe tinnitus also had more serious anxiety, depression, and insomnia. The average ages in the four groups were statistically different, and the average age of the 292 patients with slight disability was 40.67 ± 13.46 years old, which was significantly older than that of the 1017 patients in the severe disability group (35.05 ± 11.64 years) (Table 2). The proportions of male and female patients showed no differences in the four groups. Notedly, the numbers of patients diagnosed with anxiety and depression according to the HADS were significantly greater in the severe (756, 74.3 %) and moderate (257, 33 %) disability groups compared to the slight (75, 11.4 %) and mild (11, 3.8 %) disability groups. Similarly, patients with insomnia were much more common in the severe disability group (861, 84.7 %) compared to the slight (287, 43.8 %) and mild (58, 19.9 %) disability groups. In line with our expectations, only 8 patients (0.8 %) in the severe disability group were sorted as grade I, while 599 (58.9 %) patients were sorted as grade IV on the tinnitus severity assessment scale.

3.3. *Efficacy in 2744 patients with tinnitus*

The overall efficacy of sound therapy was significant as measured by almost every scale. As shown in Fig. 3, the maximum scores of all the scales declined from baseline to the 3-month follow-up, as did the 25th percentile, median, and 75th percentile. Thus, FTRS sound therapy appeared to be effective in tinnitus patients with or without severe accompanying symptoms. Interestingly, the maximum scores at baseline were the same as the 1-month follow-up for all scales, and only the 25th percentile, median, and 75th percentile for the THI and HADS-D decreased progressively along with follow-up. The 75th percentile scores of THI were 72 at baseline, 64 at 1 month, and 46 at 2 months, thus showing a sharp decrease. We used one-way ANOVA to perform multiple comparisons, and the median at the 3-month follow-up was much lower than at baseline for THI (from 50 to 32), HADS-A (from 6 to 4), and HADS-D (from 6 to 3). These results indicate the apparent efficacy of FTRS sound therapy for tinnitus patients, and the trend for a decline in THI suggests its efficacy even in severe patients.

Table 1
Descriptive analysis of general information and tinnitus profiles in 2744 patients using the FTRS app.

		Male (n = 1642)	Female (n = 1102)	p
Age (years)		37.19 ± 12.56	36.78 ± 12.78	0.407
THI (%)	Slight	180 (11.0)	112 (10.2)	0.677
	Mild	396 (24.1)	260 (23.6)	
	Moderate	472 (28.7)	307 (27.9)	
	Severe	594 (36.2)	423 (38.4)	
HADS-A (%)	Positive	690 (42.0)	409 (37.1)	0.011
	Negative	952 (58.0)	693 (62.9)	
HADS-D (%)	Positive	561 (34.2)	324 (29.4)	0.01
	Negative	1081 (65.8)	778 (70.6)	
AIS (%)	No	316 (19.2)	219 (19.9)	0.194
	Suspicious insomnia	279 (17.0)	214 (19.4)	
	Insomnia	1047 (63.8)	669 (60.7)	
Main frequency of tinnitus (Hz)	125	85 (5.2)	121 (11.0)	<0.001
	250	67 (4.1)	90 (8.2)	
	500	50 (3.0)	47 (4.3)	
	1000	40 (2.4)	60 (5.4)	
	2000	51 (3.1)	39 (3.5)	
	3000	61 (3.7)	25 (2.3)	
	4000	92 (5.6)	37 (3.4)	
	5000	133 (8.1)	66 (6.0)	
	6000	171 (10.4)	102 (9.3)	
	8000	252 (15.3)	127 (11.5)	
	10,000	272 (16.6)	153 (13.9)	
	12,000	368 (22.4)	235 (21.3)	
Tinnitus position (%)	Tinnitus cerebri	161 (9.8)	111 (10.1)	0.561
	Bilateral	713 (43.4)	461 (41.8)	
	Right side	376 (22.9)	242 (22.0)	
	Left side	392 (23.9)	288 (26.1)	
Tinnitus duration (months)		32.50 ± 65.12	20.30 ± 39.05	<0.001
Tinnitus severity grade (%)	I	124 (7.5)	99 (9.0)	
	II	413 (25.2)	267 (24.2)	0.7
	III	476 (29.0)	314 (28.5)	
	IV	629 (38.3)	422 (38.3)	

3.4. Further analysis of 54 patients

Sound therapy in the FTRS app could significantly reduce the number of patients with severe tinnitus. We collected complete THI, HADS-A, HADS-D, and AIS scores from 54 patients at all three follow-up time points, and we used them as indicators of quality of life. Among them, there were 19 patients with severe disability and 9 with moderate disability, which together made up more than half of the 54 total patients. After 1 month of FTRS sound therapy, the patients with severe disability decreased from 19 (35.2 %) to 8 (14.8 %), while the number of tinnitus patients without disability or with slight disability increased from 6 (11.1 %) to 13 (24.1 %). After 2 months of treatment, patients without disability further increased to 20 (37.0 %), and the number of patients with severe disability further decreased to 3 (5.6 %) (Fig. 4).

The quality of life of tinnitus patients was significantly improved and was accompanied by relief from tinnitus. The mean THI score of the 54 patients at baseline was 51.5, and this decreased to 44.6 only a month later (Table 3). At the 3rd month follow-up, the mean THI score had decreased to 33.8, and this was consistent with the change in the proportion of severe patients. The mean HADS-D score was 6.38 at baseline, 5.59 at the 1-month follow-up, and 3.78 at the 3-month follow-up, thus also showing a progressive decline. Similarly, the HADS-A score decreased from 6.93 at baseline to 4.56 at the 3-month follow-up, and the AIS also showed an apparent decrease of 1.73 points after 2 months of FTRS sound therapy. Generally, changes in THI scores indicated that tinnitus symptoms eased after FTRS sound therapy, and the reductions in HADS-A, HADS-D, and AIS scores suggested an improvement in the tinnitus patients' quality of life. The multi-dimensional evaluation showed significant efficacy in tinnitus patients, especially severe cases, and longer duration of sound therapy was associated with better efficacy (Fig. 5).

Table 2
Correlation analysis of 2744 patients using the FTRS app grouped by tinnitus-related disability level sorted by THI scores with general information and different scales.

	Slight (n = 292)	Mild (n = 656)	Moderate (n = 779)	Severe (n = 1017)	p
Age	40.67 ± 13.46	39.05 ± 13.81	36.53 ± 12.04	35.05 ± 11.64	<0.001
Gender (%)					
Male	180 (61.6)	396 (60.4)	472 (60.6)	594 (58.4)	0.677
Female	112 (38.4)	260 (39.6)	307 (39.4)	423 (41.6)	
HADS-A (%)					
Positive	11 (3.8)	75 (11.4)	257 (33.0)	756 (74.3)	<0.001
Negative	281 (96.2)	581 (88.6)	522 (67.0)	261 (25.7)	
HADS-D (%)					
Positive	11 (3.8)	44 (6.7)	178 (22.8)	652 (64.1)	<0.001
Negative	281 (96.2)	612 (93.3)	601 (77.2)	365 (35.9)	
AIS (%)					
No	162 (55.5)	210 (32.0)	107 (13.7)	56 (5.5)	<0.001
Suspected insomnias	72 (24.7)	159 (24.2)	162 (20.8)	100 (9.8)	
Insomnia	58 (19.9)	287 (43.8)	510 (65.5)	861 (84.7)	
Tinnitus severity grade (%)					
I	106 (36.3)	88 (13.4)	21 (2.7)	8 (0.8)	<0.001
II	79 (27.1)	219 (33.4)	226 (29.0)	156 (15.3)	
III	71 (24.3)	218 (33.2)	247 (31.7)	254 (25.0)	
IV	36 (12.3)	131 (20.0)	285 (36.6)	599 (58.9)	

3.5. Longitudinal analysis on 784 patients of different scales over time and at the individual level

The relationship between different scales with sound treatment duration, tinnitus duration, sex, and age were assessed in the longitudinal models.

Compared with the null models that only focused on the variance of the tinnitus scale scores at individual level, final models controlling significant predicators were improved ($AIC_{THIfinal} = 6782.950$, $R^2_{THIfinal} = 0.784 > R^2_{THInull} = 0.738$). Based on the results, time was a negative predictor of THI ($P < 0.001$). For every one day of receiving sound treatment on the app, the THI decreased by 0.03 points [β(THI-time) = −0.03, 95%CI: −0.05 to −0.02]. Older tinnitus patients presented lower scores on the THI [β(THI-age) = −0.22, 95 %: −0.41 to −0.03] and HADS-D [β(HADSD-age) = −0.04, 95%CI: −0.07 to −0.01] ($P < 0.05$). The duration of tinnitus seemed to be the only significant predictor of tinnitus scale scores. Longer duration had a positive effect on THI scores [β(THI-duration) = 0.09, 95%CI: 0.04–0.14] (Table 4).

We found a decreasing trend for THI score with increasing length of sound treatment. (Fig. 6). The scores on the other scales also decreased at the beginning. However, after 2 months the scores for HADS-A, HADS-D, and AIS began to increase again.

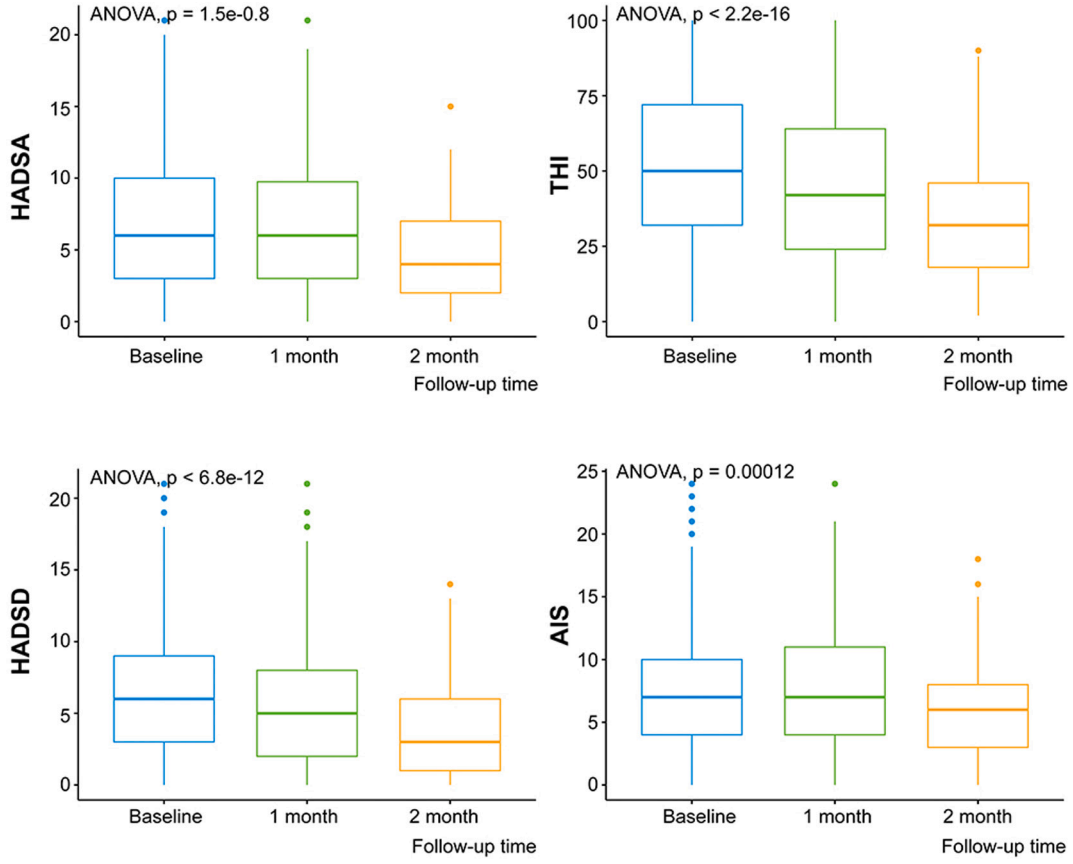
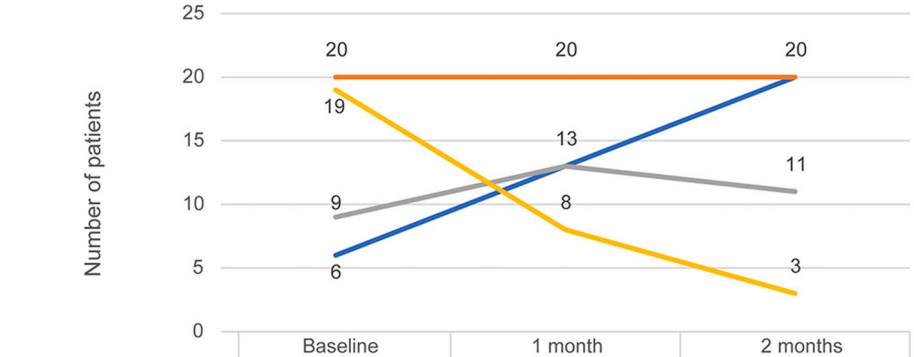


Fig. 3. Changes in scores on the different questionnaires at the three time points. All scales showed a statistically significant difference using one-way ANOVA ($p < 0.05$), and scores at the 3-month follow-up were significantly lower than at baseline.



	Baseline	1 month	2 months
No disability	6	13	20
Mild disability	20	20	20
Moderate disability	9	13	11
Severe disability	19	8	3

Fig. 4. The change in patient numbers in different disability levels. A total of 54 patients were recruited for this analysis, and the THI scores of tinnitus patients with severe disability markedly decreased.

Table 3
Efficacy in 54 patients with tinnitus measured by descriptive analysis of THI, HADS-D, HADS-A, and AIS.

	THI	HADS-D	HADS-A	AIS
Baseline	51.5 ± 25.0	6.38 ± 4.44	6.93 ± 4.57	7.65 ± 4.69
1st month	44.6 ± 25.8	5.59 ± 4.23	6.49 ± 4.61	7.87 ± 4.90
3rd month	33.8 ± 20.6	3.78 ± 3.03	4.56 ± 3.48	5.92 ± 3.76

4. Discussion

To our knowledge, this is the largest study ever to evaluate the efficacy of a mobile app for tinnitus management, including diagnosis and treatment. The results support our main hypothesis, showing that 2 months of FTRS use resulted in greater reductions in tinnitus symptom severity compared to baseline. In the descriptive analysis of patient information, we found that the frequency and perceived severity of tinnitus were significantly heterogeneous by sex. The proportion of low-

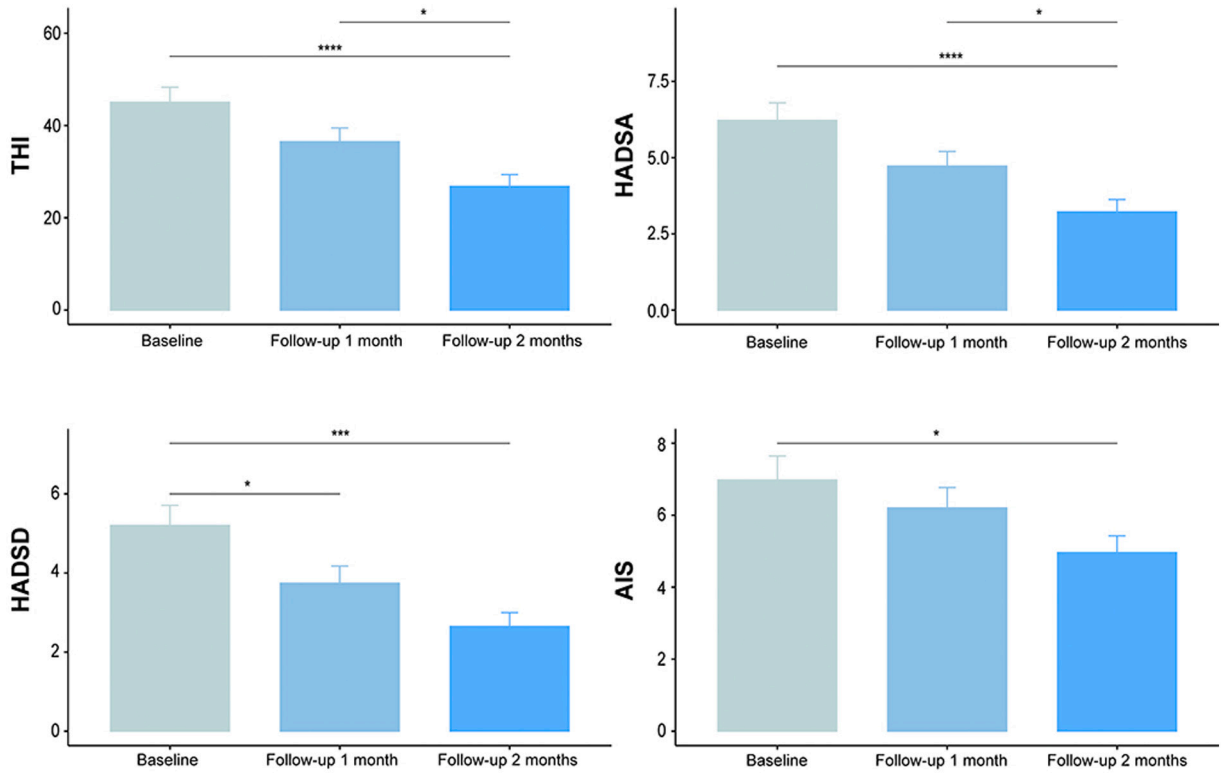


Fig. 5. The quality of life of 54 patients at all follow-up time points. The scores of THI, HADS-A, HADS-D, and AIS were significantly improved at 3-month follow-up compared with baseline, indicating that the quality of life of the patients was improved.

Table 4
Longitudinal analysis of different scales over time and at the individual level.

	Beta	95%CI	p	AIC	R^2
THI				6782.950	0.784
Sound treatment time (days)	−0.03	−0.05 to −0.02	<0.001		
Sex-Male (Female as reference)	−2.76	−8.02–2.50	0.304		
Age (years)	−0.22	−0.41 to −0.03	0.023		
Tinnitus location (Left as reference)					
Right	−5.22	−12.75–2.31	0.174		
Bilateral	−5.69	−12.30–0.92	0.091		
Tinnitus cerebri	0.21	−9.23–9.65	0.965		
Tinnitus duration (months)	0.09	0.04–0.14	<0.001		
HADS-A				4215.075	0.749
Sound treatment time (days)	−0.00	−0.01–0.00	0.144		
Sex-Male (Female as reference)	0.37	−0.59–1.34	0.449		
Age (years)	−0.02	−0.06–0.01	0.250		
HADS-D				4137.239	0.767
Sound treatment time (days)	−0.00	−0.01–0.00	0.175		
Sex-Male (Female as reference)	0.36	−0.55–1.28	0.435		
Age (years)	−0.04	−0.07 to −0.01	0.020		
AIS				4167.331	0.810
Sound treatment time (days)	−0.00	−0.01–0.00	0.139		
Sex-Male (Female as reference)	0.47	−0.57–1.52	0.374		
Age (years)	0.01	−0.03–0.04	0.743		

frequency tinnitus in female patients was much higher, while the proportion of anxiety and depression related to tinnitus was higher in males and the duration of disease was longer than in females. In the present study, there was no significant difference in THI or AIS scores between male and female patients, while the HADS-A and HADS-D scores of male patients were more severe than for female patients. Another study showed that severe depressive symptoms were associated with tinnitus severity in both sexes, but stress intensity was associated with tinnitus severity only in male patients (Han et al., 2019). In contrast, Seydel et al. (2013) found that tinnitus-related stress was related to the patient's age and tinnitus duration and that female patients, especially elderly women (≥60 years of age), reported more somatic complaints, including sleep disturbances, than older men. Women had more accompanying symptoms and coped less efficiently than men, except for younger patients (<45 years of age). Niemann et al. (2020) used different scales to evaluate sex-related tinnitus symptoms and found that the tinnitus frequency and the related stress and depression levels of female patients were higher than those of male patients. A study focusing on suicide attempts associated with tinnitus found that severe tinnitus was associated with suicide attempts in females but not in males (Lugo et al., 2019).

We found significant improvements in tinnitus severity using various scales, and similar results in THI score were reported in a study by Kim et al. (2017) using a smartphone app to deliver notched music. Also, Tyler et al. (2018) reported a reduction in tinnitus-related distress after smartphone app-based sound therapy in cochlear implant patients. Another study used partial sound masking to treat tinnitus patients and saw an improvement on Tinnitus Primary Functions Questionnaire scores (Tyler et al., 2020). Our study not only found a significant improvement in THI score, a commonly used questionnaire, but also used anxiety, depression, and sleep scales to comprehensively evaluate the patient's situation. From multiple perspectives of the impact of tinnitus on daily life, our study verified the effectiveness of FTRS sound therapy.

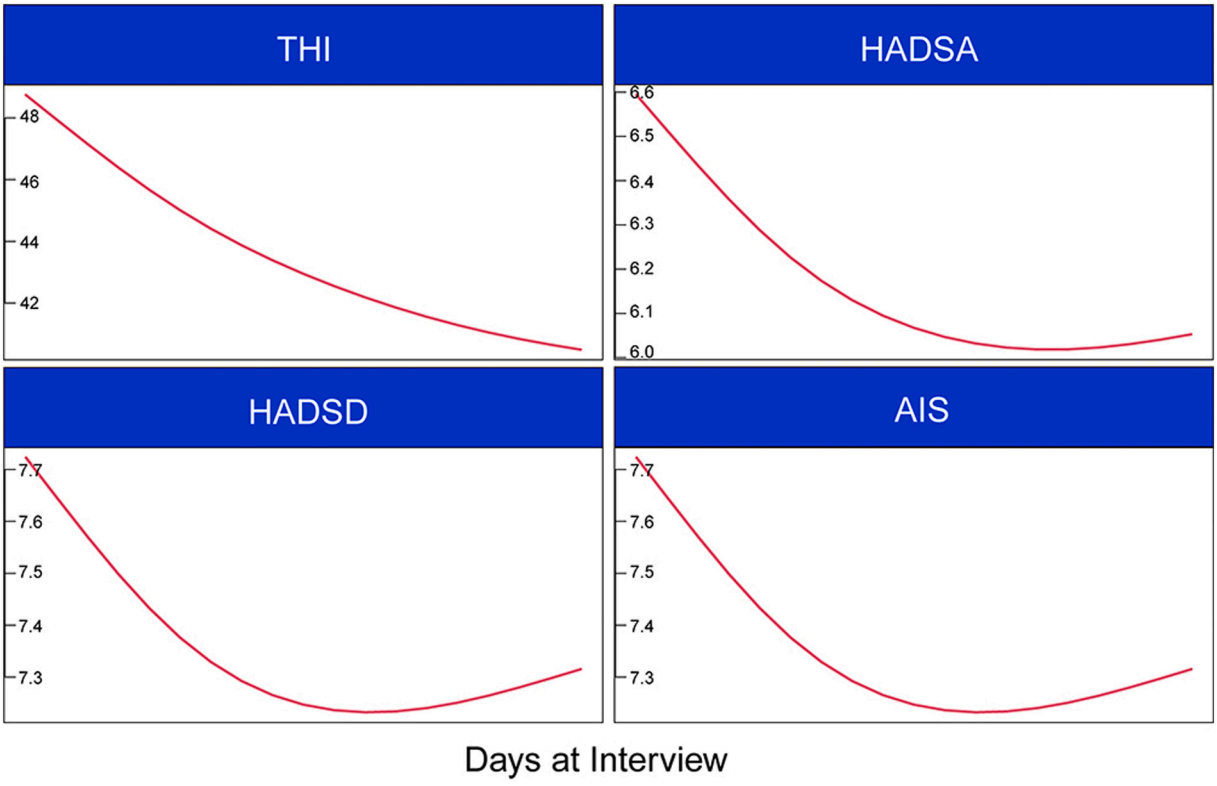


Fig. 6. Correlation graph of the sound treatment time for the different scales. The y-axis is the mean score of the THI, HADS-A, HADS-D, and AIS, and the x-axis is the number of days of sound therapy. There were significant negative correlations between the scores and follow-up time for the THI, while HADS-A, HADS-D, and AIS showed a rising trend after about 100 days.

A systematic review included tinnitus sound therapy apps based on a web-based survey of patient opinions (Sereda et al., 2019), which reflects the high acceptance of usage of apps. Our study showed statistically significant differences in the perceived intensity of tinnitus and its impact on quality of life after using sound therapy based on the FTRS app. It is more flexible and portable than sound generators, and because it can be updated and modified, patients can more easily customize the sound therapy music fitting their own needs and tinnitus features. In addition, the app is free, and we are continuously collecting feedback from patients in order to improve the user interface and process and to create a better interactive experience, which also helps to expand the number of users and helps achieve better results.

It should be noted that participants may undergo a "placebo effect", that is to say, some people may think that as long as clinicians pay attention to their tinnitus then sound therapy or anything else will help them anyway. Such a situation was reported in a previous study, which also showed that participants recruited from a website were willing to try anything to reduce the prominence of their tinnitus (Tyler, 2012). Before initiating a study, clarifying the importance of continuous sound therapy with patients and offering patients the experience of different treatment methods before participating in sound therapy might avoid this placebo effect.

It is notable that the population of patients completing the continuous follow-up process was relatively small mainly due to the consideration of user's convenience and compliance during app development, and they were not required to fill out the multi-dimensional tinnitus evaluation scale, which resulted in the loss of follow-up data. In addition, the duration and frequency of follow-up time points were different among patients. For example, some users filled out the questionnaires at an interval of several months to one year beyond 3 months, resulting in the loss of a number of users with continuous follow-up data. In the future, we will encourage more doctors to use the FTRS app for tinnitus matching, sound therapy, follow-up evaluation, and other functions in order to improve this loss of follow-up situation and thus provide more data to support the use of the mobile phone app to explore the efficacy of tinnitus treatment and chronic disease management.

5. Conclusion

The multi-dimensional standardized questionnaires showed that the FTRS app helps to reduce the severity of tinnitus and that it is also effective for patients with severe tinnitus. In addition, the quality of life of patients was greatly improved. In order to determine if this app can have long-term efficacy in patients, future studies should focus on long-term follow-up and should explore the relationship between treatment duration and symptom improvement.

CRediT authorship contribution statement

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

Declaration of competing interest

The authors declare that no conflict of interest exists.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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