Tinnitus-related fear

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Research Paper

Tinnitus-related fear: Mediating the effects of a cognitive behavioural specialised tinnitus treatment

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ABSTRACT

Objective: Cognitive behavioural treatments (CBT) for the reduction of tinnitus complaints have been shown to be effective; however the specific mechanisms of change are yet to be unveiled. Reductions in tinnitus-related fear have been indicated to be an important factor in alleviating tinnitus suffering. The role of tinnitus-related fear has been proposed as a mediator explaining the cognitive behavioural treatment effects on tinnitus severity, tinnitus-related impairment and general quality of life of tinnitus patients.
Methods: A two-group, single-centre RCT was carried out with adult tinnitus patients ($n = 492$), with 3 follow-up assessments up to 12 months after randomization. Patients were randomly assigned to Usual Care (UC) or Specialised cognitive behavioral stepped Care (SC). A repeated-measures design, with group as a between subjects factor, and time as the within-subject factor, was used in an intention-to-treat analysis. Mixed regressions for assessing mediation effects were performed with general health, tinnitus distress, tinnitus related impairment as the dependent variables and tinnitus related fear as the mediator variable.
Results: Tinnitus-related fear appears to mediate part of the treatment benefits of specialized CBT for Tinnitus, as compared to usual care, with respect to increased quality of life ratings, and decreased tinnitus severity and tinnitus related impairments.
Conclusions: The effectiveness of specialized cognitive behavioural treatment approaches for tinnitus might be partly explained by significant reductions in tinnitus-related fear. These results are relevant in that currently, though CBT approaches in tinnitus management have been proven to lead to decreased suffering of tinnitus patients, the psychological mechanisms causing these benefits are still to be discovered.

1. Introduction

Up to 21 percent of the adult population is at one point in life bothered by tinnitus, an internally generated noxious sound (Krog et al., 2010). Most people habituate to the tinnitus fairly easily, though for an unfortunate few it becomes a continuous pernicious perception, negatively impacting all aspects of daily living. (Cima, Vlaeyen, Maes, Joore and Anteunis, 2011b; Erlandsson and Hallberg, 2000). Chronic tinnitus is often accompanied by severe anxiety, depression, insomnia, and concentration problems (Langguth et al., 2011). Severe tinnitus complaints often coincide with distressing catastrophic thoughts, and though suicide is rare, suicidal thoughts are common amongst severe sufferers (Pridmore et al., 2012; Javaheri et al., 2000). Psychological distress as a result of the tinnitus are most troubling in patients and are considered the key factors in predicting the level of tinnitus suffering and the decrease in quality of life (McKenna et al., 2014; Andersson and Westin, 2008; Erlandsson and Hallberg, 2000; Hallam et al., 2004).

Evidence corroborates cognitive misinterpretations, negative emotional reactivity, maladaptive behavioral responses and

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dysfunctional attentional processes are of main importance in predicting dysfunctional tinnitus habituation, leading to the severe tinnitus condition (Andersson et al., 2006; Cima, Crombez and Vlaeyen, 2011a; Erlandsson and Hallberg, 2000; Handscomb et al., 2016; Kleinstauber et al., 2012; McKenna et al., 2014). Conversely, the psychoacoustic parameters (i.e. the audiometric properties, such as loudness or pitch) of the subjective tinnitus-perception hardly predict annoyance of the tinnitus or impact of tinnitus on daily living (Andersson, 2003; Hiller and Goebel, 2006, 2007; Hiller and Haerkötter, 2005).

Considering these cognitive behavioural mechanisms, cognitive-behavioural accounts for tinnitus have been postulated (Cima, Crombez and Vlaeyen, 2011a; Hallam et al., 1984; Kleinstauber et al., 2012; McKenna et al., 2014; Hesser, 2013; Jastreboff et al., 1996) and the merits of Cognitive Behavioural Treatments (CBT) for tinnitus have shown to decrease tinnitus disability and distress for a large group of patients (Cima et al., 2014; Hesser et al., 2011; Hoare et al., 2011). However, the underlying processes of change, targeted by these CBT methods and hypothesized to be the cause of therapeutic changes, are much less investigated (Andersson and Westin, 2008; Vlaeyen and Morley, 2005). Below, we briefly describe 4 theoretical models explaining chronic tinnitus distress: namely the habituation model, the neurophysiological model, the cognitive model, and the fear-avoidance model and conceptual overlap and differences.

One of the first cognitive behavioural accounts for tinnitus might be the habituation-model proposed by Hallam et al. (1984). Hallam suggested that the negative interpretation of the signal, and related heightened autonomic arousal levels would lead to dysfunctional cognitive processing and therefore would disrupt habituation. Research to date indicates mixed evidence in support of the habituation model (Baguley et al., 2013). Hallam's model partly inspired Jastreboff (Jastreboff, 1990; Jastreboff et al., 1988a), who postulated that classical conditioning explained the association between tinnitus and aversive emotional states. Classical (or Pavlovian) conditioning (Pavlov, 1927) refers to a process whereby two stimuli, a neutral and a biologically relevant one, are presented contingently (famously illustrated by the dog, presented with both a bell and meat-powder). Repetitive presentations of these stimuli will lead to an organism to learn that the two stimuli, previously unrelated, are associated (i.e. 'if bell, then meat'). Subsequent presentations of the originally neutral stimulus alone (the bell, which is the conditioned stimulus), even without the meat (the unconditioned stimulus), proved to suffice to trigger the same response (salivating, which is the conditioned response).

The neurophysiological model (NP-model) for chronic tinnitus is based on the premise that classically conditioned fear-responses elicited by the tinnitus-stimulus are the cause of the tinnitus becoming bothersome (Jastreboff, 1990; Jastreboff and Hazell, 1993). The hypotheses were tested in animal research, in which conditioning paradigms were used to induce tinnitus-like fearful behaviour in rats (Jastreboff et al., 1988a; b). The NP-model distinguishes 3 stages: 1. generation of the auditory stimulus in the auditory periphery; 2. detection of the tinnitus-related signal; 3. perception-evaluation of tinnitus. The NP model is mainly a model of tinnitus generation/detection, based on neurophysiological mechanisms, and the hypotheses concerning the processes of change to target are aimed at the first to stages, the generation and perception of the tinnitus-signal.

An alternative conceptual "cognitive" model was recently proposed by McKenna and colleagues (McKenna et al., 2014). The model is based on a cognitive model of distress to explain insomnia (Harvey, 2002), and purports that it is mainly the negative cognitive misinterpretations of the tinnitus-signal which provoke distress and bodily arousal, leading to mis-evaluations of sensory activity and distorted perceptions. It is proposed that the resulting stress and hypervigilance exacerbates the distress associated with flawed sensory processing; of which tinnitus may be a major component. The model attributes a fundamental role to the negative evaluation of tinnitus. Clinical trials in which this model is applied to treatment have not taken place yet. However, supporting evidence exists that cognitive processes, such as catastrophic interpretations (Weise et al., 2013; Cima, Crombez and Vlaeyen, 2011a), attention and memory, are indeed involved in chronic tinnitus suffering (Andersson, Hesser, Cima and Weise, 2013; Rossiter, Stevens and Walker, 2006; Stevens, Walker, Boyer and Gallagher, 2007), though these studies were not specifically aimed at validating the model.

Fear-related safety-seeking behaviours have been postulated to be of key importance as well in explaining increased suffering in tinnitus patients. Evidence has been found that the tendency to avoid so-called 'unsafe' stimuli or events because of the tinnitus, mediates the association between tinnitus severity and quality of life (Westin et al., 2008a; b; Westin et al., 2011). This was corroborated in a study, which showed that fear of bodily sensations was strongly related to tinnitus distress, again fully mediated by tinnitus-related avoidance behaviours (Hesser and Andersson, 2009). Additionally, a study where 'acceptance', which is defined as a willingness to experience inner sensations without engaging in controlling or avoiding behaviours (Hayes et al., 1999), was found to predict processes of change in an Acceptance and Commitment Therapy (ACT) approach as well as a more traditional CBT approach (Hesser et al., 2014). It was shown that the ability to pursue activities of value ('activity engagement'), did indeed mediate the positive effects of both ACT and CBT (Hesser, Westin and Andersson, 2014). These results seem to support the idea that the less the individual is engaging in safety-seeking, i.e. controlling or avoiding certain behaviours, the more positive the outcome.

These findings indicate tinnitus-related fear and consequent behavioural avoidance behaviour as important mechanisms, possibly explaining why in some but not all patients, severe tinnitus suffering is such a persistent condition. Indeed, it has been indicated earlier that tinnitus-related fear has a mediating role in explaining decreased quality of life (Cima et al., 2011a). Interestingly, fear and fear-related safety-seeking behaviours are seen as a key mechanism in chronic pain suffering, and parallels between chronic pain and tinnitus have been suggested repeatedly (Cima et al., 2011; Folmer et al., 2001; Jastreboff, 1990; Tonndorf, 1987). Both chronic pain and chronic tinnitus conditions cannot be understood on biomedical grounds only, complete recovery is very rare, and complaints unfortunately persist over long periods of time. The fear avoidance (FA) model of chronic pain predicts that, if pain is (mis-) interpreted as threatening, it will elicit specific pain-related fear associated with protective escape and avoidance behavior (Crombez et al., 2012; Leeuw et al., 2007; Vlaeyen and Linton, 2000, 2012). These safety-seeking behaviors may be helpful in the short-term, but worsen the problem in the long run by increasing disability and negative mood (Gheldof et al., 2010). There is ample empirical support for the role of pain-related fear in the development and maintenance of the suffering of patients with chronic pain, both experimentally as well as clinically (Asmundson et al., 1997; Crombez et al., 1999; Dawson et al., 2011; de Jong, Vlaeyen, Onghena, Goossens, et al., 2005b; den Hollander et al., 2010; Gheldof et al., 2010). Moreover, previous evidence seems to indicate that pain-related fear acts as a mediator on the association between pain severity and negative affect (Gheldof et al., 2006), explains why women but not men report more pain intensity, and pain unpleasantness (Meulders et al., 2012), and fear of pain might explain why some individuals experience more pain intensity and unpleasantness (Meulders et al., 2016).

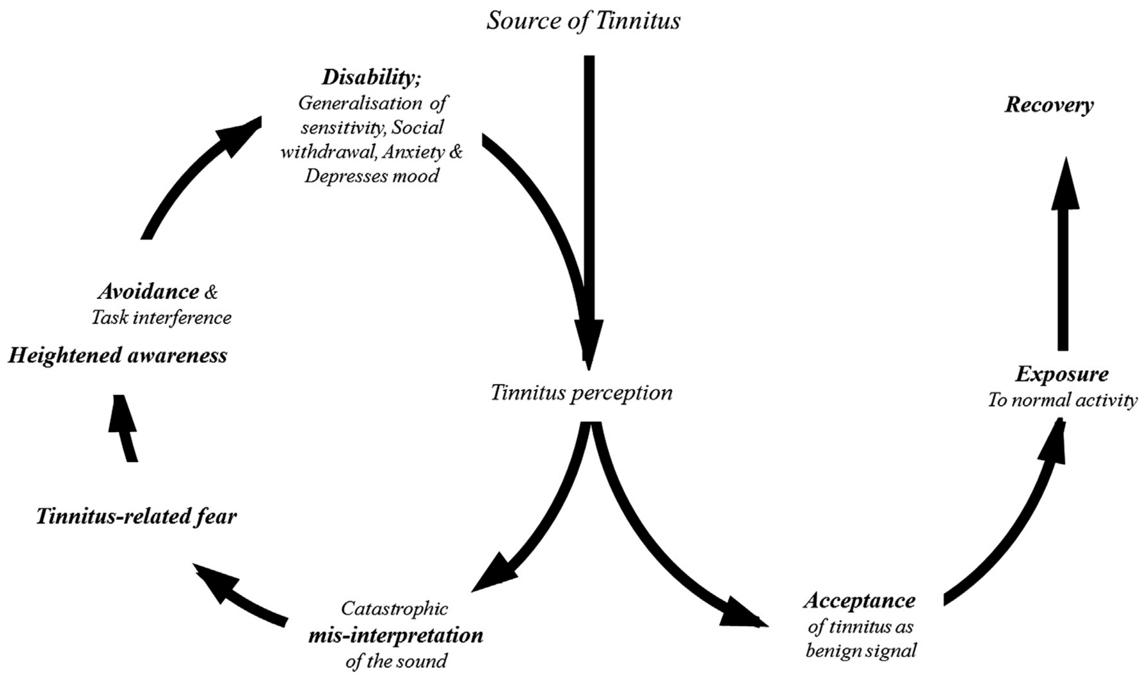


Fig. 1. The fear-avoidance model for bothersome tinnitus (based on Vlaeyen & Linton 2000).

A fear-avoidance model (FA-model) for bothersome tinnitus (Cima et al., 2011a; Kleinstauber et al., 2012), offers predictions about the behavioural components in the maintenance of tinnitus-disability. Additionally, the FA-model (Fig. 1) for tinnitus offers explanatory predictions about both the cognitive processes, as well as the behavioural mechanisms. It predicts that individuals perceiving the tinnitus-signal are subject to automatic emotional and sympathetic responses. These symptoms are misinterpreted as harmful or threatening. If the signal persists, the coinciding threatening (alarm) states, which indicate malignance of the signal, elicit conditioned, both classical and operant, fear-responses, (i.e. fear and increased attention), and safety seeking, (i.e. avoidance and escape behaviours). These safety-seeking behaviours become negatively reinforced through instant decreased fear, which is adaptive in the acute phase. In other words, by avoiding, or not exposing themselves to tinnitus-related perceptions, patients learn that their fear instantly diminishes. However in the long run, through persistent avoidance of the tinnitus, as well as tinnitus-eliciting, or tinnitus-increasing stimuli, the heightened fear and fear-responses, such as hypervigilance and safety-seeking, are maintained. Avoidance behaviours subsequently may lead to task interference and functional disability (Blaesing and Kroener-Herwig, 2012; Hesser et al., 2009). The maintained high threat-value of the tinnitus leads to increased tinnitus-severity and distress, feeding into an endless circle of increased disability (Cima et al., 2011b).

A typical feature of the FA-model for bothersome tinnitus is that it predicts, next to the maladaptive pathway (leftward), an alternative, and more adaptive pathway (turning right), whereby a positive or neutral evaluation of the tinnitus results in no- or low fear of the tinnitus, and no or lowered distress. In other words, following the model to the right, the tinnitus sound is 'accepted' by the system as being benign. Therefore, no unwanted attentional resources are needed; daily tasks are approached rather than avoided, with swift recovery as the outcome.

Accumulating evidence indicates that exposure to the tinnitus-sound, which is a cognitive-behavioural treatment, leads to reappraisal or significantly reduces tinnitus-distress, and improves daily functioning and quality of life in tinnitus-patients (Andersson, 2002; Andersson and Lyttkens, 1999; Andersson et al., 2002; Cima et al., 2012; Hesser et al., 2011; Hoare et al., 2011; Martinez-Devesa et al., 2010). However, the cause-effect relationships of specific learning-mechanisms are still unknown (Cima, Crombez and Vlaeyen, 2011a; Henry et al., 2005; Kleinstauber et al., 2012).

In the current study we tested whether aversive reactions as a result of the tinnitus perception, and tinnitus-related fear in particular might be indeed the key factor in predicting tinnitus disability and its impact on daily living. We expect that tinnitus-related fear might not only be the mediating factor in the maintenance of chronic tinnitus distress, but its reduction could also explain the beneficial effects of CBT on tinnitus severity, tinnitus related impairment and quality of life, as was shown in a recent RCT (Cima et al., 2012). The effectiveness of this *Specialised CBT for Tinnitus* (CBT4T)[1] was demonstrated by improved quality of life, decreased tinnitus severity and daily life impairment by tinnitus as compared to the treatment as usual. Moreover, the CBT4T generated greater improvements in co-morbid anxiety and depression, level of tinnitus-related cognitive impairments, and tinnitus-related fear (Cima et al., 2012). The CBT4T mainly focussed on Exposure-treatment, in combination with cognitive restructuring methods, applied relaxation, movement exercises, and stress-relief techniques with use of elements from Acceptance and Commitment and Mindfulness (Bailey et al., 2010).

2. Methods

In the present study, data were used obtained from an earlier randomized controlled study, in which the effectiveness of CBT4T (Specialised Care = SC) was compared to usual tinnitus care (UC)

[1] This specialised CBT for tinnitus included audiological diagnostics and counselling, and was organised in 2 steps, increasing the level of treatment intensity as complaints were more severe (Von Korff and Moore, 2001).

(Cima et al., 2012). Brief descriptions of the study design, participants, intervention procedures, outcomes, and statistical procedures, relevant for the present study, are provided below.

2.1. Study design

A two group, 2- stepped care, single-centre randomized controlled trial was carried out with adult tinnitus patients, with 3 follow-up assessments up to 12 months after randomization, with a no-contact period in the last 4 months in the trial, between follow up 2 and follow up 3. Tinnitus patients referred to our specialised tinnitus centre were, after screening, invited to participate during a time period of 16 months. Patients willing to participate were invited for a first off-centre assessment contact, after which they were randomly allocated to either to Usual Care (UC) or Specialised Care (SC). See Fig. 2 for the trial profile of the flow of participants.

2.2. Participants

Patients referred to our centre who reported subjective tinnitus complaints, aged 18 years and older, were eligible for inclusion. After screening, patients were excluded when unable to read and write in Dutch or when medical conditions prevented them to participate. Also excluded were patients who visited our centre within 5 years prior to trial enrolment. An ENT physician assessed all patients before entering the trial, and examined the presence of acute audiological conditions, requiring immediate medical care. Written informed consent was obtained before assessment and trial entry and both patients and assessors were blinded for treatment allocation.

2.3. Intervention procedures

2.3.1. Care as usual (UC)

The Usual Care procedure entailed a standardized protocol modelled after the average care as is usually provided by secondary care audiological centres across the Netherlands. Step-1 of UC treatment consisted of a standard audiological intervention (sound-generators were prescribed when specifically asked for by the patient). For patients with mild complaints, treatment ended after step 1, and they remained in the trial without additional treatment. In case tinnitus suffering was more severe (as measured at baseline and after audiological counselling); patients were advised to enter a second step of treatment for 12 weeks maximally (Cima et al., 2012). The Usual care step 2 treatment consisted of counselling sessions with a social worker focused on coping strategies, work-related problems and daily structuring.

2.3.2. Specialised Care (SC)

Specialised Care (or CBT4T) consisted of comprehensive multidisciplinary audiological and psychological diagnostics and CBT4T. Step 1 treatment consisted of an audiological and psychological assessment and primary counselling, carried out in a cognitive behavioural framework (including audiological rehabilitation when necessary). For patients with mild complaints this basic intervention was expected to suffice, and they were measured for follow-ups only and remained in trial without extra care. When tinnitus suffering was more severe (as measured at baseline and after psychological screening), patients could enter step 2 treatment, which consisted of three different 12-week CBT4T group-treatment options (Cima et al., 2012).

2.4. Outcomes

2.4.1. Stratification assessment

To assess *hearing impairment* pure tone audiometry was performed bilaterally on 1, 2, and 4 kHz, using a mobile audiometer (Interacoustics AS208) with audiometry headphones (Telephonics TDH-39, Peltorcapped) and the pure tone average (PTA) for 1, 2 and 4 kHz (stratification cut-off point at 60 dB hearing level in worst ear) was calculated. The Tinnitus Questionnaire was used to assess *Tinnitus-severity* at baseline (stratification cut-off point at a score of 47) (Rief et al., 2005).

2.4.2. Outcome measures

The HUI mark III is a 17 item questionnaire to assess *Health related quality of life or Generic Health* on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Each question has five or six levels, and 972.000 possible health states can be computed. Possible utility scores range from $-0{\cdot}36$ to $1{\cdot}00$ (Feeny et al., 2002) for the HUI mark III. The HUI has shown adequate responsiveness in the tinnitus population (Maes et al., 2011). *Tinnitus severity* or distress due to the tinnitus was assessed with the Tinnitus Questionnaire (TQ) (Hallam et al., 1988). The TQ consists of 52 items rated on a 3-point scale and assesses the psychological distress associated with the tinnitus. Psychometric properties of the TQ have proven excellent in different languages (Baguley et al., 2000; McCombe et al., 2001). The tinnitus handicap inventory (THI) is a 25-item instrument scored on a 3 point Likert scale. The THI assesses *Tinnitus related impairment*, or negative responsiveness as a result of the tinnitus on 3 domains; functional, emotional and catastrophic (Newman et al., 1996). Both overall and subscale internal consistency were found to be good (Newman et al., 1998). The Fear of Tinnitus Questionnaire (FTQ) measures *Tinnitus-related fear*. In the development of this novel measure, items were included that were believed to capture worries and fears of patients experiencing tinnitus (see appendix A for all FTQ items). Some of the FTQ items were derived from the Tampa scale for Kinesiophobia (Roelofs et al., 2007) and the Pain Anxiety Symptoms Scale (McCracken et al., 1992). The FTQ was pretested on a patient-sample in an earlier study with excellent reliability (Cima et al., 2011a). The FTQ has 17 items to be rated on a true or false scale. Internal consistency of the total FTQ score in the current sample was excellent as well (Cronbach's alpha = ·82). *Demographic data* were gathered by means of a 5-item questionnaire to establish gender, age, duration of complaints, educational level and residence.

2.5. Statistical analysis

All statistical analysis were performed with SPSS statistical software, version 24·0 (SPSS, 2016).

2.5.1. Treatment outcome: intention-to-treat analyses

Intention-to-treat analyses were employed. That is, all patients who were measured at baseline and allocated to treatment initially were included, irrespective of their participation in subsequent treatment or follow up measurements. A series of mixed (multilevel) regression analyses was carried out on all available data, using maximum likelihood estimation without imputation of missing data. The outcome measures were used as dependent variables in a repeated measures mixed regression analysis with group (UC, SC) as the between-subject factor and time (Baseline, follow up 1, follow up 2 and follow up 3) as the within-subject factor. Age, gender, education, and the stratifiers were included as covariates to increase statistical power. Since duration of complaints was a potentially relevant prognostic variable, this was

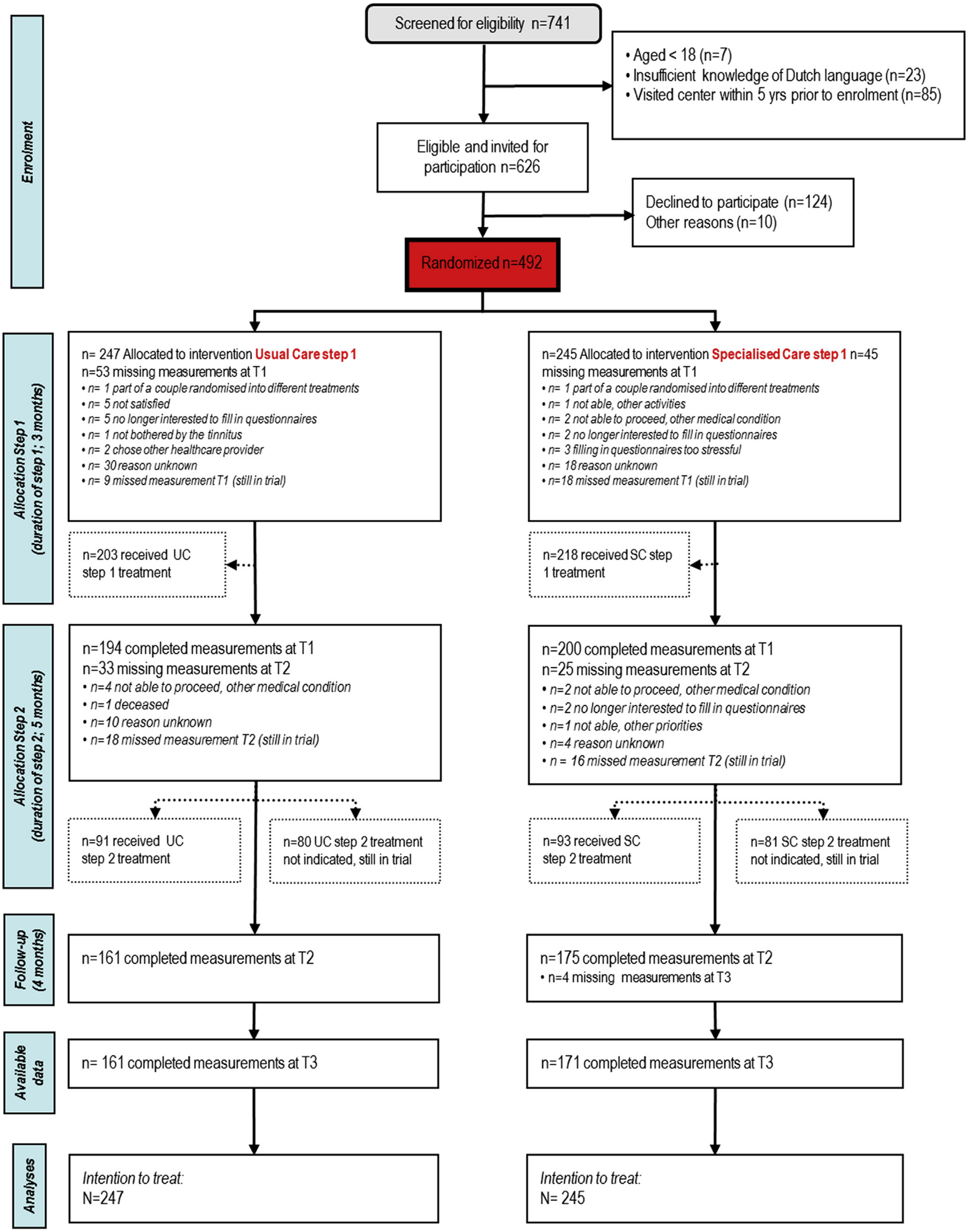


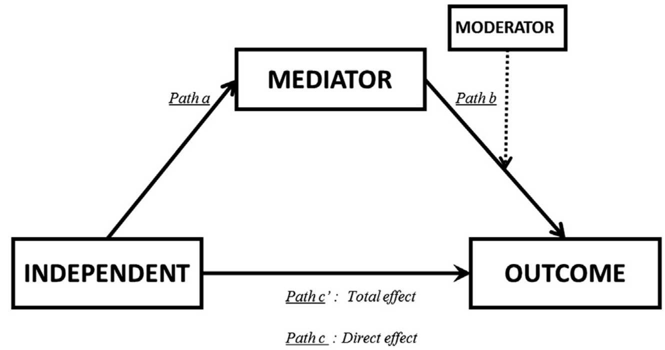
Fig. 2. Consort flow chart.

added to the model as well.[2] Further, the initial mixed model also included quadratic effects of the quantitative covariates age and duration of complaints, and interactions of group and of all covariates with time. The set of interactions of age, gender, education and duration with time was deleted from the model if not significant according to a likelihood ratio (LR) test of the model with versus without these interactions, using $\alpha = 0.05$ (for details of LR testing in mixed models, see Verbeke and Molenberghs, 2000). The same procedure was subsequently applied to the interactions of the stratifiers with time, and to the quadratic effects of age and duration. Further, the effect of time was modelled using dummy indicator coding with baseline as reference category and a dummy per time point to allow nonlinear change within each treatment group. However, for the interaction of group with time, time was included as a single quantitative factor coded 0, 1, 2, 2 for the respective time points in view of the finding in the original effect publication (Cima et al., 2012) that the outcome difference between groups increased linearly from baseline through 3 months to 8 months and then became stable from 8 to 12 months. The group by time interaction of interest was thus represented by a single regression parameter. This model reduction was validated by a LR test of it against the model with dummy coding of time for main as well as interaction effects of time. Throughout these analyses, an unstructured covariance matrix for the repeated outcome measures was assumed (i.e. allowing the outcome variance to differ between time points and the correlation between repeated measures to differ between pairs of time points). No valid reduction to a more simple structure such as compound symmetry or random intercept, random slope and autoregressive error was found.

2.5.2. *Mediating mechanisms*

Fig. 3 graphically represents the mediator model. To test whether changes in tinnitus-related fear mediated the treatment effect (SC versus UC) on the outcomes, we followed the joint significance test procedure of MacKinnon et al. (2002) which was shown by these authors to perform well in terms of type I error risk and power and consisted of two separate analyses. First, the effect of the treatment on the potential mediator tinnitus-related fear was tested, using the same mixed regression modelling procedure as before, but now with tinnitus-related fear (the FTQ) as an outcome variable. (Cima et al., 2012). Second, we tested the effect of the mediator tinnitus-related fear on the primary outcomes; general health, tinnitus severity, and tinnitus related impairment, controlling for treatment. This was done by adding the mediator FTQ to the final mixed models for the HUI, the TQ, and the THI as a time dependent (within-subjects) covariate. So the baseline mediator value served as a covariate for the baseline outcome measurement, the first follow up value of the mediator as a covariate for the first follow up of the outcome and so forth. This analysis also checked the presence of mediator by time interaction by adding the product term of mediator and time as predictor.

Joint significance holds if the associations between treatment and mediator in the first analysis (path a), and between mediator and outcome in the second analysis (path b), are both significant. Of course, interpreting such significance as evidence for mediation can only occur under the assumption that there are no hidden confounders affecting mediator and outcome simultaneously. This



Total effect = Direct effect + Indirect effect
c' = c + ab

Fig. 3. The mediator model.

assumption is actually made in all analyses of nonrandomized studies, and also in all analyses of randomized studies were a post-randomization variable (e.g. a mediator) is used as a predictor of an outcome measure.

A delay in effect of the mediator on the outcomes was investigated as well, by using the mediator value at time point t as well as the mediator value at time point $t+1$ as predictors of the outcome at time $t+1$ in the same mixed model, thereby preventing spurious correlation between the mediator at time t and the outcome at time $t+1$ due to their correlations with the mediator at time $t+1$. In these analyses only part of the data could be used since there is no mediator available for the outcome at baseline and there is no outcome available for the mediator at the last time point. So the baseline mediator value served as a covariate for the first outcome measurement, the first follow up value of the mediator as a covariate for the first and second follow up of the outcome, and so forth.

A moderating effect of step 2 treatment (i.e. whether or not patients actually had received treatment in the 2nd step or not after follow up 1) on the mediating role of fear was investigated, by repeating the mediation analyses on the outcomes HUI and THI, and adding as predictors the moderator itself and the interaction term (moderator x mediator) to the final model of the mediation analysis (Emsley et al., 2010).

Finally, to check the correlational pattern of outcome and mediator over time and to test reverse causation (from outcome to mediator), bivariate mixed regression models were run following the method proposed by Bauer, Preacher and Gil (2006), with the outcome and mediator as two dependent variables.

3. Results

Results obtained in the earlier RCT, the flow of participants and the treatment outcome analyses, which are relevant for current analyses, are described briefly below first (Cima et al., 2012).

3.1. *Flow of participants and treatment outcome analyses*

Of the 741 participants who were screened for eligibility, 626 were invited for participation, and 492 completed baseline measurements and were then randomized to treatment step-1; of whom 247 were allocated to UC, and 245 to SC treatment. Randomization and allocation started in September 2007 and ended in December 2009. Follow-up measurements were completed in January 2011.

Non-response and drop-out rates per time point did not differ

[2] Categorical covariates were entered in the model using dummy coding, for Gender: 0 = male, 1 = female; Education dummy 1: 0 = low, 1 = middle, 0 = high; education dummy 2: 0 = low, 0 = middle, 1 = high. Each quantitative covariate was first entered centred (Cov − sample mean = CovCen), and subsequently we added its square (CovCen * CovCen = CovCen2) to the model to assess possible nonlinear effects of the covariates on the outcomes.

between groups ($\alpha = \cdot 01$, $p > \cdot 20$ on any of the time points, and did not appear to be related to demographics or outcomes, according to logistic regression per time point, using non-response and drop-out per time-point (0 = not missing, 1 = missing) as the outcome variable, and treatment group, all covariates (age, gender, education, duration of complaints, tinnitus-severity at baseline and hearing loss) and scores on the HUI, the TQ and the THI on the previous time-point as independent variables. Table 1 presents a summary of demographic characteristics of the study sample.

Table 2 displays the observed means and standard deviations of the HUI, the TQ, the THI, and the FTQ for all 4 time points (baseline, follow up 1, 2, and 3). Table 3 shows the estimated group differences, more specifically, the regression weight of the group by time interaction term, as well as the confidence intervals and effect sizes for all follow up measurements, based on the final mixed model for each outcome, which included no covariate by time interactions or quadratic effects of age or duration of complaints, as these effects were never significant for any outcome.

3.2. Mediation by tinnitus-related fear

It has been already shown that there was a significant treatment effect on the presumed mediator, tinnitus related fear (path a), as SC treatment was more effective in reducing tinnitus related fear than UC treatment (see Table 3). With respect to the relationship between fear of tinnitus as the mediator and the primary outcomes (HUI, TQ and THI), controlling for the SC-treatment effects on all 3 follow up assessments, we found a mediating effect of tinnitus related fear on all three primary outcomes ($p < 0.001$ for all three), and almost half of the total treatment effects as shown in Table 3 (paths c'), were mediated by tinnitus related fear (42, 50, and 48% for HUI, TQ and THI respectively) and the remaining parts were direct effects (paths c). Table 4 gives the path coefficients (a, b, c and c') for each of the three primary outcomes. This mediating effect was not moderated by time ($p > 0.40$ for the mediator by time interaction for all outcomes) and the effects reported above and in Table 4 are therefore based on the model without that interaction. As said before, interpreting the relations between tinnitus related fear and the other three outcomes as mediation rests of course on the assumption of a specific causal model (as in Fig. 3) and absence of hidden confounding.

3.3. Delayed mediation by tinnitus-related fear

After we found a cross-sectional mediating effect of tinnitus-related fear on the HUI, the THI and the TQ, the mediation analyses were repeated with FTQ at the same time point and at the previous time point as simultaneous predictors of TQ resp. THI resp. HUI to investigate delayed mediating effects of tinnitus-related fear on quality of life, tinnitus-related impairment, and tinnitus severity, controlling for cross-sectional effects. So in this model the mediator measures at t and $t+1$ were used as predictors for the outcome at $t+1$. Consequently, the baseline outcome recording was left out and so was one time indicator dummy. A delayed effect of fear of tinnitus was not found for health related quality of life (HUI, $p > 0.90$), but was found for tinnitus related impairment (THI) and for tinnitus severity (TQ) (both $p < 0.001$), although the effect was much smaller than the cross-sectional effect, that is, about 25% of the cross-sectional effect for TQ and 16% for THI.

3.4. Moderated mediation of tinnitus-related fear

We tested whether the mediation of treatment effects on HUI, TQ and THI by tinnitus related fear was moderated by whether or not participants received step 2 treatment after the first follow-up. by including as moderator the indicator for step 2 care and its interaction with the mediator. The moderator was coded as (0,0,1,1) on the four successive time points for patients receiving step 2 care after the first follow-up and as (0,0,0,0) else, irrespective of treatment condition, i.e. for both UC and SC. Moderated mediation was not found for the HUI ($p > 0.80$), but was found for the THI ($p < 0.001$) and possibly also for the TQ ($p = 0.017$). However, the mediator effect was of the same sign and similar magnitude for those with step2 care as for those without (2.3 versus 3.0 for THI, 2.8 versus 3.1 for TQ). For simplicity this moderation was therefore ignored in the final bivariate mixed regression.

Table 1
Summary of demographic characteristics, baseline mean values on primary and secondary outcome measures, tinnitus characteristics, and audiometric data of the all participants, and for each group separately.

	Total (n = 492)		UC (n = 247)		SC (n = 245)	
Age in yrs (SD)	54.19 (11.54)		54.63 (12.02)		53.74 (11.05)	
Gender (% male)	62.6		60.7		64.6	
Education (%)						
Low	45.7		47.3		44.0	
Middle	27.7		24.5		30.9	
High	26.6		28.2		25.1	
Employment (% yes)	53.4		50.2		56.6	
Duration (%)						
less than 1 yr	29.9		32.7		27.2	
1–5 yrs	38.9		37.9		39.9	
more than 5 yrs	31.1		29.4		32.9	
Mild complaints TQ < 47 (%)	45.5		45.3		45.7	
Tinnitus sound: pure tone (%)	14.5		9.9		17.8	
Tinnitus left (ear/head) (%)	25.0		24.8		25,2	
Tinnitus right (ear/head) (%)	19.9		19.6		20.1	
Continuous tinnitus (%)	83.9		83.3		84.5	
Interval tinnitus (%)	6.9		3.0		10.7	
Fitting of hearing aid (% yes)	18.5		18.2		18.6	
Fitting of sound generator (% yes)*	18.9		18.6		19.2	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
PTA right ear	29.74	19.40	30.30	20.58	29.18	18.15
PTA left ear	31.05	20.64	30.96	20.25	31.14	21.06
PTA bilateral	30.57	17.60	30.77	17.85	30.37	17.38

UC = Usual Care, SC = Specialized Care, PTA = Pure tone average (for 1, 2 and 4 kHz) *Sound generators were fitted by using a small band noise around the Pitch Match Frequency presented slightly below the tinnitus masking level (UC), or just above the hearing threshold, as measured with the small band noise of the sound generator (SC).

Table 2
Observed means and standard Errors (SE) based on all available data for the outcomes at baseline, follow up 1 (after step 1, 3 months after baseline), follow up 2 (after step 2, 8 months after baseline) and follow up 3 (4 months follow up, 12 months after baseline).

Outcome Measures	Baseline UC (n = 247) Baseline SC (n = 245)		Follow up 1 UC (n = 194) Follow up 1 SC (n = 200)		Follow up 2 UC (n = 161) Follow up 2 SC (n = 175)		Follow up 3 UC (n = 161) Follow up 3 SC (n = 171)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Health related QoL (HUI)								
UC	0.641	0.019	0.640	0.021	0.634	0.023	0.631	0.022
SC	0.628	0.018	0.620	0.019	0.656	0.019	0.681	0.019
Tinnitus Severity (TQ)								
UC	48.87	1.22	45.51	1.41	42.36	1.55	42.12	1.56
SC	49.39	1.18	42.01	1.40	36.47	1.32	33.43	1.29
Tinnitus impairment (THI)								
UC	38.73	1.48	37.38	1.71	34.14	1.95	33.51	1.84
SC	39.25	1.45	34.25	1.66	28.85	1.55	26.45	1.45
Tinnitus related fear (FTQ)								
UC	7.32	0.23	6.60	0.27	6.19	0.32	6.04	0.32
SC	7.19	0.23	5.60	0.27	4.52	0.26	4.20	0.24

QoL = Quality of life. UC = Usual Care. SC = Specialized Care. SE = Standard Error. HUI = Health utilities index. TQ = Tinnitus questionnaire. THI = Tinnitus handicap inventory. FTQ = Fear of tinnitus Questionnaire.

Table 3
Estimated Group difference (B) and 95% confidence intervals (C.I.) on outcomes at follow up 1 (3 months), follow up 2 (8 months), and follow up 3 (12 months), based on intention to treat analysis and using the models intended to perform current mediator-moderator analyses.

Primary outcomes	B	95% C.I.		P	E.S. (absolute values)
Health related QoL (HUI)[a]					
3 months	0.028	0.007	0.047	0.01	0.11
8 and 12 months	0.056	0.014	0.094	0.01	0.22
Tinnitus Severity (TQ)					
3 months	−3.767	−5.036	−2.498	<0.0005	0.20
8 and 12 months	−7.534	−10.072	−4.996	<0.0005	0.40
Tinnitus impairment (THI)					
3 months	−3.752	−5.286	−2.217	<0.0005	0.22
8 and 12 months	−7.504	−10.572	−4.434	<0.0005	0.44
Tinnitus related fear (FTQ)					
3 months	−0.716	−1.026	−0.406	<0.0005	0.23
8 and 12 months	−1.432	−2.052	−0.812	<0.0005	0.46

QoL = Quality of life. UC = Usual Care. SC = Specialized Care. SD = Standard Deviation. HUI = Health utilities index. TQ = Tinnitus questionnaire. THI = Tinnitus handicap inventory. FTQ = Fear of tinnitus Questionnaire.
[1] Since UC is coded as 0 and SC as 1. a negative B shows lower scores in UC than SC at the follow up measurements. The B's displayed are the group * time effects. where time = 0 for baseline· time = 1 for follow up 1, time = 2 for follow up 2. and time = 2 for follow up 3.
[2] E.S. = Effect size, calculated by dividing the B's (ignoring their sign) by the square root of the average of residual variances at follow up 1, 2 and 3, giving a mixed regression version of Cohen's d.
[a] Adjusted for the main effects of both stratifiers (hearing loss and, except for TQ, also tinnitus severity at baseline, and for the time effect (using dummy coding with baseline as reference category) and the main effects of age, gender, education and duration of complaints.

Table 4
Regression weights used to calculate paths a, b, c and c' of the mediation models for all three main outcomes.

Path	Term	HUI	TQ	THI
A (x to m)	Group*time	−0.7162	−0.7063	−0.7162
B (m to y)	Mediator	−0.0159	2.8557	2.4997
C = direct	Group*time	0.0156	−1.8759	−1.9543
C' = total	Group*time	0.0268	−3.7668	−3.7515

3.5. Bivariate mixed regression of outcome and mediator: bi-directional and delayed effects

Following the method of Bauer, Preacher and Gil (2006) mediation was finally assessed by bivariate mixed regression of each primary outcome and the mediator FTQ on baseline covariates, group, time and group by time, which allowed testing effects of mediator on outcome and vice versa, both cross-sectionally and time-lagged (i.e. delayed mediation). These analyses involved 8 repeated measures (4 of the outcome, 4 of the mediator), thus giving 8 variances and 28 correlations to model, making the unstructured covariance model of the univariate analyses impractical. The outcome was therefore rescaled to have the same variance as the mediator by multiplying the outcome at each time point with a factor $\sqrt{}$(mean outcome variance/mean mediator variance), where the mean was taken over the four variances. The resulting 8×8 covariance matrix of repeated measures could subsequently be approximated by a combination of a random intercept for the outcome and a random intercept for the mediator (allowing both intercepts to correlate) for the level-2 (between-subject) variance, with an ARMA11 structure for the level-1 (within-subject) variance.

A cross-sectional effect of the mediator on the outcome could be included into this model and was found to be significant for each outcome (HUI, TQ, and THI). Likewise, a reverse cross-sectional effect of the outcome on the mediator could be included and was found, but simultaneous inclusion of both effects led to nonconvergence, redundant (unidentifiable) parameters and bad model fit, and the same held for any attempt to let the effect of the mediator on the outcome vary randomly between persons, probably due to the rather high correlations between mediator and outcomes. The problem was resolved by moving to delayed mediation, leaving the baseline measurement out and including the mediator at time t and $t+1$ as predictor of the outcome at time $t+1$, and simultaneously including the outcome at time t and $t+1$ as predictor of the mediator at time $t+1$. This combination captured the cross-sectional and lagged correlations between outcome and mediator without requiring either an autoregressive model for the within-subject variance, or a correlation between the random intercepts for the between-subject variance, and did not give any convergence or identifiability problem. For the HUI, this model showed significant ($p < 0.001$) cross-sectional effects of similar size (i.e. about -0.30) in both directions, from mediator to outcome and vice versa, but no delayed effects ($p > 0.05$). For the TQ, the model showed a cross-sectional as well as delayed effect of the mediator on the outcome (effects 0.56 resp 0.17, both $p < 0.001$) but only a cross-sectional effect of the outcome on the mediator (effect 0.76, $p < 0.001$). Likewise, the THI showed a cross-sectional plus delayed effect of mediator on outcome (effects 0.51 resp 0.17, bot $p < 0.001$), but only a cross-sectional effect of outcome on mediator (effect 0.71, $p < 0.001$). In interpreting these effects remember that the outcome was rescaled to have the same variance as the mediator in these analyses, making the effects reported here standardized regression weights.

4. Discussion

The present study suggests that tinnitus-related fear plays a partially mediating role in the benefits of a specialized CBT for tinnitus (SC), when compared to usual tinnitus care (UC). Patients in the specialised CBT4T group increased their quality of life, decreased in tinnitus severity, and were significantly less impaired by their tinnitus, as compared to patients in the usual care group. They also showed less tinnitus-related fear, and including this fear as mediator into the outcome analyses reduced the treatment effect by almost 50%, thus suggesting partial mediation. Extending the model with the previous timepoint measurement of fear as mediator showed a delayed mediation effect on top of the cross-sectional effect for the TQ and THI but not for the HUI. These delayed effects were small compared with the cross-sectional effects, however moderation analysis furthermore showed that the mediating effect of tinnitus related fear on treatment effects as measured with the THI was different for patients who participated in step 2-treatment than for those who did not, but this moderation effect was relatively small. An even smaller moderation effect was also found for the TQ.

The lack of any moderated mediation effect on the HUI can perhaps be explained by the generality of this instrument as a measure of quality of life. This HUI might be less sensitive to pick up the more specific tinnitus-related mechanisms of change (Maes et al., 2011).

A final interesting finding, resulting from bivariate mixed regression, was that at least the cross-sectional effects between fear and the primary outcomes appear to be bidirectional, but that the delayed effects (which are much smaller) are 1-directional, from tinnitus related fear to the outcomes, and not vice versa. However, this finding deserves replication before drawing any firm conclusions.

In sum, decreased tinnitus-related fear may partly explain why the Specialized CBT4T significantly increased quality of life, and decreases tinnitus severity and impairment, when compared to the Usual Care treatment group, irrespective of whether patients were treated in step 1 only, or were treated with the additional step 2. These findings corroborate the notion that a CBT4T, including exposure-treatment has an attenuating effect on tinnitus related fear and fear related behaviours, thereby decreasing tinnitus complaints significantly.

In the past, the CBT approach, with a focus on dysfunctional beliefs about tinnitus and associated safety-seeking behaviours, have been widely applied and studied (Henry et al., 2007; Martinez-Devesa et al., 2010; Phillips and McFerran, 2010) and cognitive-behavioural accounts of tinnitus suffering have been hypothesized earlier (Cima, Crombez and Vlaeyen, 2011a; McKenna et al., 2014). The FA model for tinnitus incorporates the dysfunctional behavioural consequences of heightened tinnitus distress. Safety-seeking behaviours, e.g. such as avoiding loud environmental noise or silence, including using sound-enrichment or tinnitus masking devices to prevent the full perception of the tinnitus, are hypothesized to temporarily reduce the threat value of the tinnitus sound, but paradoxically may reinforce fearful responding and increase tinnitus related disability in the long run. The Fear-avoidance approach seems a valid model for chronic tinnitus, for both directing new treatment avenues as well as in formulating hypotheses in future experimental and clinical research (Hesser et al., 2009; Cima, Crombez and Vlaeyen, 2011a; Blaesing and Kroener-Herwig, 2012; Kleinstauber et al., 2012). *First*, self-reported and fear-related avoidance behaviours have been found to, at least partly, mediate the association between tinnitus severity and quality of life, moreover, such avoidance behaviour was found to mediate the association between fear of bodily sensations and tinnitus related disability. Additionally, tinnitus-related fear has been found to mediate the association between cognitive misinterpretations of tinnitus and decreased quality of life. (Cima, Crombez and Vlaeyen, 2011a; Hesser and Andersson, 2009; Westin et al., 2008a; Westin et al., 2011). Moreover, acceptance, operationalised as a willingnes to engage in goal-directed behaviour despite fear, as opposed to a fear-induced safety-seeking, has also been shown to mediate the effects of both ACT and traditional CBT (Hesser, Westin and Andersson, 2014). Since ACT targets increased acceptance directly and traditional CBT approaches do not, these results might seem counterintuitive, expecting a more dramatic mediating effect of acceptance in the ACT treatment group. An alternative explanation might be that findings indicate that decreases of fear in both treatment approaches might be the important underlying mechanism in explaining increased acceptance, whether or not targeted directly.

In overview, consensus between the theoretical models exists about the premise that a neutral acoustic signal receives negative valence by means of classical conditioning, in which an individual learns that the signal becomes predictive for negative states (‘false alarms’) as a result of automatic negative responses elicited by this signal (Jastreboff and Jastreboff, 2006; Vlaeyen and Linton, 2000, 2012). Both the NP and McKenna's model highlight the importance of cognitive processes, and although behavioural consequences are mentioned and considered of importance, they are considered secondary in the treatment of chronic tinnitus-suffering. Changes of conscious cognitive processes are emphasized in these models, as these constitute the main therapeutic targets in treatments stemming from these models.

Following the lines of theoretical reasoning, it can be postulated that conditioned negative responses are the main cause of the suffering (Jastreboff and Jastreboff, 2006), and that these aversive responses towards the tinnitus sound lead to misinterpretations feeding back into negative evaluations, and fear-responses (Hallam et al., 1988; Hallam et al., 1984; P. J. Jastreboff, 2007; McKenna et al., 2014). Building on these principles, the FA model offers predictions about fearful-responses (emotional and attentional) and behaviours (Cima et al., 2011a), which explain the maintained tinnitus-distress in the long run. This latter premise is based on an operant component in learning theory terms and the FA-model provides more specific predictions on this level, compared to the other models, which might well be the main difference between the models.

Whereas the NP-model is mainly a model of tinnitus generation and detection, and the habituation and cognitive model emphasize that the voluntary conscious processing of the tinnitus should be of main concern in treatment endeavours, the FA model offers avenues for the more behavioural exposure treatment-element of CBT. The main conceptual overlap might lie at the level of the detection/perception and interpretation level, and the classical learning principles involved, as was described above. Even though the models differ in explaining how these classical and operant learning principles contribute to tinnitus-suffering, there exists a large conceptual overlap between them. Both in the NP-, and the cognitive model it is hypothesized that effortful conscious alteration of negative interpretations mainly will decrease arousal and distress as a result of the tinnitus, with less emphasis on the behavioural processes, as compared to the FA model. The FA model, which is based on associative-learning principles, offers explanatory predictions about both the classical and additionally the consequent behavioural mechanisms. This fear-avoidance approach integrates previous conjectures and might prove helpful, both to discover new venues for investigations, as well as to offer a means of discovering why not only cognitive, but also behavioural treatment approaches are repeatedly found to be successful, and offers means for discerning which components work best for whom.

The present findings support the fear-avoidance approach and the importance of addressing tinnitus-related fear more systematically in research and management of patients with disabling tinnitus. Our findings also support the conjecture that initial fearful responses towards the tinnitus sound, and as a result safety-seeking behaviours, may lead to more severe problems in the long run, not only decreasing chances for tinnitus habituation, but also maintaining the tinnitus impairment as such. Also, treatment effects might even be magnified when aiming treatment elements specifically at decreasing these fearful responses in cognitive behavioural exposure approaches, as has been shown currently. Likewise, treatments aimed at fear reduction, such as exposure in vivo with behavioural experiments, have shown to be quite successful in the management of chronic pain (Bailey et al., 2010; de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005; Vlaeyen et al., 2002), and its application in tinnitus patients is warranted.

There are some considerations worth mentioning about the current study. *First*, the current CBT-based treatment consisted of a combination of CBT treatment elements, which of those contributed most to the overall effects, and specifically reductions in tinnitus related fear has remained unclear. A dismantling approach is recommended, leaving out potentially redundant treatment components in subsequent trials. *Second*, next to longitudinal studies, relying mostly on self-report measures, a more experimental approach, using behavioural and physiological measures, examining the nature of the threat value of the tinnitus sound, the fearful responses and behavioural reactions, will provide more fundamental insights into these processes. *Third and last*, although we have found some evidence for a mediating role of tinnitus-related fear, the finding of at least cross-sectional effects in the opposite direction (from primary outcomes to fear) and the risk of hidden confounding in any mediation analysis prevent strong conclusions about mediation from this study. Replication as well as more advanced designs and methods for causal inference will be needed for that.

In conclusion, our findings provide evidence that the effectiveness of specialised CBT might be partly explained by significant reductions in tinnitus-related fear. Tinnitus related fear might explain why only a small part of individuals experience the heightened tinnitus distress and suffer prolonged chronic tinnitus, whereas for the larger part the tinnitus is hardly bothersome, since in them these fearful reactions might be absent. Exposure-based CBT methods have been successfully applied to a range of anxiety related disorders, such as Phobia, Post-Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), and chronic pain and mechanisms are studies widely (Bailey et al., 2010; Foa and McLean, 2016; Meulders et al., 2016). Current findings might contribute to the development of novel intervention approaches, and the much-needed more fundamental research into the behavioural mechanisms of change in tinnitus research as well.

The results of the current study are relevant for clinical practice as well. CBT approaches in tinnitus management have been effective in decreasing suffering of patients; even though at present patients and clinicians alike are confronted with a lack of treatment guidance, and fragmentized and costly treatment trajectories (Cima et al., 2009; Hoare and Hall, 2011; Fuller et al., 2017). The lack of or incorrect information at the time of tinnitus onset, and mis-indication or delay of appropriate treatment, is augmenting tinnitus related fear and fearful reactions, aggravating tinnitus severity and suffering in a large group of patients.

5. Compliance with ethical standards

The Medical Ethical Board of the Rehabilitation Foundation Limburg reviewed and approved of the study protocol (METC-SRL: 11/09/2006).

Funding and trial registration

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Contributors

The trial project members RFFC (principal investigator and main author), and JWSV (project leader) designed the study and obtained funding. The statistical analysis plan was set up by RFFC, JWSV, and GJPB (advisor statistical analyses). The statistical analyses were carried out by RFFC, supported by GJPB. Data interpretation was carried out by RFFC and GJPB. Trial treatments and the UC and SC treatment teams were coordinated and monitored by RFFC. RFFC, JWSV, and GJBP were involved in the writing of the current manuscript, the design of tables, figures, appendices and panels. RFFC was responsible for writing and for the decision to submit the final paper for publication.

Conflicts of interest

All authors declare to have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heares.2017.10.003.

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