Tinnitus and stress in adults: A scoping review

Introduction

Tinnitus is the perception of sound in absence of any external acoustic stimulation, and is associated with otological and non-otological disorders (Baguley et al., 2013). Tinnitus signals are varied in loudness, pitch, and spectral contents (psychoacoustic characteristics) among those who experience it (Cederroth et al., 2019), which can impact the emotional and mental status of the person differently (Møller, 2016; Hall et al., 2018a). A relationship between tinnitus and stress is frequently reported in literature (including fiction), patient information leaflets, and online tinnitus information. Stress is a recognised risk factor for several systemic illnesses and psychological disorders such as heart diseases, depression, and anxiety potentially through changes in metabolic and immune activity, adoption of unhealthy behaviours, or alteration in neuronal networks involved in the regulation of emotion and cognition (Duric et al., 2016). Although it is not clear if stress is a risk factor for, or a consequence of tinnitus (Pattyn et al., 2016), changes in neuronal networks is a possible explanation for a relationship. Tinnitus perception is maintained by non-auditory neuronal circuits (Rauschecker et al., 2010). Excessive neuronal activity in the limbic system, para-limbic structure, frontal and temporal lobes are commonly found in tinnitus patients (Henry et al., 2014; Kreuzer et al., 2013). Similarly, these areas have shown stress-related structural and functional changes (Henry et al., 2014; Kreuzer et al., 2013). Cognitive functions are mainly regulated by different limbic structures such as prefrontal cortex, amygdala, and hippocampus (Rajmohan and Mohandas, 2007). Cognitive functions can be affected by stress (Boals and Banks, 2012; Fisher et al., 2017) and tinnitus (Tegg-Quinn et al., 2016; Clarke et al., 2020; Mohamad et al., 2016; Andersson and McKenna, 2006). Additionally, Stress-related psychological disorders, mainly anxiety and depression, are highly prevalent in tinnitus patients (Milerova et al., 2013; Crocetti et al., 2009; Pattyn et al., 2016; Pinto et al., 2014; Durai and Searchfield, 2016). Presumably, stress and tinnitus share many features and occur simultaneously, which suggests a relationship.

Although there is some evidence for a relationship between stress and tinnitus, there are still questions about the extent of the contribution of stress to tinnitus pathogenesis, and the direction of this relationship, which need to be clarified (Hébert et al., 2017). This is a complex area of research given the complexity of stress concept. For any given individual, stress can be defined as the feeling of mental and emotional strain, tension, and worry associated with a stressful or demanding event. In psychology, stress is defined as the biophysiological changes that occur in response to exposure to a demanding event (i.e. response-based concept) (Saxena, 1980; McEwen, 2005). These responses include activation and inhibition of several neuroendocrine axes, mainly the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary axis. Both, in turn, regulate different metabolic and immunological functions like lipolysis and glycogenolysis (Schneiderman et al., 2005) through their end effectors, mainly cortisol, epinephrine (EPI), and norepinephrine (NE). Thus, stress can be measured by assessing the level of stress mediators and their physiological effects on the body (Rice, 2012; Saxena, 1980). Stress is also defined as an event that a person experiences which stimulates physical and psychological adaptive effects on the body, for example, job-related stress (Papathanasiou et al., 2015). This definition is the stimulus-based concept of stress in which stress is measured by the intensity and duration of the event, for example using the Daily Hassles Scale (Kanner et al., 1981), the Social Readjustment Rating Scale (Holmes and Rahe, 1967), or Interview-based assessment of life events (Monroe, 2008). The third definition of stress is the interaction between stressors (internal or external), an individual's perception and interpretation of the stressors, and the available resources for coping with the stressors. In other words, stress is modulated by cognition and coping (Lazarus and Folkman, 1984). This transactional model hypothesises that the key component in developing diseases is perceived stress, which is measured by different instruments such as the Perceived Stress Scale (PSS) (Cohen et al., 1983), Perceived Stress Questionnaire (PSQ) (Levenstein et al., 1993), or the Depression Anxiety Stress Scale (DASS) (Lovibond and Lovibond, 1995). Tinnitus can be measured by self-reported questionnaires (psychometric instruments) that assess “tinnitus reaction” and by psychoacoustic measurements that assess “tinnitus perception” (Henry et al., 2019). Therefore there are multiple different ways in which stress and tinnitus can be measured and assessed, which could in turn affect the supposed relationship between tinnitus and stress. Consequently, in order to build an understanding of the current position of the research in stress and tinnitus, there is a need to identify research evidence and gaps in existing knowledge on the relationship between tinnitus and stress in adults. The evidence could be used to improve clinical practice for tinnitus and identify whether stress management should be prioritised, and identify specific research questions and elements that should underpin the design of any new studies or systematic review.

When there is limited evidence on the current position of research on a topic (e.g. the relationship between tinnitus and stress), and the potential research gaps within the existing literature to know the value of undertaking a systematic review and to be able to form the precise research question needed for a systematic review, scoping reviews are often conducted as a precursor to a systematic review. Scoping review methodology enables broad research questions to be addressed, examining the extent of evidence across large and diverse range of topics and study designs, whilst still incorporating rigorous methodological practices throughout the process similar to that used in a systematic reviews (Peters et al., 2015). This scoping review methodology therefore allows us to undertake an inductive approach to conduct an in-depth exploration of the complex relationship between tinnitus and stress, taking into account the complexity of the stress concept and the variety of assessment instruments used from a broad range of study designs. Therefore, the aim of this scoping review is to catalogue research to date on the relationship between tinnitus and stress in adults (in all three concepts of stress described above), and specifically the contribution of stress to the prevalence of tinnitus, reported stress-related biophysiological changes in tinnitus patients, perceived stress levels in tinnitus patients, and the effect of tinnitus management on stress and vice versa.

Methods

This review was conducted and reported in accordance to scoping review protocol guidelines by Arksey and O'Malley (2005) and Levac et al. (2010). As per guidelines, we followed a five-stage framework for the conduct of scoping reviews. This involve (i) identifying the review question, (ii) identifying the relevant studies, (iii) study selection, (iv) charting the data, (v) collating, summarising and reporting the results. This method is in accordance with the PRISMA-ScR checklist for scoping reviews (Tricco et al., 2018).

Stage i: Identifying the question

The key question of this scoping review is “What is known about the relationship between stress and tinnitus?” It was formed to guide the search and identify the inclusion criteria.

Stage ii: Identifying the relevant studies

Eligibility criteria

The inclusion criteria were (1) original articles published in English, (2) conducted in adult humans (18 years and above, no upper age limit), and (3) both tinnitus and stress were measured separately as in a specific construct of stress was measured and this was independent of measurements of the construct tinnitus symptom severity (which may contain some items referring to tinnitus-related stress). The last inclusion criteria was essential to compare levels of stress with level of tinnitus. There are various classification systems for tinnitus such as primary vs secondary, and subjective vs objective. All classifications of tinnitus were eligible in this review.

Review articles including systematic reviews, epidemiology articles, and any sources reporting personal/expert opinions were excluded. Records relating to basic scientific research in animals, Posttraumatic Stress Disorder (PTSD), trauma, and stress reactivity (oxidative stress) were also excluded. Where multiple eligible unique records pertaining to a single trial were identified, the record that was published first was included and any secondary analyses of the data were excluded.

Search strategy

Literature searches were undertaken in relevant electronic databases, namely PsycINFO (OVID), Medline (OVID), EMBASE (OVID), PILOTS, CINAHL, Web of Science, Pubmed, Scopus and Google scholar. ProQuest Dissertations and Theses, and Nottingham eTheses and EThOS were searched for grey literature. The search strategy varied by database (example in Table 1).

<Table 1>

Using the search terms tinnitus AND stress* AND adult AND human, the searches for each term were conducted separately and then search results were combined. When possible, the search was limited to English. The search was not limited to any specific date. Additionally, reference lists of any review articles from the electronic search and the table of contents of the last 6 months of key journals were hand-searched for potentially relevant articles. The initial searches were conducted in October 2017. The final electronic search was conducted in July 2019 and hand-search in November 2019.

Stage iii: Study selection

Records identified through electronic and hand searches were exported into Endnote and duplicates were removed. Study selection had two stages. In the first stage, titles and abstracts were screened independently by two reviewers, one of those is the primary author (AE) and one of the co-authors (KF, DB, or DH). Disagreements between reviewers resolved through discussion. All records that held the possibility of relevant findings were retained for full-text screening. Full texts were screened independently by two reviewers against the inclusion/exclusion criteria. Disagreements were resolved through discussions or the involvement of a third reviewer.

Stage iv: Charting the data

A data extraction form was developed in Microsoft Excel and modified following piloting with two included studies. Two reviewers (AE, the primary author, with KF, DB, or DH) extracted data from each record independently and compared the results. Any disagreements in the extracted data were resolved through discussion and revisiting the record. Data was extracted on study identifiers (authors' names, date of publication, title, and type of the study), study characteristics (aims, sample size, participants age, presence of hearing loss and tinnitus) assessment instruments used to measure tinnitus and stress, and any reported relationship between tinnitus and stress as reported in the findings of the study.

Stage v: Collating, summarizing and reporting results

The extracted data on the study characteristics and assessment instruments were initially summarised and tabulated. Further to this, the information related to the assessment instruments, results of the study and the relationship between tinnitus and stress was subjected to thematic analysis in order to catalogue and summarize similar findings into four themes: assessment instruments used, evidence of a relationship, biomarkers of stress in tinnitus, and changes after an intervention.

Results

Initial database searches produced 4911 records. After removing duplicates, title, and abstract screening, 131 records were selected for full-text screening. Following full-text screening, an additional 93 records were excluded, leaving 38 included records retrieved for data extraction. From our updated literature searches in July 2019 and November 2019, a further 12 records were identified as eligible for data extraction (Figure 1). Studies were in general excluded because stress was not measured, or they included participants younger than 18 years old. Details of the study design, age of the participants, and tinnitus and stress measurements summarised in Supplementary Table.

<Figure 1>

Hearing was assessed in 32 studies. The other 19 studies did not report whether hearing was assessed or not. Audiometric tests were used in 18 studies (mainly pure tone audiometry). Eight studies used self-report instruments (i.e. participants answered questions about hearing impairment) and reported the percentages of participants who had hearing impairment. Only five studies measured hearing but did not report the results. Few studies were designed to examine tinnitus associated with hearing impairment. Those that were had specific populations who had either sudden sensorineural hearing loss (Schmitt et al., 2000), single sided deafness (Haussler et al., 2019), or used cochlear implants (Olze et al., 2012; Olze et al., 2011a; Olze et al., 2011b; Ketterer et al., 2018) (see also Supplementary Table).

Among included studies, only 25 were specifically designed to assess stress within tinnitus population. The aims were to assess psychological and biophysiological stress in tinnitus patients, to describe the modulating factors of the relationship between tinnitus and stress, to assess the effect of management on tinnitus and stress, to measure the occurrence of stress in tinnitus patients, or to evaluate the effect of stressful life events on tinnitus patients. The remaining 18 studies had different aims that included testing the effect of tinnitus managements on tinnitus, describing tinnitus features in a group of tinnitus patients, tinnitus questionnaire validation, and others.

Measurements used in the included studies

The most frequently used standardised stress instruments in all included studies were the PSQ, stress Visual Analogue Scales (VAS), and the DASS which are perceived stress measurements. Stimulus-based stress measurements were used in three studies. Biophysiological markers of stress were measured in 15 studies. Four studies assessed the occurrence of stress symptoms among people who have tinnitus. Only two studies assessed job-related stress (Abbott et al., 2009; Saruhanoglu et al., 2017).

Tinnitus symptom severity was measured in all studies; in most of them two instruments were used. The most frequently used instruments were VAS, the Tinnitus

Handicap Inventory (THI) (Newman et al., 1996), the Tinnitus Questionnaire (TQ) (Hallam et al., 1988), or the Tinnitus Reaction Questionnaire (TRQ) (Wilson et al., 1991). The Tinnitus Functional Index (TFI) (Meikle et al., 2012) was used in five studies. Regarding the psychoacoustic properties of tinnitus, we found that they were measured in ten studies but were rarely used in the analysis. Residual Inhibition (RI) was not measured. Details of the frequency of using each instrument are summarized in Table 2.

<Table 2>

Evidence of a relationship

Evidence of a relationship between stress and tinnitus was collected in 26 studies. These studies reported association between the (a) onset of tinnitus and stress, (b) levels of stress and its effects in those with tinnitus, or (c) a statistical correlation between self-reported tinnitus and stress levels.

a) Onset of tinnitus and stress

Three studies reported the percentage of patients who associated the onset of their tinnitus with stress. These percentages were 13.5% (n=200) (Yıldırım et al., 2017), 14.2% (n= 260) (Muller et al., 2016), and 28.3% (n= 350) (Probst et al., 2017). In Yıldırım et al. (2017), patients clearly described the occurrence of at least one stressful event that induced or worsened their tinnitus.

b) Stress levels and effects

Tinnitus patients tended to report a moderate level of stress in their lives (Dineen et al., 1997). Patients with high self-reported tinnitus severity had significantly higher levels of stress as measured by PSQ vs TQ-52 (Olze et al., 2011) and MPS-9 (Psychological Stress Measurement) vs THI (Frachet et al., 2017). Higher levels of subjective stress were associated with louder and more distressing tinnitus (Probst et al., 2017). Tinnitus patients showed higher PSQ scores than healthy controls (Betz et al., 2017). Gomaa et al. (2014) stated that 73% of tinnitus patients, who also had hearing loss, suffered from stress. They described a correlation between the duration and severity of tinnitus and the severity of stress. In a group of workers at a call centre aged 22-45 years, 33.1% reported tinnitus and 62.1% described high job-related stress level (Saruhanoglu et al., 2017).

c) Stress-related symptoms in tinnitus

Stress-related symptoms such as headache, tension in facial muscles and sleep disturbance were more frequent when the level of tinnitus was high. This is reported by Lindberg et al. (1984) who assess the grade of tinnitus by using Klockhoff and Lindblom grading system (1967). The authors concluded that the frequency of these symptoms strongly correlate with the grade of tinnitus. Similarly, Ciminelli et al. (2018) reported that 65% of participants described presence of stress symptoms (Lipp's Inventory for Symptoms of Stress (ISSL)), and this percentage is higher in patients who had higher scores on THI. On the Life Event Scale and the Daily Hassles Scale, patients with sudden sensory hearing loss and tinnitus had significantly higher scores than those in control group (Schmitt et al., 2000).

d) The effect of stress on tinnitus perception

The effect of stress on tinnitus was reported in six studies. 53.8% of tinnitus patients reported that stress intensified their tinnitus (Muller et al., 2016). Hebert and Lupien (2009) described increase in the subjective stress and salivary cortisol after exposure to noise, accompanied by an increase in ‘intensity’ of tinnitus. Ecological Momentary Assessment (EMA) showed that tinnitus (bothersomeness and loudness) and stress changed together across time (Goldberg et al., 2017); the author concluded that temporary changes in bothersome tinnitus is strongly associated with levels of perceived stress. (Probst et al., 2016; Probst et al., 2017) also measured stress and tinnitus (loudness and distress) at different times of the day using $VAS_{0-1,}$ and reported that stress mediated the association between tinnitus loudness and tinnitus distress (Probst et al., 2016).

e) Correlations between self-reported stress and tinnitus

Positive correlation between self-reported tinnitus and stress measurements were reported in 15 studies (Muller et al., 2016; Bencsik et al., 2015; Ahmed et al., 2017; Panagiotopoulos et al., 2015; Park et al., 2017; Salviati et al., 2013; Brueggemann et al., 2019; Frachet et al., 2017; Han et al., 2019; Olze et al., 2011; Jackson, 2019; Gerber et al., 1985; Dineen et al., 1999). The strength of this correlation varied according to the instruments used from 0.26 (FTQ and PSQ-30) to 0.67 (THI and SVS) (Table 3).

<Table 3>

Non-significant correlations were found between TRQ and DSP scores (Dineen et al., 1999), between the Stressful Life Events scores and tinnitus severity questionnaire scores (not specified) (Gerber et al., 1985), and between Tinnitus VAS_{1-100} on one hand and Severity of Recent Life Event (SRLE) and PSS-10 on the other (Jackson, 2019).

Biomarkers of stress in tinnitus

a) Cortisol

Cortisol, either in saliva or blood, was the most commonly assessed biomarker (n=6 studies). Kim et al. (2013) reported that single-point blood cortisol levels did not correlate with the VAS, THI, or Korean-Brief Encounter Psychosocial Instrument (K-BEPSI). Tinnitus participants who had high TRQ scores (>18) presented chronically above median salivary cortisol (CAMC) i.e. their cortisol were more frequently elevated than low distressed and healthy controls (Hebert et al., 2004). Salivary samples were taken five times across the day to assess CAMC. Cortisol Awakening Response (CAR) was assessed by measuring the Area Under The Curve with respect to increase (AUCi) (Jackson, 2019). Distressed tinnitus participants (TFI scores >25) had significantly lower AUCi than non-distressed tinnitus participants (TFI <25) and controls. Jackson 2019 also found that AUCi levels and tinnitus distress levels (VAS_{0-100}) measured at awakening, after 6 hours and after 12 hours had moderate negative and statistically significant correlation. This indicates that AUCi levels may predict tinnitus distress levels later in the day.

Salivary cortisol, that measured at different points after exposure stress or noise, displayed a blunted and delayed response (Hebert and Lupien, 2007; Hebert and Lupien, 2009). Aydin and Searchfield (2019) did not found significant changes in cortisol and cortisone levels after exposure to BBN and Nature sound in tinnitus particiants. However, their finding was based on a single point measurement before and after exposure, and they reported higher variation in cortisol levels among the participants.

Tinnitus patients' response to a dexamethasone suppression test was stronger than healthy participants; the percentage reduction in salivary cortisol after dexamethasone was significantly higher than that of healthy controls despite similar basal cortisol levels, implying an increase in glucocorticoid sensitivity in tinnitus patients (Simoens and Hebert, 2012).

b) Other biomarkers

Stress-related immunological biomarkers (cytokines, Tissue Necrotic Factor, interleukins [IL-6, IL-10]) were compared in patients with chronic tinnitus and healthy participants; only levels of IL-6 were higher in tinnitus patients (Weber et al., 2002). Elevated NE or 5-HIAA were more frequently observed in tinnitus patients than controls, and ranged widely among patients, but differences were not statistically significant (Kim et al., 2013).

Indicators of sympathetic activity were assessed in six studies. (Betz et al., 2017) reported no difference between tinnitus and non-tinnitus group, and no relationship between heart rate variability and TQ scores. Ylikoski et al. (2017) reported decrease in heart rate variability after TRT (Aydin and Searchfield, 2019) reported decrease in Blood pressure after BBN and nature sound. Crocetti et al. (2018), Kirsch and Blanchard (1987), Weise et al. (2008) assessed muscle tension, skin conductance, and change in temperature and they did not report any significant findings.

Change in tinnitus and stress after intervention

Stress and tinnitus were assessed before and after tinnitus management in 22 studies. The reported changes were inconsistence as seen in Table 4.

<Table 4>

Cognitive Behavioural Therapy (CBT) was used in four interventional studies. CBT was part of a multimodal treatment in Brüggemann et al. (2018) who reported improvement in TQ and PSQ after 7 days of multimodal treatment and this improvement was maintained in 5 years follow-up. In Hesser et al. (2012) THI and PSS scores improved after internet-delivered CBT and Acceptance and Commitment Therapy (ACT); there was a significant linear decrease in tinnitus distress and PSS scores. Li et al. (2019) introduced CBT with masking therapy and found that cortisol and tinnitus (THI) levels become lower after treatment, but interleukins (IL-2) level become significantly higher. In contrast, Abbott et al. (2009) found no significant changes in TRQ or DASS stress scores (both were low at baseline) after CBT.

Changes in the level of stress and tinnitus after relaxation therapy were reported in four studies. Kirsch and Blanchard (1987) used progressive relaxation training and biofeedback therapy with six patients. A reduction in tinnitus severity and stress level was reported but was non-concomitant. Another study showed a reduction in tinnitus and stress levels after weekly yoga sessions (Koksoy et al., 2017).

Tinnitus and stress levels decreased after progressive muscle relaxation (Weber et al., 2002); PSQ scores and Tissue Necrotic Factor alpha (TNF-α) levels decreased significantly in tinnitus patients compared to non-tinnitus controls. Weise et al. (2008) measured tinnitus severity using the TQ, the electromyogram (EMG), and skin conductance before and after biofeedback management. No relationship analyses were reported, as the main aim of this study was to assess the test-retest reliability of EMG and skin conductance.

Sound-based management, which aims to mask or distract the patient from tinnitus, was the intervention of choice in eight studies. In four different records, Olze et al. (2012; 2011), Haussler et al. (2019) and Ketterer et al. (2018), the effect of cochlear implants (CI) on tinnitus and stress levels was assessed. Both decreased after CI when patients initially had high levels of tinnitus distress and stress (PSQ higher than 0.33). Ketterer et al. (2018) reported no change in PSQ after 6- and 12-month post-CI (initial PSQ scores were 0.3±18).

Durai and Searchfield (2017) used broadband noise and described a decrease in stress and tinnitus scores. On the other hand, no change occurred in stress level after music-based treatment in Attanasio et al. (2012) but tinnitus intensity improved significantly. No changes occurred after broadband noise exposure in Dineen et al. (1999).

Tinnitus Retraining Therapy (TRT) (Jastreboff and Hazell, 2008) decreased both tinnitus and stress levels. In Seydel et al. (2010), more improvement was noticed in participants with higher level of stress. The improvement in TQ and PSQ scores were maintained 5 years post-multimodal TRT (Brüggemann et al., 2018).

Two studies used a pharmacological intervention. Aoki et al. (2012) aimed to evaluate whether the use of lyophilised powder of enzymolysed honeybee larvae provides a therapeutic effect on tinnitus-related symptoms. They reported a decline in cortisol/dehydroepiandrosterone sulfate (DHEA) ratio after this treatment but tinnitus distress did not improve. Frachet et al. (2017) studied the effect of Auditism® (a combination of Ginkgo Biloba, melatonin, magnesium, zinc) which improved the level of tinnitus in 40.1% and level of stress in 21.8% of the participants. Ylikoski et al. (2017) reported an improvement in HRV after transcutaneous vagal nerve stimulation (tVNS), but they did not indicate if there was a change in tinnitus distress.

Discussion

The aim of this scoping review was to catalogue research to date evaluating the relationship between stress and tinnitus. We first reviewed measurements used in the included studies, which typically focused on one psychological concept of stress at a time, most often perceived stress. Psychoacoustic measures of tinnitus were rarely analysed in the included studies. None of these studies provided a clear rationale for not including these measures in the analysis, therefore no conclusion could be drawn about the effect of stress on the perceptual qualities of tinnitus. A number of tinnitus instruments were used in the included studies. For these instruments, there is varied evidence for the reliability and validity. For example, questions have been raised on the questionnaire structures, overlap of content and depth of information being measured

(Tyler et al., 2007; Fackrell et al., 2016; Newman et al., 2014; Kamalski et al., 2010).

In this review, we asked whether exposure to stress plays a role in the pathophysiology of tinnitus. As the association between an outcome and an exposure is a first step toward defining a cause-effect relationship and it should be studied for consistency and specificity (Lucas and McMichael, 2005), we need to find whether stress acts as stimulus and causes tinnitus, and/or whether exposure to stress modulate tinnitus. The collated evidence showed that up to 29% of tinnitus patients associated the onset of tinnitus with stress, as per question number 7 in the Tinnitus Sample Case History questionnaire (Langguth et al., 2007). However, no guiding definition of stress is given in this question. Therefore, it is not clear if the tinnitus was associated with the occurrence of events or with the emotional distress that occurred when the event was perceived as stressful. As advised by Cohen et al. (1995), the best strategy to associate the onset of any disorder with stress is to assess it with a stimulus-based instruments. These instruments were used in just three studies (Gerber et al., 1985; Schmitt et al., 2000; Jackson, 2019), neither of which examined the onset of tinnitus with the occurrence of stressful event. Schmitt et al. (2000) reported higher Life Events Scale and Daily Hassles scores in those with sensorineural hearing loss and/or tinnitus than controls. But, they did not report the findings in the ‘tinnitus only’ group separately. Jackson (2019) reported negative, but non-significant, correlation with the severity of tinnitus.

It is obvious at this stage that not all tinnitus patients associated the onset of tinnitus with stress. This may be because the effect of daily hassles and recent life events on the onset of tinnitus was overlooked, or the inclusion of participants with long-term tinnitus resulting in a recall bias. Moreover, as tinnitus is a multifactorial and heterogeneous disorder with many different complaints associated with it, as previously reported

(Sanchez and Stephens, 1997; Sanchez and Stephens, 2000; Tyler and Baker, 1983; Watts et al., 2018), any study conducted in tinnitus is often rich in confounding factors. Similarly, most studies did not provide extensive detail about stress, e.g. whether it was associated with disease, or was acute or chronic. Therefore, this association will not simply imply a causal relationship between tinnitus and stress.

Several studies in this review showed that stress increased the bothersomeness and loudness of tinnitus. This is consistent with Baigi et al. (2011) who suggested that stress is a key factor in modulating the severity of tinnitus, in this study no instrument was used to assess the levels of stress and tinnitus. Studies included in this review used different methodological approach. In two included studies (Muller et al., 2016; Yıldırım et al., 2017), participants were asked whether stress intensified their tinnitus, around half of the patients, answered the question positively. Other studies indicated a simultaneous fluctuation of tinnitus and stress levels based on daily monitoring. Their finding supports the notion that stress modulates tinnitus perception, but they also asked participants whether they felt stressed without providing a definition of stress. We observed that not all the participants associated tinnitus and stress, and there is variability in cortisol levels in tinnitus population. This may indicate a possibility to use stress levels to split tinnitus population into groups. Comparing these groups may reveal additional factors that likely mediate this relationship.

The biophysiological markers of stress are objective measures, and the measured response in tinnitus participants was different from non-tinnitus controls. Levels of IL-6 were higher in tinnitus patients than a younger control group (Weber et al., 2002). In general, IL-6 increases with age (Puzianowska-Kuźnicka et al., 2016; Hager et al., 1994) which may indicate that this finding is not specific to tinnitus. Salivary cortisol secretion in tinnitus patients exposed to short-term mental stress or noise was blunted and delayed in comparison to age-matched controls and was more so in those with higher tinnitus distress. This implies a dysregulation in the Hypothalamus-Pituitary-Adrenal axis (Mazurek et al., 2015). This is a momentary measurement and the assessment of long-term cortisol levels will reveal the significance of this finding. Other sampling techniques like 24-hour urine collection, which provides cortisol level over an entire day (Dantzer et al., 2014), and hair analysis, which gives reliable retrospective cortisol levels up to 5 months (Stalder et al., 2017), are examples of sampling techniques to assess long-term cortisol secretion.

The indicators of the sympathetic-adrenal-medullary axis response (Skin conductance, EMG, and HRV) were also assessed. According to Crocetti et al. (2018), attention focus on tinnitus does not seem to produce sympathetic activation. Only HRV in tinnitus patients was different from healthy controls and improved after tVNS treatment in patients who had high levels originally (Ylikoski et al., 2017). But these findings are limited by the effect of confounders as HRV is not an exclusive biomarker of the autonomic nervous system and affected by many factors such as the age, physical activity, and blood pressure (Valentini and Parati, 2009). It is noteworthy that none of the previous studies examined changes in stress biomarkers in patients with recent onset tinnitus, at least as a separate group.

Many included studies reported a positive correlation between measurement of tinnitus and perceived stress measurements. However, this probably resulted from the overlap of psychological constructs of these questionnaires (Hall, 2017). This is noticeable by looking at the difference in the strength of the correlation (Table 2). A moderate correlation was found between perceived stress measurements and tinnitus measurements that mainly assess distress in tinnitus patients (THI, TFI, TQ, TRQ), and a weak correlation was between PSQ and both the FTQ and TCS which assess tinnitus-related fear. These studies used similar statistical testing, which opens the field for a systematic synthesis for the strength of this correlation.

Yet, self-reported levels of stress were higher in tinnitus patients than non-tinnitus controls (Betz et al., 2017). Patients with decompensated tinnitus had higher stress scores than patients with chronic pain (Zirke et al., 2013). Stress manifested with different symptoms. These symptoms occurred more frequently in those with tinnitus than those without, and were much more common when the subjective grading of tinnitus was higher. Likewise, van Dijk et al. (1987) reported an interrelation between tinnitus and the frequency of stress symptoms. These findings could be considered as evidence of a relationship. However, due to the potential overlap in contents between the questionnaires, these conclusions do need to be interpreted with caution. These findings and the similar statistical testing do however indicate the need for a systematic review to examine and synthesise the evidence across studies and for future studies to focus on comparing the level of perceived stress and stress symptoms in tinnitus patients with other patient populations e.g. patients with fibromyalgia). It is important to consider confounders and shared underlying variables that may affect the correlation between tinnitus and stress measurements. In addition, stress questionnaires are prone to different kinds of method bias which may affect the estimate of the relationship between two constructs (Podsakoff et al., 2012; Weckesser et al., 2019).

We also catalogued how tinnitus management affected the level of stress and tinnitus. The type of tinnitus management, whether it was stress- or sound-based management did not seem to influence how their levels changed. The most effective management of tinnitus has not been established and the efficacy of most tinnitus managements lacks supportive evidence (Makar et al., 2017; Hoare et al., 2011). It appears that changes after CBT (Hesser et al., 2012) and CI (Olze et al., 2011; Olze et al., 2012) were more likely to occur if the baseline level was high, and less likely to occur if the baseline level was low (Abbott et al., 2009). Thus, it is questionable if the baseline levels of tinnitus and stress have an influence on the outcome of intervention. This requires further investigation to estimate whether the selection of participants with high tinnitus level influences the outcome.

It was not possible to conduct a critical appraisal which is an optional step in scoping review methodology and not an essential aim (Munn et al., 2018; Tricco et al., 2018). Quality assessment does not form part of the scoping review which is a limitation of the method (Arksey and O'Malley, 2005). But this does not affect their ability to identify sources of the literature and makes it a robust method (Davis et al., 2009).
We decided prospectively not to appraise studies as it was not relevant to the stated purpose of the review; to catalogue the evidence of the relationship. In addition, the included studies varied in design and outcome measures which would require a complex set of tools to conduct a meaningful appraisal. As such we also cannot in this review provide specific methodological recommendations considering tinnitus research; the reader is referred to general methodological considerations in Hall et al. (2018b) and Tyler et al. (2007).

Recommendations and future directions

This review can be used as guidance to conduct a systematic review of the use of specific stress instruments in this population or to design a study to assess the relationship under review. The suggestions and recommendations for future studies are:

1. To associate the onset of tinnitus with stress, it is important to use stimulus-based instruments or structured interviews, and study the association in recent-onset tinnitus patients.

2. We recommend the use of a guiding definition of stress to ensure participants and readers clearly understand the stress concept being investigated in the same manner.
3. When studying the changes in stress biomarkers in tinnitus patients, it is important to also consider psychological (depression and anxiety) and physical co-morbidities that may affect long-term and short-term stress biomarkers. Also, confounding factors, such as age, and hearing impairment, should be considered in the analysis.
4. It is important to compare stress-related biomarkers in age-matched groups, be measured at different points, and correlated with the changes in tinnitus severity.
5. We recommend to include the psychoacoustic measurements of tinnitus in the analysis if they were used, and to report the findings.
6. It should be acknowledged that psychometric tinnitus measurements assess the impact of tinnitus on various constructs or domains of quality of life (Kennedy et al., 2004). Therefore, the interpretation of the tinnitus severity should be based on the psychometric properties of the instruments they used.

There are opportunities to design studies and to conduct reviews that broaden our understanding of the role of stress in developing tinnitus. Many alternative methodological approaches should be considered. For example, studying more than one concept of stress using reliable measurements rather than focusing on one psychological concept of stress at a time. Daily monitoring and measuring of long-term self-reported stress and biomarkers levels may lead to significant findings as the stressful events that a person faces are varied in magnitude and quantity day-by-day. An additional consideration is to compare stress levels between different groups such as tinnitus and non-tinnitus groups, recent-onset and chronic tinnitus, or distresses and non-distressed tinnitus groups. This may reveal that not all tinnitus patients are vulnerable to stress or the existence of other confounding factors.

There are some reviewed studies that have fulfilled some of the abovementioned recommendations. For example, Jackson (2019) measured stress in its three different concepts. He used salivary cortisol as a biophysiological marker, SRLE as a stimulus-based instrument, and PSS-10 to measure the perceived stress. Based on the findings of this scoping review, we are also conducting a study in which we used DHS, RLCQ, DASS and hair cortisol (Elarbed et al., 2019). We also measured tinnitus loudness psychoacoustically for inclusion in the final analysis. With the existence of a wide variety of stress and tinnitus instruments, that future research uses them widely and simultaneously.

Limitation

The inclusion criteria of this review was limited to studies published in English only and relevant studies published in non-English languages would have been missed. However, the included studies were conducted in English and non-English speaking countries. We put a limitation on the age of participants and this led to the exclusion of 13 studies where at least some adults were included. For a systematic review, we recommend that data should be included by separating out the adult from child data. That was beyond the aim of this scoping review. Lastly, we included studies that measured stress and tinnitus separately. This lead to exclude studies that assessed stress in tinnitus population but did not assess the level of tinnitus.

Conclusion

The inconclusive results is enhancing understanding of the relationship, as the evidence suggests as it stands that the relationship between stress and tinnitus could go either way and that more research is needed on investigating the relationship, which recommendations are provided from the review as to the gaps in research. Several questions remain to be answered, such as the direction of this relationship, the effect of stress on the characteristics of tinnitus, and the role of stress mediators in tinnitus physiopathology. There is considerable room for improvement and for conducting further research about this relationship. This review highlighted some shortcomings and possible solutions that can be used as a reference point when designing studies investigating the relationship between stress and tinnitus.

Conflicts of interest

No conflict is declared**.**

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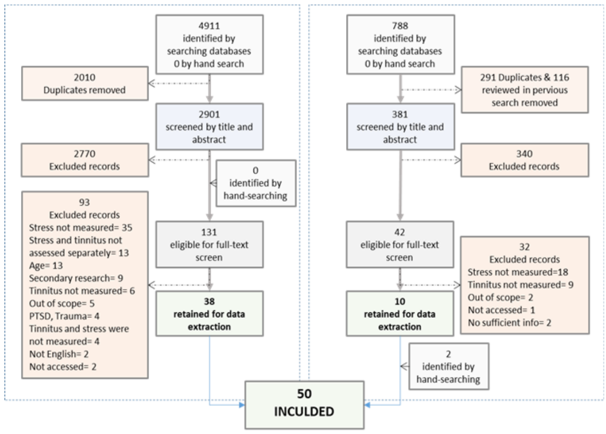

Fig. 1. Flow diagram details search process and count of included and excluded records of each stage of the review. We repeated the same steps in the updated search in July.

Table 1: Search strategies examples

Database	Search term
Pubmed	Tinnitus AND stress* AND adult AND human
PsychoINFO	tinnitus.mp. or exp tinnitus/ stress*.mp. or exp psychological stress/or exp stress/ 1 and 2 limit 3 to (human and English language)

Table 2: List of measurements used in the included studies.

Perceived Stress Measurements		**frequency of using**
Perceived Stress Questionnaire	PSS	11
Visual analogue Scale	VAS	6
Depression Anxiety Stress Scale	DASS	5
Perceived Stress Scale	PSS	4
Korean-Brief Encounter Psychosocial Instrument	K-BEPSI	3
Derogatis Stress Profile	DSP	2
Psychological Stress Measurement	MSP	2
Stimulus-based Stress Measurements		
Recent Life Changes	RLC	2
Severity of Recent Life Event	SRLE	1
Daily Hassles Scale	DHS	1
Symptoms of Stress Measurements		
Stress Vulnerability Scale	VRS	1
Lipp's Inventory for Stress Symptoms	ISSL	1
Stress Symptoms Scale	SSS	2
Stress Biophysiological Measurements		
Cortisol	CORT	9
Cortisone	CORTn	1
dehydroepiandrosterone Sulphate	DHEAS	1
Interleukins (2, 6, 10)	IL	3
Epinephrine & norepinephrine	NE, EPI	1
Tissue Necrotic Factor a	TNFa	1
Blood Pressure	BP	1
Heart Rate & Heart Rate variability	HR, HRV	4
Skin Conductance	SkD	2
Electromyogram (Muscle contraction)	EMG	3
Temperature	Temp	3
Tinnitus Psychometric Measurements		
Tinnitus Handicap Inventory	THI	17
Tinnitus Questionnaire	TQ	13
Tinnitus Reaction Questionnaire	TRQ	7
Visual analogue Scale	VAS	6
Tinnitus Functional Index	TFI	5
Fear of Tinnitus Questionnaire	FTQ	1
Tinnitus Catastrophic Scale	TCS	1
Tinnitus Handicap Questionnaire	THQ	1
Global Rating Bother Scale	GBS	1
Tinnitus Severity Questionnaire	TSQ	1
Tinnitus Acceptance Questionnaire	TAQ	1
Tinnitus Fragebogen	TF	1
Tinnitus Psychoacoustic Measurements		
Pitch Matching	PM	**8**
Loudness Matching	LM	**6**
Minimum Masking Level	MML	**5**

Table 3: Correlation between tinnitus and stress subjective measurements.

Author	**Tinnitus measurements**	**Stress measurements**	**Statistical analysis**	**r**	**p**
Ahmed et al. (2017)	THI (male)	DASS (male)	NR	0.54	<0.001
	THI (female)	DASS (female)	NR	0.53	<0.001
Bencsik et al. (2015)	THI	PSS-4	PC	0.55	<0.01
Betz et al. (20017)	TQ	PSQ	PC	0.62	=0.005
Brueggemann et al (2019)	TQ	PSQ	PC	0.53	<0.01
Frachet et al. (2017)	THI	MPS-9	PC	0.67	<0.000
Han et al. (2019)	THI (male)	K-BEPSI (male)	PC	0.59	<0.01
	THI (female)	K-BEPSI (female)	PC	0.29	ns
Muller et al. (2016)	THI	PSQ-30	SC	0.47	<0.01
	TFI	PSQ-30	SC	0.41	<0.01
	TCS	PSQ-30	SC	0.34	<0.01
	FTQ	PSQ-30	SC	0.26	<0.01
Olze et al. (2011a)	TQ	PSQ	SC	0.58	<0.001
Olze et al. (2011b)	TQ	PSQ	SC	0.44	<0.05
Panagiotopoulos et al. (2015)	TQ-mini	PSS	PC	0.35	<0.000
Park et al. (2017)	THI	K-BEPSI	PC	0.42	<0.001
Salviati et al. (2013)	THI	SVS	SC	0.67	<0.000

DASS=Depression Anxiety Stress Scale, FTQ=Fear of Tinnitus Questionnaire, K-BEPSI=Korean-Brief Encounter Psychosocial Instrument, LM=Loudness Matching, MPS=Psychological Stress Measurement, NR=Not Reported, ns=Not Significant, PC=Pearson's correlation, PSS=Perceived Stress Scale, PSQ=Perceived Stress Questionnaire, PM= Pitch Matching, SC=Spearman's correlation, SRLE=Survey of Recent Life Experiences, SVS=Stress Vulnerability Scale, TCS=Tinnitus Catastrophizing Scale, THI=Tinnitus Handicap Inventory, TFI=Tinnitus Functional Index, TQ=Tinnitus Questionnaire, VAS=Visual Analogue Scale..

Table 4: Studies assessed the effect of interventions on tinnitus and stress. Describing the type of the intervention and the measurements used in each study, and reporting any changes after the intervention.

Study	Intervention	Tinnitus Measure	Type	Significant Change	Stress Measure	Type	Significant Change
Dineen et al. (1999)	BBN	TRQ	PsM	N	DGS	PsM	N
Durai and Searchfield (2017)	BBN	TFI & MML	PsM & PsA	Y & NR	DASS	PsM	Y
Weise et al. (2008)	BIO	TQ	PsM	NR	EMG, SKC	BPh	NR
Abbott et al. (2009)	CBT	TRQ	PsM	N	DASS	PsM	N
Bruggemann et al. (2018)	CBT (multimodal)	TQ	PsM	Y	PSQ	PsM	Y
Hesser et al. (2012)	CBT, ACT	THI, TAQ	PsM	Y	PSS	PsM	Y
Li et al. (2019)	CBT & sound	THI	PsM	Y	CORT IL-2	BPh	Y N
Haussler et al. (2019)	CI	TQ	PsM	Y	PSQ	PsM	Y (ns)
Ketterer et al. (2018)	CI	TQ	PsM	Y	PSQ	PsM	M
Olze et al. (2011a)	CI	TQ	PsM	Y	PSQ	PsM	Y
Olze et al. (2011b)	CI	TQ	PsM	Y	PSQ	PsM	Y
Olze et al. (2012)	CI	TQ	PsM	Y	PSQ	PsM	Y
Frachet et al. (2017)	MedT	THI	PsM	Y	MPS	PsM	Y
Aoki et al (2012)	MedT	THI	PsM	N	CORT/DHEA	BPh	Y
Attanasio et al. (2012)	Music	THI, VAS	PsM	Y	MSP	PsM	N
Kirsch & Blanchard (1987)	PMR & BIO	Weekly tinnitus disturbance, LM, MML	PsM, PsA	M	EMG, Reported	BPh & PsM	M
Weber et al. (2002)	PMR	TQ	PsM	Y	PSQ, Immuno-biomarkers	PsM, BPh	Y
Bruggemann et al. (2019)	TRT (multimodal)	TQ	PsM	Y	PSQ	PsM	Y
Crocetti et al. (2018)	TRT	THI	PsM	Y	EMG, SKC, HRV	BPh	N
Seydel et al. (2010)	TRT	TQ & PM,LM	PsM & PsA	Y & NR	PSQ	PsM	Y
Ylikoski et al. (2017)	tVNS	THI, mini-TQ	PsM	NR	HRV	BPh	Y
Koksoy et al. (2017)	Yoga	THQ	PsM	Y	SSS	PsM	Y

ACT=Acceptance and Commitment Therapy, BBN=Broadband Noise, BIO=Biofeedback, BPh=Biophysiological measurement, CBT=Cognitive Behavioural Therapy, CI=Cochlear Implants, CORT=Cortisol, CORT/DHEA=cortisol/ dehydroepiandrosterone ratio, DASS=Depression Anxiety Stress Scale, DGS=Derogatis Stress Profile, EMG= Electromyogram, HRV=Heart Rate Variability, LM=Loudness Matching, M=Mixed, MedT=Medical treatment, MML= Minimum Masking Level, MSP=Measure du Stress Psychologique Questionnaire, N=No, ns=not significant, NR=Not Reported, PM=Pitch Matching, PMR=Progressive Muscle Relaxation, PsA=Psychoacoustic measurement, PsM= Psychometric measurement, PSS=Perceived Stress Scale, PSQ=Perceived Stress Questionnaire, SKC=Skin Conductance, SSS=Stress Symptoms Scale, TAQ=Tinnitus Acceptance Questionnaire, TFI=Tinnitus Functional Index, THI=Tinnitus Handicap Inventory, THQ=Tinnitus Handicap Questionnaire, TQ=Tinnitus Questionnaire, TRQ= Tinnitus Reaction Questionnaire, TRT=Tinnitus Retaining Therapy, tVNS=transcutaneous vagal nerve stimulation, VAS=Visual Analogue Scale, Y=Yes.