A New Approach Toward Understanding the Relationship Between Tinnitus and Stress

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Abstract

This thesis examined the relationship between tinnitus and stress. Chapter 1 provides an overview of tinnitus and stress in terms of definitions, terminologies, mechanism, classification, assessment, and management. Chapter 2 describes the similarities between tinnitus and stress. It is divided into three sections. In the first section, I explain how both tinnitus and stress are associated with changes in brain function and structure, are associated with several diseases, and affect cognition. The second section summarises the findings of a scoping review of research on tinnitus and stress. It revealed discrepancies in the findings and limitations in the methodologies of reviewed studies. Cortisol was commonly studied. Thus, the third section describes the methods and findings of studies that assessed cortisol in tinnitus. The findings in this chapter informed the empirical studies described in the remaining chapters.

Chapter 3 describes an observational study that assessed stress (as a stimulus, a response, and perceived stress) in tinnitus and non-tinnitus participants. The primary outcome measure was hair cortisol. I found no differences in stress levels between tinnitus and non-tinnitus participants. Impact of tinnitus on the sense of control and sleep was associated with cortisol level. Daily hassles and perceived stress were associated with tinnitus-related emotional distress. Changes in tinnitus levels were not associated with changes in stress levels. Recent life changes did not affect tinnitus, nor did stress have any effect on the psychoacoustic characteristics of tinnitus.

Chapter 4 explored how tinnitus patients define the word ‘stress’. I conducted a concept mapping study which had a mixed-method design. It revealed that people with tinnitus expressed the meaning of the word ‘stress’ in various ways. Almost half of the participants defined stress as ‘internal factors’, the other half defined it as ‘external factors’ and an ‘individualised experience’. The findings of this study highlighted the importance of using validated stress instruments or defining stress in research. So, it could clarify which aspect of stress is associated with the disorder being studied.

Chapter 5 describes a service evaluation study to define how stress is assessed and managed in tinnitus clinics. Health professionals defined stress differently to non-health professionals. They face challenges in

assessing and managing stress in their clinics that result from the lack of understanding of stress and lack of proper advice on how to manage stressed patients.

Chapter 6 then provides the key findings of the studies which highlighted the importance of refining the methodologies to identify links between tinnitus and stress. Furthermore, it clarified the importance of using a proper definition to the word '*stress'* and how stress is defined by people who have tinnitus and by their clinical carers. This new understanding could help in improving the management of stress in tinnitus clinics.

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Abbreviations

11β-HSD1	11β-hydroxysteroid dehydrogenase type 1
2D	Two Dimensional
5-HT	5-hydroxytryptamine
A1	First centimetre of hair collected on the first visit
A2	Second centimetre of hair collected on the first visit
A3	Third centimetre of hair collected on the first visit
A4	Fourth centimetre of hair collected on the first visit
ABR	Auditory Brainstem Response
ACTH	Adrenocorticotropic Hormone
AE	Asma Elarbed
AN	Arcuate Nucleus
ANOVA	Analysis of Variance
App	Smartphone Application
AT-II	Angiotensin-II
AUC	Area Under the Curve
AUCi	Area Under the Curve with respect to increase
AUDIT	Alcohol Use Disorders Identification Test
AVM	Audio-vestibular Medicine
AWAM	Automated Working Memory Assessment
B1	First centimetre of hair collected on the second visit
B2	Second centimetre of hair collected on the second visit
B3	Third centimetre of hair collected on the visit
BBN	Broadband Noise
BCIG	British Cochlear Implant Group
BDNF	Brain-derived Neurotrophic Factor
BMI	Body Mass Index
BTA	British Tinnitus Association
CAMC	Chronically Above-Median Cortisol
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAR	Cortisol Awakening Response
CBT	Cognitive Behavioural Therapy
CBTT	Corsi Block Tapping Test
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
C-I	Cochlear Implant
CORE-OM	Clinical Outcomes in Routine Evaluation–Outcome Measure
CRH	Corticotrophin Releasing Hormone
CRHR	Corticotrophin Releasing Hormone Receptors
DASS	Depression, Anxiety and Stress Scale
DASS-A	Depression Anxiety Stress Scale-Anxiety
DASS-D	Depression Anxiety Stress Scale-Depression
DASS-S	Depression Anxiety Stress Scale-Stress
DB	David Baguley
dB	Decibel
dBSL	Changed dB Sound Level
DH	Derek Hoare
dHCC	Changes in HCC
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone Sulphate
DHS	Daily Hassles Scale
DHS-N	Daily Hassles Scale-Number
DHS-S	Daily Hassles Scale-Severity
DSB	Digit Span Backward

DSM-5®	Diagnostic and Statistical Manual of mental disorders
DSP	Derogatis Stress Profile
dTFI-T	Change in TFI-T
EEG	Electroencephalography
e.g.	*exempli gratia* (for example)
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	Ecological Momentary Assessment
EMG	Electromyography
ENT	Ear Nose Throat
EPI	Epinephrine
etc	*et cetera* (and the rest)
FMHS-REC	Faculty of Medicine and Health Science Research Ethics Committee
FTQ	Fear of Tinnitus Questionnaire
GABA	Gamma-Aminobutyric acid
GAQ	General Assessment Questionnaire
GAS	General Adaptation Syndrome
GBS	Global Rating Bother Scale
GCM	Group Concept Mapping
GCR	Glucocorticoid receptors
GCSE	General Certificate of Secondary Education
GLM	General Liner Model
GP(s)	General Practitioner(s)
HADS	Hospital Anxiety and Depression Scale
HCC	Hair cortisol concentration
HPAA	Hypothalamus-Pituitary-Adrenal Axis
HR	Heart Rate
HRV	Heart Rate variability
Hz	Hertz
Ibid	*Ibīdem* (in the same source)
IAPT	Improving Access to Psychological Therapies
i.e.	*id est* (that is)
ID	Identification
IGF-1	Insulin-like growth factor-1
IHC	Inner Hair Cells
IHR	Institute of Hearing Research
IL-1	Interleukin-1
IL-6	Interleukin-6
JCQ	Job Control Questionnaire
kHz	Kilo Hertz
K-BEPSI	Korean-Brief Encounter Psychosocial Instrument
KF	Kathryn Fackrell
KJCQ	Karasek Job Control Questionnaire
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LCU	Life Change Unit
LEDS	Life Events and Difficulties Schedule
LES	Life Experiences Survey
LM	Loudness Matching
M	Mean
MCRs	Mineralocorticoid Receptors
MDS	Multidimensional Scaling
Mg	Milligram
MGN	Medial Geniculate Nucleus
MLR	Multilinear Regression analysis
MML	Minimum Masking Level

MRI	Magnetic Resonance Imaging
MSP	Psychological Stress Measurement
N	Number
NE	Norepinephrine
Ne-SS	negative social support
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR Nottingham BRC	National Institute of Health Research Nottingham Biomedical Research Centre
NR	Not reported
NTP	Non-Tinnitus Participants
NUH	Nottingham University Hospitals
PC	Pearson's product moment correlation
PEBL2	The Psychology Experiment Building Language
PFC	Prefrontal Cortex
pg	Picogram
PM	Pitch Matching
PMR	Progressive Muscle Relaxation
Po-SS	Positive Social Support
PPI	Patients and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSQ	Perceived Stress Questionnaire
PSS	Perceived Stress Scale
PTSC	Posttraumatic Stress Disorder
PVN	Paraventricular Nucleus
QCA	Qualitative Content Analysis
QMC	Queen Medical Centre
RI	Residual Inhibition
RLCQ	Recent Life Changes Questionnaire
rTMS	Repetitive Transcranial Magnetic Stimulation
SAM	Sympathetic-adrenal-medullary
SC	Spearman's rank correlation
SCL	Skin Conductance Level
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SEPRATE	Structured Event Probe and Narrative Rating
sig.	Significance level
SkD	Skin Conductance
SLI	Structured Life Events Inventory
SNHL	Sensorineural Hearing Loss
SON	Supraoptic Nucleus
SPSS	Statistical Package for the Social Sciences
SRLE	Severity of Recent Life Event
SRRS	Social Readjustment Rating Scale
SSS	Stress Symptoms Scale
S-VAS	Stress visual analog Scale
T3H	Triiodothyronine
T4H	Thyroxine
TA	Thematic Analysis
TAQ	Tinnitus Acceptance Questionnaire
TCS	Tinnitus Catastrophic Scale
Temp	Temperature
TF	Tinnitus Fragebogen
TFI	Tinnitus Functional Index

TFI-T	Tinnitus Functional Index-Total
TFI-A	Tinnitus Functional Index-Auditory Difficulties
TFI-C	Tinnitus Functional Index-Cognitive Interference
TFI-E	Tinnitus Functional Index-Emotional Distress
TFI-I	Tinnitus Functional Index-Intrusiveness
TFI-QoL	Tinnitus Functional Index-Quality of Life
TFI-R	Tinnitus Functional Index-Relaxation
TFI-SC	Tinnitus Functional Index-Sense of Control
TFI-S	Tinnitus Functional Index-Sleep Disturbance
THI	Tinnitus Handicap Inventory
THQ	Tinnitus Handicap Questionnaire
TNF-α	Tumour Necrosis Factor-alpha
TP	Tinnitus Participants
TQ	Tinnitus Questionnaire
TRN	Thalamic Reticular Nucleus
TRQ	Tinnitus Reaction Questionnaire
TRT	Tinnitus Retraining Therapy
TSCHQ	Tinnitus Sample Case History Questionnaire
TSQ	Tinnitus Severity Questionnaire
TSST	Trier Social Stress Test
T-VAS	Tinnitus Visual analog scale
UK	United Kingdom
ULOQ	Upper Limit of Quantification
USA	United State of America
UV	Ultraviolet
VAS	Visual Analog Scale
VRS	Stress Vulnerability Scale
vs	versus
w	weighted Ranks
WSCT	Wisconsin Sorting Card Test
Y	Year

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CHAPTER 1 OVERVIEW OF THESIS TOPICS

1.1 INTRODUCTION

Tinnitus refers to the phenomenon of hearing sound in the ears or the head without an external source of this sound (Baguley et al., 2013, Noreña, 2015). About one in eight adults are affected by tinnitus and the number is on the rise (Ramage-Morin et al., 2019). It is linked to many disorders and risk factors, stress being one of these. Research on psychological stress has not determined whether stress causes tinnitus and/or the other way around. Establishing the direction of any relationship between stress and health disorders is complicated because the concept of stress is ambiguous and there are limited methods of determining the level of stress. Similarly, tinnitus definitions and assessment methods are varied and many.

In this chapter, I will highlight the complexities in tinnitus and stress in terms of a standard definition, appropriate measurements, and the important research-related issues that affect the study of the relationship between stress and tinnitus.

1.2 TINNITUS

1.2.1 Definition and classification of tinnitus

Tinnitus is generally defined as the perception of sound in the absence of external acoustic stimulation (Baguley et al., 2013). Those who experience tinnitus usually describe the sound as whistling, buzzing, etc. The simplicity of this definition and the lack of descriptive

characteristics of tinnitus carry negative implications for research. The estimation of tinnitus prevalence, for example, can vary according to the question used or criteria applied in different studies (Martinez et al., 2015, McCormack et al., 2016). Some studies asked about tinnitus that last for more than 5 min at a time, other may ask whether the participants have permanent tinnitus all the time. In general, the prevalence of tinnitus in adult populations was reported between 10% and 15% (Baguley et al., 2013) and as high as 30% of the population in other studies (Martinez et al., 2015). What are considered a clinically important finding in epidemiological studies is that 0.5% of adults describe tinnitus as severe enough to affect their ability to lead a normal life, 1.6% describe it as severely annoying, and the prevalence of tinnitus increases with age (Baguley et al., 2013, Shargorodsky et al., 2010, Dawes et al., 2014, McCormack et al., 2016). However, a recent report of data collected through the Canadian Health Measures Survey (CHMS) found that the prevalence of tinnitus among 19-29 year olds to be higher than in its older age groups, which suggests that tinnitus prevalence will increase in the future as the aged population continues to grow (Ramage-Morin et al., 2019).

Various classifications of tinnitus have been proposed based on the underlying pathology, duration, clinical severity, laterality, or psychoacoustic characteristics (Cianfrone et al., 2015). For diagnostic purposes, tinnitus is generally classified as subjective, when the tinnitus is only perceived by the patient, or objective when tinnitus can also be heard by an examiner (Baguley et al., 2013). Objective tinnitus is mainly

related to vascular defects (pulsatile tinnitus) or muscular contraction (myoclonus) (Cianfrone et al., 2015). However, objective tinnitus is not common and pulsatile tinnitus can be subjective (i.e. in some cases the examiner cannot hear it) (Topal et al., 2008).

Tinnitus is also classified as primary when it is idiopathic or generated within the auditory pathways (usually co-morbid with sensorineural hearing loss (SNHL)), or secondary when it has an identifiable underlying cause (other than SNHL) such as impacted ear wax in the external ear canal, Acoustic Neuroma (a benign tumour develops on the eighth cranial nerve), and middle ear diseases (Tunkel et al., 2014, Henry, 2016). Another classification is based on self-reported measurements. Tinnitus is subtyped into bothersome and non-bothersome, which has more clinical value in terms of assessment and follow-ups. Finally, tinnitus can be continuous or intermittent, and some people report occasional episodes of tinnitus. In general, the characteristics of each tinnitus subtype are not related to a known aetiology (Martines et al., 2010) and cannot be used to localise a defect in the auditory pathway (Møller, 2016). Tinnitus is therefore a markedly heterogeneous disorder, and patients may present diverse clinical profiles that cannot be related to a certain subtype (Cederroth et al., 2019) which makes these classifications less valuable.

1.2.2 Pathophysiology of tinnitus

Most people who do not experience tinnitus hear tinnitus-like sounds if they were in a sound-proofed room or silent environment (Heller and Bergman, 1953, Tucker et al., 2005). This might indicate that normal

underlying activities in the auditory pathway are perceived as sound which might be faint and masked by ambient noise. Thus, tinnitus may be an awareness of exacerbation or change in neural activities within the auditory system that may be a symptom of underlying pathologies (Jastreboff, 1990, Baigi et al., 2011, Han et al., 2009).

The pathophysiology of tinnitus cannot be summarised in a single explanation; there are multiple theories. Almost all theories state that tinnitus signals are triggered by an abnormal activity (increase firing signals, hyperactivity, or abnormal synchrony) or damage (deprivation of sensation or deafferentation) in the peripheral auditory system that is interpreted by central auditory systems as sound (Jastreboff, 1990). The neurophysiological model of tinnitus states that the abnormal activity may be a continuous or spontaneous firing of cochlear fibres to the brain resulting from damaged cochlear hair cells (Jastreboff, 1990). Eggermont and Roberts (2004) proposed that a lesion in the cochlea leads to a loss of the input from the lesioned area and corresponding afferent nerves. This loss leads to an overrepresentation of lesion-edge frequencies in the central auditory cortex that leads to perceiving tinnitus.

Tinnitus related activity may not only occur in auditory areas. Evidence suggests that tinnitus is linked to excessive neural activity in non-auditory brain networks, mainly limbic, parietal, and frontal regions (Figure 1.1) which are involved in arousal, emotion, stress, and motor control (Chen et al., 2017b, Henry et al., 2014, Kreuzer et al., 2013).

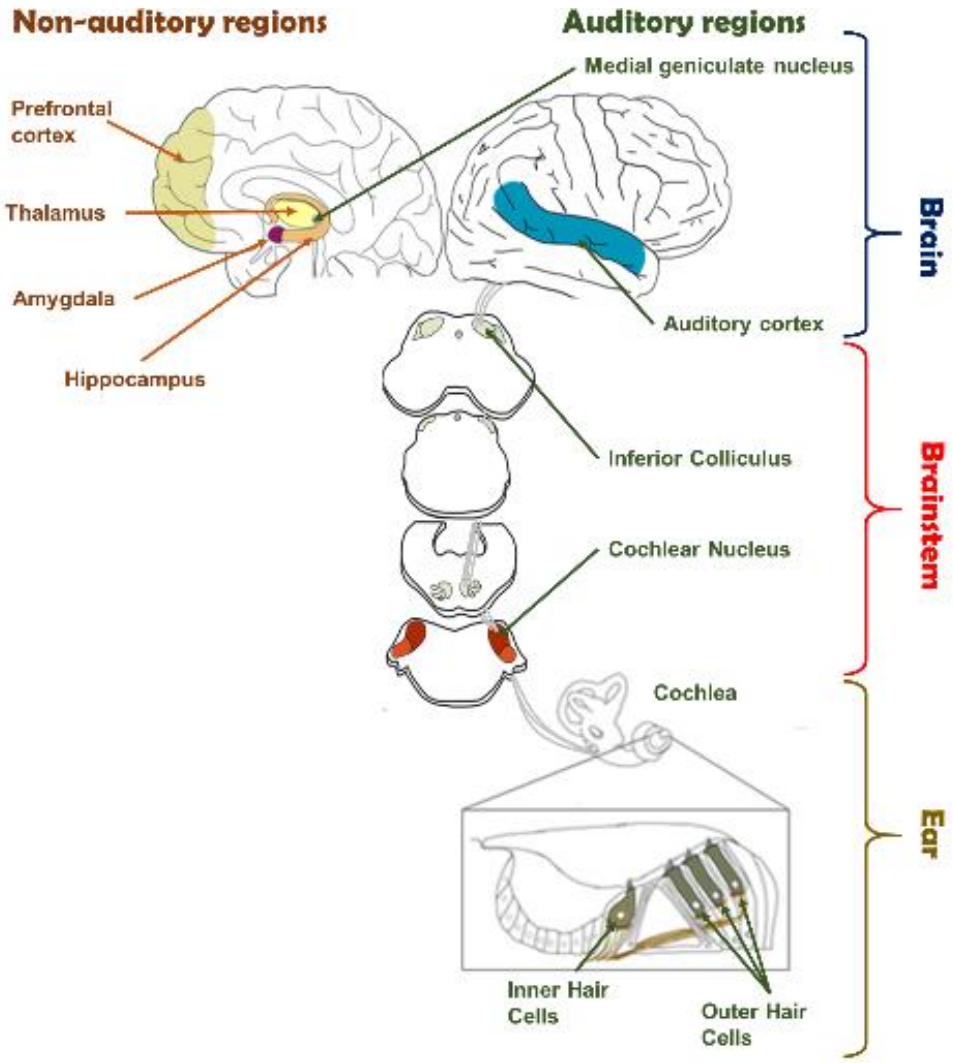


Figure 1.1 Auditory and non-auditory neuronal structures associated with the pathogenesis of tinnitus.
Auditory areas are listed on the right side of the figure, and non-auditory areas are listed on the left. The cochlea is the inner part of the ear where the inner hair cells are the sensory receptors of the sound are located.

This link between auditory and non-auditory areas might explain why tinnitus is bothersome for some patients and not others. Jastreboff (1990) suggested that tinnitus signals are processed in the limbic system that in turn stimulate the autonomic nervous system. This leads to increased symptoms of anxiety that makes tinnitus sounds louder. Another explanation was proposed by Rauschecker et al. (2010). They

hypothesised that tinnitus signals in non-sufferers are cancelled out by an inhibitory feedback loop, which originates in para-limbic structures and inhibits the medial geniculate nucleus (MGN; part of the central auditory pathway) in the thalamus. A defect in this loop (in the para-limbic structure) may lead to failure in inhibiting tinnitus signals, which are subsequently perceived at the auditory cortex as sound. They called this theory the “inhibitory gating mechanism.”

Adjamian et al. (2014) reviewed several radiological studies that reported changes in the central structures, including the prefrontal cortex (PFC) and the amygdala, in patients with tinnitus. They concluded that tinnitus onset might be facilitated by hearing loss, but its perception likely requires an interconnected neuronal circuity that involves auditory, limbic, and possibly other structures. Subsequently, long-term maintenance of tinnitus (chronic tinnitus) results from neuronal and synaptic changes i.e. neuroplasticity (Henry et al., 2014, Møller, 2016, Bruggemann et al., 2016). This means that the inhibition of the input from the peripheral auditory pathway might lead to neuroplastic changes in the related auditory areas. Neural changes can occur at the level of synapses between inner hair cells (IHC) in the ears and the auditory nerve and at multiple levels of the central auditory pathway (Henry et al., 2014).

Resting-state imaging studies have shown that the interaction between multiple brain networks, such as the auditory network, default mode network, attention network and visual network, correspond to various aspects of tinnitus (Chen et al., 2017a). Attention networks (Petersen

and Posner, 2012) may be important in gating, synchronising or manipulating information across different cognitive processes (Gu et al., 2015) and stronger connectivity within attention networks was observed in those who had bothersome tinnitus compared to those who had mild tinnitus (Shahsavarani et al., 2021, Burton et al., 2012). This suggests that plastic changes within the attention networks might result in habituation to tinnitus (Husain, 2016, Shahsavarani et al., 2021) and /or control the cognitive and emotional impact of tinnitus (Khan and Husain, 2020).

Emerging studies indicate that tinnitus results from defects in the higher-order neuronal feedback signals (top-down) and sensory signals (bottom-up). Sedley et al. (2016) proposed the “sensory precision tinnitus model.” This model is based on the “hierarchical predictive coding model” of visual processing (Rao and Ballard, 1999) in which the visual cortical area sends “prediction” signals to lower neuronal connections (top-down) and the retina sends the sensory stimuli (bottom-up). The neuronal connections carry up “the residual errors of prediction” which is the remaining component of the input signals after removing the prediction signals (Huang and Rao, 2011, Rao and Ballard, 1999). In the sensory precision tinnitus model, spontaneous activity of the auditory higher-order neurons constitutes a ‘tinnitus precursor’ and considered as top-down predictions that are normally ignored against the usual percept of silence. Tinnitus is perceived in the absence of structured auditory input to remove the prediction, or when the postsynaptic gain within the neuronal connections rises sufficiently

to overcome auditory input. Transient elevation in precision may occur as a result of changes in neurophysiological, hormonal, and/or neurochemical factors including in attention, illness, and stress (Sedley et al., 2016).

Theories of tinnitus pathophysiology are based on findings in animal studies. In these studies, induced injury to the inner ear (by exposing the animal to noise or ototoxic agents) leads to hearing loss and behavioural evidence of tinnitus (Haider et al., 2018). Therefore, the assumption that a peripheral auditory lesion is a key element in the pathophysiology of tinnitus is uncertain. Tinnitus may be triggered by other pathologies in the central nervous system. There is growing evidence to support the hypothesis that tinnitus results from changes in the central nervous system which may or may not be triggered by changes in the peripheral auditory pathway (Henry et al., 2014, Adjamian et al., 2014, Noreña and Farley, 2013, Noreña, 2015). The role of the peripheral lesion is not fully supported by evidence. Adjamian et al. (2014) reported that changes in central structures were associated with hearing loss in some studies, however, it was not necessarily associated with hearing loss in others. Auditory brainstem response (ABR) studies in patients with tinnitus and normal hearing indicate a reduced excitation of the auditory nerve fibres (Konadath and Manjula, 2016), and indicates a lesion in the central auditory pathway up to the inferior colliculus region (Ravikumar and Murthy, 2016). These abnormalities were reported only in 40% of these patients. Therefore, it is possible to have severe tinnitus with no evidence of pathology in the

ears (Phillips and McFerran, 2010). Although most patients with tinnitus have peripheral hearing loss when measured by standard and high-frequency audiogram, not all patients with SNHL develop tinnitus (Rauschecker et al., 2010) which means that tinnitus can occur without a predisposing lesion in the ear.

1.2.3 Symptoms and diseases associated with tinnitus

Tinnitus is an auditory symptom. However, it is associated with otological (i.e. ear-related) and non-otological diseases (Martinez et al., 2015, Tunkel et al., 2014) as summarised in Table 1.1.

Table 1.1 Diseases and disorders associated with tinnitus

		Diseases or conditions
Otological	Infectious	Otitis media, labyrinthitis, mastoiditis.
	Neoplastic	Vestibular schwannoma (Acoustic neuroma), meningioma.
	Labyrinthine (Inner ear)	Sensorineural hearing loss, Ménière's disease, Vestibular vertigo.
	Other	Impacted ear wax, otosclerosis, presbyacusis (Age-related hearing loss), noise exposure.
	Ototoxic Medications	Analgesics, antibiotics, antineoplastic, corticosteroids, diuretics, immunosuppressive, non-steroidal and steroidal anti-inflammatory drugs.
Non-otological	Neurological	Meningitis, migraine, multiple sclerosis, epilepsy.
	Traumatic	Head or neck injury, loss of consciousness.
	Musculoskeletal	Temporomandibular joint disorder, cervical spondylosis,
	Cardiovascular	Hypertension, angina, myocardial infarction,
	Rheumatological	Rheumatoid arthritis, osteoarthritis,
	Immune-Mediated	Systemic lupus erythematosus, systemic sclerosis.
	Endocrine and Metabolic	Diabetes mellitus, hyperinsulinaemia, hyperlipidaemia, hypothyroidism, hyperthyroidism, pregnancy.
	Psychological	Anxiety, depression, emotional trauma.

Sources : Baguley et al. (2013), and Kim et al. (2014)

Otological pathologies can lead to damage to the auditory apparatus and this might explain their association with tinnitus. But the link between non-otological disorders and tinnitus is not clear. Yet, the poor psychological well-being of individuals with tinnitus has been documented (Milerova et al., 2013). First, a high prevalence of psychiatric disorders, mainly anxiety and depression, have been reported in tinnitus populations (Durai and Searchfield, 2016, Pattyn et al., 2016, Pinto et al., 2014, Crocetti et al., 2009). Second, the severity of depression correlates significantly with tinnitus severity and annoyance (Folmer et al., 1999, Pinto et al., 2014). Third, the presence of either major depressive disorder or generalised anxiety disorder increases the risk of reporting tinnitus later in life (Shargorodsky et al.,

2010). However, anxiety and depression may be a consequence of tinnitus rather than a predisposing factor (Hebert et al., 2004). So, the association may be bidirectional.

Besides hearing loss, tinnitus is sometimes comorbid with other auditory conditions such as hyperacusis (reduced sound tolerance), misophonia (perception of specific noises as unpleasant), or phonophobia (fear of specific noises) (Al-Swiahb and Park, 2016, Kreuzer et al., 2013). Tinnitus is also associated with concentration difficulties, insomnia, decreased speech discrimination, and impaired cognitive performance (Han et al., 2009, Andersson et al., 2000, Crönlein et al., 2016, Folmer and Griest, 2000).

1.2.4 Measurements of tinnitus

Tinnitus has two main attributes. These are the tinnitus percept and the tinnitus reaction (Henry et al., 2019b, Hall et al., 2018). Tinnitus percept refers to its psychoacoustic characteristics (loudness, pitch, and timbre/spectral content). Tinnitus reaction refers to various domains such as emotional distress (i.e. the negative emotional effects of tinnitus (Meikle et al., 2008)) and sleep disturbance which are measured by psychometric instruments (Møller, 2016, Hall et al., 2018). Therefore, tinnitus is measured using psychoacoustic procedures to assess the subjective ‘amplitude’ or pitch of the perceived sound, and psychological self-reported measurements to measure the type and degree of distress it is causing.

1.2.4.1 Psychoacoustic measurements

1. Pitch Matching (PM): Tinnitus pitch refers to the perceived frequency of tonal tinnitus or centre frequency of non-tonal tinnitus (Henry, 2016). In patients with hearing loss, tinnitus pitch often corresponds to the frequency range neighbouring or within the hearing loss region (McNeill et al., 2012). The patient is asked to match their tinnitus pitch to the pitch of an external sound or the pure tone frequency that is closest to the perceived tinnitus frequency. PM has poor reliability (Henry et al., 2019b). PM can be used in clinical evaluation (Cima et al., 2019) but the UK tinnitus guidelines (NICE, 2020) do not give advice about the use of PM in clinics.
2. Loudness Matching (LM): An auditory stimulus (usually a pure tone at 1000 Hertz) is presented and the patient is asked to adjust the loudness of the stimulus to match the perceived loudness of their tinnitus (Henry, 2016, Meikle et al., 2008). Although most tinnitus patients reliably produce LM (Meikle et al., 2008), it has low clinical value in terms of diagnosing and assessing the severity of tinnitus (Henry, 2016).
3. Minimum Masking Level (MML): This refers to the minimum level of broadband noise (BBN) required to mask a person's tinnitus (i.e. make their tinnitus "inaudible") (Henry, 2016). The noise is adjusted in small steps (1-2 decibel). MMLs are used to determine the effectiveness of masking therapy as a treatment, but MML testing has little value for tinnitus assessment. They do not predict the level

of emotional distress or functional consequences of tinnitus. For example, high MML are not associated with a substantial annoyance to the patient (Henry, 2016). Also, the MML procedure may exacerbation tinnitus (Meikle et al., 2008) which limits their use in the clinical assessment (NICE, 2020).

4. Residual inhibition (RI) refers to the temporary suppression of tinnitus that often occurs immediately after auditory stimulation (Henry, 2016), which can last from seconds to hours (Roberts et al., 2008).

1.2.4.2 Self-reported measurements

1. Rating scale: One example is the Visual Analog Scale (VAS) which is used to evaluate tinnitus severity, loudness, or awareness. When it was used to assess perceived loudness, it tended to correlate with the degree to which tinnitus impacted the patient (Henry, 2016). Therefore, it was advised that VAS as a measure of severity or loudness should be interpreted cautiously and used with other measures of tinnitus (*ibid*).
2. Questionnaires and inventories have been developed to measure tinnitus and used in clinics to identify and to monitor specific areas of the patient's life that are affected by tinnitus (Haider et al., 2016). Each questionnaire covers multiple overlapping tinnitus-related complaints (Møller, 2016, Haider et al., 2016, Kennedy et al., 2004). For example, the Tinnitus Reaction Questionnaire (TRQ; Wilson et al., 1991) measures the emotional consequences of tinnitus. The Tinnitus Handicap Inventory (THI; Newman et al., 1996) , Tinnitus

Questionnaire (TQ; Hallam et al., 1988) , and Tinnitus Functional Index (TFI; Meikle et al., 2012) are the most frequently recommended tool in clinical guidelines (Fuller et al., 2017, NICE, 2020) and the commonly used in the UK (Hoare et al., 2015). The THI is used to quantify the functional and psychosocial consequences of tinnitus and its impact on daily life (Salviati et al., 2013). The TQ measures tinnitus-related distress, or severity, as perceived by patients (Zeman et al., 2012). The TFI will be explained in 3.3.5.3. Tinnitus questionnaires are recommended for clinical evaluation (Cima et al., 2019, NICE, 2020, Møller, 2016). However, they are subjective and affected by the patients' response and interpretation. Also, the psychoacoustic and psychometric measurements of tinnitus do not usually correlate (Manning et al., 2019, Basile et al., 2013, Hoare et al., 2014).

Each tinnitus instrument measures different tinnitus domains (Hall et al., 2018) and tinnitus level is described according to the instrument used. For example, TQ generally describe the psychological impact of tinnitus, thus it describes tinnitus distress (Zeman et al., 2012). In this thesis, tinnitus level will be used to describe tinnitus scores measured by different instruments. Tinnitus impact will describe the scores measured by the TFI. Tinnitus assessed by T-VAS will be described according to the domain it measures. For example, T-VAS annoyance will describe the level of tinnitus annoyance.

1.2.4.3 Other measurements of tinnitus

There are many attempts to use audiology measurements (such as ABR and otoacoustic emissions), and non-audiological measurements (such as blood biomarkers, radiology, and imaging tests) to assess the severity of tinnitus (Milloy et al., 2017, Jackson et al., 2019, Dadoo et al., 2019). However, there is poor evidence to support the value of using these tests as objective measurements for tinnitus (Jackson et al., 2019).

1.2.5 Management of tinnitus

The first step in managing tinnitus is treating any underlying disorders (listed in Table 1.1). Yet in many cases, the possible cause of tinnitus is irreversible, as with ototoxicity and age-related hearing loss (presbyacusis), or after acoustic neuroma excision (Jason et al., 2016). So, the management aims to alleviate tinnitus distress and its effect on daily life.

Tinnitus management targets either the perception of tinnitus and/or its negative consequence (Hobson et al., 2012, McFerran et al., 2019). Because tinnitus is a multifactorial condition, a single treatment cannot be expected to treat all forms (Møller, 2016, Henry et al., 2019a, NICE, 2020). All the available treatments (Table 1.2) have been subjected to trials and studies, and none of them effectively treat tinnitus in all individuals.

Table 1.2 Management of tinnitus.
Pharmacological and non-pharmacological treatments of tinnitus with short explanation of their principles and mode of action.

Non-pharmacological	Characteristics of the treatment
Tinnitus retraining therapy (TRT)	- Based on the neurophysiological approach (Jastreboff, 1990). - Aims to change the negative emotional response associated with tinnitus (Jastreboff and Hazell, 2008). - Acoustic stimulation (broadband ear-level sound generator are used to mask the tinnitus partially) combined with educational counselling (Kreuzer et al., 2013). - Changes the perception of tinnitus from a negative stimulus to a neutral stimulus (Martz, 2016).
Sound therapy (masking)	- External noise is used to mask tinnitus completely or partially and distract patients from tinnitus (Pienkowski, 2019). - Individually tailored (Hobson et al., 2012).
Hearing aids	- Amplification with hearing aids may distract the patient from tinnitus and enabling masking (McNeill et al., 2012). - Improves auditory input in the affected region (Kreuzer et al., 2013) and the quality of life related to hearing difficulties (McNeill et al., 2012).
Cochlear implants	- Partial or total suppression of tinnitus was noticed in cochlear implants users (Quaranta et al., 2004). Its use may reduce tinnitus-related distress (Knopke et al., 2017).
Neuromodulation	- The generated tones can be modified according to tinnitus pitch-matching (Teismann et al., 2014, Bastos and Sanchez, 2017).
Repetitive transcranial magnetic stimulation (rTMS)	- Magnetic field is produced by magnetic coils placed above the scalp. It believes to inhibit cortical excitability localised within 2 cm distance (Meng et al., 2011).
Cognitive behavioural therapy (CBT)	- Aims to promote habituation and to alter the cognitive distortions associated with having tinnitus (Martz, 2016). It improves tinnitus-related distress and quality of life (Hébert et al., 2012b). - It is not clear if it acts directly on tinnitus or improving the associated psychological conditions (Martinez-Devesa et al., 2010). - CBT may reduce the impact of tinnitus on quality of life as measured by THI (Fuller et al., 2020).
Mindfulness	- It is a process of purposefully paying attention to what is happening now without being distracted by the associations attached to those thoughts or sensations (Kabat-Zinn et al., 1987). - Enhance the effect of psychoeducation and maintained its benefit (Philippot et al., 2012)
Low-level laser therapy	- A low-power laser targets the cochlea through the external auditory canal (Cuda and De Caria, 2008).May increase cell proliferation and blood flow to the inner ear (Fioretti et al., 2011). - Worsening of tinnitus can occur beside other side effects (Salahaldin et al., 2012).
Acupuncture	- Modifies the production of neurotransmitters released in the central nervous system. Not enough evidence of its effectiveness in tinnitus (Kim et al., 2012).
Pharmacological	
Ginkgo biloba	- Increases blood flow, prevents platelets aggregation and protects against free radicles (Hilton et al., 2013). - Side effects range from mild gastrointestinal disturbance up to bleeding problems, interaction with anticoagulant medication and seizures (Hilton et al., 2013).
Anticonvulsants	- Inhibits the central auditory system by inhibiting the production of glutamate and inhibits cell depolarisation (Hoekstra et al., 2011).
Antidepressants	- Acts by improving the underlying psychological symptoms. It may act on receptors implicated in the mechanism of tinnitus (Baldo et al., 2012).
Melatonin	- Has antioxidant properties and it seems to improve tinnitus-related sleep disturbance (Miroddi et al., 2015)

Systematic reviews concluded that there is no evidence for the effectiveness of Tinnitus Retraining Therapy (TRT) (Phillips and McFerran, 2010), sound therapy or masking (Hobson et al., 2012), hearing aids (Sereda et al., 2018), repetitive transcranial magnetic stimulation (rTMS; Meng et al., 2011) , Ginkgo biloba (Hilton et al., 2013), anticonvulsants (Hoekstra et al., 2011), antidepressants (Baldo et al., 2012), or acupuncture (Kim et al., 2012) in managing tinnitus. Some individual studies have shown promising effects. In a single study, TRT was more effective than tinnitus masking in reducing tinnitus level (Henry et al., 2006).

Pharmacotherapy is restricted to treat comorbidities such as anxiety disorders, sleep disorders, and depression (Kreuzer et al., 2013). Cognitive Behavioural Therapy (CBT) has a positive effect on the management of tinnitus as it improves depression score or reduces depression symptoms (Fuller et al., 2020). Aazh et al. (2016) surveyed patients views on their different tinnitus treatments and reported that client-centred counselling helped the patients in managing their tinnitus, and was superior to CBT, counselling, hearing aids, or broadband noise generators.

There are many obstacles to tinnitus research that prevent reaching an effective cure or management. These include the lack of objective outcome measures and the uncertainty about the duration required to achieve a measurable improvement (McFerran et al., 2019). Phillips et al. (2018) reviewed the prognosis of tinnitus in the no-treatment arms in clinical trials assessing tinnitus interventions and they found that these

groups of participants generally demonstrate a small but statistically significant improvement in self-reported global tinnitus severity scores over time. This indicates that tinnitus patients may exhibit improvement in tinnitus levels over time without receiving any intervention, which makes the effect of any management questionable.

1.3 STRESS

Stress is a term commonly used to describe any situation that makes a person feels helpless or worried (Koolhaas et al., 2011). The ambiguity of this definition does not provide for measurable variables which can be used in assessing the relationship between stress and illnesses (Kagan, 2016, Karatsoreos, 2018). Stress is a complex concept and acknowledging this complexity is required for stress-related research (Arthur, 2004, Lazarus, 2000). In psychology, three concepts have been suggested to enable researchers to measure the contribution of stress in developing illnesses.

1.3.1 Concepts of stress in psychology

1.3.1.1 Stimulus-based concept

This environmental concept describes stress as a life event that a person experiences which provokes physical and psychological adaptive effects on the body (Papathanasiou et al., 2015). The event may have a definable starting point (Harkness and Monroe, 2016). These events may be irritating or distressing day-to-day difficulties or demands (daily hassles), significant incidents that result in changes in life circumstances (major events), or catastrophic events. Here, the

intensity and duration of the stressful events determine the level of stress which may have a cumulative effect (Cohen et al., 2016, Epel et al., 2018). This model assesses the occurrence of environmental events or experiences but ignores the assessment of individuals' variations and whether they perceive the event as stressful. To overcome these limitations, Cohen et al. (2019) recently proposed an alternative theoretical perspective on what can be classified as a "*stressful event*." In this perspective, the stressfulness of an event depends on four factors. These are (1) the amount of adaptation required to overcome this event, (2) the level of threatening or harmfulness of the event, (3) the balance between demand and resources, and/or (4) interruptions of an individual's major goals. These perspectives overlap and none of them can completely embrace the meaning of "stressful event", and the necessary criteria are for classifying the event as "stressful" remains unclear (Cohen et al., 2019).

The stimulus-based concept was based on observations that physical illness is associated with the occurrence of a recent major event (Cohen et al., 1995), or with an increase in daily hassles (Delongis et al., 1988). Despite the fact that these observations resulting from uncontrolled cross-sectional studies in patients (non-representative samples), and that most people who experienced stressful events do not necessarily develop an illness (Cohen et al., 2019), the effect of life events and daily hassles on health is still accepted as a concept of stress (*ibid*).

1.3.1.2 Response-based concept

This concept describes the biophysiological changes in response to exposure to physical and psychological demands. These changes are mediated by the Sympathetic Nervous System (SAM; see 1.3.4.1) and the Hypothalamus-Pituitary-Adrenal Axis (HPAA; see 1.3.4.2). The response to stress/threat was described as “fight or flight” response by Cannon (1923) who explained the effects of emotional arousal (fear) on neuroendocrine and sympathetic activity (Cannon, 1923, Gerin, 2011). Selye (1956) defined stress response as “a non-specific response of the body to any demand” and called the response the General Adaptation Syndrome (GAS) which is formed of three stages (Selye, 1956, Saxena, 1980, Gerin, 2011). In each stage, the amount of stress hormones released, such as adrenaline and cortisol, is different and therefore the physiological responses vary. These stages are:

1. Alarm stage: A surge of stress hormones and mediators leads to an increase in heart rate, glucose level in blood, and alertness state, to help the body to “fight or flight” the stressful situation.
2. Resistance stage: Chronic exposure to stressors leads to physiological changes that promote full adaptation and this may lead to deleterious effects on different organs.
3. Exhaustion stage: If the demand is severe or prolonged beyond the ability of the body to physiologically adapt or overcome this effect, vulnerable organs will collapse, and stress-related disorders appear.

The development of GAS was based on Selye’s observations of changes in rats exposed to “non-specific nocuous agents” such as

exposure to extreme cold, or excessive muscular exercise for a relatively short duration (Selye, 1936). This model was criticised because it explained the effect of a negative (threat) but not positive (happy) event (Aldwin, 2007). However, Selye (1956) subsequently modified his theory and classified the stimuli into eustress (good) and distress (bad), so the patterns of response vary according to the type of stressor and not all stressor leads to damaging effects (Saxena, 1980, Kagan, 2016). The model also has been criticised for failing to consider the individual differences in physiological and psychological responses to the stressors (McEwen, 2005), which is a major limitation.

To overcome this major limitation of Selye's model of stress, McEwen and Stellar (1993) proposed a different approach to explain the stress response. They coined the terms allostasis, allostatic loads, and allostatic overloads which refer to the "wear and tear" response that the body experiences during repeated stressful situations (McEwen and Stellar, 1993). Allostasis refers to the biophysiological responses to everyday demands and activation of neural, neuroendocrine, and immune systems that contribute to adaptation and stability of homeostasis and do not necessarily have a damaging effect (McEwen and Akil, 2020). When the body is exposed to a new stressor, additional physiological and biological changes occur. If these responses are overused due to frequent or prolonged activation they lead to maladaptation to the changes. Subsequently, the cumulative cost to the body leads to allostatic load and overload which lead to the

development of stress-related diseases (Karatsoreos and McEwen, 2011, Cohen et al., 2016).

McEwen (1998) indicated that the perception of threat and the mobilisation of the allostatic process are affected by individual differences, such as genetics, development, experience, behavioural, and experiences of early-life major events (Figure 1.2). Thus, they acknowledged the individual variations in developing stress-related diseases.

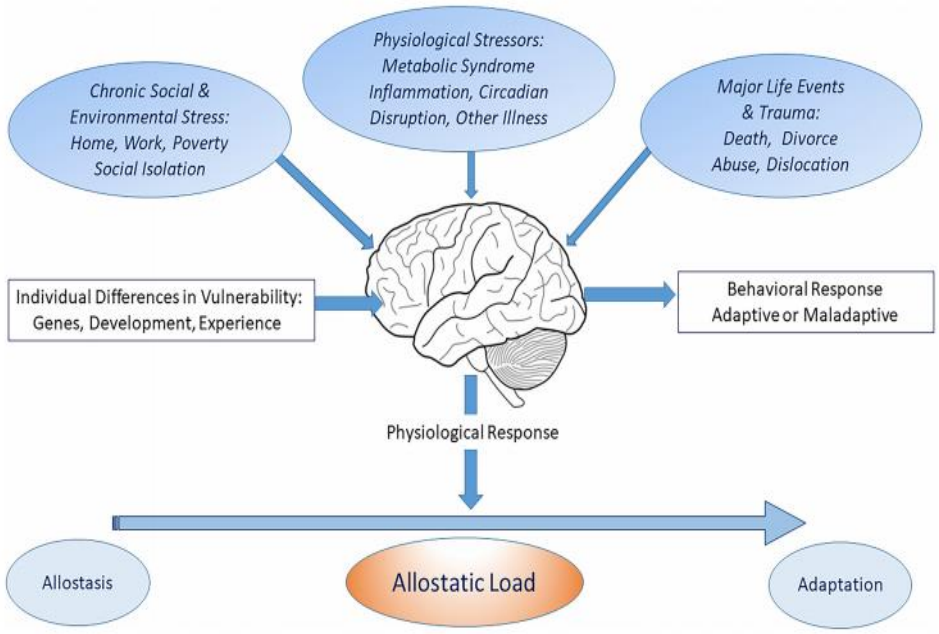


Figure 1.2 The stress response and development of allostatic load Experiencing a stressful event initiates neuronal response that lead to allostasis and adaptation. Accumulation of allostatic load and stress mediators can lead to developing diseases and disorders. Source: McEwen and Akil (2020).

1.3.1.3 Transactional concept of stress

This concept emphasises the importance of an individual's perception of the stressor. Lazarus & Folkman (1984) explained that stress is an interaction between stressors (external or internal events), individual's appraisals (perception and interpretation), and the internal or external resources available to overcome the effect of the stressor. The response will depend on the vulnerability of the person and the characteristics of the environmental factor (Morrison and Bennett, 2009, Cohen et al., 2016). In the transactional concept of stress, individual variations, and the role of appraisal in modulating the perceived stress are considered. The appraisal is a cognitive process that evaluates the event and determines whether and to what extent it was stressful. So,

the individual assesses or appraises the event as a threat, challenge, or irrelevant (i.e. having no implications for the person's well-being); this is called primary appraisal. In secondary appraisal, the person assesses resources and abilities to determine the possibility of coping (managing the demands and related emotions) or eliminating or diminishing the effects of the event (Lazarus and Folkman, 1984, Cohen et al., 1995). The event will be perceived as stressful if it is appraised as challenging or threatening, if the coping abilities are insufficient to meet the demands of the event, and if it is accompanied by negative emotional responses (Rice, 2012, Cohen et al., 1995). The role of stimulus, emotional and behavioural response, individual differences, and the external environment in perceiving stress are considered in determining the impact of the event (Cohen et al., 1983). This concept was later developed into the transactional model of stress and coping (Lazarus and Folkman, 1987) to emphasise the role of coping in modulating the perceived stress. It explains the reappraisal of the event in which the person would engage if they failed to cope with the event (Rice, 2012, Denovan and Macaskill, 2013).

In terms of definition, stress cannot be comprehensively defined by one concept. For instance, there is a link between stimulus-based stress and perceived stress (Monroe, 2008), in particular, the recognition of the effect of demand and the required adaptation as integrated parts in classifying the event as stressful (Cohen et al., 2019). Also, there are contradictions between the models. Lazarus's concept is solely based on the subjective assessment of stress and the ability of the person to

modulate stress. On the other hand, Selye's model depicts stress as an unavoidable non-specific response to a change in the environment. The stimulus-based concept only assesses the occurrence and the strength of the event.

In these models, stress is depicted as a unidirectional process. However, stress can be bidirectional, as explained in the transactional model of stress. The appraisal of the event as challenging can bring a positively perceived stress resulting in positive outcomes such as reprioritisation of life goals, increased feeling of self-esteem and self-efficacy (Cohen et al., 1995). These may in turn enhance the positive appraisal of later events as the person will adopt new coping strategies.

In this thesis, the working definition of stress is the bidirectional and continuing transaction between the person and the environment that can be modulated by cognitive appraisal and affected by the nature of the related event or change. It leads to bio-physiological changes to preserve homeostasis of the body. Thus, stress should be measured as three variables: bio-physiological changes, the occurrence of the event, and the perceived stress.

1.3.2 Acute and chronic stress

In Selye's early experiments (Selye, 1936), the exposure to an acute stressor (such as exposure to extreme cold or electrical shock for few hours) elicited the alarm response but when the same stressor was used for a longer duration or repeatedly (over 1 to 3 months) with relatively low intensity it elicited the resistance response; damage

occurred only when the intensity of the stressor increased. These results gave a glimpse of the effects of exposure to short- and long-term stressors. So, the effect of stress depends on the duration of exposure to stressors, and differentiation between acute and chronic stress is important in studying the relationship between stress and illness (Cohen et al., 1995, Schommer et al., 2003).

Stress can be classified as acute when it is in response to a single, time-limited event, intermittent when the body is exposed to the same stressor more than once, and chronic when it persists for a long time (Kovacs et al., 2004, Baum et al., 1999, Cohen et al., 2019). This classification is based on the duration of the event but not the duration of the response. Cohen et al. (1995) suggested three parameters to define the duration of stress based on all psychological concepts: the duration of the event, duration of perceived threat, and duration of stress response. However, a time-frame which determines the chronicity of stress does not exist (Bloch et al., 2004) as it is affected by many factors that influence these parameters such as individual's appraisal of the event and coping abilities, as explained by Lazarus and Folkman (1987). Also, defining the duration of each parameter is challenging. For example, daily hassles (duration-of-event parameter) could be acute as they occur for a short-time, but also chronic because they occur repeatedly over a long time.

In general, it is accepted that stress has a cumulative effect on the body and each additional stress adds to the overall burden of the required adaptation (Cohen et al., 2016). Regardless of the timescale of the

event, stress levels are influenced greatly by social context e.g. someone who experiences long-term stress is more likely to report a greater number of daily stressors and greater general perceived stress at any time point (Epel et al., 2018).

1.3.3 Stress, stressor, or stress response

Stressor, stress stimulus or event, can be defined as the external or internal change in the environment that is sensed by an organism (Steckler et al., 2004) and can be classified into psychological and physical (internal such as inflammation or external such as burn or electrical shock). Physical stressors are sensed by internal and external receptors and transmitted through ascending visceral and somatosensory pathways, and activates subcortical autonomic circuits which directly affect motor neurons without significant cortical contribution (Steckler et al., 2004, Kovacs et al., 2004). Psychological stressors on the other hand require cognitive and emotional processing, involve higher brain areas such as the hippocampus (Steckler et al., 2004, Conrad, 2011), and involve complex somatosensory and neuronal response mechanism (Kovacs et al., 2004). However, the distinction between these two types of stressor is not clear as physical stressors can involve a cognitive and learning function in the brain. Therefore, stressors are mostly a combination of the psychological and physical (Steckler et al., 2004, Li et al., 2019b, Finnell et al., 2017).

Exposure to a stressor causes physiological and psychological changes according to the intensity and duration of the stressor, and the vulnerability of the recipient (as explained in 1.3.1). The body will

respond by various mechanisms including behavioural, psychological and bio-physiological, to restore the equilibrium of the body and reduce or eliminate the effects of the stressor (Bali and Jaggi, 2015, Steckler et al., 2004). What is defined as a response in the response-based concept is different from the response in the transactional model of stress. In the former, the response is entirely bio-physiological and inevitable (explained in 1.3.4) whereas in the later the response is the perceived stress (explained in 1.3.1.3), so it can be modulated by cognitive appraisal. Unsurprisingly, the bio-physiological and the psychological responses are linked and interrelated as the stress-related hormone and mediators play a role in activation of brain circuits related to stress. In the stimulus-based and response-based concepts the response starts once the organism is exposed to the stressor. However, in the transactional model of stress the response is psychological and behavioural and there is a difficulty in establishing the exact beginning of the response as there is an overlap between the primary and secondary appraisal (Morrison and Bennett, 2009). In addition, it is not clear whether the cognitive appraisal or anticipation of an event change the stress mediators' level or the change in stress mediators effects the cognitive function (Aldwin, 2007, Aschbacher et al., 2013).

In this thesis, the words "stressor" and "events" will be used interchangeably to indicate the environmental changes or demands that provoked the response. The word "response" will indicate the bio-

physiological changes. The perceived stress will indicate the perception of a situation as stressful or challenging.

1.3.4 Stress and bio-physiological changes

Preserving homeostasis of the body after transaction with environmental demands is vital. The major players in homeostasis are the neuroendocrine system and the sympathetic nervous system. Both regulate the excretion of hormones and mediators that activate pathways involved in metabolism, immunity, and cell proliferation (Finnell et al., 2017, Fink et al., 2012).

1.3.4.1 Sympathetic-adrenal-medullary (SAM) axis

The SAM axis is one of the main pathways that is activated by stress and provides rapid response to stressful stimuli (Aguilera, 2012, Tsigos and Chrousos, 2002). The SAM axis is a direct connection between the sympathetic nervous system and the medulla of the adrenal gland, and activation leads to the release of catecholamines, namely adrenaline and noradrenaline, into the vascular circulation (Aldwin, 2007, Wosu et al., 2013). Sympathetic activation enhances renin and subsequently angiotensin-II (AT-II) production. AT-II receptors are highly expressed in the hypothalamic-pituitary-adrenal axis (see 1.3.4.2), hippocampus, and the amygdala (Saavedra et al., 2011) and their activation increases adrenocorticotropic hormone (ACTH) and glucocorticoid secretion. AT-II enhances secretion of vasopressin, a weak stimulator of ACTH (Bale and Vale, 2004) which indicates an interaction between AT-II activities and the HPAA (Huber et al., 2017). Therefore, SAM axis and HPAA are connected, which indicates the complexity of the stress response.

1.3.4.2 Neuroendocrine system

The neuroendocrine system consists of neurons, glands and supportive tissues which function in an integrated manner to release hormones and humoral signals. Collectively, they regulate the physiological or behavioural state in response to internal or external changes (Fink et al., 2012). A crucial component of this system is the hypothalamus which is a part of the limbic system and located in the forebrain. It is formed of a group of nuclei (about 16), and receives and sends projections to different parts of the central nervous system (Levine, 2012), mainly to other parts of the limbic system and brainstem. Thus, it plays a role in regulating body temperature, thirst, hunger, osmotic balance, and the autonomic system (Aguilera, 2012). This means that the hypothalamus is an important neuronal hub that connects brain regions concerned with sensory processing, memory, and emotion with brain regions that produce appropriate alterations in hormone secretions and neural signals that maintain the bodily homeostasis (Levine, 2012).

In response to stress, the paraventricular nucleus (PVN), arcuate nucleus (AN), and supraoptic nucleus (SON) produce “releasing hormones”, such as corticotrophin releasing hormone (CRH; a neuropeptide secreted from the PVN), that act directly via the hypophyseal portal system to activate the pituitary gland (Levine, 2012). The pituitary gland is the other major part of the neuroendocrine system. It is formed by the anterior lobe (also known as adenohypophysis) and posterior lobe (neurohypophysis) and secretes “tropic hormones” such as ACTH into the peripheral circulation and

stimulates other glands to secrete hormones (Aguilera, 2012, Fink et al., 2012). This cascade of hormone secretion from the hypothalamus, pituitary gland, and other body glands is known as axis. The main neuroendocrine axes and their end effectors are summarised in Figure 1.3. These axes are either activated or inhibited in stress. This can be a direct effect of the hypothalamus or result from interactions with HPAA mediators. CRH stimulates the anterior pituitary to secrete ACTH into the peripheral circulation, which triggers the adrenal cortex to release glucocorticoids (Conrad, 2011, Wosu et al., 2013, Levine, 2012). Glucocorticoids secretion in acute stress transiently enhances the hypothalamic-pituitary-thyroid axis and hypothalamic-pituitary-growth axis. In chronic stress the production of thyroid releasing hormone and insulin-like growth factor-1 (IGF-1) is inhibited by glucocorticoids and somatostatin (growth-hormone-inhibiting hormone that is produced by the hypothalamus). The hypothalamic-pituitary-gonadal axis is inhibited in chronic and acute stress by CRH (Aguilera, 2012, Scott and Lindberg, 2000, Stengel and Taché, 2017). The HPAA has a reciprocal interaction with the immune system. Cortisol has profound inhibitory effects on the inflammatory process (Scott et al., 2012). Conversely, inflammatory cytokines, tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) can stimulate HPAA (Tsigos and Chrousos, 2002, Scott et al., 2012).

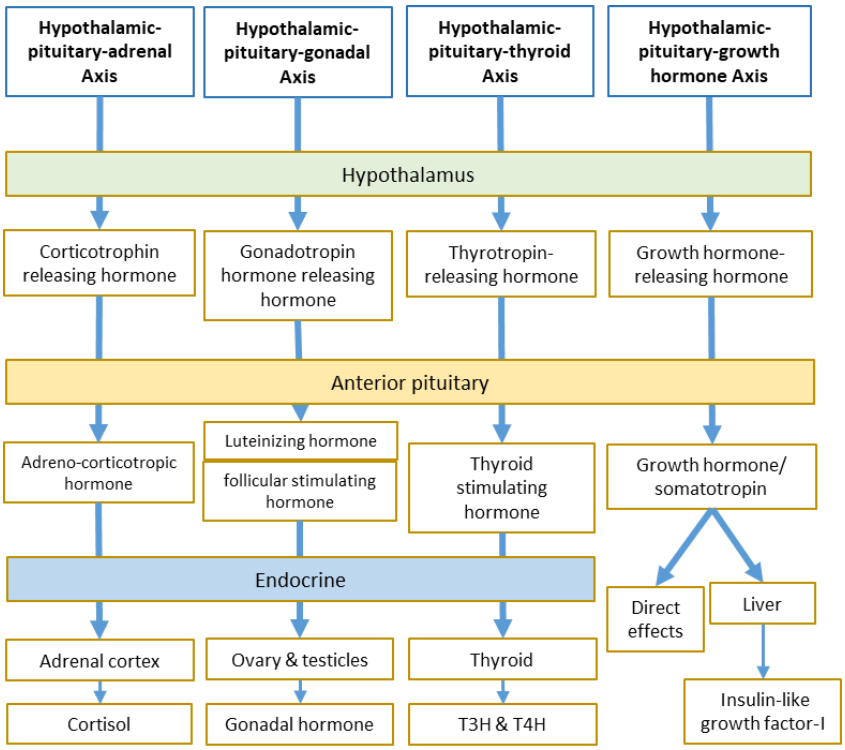


Figure 1.3 Main neuroendocrine axes and their end effectors
Sources: Aguilera (2012), Scott et al. (2012).
T3H= Triiodothyronine, T4H= Thyroxine.

The complexity of the stress response goes beyond the interactions between neuroendocrine axes. For example, it was found that CRH is also expressed in neuronal structures other than the HPAA such as the limbic system and cortical areas (Aguilera, 2012). CRH receptors (CRHR) are not only found in the anterior pituitary gland but also in the limbic system, some hypothalamic nuclei, and cerebellar cortices (Ventura-Silva et al., 2020, Wynn et al., 1984). This may indicate that CRH has other functions that are not related to HPAA such as fear mediating stress-induced anxiety. It may explain the various behavioural and emotional changes that are controlled by the limbic system and associated with stress not explained by changes in glucocorticoids levels (Ventura-Silva et al., 2020).

1.3.5 Measurements of stress

1.3.5.1 Psychological measurements

Psychological measurements are based on the stimulus-based and transactional-based approach.

1. Stimulus-based measurements: measuring the occurrence of major life events and daily hassles. They are based on the assumption that stressful events have a cumulative effect on health (Gouin et al., 2012). Holmes and Rahe (1967) developed the Social Readjustment Rating Scale (SRRS) in which each stressful life event is given a Life Change Unit (LCU) to measure its intensity (Miller and Rahe, 1997). The SRRS was found to have a weak association with disease when used in prospective studies which contradicts the universal belief in the role of stress in developing diseases (Morrison and Bennett, 2009). Other drawbacks of the SRRS are that some events may not be applicable to all individuals, and it does not consider cultural or contextual differences in reacting to certain life events.

   Another self-report checklist is the Life Experiences Survey (LES) developed by Sarason and Johnson (1976) which asks respondents to rate the severity of the listed events. However, the rating of the response leads to an overlap between the stimulus and perceived concepts of stress as it reflects the exposure to life events and the subjective assessment of the event (Harkness and Monroe, 2016). Kanner et al. (1981) developed the Daily Hassles Scale (DHS). They found that psychological and physical symptoms of diseases

were better predicted by the frequency of daily hassles than by occurrence of major life events, especially if they were repeated over time.

Stimulus-based self-reported questionnaires or checklists have their limitations, for example people recall less events when they retrospectively report events happened over a period of time than events reported on a monthly basis for the same period (Raphael et al., 1991). These checklists combine a heterogeneous range of life events into one overall score. However, not all types and timings of life events are equally relevant for all disorders, and it is not possible to list all the events that may happen in a person's life (Harkness and Monroe, 2016). These checklists do not address whether the event is independent or a consequence of a major life event that occurred beforehand. For example, stressful financial and social events might have arisen from long-term unemployment. Lastly, assessing the reliability and validity of these questionnaires is challenging although usually indicates a modest test–retest reliability (Harkness and Monroe, 2016, Anderson et al., 2011).

The limitations of stimulus-based self-reported questionnaires led to development of Interview-based assessment of life events (Monroe, 2008), a structured interview used to examine the reported events and their surrounding context in details (Cohen et al., 2016). Examples of these structured interviews are: the Life Events and Difficulties Schedule (LEDS; Brown and Harris, 1989) , the Structured Event Probe and Narrative Rating (SEPRATE;

Dohrenwend et al., 1993), and The Structured Life Events Inventory (SLI; Wethington et al., 1993). However, the Interview-based assessment is not widely used as it is complex, requires extensive and costly training for rating and administration, and imposes a burden on the interviewee and the researcher in terms of the time required for the interview (Anderson et al., 2011). Also, they are at risk of recall bias and potential unwillingness to disclose sensitive information by the interviewee (Ludwig et al., 2018).

2. Transactional-based measurements: These scales are based on the concept of the transactional model and focus on personal reactions to stress. The Perceived Stress Scale (PSS; Cohen et al., 1983) is commonly used and measures the degree to which a situation is appraised as stressful. It correlated moderately with the life events scales (Farag et al., 2008, Cohen et al., 1983, Bell and Lee, 2002). The Perceived Stress Questionnaire (PSQ) is another measurement of perceived stress (Levenstein et al., 1993) similar to the PSS and commonly used in research. The Depression, Anxiety and Stress Scale (DASS; Lovibond and Lovibond, 1995) measures the negative emotional status and severity of depression, anxiety and stress (chronic non-specific arousal). It discriminates between these three states and indicates severity.

In addition to the above-mentioned instruments that assess general perceived stress, there are instruments designed to assess perceived stress within certain environment. For example, the

Karasek Job Control Questionnaire (JCQ; Karasek, 1981) assess perceived stress related to employment (Cohen et al., 2016).

These instruments assess stress retrospectively so when they are used to study the relationship between stress and disease they do not differentiate between cause and effect, and are influenced by a range of internal and external factors (Levenstein et al., 1993, Monroe, 2008). However, both stimulus-based and transactional-based measurements have been useful in predicting subsequent risk of morbidity and mortality (Cohen et al., 2016), which makes them valuable in research.

1.3.5.2 Physiological and biological measurements

The response-based model of stress describes bio-physiological changes. There are several stress mediators have been examined (examples in Table 1.3) some of which are the end effectors of stress-related axes, whilst others result from the metabolic and immunological changes associated with stress. The stress hormones epinephrine, norepinephrine, and cortisol (explained in 1.4) and their antagonists Dehydroepiandrosterone (DHEA), in conjunction with inflammatory cytokines (e.g., IL-6, TNF-α) are referred to as the primary mediators (McEwen, 2003).

Table 1.3 Physiological and biomarkers used to measure stress

Physiological markers	Biomarkers	
Heart rate	Cortisol, ACTH	Interleukins 1, 6
Blood pressure	Alpha amylase	Tissue necrotic factor
Heart rate variability	Dehydroepiandrosteron	(TNF)
Respiratory rate	e (DHEA)	Lymphocyte count
Skins conductivity	Cathecholamines	(CD4, CD8)
Muscle tension	Dopamine	CD4/ CD8 ratio
	Oxytocin	C-reactive proteins
	Gonadal hormones	Neuropeptide
	Lipoproteins	5-hydroxytryptamine
	Growth hormone, IGF-1	(5-HT)
	Thyroid hormones	Glycated
	Albumin	haemoglobin
		Creatinine

Sources: Aigrain et al. (2018), Smith and Vale (2006), Steckler et al. (2004).

Each stress response has its characteristic, spatial and temporal domains (Joëls and Baram, 2009). Physiological measures can be a reliable method for studying the consequences of stress (Rice, 2012) but lack specificity because they are also used to evaluate stress-related diseases or the disease outcome under study (Harkness and Monroe, 2016). For example, interleukins, which keep the body biologically safe and protected from foreign pathogens, are also involved in stress response (Slavich, 2020). Some measures that can indicate stress, such as heart rate variability and skin conductivity, are transient and so only used in research (Kim et al., 2018).

1.4 CORTISOL

Cortisol is the active form of glucocorticoids and secreted from the adrenal cortex into the bloodstream. The inactive form of glucocorticoids in human is cortisone which is activated by the action of 11β-hydroxysteroid dehydrogenase type 1 enzyme (11β-HSD1) into the

active form, cortisol (Cooper and Stewart, 2009). This enzyme has an equivalent in animals. In rodent, for example, 11β-hydroxysteroid dehydrogenase enzyme converts 11-dehydrocorticosterone to the active form corticosterone (*ibid*). Cortisol maintains homeostasis in the body by regulating metabolism (enhance gluconeogenesis) and downregulating the immune response (Wosu et al., 2013, Scott et al., 2012).

1.4.1 Cortisol secretion

Cortisol is the end effector of the HPAA which is normally under circadian rhythm i.e. a cycle that repeated every 24 hours (Spiga and Lightman, 2020). The circadian rhythm is regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus which receives afferent neurons from the retina and is the key regulator of sleep/awake cycle. The HPAA is inhibited by elevated cortisol level and glucocorticoids levels provide negative feedback inhibition to maintain a basic cortisol level that is enough for homeostasis (Smith and Vale, 2006). After exposure to an unpredicted event, the HPAA is activated, cortisol levels are elevated temporarily, and return to the baseline levels once this event ends (Smyth et al., 2013, Duric et al., 2016). Repeated exposure to the same event leads to habituation and a gradual decrement in HPAA response; the baseline level changes only slightly but responses to stimuli are attenuated (Kovacs et al., 2004, Grissom and Bhatnagar, 2009). A change in the context in which stress is experienced can diminish the magnitude of the habituated HPAA response (Grissom and Bhatnagar, 2009).

1.4.2 Glucocorticoids and mineralocorticoid receptors

Cortisol binds to mineralocorticoid receptors (MCRs) with high affinity, and to glucocorticoid receptors (GCRs) with low affinity (Conrad, 2011). Almost every cell in the body expresses GCRs, MRCs or Both in different quantities (De Kloet et al., 2009, Conrad, 2011, McEwen and Akil, 2020). GCRs and MCRs produce two types of reaction. The first is a non-genomic reaction which rapidly effects the excitability and activation of neurons. For example, glucocorticoids directly stimulate the glutamate release which then feedback on glutamate and GABA release. They also act in mitochondria to affect Calcium ion buffering and free radical formation. The second is a genomic reaction which facilitates the transactivation or trans-repression of selected genes i.e. epigenetic regulation of gene expression (Groeneweg et al., 2011, McEwen and Akil, 2020, Joëls et al., 2012).

GCRs are expressed widely in the brain with the highest levels found in the PVN and hippocampus (McEwen and Akil, 2020, Smith and Vale, 2006). MCR expression is mostly restricted to neurons in limbic areas, with moderate levels in the PFC and the amygdala, and high levels in the hippocampus (Groeneweg et al., 2011, McEwen and Akil, 2020, Joëls and Baram, 2009, Smith and Vale, 2006). Regarding the cochlea, MCRs are also predominant in the stria vascularis and spiral ganglion neurons in the cochlea (inner ear). Increased activation of MCRs may lead to an imbalance of potassium-sodium levels in the scala tympani (Al-Mana et al., 2008, Mazurek et al., 2012). This raises the possibility that glucocorticoids cause damage to or dysfunction of the cochlea by

influencing endolymphatic homeostasis (Horner, 2003, Salviati et al., 2014).

1.4.3 Measuring cortisol

Cortisol is an important biological variable and is considered the main biomarker in stress research (Wosu et al., 2013, Hellhammer et al., 2009, Monroe, 2008). It can be measured by different methods and sampling techniques (Dantzer et al., 2014). Each method, which will be discussed below, is affected by the sampling procedure, diurnal levels, and/or sample storage requirements (Russell et al., 2012).

1.4.3.1 Salivary cortisol

Salivary sampling is the most commonly used method to measure the cortisol production in the short-term (Smyth et al., 2013). The time of collecting the sample reflects different parameters of salivary cortisol level. For example, samples collected on awakening assess the Awakening cortisol and Cortisol awakening response; and samples collected at different times of the day assess the Diurnal cortisol slope and the Area under the daytime cortisol curve, samples collected after exposure to a momentary stressor assess cortisol reactivity (Adam and Kumari, 2009). As it depicts the fluctuation in cortisol secretion over a short time, salivary cortisol measurement is a useful method to investigate the functional dynamics of the HPAA (Roerink et al., 2018). Besides the factors that affect cortisol levels in general (such as steroid use or diabetes), there are many modulating factors that can affect salivary cortisol such as having an illness on the day of testing, alcohol consumption or heavy exercise within 24 hours of the testing, or eating

and drinking within 1 hour of the testing (Smyth et al., 2013, Adam and Kumari, 2009). All of these factors should be considered when salivary cortisol is measured (Hellhammer et al., 2009). One limitation of salivary cortisol measurement is that it is impractical and time-consuming if there is a need to measure cortisol secretion over longer periods as multiple samples are required.

1.4.3.2 Circulating cortisol

Cortisol is also measured in blood plasma and serum. Like salivary cortisol, circulating levels of cortisol are subjected to circadian effects. As only 5-10% of cortisol is biologically active ('free'), and the rest is bound to specific circulating protein which is the corticosteroid-binding globulin (Smyth et al., 2013), blood cortisol levels indicate both the free and binding cortisol (Hellhammer et al., 2009). It means that it is affected by the level of blood proteins, i.e. low levels of circulating proteins may be associated with the increased level of free cortisol (Sauve et al., 2007, Abell et al., 2016). This should be considered when interpreting the level of blood/ serum cortisol. In addition, blood samples are obtained by venepuncture which, controversially, may induce cortisol responses stress and lead to increase in the cortisol levels in response to physical stress related to venepuncture or in response to fear of needles (Weckesser et al., 2014).

1.4.3.3 Urinary cortisol

Excess free circulating cortisol is excreted in urine which can be collected over various periods and interpret accordingly. A 24-hour collection of urine reflects the level of free cortisol over a day (Kraan et

al., 1998). It can also be collected over a 12-hour period or collected at a single point in the morning. Urinary cortisol has a clinical value in diagnosing Cushing's syndrome, which is characterised by the excessive production of cortisol by the adrenal gland (Turpeinen and Hämäläinen, 2013). Urinary cortisol has been measured in psychobiological research (Levine et al., 2007). For example, some studies reported that an increase in 24-hour urinary cortisol is associated with impairment of cognitive function (Karlamangla et al. (2005), and with depression and PTSD (Maes et al., 1998).

Unlike salivary and circulating cortisol, urinary cortisol is not affected by diurnal variation of cortisol secretion or the level of proteins in serum (Turpeinen and Hämäläinen, 2013). Free cortisol in urine is about 53-fold higher than in diurnal saliva specimens which increases the power to detect change in cortisol levels (Sarkar et al., 2013). However, urinary cortisol is positively associated with urine volume and fluid intake (Fenske, 2006, Shi et al., 2008), and urinary free cortisol excretion rate is significantly reduced in patients with moderate to severe renal impairment (Chan et al., 2004). These factors should be considered when conducting research using urinary cortisol.

1.4.3.4 Hair cortisol

In contrast to salivary and blood cortisol, hair cortisol concentration (HCC) provide a measure of long-term secretion of cortisol (Manenschijn et al., 2011, Raul et al., 2004). Hair cortisol sampling is a non-invasive technique, and gives the retrospective and cumulative level of cortisol (Raul et al., 2004, Abell et al., 2016, Dantzer et al., 2014,

Greff et al., 2019, Kalliokoski et al., 2019). HCC is positively correlated with salivary cortisol and increases with stress, more with ongoing or recent stress than past stress (Stalder et al., 2017, Kalliokoski et al., 2019). HCC analysis has its limitations; it is affected by multiple confounders such as gender and race. Also, exposure to sun and artificial UV light, hair washing frequency, and the use of certain hair products leads to loss of cortisol from the hair shaft, (Abell et al., 2016, Greff et al., 2019, Stalder et al., 2017, Noppe et al., 2015). This is known as the wash-out phenomena. HCC does not consistently correlate with self-reported measures of perceived stress (van den Heuvel et al., 2020, Koumantarou Malisiova et al., 2020), and it cannot be used to detect changes in the circadian rhythm of cortisol (Stalder et al., 2017, Prado-Gascó et al., 2019). However, it can be used in clinical diagnosis and in research as a biomarker of stress (Greff et al., 2019, van den Heuvel et al., 2020) as it can be used to assess cortisol levels over a month or months basis (Manenschijn et al., 2011). For instance, hair cortisol analysis may have value in the diagnosis of Cushing's syndrome, a pathological increase in glucocorticoids either from an exogenous source or from an excessive endogenous production of cortisol (Hodes et al., 2017, Wester et al., 2017).

1.5 STRESS AND DISEASES

1.5.1 Stress as a risk factor

Stress is believed to be a risk factor or exacerbating factor in disorders such as cardiovascular diseases, cancer, anxiety, depression, asthma, and autoimmune diseases (Steptoe and Ayers, 2004). Exposure to

stressors may affect health behaviours, hormones secretion, and/or the function of the nervous system. However, whilst the evidence derived from observational studies supports the presence of associations, they do not demonstrate a cause-effect relationship (Cohen et al., 2007, Smyth et al., 2013). Nevertheless, various sociodemographic and behavioural risk factors like adapting unhealthy coping strategies may mediate this relationship (McIntosh, 2005).

Stress might have a significant effect on cells and organs (Karatsoreos, 2018) and it affects different organs through different mechanisms. Stress hormones and mediators target specific receptors that are widely distributed in the human body and brain. For example, it leads to rearrangement of neuronal connections and morphological changes in the hippocampus, PFC, and the amygdala which may explain the association with psychological disorders (Karatsoreos, 2018). It is possible that stress exacerbates an existing or premorbid disease state by tipping the balance of an already vulnerable system. In other words, cumulative stress may increase disease risk through progressive biological wear and tear (Cohen et al., 2019, Juster et al., 2010).

1.5.2 **The role of stress mediators in developing diseases**

Stress is considered a cumulative process in individuals usually exposed to a variety of stressors (Herman et al., 2016) whereby the development of disease is attributed to an inadequate or a prolonged activation of the neuroendocrine axes (Smith and Vale, 2006, Myers et al., 2012). Cortisol, thyroid hormones, growth hormone, and IGF-1 regulate metabolism and shift energy from body storage in acute stress.

Vasopressin regulates water retention and vascular circulation, which regulates blood pressure (Aguilera, 2012). These mediators are transiently elevated in acute stress and their effects are temporary and differ from the prolonged response (Fulford and Harbuz, 2005). Elevated levels of circulating glucocorticoids in chronic stress affects the limbic system and the mood-regulating neurocircuitry (Duric et al., 2016). It decreases cell proliferation and differentiation and the survival rate of neurons in the hypothalamus and PFC (Conrad, 2011), and increases the number of dendritic projections in the amygdala (Aguilera, 2012). Glucocorticoids and prolonged exogenous administration of corticosterone can alter the rate of birth and rate of survival of hippocampal neurons (Karatsoreos and McEwen, 2011, McEwen and Akil, 2020, Kino, 2015).

Catecholamines control a wide range of functions. Epinephrine increases heart rate and respiratory rate, and elevates blood glucose by enhancing lipolysis and glycogenolysis (Schneiderman et al., 2005). Norepinephrine activates the amygdala (Tsigos and Chrousos, 2002) and is important for modulating attention, arousal, and cognition (Schwarz and Luo, 2015). Hence, stress is associated with somatic, behavioural, mental and cognitive changes which can be considered symptoms of stress (Aguilera, 2012) summarised in Table 1.4.

Table 1.4 Behavioural, emotional and cognitive symptoms of stress.

	Symptoms
Somatic	- Increased heart rate, blood pressure. - Rapid or shallow breathing, chest pain. - Upset stomach, change in bowel habit, nausea. - Muscle, clenched jaw & grinding teeth. - Low immunity, frequent infection. - Headache. - Chronic fatigue. - Skin irritations.
Behavioural	- Change in appetite & eating behaviour. - Increase alcohol, tobacco, or drugs consumption. - Avoiding responsibilities. - Nail biting, fidgeting, pacing. - Insomnia.
Emotional	- Arousal & increased awareness. - Agitated, frustrated, moody & depressed - Irritability & panic attacks. - Losing control. - Difficulty relaxing & quieting your mind. - Low self-esteem, worthless, and loss of confidence.
Cognitive	- Constant worrying and racing thoughts - Muddled thinking and forgetfulness. - Disorganisation and inability to focus. - Poor judgment and hasty decisions. - Being pessimistic.

Summarised from Elo et al. (2003) and Köhn et al. (2013)

The role of elevated stress hormones in developing disease can be attributed to:

- Long-term dysregulation of HPAA (Fink et al., 2012, Wosu et al., 2013);
- Metabolic and immune changes (Abell et al., 2016, Duric et al., 2016);
- Alteration in affective regulation like elevated level of anxiety, fear, and depression (Cohen et al., 2019, McEwen and Akil, 2020);
- Increased stress oxidative damage (Aschbacher et al., 2013);
- Glucocorticoids receptors resistance (Cohen et al., 2012);

- Epigenetic regulation of genetic information (McEwen and Akil, 2020);
- Changes in health practices such as smoking and eating behaviours (Schneiderman et al., 2005, Cohen et al., 2019, Park and Iacocca, 2014, Scott et al., 2012).

1.6 AIM AND OBJECTIVES

At this point, I have described the role of stress in affecting health. It is strongly evident that stress affects the neuronal structure within the central nervous system, and tinnitus is possibly a disorder of higher neuronal pathways.

The aim of this thesis is to examine the relationship between tinnitus and stress. The objectives were:

1. To catalogue the evidence of a relationship between stress and tinnitus, and how it is approached in research by conducting a scoping review (Chapter 2).
2. To examine whether hair cortisol plays a role in tinnitus pathogenesis; a cross-sectional study was conducted to compare hair cortisol concentration in tinnitus patients and healthy controls, and to examine whether hair cortisol level correlates with the level of self-reported tinnitus and self-reported stress. Also, the change in hair cortisol levels in tinnitus patients when tinnitus becomes bothersome was examined (Chapter 3).
3. To examine whether changes in hair cortisol level and tinnitus levels are associated with a change in cognitive performance (Chapter 3).

4. To examine the effect of anxiety, depression, and social factors on the relationship between tinnitus and stress (Chapter 3).
5. To test whether cortisol production is consistent over time in chronic tinnitus and therefore whether it can be used as an objective tool (Chapter 3).
6. To explore how tinnitus patients, conceptualise stress using a concept mapping technique (Chapter 4).
7. To examine how health carers, define, assess, and manage tinnitus-related stress by conducting a service evaluation (Chapter 5).

CHAPTER 2 PREVIOUS RESEARCH ON THE RELATIONSHIP BETWEEN TINNITUS AND STRESS

2.1 INTRODUCTION

A relationship between tinnitus and stress is frequently reported (Mazurek et al., 2015). Stress is considered a key risk factor in the transition of tinnitus from being a mild to a severe problem (Baigi et al., 2011), i.e. it can be an exacerbating factor for tinnitus. However, tinnitus is also considered a source of distress. Furthermore, there are neuronal links between auditory and non-auditory areas that are part of stress neuronal circuits. This supports the possibility of a relationship between tinnitus and stress.

Herein, I will summarise the main similarities between stress and tinnitus. This chapter is divided into three sections. Section 2.2 is an overview of the anatomical and physiological changes, cognitive changes, and comorbidities in stress and tinnitus. Section 2.3 provides a summary of findings and representative examples from a scoping review of studies that have measured both stress and tinnitus. Section 2.4 reports the findings from studies that assessed cortisol in tinnitus participants.

2.2 SIMILARITIES BETWEEN TINNITUS AND STRESS: LITERATURE REVIEW

As explained in chapter one, stress and tinnitus are associated with functional and structural changes in neuronal structures, and both are

associated with several health-related disorders. These changes and disorders have been researched in each domain independently. I will summarise the main similar findings of these studies that provide evidence for the relationship between tinnitus and stress.

2.2.1 Anatomical and physiological changes within the brain

Many studies have reported several changes in the hippocampus, the PFC, and the amygdala that occur in tinnitus as well as in stress. In the hippocampus, stress leads to loss of spine and dendritic shrinkage in hippocampal neurons (McEwen, 2017). Disruption of hippocampal white matter tract was reported in tinnitus (Gunbey et al., 2017). Also, adult neurogenesis and grey matter concentration decrease in tinnitus (Landgrebe et al., 2009), and because of exposure to stress (Kino, 2015). Tae et al. (2018) reported a negative correlation between tinnitus symptom severity measured by the THI and the thickness of the hippocampus (measured by local surface distance on the MRI). So, there is similar changes within the hippocampus in tinnitus and stress that correlate negatively with both.

In tinnitus patients, neuroplasticity and grey matter volume in the PFC is decreased and white matter is increased compared to controls (Adjamian et al., 2014, Leaver et al., 2011, Leaver et al., 2012) which overall leads to a significant decrease in cortical thickness (Aldhafeeri et al., 2012). PFC atrophy and loss of its complexity occur also with stress (Karatsoreos and McEwen, 2011). Chronic stress is associated with

debranching and shrinkage of dendrites of the medial-PFC neurons (McEwen, 2017).

Synaptic transmission in the amygdala increase in stress due to increase in synaptic plasticity in the amygdala of rats (Vouimba et al., 2004). Electrical neuronal activity as measured by the Electroencephalography (EEG) is higher in the amygdala in distressed tinnitus participants than non-distressed participants (Vanneste et al., 2010). However, the cortical thickness of the amygdala decreases in tinnitus subjects compared to non-tinnitus controls (Aldhafeeri et al., 2012), whereas in contrast, it increases in stress (Karatsoreos and McEwen, 2011).

The effect of stress on auditory pathway structures that are involved in the pathogenesis of tinnitus has not been investigated. Dagnino-Subiabre (2013) reported “stress-induced dendritic atrophy” in the inferior colliculus (part of the auditory pathway) and auditory cortex in rats and concluded that chronic stress may affect the auditory pathway.

2.2.2 Cognitive function in tinnitus and stress

Stress is known to impact cognitive functions (Boals and Banks, 2012). The impact of stress on cognition can be a U-shaped or a linear relationship depending upon the intensity of stress and the type of cognitive function measured (Sandi, 2013). Tinnitus patients also appear to have an impaired capacity to perform certain cognitive tasks (Andersson and McKenna, 2006). For example, evidence suggests that tinnitus has an impact on the executive control of attention and memory

(Tegg-Quinn et al., 2016, Trevis et al., 2018, Mohamad et al., 2016). The increase in tinnitus severity may associate with increase in error rates and longer response time in performing the executive functioning tasks (Clarke et al., 2020).

The effects reported here can be explained by changes in the neuronal structures that are integral elements of the cognitive function pathways. The hippocampus is important for learning and memory. The PFC controls and mediates several higher cognitive functions, for example, sustained attention and information processing (Miller and Cohen, 2001). The amygdala regulates emotionality, aggression, fear learning and memory (LeDoux, 2007). Therefore, it can be assumed that stress and tinnitus lead to neurological changes that affect the cognitive functions.

2.2.3 Comorbidities of both tinnitus and stress

Stress is linked to several psychological and somatic disorders (Schneiderman et al., 2005) which are prevalent in tinnitus as well. Anxiety, depression (Gomaa et al., 2014, Cho et al., 2013, Stohler et al., 2019, Pattyn et al., 2016), and post-traumatic stress disorder (Fagelson, 2007) have been reported in tinnitus patients. Sleep disturbance is also associated with tinnitus (Burgos et al., 2005, Stohler et al., 2019), and with stress (Van Reeth et al., 2000). These psychological disorders have been linked to the functional changes in the amygdala (Karatsoreos and McEwen, 2011) which receives efferent neurons from the dorsomedial thalamus directly. According to the inhibitory gating mechanism theory of tinnitus (Rauschecker et al.,

2010), the thalamus is a major hub in tinnitus inhibitory feedback loop (explained in 1.2.2).

Stress symptoms such as headaches are frequently reported with tinnitus (Lindberg et al., 1984, van Dijk et al., 1987, Lugo et al., 2020). Stress-related diseases such as diabetes mellitus, hypertension, and cardiovascular diseases which are thought to be resulted from neuropathy, hyperlipidaemia, and/or micro-angiopathy (Al-Hariri, 2016), can co-occur with tinnitus (Table 1.1). Recently, Stohler et al. (2019) reported that irritable bowel syndrome and fibromyalgia, which are also stress-related disorders (Van Houdenhove and Luyten, 2006, Mayer et al., 2001), were statistically associated with the risk of being diagnosed with tinnitus. However, Stohler et al. (2019) did not observe any meaningful increased or decreased risk of being diagnosed with tinnitus in patients with cardiovascular comorbidities (such as arrhythmia, hypertension, and stroke), hyperlipidaemia, or thyroid disorders.

2.2.4 Summary

Although stress and tinnitus have similarities that may indicate shared pathophysiology or cause-effect relationship, studies cited in this section have not accounted to the effect of stress on tinnitus and vice versa. This means that when tinnitus was the subject of the study, stress was overlooked and was not measured. Also, tinnitus is not a factor that is commonly assessed when stress is the subject under investigation which makes it difficult to interpret whether any observed findings are purely stress-related or might be tinnitus-related. In the

view of this drawback, a scoping review of studies that both stress and tinnitus assessed by using separate instruments was required.

2.3 A SCOPING REVIEW OF THE RELATIONSHIP BETWEEN TINNITUS AND STRESS

In the first section of this chapter, I gave an overview of the major similarities between tinnitus and stress as reported in studies that assessed each topic separately. These similarities highlighted the significance of understanding the role of stress in tinnitus and whether stress mediators are determining factors for the pathogenesis of tinnitus. Here, I conducted a scoping review to map the literature and identify gaps in knowledge regarding this topic.

Scoping reviews are used to examine the extent of evidence on a topic. They have a rigorous and valid approach throughout the entire process (Munn et al., 2018, Pham et al., 2014). They are distinct from systematic reviews, and they are conducted for different purposes (Munn et al., 2018). Arksey and O'Malley (2005) identified the potential reasons to conduct scoping reviews, these are:

- To examine the extent and nature of research activity.
- To identify whether a systematic review is necessary.
- To summarise and disseminate research findings.
- To identify potential research gaps within the existing literature.

This scoping review catalogued research to date on the relationship between tinnitus and stress in adults.

2.3.1 Methods

I followed the five-stage framework for conducting scoping reviews developed by Arksey and O'Malley (2005) and updated by Levac et al. (2010). Also, I revised these steps in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for scoping reviews (Tricco et al., 2018). The framework involves the following steps:

2.3.1.1 Identifying the question

I identified the key question of this scoping review as *"what is known about the relationship between stress and tinnitus?"* This key question was formed to guide the search strategy and inclusion criteria.

2.3.1.2 Identifying the relevant studies

I used the search terms (tinnitus AND stress* AND adult AND human), which were conducted line-by-line: this means that the searches for each term were conducted separately, and then search results were combined. When possible, the search was limited to English, but was not limited to any specific date.

I undertook the literature search in October 2017 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 the database (example in Table 2.1).

Table 2.1 Search strategies examples in two databases

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)

Additionally, reference lists of any review articles from the electronic search and the table of contents of the last six months of key journals were hand-searched for potentially relevant articles.

2.3.1.3 Study selection

Studies were included if they were original studies published in English and assessed tinnitus and stress by using separate instruments. The last inclusion criteria was essential to compare levels of stress with level of tinnitus, i.e. 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. Studies relating to basic scientific research in animals, Posttraumatic Stress Disorder (PTSD), trauma, oxidative stress, and reviews were excluded.

The title and the abstract were screened first. Then, all identified records that held the possibility of relevant findings were retained for full-text screening. Two reviewers (AE and KF, DB, or DH) independently screened the records in both stages. Any disagreements between the reviewers were resolved by discussion or by a third reviewer.

2.3.1.4 Charting the data

Data were extracted into an Excel spreadsheet, which included general data regarding study identifiers (authors' names, date of publication, title, and study design); the aim of the study; the sample size and the age of the participants; the presence of hearing loss and any confounder factors, instruments used to measure tinnitus and stress, and the results of the study; and any reported relationship between tinnitus and stress as mentioned in the findings of the study.

2.3.1.5 Collating, summarising and reporting results

The results are presented in two formats. The first is tabular to summarise the characteristics of the studies. The second is thematic in which results are described under three themes:

- Instruments that were used in the reviewed studies.
- Associations between subjective measurements of stress and tinnitus.
- Effect of tinnitus management on tinnitus and stress.
- Stress as a risk factor for tinnitus.
- The association between psychoacoustic measurements of tinnitus.
- Self-reported tinnitus levels, and stress.
- The bio-physiological parameters of stress in tinnitus patients.

According to Tricco et al. (2018) critical appraisal of the reviewed studies is an optional step. I opted not to conduct one as the included studies varied substantially in design.

2.3.2 Results

Initial database searches produced 4911 records (Figure 2.1). After removing duplicates, and conducting title and abstract screening, 131 records were forwarded to the full-text screening where an additional 79 records were excluded.

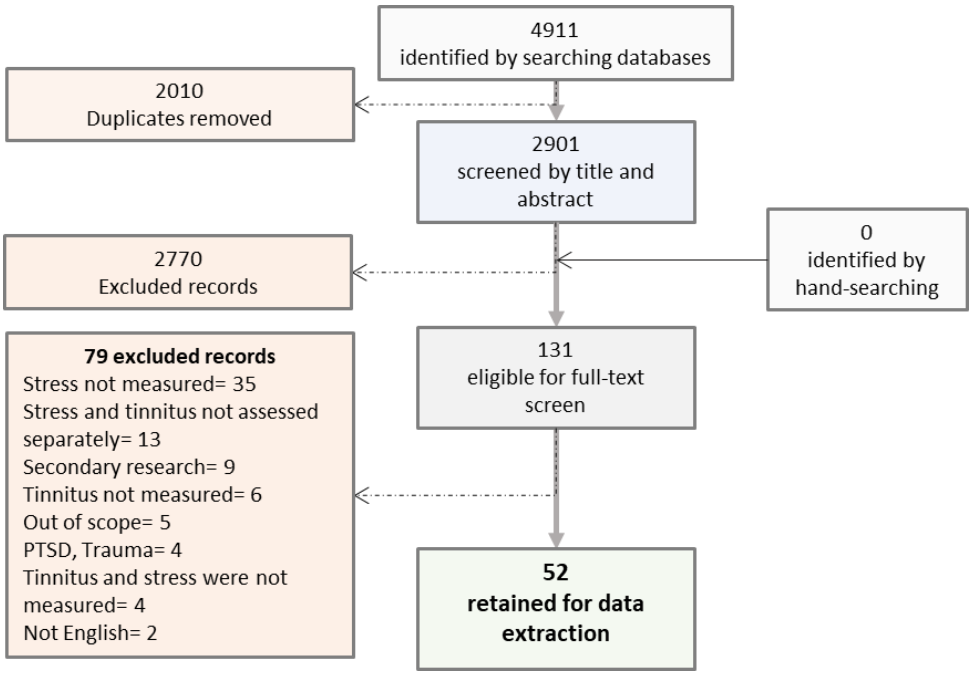


Figure 2.1 Flow diagram details search process.
Count of included and excluded records in each stage of the study selection stage of the review are reported in the boxes.

Data were extracted from the remaining 52 records. Among those, only 18 studies specified an aim to examine the relationship between stress and tinnitus. The remaining 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. Thirty-five studies were excluded because stress was not measured, or stress was assessed using tinnitus instruments i.e. the study reported stress as tinnitus-related distress which prevented comparing stress and tinnitus levels.

2.3.2.1 Tinnitus and stress instruments used in the reviewed studies

The frequency of using tinnitus and stress instruments in the reviewed studies are detailed in Table 2.2. The most frequently used stress

instruments were the perceived stress measurements namely, PSQ, Stress Visual Analog Scale (S-VAS), the DASS, and the PSS. Biomarkers of stress were measured in 11 studies. Measurements of stress as a stimulus were used only in two studies (Schmitt et al., 2000, Gerber et al., 1985). The psychometric properties of tinnitus were measured in all studies; in most of these, two instruments were used. The most frequently used measures were T-VAS, THI, TQ and TRQ. TFI was used in three studies. The psychoacoustic properties of tinnitus were measured in 10 studies. PM and LM were measured in nine studies, MML was measured in six studies, RI was not measured.

Table 2.2 List of measurements used in the reviewed studies

Perceived Stress Measurements	**frequency of using**
Perceived Stress Questionnaire	10
Stress Visual analogue Scale	7
Depression Anxiety Stress Scale	4
Perceived Stress Scale	4
Korean-Brief Encounter Psychosocial Instrument	4
Derogatis Stress Profile	1
Psychological Stress Measurement *(Mesure du Stress Psychologique)*	1
Stimulus-based Stress Measurements	**frequency of using**
Recent Life Changes Questionnaire	2
Daily Hassles Scale	1
Symptoms of Stress Measurements	**frequency of using**
Stress Vulnerability Scale	1
Stress Symptoms Scale	1
Stress Biomarkers Measurements	**frequency of using**
Cortisol	6
Dehydroepiandrosterone Sulphate	1
Interleukins (6, 10)	1
Epinephrine & norepinephrine	1
Tissue Necrotic Factor alpha	1
Heart Rate & Heart Rate variability	3
Skin Conductance	4
Electromyogram (Muscle contraction)	3
Temperature	3
Tinnitus Psychometric Measurements	**frequency of using**
Tinnitus Questionnaire	12
Tinnitus Handicap Inventory	10
Tinnitus Reaction Questionnaire	9
Tinnitus Visual analogue Scale	3
Tinnitus Functional Index	3
Fear of Tinnitus Questionnaire	1
Tinnitus Catastrophic Scale	1
Tinnitus Handicap Questionnaire	1
Global Rating Bother Scale	1
Tinnitus Severity Questionnaire	1
Tinnitus Acceptance Questionnaire	1
Tinnitus Fragebogen	1
Tinnitus Psychometric Measurements	**frequency of using**
Pitch Matching	8
Loudness Matching	10
Minimum Masking Level	3

2.3.2.2 Associations between subjective measurements of tinnitus and stress

Correlation analyses can be used to examine the expected associations between different instruments (Tsang et al., 2017, Westen and Rosenthal, 2003). The presence of a strong correlation indicates that instruments measure the same or a similar construct (convergent validity), and a weak correlation indicates that the construct measured by these instruments are likely unrelated (discriminant validity) (Swank and Mullen, 2017, Tsang et al., 2017, Kira et al., 2021). Regardless of the specific purpose of questionnaires all are subjective and measures various aspects of health-related quality of life. It should be expected therefore that measures as 'different' as those for tinnitus and stress will have some commonality and correlate to some degree (Cowin et al., 2008). Here, it found that the scores of stress instruments significantly correlated with scores on tinnitus instruments, as summarised in Table 2.3. The strength of the corelation varied according to the instrument used in the study. It ranged from very weak and negative correlation (r=- 0.08) between T-VAS$_{0\text{-}10}$ Loudness and Korean-Brief Encounter Psychosocial Instrument (K-BEPSI) (Al-Swiahb et al., 2016), to high-moderate positive correlation (r=0.67) between THI and SVS (Salviati et al., 2013). Multiple regression analysis showed a strong association between TQ and PSQ (Seydel et al., 2010).

Table 2.3 Correlations between subjective tinnitus and stress measurements

Author	N	Measurements		Statistical analysis	*r*	*p*
		Tinnitus	Stress			
Ahmed et al. (2017)	110	THI	DASS	NR	0.53	p<.001
Al-Swiahb et al. (2016)	216	THI	K-BEPSI	NR	0.45	p<.001
		T-VAS-L_{0-10}	K-BEPSI	NR	-0.08	p<.001
		T-VAS-A_{0-100}	K-BEPSI	NR	-0.06	p<.05
Bencsik et al. (2015)	72	THI	PSS-4	PC	0.55	p<.01
Betz et al. (2017)	38	TQ	PSQ	PC	0.62	p=.005
Bruggemann et al. (2016)	531	TQ	PSQ	PC	0.46	p<.01
Lee et al. (2014)	129	THI	K-BEPSI	SC	0.40	p<.01
Muller et al. (2016)	260	THI	PSQ-30	SC	0.47	p<.01
		TFI	PSQ-30	SC	0.41	p<.01
		TCS	PSQ-30	SC	0.34	p<.01
		FTQ	PSQ-30	SC	0.26	p<.01
Olze et al. (2011b)	32	TQ	PSQ	SC	0.44	P<.05
Olze et al. (2011a)	43	TQ	PSQ	SC	0.58	p<.001
Panagiotopoulos et al. (2015)	301	mini-TQ	PSS	PC	0.35	p<.001
Park et al. (2017)	140	THI	K-BEPSI	PC	0.42	p<.001
Salviati et al. (2013)	467	THI	SVS	SC	0.67	p<.001

BEPSI=Korean-Brief Encounter Psychosocial Instrument, DASS=Depression Anxiety Stress Scale, FTQ=Fear of Tinnitus Questionnaire, K- N=Number of participants, NR=Not Reported, p= Significance level, PC=Pearson's product moment correlation, PSS=Perceived Stress Scale, PSQ=Perceived Stress Questionnaire, r= correlation coefficient, SC=Spearman's rank correlation, SVS=Stress Vulnerability Scale, TCS=Tinnitus Catastrophizing Scale, TFI=Tinnitus Functional Index, THI=Tinnitus Handicap Inventory, T-VAS-A_{0-100}= Tinnitus Visual Analog Scale Awareness on scale 0f 0-100%, T-VAS-L_{0-10}= Tinnitus Visual Analog Scale Loudness on scale of 0-10, TQ=Tinnitus Questionnaire.

Patients highly distressed by tinnitus reported a higher level of stress than patients with low distress with tinnitus (Dineen et al., 1997, Olze et al., 2011b) or patients with chronic pain (Zirke et al., 2013).

2.3.2.3 Effect of tinnitus management on tinnitus and stress

Associations between changes in stress measurements and tinnitus measurements after intervention (Table 2.4) including CBT (Attanasio et

al., 2012, Hesser et al., 2012), cochlear implantation (Olze et al., 2012), muscle relaxation therapy (Weber et al., 2002) and TRT (Seydel et al., 2010) were reported, most notably in highly distressed patients.

Tinnitus visual analogue Scales (T-VAS), which was used mainly to describe the participants' characteristics in term of subjective tinnitus loudness, annoyance, awareness, severity and/or intensity of tinnitus, showed mutual changes with stress instruments used in interventional studies (Aoki et al., 2012, Attanasio et al., 2012, Durai and Searchfield, 2017, Koksoy et al., 2017).

Table 2.4 Studies that assessed the effect of interventions on tinnitus and stress measurements

Study	Intervention	Tinnitus Measure	Type	Sig. C	Stress Measure	Type	Sig. C
Counselling or psychological management							
Abbott et al. (2009)	CBT	TRQ	PsM	N	DASS	PsM	N
Hesser et al. (2012)	CBT, ACT	THI, TAQ	PsM	Y	PSS	PsM	Y
Kirsch and Blanchard (1987)	PMR & BIO	Tinnitus disturbance, LM, MML	PsM, PsA	N	EMG, Self-reported	BPh PsM	M
Koksoy et al. (2017)	Yoga	THQ	PsM	Y	SSS	PsM	Y
Weber et al. (2002)	PMR	TQ	PsM	Y	PSQ, Immuno-biomarkers	PsM, BPh	Y
Weise et al. (2008)	BIO	TQ	PsM	NR	EMG, SKC	BPh	NR
Sound-based management							
Attanasio et al. (2012)	Music	THI, VAS	PsM	Y	MSP	PsM	N
Dineen et al. (1999)	BBN	TRQ	PsM	N	DGS	PsM	N
Durai and Searchfield (2016)	BBN	TFI	PsM	Y	DASS	PsM	Y
		MML	PsA	NR			
Olze et al. (2011a)	C-I	TQ	PsM	Y	PSQ	PsM	Y
Olze et al. (2011b)	C-I	TQ	PsM	Y	PSQ	PsM	Y
(Olze et al., 2012)	C-I	TQ	PsM	Y	PSQ	PsM	Y
Others							
Aoki et al. (2012)	MedT	THI	PsM	N	CORT/DHEA	BPh	Y
Seydel et al. (2010)	TRT	TQ	PsM	Y	PSQ	PsM	Y
		PM, LM	PsA	NR			
Ylikoski et al. (2017)	tVNS	THI, mini-TQ	PsM	NR	HRV	BPh	Y

ACT= Acceptance and Commitment Therapy, BBN= Broadband Noise, BIO= Biofeedback, BPh= Biophysiological measurement, C-I= Cochlear Implants, CBT= Cognitive Behavioural Therapy, CORT/DHEA= cortisol/ dehydroepiandrosterone sulphate 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, N= No, NR= Not Reported, PM= Pitch Matching, PMR= Progressive Muscle Relaxation, PsA= Psychoacoustic measurement, PsM= Psychometric measurement, PSQ=Perceived Stress Questionnaire, PSS=Perceived Stress Scale, Sig C= Significant changes, SKC= Skin Conductance, SSS= Stress Symptoms Scale, TAQ=Tinnitus Acceptance Questionnaire, TFI=Tinnitus Functional Index, THI=Tinnitus Handicap Inventory, THQ= Tinnitus Handicap Questionnaire, TRQ= Tinnitus Reaction Questionnaire, TQ=Tinnitus Questionnaire, tVNS= transcutaneous vagal nerve stimulation, VAS=Visual Analogue Scale, Y= Yes.

2.3.2.4 Is stress a risk factor for tinnitus?

Few studies have assessed stress at the onset of tinnitus. In a group of patients with sudden SNHL and tinnitus, life events and daily hassles were significantly more frequent before the onset of sudden SNHL than the control group. These patients showed significantly higher scores on both measures of stress than those in the clinical control group (Schmitt et al., 2000). Yıldırım et al. (2017) reported that only 13.5% of participants clearly described one event that induced or worsened their tinnitus. SRRS scores were not correlated with the severity of tinnitus (Gerber et al., 1985).

Different studies have reported that stress increases tinnitus distress. Probst and his colleagues conducted two studies using Ecological Momentary Assessment (EMA). One showed that self-reported tinnitus loudness had an impact on tinnitus distress (Probst et al., 2016). Stress level partially mediated this relationship as patients perceived their tinnitus louder and more distressing during the night and early morning, in contrast, stress level was higher in the mornings and afternoons (Probst et al., 2017). However, not all people who have tinnitus associated it with stress. Only 26.48% tinnitus patients reported stress in Park et al. (2014). The percentages of tinnitus participants who associated worsening of tinnitus with exposure to stress were 53.8% in (Muller et al., 2016) and 29% in Stouffer et al. (1991) regardless of the question asked.

2.3.2.5 Association between psychoacoustic measurements, self-reported measurements of tinnitus and stress

Psychoacoustic measures of tinnitus (LM, PM) were assessed in 10 studies, but rarely used in analyses. Changes in tinnitus MML have not always corresponded to increases or decreases in diary ratings of tinnitus disturbance (Kirsch and Blanchard, 1987). Tinnitus PM does not correlate with THI or TQ total score, while LM correlates with the TQ subscales “hearing problems” and “intrusiveness of tinnitus.” (Bruggemann et al., 2016) and the THI total score (Bencsik et al., 2015). T-VAS loudness has been found not to correlate with PM, LM (Dineen et al., 1997), nor MML (Durai and Searchfield, 2017).

Changes in stress (measured by DASS) and tinnitus (measured by TFI) were not accompanied by a change in the MML after sound therapy (BBN, and nature sound) (Durai and Searchfield, 2017). Besides, MMLs and self-reported loudness were not significantly correlated with self-reported tinnitus severity as assessed by a set of questions (Folmer et al., 1999).

2.3.2.6 Bio-physiological parameters of stress in tinnitus patients

Six studies assessed the autonomic nervous system response in tinnitus patients. Changes in muscle tension as measured by Electromyography (EMG) in a response to stressful situation were reported, but no changes were recorded in the Skin Conductance Level (SkD), a measure of SAM response (Heinecke et al., 2009, Heinecke et al., 2008, Weise et al., 2008, Kirsch and Blanchard, 1987). Baseline

mean heart rate and heart rate variability (variation in the beat-to-beat interval) were lower in tinnitus patients but did not differ significantly from healthy control (Betz et al., 2017, Ylikoski et al., 2017).

Weber et al. (2002) used cytokines, TNF-α, IL-6 and IL-10, to assess the effect of progressive muscle relaxation (PMR) on tinnitus. IL-6 was higher in tinnitus participants at the baseline. They reported decrease in the TQ, and cytokines levels post PMR.

Cortisol was assessed as a biomarker in six studies. Kim et al. (2014) reported that levels of stress-related hormones in the blood (cortisol, epinephrine, and norepinephrine) varied widely and did not correlate with psychological measurements of stress and tinnitus. Changes in serum cortisol level did not correlate with changes in tinnitus perception (Aoki et al., 2012). Simoens and Hebert (2012) reported that tinnitus and the non-tinnitus participant had similar basal cortisol levels. However, when salivary cortisol was measured and averaged over the course of a day, the chronically above-median cortisol (CAMC) was higher in the highly distressed tinnitus patients than in low-distressed patients and controls (Hebert et al., 2004). Increased salivary cortisol in response to a stressor was accompanied by increased tinnitus intensity and subjective level of stress (Hebert and Lupien, 2009) The overall cortisol reactivity In response to Trier Social Stress Test (TSST) was delayed (the peak of cortisol secretion in tinnitus patients happened 10 minutes after the controls) and significantly lower than healthy controls, which indicates a disturbance in HPAA function (Hebert and Lupien, 2007).

2.3.3 Scoping review discussion and conclusion

In this review we examined the extent of research conducted on this topic. We found that the majority of the included studies assessed perceived stress only and reported moderate correlations between perceived stress measurements (PSQ, PSS, DASS) and tinnitus measurements that mainly assess distress in tinnitus patients (THI, TFI, TQ). Muller et al. (2016) reported moderate correlations between the PSQ and both the TFI and the THI, and a weak correlation between the PSQ and both the Fear of Tinnitus Questionnaire (FTQ) and the Tinnitus Catastrophic Scale (TCS). Given that each tinnitus instrument measures different domains, the correlation between subjective stress and subjective tinnitus might be a correlation between the domains within the instruments. This should be expected as many instruments assess the impact of disorder on various overlapping domains e.g. emotional distress is the main domain assessed by the TQ, THI, TRQ and THQ (Kennedy et al., 2004).

Tinnitus has been reported to start after exposure to an emotional stressor (Baldo et al., 2012), and work-related stress is associated with tinnitus (Hasson et al., 2011, Lin et al., 2010). However, a history of exposure to stress does not appear to be a common finding in tinnitus patients nor to worsen tinnitus in *all* patients. This indicates that there is a group of patients who are susceptible to stress and they might be identified by changes in stress mediators. This, however, may be related to other factors such as personality (Biehl et al., 2020), sleep difficulties (Hébert and Carrier, 2007, Fioretti et al., 2013, Alster et al.,

1993), social isolation and lack of social support (Schaaf et al., 2014, Schneider et al., 1994). The other issue with the response to the question about the history of exposure to stress is that there is no standard working definition of the word '*stress*'. Therefore, it is not clear whether the response is related to the event that happens in a person's life or how they perceived the event as stressful.

There is a lack of reporting of stress effects on the psychoacoustic measurements of stress. This may be because they are poorly associated with the self-reported measures of tinnitus distress (Raj-Koziak et al., 2019, Hall et al., 2017). Biomarkers in the included studies are not stress-specific and may be affected by age. For example, immunological factor IL-6 increases with age (Puzianowska-Kuźnicka et al., 2016, Hager et al., 1994). Weber et al. (2002) reported that IL-6 was higher in tinnitus participants who were older than the control group of the study. HPAA and SAM responses in tinnitus patients were described as blunted and delayed (Betz et al., 2017, Hebert and Lupien, 2007), yet this applied only to the short-term stress response and it is not clear how this blunted response affects the levels of stress mediators over a prolonged period.

This scoping review can inform those who are interested in or intending to conduct systematic reviews about stress measurements in tinnitus research by providing a catalogue of the research studies available from which they might answer their review question. It showed there is sufficient published data to conduct a systematic review about measurements of perceived stress in tinnitus populations. However,

many methods such as measurement of sympathetic activities or immune biomarkers and use of stimulus-based instruments were rarely used. Therefore, it is not feasible to conduct a systematic review of data using these methods in tinnitus research. To summarise, this review identified gaps in research on the relationship between tinnitus and stress. These gaps include data on the effect of stress on the psychoacoustic properties of tinnitus, on stress in recent onset tinnitus, and on the effect of stressful life events on tinnitus.

The reviewed studies signposted that cortisol was the most investigated stress biomarker. In the next section, I will review studies that assessed cortisol in tinnitus populations and were either excluded from the scoping review or has been published after October 2017. An updated version of this scoping review was subsequently published (Elarbed et al., 2020)

2.4 FURTHER REVIEW OF CORTISOL IN THE TINNITUS POPULATION

Studies that included only tinnitus participants reported non-conclusive findings in term of cortisol level. Savastano et al. (2007) assessed blood cortisol in 85 tinnitus participants. They reported correlations between cortisol levels and *Mesure du Stress Psychologique* (MSP; Lemyre & Tessier (1988)). But they did not report any findings that add to the relationship between tinnitus and stress (this study was excluded from the scoping review because it did not used tinnitus measurements). Blood cortisol levels range widely in tinnitus (Kim et al., 2014). In line with Aoki et al. (2012), Li et al. (2019a) reported a significant decrease

in tinnitus levels and serum cortisol after CBT for tinnitus by comparing two tinnitus groups (treatment vs non-treatment). Aydin and Searchfield (2019) studied the effect of broadband noise and nature sounds on salivary cortisol. The cortisol levels before and after exposure to these sounds were not statistically different, but they showed a high variation among participants. Frederiksen et al. (2016) analysed datasets from a cross-sectional survey (n= 632) and they found no associations between tinnitus and different parameters of salivary cortisol measurements (awakening cortisol, awakening+30 cortisol, cortisol awakening response, evening cortisol, cortisol slope and area under the curve).

When they compared tinnitus with control participants after exposure to the stimulus, Hebert and Lupien (2007) reported a delayed and blunted salivary cortisol reactivity after mental stress, and they reported an overall lower salivary cortisol levels after exposure to sound (Hebert and Lupien, 2009). Alsalman et al. (2016) assessed salivary cortisol levels after mental stress and reported no differences between these two groups. However, there were fundamental differences between the studies in terms of the age of the participants, the length of the exposure to the stimulus, the time of the experiment, and the time of collecting the samples after exposure. These are summarised in Table 2.5.

Table 2.5 Comparison between studies assessed salivary cortisol levels overtime after exposure to sound and Trier Social Stress Test

	Hebert and Lupien (2009)	Aydin and Searchfield (2019)	Hebert and Lupien (2007)	Alsalman et al. (2016)
Participant	20 tinnitus, 20 non-tinnitus Men and women	21 tinnitus, Men and women	18 tinnitus, 18 non-tinnitus Men and women	10 tinnitus, 10 non-tinnitus Men only
Age in years (SD)	Tinnitus= 67.9 (6.1) Non-tinnitus= 68.8 (5.5)	Tinnitus= 47.2 (13.7)	Tinnitus= 68.8 (5.7) Non-tinnitus= 68.9 (5.5)	Tinnitus= 23.9 (3.78) Non-tinnitus= 23.6 (4.47)
Tinnitus duration in years (SD)	14.5 (9.7)	Not reported	14.67 (10.6)	3.30 (1.63)
Hearing level measured by Pure tone Audiogram	Tinnitus participants had higher hearing thresholds than non-tinnitus	Slight high frequency hearing loss	Tinnitus participants had higher hearing thresholds than non-tinnitus	No difference between tinnitus and non-tinnitus
Tinnitus level (SD)	TRQ= 19.9 (10.3) Mild	TFI= 33.1 (15.1) Mild-moderate	TRQ= 20.2 (17.7) Mild	TSI= 19.2 (6.90) Not bothersome
Stimulus	Low-frequency flat spectrum hissing sound (125–2000Hz)	BBN and Nature sounds	TSST	TSST
Procedure	Noise for 20 min	Each sound for 30-min listening sessions	10-min anticipation followed by 10-min free speech and mental task	Mental tasks, up to 5 min
Time of testing	12:30 or 3:00 pm	2:00 pm	Either at noon or at 3:30 pm	At 6:00 pm
Sampling time	Baseline, and 10, 20, 30, 40, 60 min post test	Before and after exposure to each sound (0, 30, 60 min)	Baseline, and 10, 20, 30, 40, 60 min post test	Baseline, and 5, 30, 60 min post test
Baseline salivary cortisol level	Not reported	Not reported	Not reported	No difference between tinnitus and non-tinnitus
Salivary cortisol levels overtime	Tinnitus group had an overall lower cortisol level	No difference in cortisol level before and after exposure to each sound	Tinnitus group displayed a blunted and delayed response	No difference between tinnitus and non-tinnitus.

BBN= Broadband Noise, TFI= Tinnitus Functional Index, TRQ= Tinnitus reaction Questionnaire, TSI= Tinnitus Severity Index, TSST= Trier Social Stress Test.

Cortisol levels have also been evaluated in a non-experimental setting.

Hebert et al. (2004) found that CAMC measure in highly distressed

tinnitus patients was higher than in low-distressed patients and non-tinnitus controls, but they did not report different in cortisol awakening responses. Jackson (2019) assessed the Cortisol Awakening Response (CAR) and measured the area under the curve with respect to increase (AUCi). Tinnitus participants who had TFI scores more than 25 had significantly lower AUCi than controls and tinnitus participants who had TFI scores less than or equal to ≤25. Also, AUCi levels and tinnitus distress levels ($T\text{-}VAS_{0\text{-}100}$) measured at awakening, after 6 hours and after 12 hours had a moderate negative and statistically significant correlation. This indicates that AUCi levels predict tinnitus distress levels later in the day.

2.5 CHAPTER DISCUSSION

In this chapter, I highlighted the main similarities between tinnitus and stress, starting with similar anatomical and functional changes in the amygdala, hippocampus, and PFC that occur in stress and tinnitus and may affect cognitive function. Psychological comorbidities common to both tinnitus and stress is further evidence of a relationship. Stress mediators may cause structural and functional changes in the brain which in turn may play a role in the pathogenesis or severity of tinnitus. It also might modulate the severity of tinnitus. For example, regional atrophy of the amygdala affects the tinnitus-related emotional distress (Tae et al., 2018). However, some of these anatomical changes were recorded in distressed tinnitus patients (Adjamian et al., 2014), so it was not clear if they are caused by stress or tinnitus. Besides, they are not

specific to tinnitus and can occur with other disorders such as chronic pain (Vanneste et al., 2010).

Most of the reviewed studies have only focused on one psychological concept of stress at the time, mainly perceived stress. Some of those reported a moderate positive correlation between tinnitus and stress. However, many self-reported tinnitus instruments assess patient-reported complaints that overlap with stress-related complaints (Hall, 2017). These include sleep difficulties, impact on life, and cognition. Therefore, this positive correlation might result from the overlap in the construct between tinnitus and stress self-reported instruments (Hall, 2017).

When stress was considered as a stimulus, exposure to stress initiated or worsened tinnitus but not in all tinnitus patients. In these studies, stress was assessed using a single question with no clear definition of the concept of stress. Stimulus-based measurements of stress have rarely been used. Jackson (2019) reported negative, but non-significant, correlation (r =−.207; p>0.05) between Severity of Recent Life Event (SRLE) and severity of tinnitus as measured by T-VAS at the time of cortisol collection. No study has used interview-based assessment of life events. Therefore, the use of these instruments may reveal more meaningful associations between tinnitus and stress.

Stress biomarkers are objective indicators of stress levels. Measuring stress-related biomarkers in tinnitus patients has so far revealed little about their effect on tinnitus patients. Although cortisol is affected by many factors (Jackson, 2019, Adam and Kumari, 2009), it might be a

mediator that connects stress and tinnitus. Exposure to stress leads to increased cortisol levels which may affect the auditory and non-auditory circuits in the brain by downregulating or upregulating GCRs and MCRs (1.4.2) which in turn explain the similar neuronal changes in tinnitus and stress. Thus, it may explain the role of stress in tinnitus. Cortisol secretion is in a rapidly fluctuating and dynamic state (Lightman and Conway-Campbell, 2010). In tinnitus patients, HPAA and cortisol secretion responses were described as blunted and delayed (2.3.2.6) which might decrease cortisol in a longer term. The long-term secretion of cortisol can be assessed in hair (1.4.3.4), which has not been studied in tinnitus patients. Additionally, the effect of stress on psychoacoustic characteristics of tinnitus and whether the level of cortisol and/or perceived stress can affect the perception of tinnitus are unknown.

In summary, the direction of any relationship between tinnitus and stress and requires thorough investigation. All three concepts of stress should be considered and measured using reliable tools. Long-term changes in cortisol levels, and their role in tinnitus pathophysiology should be investigated, as should the effect of stress on the psychoacoustic measures of tinnitus.

CHAPTER 3 TINNITUS AND STRESS: THE ROLE OF CORTISOL

The aim of this chapter is to examine the role of stress and cortisol in tinnitus compared to people who do not have tinnitus.

3.1 INTRODUCTION

The impact of tinnitus is generally assessed using subjective self-report instruments (e.g. TFI, THI, and TQ) and as yet there is no objective measure to evaluate the severity of tinnitus or the effects of any treatment (Henry, 2016, McFerran et al., 2019). Given the similarities between tinnitus and stress, and the differences in salivary cortisol reactivity to stress between tinnitus and non-tinnitus participants (as reviewed in 2.4), one can propose an association or a cause-effect relationship between the impact of tinnitus and cortisol levels. The question raised here is whether cortisol can predict the impact of tinnitus on an individual.

The long-term secretion of cortisol can be assessed in hair shafts. The earliest protocol to extract and detect the physiological concentrations of cortisol in hair was published in the 2000s (Cirimele et al., 2000, Raul et al., 2004). Since then, hair cortisol analysis has been used in research about general health (Henley et al., 2013, Jackson et al., 2017, Ling et al., 2020), psychological disorders (Mewes et al., 2017, Heinze et al., 2016), and diseases (Gow et al., 2011, Hodes et al., 2017). It is considered a promising methodological approach that can

be applied in large population studies (Abell et al., 2016). Yet, it has not been studied in people with tinnitus.

HCC were previously found to be low in PTSD and General Anxiety disorder, to be high in stress-exposed participants, or to be equivalent in patients compared to controls in some studies (Stalder et al., 2017). In tinnitus patients, any of these patterns is expected (i.e. hair cortisol in people who have tinnitus can be higher than, lower than, or not different from those who do not have it.

3.2 STUDY AIMS AND OBJECTIVES

The main aim of this study is to determine whether cortisol has a role in the pathogenesis of tinnitus and/or making tinnitus more bothersome. To achieve this aim, I set primary and secondary objectives.

3.2.1 Primary objectives

1. To compare HCC in tinnitus patients and non-tinnitus controls.

   Null hypothesis: No differences in HCC in those who have tinnitus and those who do not.

   Alternative hypothesis: HCC differs (is higher or lower) in people who have tinnitus than people who do not.

2. To examine the changes HCC in tinnitus patients when tinnitus becomes bothersome

   Null hypothesis: No differences in HCC around the changes in tinnitus bothersome.

Alternative hypothesis: HCC is higher when tinnitus become more bothersome.

3.2.2 Secondary objectives

1. To examine whether HCC correlates with the severity of self-reported level of stress, self-reported tinnitus levels, and the pitch and loudness of tinnitus (psychoacoustic properties of tinnitus).
2. To examine the effect of anxiety, depression, and social factors on the relationship between tinnitus and stress.
3. To examine whether the occurrence of life events (stimulus-based stress) is associated with psychometric and psychoacoustic tinnitus levels.
4. To examine the effect of tinnitus management on HCC. This will help to understand whether HCC can be used as a tool (objective biomarker) to monitor the progress of the management in the clinical setting.
5. To examine whether changes in HCC and tinnitus levels are associated with changes in cognitive performance.

3.3 MATERIALS AND METHODS

3.3.1 Study design and setting

This study was an observational, single-centre study formed of two studies:

1. A cross-sectional study aimed to measure HCC in people who have tinnitus and non-tinnitus participants.

2. A longitudinal study to assess the effect of tinnitus management on HCC. Participants in the tinnitus group were asked to attend two visits 3 months apart.

Although it was possible to record changes in TFI scores after 3 months (Fackrell et al., 2018), there is no evidence to what the optimal interval is to achieve a measurable change in tinnitus levels in longitudinal studies. The length of the interval can vary from 1 week to 5 years. I accounted for other factors that may affect HCC, like the seasonal effect, to set the time between the two visits. Post-intervention changes have been reported in HCC after 1 month (Goldberg et al., 2014).

The study started in November 2018 and closed in March 2020. The visits took place in the National Institute of Health Research Nottingham Biomedical Research Centre (NIHR Nottingham BRC) in Ropewalk House and the Institute of Hearing Research (IHR) building at the University of Nottingham.

3.3.2 Ethics approval

This study was approved by the West Midlands-Solihull Research Ethics Committee, reference number: 18/WM/0283.

3.3.3 Study participants

Participants were recruited into two groups: non-tinnitus (NTP) and chronic tinnitus (TP).

3.3.3.1 Sample size and justification

Sample size estimation was conducted using nQuery v4.0 software. It was based on previous studies finding a difference in HCC between

patients' groups and controls. Pochigaeva et al. (2017) described differences of 44.2% between patients with major depressive disorder and non-patient group. Stalder et al. (2017) in their meta-analysis reported that exposure to physical stressors can result in a 52% increase in HCC. They estimated a 29% decrease of HCC between the first 3-cm and second 3-cm segments of hair due to the wash-out phenomena (explained in 1.4.3.4). Therefore, the differences in HCC can vary between 29% up to 52%.

For this study, a power calculation determined that a sample of 84 participants (42 per group) would be required to detect a 50% increase in HCC and an effect size of 0.443 (a two-sided significance level of 5% to detect higher or lower level of cortisol, and power of 80% with equal allocation to each group). This increased to 46 participants in each group to overcome an estimated 10% drop of number of tinnitus participants in the second visit. Therefore, 92 TP and NTP in total were targeted for recruitment.

Following preliminary analysis HCC from the first 21 participants (TP= 11, NTP= 10), the sample size was recalculated using the same criteria mentioned above. The mean (M) and standard deviation (SD) for TP was 0.799±0.442 (ranged 0.31-1.69), and for NTP was 0.505±0.194 (ranged 0.14-0.83). Although TP group had higher mean HCC, it was not statistically significant. However, the sample size estimate based on these means showed that 23 participants in each group (in total, 46 participants were needed to reach a reliable significance level).

3.3.3.2 Inclusion and exclusion criteria

3.3.3.2.1 Inclusion criteria

- 18 years old and above.
- Native English speakers or had sufficient command of English.
- Able and willing to give informed consent.
- Hair length longer than 1 cm in the vertex area (back of the head), that was not heavily bleached or dyed.
- For chronic tinnitus group, participants should have subjective tinnitus for more than six months.

3.3.3.2.2 Exclusion criteria

1. Body Mass Index (BMI) equal to or more than 30 kg/m^2 as it is positively correlated with HCC (Stalder et al., 2017, Jackson et al., 2017).
2. Diseases or disorders known to cause pathological changes in cortisol levels, namely, Cushing's syndrome (hypercortisolism) or Addison's disease (hypocortisolism).
3. Psychological disorders associated with changes in HCC namely PTSD, General Anxiety Disorder, or Major Depressive Disorder.
4. Pregnancy and nursing, diabetes mellitus, and hypertension as these interfere with the function of HPAA.
5. On continuous corticosteroid therapy.
6. Otitis Media, labyrinthitis, mastoiditis, Meniere's disease, Vestibular schwannoma, meningioma, otosclerosis, multiple sclerosis, epilepsy, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, systemic sclerosis, decrease or increase thyroid hormone secretion (hypothyroidism and hyperthyroidism).

3.3.3.3 Participants recruitment

Participants were recruited from National Health Service (NHS) sites and non-NHS sites. Those who were willing to take part contacted me either by email or on phone. They confirmed that they read the information sheet and they did not have any reason to be excluded from the study.

3.3.3.3.1 Recruitment from clinical sites

Tinnitus patients at the audiology clinics at the Ropewalk House (main audiology clinic within Nottinghamshire Healthcare NHS Foundation Trust) and the ENT clinic at the QMC were asked by their usual care team if they were interested in taking part in the study. I approached those who were interested and explained the study. I asked them to read the information sheet and to take their time to think about their decision. Posters were displayed in Ear Nose Throat (ENT) department and audiology clinics in the Queen Medical Centre (QMC), Ropewalk House, and King's Mill audiology department. Posters were sent to General Practitioners (GPs) surgeries across Nottingham.

3.3.3.3.2 Recruitment from non-clinical sites

Invitations were emailed to people registered in NIHR Nottingham BRC hearing research database on three occasions during the study period. A digital copy of the information sheet was attached. Emails were sent to tinnitus support groups and to different email list moderators within the University of Nottingham asking for permission to send invitations through their email list. I received positive response from several administrators and the invitation were sent to their departments.

The study was publicised on social media platforms (NIHR Nottingham BRC Hearing Twitter account), at public events (e.g. University of Nottingham Wonder event 2019) and at British Tinnitus Association (BTA) conferences. I gave short talks to tinnitus support groups members to advertise the study. Posters were also displayed in different buildings at the University of Nottingham (Jubilee campus, University Park campus and Medical school).

3.3.4 Visits schedule

The visit was divided into four tasks as illustrated in Figure 3.1. Before starting the tasks, I discussed the information provided and answered any queries before gaining written consent from the participants. In task 1, participants completed the General Assessment Questionnaire (GAQ), RLCQ, DHS, and DASS. Participants then completed the cognitive testing in task 2. Task 3 was dedicated to assessing tinnitus and only participants in this group completed the Tinnitus Sample Case History Questionnaire (TSCHQ), TFI and performed the Tinnitus Tester. In task 4, hair samples were collected. Participants in the non-tinnitus group completed tasks 1, 2 and 4 and the whole visit lasted less than 2 hours. They attended one visit only. Tinnitus participants attended either one or two visits. Each visit lasted less than 3 hours. In the second visit participants followed the same steps as visit 1 except they did not complet the GAQ and TSCHQ. The interval between visits was 3 months. Looking at tinnitus interventional studies collectively, there is no standard in the length of the interval between the start of the management and the treatment endpoint. This interval can range from

weeks (trials of talking therapies for example) or 2 years (trials of TRT for example). Three months, however, is a standardised interval used to review important outcomes in Cochrane systematic reviews of tinnitus treatments (Hesse, 2016).

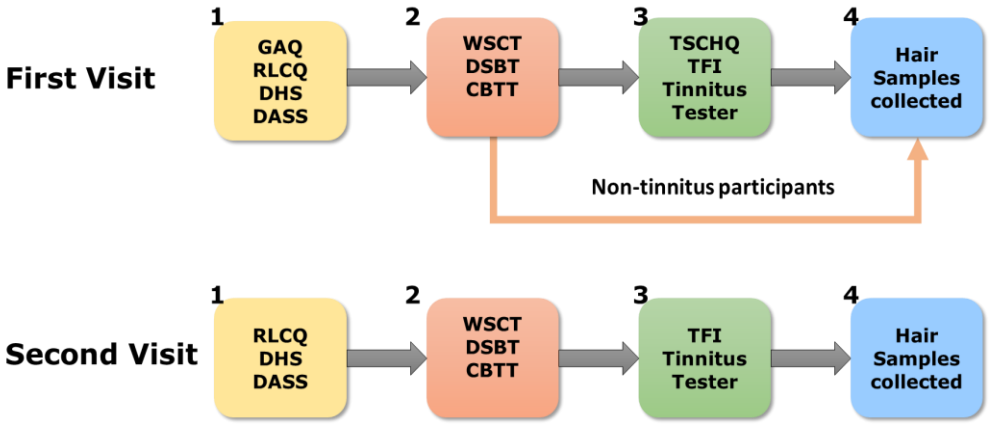


Figure 3.1 The schedules of first and second visits of the study.
All participants completed the tasks in the same given order. Non-tinnitus participants were not required to complete tinnitus assessment and they completed tasks in 1, 2 and 4. Hair samples were collected by the researcher (AE).
GAQ=General Assessment Questionnaire, RLCQ=Recent Life Changes Questionnaire, DHS=Daily Hassles Scale, DASS=Depression Anxiety Stress Scale, WSCT=Wisconsin Sorting Card Test, DSBT=Digital Span Backward Test, CBTT=Corsi Block Tapping Test, TSCHQ=Tinnitus Sample Case History Questionnaire, TFI=Tinnitus Functional Index.

Data therefore were collected at two points: the first visit (A) and the second visit (B). However, data collected assessed different time frames (i.e. retrospective, chronic, and single point, as described in Figure 3.2). For example, HCC in the third centimetre of hair collected in B corresponds to self-reported measures that were collected in A. This will be considered during data interpretation. Figure 3.2 also shows the timeframe for each measurement. Cognitive testing and tinnitus tester recorded the findings on the day of the visit. DHS, DASS, TFI, and few items in TSCHQ (that assess loudness awareness and bothersome) covers the week before the visit. RCLQ measures the occurrence of the events over 6 months. The GAQ and most items in the TSCHQ describe participants characteristics and have no specified timeframes.

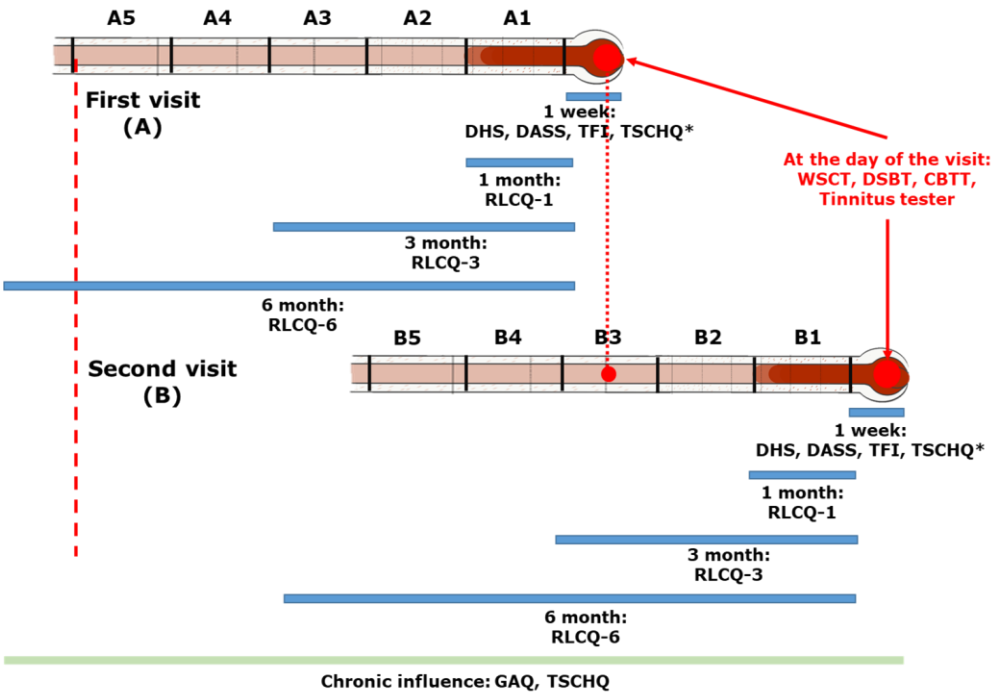


Figure 3.2 Timeframe of collected data
Data collected in visit 1 (A) has corresponding points with data collected in visit 2 (B). Data collected in the first visit that measures the changes within a week from the visit (namely DHS, DASS, TFI and few TSCHQ items), and the tests conducted on the same day corresponds with the hair cortisol level in the third centimetre collected in the second visit. The first centimetre of hair collected in the first visit corresponds with the fourth centimetre of hair collected in the second visit.
GAQ=General Assessment Questionnaire, RLCQ=Recent Life Changes Questionnaire, DHS=Daily Hassles Scale, DASS=Depression Anxiety Stress Scale, WSCT=Wisconsin Sorting Card Test, DSBT=Digital Span Backward Test, CBTT=Corsi Block Tapping Test, TSCHQ=Tinnitus Sample Case History Questionnaire, TFI=Tinnitus Functional Index.

3.3.5 Variables and data sources

The variables used in this study were chosen based on the findings of the scoping review (2.3) and a review of studies that assessed cortisol in tinnitus (2.4). Reviewed studies showed that many instruments have not been used in tinnitus. For example, hair cortisol had never been studied in tinnitus before. The TFI was used only in three previous

studies and its scores correlated positively with PSQ scores (Table 2.3). The review demonstrated that in previous studies stress was almost always measured according to only one or two concepts which indicated the need to measure stress according to all three concepts. We found that there was a lack of reporting on the effect of stress on the psychoacoustic measurements of tinnitus, and assessment of stress using stimulus-based instruments. However, the scoping review did not inform the choice of cognitive tests as they were out of the scope of the review. The justification of using the following instruments is explained the relevant section.

3.3.5.1 Hair samples for cortisol analysis

Hair samples allows one to measure retrospective cumulative cortisol levels up to 5 months (Abell et al., 2016, Dantzer et al., 2014) and thus, observe change that may be related to change in severity of tinnitus. This has not been investigated previously. Hair sample collection is convenient, safe and avoids methodological issues associated with collecting plasma, urine, or saliva for cortisol analysis (D'Anna-Hernandez et al., 2011). It does not require prior instruction such as avoiding certain foods or physical exercise (as detailed by Salimetrics and SalivaBio (2011) manual for collecting saliva). Additionally, hair samples can conveniently be stored at room temperature (Raul et al., 2004).

Nevertheless, this method has some technical challenges that should be considered when conducting the study and interpreting the results (Figure 3.3). First, the “wash-out phenomena” which means that HCC in

the proximal segments is higher than in the distal segments (Stalder et al., 2017, Dettenborn et al., 2012). Second, HCC is universally agreed to be reliable in the first five centimetres. Therefore, I collected only the proximal part of hair strands. Third, cortisol in the hair follicle and adjacent hair shaft that cannot be cut by the scissors represents cortisol secretion over the last 2 weeks (LeBeau et al., 2011). Last, a small amount of hair cortisol comes from sweat and sebaceous glands in the scalp and attaches to the outer layer of the hair shaft (Russell et al., 2012) and as such any detected level of cortisol is not fully attributed to the free cortisol in the blood (Meyer and Novak, 2012).

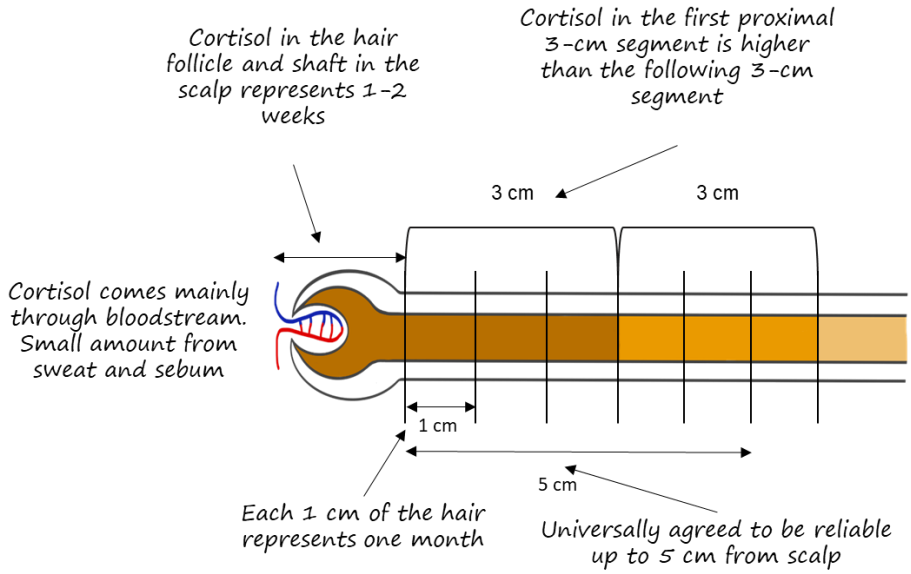


Figure 3.3 Important concerns regarding hair cortisol analysis.

The reference value of normal HCC can vary according to the analytic test being used (Binz et al., 2018). For example, Manenschijn et al. (2012) reported HCC of 75.90 pg/mg (measured by Enzyme-linked Immunosorbent Assay (ELISA)) as a cut-off value to diagnose Cushing's disease, which is one of the exclusion criteria in this study. There are no reference values reported for the mass spectrometry technique which was used in this study. Given that those who have any chronic illness associated with changes in cortisol were excluded from the study, only HCC data above the upper limit of quantification (ULOQ) was excluded from the statistical analysis. The ULOQ is a parameter of analytic test validation and indicates the maximum concentration of a sample that can be quantified without compromising the precision and accuracy of the test (Peters et al., 2007), therefore any value above the ULOQ could bias the results.

HCC is considered as a reliable measure for cortisol secretion. It has been shown to significantly correlate with salivary cortisol area under the curve (AUC) (r=0.45 as reported by D'Anna-Hernandez et al. (2011) and r=0.398 as reported by Vanaelst et al. (2012)). Sugaya et al. (2020) reported a positive correlation between HCC in the first hair and 30-day integrated salivary cortisol (r= 0.41). HCC also correlated positively with cortisol in 24-hour urine samples (r=0.33) (Sauve et al., 2007). Repeated hair cortisol analysis across 2- and 4 month intervals showed a strong test-retest reliability; correlation coefficient ranged between 0.68 and 0.79, p<0.001 (Stalder et al., 2012). Therefore, HCC is an appropriate measurement to assess the differences in cortisol levels between patient and control groups.

3.3.5.2 Self-reported measurements of stress

3.3.5.2.1 Recent Life Changes questionnaire

Miller and Rahe (1997) updated the Social Readjustment Rating Scale (SRRS; developed by Holmes and Rahe (1967)) to develop the Recent Life Changes Questionnaire (RLCQ). This means that the RLCQ is a measure of change caused by events that may disturb the person's life over a certain period of time (Schroeder and Costa, 1984). This questionnaire consists of a checklist of events that covers health, work, home and family, personal and social life, and finances (Appendix III). The respondents are required to report events that happened in the prior year. Miller and Rahe (1997) used a proportional scaling method to quantify the magnitude of each event and that is termed as Life Change Units (LCU). They chose one item (marriage) as an arbitrarily

"module" and a mid-range score (50) was assigned to the module event. All other items on the list are scaled in proportion to this module item. The total score represents the level of stressful events in the person's life. In general, a 6-month score of 300 or more, or a year score of 500 or more, indicates high stress in a person's life (Miller and Rahe, 1997). Sobell et al. (1988) reported that test re-test reliability correlation of RLCQ (scores in period of 6-month) was high (r=0.85) when the participants re-called events retrospectively.

In this study, I asked the participants to report events that happened over the last 6 months and report the month when the event happened in order to estimate the effect of recent life changes on cortisol levels over months and per month.

3.3.5.2.2 Daily Hassles Scale

To assess the occurrence of daily events, participants were asked to complete the Daily Hassles Scale (Kanner et al., 1981, Wright et al., 2019). It is formed of a list of 119 daily events that may or may not occur in their lives (Appendix IV). Each event had a rating of severity that ranged from "*somewhat severe*:1" to "*extremely severe*:3." Participants were asked to circle the severity of the hassles that they were "currently" experiencing. As there is no option of "not stressful" (Wright et al., 2019), the participants are asked to skip events that are not relevant to them. At the end of the questionnaire, they were asked to declare whether they were facing a recent event that may affect how they completed the DHS. The scoring of the scale covers the daily hassles number (DHS-N) and severity (DHS-S) both independently

associated with psychological distress (Reich et al., 1988). The scale is a checklist and there are no reference values or cut-off scores.

3.3.5.2.3 Depression anxiety and stress scale

The 42-item Depression Anxiety Stress Scale (DASS-42; Lovibond and Lovibond, 1995) is widely used scale to assess the core symptoms of depression anxiety and stress (Appendix V). Each item in DASS-42 measures the symptoms of either depression, anxiety, or stress and is scored by participants selecting one of four options: "*Did not apply to me at all"*= 0, "*Applied to me to some degree, or some of the time"*= 1, "*Applied to me to a considerable degree, or a good part of time"*= 2, *and "Applied to me very much, or most of the time"*= 3. The scores for depression, anxiety, and stress are the sum of 14 items that are relevant to each sub-scale.

The interpretation of the score varies among the sub-scales. On DASS-D, a score of 0-9 considered as normal, 10-13 is mild, 14-20, moderate, and more than 20 is severe. On DASS-A, a score of 0-7 is interpreted as normal, 8-9 is mild, 10-14 is moderate, and more than 14 is severe. On DASS-S, a score of 0-14 considered as normal, 15-18 is mild, 19-25 is moderate, and more than 25 is severe.

Validations in clinical and community settings have showed that the DASS-42 has acceptable reliability with Cronbach' s alphas score of more 0.90 for each sub-scale (Antony et al., 1998). Similar reliabilities of the DASS scales have been also reported among general adult UK population Crawford and Henry (2003). Although it was designed to discriminate between its subscales, studies have shown that DASS-42

has moderate convergent and discriminant validity (Crawford and Henry, 2003, Imam, 2008).

3.3.5.3 Measurements of tinnitus

3.3.5.3.1 Tinnitus Functional Index

Tinnitus Functional Index (TFI, Meikle et al., 2012) is a 25-item questionnaire that cover eight subscales: Intrusiveness (TFI-I), Sense of Control (TFI-SC), Cognitive Interference (TFI-C), Sleep Disturbance (TFI-S), Auditory Difficulties (TFI-A), Relaxation (TFI-R), Quality of Life (TFI-QoL), and Emotional Distress (TFI-E). Each item is scored on an 11-point scale, with descriptors at either end of the scale (Appendix VI).

The total scores of TFI were calculated according to Meikle et al. (2012). The sum of all responses is divided by the number of the valid items and multiplied by 10 to give a total score range between 0 -100. The same process is followed to calculate the total scores for each subscale (total score 0 -100) which can indicate the impact of tinnitus on different domains. Also, the total score can be stratified into five or three categories to indicate “tinnitus impact”. The scores can be classified into no problem (0-7), small problem (8-28), moderate problem (29-47), big problem (48-65), or very big problem (66-100). This classification was developed by Fackrell et al. (2018) for UK-based population. Therefore, it will be followed in this study.

TFI has an internal consistency of 0.80 (Cronbach’s α), reliability of 0.90 (Inter Class Correlation), and significantly correlates with THI (r=0.82) and THQ (r=0.82) in non-clinical setting (Fackrell et al., 2016).

3.3.5.3.2 Tinnitus Sample Case History Questionnaire

Tinnitus Sample Case History Questionnaire (TSCHQ; Langguth et al., 2007) was compiled by tinnitus experts during a consensus workshop on tinnitus assessment in 2006. I modified the TSCHQ for this study by removing some repeated questions (age and gender) and moving the hearing-related questions to the GAQ.

The modified TSCHQ contained 29 items (Appendix VII). While most items are multiple-choice, dichotomous, or verbal description format, three items require the patient to rate their tinnitus loudness (scale 1–100), awareness (percentage of the awake time), and annoyance (percentage of the awake time). TSCHQ is limited in terms of collecting data about all tinnitus comorbidities and factors that are possibly associated with tinnitus (Genitsaridi et al., 2019), however, people who had these comorbidities were excluded from the study and the possible related factors were collected in the GAQ; see 3.3.5.4.

3.3.5.3.3 Pitch Matching and Loudness Matching

Tinnitus Tester software is a computerised procedure used to assess the quality of the tinnitus sensation (Roberts et al., 2008). Participants are required to complete a 5-minute introduction session to understand how to use software and answer the questions during the testing session. Next participants are asked to localise their tinnitus (right ear, left ear, or both), to determine its bandwidth (tonal, ringing, or hissing) and its temporal properties (steady or pulsing), and to rate its loudness (T-VAS Loudness 0-100). In the second section, they attempt to match

the loudness and pitch of their tinnitus to the loudness and pitch of eleven different sounds presented over headphones that have centre frequencies of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 kHz.

LM is reported as the PA5 attenuator value, zero attenuation (maximum output of the system) was 96 dB SPL. Sounds are presented 22 times in a random order during LM. Each frequency is presented twice, and the participant adjust the loudness to match the loudness of their tinnitus; the average loudness rating at 1000 Hz was taken as representative of their tinnitus loudness.

PM are rated on a 100-point matching scale from 0 (not at all) to 100 (identical). Each sound is presented three times (total 33 trials), participants rate its similarity to the pitch of their tinnitus on a 1-100 likeness scale and the highest average percentage likeness is taken as the representative PM at each frequency.

3.3.5.4 General assessment Questionnaire

A 32-item general assessment questionnaire was devised and formed of six sections. It was created to assess social and physical moderators and confounders that may affect the HCC. These sections and items are detailed in Table 3.1. Social mediators such as socioeconomic status, behavioural trait, and social support are important mediators in the interaction between stress and health (Hawkley et al., 2011, McEwen and Akil, 2020). Chronic social stress can lead to HPAA dysregulation (Scott et al., 2012). As such, they can affect the primary or secondary appraisal in the transaction between the event and the

individuals (McKimmie et al., 2019). They can be protective factors if they enhance the resilience to stress. For example, supportive family structures and maintenance of a physically active lifestyle allow one to withstand or bounce back from stress (Epel et al., 2018). Thus, it was important to assess these confounder factors.

Table 3.1 Items within the General Assessment Questionnaire (GAQ)

SOCIOECONOMIC STATUS

1. What is the highest degree or level of school you have completed/ received? Higher education & professional/ vocational equivalents; A levels, vocational level 3 and equivalents; GCSE/O Level grade A*-C, vocational level 2 and equivalents; Qualifications at level 1 and below; Other qualifications: level unknown (including foreign qualifications); No qualifications

2. What is your current employment status? Employed full time; Employed part time; Unemployed and currently looking for work; Unemployed and not currently looking for work; Self-employed; Student; Retired; Unable to work; Other.

3. What is your marital status? Single/ never married; Married or domestic partnership; widowed; divorced; Separated.

MEDICAL HISTORY

4. Are you being treated for any medical condition at the present or have you been treated within the past 5 months? Yes/No

5. If yes, please list these conditions and the length of the condition? ----------

6. Are you taking any medications, non-prescription drugs or herbal supplements of any kind? Yes/No

7. If yes, please list ----------

HEALTH BEHAVIOUR

8. How often do you have a drink containing alcohol? Never; Monthly or less; 2-4 times per month; 2-3 times per week; 4 times and more per week.

9. How many units do you drink on a typical day when you are drinking? 1-2; 3-4; 5-6; 7-9; 10+

10. Do you smoke? Never; yes; ex-smoker

11. If yes, how many a day: ----------

12. How much is your Height? ……. Inches ……cm

13. How much is your weight? ……. pounds ……Kgs

14. Do you take regular exercise? Yes/ No

15. In a typical week, on how many days do you exercise? 1-3 days; 4-5 days; 6-7 days

16. How much time do you spend doing exercise in a typical day? Less than 1 hour; 1-2 hours; More than 2 hours.

HAIR (HAIR-RELATED PARAMETERS)

17. Do you describe your natural hair colour as: white; blond; red; brown; black

18. In a typical week, how often do you wash your hair? 1-3 times; 4-5 times; 6-7 times

19. How often do you use hair styling products? Every day; Twice in the week; Once in the wee; Never

20. Which of these treatments have you done for your hair in the last 5 months? Dyed; bleached; Permed/ straightened; None.

HEARING AND AUDIOLOGICAL SYMPTOMS

21. Do you think you have a hearing problem? Yes/ No

22. Do you wear hearing aids? Right; left; both; none

23. Do you have difficulty in understanding what others were saying in noisy or crowded places? Yes/ No

24. Do you have a problem tolerating sounds because they often seem much too loud? That is, do you often find too loud or hurtful sounds which other people around you find quite comfortable? Never; Rarely; Sometimes; Usually; Always

Please, list two examples of sounds that are too loud or uncomfortable for you, but seems normal to others ----------

25. Do sounds cause you pain or physical discomfort? Yes; No; I don't know

SOCIAL SUPPORT

26. How much do people around you really understand the way you feel about things? A lot; some; a little; not at all.

27. How much can you rely on them if you have a serious problem? A lot; some; a little; not at all.

28. How much can you open up to them if you need if you need to talk about your worries? A lot; some; a little; not at all.

29. How much do they criticise you? A lot; some; a little; not at all.

30. How much do they let you down when you are counting on them? A lot; some; a little; not at all.

31. How much do they get on your nerves? A lot; some; a little; not at all.

32. How often do they make too many demands on you? A lot; some; a little; not at all.

Some of these questions were adapted from other self-reported instruments:

1. The two questions assessing alcohol intake (items 8 and 9) were extracted from the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) which is a 10-item screening tool used to effectively identify people with at-risk or harmful drinking. It is recommended by WHO (2019). The English version has been shown to be a reliable measure (Reinert and Allen, 2002, Fiellin et al., 2000, Wardell et al., 2020).
2. The five questions on hearing and audiological symptoms were extracted from the TSCHQ (Langguth et al., 2007).
3. Social Support was assessed using items adapted from a questionnaire measuring the effect of positive social support (Po-SS) and negative social support (Ne-SS) on HCC (Iob et al., 2018). In this questionnaire, Po-SS and Ne-SS are assessed on a 4-point scale (*Not at all*: 1, *a little*: 2, *some*: 3, and *a lot*: 4) the average score for each type is calculated and categorised into three categories. The 3-item Po-SS scores are categorised into low for scores <2, medium for scores 2-3, and high for scores >3. The 4-item Ne-SS scores are categorised into low for score <1, medium for scores 1-3, and high for scores >3. In this study, the raw scores of the social support items were used in the regression analysis.

3.3.5.5 Cognitive tests

Impaired capacity to perform certain cognitive tasks in tinnitus patients has been reported (Andersson and McKenna, 2006, Mohamad et al.,

2016). For example, tinnitus has showed a strong effect on attention and memory (Mohamad, 2015). As explained in Chapter 2, some functional and structural changes in brain areas (limbic system) that regulate higher cognitive functions were observed in tinnitus and stress. These areas include the prefrontal cortex which regulates executive functions (Ball et al., 2011, Yuan and Raz, 2014), the hippocampus and the amygdala which regulate memory (Kumaran, 2008, Sheldon and Levine, 2016, Schaefer et al., 2006, Ghosh et al., 2013). Therefore, these two (executive function and memory) were the constructs of interest in this study. The aim of assessing cognitive function in this study was to determine whether changes in HCC relate to changes in the cognitive performance of tinnitus patients.

3.3.5.5.1 Wisconsin Sorting Card test

The Wisconsin Sorting Card Test (WCST) was developed by Grant and Berg (1948). It is a well-established test of executive function which is a specific aspect of cognitive functions and is considered as the primary function of the prefrontal cortex (Glisky, 2007, Diamond, 2013, Brown, 2000, Rhodes, 2004). The WSCT has 10 parameters, as listed by Yates et al. (2013). The description and interpretation of these parameters are summarised in Figure 3.4.

Description and Interpretation of the Wisconsin Card Sorting Test scores

Score	Description	Interpretation
Total number of trials administered	Total number of cards used.	The lower the score, the greater the efficiency of the examinee in the task.
Total number of correct responses	Number of successes in combinations according to the current category.	The greater the score, the better the performance (considering the number of trials administered).
Total number of errors	Number of incorrect combinations, done despite the examiner´s feedback.	The greater the score, the worse the performance.
Perseverative responses	Number of correct and incorrect combinations done by combining with a determined standard.	The greater the score, the worse the performance.
Perseverative Errors	Number of incorrect combinations done by combining with an incorrect combination standard.	The greater the score, the worse the performance. It indicates the mental inflexibility and *insight* difficulty.
Conceptual level responses	Consecutive correct answers which occur in a number of three or more.	The greater the score, the better the performance. It indicates *insight* about the correct principle of cards combination.
Number of completed categories	Number of categories (each sequence of 10 consecutive correct combinations according to the classification criteria) which the examinee completes successfully along the test.	The greater the score, the better the performance in the task.
Trials to complete the first category	Number of attempts needed to complete the first category successfully.	The greater the score, the greater the difficulty the examinee has to perceive the current category and combine accordingly.
Non-perseverative errors	Number of errors which occur in a non-perseverative way, that is, number of errors that do not persist in an incorrect combination standard.	The greater the score, the worse the performance. It indicates difficulties on forming concepts and having insights even with flexible answers.
Failure to maintain set	Number of times the examined individual makes five or more consecutive correct combinations, but makes an error before completing a category.	The greater the score, the worse the performance on keeping the correct responses in sequence.

Figure 3.4 Wisconsin sorting card test parameters and their interpretations.
Source: Yates et al. (2013)

According to Greve and Bianchini (2002), a group of parameters reflects a certain aspect of executive function. For example, the disruption in problem-solving function is assessed by the perseverative errors, perseverative responses, and total errors reflect response inflexibility. The percent conceptual level responses, categories completed, and total correct responses parameters. The number of categories completed (scored from 0-6) reflects the global performance of executive functions (Shan et al., 2008). Response maintenance and

distractibility (i.e. the inability to maintain focus on a task) are assessed by Failure to Maintain Set (Figueroa and Youmans, 2013) which is scored from 0-5. A score more than 3 is relatively rare even in patients with dementia and stroke (Greve et al., 2009).

The choice of parameter depends on the study aim and the disorder being assessed. Shan et al. (2008) advised the use of “percent-form” of the parameters to standardise the measurement of the WCST index response. Martin et al. (1991) reported that higher levels of depression are associated with poor performance in percent perseverative errors, percent conceptual level responses, total errors, failure to maintain set, and percent perseverative responses. Participants with schizophrenia recorded higher number of trials, total error, and percent conceptual level responses than non-patient group (Singh et al., 2017). Considering that the aim is to examine the effect on HCC on the cognitive function in tinnitus, all parameters will be assessed in this study.

3.3.5.5.2 Digital Span Backwards Test (Visual)

Digit span is the maximum number of digits (numbers) that are correctly recalled after administrating a series of digits (Blackburn and Benton, 1957). There are a variety of span tests and each type assesses different constructs of cognitive performance. Recalling the number in reverse order is called the Digit Span Backward (DSB) and measures the working memory given the need to reverse the order of the digits (Diamond, 2013, Kessels et al., 2008, Reynolds, 1997). In this study, participants completed a computerised DSB to reduced variability in the

rate and clarity of digit presentation in the non-computerised version (Woods et al., 2011). Additionally, digits were administered visually rather than verbally to reduce the effect of language bias in the testing bilingual participants (Olsthoorn et al., 2012). The scores are recorded as DSB maximum number and consecutive error. In a technical report, Croschere et al. (2012) stated that a digit span of 7 is the average number of digits people recall. Consecutive error represents the maximum number of digits recalled correctly before making two consecutive errors (Alesi et al., 2020). There is no information about the average DBS consecutive error, and they are usually less used in the studies than the DBS maximum number.

3.3.5.5.3 Corsi Block Tapping Test

The Corsi Block Tapping Test (CBTT; Corsi, 1973) was designed to assess the visuospatial short-term and working memory and is used widely in both clinical and research settings (Kessels et al., 2000, Diamond, 2013). Originally, the examiner taps a physical block in sequence and the examinee has to recall the sequence in forward or backward order. Although the backward recall may appear to be more relevant to the working memory, Kessels et al. (2008) concluded no differences between forward and backward CBTT and that they rely on the same cognitive process. Therefore, I used only the forward CBTT in this study. The blocks in CBTT are not labelled which makes it less susceptible to the use of verbal coding (Richardson, 2007). CBTT is recorded in two parameters. The span capacity or CBTT span indicates the highest level at which the participant correctly reproduced at least

one sequence, and it may range between two and nine (Farrell Pagulayan et al., 2006, Kessels et al., 2000). CBTT score is the sum of correctly reproduced sequences at all levels (*ibid*). CBTT Span appears to be a less sensitive measure than CBTT score, possibly because the range of scores is limited and does not consider the performance on both trials within each level (Kessels et al., 2000).

In general, it is recommended to use multiple validated measures in tinnitus research to avoid analysis bias (Mohamad et al., 2016). The reliability of the WSCT, CBTT, and DSB tests were assessed in tinnitus population by Mohamad (2015). Both the DSB and CBTT appear as part of known cognitive test batteries such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Automated Working Memory Assessment (AWAM) Battery (Diamond, 2013). Therefore, the DSB, CBTT, and WSCT were included in this study.

3.3.6 Test presentation

All questionnaires (GAQ, DHS, RLCQ, and DASS) were completed in a paper-and-pen format, and in the same order. The WSCT was administered using a series of test cards that were revised and standardised by Heaton (1981). The card set is formed of 128 test cards in two packs and four reference card that refer to three rules (colour, shape/ form, or the number shapes). The test cards were numbered, and they were given out accordingly. I explained to the participants at the beginning of the test that they must match one card each time to a reference card, and to do so, they had to figure the

matching rule each time. The only feedback they received was whether their decision was correct or incorrect and thereafter they had to figure out the rule for the next card. I administered the rules in the following order (Colour, Forms, Number, Colour, Forms, and Number) which forms six categories. Participants were required to give 10 successive correct answers to complete one category. The test was carried out until they completed all six categories, or they matched all 128 test cards. Scoring was computed on WSCT software (Heaton and Staff, 1993) which computes the test parameters and adjust them according to age and education.

DSBT and CBTT were performed on PEBL2 (The Psychology Experiment Building Language) software (Mueller and Piper, 2014), and run on Windows 10. Onscreen instructions were presented to the participants at the beginning of each test and I explained the steps to the participants. In DSB, a 3-trial training was provided to familiarise participants with the test. The test started with presenting a three-digit sequence. Then, the participant was instructed to type the digit in a box on the screen in the backward order. The length of the sequence increased by one if the participant responded correctly for two successive trials. The test stops once the participant fails to recall the correct order for three trials. The CBTT had no training session and participants started the test immediately. In this computerised version, nine blue squares replaced the blocks in the original test. The change of the colour from blue to yellow replaced the physical tapping of the blocks. Participants were required to remember the sequence of

change in colour. The length of the sequence started with three squares that are processed for two trials before its length increases. The test ceased once the participant failed to recall the correct sequence for three trial. The program recorded and adjusted the results to the participant's age.

Tinnitus participants completed TSCHQ and TFI in a paper format. Then, they performed the Tinnitus Tester in a sound-proofed booth which blocks the outside sounds and thus minimises the effect of external noises on the test. The room had a glass window and calling system that allowed easy communication with the examinee when it was needed. Sound was presented through an over-ear headphone to both ears at the same time (binaurally). I instructed the participants during the introductory training and they completed the test on their own. The test terminated when they completed the PM tasks, and the results were saved automatically in an Excel format.

I collected hair samples at the end of the visit from all participants following the recommendations from previous research. It is generally recommended that hair samples should be collected from the vertex region on the scalp as there is less variability in the cortisol level compared to other scalp regions (Xie et al., 2011). Sauve et al. (2007) reported that the coefficient of variation was 15.6% between hair samples obtained from the vertex which was smaller than variation within hair samples taken from different sections of the head at 30.5%. Hair grows on average about 1 cm per month (LeBeau et al., 2011). So, cortisol secretion over one month can be estimated from analysing one

centimetre of hair and the proximal hair segments represent cortisol secretion in recent months (Iglesias et al., 2015). Bundling of hair and the angle of the scissors in relation to the scalp leads to uneven cutting of the hair (LeBeau et al., 2011). To minimise the effect of this drawback, I used a large hair clip instead of a band to stabilise hair strands (Figure 3.5 A). This technique allowed me to cut the hair in a linear shape, and to make the cut parallel to the scalp as much as possible. It helped me to control hair strands shorter than 2 cm. To avoid leaving a bald spot on the back of the head, I cut the hair from three different spots on the lower vertex and the upper occipital region (Figure 3.5 B). I then cut each hair strand into 1 cm segments to estimate HCC per month (Figure 3.5 C) wrapped in 15x15 cm foil squares (Figure 3.5 D). Each sample was placed in a plastic pouch labelled by the participant's code, date and time of collection, and the sample number (Figure 3.5 E) and stored in a dark and locked cupboard at room temperature. Only the proximal five segments of hair samples were kept for the analysis.

For reporting the results, hair segments collected at the first visit were labelled as following: A1= first centimetre, A2= second centimetre, A3= third centimetre, etc. Hair segments collected at the second visit were labelled as following: B1= first centimetre, B2= second centimetre, etc. (Figure 3.5 F).

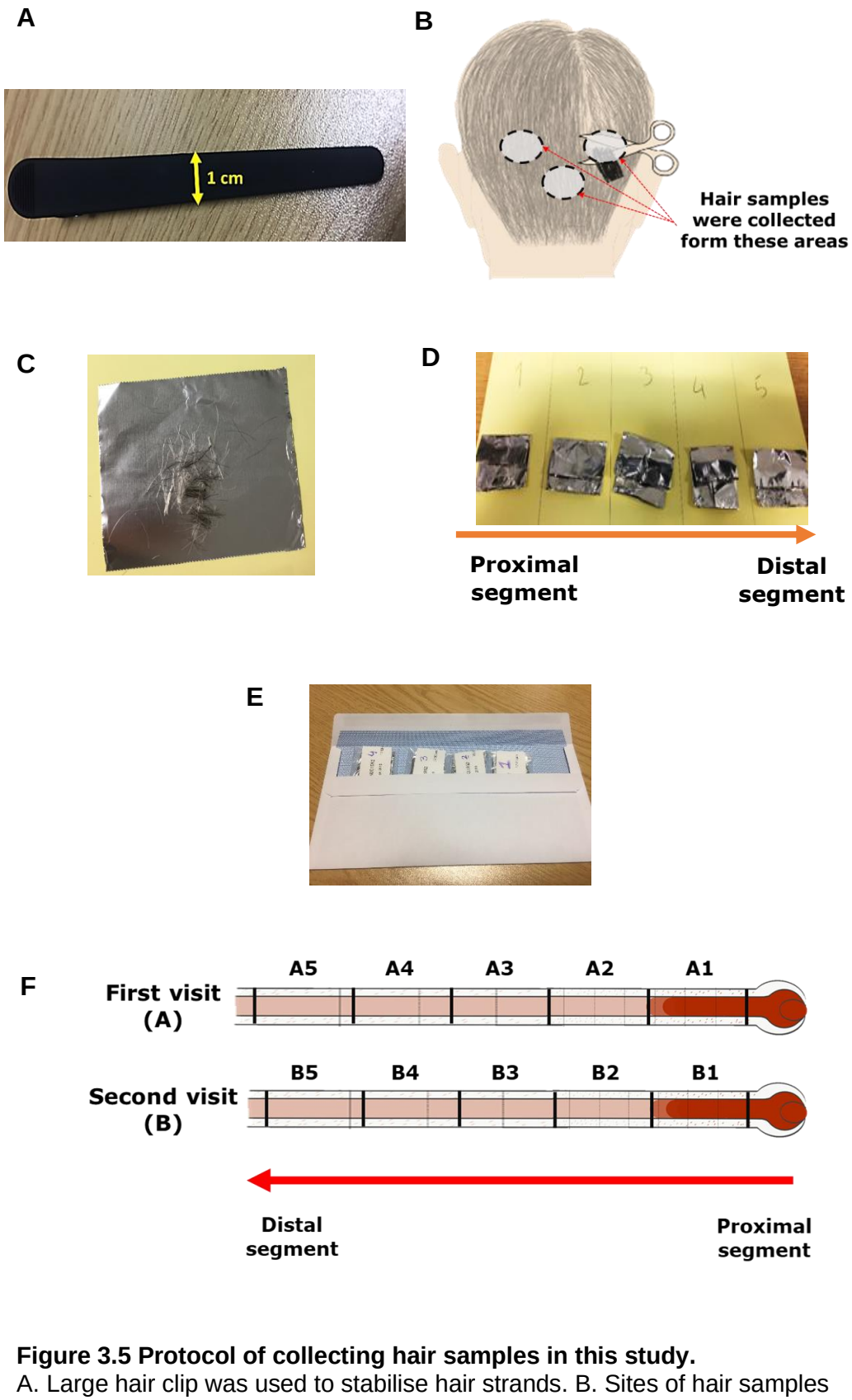


Figure 3.5 Protocol of collecting hair samples in this study.
A. Large hair clip was used to stabilise hair strands. B. Sites of hair samples collection from the back of the head. C, D. Hair strands were cut into 1-cm segments and wrapped in foil squares. E. Samples were stored in envelops and kept in dark place at room temperature. F. Hair segments labels.

3.4 HAIR CORTISOL ANALYSIS

Hair cortisol can be analysed by various analytic techniques. In this study, it was analysed using liquid chromatography tandem mass spectrometry (LC-MS/MS) which has an excellent sensitivity and specificity (Gao et al., 2016, Qi et al., 2017). This method is less subject to intra-assay and inter-assay variability than immunoassay (Russell et al., 2012, Taylor et al., 2015). A cross-reactivity between cortisol and steroids such as progesterone is a known drawback of ELISA assay (Greff et al., 2019), which may inflate HCC. The samples were sent to the Mass Spectrometry, Edinburgh Clinical Research Facility to conduct the LC-MS/MS.

3.5 STATISTICAL ANALYSIS

Participant data were recorded in Microsoft Excel 2010. Statistical analysis was undertaken using the Statistical Package for the Social Sciences (SPSS, Version 26.0, run on Windows 10). The appropriate statistical analysis was chosen based on the data. Continuous data were examined for skewness and kurtosis to determine whether they met the assumption of normal distribution. Data were examined for normality by performing the Kolmogorov-Smirnov test (66 participants were recruited in this study). The Z score was calculated to detect outliers and any value that had a z-score more or less than ±2.89 (i.e. 99% of data fell within this score) were considered outliers and were replaced with values (X) calculated as following this equation: $X= (2.98 \times SD)+M$; where M is the mean of the variable, and SD is the Standard

Deviation (Field, 2013). This step was useful to treat the scores of the Daily Hassles and Recent Life Changes Scales as they were checklists. For example, one participant reported a score of 204 (z-score= 5.179) on the DHS-S. Thus, the score was replaced with a score of 125.8.

Descriptive statistics were expressed as means and standard deviation, median, and ranges. The categorical data that describes the characteristics of the participants were expressed in frequencies and percentages. P values of less than 0.05 were reported as statistically significant.

3.5.1 Differences between the groups

Independent samples t-test for the normally distributed data, and Mann-Whitney U and Wilcoxon signed-rank for non-parametric data were performed to compare the differences in means between the tinnitus and non-tinnitus group (inter-subject differences). Comparison between the mean of the variables collected from tinnitus participants in both visits (intra-subject comparison) were performed using the Paired t-test and Wilcoxon signed-rank accordingly. Effect sizes were calculated online as: Cohen's d = $(M_2 - M_1)/SD_{pooled}$ where $SD_{pooled} = \sqrt{((SD_1^2 + SD_2^2)/2)}$. M stands for the mean of the group and SD for the standard deviation (computed on the website https://www.socscistatistics.com/effectsize/default3.aspx and Cohen's d was reported.

3.5.2 Relationships between variables

Correlations between variables were calculated using Pearson's and Spearman's rho tests. Correlations were described as weak if it were less than 0.4, moderate between 0.4-0.7, and strong if it greater than 0.7 (Dancey and Reidy, 2007, Akoglu, 2018). Repeated measure one-way ANOVA were performed to detect the changes in HCC between hair segments. The association between outcomes were assessed with linear regression analysis. Multilinear Regression analysis (MLR) was used to explore whether stress and outcomes (independent variables) predict tinnitus levels (dependent variables). Univariate General Liner Model (GLM) used to explore candidate predictors and confounders.

3.5.3 The effect of changes in HCC on tinnitus

To examine whether changes in cortisol levels are associated with changes in tinnitus levels, two methods of assessment were used:

1. Hair samples collected in visit A represents the cortisol values that secreted in the months prior to the tinnitus levels measured at visit A. The samples collected in visit B represents the cortisol levels that secreted following the tinnitus levels measured at visit A. A comparison is made between A1 and B3 hair segments which provide the cortisol level one month before and one month after assessing the impact of tinnitus in visit A (Figure 3.6 A). Four participants did not have B3 data which was replaced with the levels of B1.

2. The changes in TFI total (dTFI-T) was measured as the differences between TFI-T scores at A and B. Th changes in HCC (dHCC) was calculated as the differences between B3 and B1 (Figure 3.6 B).

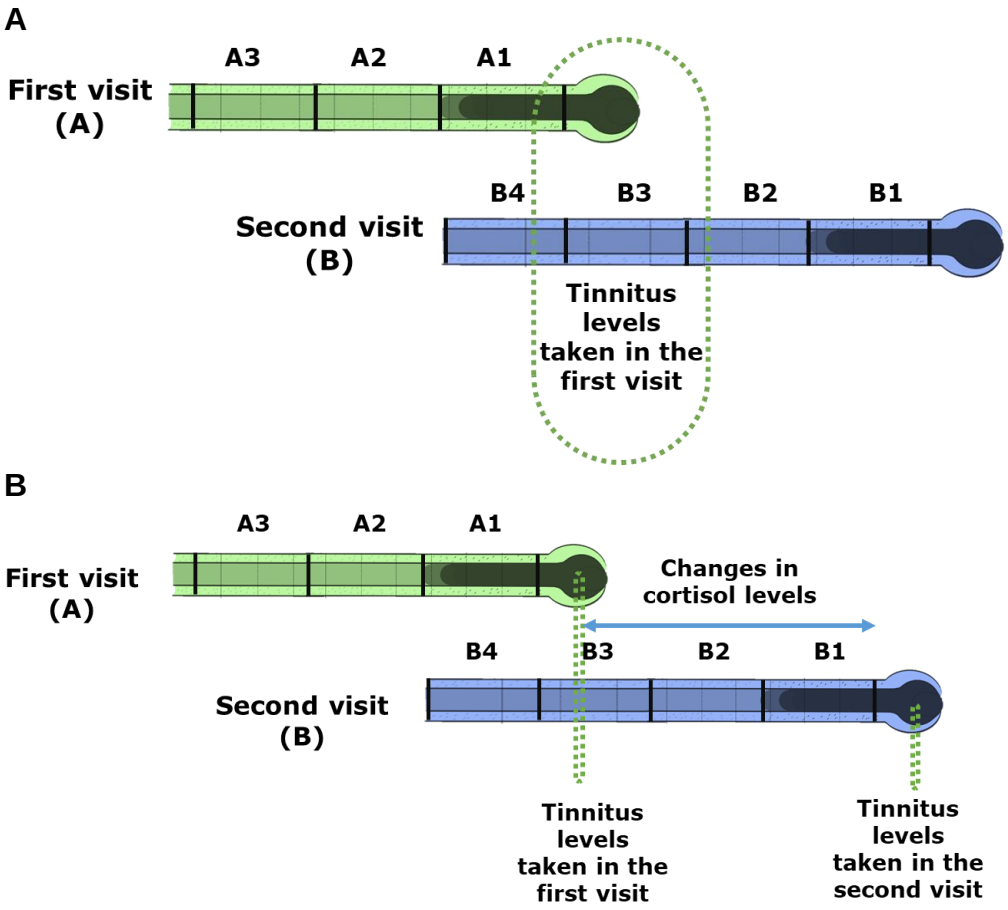


Figure 3.6 Assessing the changes in cortisol levels when tinnitus become bothersome.
(A) The first hair segment in the first visit represents the cortisol secretion before tinnitus levels. The third hair segment in the second visit correspond to the hair strand below the scalp in the first visit and therefore represents the cortisol secretion parallel to/ after the tinnitus levels measured in the first visit. (B) Two records of tinnitus levels were taken in each visit. The hair segments taken in the second visit represents the changes in cortisol levels between the two points. So, the association between the change in cortisol levels and the change in tinnitus bothersome was computed by using the changes in cortisol in the second visit and change in tinnitus levels in both visits.

3.6 RESULTS

3.6.1 Participants recruitment

Out of 165 people who showed interest in the study, only 66 participants were recruited and took part in the study. Of those, 32 were NTP and 34 were TP. Figure 3.7 shows the recruitment process from

NHS and non-NHS sites, reasons for exclusion, and the final number of participants. Only 22 tinnitus participants attended the second visit (35.3% drop-out).

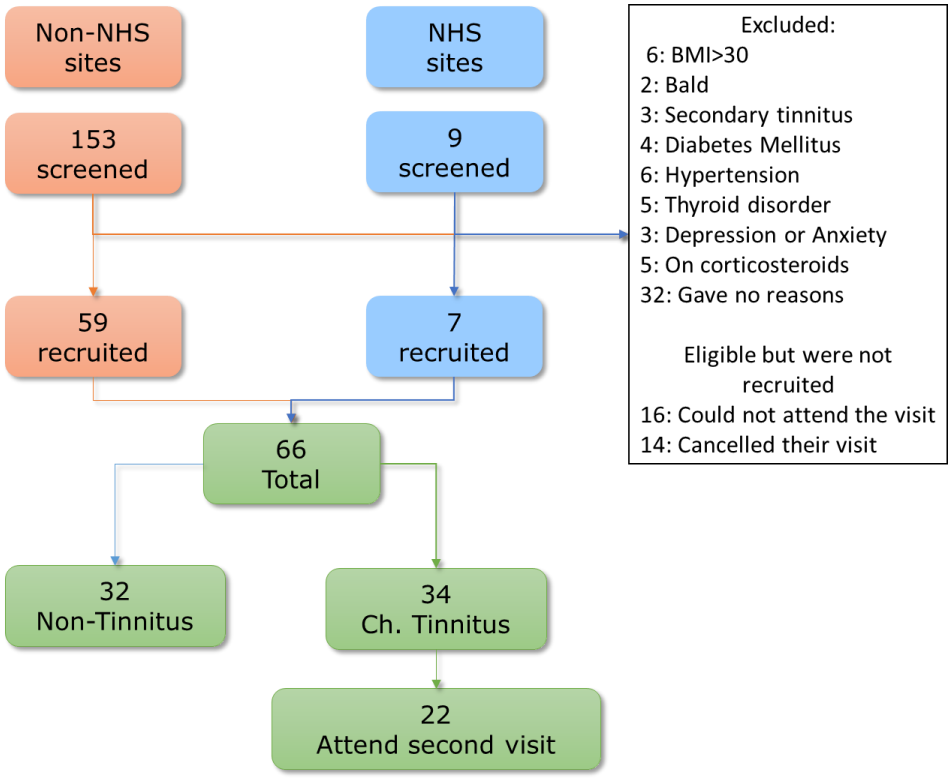


Figure 3.7 Flow chart of recruitment process.
Participants were mainly recruited from non-NHS sites. Number of excluded (96 people) and the reasons for exclusion are reported in the text box.

3.6.2 Descriptive statistics

3.6.2.1 Sample characteristics

The majority of TP were men (>75%), whilst in contrast NTP were mostly women (>65%). Table 3.2 shows the demographic characteristics of NTP and TP for both visits. The independent sample t-test showed significant difference in the age between NTP and TP ($t(64) = -2.039$, $p<0.05$).

Table 3.2 Characteristics of the participants in each group

	Non- tinnitus group A (N= 32)	Tinnitus group A (N= 34)	Tinnitus group B (N=22)
Age M±SD (range in years)	41.66±21.046 (20-73)	51.82±19.473 (21-88)	51.32±17.924 (21 –74)
Male	10 (31.3%)	**26 (76.5%)**	19 (86.4%)
Female	**22 (68.8%)**	8 (23.5%)	3 (13.6%)
Education			
Higher	**22 (68.8%)**	**21 (61.8%)**	13 (59.1%)
A level	6 (18.8%)	4 (11.8%)	3 (13.6)
GCSE	2 (6.3%)	7 (20.6%)	5 (22.7%)
Other	2 (6.3%)	1 (2.9%)	0 (0%
No qualifications	0 (0%)	1 (2.9%)	1 (4.5%)
Employment			
Full-time	2 (6.3%)	6 (17.6%)	5 (22.7%)
Part-time	2 (6.3%)	5 (14.7%)	3 (13.6%)
Unemployed	2 (6.3%)	0 (0%)	0 (0%)
Self-employed	1 (3.1%)	5 (14.7%)	2 (9.1%)
Student	**17 (53.1%)**	7 (20.6%)	5 (22.7%)
Retired	8 (25.0%)	**11 (32.4%)**	7 (31.8%)
Marital status			
Single, never married	**17 (53.1%)**	8 (23.5%)	6 (27.3%)
Married, in partnership	13 (40.6%)	**25 (73.5%)**	16 (72.7%)
Divorced	2 (6.3%)	0 (0%)	0 (0%)
Widowed	0 (0%)	1 (2.9%)	0 (0%)
Alcohol intake			
Never	5 (15.6%)	4 (11.8%)	1 (4.5%)
Yes	**27 (84.4%)**	**30 (88.2%)**	21 (95.5%)
Smoking			
Yes	0 (0%)	1 (2.9%)	1 (4.5%)
No	**23 (71.9%)**	**18 (52.9%)**	11 (50%)
Ex-smoker	9 (28.1%)	15 (44.1%)	10 (45.5%)
Exercise			
Yes	**26 (81.3%)**	**27 (79.4%)**	18 (81.8%)
No	6 (18.8%)	7 (20.6%)	4 (18.2%)

Numbers in bold fonts indicate the highest percentage in the row.
GCSE= General Certificate of Secondary Education, M=Mean, N= Number of participants, SD= Standard deviation, A= First visit, B= Second visit

Hearing problems were reported by a majority of the TP group (64.7% and 76.5% respectively), and by about half of NTP (43.8% and 53.1% respectively). However, only 22 participants (13 NTP and 9 TP) were hearing aids users (Table 3.3). Less than 50% of NTP and more than 65% of TP reported that they experienced hyperacusis, and most reported that sound did not cause pain (90.6% of NTP and 67.6% of TP).

Table 3.3 Hearing problems among participants in each group

	Non- tinnitus group A (N= 32)	Tinnitus group A (N= 34)	Tinnitus group T2B (N=22)
Hearing problems (subjective)			
Yes	14 (43.8%)	**22 (64.7%)**	**14 (63.6%)**
No	**18 (56.3%)**	12 (35.3%)	8 (36.4%)
Wearing hearing aid			
None	**19 (59.4%)**	**25 (73.5%)**	**15 (68.2%)**
One ear	0 (0%)	2 (5.9%)	1 (4.5%)
Two ears	13 (40.6%)	7 (20.6%)	6 (27.3%)
Understanding speech in noise			
Yes	**17 (53.1%)**	**26 (76.5%)**	**17 (77.3%)**
No	15 (46.9%)	8 (23.5%)	5 (22.7%)
Hyperacusis			
Usually	1 (3.1%)	4(11.8%)	3 (13.6%)
Sometimes	7 (21.8%)	15 (44.1%)	**10 (45.5%)**
Rarely	6 (18.8%)	4 (11.8%)	3 (13.6%)
Never	**18 (56.3%)**	**11(32.4%)**	6 (27.3%)
Do you feel pain or physical discomfort?			
Yes	1 (3.1%)	8 (23.5%)	6 (27.3%)
No	**29 (90.6%)**	**23 (67.6%)**	**14 (63.3%)**
Do not know	2 (6.3%)	3 (8.8%)	2 (9%)

Numbers in bold fonts indicate the highest percentage in the row.
N= Number of participants, A= First visit, B= Second visit.

NTP reported lower social support (Po-SS= 1.76±0.576 and Ne-SS= 2.98±0.617) than TP (Po-SS= 2.02±0.618 and Ne-SS= 3.13±0.680). Independent t-test showed no differences in the means between both groups (Po-SS $t(64)=1.754$, $p=0.084$; Ne-SS $t(64)=0.927$, $p=0.356$).

3.6.2.2 Hair cortisol levels

The quantity of samples obtained from the first, second, third, and fourth centimetres were 66, 59, 49, and 37 samples, respectively. Samples were obtained from the fifth and sixth centimetres obtained from less than 45% of the participants and therefore were excluded from the laboratory analysis. Data from three participants (two NTP and one TP) were above the upper limit of quantification (ULOQ) and therefore were excluded from the statistical analysis. The HCC was reported in picogram of cortisol per milligram of hair (pg/mg). Log

transformation was applied to normalise the positively skewed HCC data. The M and SD of HCC in the full hair sample from TP and NTP participants attended visit A (N=63) was 0.824± 0.374. One-way repeated measures ANOVA indicated a non-significant time effect on HCC across the four hair segments (Wilks' Lambda= 0.83, $F(3, 33)= 2.322$, $p=0.93$), and similarly, between the first (A1) and second (A2) segments (Wilks' Lambda= 0.99, $F(1, 56)= 0.402$, $p=0.529$). Figure 3.8 shows the mean concentrations of cortisol in the proximal four centimetres of hair from all participants.

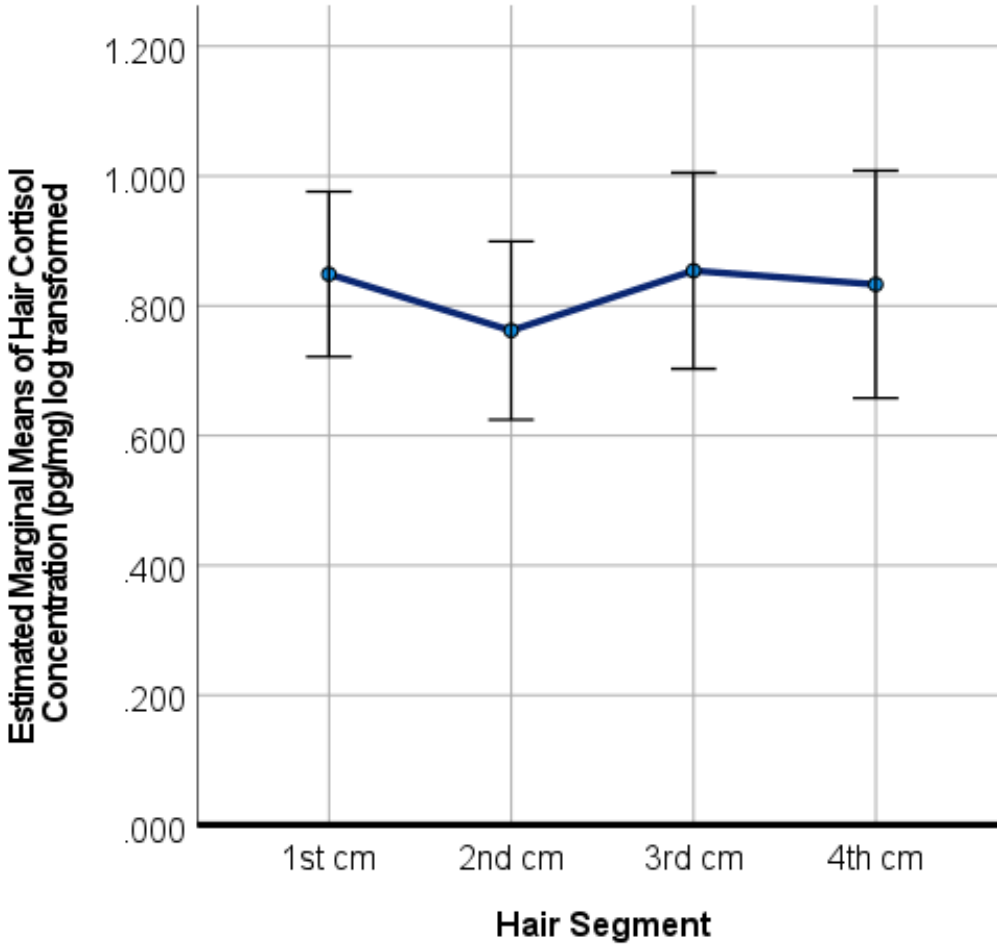


Figure 3.8 Changes in cortisol levels across the proximal four centimetres of hair
Data collected from tinnitus and non-tinnitus participants (N=63).
Error bar 95% Confidence Interval

3.6.2.3 Self-reported stress levels

Table 3.4 reports the descriptive statistics for the stress, depression, and anxiety scales. The TP group had higher levels of depression, anxiety and stress as shown by DASS subscale scores, but NTP had higher DHS and RLCQ mean scores.

Table 3.4 Means, Standard deviations, ranges and Median of self-reported measures of stress, depression and anxiety as reported by participants in the first visit.

			Non-tinnitus group (N=32)	Tinnitus group (N=34)
DASS	**Depression**	M±SD	2.89±3.808	3.64±4.424
		Median (range)	2 (0-16)	2 (0-15.68)
	Anxiety	M±SD	2.32±2.55	3.24±3.429
		Median (range)	1.5 (0-11.18)	1 (0-10)
	Stress	M±SD	5.75±5.315	7.00±5.725
		Median (range)	4 (0-22.21)	5 (0-22.12)
DHS	**Number**	M±SD	20.92±21.114	20.00±15.690
		Median (range)	14 (3-87.52)	17 (0-78)
	Severity	M±SD	29.49±29.639	26.31±21.988
		Median (range)	17.5 (3-104.86)	22.5 (0-104.86)
RLCQ	**Last month**	M±SD	43.14±74.245	31±55.868
		Median (range)	0 (0-265)	0 (0-226)
	Last 3 months	M±SD	127.10±132.557	87.02±101.703
		Median (range)	73.5 (0-461.65)	52 (0-526)
	Last 6 months	M±SD	177.65±161.013	167.70±164.613
		Median (range)	157 (0-613.96)	124 (0-613.96)

DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, M=Mean, N= Number of participants, RLCQ= Recent Life Changes Questionnaire, SD= Standard deviation.

Independent samples Mann-Whitney U and Wilcoxon W tests showed no significant differences in self-reported stress between TP and NTP groups (Table 3.5).

Table 3.5 Summary of the results from nonparametric test comparing the means of self-reported stress measurements

	Mann-Whitney U	Wilcoxon W	Z	*p*
DASS-Depression	512.00	1040.00	-0.407	.675
DASS-Anxiety	489.00	1017.00	-0.722	.471
DASS-Stress	465.00	993.00	-1.011	.309
DHS Number	504.50	1032.50	-0.507	.612
DHS Severity	530.00	1058.00	-0.160	.857
RLCQ last month	499.50	1094.50	-0.663	.508
RLCQ last 3 months	443.00	1038.00	-1.301	.193
RLCQ last 6 months	501.50	1096.50	-0.533	.585

DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, p= Significance level, RLCQ= Recent Life Changes Questionnaire.

3.6.2.4 Characteristics of tinnitus

Tinnitus duration varied from one to 45 years (M±SD= 12.91±11.109). Less than 80% of the TP had tinnitus for less than 20 years. The *M* and *SD* of the total TFI was 27.93±9.563 (range 0-84.80). Five (14.7%) participants had no problem with their tinnitus, 12 (35.3%) had small problem tinnitus, 13 (38.2%) had moderate problem tinnitus, and four (11.8%) had big problem tinnitus. None of the TP had very big problem tinnitus. The TFI-SC subscale had the highest mean out of all the subscales. Table 3.6 summaries the descriptive statistics for TFI sub-scales.

Table 3.6 Summary of Means and Standard Deviations of Tinnitus Functional Index sub-scales

TFI sub-scale	M±SD	Range
Intrusiveness	33.35±22.341	0- 86.70
Sense of control	40.92±23.464	0- 87.00
Cognitive	27.94±24.909	0- 87.00
Sleep	31.76±33.269	0-100.00
Auditory	26.67±24.899	0- 77.00
Relaxation	31.97±24.504	0- 93.00
Quality of Life	13.13±19.474	0- 85.00
Emotional Distress	15.20±17.041	0- 80.00

M=Mean, N= Number of participants, SD= Standard Deviation, TFI= Tinnitus Functional Index.

Participants rated their tinnitus loudness using the TSCHQ question and the Tinnitus Tester. The TSCHQ scores showed a mean score of 36.67(±18.71) for tinnitus loudness, whilst responses from the tinnitus tester showed a mean score of 45.91 (±26.28) for tinnitus loudness. Figure 3.9 illustrates tinnitus loudness levels and the percentage of the day when the participants were annoyed and aware of their tinnitus.

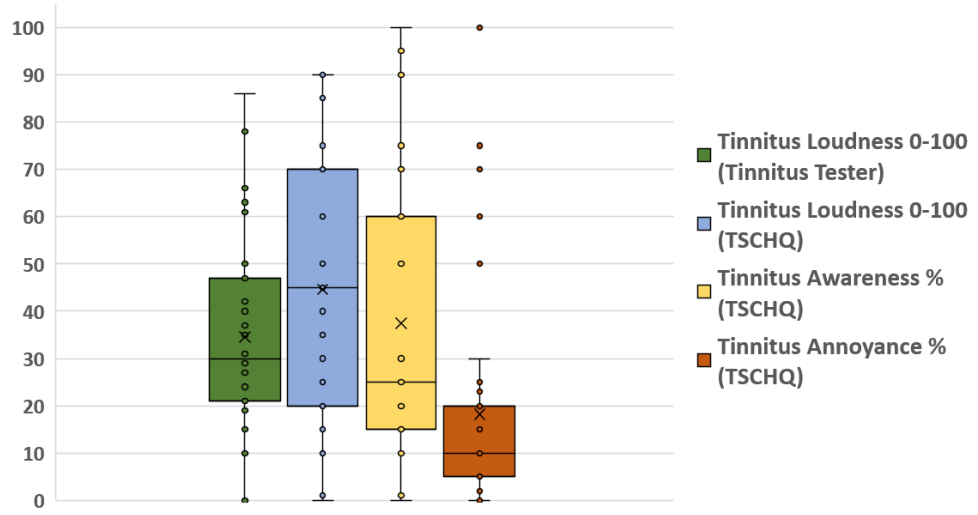


Figure 3.9 A box plot of Tinnitus Loudness, Awareness and Annoyance among 34 tinnitus participants in the cross-sectional study.
Tinnitus loudness ratings ranged from 0-100 (VAS on tinnitus tester (Borg and Borg, 2001) and Numeric Rating System on TSCHQ). Tinnitus Annoyance and Awareness are represented in percentages of the awake time.

The Tinnitus Tester was performed by 33 out of 34 of tinnitus participants at visit A (the missed case was due to technical issues). Of those, 32 participants described the temporal properties tinnitus as steady, and one described it as pulsating. The spectral properties of tinnitus were hissing (n=13), tonal (n=18), and ringing (n=2). Figure 3.10 shows that LM and PM varied among the participants.

The LM at 1kHz (LM-1kHz) has been shown to provide the most reliable results (Rabau et al., 2015, Meikle et al., 2008). Test–retest reliability of LM-1kHz shows an excellent correlation (Henry et al., 2009). Therefore, it was considered as the main parameter to be reported in this thesis. LM-1kHz ranged between 2-79 dB SL (M±SD= 34.67±21.026).

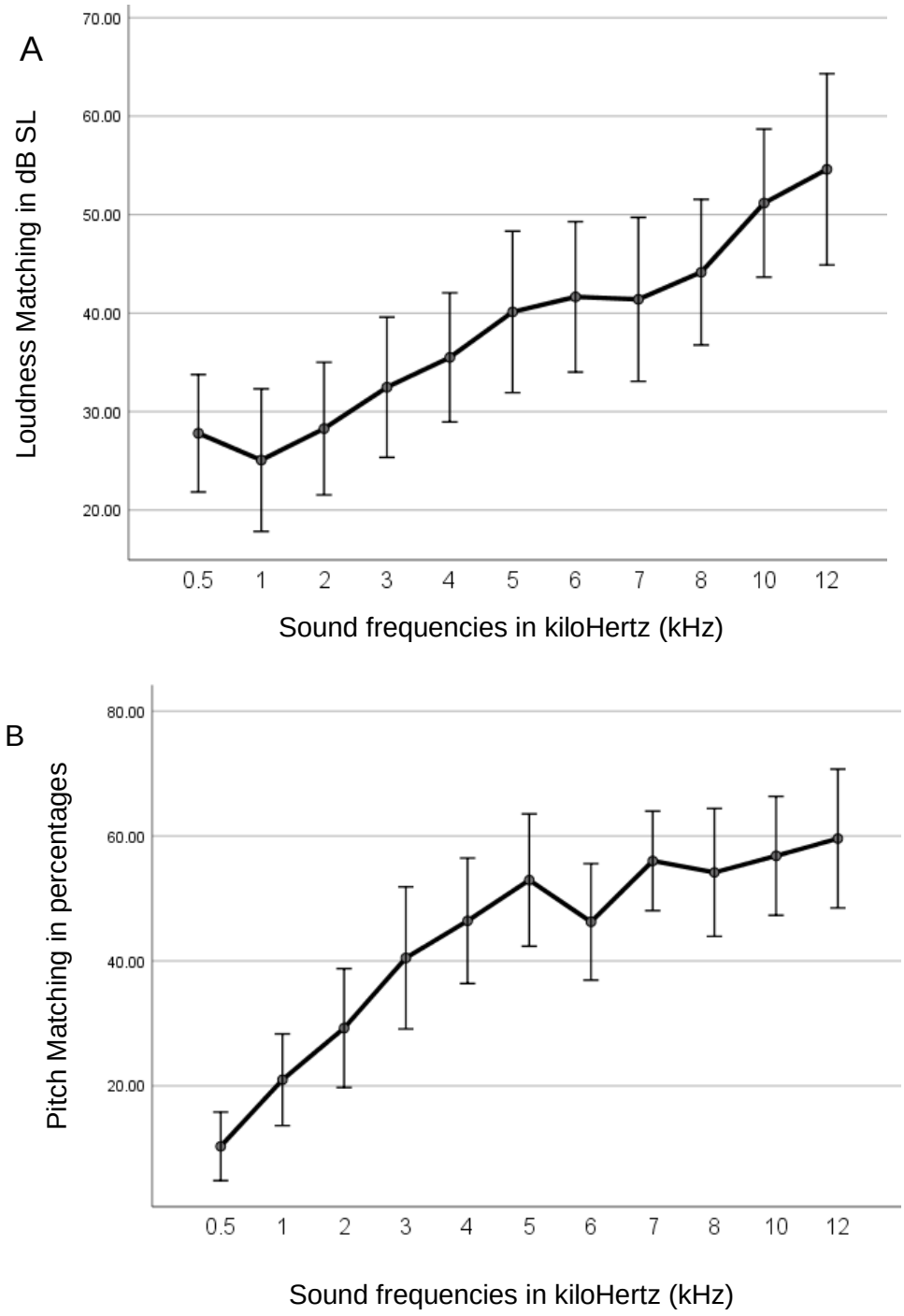


Figure 3.10 Tinnitus loudness matching and pitch matching
Loudness and pitch matching are measured at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 kHz.
Error bars 95% CI

3.6.2.5 Cognitive function

TP had slightly higher mean scores for the DSB and CBTT than the NTP but the independent t-test showed no differences between the groups (Table 3.7).

Table 3.7 Summary of the descriptive and t-test results of Digital Span Backward test and Corsi Block Tapping Test.

	Non-tinnitus group (N=23) M±SD	Tinnitus group (N=24) M±SD	*t*(45)	*p*
DSB-Max	6.17±1.497	6.33±1.522	0.362	.719
DSB-Error	5.43±1.950	6.02±2.502	1.185	.242
CBTT-Span	5.48±1.442	5.71±0.955	0.642	.525
CBTT-Score	45.44±22.817	49.91±14.755	0.790	.434

CBTT-Span= Corsi Block Tapping Test Span, CBTT-Score= Corsi Block Tapping Test Score DSB-Max= Digital Span Backward Test Maximum recall, DSB-Error=Digital Span Backward Test Errors, M=Mean, N= Number of participants, p= Significance level, SD= Standard Deviation.

Independent samples Mann-Whitney U and Wilcoxon tests showed no significant differences in the WSCT parameters between the TP and NTP groups (Table 3.8).

Table 3.8 Summary of the results from nonparametric comparison of Wisconsin Sorting task test between tinnitus and non-tinnitus groups

Test parameters	Mann-Whitney U	Wilcoxon W	Z	*p*
Number of trials	524.500	1052.500	-0.046	.963
Total number correct	492.500	1020.500	-0.466	.641
Total number error	515.500	1076.500	-0.164	.870
Perseverative responses	513.000	1074.000	-0.197	.843
Perseverative error	514.000	1075.000	-0.184	.854
Non-perseverative error	524.000	1052.000	-0.053	.958
Conceptual level responses	455.000	983.000	-0.960	.337
Categories completed	478.000	1006.000	-0.890	.374
Trials to complete first category	429.000	990.000	-1.351	.177
Failure to maintain set	507.500	1068.500	-0.291	.771
Learning to learn	392.500	827.500	-0.437	.662

p= Significance level, Z= non-parametric test statistics.

3.6.3 Main findings

3.6.3.1 Differences in hair cortisol and stress between tinnitus and non-tinnitus participants

Although TP had a higher HCC mean than the NTP group, the difference was not significant (Table 3.9). Therefore, the null hypothesis that there are no differences in HCC between TP and NTP was retained.

Table 3.9 Summary of the means, SD, and results of the independent t-test of hair cortisol concentrations.

Hair segment	HCC non-tinnitus group		HCC tinnitus group		Independent t-test			
	N	M±SD	N	M±SD	df	t	*p*	Cohen's d
A1	29	0.800±0.363	33	0.834±0.330	60	0.376	.709	.0543
A2	26	0.799±0.475	32	0.830±0.394	56	0.262	.795	.0696
A3	24	0.850±0.326	25	0.872±0.473	47	0.186	.853	.0535
A4	22	0.782±0.366	15	0.906±0.678	35	0.649	.524	.2286

A1= first centimetre of hair collected on the first visit, A2= second centimetre of hair collected on the first visit, A3= third centimetre of hair collected on the first visit, A4= fourth centimetre of hair collected on the first visit, df= Degree of freedom, HCC= Hair Cortisol Concentration, M= Mean, N= Number of participants, p= significance level, SD= Standard Deviation, t= t-test value.

3.6.3.2 Differences in hair cortisol when tinnitus become bothersome

Participants in visit B (N=22) were divided into two groups based on their TFI-T scores in visit A. Those are tinnitus participants who had TFI-T scores more than 25 (TFI>25 subgroup) and those who ad TFI scores less than or equal to 25 (TFI≤25 subgroup). HCC in TFI≤25 subgroup increased at visit B. In contrast, it decreased in the TFI>25 subgroup. However, differences in cortisol level at visit A and B in each sub-group were not statistically significant. The results are summarised in Table 3.10.

Table 3.10 Summary of paired t test results comparing hair cortisol when tinnitus become bothersome

Subgroup	N	HCC in A1 M±SD	HCC in B3 M±SD	Paired t-test df	t	*p*
TFI ≤25	9	0.789±0.344	0.857±0.524	8	0.413	.690
TFI >25	13	0.870±0.370	0.847±0.254	12	-0.221	.829

A1= first centimetre of hair collected on the first visit, B3= third centimetre of hair collected on the second visit, df= Degree of freedom, HCC= Hair Cortisol Concentration, M= Mean, N= Number of participants, p= significance level, SD= Standard Deviation, t= t-test value, , TFI= Tinnitus Functional Index.

There were only weak non-significant correlation between changes in HCC level and changes TFI-T scores ($r(20)=-0.114$, $p=.613$), changes in Tinnitus Loudness VAS ($r(12)=-0.041$, $p=.884$), and changes in LM-1KHz ($r(13)=0.320$, $p=.246$). Therefore, there was no significant differences in HCC when tinnitus became bothersome and the null hypothesis for the primary objective 2 is retained.

3.6.3.3 The association between HCC and self-reported stress

Spearman's rho showed no significant correlations between the HCC in the four hair segments and the DASS-S, DHS, and RLCQ levels. The only statistically significant but weak correlations were between HCC in A4 and the scores on the DHS-N and DHS-S (Table 3.11).

Table 3.11 Spearman's rho correlations between hair cortisol and self-reported stress levels

Hair segment	N	DASS	DHS		RLCQ		
		Stress	Number	Severity	last month	last 3 months	last 6 months
A1	62	.210	.191	.179	.174	-.027	.033
A2	58	.086	-.075	-.106	.097	-.216	-.097
A3	49	.039	-.174	-.237	.150	-.039	-.062
A4	37	-.193	**-.327***	**-.354***	.122	-.110	-.149
Average A1-A3	63	.078	-.036	-.062	.118	-.151	-.057

** p <0.05.*
A1= first centimetre of hair collected on the first visit, A2= second centimetre of hair collected on the first visit, A3= third centimetre of hair collected on the first visit, A4= fourth centimetre of hair collected on the first visit, DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, N= Number of Participants, RLCQ= Recent Life Changes Questionnaire.

3.6.3.4 The association between self-reported stress and tinnitus

Positive and weak to moderate statistically significant correlations were recorded between DASS-S and DHS-N and DHS-S with TFI-S and TFI-E (Table 3.12). Other correlations did not reach significance and were weak. RLCQ scores did not show any significant correlation with tinnitus levels. Similarly, tinnitus loudness, annoyance, and awareness scores were not correlated with self-reported stress measurements. However, correlations between DASS-S, DHS and TFI-S were not significant when computed at visit B. Instead, DHS-S and DASS-S were positively correlated with TFI-C and TFI-A. TFI-E at visit B showed positive moderate correlations with DASS-S and DHS which was also evident at visit A. All results are summarised in Table 3.12.

Table 3.12 Spearman's rho correlations between self-reported stress and tinnitus levels.

First Visit (N=34)	DASS	DH		RLCQ		
	Stress	Number	Severity	last month	last 3 months	last 6 months
TFI-Total	.248	.251	.290#	.071	-.076	.023
Intrusiveness	.114	.152	.148	.011	-.265	-.136
Sense of control	.334#	.187	.243	.090	-.056	.012
Cognitive	.334#	.267	.298#	.191	.025	.107
Sleep	**.359***	**.397***	**.455****	.080	-.017	.073
Auditory	.044	.066	.074	-.103	-.058	-.086
Relaxation	.100	.198	.198	-.081	-.052	.017
Quality of life	.196	.154	.163	.117	.054	.013
Emotion	**.382***	**.526****	**.529****	.056	.045	.197
Tinnitus Loudness NRS[1]	-.122	-.156	-.159	-.133	-.290	-.268
Tinnitus Loudness VAS[2]	172	-.052	-.006	.140	-.287	-.212
Tinnitus awareness	.001	.260	.248	.041	-.054	.054
Tinnitus annoyance	.220	.259	.162	.108	.004	.150

Second visit (N=22)	DASS	DH		RLCQ		
	Stress	Number	Severity	last month	last 3 months	last 6 months
TFI-Total	.294	.330	.402#	-.050	.209	.178
Intrusiveness	.246	.209	.334	.022	.203	.177
Sense of control	.084	.116	.052	-.294	-.178	-.203
Cognitive	**.463***	**.490***	**.488***	.075	.276	.227
Sleep	.084	-.037	.107	.004	.134	.100
Auditory	.289	.361#	**.450***	-.014	.279	.302
Relaxation	.201	.258	.319	.025	.339	.287
Quality of life	.296	.296	.355	-.033	.272	.286
Emotion	**.556****	**.564****	**.548***	-.115	.390	.316
Tinnitus Loudness VAS[2]	147	.099	.254	.110	.195	.102

*[1] Numeric Rating Scale as assessed by TSCHQ. [2] Visual Analogue Scale as assessed by Tinnitus tester. * p <0.05, ** p<0.001, #p<0.10*
DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, N= Number of Participants, RLCQ= Recent Life Changes Questionnaire. TFI= Tinnitus Functional Index.

3.6.3.5 The association between HCC and tinnitus level

Spearman's rho correlations between TFI and HCC in both visits are listed in Table 3.13. In visit A, there were positive and moderate significant correlations between TFI- SC and HCC in A1($r(31)= 0.475$, $p<0.05$), HCC in A2 ($r(30)=0.426$, $p<0.05$). There was also a positive weak but significant correlation between HCC in A1 and TFI-S ($r(31)=$

0.396, $p<0.05$). TFI-SC showed a positive weak correlation with the average HCC in the proximal three centimetres ($r(31)=0.393$, $p<0.05$). At visit B, the correlation between HCC in B1 and TFI-SC was weak and not significant ($r(20)= 0.359$, $p=0.100$), and similarly between HCC in B1 and TFI-S ($r(20)= 0.288$, $p=0.193$). It is apparent from Table 3.13 that there is a change in the direction of the correlation between HCC and TFI-E when comparing the results from visit A and B.

Table 3.13 Spearman's rho correlations between hair cortisol and tinnitus levels at first and second visits

First Visit	Hair segment				
	A1	**A2**	**A3**	**A4**	**Average A1-A3**
	n=33	**n=32**	**n=25**	**n=15**	**n=33**
TFI-Total	.301#	.273	.230	.007	.266
Intrusiveness	.316#	.272	.146	.036	.256
Sense of control	**.475****	**.426***	.234	-.091	**.393***
Cognitive	.282	.283	.093	-.005	.185
Sleep	**.396***	.311#	.140	-.204	.312#
Auditory	.208	.143	.307	.141	.194
Relaxation	.113	.058	.060	-.184	.047
Quality of life	.181	.099	.149	.017	.125
Emotion	.271	.225	.149	-.227	.202
Tinnitus Loudness NRS[1]	.119	.071	-.144	-.284	.020
Tinnitus Loudness VAS[2]	.287	.222	.069	-.033	.217
Tinnitus awareness	.294#	.175	-.005	-.096	.244
Tinnitus annoyance	.260	.159	-.006	-.262	.181
Second visit	**Hair segment**				
	B1	**B2**	**B3**	**B4**	**Average B1-B3**
	n=22	**n=20**	**n=19**	**NC**	**n=22**
TFI-Total	.132	.079	.083	---	.033
Intrusiveness	.349	.177	.154	---	.210
Sense of control	.359#	.306	.186	---	.251
Cognitive	.160	.152	.072	---	.103
Sleep	.288	.266	.310	---	.246
Auditory	.070	.020	.131	---	.014
Relaxation	.065	.-.088	-.018	---	-.031
Quality of life	.096	.104	.088	---	.019
Emotion	-.203	-.228	-.052	---	-.213
Tinnitus Loudness VAS[2]	.117	-.127	-.073	---	.217

*[1] Numeric Rating Scale as assessed by TSCHQ. [2] Visual Analogue Scale as assessed by Tinnitus tester. * p <0.05, ** p<0.001, #p<0.10.*
A1= first centimetre of hair collected on the first visit, A2= second centimetre of hair collected on the first visit, A3= third centimetre of hair collected on the first visit, A4= fourth centimetre of hair collected on the first visit, B1= first centimetre of hair collected on the second visit, B2= second centimetre of hair collected on the second visit, B3= third centimetre of hair collected on the second visit, B4= fourth centimetre of hair collected on the second visit, , N= Number of Participants, NC= Not computed.

3.6.3.6 Association between stress and psychoacoustic characteristics of tinnitus

The strength of the Spearman's rho correlations varied from negative moderate to positive weak correlation across LM and PM at different frequencies. Only the psychoacoustic properties of tinnitus (LM-2kHz,

PM-1kHz, and PM-5kHz-) showed significant moderate correlation with the stress measures (DASS-S, DHS-N, DHS-S, RLCQ-3 months, and RLCQ-6 months) as seen in Table 3.14.

Table 3.14 Summary of Spearman's rho correlations between stress levels and tinnitus tester LM and PM

			DHS		RLCQ		
	HCC-A1	**DASS Stress**	**Number**	**Severity**	**last month**	**last 3 months**	**last 6 months**
LM-1KH	.224	.085	-.069	-.020	.024	-.243	-.246
LM min/max r	.088/ .225	-.047/ .189	-.337/ -.032	-.359/ .004	-.149/ .108	-.394/ -.147	-.379/ -.199
PM min/max r	-.050/ .182	-.358/ .329	-.454/ .286	-.350/ .249	-.161/ .465	-.121/ .163	-.051/ .246
Statistically significant correlations							
LM-2kHz [2]	---	---	---	---	---	**-.394***	**-.379***
PM-1kHz [1]	---	**-.358***	---	---	---	---	---
PM-5kHz [3]	---	---	**-.454****	**-.350***	---	---	---

The maximum output of the tinnitus tester is 96 dB SLP and this led to missing values for some participants at some test frequencies. [1] n= 33, [2] n=32, [3] n=31.
** p <0.05, ** p<0.001.*
HCC-A1= Hair Cortisol Concentration in the first centimetre at the first visit, DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, LM= Loudness Matching, LM-1kHz= Loudness Matching at 1 Kilo Hertz, min= minimum, max= maximum, PM= Pitch Matching, PM-1kHz= Pitch Matching at 1 Kilo Hertz, PM-5kHz= Pitch Matching at 5 kilo Hertz, r= correlation coefficient, RLCQ= Recent Life Changes Questionnaire.

3.6.3.7 The effect of covariates on the association between tinnitus and stress

Gray et al. (2018) and Abell et al. (2016) identified age, BMI, and gender as potential confounders for HCC. In the current study, multiple linear regression showed that age and BMI had non-significant associations with HCC in A1. Linear regression showed that alcohol consumption, social support, self-reported stress, depression, and anxiety were not associated with HCC in A1 (Table 3.15).

Table 3.15 Summary of multiple linear regression of the association of HCC in the first centimetre collected on the first visit (A1) with possible co-variables

Co-variables	Adjusted R^2	F(1, 60)	*p*	B coefficient
Age	-0.016	0.038	.846	0.000
BMI	-0.005	0.701	.406	-0.010
Alcohol	0.006	1.344	.251	-0.027
Po-SS	-0.014	0.150	.700	-0.028
Ne-SS	-0.017	0.005	.943	-0.005
DASS-Depression	-0.011	0.348	.557	-0.007
DASS-Anxiety	-0.006	0.640	.427	0.013
DASS-Stress	0.019	2.197	.144	0.012
DHS-Number	-0.011	0.341	.561	0.002
DHS-Severity	-0.005	0.704	.405	0.001
RLCQ Last month	-0.001	0.925	.340	0.001
RLCQ Last 3 month	-0.014	0.139	.711	0.000
RLCQ Last 6 month	-0.016	0.150	.700	-0.028

BMI= Body Mass Index, DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, Ne-SS= Negative Social Support, p= Significance level, Po-SS= Positive Social Support, RLCQ= Recent Life Changes Questionnaire.

Categorical variables gender, health behaviour, hair nature and treatment, and hearing problems had no significant effect on HCC as assessed by General Linear Model (Table 3.16).

Table 3.16 Summary of general linear regression model assess the effect of categorical variables on HCC in the first centimetre collected on the first visit (A1)

Covariables	Adjusted R^2	df	F	*p*
Exercise	0.035	7	1.319	.260
Smoking	-0.027	2	0.210	.811
Hearing problem/ hyperacusis	-0.038	5	0.558	.731
Hair-related factors	-0.052	10	0.701	.719

df= degree of freedom, p= Significance level,

MLR was computed to explore which aspects of tinnitus level can be predicted by HCC in A1 and stress. TFI-SC was explained by HCC in A1 alone (adjusted R^2= 0.161, $F(1, 31)= 7.143$, $p<0.05$) and can be predicted by HCC in A1 (B= 25.020, $p<0.05$, 95% CI= 1.623-48.416) and the DHS-S (B=0.337, $p<0.05$, 95% CI =0.002-0.673).

HCC in A1 was also found to predict TFI-S (Adjusted R^2=0.098, $F(1, 31) = 4.469$, $p<0.05$). When adjusted for DHS-S and DASS-D scores, HCC in A1 explained 20% of variability in TFI-S scores (adjusted R^2= 0.205, $F(3, 29) = 3.750$, $p<0.05$). HCC in A1 explained 11.6% of variety in tinnitus awareness (adjusted R^2= 0.116, $F(1, 30) = 5.202$, $p<0.05$). When adjusted to the DHS-S, the effect size of the regression model increased (adjusted R^2 = 0.221, $F(2, 30) =5.544$, $p<0.05$).

The association between HCC and TFI-SC, TFI-S, and Tinnitus Awareness was retested. Models were tested to compare whether the HCC in A1 predicted tinnitus levels better than HCC in B3, or vice versa, and whether the HCC from a 1-cm segment can predict the variability in tinnitus better than the average HCC in the three centimetres.

The results are summarised in Table 3.17. Although none of these models reached significance, HCC in A1 had a slightly higher prediction value (adjusted R^2) than HCC in B3 and HCC averages in visits A and B. Regression did not reach significant levels when adjusted for age and BMI.

Table 3.17 Summary of multiple linear regression analysis

	Adjusted R^2	F(1, 20)	*p*
TFI-SC at A vs HCC-A1	0.102	3.386	.081
TFI-SC at A vs HCC-B3	0.004	1.074	.312
TFI-SC at A vs HCC (A1-A3)	0.011	1.237	.279
TFI-SC at A vs HCC (B1-B3)	-0.002	0.952	.341
TFI-S at A vs HCC-A1	0.137	4.345	.050
TFI-S at A vs HCC-B3	-0.021	0.558	.464
TFI-S at A vs HCC (A1-A3)	0.046	2.003	.172
TFI-S at A vs HCC (B1-B3)	-0.002	0.968	.377
Tinnitus Awareness at A vs HCC- A1	0.087	2.998	.099
Tinnitus Awareness at A vs HCC- B3	-0.047	0.053	.820
Tinnitus Awareness at A vs HCC (A1-A3)	-0.005	0.900	.354
Tinnitus Awareness at A vs HCC (B1-B3)	-0.049	0.024	.879

The table compares the prediction strength of HCC before and after the point when tinnitus was assessed (N=22)
HCC-A1= Hair Cortisol Concentration in the first centimetre collected in the first visit, HCC-B3= Hair Cortisol Concentration in the third centimetre collected in the second visit, p= Significance level, TFI-SC= Tinnitus Functional Index Sense of Control, TFI-S= Tinnitus Functional Index Sleep, A= First visit, B= second visit.

3.6.3.8 The occurrence of life events and association with the impact of tinnitus

72.2% of TP did not report the occurrence of life change within the last month before visit A. On examining whether the occurrence of stressful event would lead to increase in tinnitus levels or difference in the mean of psychoacoustic characteristics of tinnitus, independent t-tests showed non-significant differences in the impact of tinnitus between those who reported the occurrence of a life event and those who did not (Table 3.18).

Table 3.18 Summary of the results of independent t-test to compare tinnitus levels in relation to recent life changes

	No-RLCQ group (N=23) M±SD	RLCQ group (N=11) M±SD	df	t	*p*
TFI Total	26.19±18.325	31.56±22.420	34	0.744	0.462
Tinnitus Loudness NRS[1]	47.61±24.349	42.36±30.878	34	-0.495	0.628
Tinnitus Loudness VAS[2]	35.40±19.546	39.18±17.537	34	0.560	0.581
Tinnitus awareness	38.09±28.772	39.54±27.336	34	0.143	0.888
Tinnitus annoyance	18.26±25.214	19.82±22.934	34	0.173	0.864
LM-1kHz	33.89±20.116	36.23±23.684	17.5	-0.281	0.782

[1]Numeric Rating Scale as assessed by TSCHQ. [2]Visual Analogue Scale as assessed by Tinnitus tester.
df= Degree of freedom, *RLCQ= Recent Life Change, LM-1KHz= Loudness Matching at 1 kilo hertz, M= Mean, N=Number of participants, p= Significance level, SD= Standard Deviation, TFI= Tinnitus Functional Index.*

3.6.3.9 The effect of tinnitus management on HCC

None of TP received any new tinnitus management before visit B. Only three participants were undergoing treatment that started it before visit A, and they committed to this treatment between the visits. Of those, two used sound therapy and one used combined hearing aid (on/off for last three years). Given that 19 participants have not received any tinnitus treatment between the visits, the analysis essentially assessed changes in measures between the first and second visit rather than the effect of tinnitus management on the outcomes.

The mean TFI-Total at A was 20.14±17.41 and was higher at B (27.16±19.54). Paired t-tests showed that the difference was not significant ($t(21) = 0.905$, $p = 0.376$, 95% CI= -2.182, 6.563). RM-ANOVA showed no effect of time on the TFI (Wilks' Lambda= 0.96, $F(1, 21) = 0.818$, $p = 0.37$) nor on LM-1kHz (Wilks' Lambda= 0.891, $F(1, 13) = 1.59$, $p = 0.29$). Similarly, paired t-test showed no statistically significant differences between mean TFI sub-scale scores.

The mean cortisol level in A was lower than B but the difference was not statistically significant as tested by the paired samples *t*-test ($t(21) = 0.234$, $p=0.817$, 95% CI= -0.183-0.146). The medians of the self-reported stress measures were not significantly different as assessed by the Wilcoxon signed-rank test (Table 3.19).

Table 3.19 Summary of Wilcoxon signed-rank test

Wilcoxon signed-rank test	DASS	DHS		RLCQ		
	Stress	Number	Severity	last month	last 3 months	last 6 months
Median						
visit A	5.00	19.50	28.00	00	52.00	135.50
visit B	7.50	12.50	19.00	00	110.00	135.00
Z	- 0.963	-1.351	-.497	-.296	-1.650	-1.083
p	.335	.177	.619	.767	.099	.279

A= first visit, B= second visit, DASS= Depression Anxiety Stress Scale, DHS= Daily Hassles Scale, p= Significance level, RLCQ= Recent Life Changes Questionnaire,

3.6.3.10 The association between cognitive performance, cortisol levels, and tinnitus

The correlations between HCC and cognitive test scores are summarised in Table 3.20.

Table 3.20 summary of correlations between hair cortisol and cognitive test score in tinnitus participants.

	Hair segments			
	A1	**A2**	**A3**	**Average A1-A3**
DSB-Max	-.100	-.194	-.011	-.148
DSB-Error	-.129	-.047	.040	-.121
CBTT-Span	-.137	-.126	-.330[#]	-.189
CBTT-Score	-.092	-.103	-.327	-.146
WSCT Number of trials	-.037	.076	.041	-.027
WSCT Total number correct	-.090	.043	-.124	-.098
WSCT Total number error	-.057	.015	.041	-.052
WSCT Perseverative responses	-.067	.076	.117	-.010
WSCT Perseverative error	-.072	.026	.101	-.044
WSCT Non-perseverative error	-.031	-.019	-.043	-.068
WSCT Conceptual level responses	-.067	-.013	-.193	-.074
WSCT Categories completed	.021	-.059	-.276[#]	-.043
WSCT Trials to complete first category	-.212	-.192	-.107	-.191
WSCT Failure to maintain set	.067	.203	.113	.103
WSCT Learning to learn	-.257[#]	**-.301**[*]	**-.435**[**]	**-.303**[*]

** p <0.05, ** p<0.001, [#]p<0.10.*
A1= first centimetre of hair collected on the first visit, A2= second centimetre of hair collected on the first visit, A3= third centimetre of hair collected on the first visit, A4= fourth centimetre of hair collected on the first visit, DSB-Max= Digital Span Backward Test Maximum recall, DSB-Error=Digital Span Backward Test Errors, CBTT-Span= Corsi Block Tapping Test Span, CBTT- Corsi Block Tapping Test Score, WSCT= Wisconsin Sorting Card Test.

None of the variability in cognitive performance was explained by HCC in A1 in TP or NTP groups as assessed by MLR, even when adjusted to candidates' co-variables (alcohol score, age, DHS, depression, and anxiety levels). Only TFI-T explained the variability 20.6% of the Failure to Maintain Set in the WSCT. The regression model was significant (B=0.026, $F(1, 31)= 9.317$, $p<0.05$). The use of hearing aids (coded as 0= No and 1= Yes) was a confounder in the equation as it increased the prediction value to 26.3% (B=0.29, $F(2, 30)=6.732$, $p<0.05$) but did not increase the predictive value in the equation (B=-0.696, $p= 0.075$). HCC in A1, age, and alcohol consumption were not confounding factors.

It seems that there is no relationship between HCC, tinnitus levels and the cognitive performance, hence secondary objective 5 was rejected.

3.7 DISCUSSION

This study aimed to assess the importance of cortisol in the pathogenesis of tinnitus and worsening of its impact. The main finding was that long-term secretion of cortisol in people who have tinnitus does not differ from non-tinnitus participants. It can, therefore, be suggested that cortisol does not play a role in tinnitus pathogenesis. The groups in this study were similar in terms of socioeconomic status, health behaviours, hearing health, the level of social support, the self-reported stress levels, and cognitive testing results, but differed in age. In terms of age and HCC, Staufenbiel et al. (2015) reported a weak positive correlation between HCC and age (r=0.14 in male and r=0.21 in female participants, p<0.05), whilst Lanfear et al. (2020) reported a trend of higher HCC in older adults (60-80 years old). This may explain the slight differences in the means of HCC between tinnitus and non-tinnitus participants.

This study found no significant associations between changes in cortisol when tinnitus become bothersome when total scores were considered. However, some associations between stress and tinnitus were found in this study. It has been reported that increased tinnitus level was associated with emotional exhaustion resulting from prolonged stress (Hébert et al., 2012a), sleep disturbance (Folmer and Griest, 2000), and

decline in sense of control (Sirois et al., 2006). This was supported by the findings of the current study.

DHS and DASS-S positively correlated with TFI-E on both visits. TFI-E examines whether the person is “Anxious or worried”, “Bothered or Upset”, and/or “depressed” because of their tinnitus. The wordings of this subscale may explain the association with DASS-S and DHS-S, but not the association with the DHS-N which basically counts how many hassles the person faces daily. The potential impact of accumulated daily hassles on subsequent functioning and/or wellbeing has been reported in cross-sectional studies (Larsson et al., 2016). However, reporting daily hassles retrospectively may be affected by the recall bias and some events may become less impactful after a while (Weckesser et al., 2019) which may minimise their effects. On the other hand, the use of DHS may inflate the relationship between the daily hassles and negative well-being if overrated by the participants (Reich et al., 1988, Wright et al., 2010). These results therefore need to be interpreted with caution. Apart from Schmitt et al. (2000) who assessed daily hassles in patients with Sudden SNHL and tinnitus, the correlation between TFI and DHS and the association between daily hassles and tinnitus has not been studied before (explained in 2.3.2.2), which makes it difficult to reach a reasonable conclusion from this finding.

Other positive correlations were found between HCC in A1 and both TFI-S and TFI-SC in the first visit only. Regression analyses showed that HCC in A1 could predict the variability in TFI-S, TFI-SC, and tinnitus awareness. HCC-1 and DHS-S independently predicted TFI-SC

and tinnitus awareness and none confounded the others. TFI-SC assesses a person's ability to "control", "cope" and "ignore" their tinnitus. Sense of control is an essential tool for coping with stressful situations (Friedland et al., 1992). Coping and control are core resources for stress resilience (Schok et al., 2010) which is associated with tinnitus (Wallhäusser-Franke et al., 2014). The correlation between cortisol and TFI-SC was reported by Jackson (2019) as the strongest among all negative correlations found between AUCi and TFI-Total (and four subscales TFI-SC, TFI-I, TFI-C, and TFI-A). These findings do not contradict our findings as Sandner et al. (2020) reported a negative correlation between AUCi and HCC (r= -0.47, p=.007) in healthy participants. Higher AUCi attenuates distress responses to daily life stress (Powell and Schlotz, 2012), and it is different from AUC which correlates positively with HCC (Sugaya et al., 2020). This implies that an increase in TFI-SC is associated with an increase in HCC and a decrease in AUCi, and vice versa. There is an underlying neuronal network that may explain this association. Sandner et al. (2020) found that the neuronal activity in the dorso-anterior cingulate cortex (dACC) correlated negatively with the HCC (r=-.51, p<0.01) and positively with the AUCi (r=.38, p<0.05), but did not correlate with the activity in the amygdala and anterior insula. ACC is an important hub for the neuronal network associated with the sense of control (Hashimoto et al., 2015). It is also an area of interest in tinnitus research. Vanneste et al. (2010) suggested that dACC may be involved in persisting attention to tinnitus. Increased activity in dACC showed negative correlation with tinnitus

awareness (Song et al., 2015) and positive correlation with tinnitus distress assessed by THI (Mohsen et al., 2019). The associations between TFI-SC and cortisol may be the most relevant connection between tinnitus and stress.

TFI-S was best explained by the variability in HCC in A1, DHS, and DASS-D. The circadian rhythm of cortisol secretion and sleep cycle are linked through the SCN, as explained in 1.4.1 (Potter et al., 2016, Leng et al., 2019), with a flat circadian cortisol variation occurring after sleep deprivation (McEwen, 2019, Young et al., 2004). This variation in the circadian rhythm may affect the level of HCC. In the current study, sleep disorders were not assessed with any instrument. Therefore, whether participants had sleep disturbance that was not related to tinnitus is not clear.

Given that associations were more evident when comparing the effect of HCC of a month before the change in tinnitus levels with the month after, Changes in HCC may, to some degree, associated with changes in tinnitus awareness and its impact on sense of control and sleep The variation in hair growth rate is seen as a detrimental factor that affect the reliability of using sections of hair to capture a specific time period (Salomon et al., 2020). I assumed that using the length of 1-cm HCC (i.e. about one-month cortisol secretion) in the analysis is more reliable than using 3-cm as it assesses HCC within the time frame which is being assessed by the questionnaires. This finding and the assumption requires further investigation.

Most associations that were examined in this study were found to be non-significant. Stress was not significantly associated with the subjective tinnitus loudness that represents a specific quality of tinnitus (Wallhäusser-Franke et al., 2012, Al-Swiahb and Park, 2016). In addition, the associations with the psychoacoustic characteristics of tinnitus and stress varied across LM and PM and few were significant. It is difficult to explain these sporadic significant correlations thus they seem to be accidental. However, further work would need to look at these in more detail.

Another notable finding is that the occurrence of recent life events was not associated with any impact on psychometric nor on psychoacoustic characteristics of tinnitus. There were similarities between the lack of association between tinnitus and RLCQ in this study and those described by Herane-Vives et al. (2020). They used the RLCQ and HCC to compare stress levels in chronic fatigue and atypical major depression with a control group. They reported no differences. A possible explanation might be that recent life events had a less association with physical and psychological symptoms than accumulated daily hassles (Larsson et al., 2016). Besides, the RCLQ items were described as ambiguous as they cannot differentiate between the effect of loss and the effect of gain from certain events, for example “changes in work responsibilities” could have a positive or negative impact (Dohrenwend et al., 1978). Furthermore, individuals perceive the level of negativity and positivity of an event differently (Redfield and Stone, 1979, Hammen, 2004). Given the limitations of

RLCQ and DHS (explained in 1.3.5.1), interview-based assessment of life events could be considered to confirm this finding. For example, Basso et al. (2020) found that participants with bothersome tinnitus reported more traumatic or negative stressful experiences, assessed by a list of questions developed by the research team.

Additionally, there was no or weak correlations between HCC and self-reported stress levels, which has been found in previous studies (Staufenbiel et al., 2013, Lanfear et al., 2020, Ling et al., 2020, Faresjö et al., 2014). In general, research into the relationship between subjective and objective measure of stress show weak or no relationship (Prado-Gascó et al., 2019, Weckesser et al., 2019). It can therefore be assumed that HCC and self-reported stress measure different neurobiological influences of stress on the body.

On the question of whether changes in HCC and tinnitus levels are associated with changes in cognitive performance, this study did not find any association between stress level and cognitive functions. This outcome is contrary to that of Pulopulos et al. (2014) who found a positive relationship between HCC and DSB scores ($r(55)= .305$, $p<0.05$) and concluded that HCC was related to worse performance on working memory and short-term verbal memory. Additionally, I found that TP performance on cognitive testing was not significantly different from the NTP performance. Only the use of hearing aids was a confounding factor to the effect of tinnitus on WSCT Failure to Maintain Set which measures cognitive distractibility (Figueroa and Youmans, 2013). There are different cognitive tests for each cognitive function

available for research and for clinical use. It is possible the findings of this study would be different if cognitive test for selective, sustained attention or attention switch (Brueggemann et al., 2021, Mohamad et al., 2016) were used. Many studies showed that people who have tinnitus performed poorly at least in one or two domains of attention (Vasudevan et al., 2021). Examples of cognitive tasks used in these studies were the Stroop task and the Digit Span test which are commonly used in research (Rabin et al., 2016). These tests have demonstrated an adequate sensitivity and specificity in detecting the executive function deficit that are related to some neurological disorders (Homack and Riccio, 2004, Schroeder et al., 2011, Babikian et al., 2006). This may explain why they are commonly used in research. Tinnitus-related distress can mediate the relationship between tinnitus and attention, as reported by Leong et al. (2020) who used Stroop test and vigilance task. One of the limitations of these tests is the lack of specificity in measuring only one domain of attention which can be a disadvantage for experimental paradigm (Treviño et al., 2021). There are few cognitive tasks that measures one domain of attention, for example, the Gradual Onset Continuous Performance Test which assesses the sustained attention and is sensitive to individual differences (Rosenberg et al., 2013, Fortenbaugh et al., 2015), and the Multiple Object Tracking Test (Pylyshyn and Storm, 1988) which assesses the selective attention. These tests could be used in further research about this the relationship between tinnitus and cognitive functions is therefore recommended (See 6.4.5).

3.8 LIMITATIONS

The main limitation of this study was the small sample size. Although the second power calculation that based on the first samples collected was met, few more participants would lead to achieve a significant difference between the means of both groups. The small sample size may affect in particular the regression analysis as small sample size may lead to overfitting of the model (Riley et al., 2019). Therefore, the findings of this study should be considered as exploratory in nature and not conclusive. However, it is important to mention that there is an issue with a large sample size (hundreds or thousands of participants) as it makes very small effect sizes or weaker correlations statistically significant (Armstrong, 2019).

The role of cortisol in developing tinnitus could be assessed by measuring the changes in HCC around the onset of tinnitus. I attempted in this study to do so. However, recruiting participants with recent onset tinnitus was challenging. Despite most exhaustive efforts, no participants were recruited in this group.

Another limitation is that the participants volunteered themselves to take part in the study which may have led to selection bias (Tripepi et al., 2010). Their interest in or opinion about the research topic may influence their responses. This also prevented recruiting matched participants in the tinnitus and no tinnitus groups. The tinnitus group were mainly men aged between 60 and 80 years, while the non-tinnitus group were mainly women and slightly younger. Regression analysis showed that age and gender had no effect on HCC nor were they had a

confounding effect in this study. However, there are many confounding factors that may had affected the measured variables such as sleep pattern and difficulties, personality, and others that were not measured and were not controlled for in this study. Each of these confounders could be measured by using specifically designed instruments. For example, sleep difficulties can be measured by the Pittsburgh Sleep Quality Index (Buysse et al., 1989) which is a commonly used questionnaire in sleep study (Fabbri et al., 2021). This questionnaire has been used in tinnitus research (Fabbri et al., 2021, Hébert et al., 2011, Li et al., 2021, Lu et al., 2020). These studies showed that poor sleep quality was a common feature among tinnitus patients and might increase tinnitus severity. The personality trait of neuroticism is also associated with increased tinnitus severity (Simões et al., 2019). Neuroticism and poor sleep quality independently affecting tinnitus severity (Inagaki et al., 2021). In addition, recent studies showed that higher HCC could be predicted by higher values of neuroticism (Erickson et al., 2021, Engert et al., 2021). High HCC is possibly associated with sleep disorder as reviewed by El Mlili et al. (2021). So, the level of HCC and tinnitus severity can be mediated by the severity of sleep disorders and/or personality trait of neuroticism. This means if these confounders were measured in this study, it would have led to better understanding of their effect on tinnitus and stress. Future studies could reveal other confounders that are not measured yet.

3.8.1 COVID-19 Impact Statement

The suspension of research because of the COVID-19 pandemic had a minor impact on the study as it happened at a late stage of the study. It was planned to end the study at the end of March. The study was ended on the 15 March 2020 before the announcement of the first national lockdown. This led to cancellation of the second visit of three tinnitus participants, and the first visit of two tinnitus participants. It was not possible to extend the study to include more participants. I was able to send the remaining hair samples for lab analysis, but they were unable to conduct the analysis until the end of August when the first lockdown was lifted. This delayed the statistical analysis by 6 months.

3.9 CONCLUSION

Taking the findings together, the reported relationship between tinnitus and stress may result from an association between some stress measures (cortisol secretion and daily hassles) and some tinnitus domains (the impact of tinnitus on sleep, emotion and sense of control, and tinnitus awareness). The findings of this study support the idea that cortisol plays a role in maintaining the impact of tinnitus on sense of control which raise an intriguing question about the neurological basis of this associations.

CHAPTER 4 THE CONCEPT OF STRESS AS UNDERSTOOD BY TINNITUS PATIENTS: CONCEPT MAPPING STUDY

The aim of this chapter is to explore how tinnitus patients define the word "stress."

4.1 INTRODUCTION

The nature and the direction of the relationship between tinnitus and stress requires clarification and more research (Hébert et al., 2017). Upon reviewing the previous research in the relationship between tinnitus and stress (reviewed in 2.3), it was found that some of these studies reached their findings by asking participants to rate their stress-levels by using tinnitus questionnaires. Most of these questionnaires assess stress-related tinnitus. For example, item 24 in the THI (Newman et al., 1996) asks whether tinnitus gets worse when the person is "*under stress*", and item 27 in the THQ (Kuk et al., 1990) asks whether "*tinnitus causes stress*". Other studies have used patient's case history questionnaire such as the TSCHQ (Langguth et al., 2007) , in which the participants were asked about the factors associated with the onset of tinnitus and stress (item 7 in the TSCHQ), and whether "*stress influences their tinnitus*" (item 24 in the TSCHQ).

However, there is no consensus on a single definition of stress in the psychological fields and people usually refer to themselves as "*stressed*" in different situations. Therefore, its meaning has acquired a level of ambiguity that limits its usefulness (Kagan, 2016, McEwen, 2017). Many sources, such as health-related websites (e.g. BTA and

NHS) and information leaflets provide information about stress in terms of meaning, management, and impact on health. Some of these sources rely on scientific publications and translate scientific terms into more broadly understandable words, but not all publicly available information is accurate or reliable, and the completeness and quality of information can be compromised (Zimmermann and Jucks, 2018). As a result, the working definition of stress may vary between individuals and it will be based on the knowledge that they gained from different sources which themselves vary in terms of the accuracy, completeness, and quality of their information.

The discrepancy and the ambiguity in understanding the meaning of the word *"stress*" may affect how patients project their feelings about "being stressed" to clinicians. In other word, the meaning of the word "*stress*" for a patient might be different to the meaning their clinician assigns to the word "*stress*". The National Institute for Health and Care Excellence (NICE) tinnitus guidelines (NICE, 2020) and the European clinical practice guideline for tinnitus assessment (Cima et al., 2019) recommended that stress should be considered in history taking and patient assessment. Besides, stress is frequently reported by clinical experts as relevant to tinnitus (Cima et al., 2020). Therefore, there is a need to remove the ambiguity of the word stress during clinical evaluation and research of tinnitus.

4.2 THE AIM OF THE STUDY

The purpose of this study was to develop an understanding of the concept of stress as it relates to tinnitus, i.e. how do people with tinnitus understand the word "*stress*". Data were used to generate a conceptual framework for how stress maps onto tinnitus, based on the participants' point of view. The main aims were therefore to explore:

(i) How people with tinnitus understand the concept of stress,

(ii) Whether "*stress*" is conceptualised as one dimensional or a complex multi-dimensional construct,

(iii) Whether clusters of related ideas about *stress* are similar to the main concepts of stress reported in the literature.

4.3 METHODS AND MATERIALS

4.3.1 Concept mapping method overview

A concept mapping technique (Kane and Trochim, 2007) was used to determine the understanding of "*stress*" among people with tinnitus, and clarify the views of this population. Cluster or Group Concept Mapping (GCM; Trochim, 1989) is a mixed-method approach to collecting and organising qualitative data from the participants' own words built on their previous knowledge. The findings are interpreted through quantitative techniques and used to generate visual representations (Conceição et al., 2017). GCM is widely used in different fields to achieve various aims which include planning and evaluation of a programme or process (Conceição et al., 2017), or developing a measure or scale to be adopted into instruments (Trochim and

McLinden, 2017). The method has a structured approach involving different stages or activities and offers flexibility to adjust the study to serve the defined purpose (Kane and Trochim, 2007). For example, the study can be run either face-to-face or online. The present study consisted of three stages referred to here as Activities. The roles of the participants and initiator/ researchers within each activity are clearly defined (Figure 4.1). I prepared the study, edited, and synthesised the generated ideas, and conducted the statistical analysis. Participants generated statements online in Activity 1, sorted and rated a merged set of statements online in Activity 2, and a smaller number of participants attended a consensus meeting in Activity 3. The final interpretation of the results was conducted by both researcher and participants. The study lasted for 11 weeks; from 21 August 2019 to 29 November 2019.

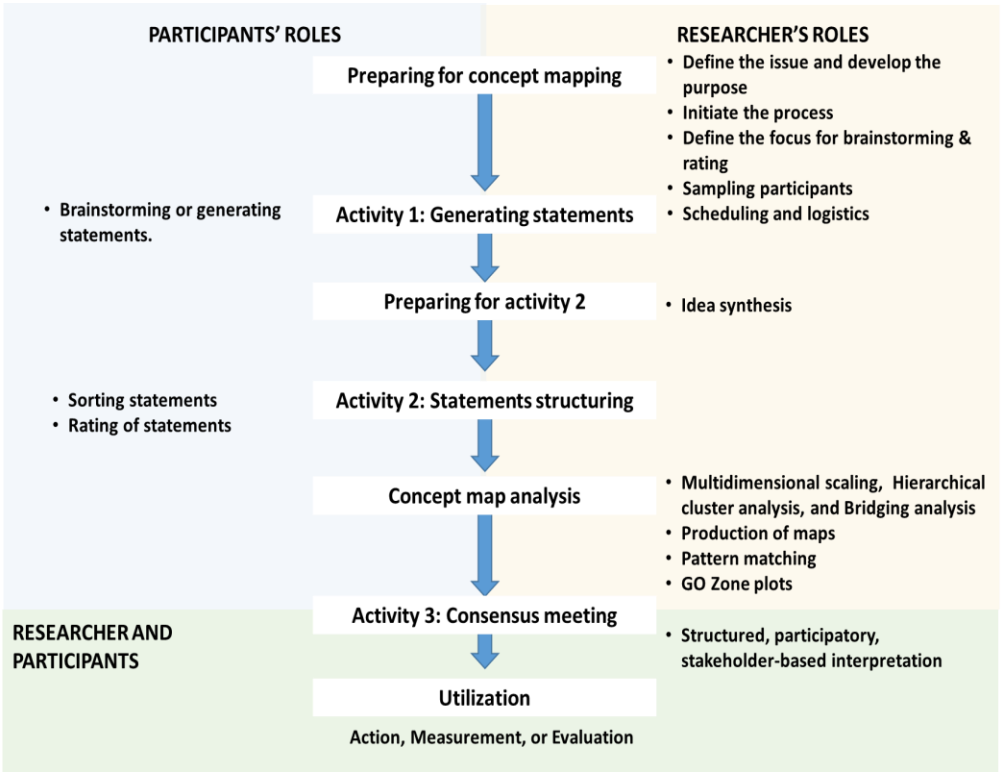


Figure 4.1 Researchers and participants' roles in the Group Concept Mapping process

4.3.2 Ethical approval

This study was approved by the Faculty of Medicine and Health Science Research Ethics Committee (FMHS-REC) on 19 August 2019, reference number: 351-1907. It was explained to potential participants that entry into the study was entirely voluntary and that their treatment and care would not be affected by their decision to participate or not, that they could withdraw at any time but data collected could not be erased and would be used in the final analyses.

4.3.3 Participants Recruitment

4.3.3.1 Sample size

There is no guidance on the sample size calculation for GCM, and there is no strict limit on the number of participants (Kane and Trochim,

2007). The sample size of early face-to-face studies ranged from 10-20 participants (Trochim, 1989) and it ranged between 20-649 in subsequent studies as reported by Rosas and Kane (2012). Donnelly (2017) reviewed doctoral theses that used GCM and reported that the average number of participants in each stage was about 48 in generating statements, 34 in structuring, and nine in interpretation activities. In conclusion, there is no solid basis to ensure this sample size is sufficient (Chan et al., 2012). Based on previous studies that used this method, I estimated the number of participants in each activity as the following:

Activity 1: As each participant can generate between 2-20 statements, it was not possible to anticipate how many statements would be provided by the participants. The minimum sample size for this activity was set at 20 participants as it was the minimum number reported in previous research (Börner et al., 2010).

Activity 2: The sample size required to conduct a weighted nonmetric multidimensional scaling, the statistical analysis conducted in the R-CMap (explained in 4.3.7.3) can be as small as 14 (Rodgers, 1991). Studies with fewer than 15 participants are more likely to generate less reliable concept maps as indicated by the stress index (explained in 4.4.2.8) (Rosas and Kane, 2012). Thus the minimum number recommended for the sorting is at least 15 participants (Bennett et al., 2018). However, to ensure that there was a sufficient sample size for the analysis and groupings, without overpowering the analysis, I

decided to recruit a minimum of 40 participants, but no more than 500 participants for this activity.

Activity 3: Based on Kane and Trochim (2007) recommendation for on-site activities, a minimum of 10 people was set as the required sample size for the face-to-face consensus meeting.

4.3.3.2 Recruitments strategies

Recruitment included email invitations to members of the NIHR Nottingham BRC participant database and emailing the leaflets to BTA Tinnitus Support Groups. The study was advertised at public events such as BTA Annual Conference (September 2019), on the University of Nottingham campus poster boards, and online through posts on social media platforms (Twitter and Facebook).

4.3.3.3 Inclusion criteria

Participants were included in the study if they were 18 years or older, native English speakers, self-reported having tinnitus for more than 6 months (i.e. chronic tinnitus) and were able to give informed consent.

4.3.4 Survey development and administration

Online study forms were developed on Jisc Online Survey (previously named Bristol Online Survey). They were distributed through the University of Nottingham email. I designed short surveys that the participants completed at the beginning of each activity (detailed below) All study materials were reviewed by the research team for readability and clarity.

4.3.5 Registration

Activity 1 was proceeded by an online registration period that lasted until the last week of Activity 2. Potential participants were required to complete the registration form that collected minimal details including their name, age, email address, and were asked to indicate where they found out about the study (Appendix VIII). Participant initials and age were used to generate an identifier code. The first page of the registration form included a consent for registration in the study and confirmation that the respondents fitting the inclusion criteria. The form also included a link to the information sheet. On the registration form, participants were asked to confirm that they read and understood the information sheet before registration. The stages and timeline of the study are outlined in Figure 4.2.

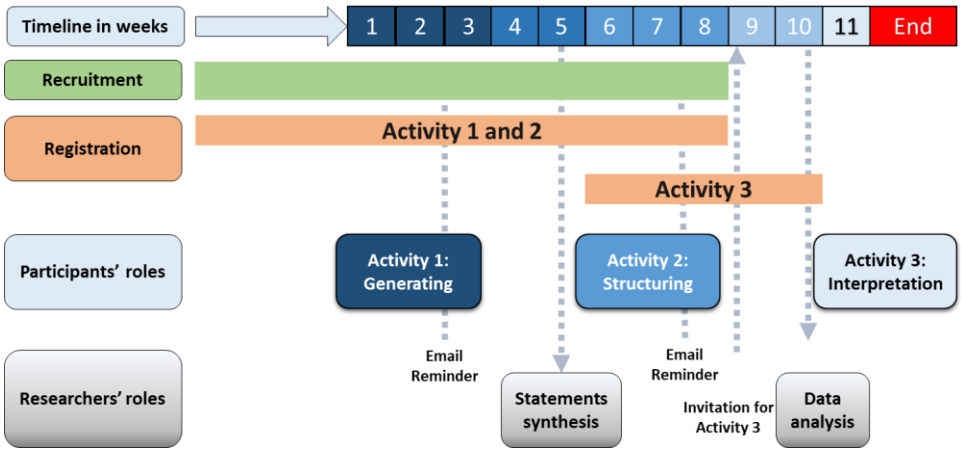


Figure 4.2 Study stages and timeline.
The study lasted for 11 weeks. Activity 1 lasted 3 weeks followed by 2- week preparation period for Activity 2. Activity 2 also lasted 3 weeks followed by a 2-week preparation period for Activity 3. On the 11th week, Activity 3 took place.

4.3.6 Activity 1: Generating statements (online)

4.3.6.1 Activity 1 tasks

Registered participants were emailed the link to Activity 1. They confirmed that they fit the inclusion criteria and signed an online consent which was in form of a seven-item checklist. The consent was considered as signed when the participants selected the 'consent to participate' button shown on the introductory screen. Consent was captured electronically on the survey database.

Upon starting the online activities, an introductory page reiterated key information previously provided in the Participant Information Sheet. Following this, participants answered a short survey that included questions about their age, gender, education level, and tinnitus. Participants were then asked to write sentences that represent the meaning of the word stress (brainstorming). They were given the pre-set prompt "*Stress may worsen tinnitus, and the word stress means...*"

For this purpose, the form contained 20 lines for free text in which participants wrote these sentences. They were asked to write as many sentences as they wanted and there were no restrictions. This activity stayed open for 3 weeks.

4.3.6.2 Activity 1 statistical analysis

Descriptive analysis of data collected through the surveys was performed in SPSS (v.26.0). Sentences generated by the participants was exported to Microsoft Excel and qualitatively analysed.

4.3.6.2.1 Thematic analysis of sentences generated in Activity 1

The purpose of conducting thematic analysis was to generate a smaller number of representative statements for Activity 2 (Kane and Trochim, 2007). The analysis conducted in activity 1 was as following:

1. All generated sentences were reviewed and those that did not answer the research question (i.e. did not provide a definition or were ambiguous) were excluded.
2. I (AE) conducted a first four steps of thematic analysis (explained in 5.3.3.2). I coded the included sentences were coded and create themes.
3. According to GCM method, similar sentences (those semantically similar) were merged, and duplicates were removed to create an “umbrella statement” that represents a group of generated sentences. All umbrella statements were edited for clarity to form a final list of statements.

4. The final list of “umbrella” statements was reviewed by the research team (DH and KF) and two Patients and Public Involvement (PPI) contributors. They commented on the readability of the statements. They reviewed the original sentences and the excluded sentences written by the participants before any changes to validate the exclusion decision.
5. Each umbrella statement was given a number which will be referred to as “Statement ID.”

4.3.7 Activity 2: Statements structuring (online)

4.3.7.1 Activity 2 tasks

Participants who registered before the final week of Activity 2 were emailed the link for this activity. They signed the seven-item checklist consent (following the same steps as for Activity 1), and completed a short survey (age, gender, and education level). Beside questions about tinnitus duration, onset, and the features of the sound, participants were asked to rate the loudness and bothersome of their tinnitus on scale of 0-100 (NRS). They also answered a set of questions about their hearing status and their opinion regarding the relationship between tinnitus and stress by asking if they agreed with one of the statements listed in Table 4.1. The purpose of these question was to determine whether the participants agreed that stress is the effector, tinnitus is the effector, or there is no relationship between stress and tinnitus. Those who disagreed with all the statements were given the option to explain why (item 13 in Activity 2 form).

Table 4.1 The wording of each choice that reflect different points of view.

Point of view	Wording of the statements
Stress is the effector	*Stress causes tinnitus* *Stress causes and worsens tinnitus* *Stress worsens tinnitus but it is not a cause*
Tinnitus is the effector	*Tinnitus increases stress*
No relationship	*There is no relationship between tinnitus and stress* *I disagree with all the above*

Participants were asked "*Which statement do you most agree with*"

Following this, participants then completed three tasks for activity 2:

1. Rating (multiple-choice questions): Participants rated each umbrella statement on a five-point Likert-scale. The rating was in response to the prompt "*rate each potential statement on a scale in terms of how strongly you think the statement is representing the definition of stress, where '1' means 'Not at all' '3' means 'Moderately representing the definition,' and '5' means 'strongly representing the definition*".
2. Ranking (free text question): Participants were asked to list and rank 10 statements that best represented the definition of stress in their opinion.
3. Sorting (free text question): Participants were asked to sort the statements into groups by similarity and to give each group a name. They had overall control on the number and names of these groups. There was no limit to the number of groups that participants could submit in their response. They were instructed to sort all statements into at least two groups (i.e. they must not put all statements into a single group), and that each statement could only be placed in one group (i.e., a statement could not be placed in two groups at the

same time). The statements list was provided as “link open in new window” on the screen to be used as a reference.

At the end of Activity 2, participants were asked to register their interest to attend Activity 3 (face-to-face consensus meeting).

4.3.7.2 Activity 2 statistical analysis

Data collected through the surveys was analysed by SPSS (26.0) to produce descriptive statistics. The responses to ranking task were transferred into Excel spreadsheet. The statements were given a weight between 1 and 10 if they were ranked by the participant, and 0 if they were not ranked. Weights were applied in reverse or a descending order, i.e. the first ranked statements were given a score of 10 and the last ranked statements were given a score of 1. The average ranking was calculated by dividing the summation of weighted ranks (w) multiplied by response count for answer choice (x), by the total number of responses, as follows,

$$Average\ ranking = \frac{\mathrm{x1w1\ +\ x2w2\ +\ x3w3\ldots.x10w10}}{\mathrm{Total\ number\ of\ participants}}$$

4.3.7.3 R-CMap built-in statistical analysis and visual products

Statistical analysis of data after the sorting task in Activity 2 was computed by R-CMap software (Bar and Mentch, 2017) using a sequence of three steps:

1. A similarity binary matrix was constructed from data generated from sorting task in activity 2 (for any two statements, “1” will be placed in

the individual matrix if they are sorted in the same pile by the sorter, and “0” if they were not sorted together).

2. The similarity binary matrix was analysed by the multidimensional scaling (MDS) analysis.
3. Hierarchical cluster analysis using Ward's algorithm was used to cluster the statements on this map into groups. The number of these groups, which is called the cluster solution, can be as many as there are statements (Kane and Trochim, 2007). However, the R-CMap gives the option to choose a cluster solution between 2 and 20 clusters.

The R-CMap computed the average ratings for each statement and for each group (Kane and Trochim, 2007) which is used to run an analysis of variance (ANOVA) test to compute the differences in mean rating across several clusters (Bar and Mentch, 2017).

GCM emphasises the value of the visual product (Trochim and McLinden, 2017) and the results are generally presented in the form of lists and maps. R-CMap software is designed to produce the visual products of the GCM. The main maps produced is the two-dimensional (2D) point map on which each point represents a statement. The distance between two points indicates the frequency of sorting two statements represented by these points into one group. To explain, when two participants put two statements into one group, these two statements become closer on the point map (Figure 4.3). Therefore, the proximity of statements to one another suggests that these statements belong to the same group (Kane and Trochim, 2007).

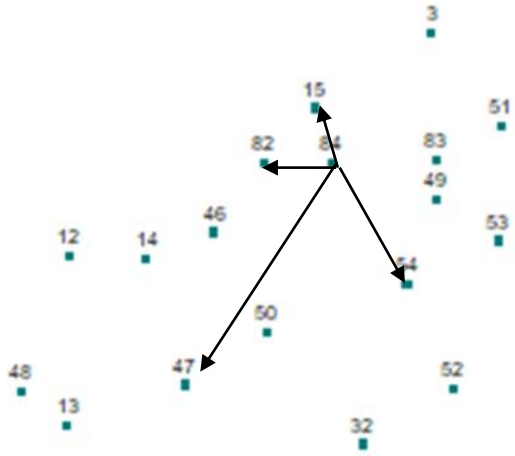


Figure 4.3 An example of the distance between two points on the point map.
The figure is cropped from a larger point map to show how the frequency of sorting the same statement into groups affects the distance on the map. The numbers on the figure represent the statements ID. In this example, statement 84 was sorted in the same group 11 times with the statement 15 and 82. It was sorted 7 times with statement 54, and 5 times with statement 47. The arrows on the figure represent the distances between the points. Statement 84 is closer to statements 15 and 82 than statements 54 and 47. The distances between these statements is also affected by the frequency of sorting them with other neighbour statements (e.g. statements 46, 50, 49, 83, and 14 on this map) (Based on data from the current study).

The strength of the MDS is assessed by calculating the stress index or factor which is a quantitative measurement of how well the relation between the input data from the sorting task and the distances on the map is maintained and represented to the best level possible (Kruskal, 1964). Stress index is a measure of goodness of fit (Bennett et al., 2018) and its values lay between zero and one. A map with a smaller stress index will produce a more reliable clustering as it represents the input data better (Bar and Mentch, 2017, Jaworska and Chupetlovska-Anastasova, 2009). Kane and Trochim (2007) advise that a stress index value between 0.205 and 0.365 is acceptable as approximately 95% of concept mapping projects tend to yield a stress index within this range.

There are many factors that can affect a stress index value, for example a higher number of points on the map generally increases the stress index (Borg and Groenen, 2005).

The other visual products generated by the cluster analysis and rating are:

1. The cluster map that is produced by the hierarchal cluster analysis showing group borders.
2. The dendrogram, a graphical tool to assess which map is most appropriate for the sorted statement data (Bar and Mentch, 2017).
3. The univariate rating by-clusters (cluster rating) map which shows the average cluster ratings.
4. The univariate rating by-statements (point rating) map which represents the “value dimension” of these statements (Kane and Trochim, 2007).

GCM can produce other types of graphs called pattern matching and a go-zones graph if statements are rated on two different prompts. I used one prompt for rating. Therefore, those graphs were not produced in this study.

4.3.8 Activity 3: Face-to-face consensus meeting

4.3.8.1 Preparing for Activity 3

Participants who registered their interest to attend the consensus meeting were emailed a supplementary information sheet with details about the schedule, the address of the venue, what would be expected from them, and initial instructions. The explanatory materials were

prepared before the meeting. These included PowerPoint presentations, printouts of statements list, and individual statements on cards. PPI contributors reviewed and helped prepare these materials. This activity was an interactive discussion among the invited group of the participants, and it was an important step to clarify the views of the participants. This group acted as a consulting group to finalise the results.

4.3.8.2 Activity 3 tasks

Activity 3 took place face-to-face at the NIHR Nottingham BRC. Consent for Activity 3 (face-to-face consensus meeting) was in a written format. Participants signed and dated two copies of the consent form at the start of the session. They kept one copy and the other copy was retained in the study records.

At the beginning of the activity, I presented the statements list and the five highest rated statements arising from Activity 2. Participants reviewed the structure and readability of these statements. Then, they discussed and gave their opinion whether these statements could be used in the clinics and in research. Next, I explained how the statistical analysis led to development of the point map. Participants were given time to identify four statements on the map that were close, and to each other on the point map. Then, they were asked to examine the wording of those statements. The aim of this step was to help the participants to understand the meaning of each point on the map. We then looked at the clusters that were generated through the statistical analysis and

attempted to reach a consensus on the name for each cluster and the total number of clusters that made sense to the participants.

For later reference, the session was recorded, and written notes were taken during the meeting. The PPI Manager and two PPI contributors co-facilitated the meeting. PPI contributors also acted as “buddies” during the meeting to offer a friendly ear to any participant who needed to step out of the meeting and take a break from the discussion for any reason.

4.4 RESULTS OF GCM STUDY

4.4.1 Activity 1: Generating statements

4.4.1.1 Participants

A total of 84 participants completed Activity 1. Participants included 36 men (42.9%) and 48 women (57.1%), with the majority aged from 61 to 80 years old (60.7%) and having a higher education (71.4%). More than half the participant had experienced tinnitus for more than 10 years (69.3%) with most reporting a gradual onset to their tinnitus (53.6%). Table 4.2 summarises the characteristics of participants in this stage. The participants submitted 513 sentences. The number of sentences submitted by individual participants ranged from 1-20 sentences (median=5).

Table 4.2 Summary of participants' characteristics in Activity 1

Age	N (%)
21-30	1 (1.2)
31-40	3 (3.6)
41-50	12 (14.3)
51-60	13 (15.5)
61-70	31 (36.9)
71-80	20 (23.8)
>80	4 (4.8)

Education	N (%)
Higher education	60 (71.4)
A Level or GCSE	15 (17.9)
Other qualifications	3 (3.6)
No qualifications	5 (6.0)
prefer not to say	1 (1.2)

Tinnitus duration	N (%)
<1	0 (0)
1-5	19 (22.6)
5-10	16 (19.0)
10-15	17 (20.2)
15-20	10 (11.9)
>20	22 (26.2)

Tinnitus Onset	N (%)
Gradual	45 (53.6)
Sudden	32 (38.1)
Other	7 (8.3)

GCSE= General Certificate of Secondary Education, N= Number of the participants.

4.4.1.2 Refinement and categorisation of statements

Of the 513 sentences, 123 sentences (23.9%) were excluded either because they were ambiguous, described effects of stress rather than a definition (these included expressions like "*stress (can) make*…", "*stress (can) cause*….", "s*tress affects*…"), or they represent opinion rather than a definition. Out of 84 participants who submitted sentences in Activity 1, 76 participants generated sentences that answered the research question and were included in the study. Responses from eight participants were excluded because their statements reflect either their opinion about the relationship between tinnitus and stress (e.g. *"Stress definitely makes my tinnitus worse"*) or their experiences with tinnitus (e.g. "*Noises make my tinnitus worse*"). In other words, their statements did not give a possible meaning for the word *'stress'*. The remaining 390 sentences were subjected to thematic analysis which resulted in a list of 85 umbrella statements and 17 categories. Table 4.3 shows these categories, an example of an umbrella statement, and the

total number of statements within each category. These categories were used as a reference to support later analyses. Participants in Activity 2 were blinded to this categorisation. Figure 4.4 provides examples on the process of merging the sentences in thematic analysis. The full list of original and umbrella statements available in Appendix IX.

Table 4.3 The name of the categories that resulted from the thematic analysis

Category	Example of an umbrella statement	Number of Statements
General definition	Stress is a significant burden to some people but has insignificant effect on others	7
Response	Stress is an emotional response to outside influences	4
Pressure (general)	Stress means feeling (or being) under pressure	8
Pressure (time)	Stress is being time-pressured	4
Pressure (from other people)	Stress is feeling (or being) pushed to your limit at home, in work, or in another external environment	3
Relationship issue	Stress means increased anxiety (worrying) especially about relationships with people in general	5
Anxiety and worry	Stress means heightened anxiety and emotional strain	6
Overthinking	Stress is overthinking about something	1
Workload and overwhelmed	Stress is being (or feeling) constantly having excessive workload	7
Difficulties with relaxation and sleep	Stress is not being able to completely relax even when completely feeling tired	6
Coping	Stress is being (or feeling) unable to cope with situations	2
Sense of control	Stress is feeling out of control over everything	4
Environment and events	Stress is external factors or new situations that intrude in someone's life	9
Negative feelings	Stress means feeling vulnerable or upset	10
Health/ physical related	Stress is feeling pain (continuous, uncontrollable, or unbearable)	2
Tinnitus/hearing loss	Stress means feeling overwhelmed by circumstances and usually when overtired and at those times tinnitus seems louder	2
Other	Stress is being out of one's comfort zone	3

With statement example of each category and the total number of the statements within each category

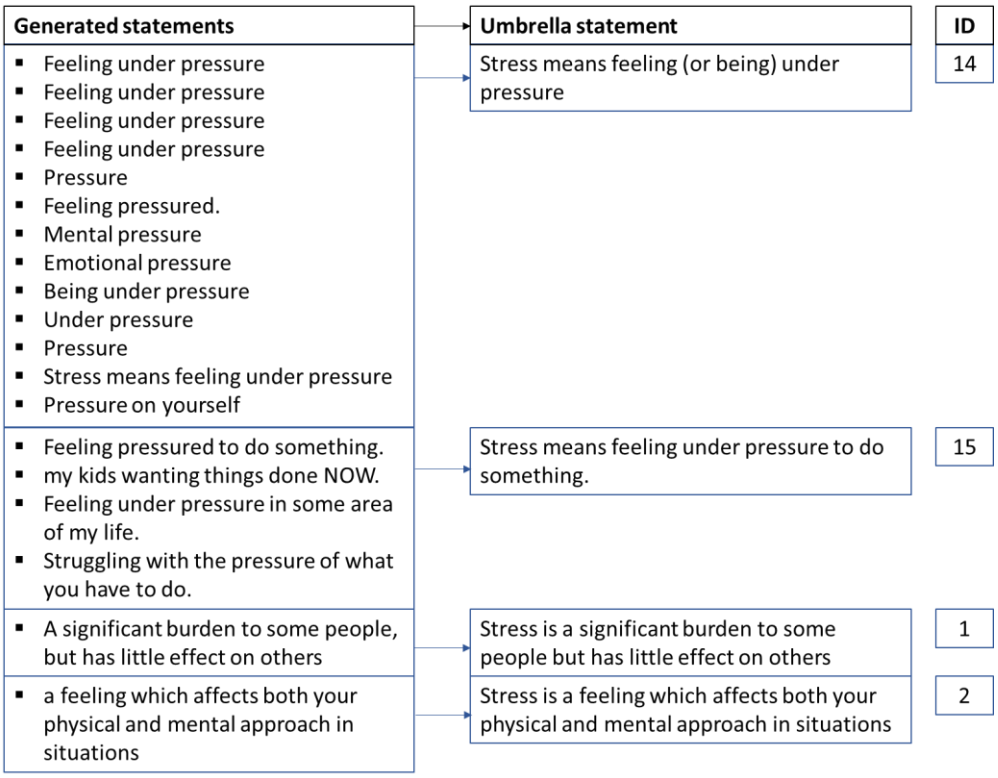


Figure 4.4 Examples of merging generated sentences to create an umbrella statement.
The set of boxes on the left represent the sentences generated by the participants. The second set of boxes on the right shows the final umbrella statement the resulted from the thematic analysis and the "Statement ID" reference number. Statement 14 was generated by merging participants' inputs that were similar in structure and meaning. Statement 15 was generated by merging sentences that had similar meaning. Some statements originally held more than one meaning and those kept in their original form, as seen with statements 1 and 2.

4.4.2 Activity 2: Statements rating and sorting

4.4.2.1 Participants

A total of 43 participants rated, ranked, and sorted the 85 umbrella statements in this activity. Twenty participants were men (46.5%) and 23 were women (53.3%), with majority aged between 61 and 80 (69.8%) and in the higher education category (79.1%). Table 4.4 summarises the characteristics of participants for activity 2.

Table 4.4 Participant characteristics in Activity 2

Age	N (%)
21-30	2 (4.7%)
31-40	2 (4.7%)
41-50	2 (4.7%)
51-60	4 (9.3%)
61-70	16 (37.2%)
71-80	14 (32.6%)
>80	3 (7.0%)

Education	N (%)
Higher education	34 (79.1%)
A Level or GCSE	6 (14.0%)
Other qualifications	2 (4.7%)
No qualifications	1 (2.3%)
prefer not to say	0 (0%)

GCSE= General Certificate of Secondary Education, N= Number of the participants.

4.4.2.2 Characteristics of tinnitus

As summarised in Table 4.5, tinnitus duration varied among the participants with the majority having tinnitus for 5-10 years and none of them had tinnitus for less than 1 year. Participants reported ratings of tinnitus loudness that ranged from 10 to 100/100 (mean 56.46, *SD* 25.32). Similarly, how bothersome tinnitus was, was rated from 5 to 100/100 (mean 53.56, *SD* 26.73).

Table 4.5 Tinnitus duration, onset, and perception among participants in Activity 2

Tinnitus duration	N (%)
<1	0 (0%)
1-5	7 (16.3%)
5-10	14 (32.6%)
10-15	9 (20.9%)
15-20	3 (7.0%)
>20	10 (23.3%)

Tinnitus Onset	N (%)
Gradual	24 (55.8%)
Sudden	19 (44.2%)
Other	0 (0%)

Tinnitus perception	N (%)
Tonal	7 (16.3%)
Hissing	21 (48.8%)
Ringing	7 (16.3%)
Other	8 (18.6%)

4.4.2.3 Hearing status among participants

Most participants had hearing problems (33 participants, 76.7%), and difficulties in understanding speech in noise (34, 79.1%). 24 participants (55.8%) were hearing aid users, and none had a cochlear implant.

4.4.2.4 How did the participants view the relationship between tinnitus and stress?

All participants (N= 43, 100%) answered the question about the relationship between tinnitus and stress. Only one participant (2.3%) believed that stress causes tinnitus, and five participants (12%) chose two answers to show that there is a reciprocal relationship (stress worsens tinnitus and tinnitus increases stress). Fifteen participants (34.9%) believe that "*Stress worsen tinnitus but it not a cause*" (Figure 4.5). Twenty-two participants (51.2%) believe that stress is the effector in the relationship. In contrast, seven participants (16.3%) believe that tinnitus is the effector. Five participants (11.6%) believe that there is a reciprocal relationship. Out of the nine participants (20.9%) who believe that there is no relationship, seven (16.3%) gave valid responses to item 13 in the Activity 2 form. Only three participants (6.9%) selected to "*disagree with all*", and one participant selected "*there is no relationship*."

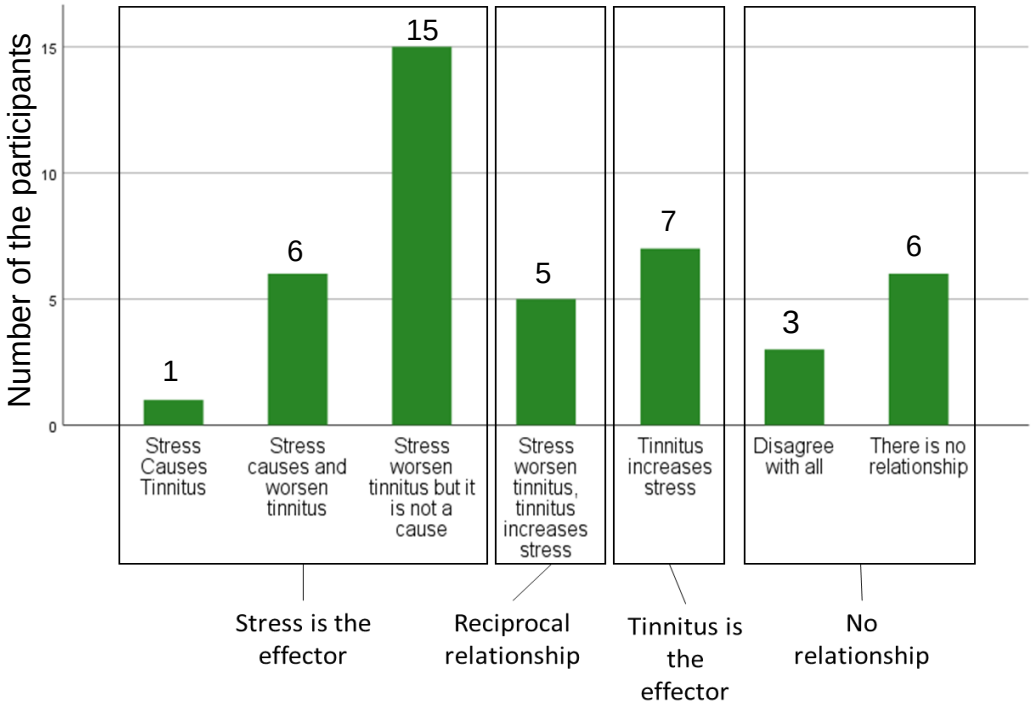


Figure 4.5 Participants opinion about the direction of the relationship between tinnitus and stress.
Participants were asked which of the statements they agreed with.

4.4.2.5 Results of statements rating task

All statements were rated by the participants. The means and SD for statement ratings are reported in Appendix X. The rating scores for the statements ranged from a mean of 4.4 (SD 0.79) to a mean of 2.12 (SD 1.22). Only 19 statements were rated more than 3.5 and of those, nine statements were rated more than 3.75 (Table 4.6).

Table 4.6 Statements rated more than 3.5 in terms of the meaning of the word "*stress*"

ID	Statement	M	SD
6	Stress includes tiredness (mentally and/or Physically), worry, anxiety, tension, irritability, mental pressure, unpleasant feelings and/or unusual situations	**4.4**	0.79
2	Stress is a feeling which affects both your physical and mental approach in situations	**4.07**	1.1
31	Stress is not being able to completely relax even when completely feeling tired	**3.98**	1.03
77	Stress means heightened anxiety and emotional strain	**3.93**	1.14
33	Stress is feeling tense and opposite of calm and relaxed	**3.88**	1.03
30	Stress is feeling trapped in a situation and unable to escape	**3.86**	1.01
43	Stress means having the likelihood of becoming more aggressive, irritable, agitated, annoyed, edgy, tense, and loss empathy with others	**3.84**	1.04
66	Stress means feeling overwhelmed by circumstances and usually when overtired and at those times tinnitus seems louder	**3.81**	1.24
34	Stress is having difficulty getting to sleep, lack of sleep, or not sleeping well	**3.77**	1.04
1	Stress is a significant burden to some people but has little effect on others	**3.74**	1.07
37	Stress is being (or feeling) unable to cope with situations	**3.72**	1.14
8	Stress is an emotional response to outside influences	**3.7**	0.96
14	Stress means feeling (or being) under pressure	**3.65**	0.95
21	Stress is experiencing upsetting events or problems requiring urgent attention that someone feels powerless to resolve	**3.63**	1.02
40	Stress is feeling (or being) not in control of a situation, thoughts, or feelings	**3.63**	1.23
12	Stress means enduring pressure, often without being consciously aware	**3.57**	1.11
39	Stress is feeling out of control over everything	**3.56**	1.37
54	Stress is feeling (or being) pushed to your limit at home, in work, or in another external environment	**3.56**	1.12
11	Stress is pressure (from outside sources or self-generating) causing a physical reaction	**3.51**	1.08

The statements are sorted in a descending order according to the mean of the rating.
ID= statement's identification number, M= mean, SD= Standard Deviation

4.4.2.6 Results of statements ranking task

Participants chose 10 statements that best represented the meaning of stress for them and listed those statements in order of relevance and representative of stress. The top 10 ranked statements are shown in Table 4.7. The table shows the statements' ID, and how many participants ranked the statement in their top ten. The weighted ranking is listed in the last column resulted from the analysis conducted by using the equation mentioned in 4.3.7.2.

Table 4.7 The 10 top ranked statements

Rank	ID	Statements	Number of participants	Weighted ranking
1	6	Stress includes tiredness (mentally and/or Physically), worry, anxiety, tension, irritability, mental pressure, unpleasant feelings and/or unusual situations	18 (41.86%)	3.37
2	26	Stress is to be aware of tinnitus day and night and the mental effort to ignore it and not being able to hear "quiet"	11 (25.59%)	2.26
3	2	Stress is a feeling which affects both your physical and mental approach in situations	15 (34.88%)	1.95
4	30	Stress is feeling trapped in a situation and unable to escape	13 (30.24%)	1.79
5	34	Stress is having difficulty getting to sleep, lack of sleep, or not sleeping well	11 (25.58%)	1.60
7	10	Stress is mental, physical, emotional and psychological responses to things rather than rational, objective responses (losing the sense of reasoning)	11 (25.58%)	1.53
6	77	Stress means heightened anxiety and emotional strain	10 (23.26%)	1.53
8	21	Stress is experiencing upsetting events or problems requiring urgent attention that someone feels powerless to resolve	11 (25.58%)	1.44
9	1	Stress is a significant burden to some people but has little effect on others	11 (25.58%)	1.42
10	14	Stress means feeling (being) under pressure	10 (23.26%)	1.42

The table shows the number and the percentages (%) of participants who put the statements in the corresponding rank. The weighted rank is based on the computing the equation mentioned in 4.3.7.2.
ID= statement's identification number.

4.4.2.7 Statements sorting

None of the participants sorted all the statements into a single group as they were instructed. Statement 6 was sorted into a group by 32 participants (74.4%) which was the highest rate. In contrast, statement 69 was the least sorted statement, which was sorted into a group by only 19 participants (44.2%). Nevertheless, the frequency of sorting the statements was almost equivalent across the whole list (Figure 4.6). The number of groups created by participants ranged from two to seven with a median of three.

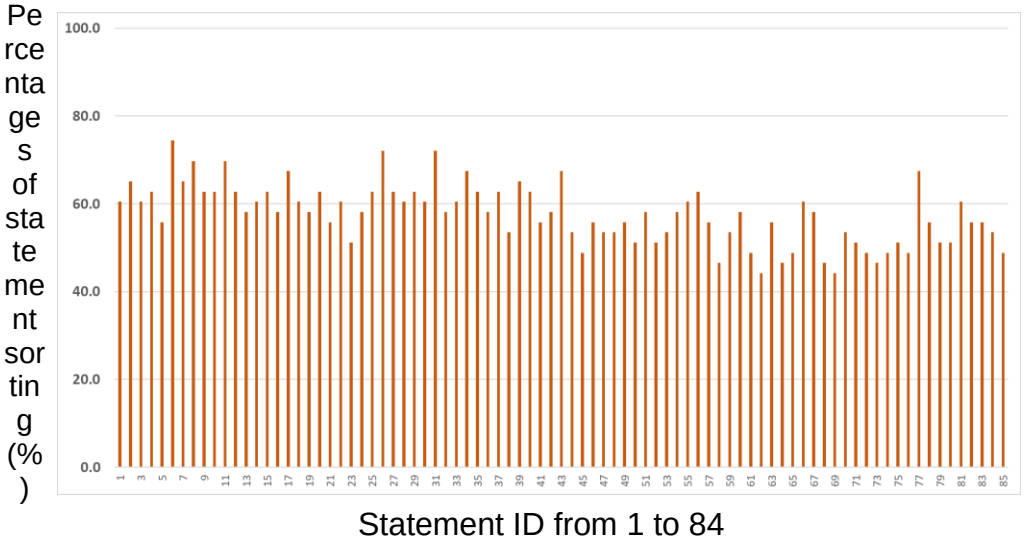


Figure 4.6 Frequency of sorting each statement across the list. The X axis represents the statement's identification number on the list. The Y axis represents the percentage of sorting each statement into a group as resulted from percentage of participant sorted the statement into a group of the total number of participants.

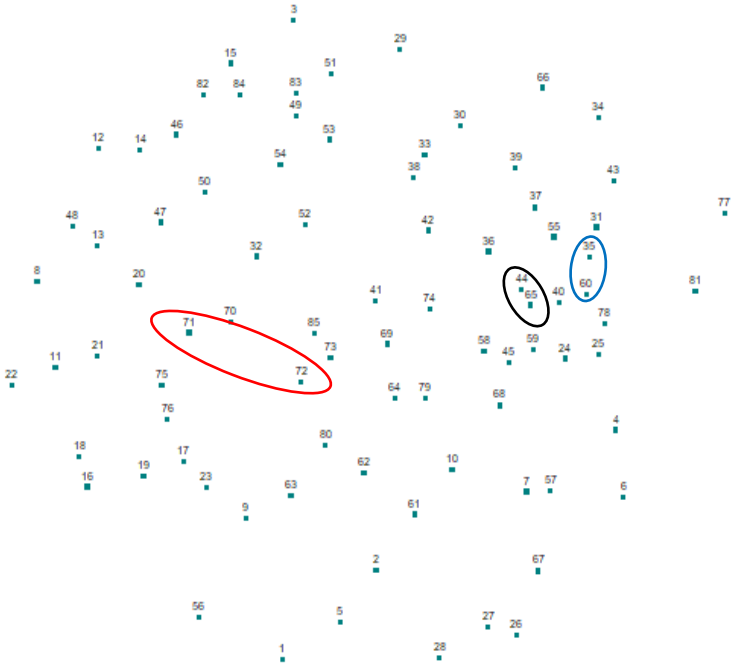
4.4.2.8 Visual product of Group Concept Mapping

Visual products were generated by the R-CMap software. The first product was a 2D point map generated by MDS analysis (Figure 4.7 A). As explained in 4.3.7.3, the distance between two points on the map reflects how many times those two statements were sorted together by different participants (examples in Figure 4.7 A). The stress index of this point map was 0.304, which is an acceptable stress index value (Kane and Trochim (2007). The cluster map and the dendrogram are also visual products (Figure 4.7 B, Figure 4.8) that were generated by hierarchal cluster analysis that grouped statements into clusters that reflected similar ideas.

To decide which cluster solution should be taken forward to Activity 3, a number of different possible cluster solutions were examined to identify

the cluster solution that produced the smallest number of clusters and the most reliable distinction between the clusters even when the statements look close on the point maps. To explain, if two statements were very close on the point map, they might belong to two different clusters on the cluster map; for example point 35 belongs to cluster 7 and point 60 belongs to cluster 3 (Figure 4.7 A and B). The dendrogram shows clearly that points 35 and 60 are far apart (Figure 4.8).

A



B

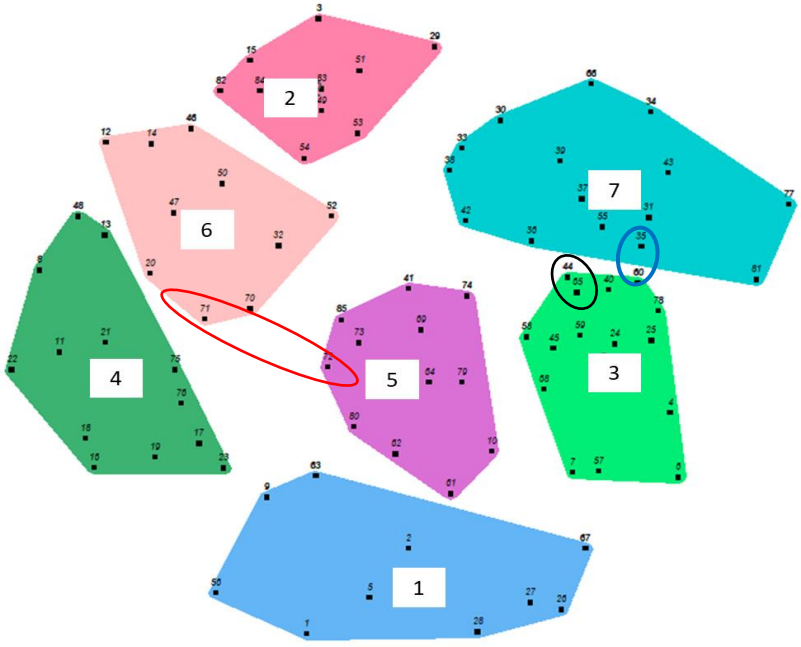


Figure 4.7 Point map and Cluster map
(A) Point map shows the proximity of the statements with each other. The black and blue circles indicate examples of two pairs of statements (44, 65 and 35, 60 respectively) that were grouped by participants more often than statements 71 and 72 (red circle). (B) Cluster map. The hierarchal analysis shows the boundaries between 7 groups and that statements 44, 65 (black circle) belong to the same cluster. However, statements 35, 60 (blue circle) belong to different groups despite being close on the point map. Statements 71, 72 belong to different groups.

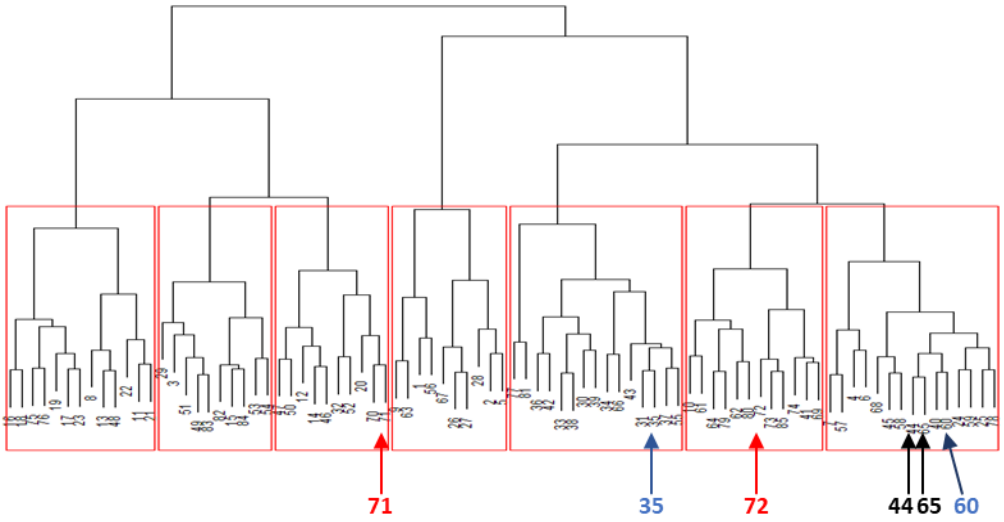


Figure 4.8 Dendrogram of group concept map
The dendrogram shows the location (arrows) of each statement given as examples. The red circled (71, 72) in red, the blue circled (35, 60) in blue, and the black circled (44, 65) in black.

An ANOVA test showed a statistically significant differences between the seven clusters ($F(6) = 3.7885$, $p < 0.05$). In contrast, the clusters in the 6-cluster solution did not significantly differ from each other ($F(5) = 0.70563$, $p = 0.6209$). Therefore, the seven-cluster solution was deemed the most appropriate fit for the data. All members of the research team (AE, KF, DH) reviewed and agreed that the seven-cluster solution was the best fit of the data to take forward to Activity 3. T cluster rating map and point rating map are given in Appendix XI.

4.4.3 Activity 3: Face-to-face consensus meeting

4.4.3.1 Participants

Invitations were emailed to 28 participants who registered their interest in attending the consensus meeting. Of these, eight participants attended the meeting. They were aged 62-80 years old and had all experienced tinnitus for more than 10 years (Table 4.8).

Table 4.8 Details of the participant who attended Activity 3

ID	Age (y), gender	Education	Tinnitus duration (y)	Hearing problems	Opinion on the relationship*
1	62, male	A level	10-15	Yes	Disagree with all
2	71, male	Higher	>20	Yes	Disagree with all
3	84, male	Higher	>20	Yes	There is no relationship
4	80, male	Higher	15-20	Yes	Tinnitus increases stress
5	77, female	Higher	15-20	No	Stress worsens tinnitus but it is not a cause
6	70, male	A level	10-15	Yes	Stress worsens tinnitus but it is not a cause
7	73, male	Higher	>20	Yes	Stress worsens tinnitus but it is not a cause
8	76, male	Other	>20	Yes	Stress worsens tinnitus, Tinnitus increases stress

*Based on the participant's answer to the question *"Which statement do you most agree with".* Listed in Table 4.1.
Y= Year.

4.4.3.2 The highest rated statements

The five highest rated statements from Activity 2 and their rating scores are listed in Table 4.6. Participants reviewed and discussed each of the five statements, stating whether they agreed or disagreed with the statement and what it meant to them.

The highest rated statement was Statement 6 "***Stress includes tiredness (mentally and/or physically), worry, anxiety, tension, irritability, mental pressure, unpleasant feelings and/or unusual situations***" and was generated in Activity 1 by merging three sentences with the main concept of involving "mental" association. Participants generally agreed that this statement represents the meaning of the word "*stress.*"

It includes stress-related feelings (tiredness, worry, anxiety, tension, irritability, mental pressure, and unpleasant feelings), and it acknowledges the effect of external concept (unusual situations).

Participants commented on the possible overlap in the meanings of anxiety, worry, and tension. They also suggested separating the internal and external concepts and putting them into two sentences. In addition, they acknowledge that tiredness makes it difficult to sleep which can increase stress.

Participants noticed that the third highest rated statement 31 "***Stress is not being able to completely relax even when completely feeling tired***" and the fifth highest rated statement 33 "***Stress is feeling tense and opposite of calm and relaxed***" are related to inability to relax.

Participants agreed that the fourth highest rated statement 77 "***Stress means heightened anxiety and emotional strain***" may represent the concept of anxiety. Participants agreed that this statement represents only some aspects of stress which can "*be other things*."

Participants criticised the second highest rated statement 2 "***Stress is a feeling which affects both your physical and mental approach in situations.***" They argued that stress affects either physical or mental approach, so this statement should read "…*physical and/or mental*…" There was a divergence in opinion about the use of the word "approach," which may mean either reaction or lack of control over a behaviour. One participant criticised the statement as tinnitus in his opinion comes from the brain and is more a mental rather than physical entity if compared to external noise.

4.4.3.3 Suggestions from participants

Participants suggested possible rewording of all statements. They suggest that instead of starting with "*Stress is…"* or "*Stress means…,"* statement could be re-worded to read "*stress can include…"* and "*Stress can be….*" They also suggested some statements end with the phrase "*… can be stress*" instead of starting with a phrase about stress.

Participants were consulted about the cluster numbers and names. They reviewed the generated clusters based on 7-cluster solution. They concluded that some statements should be moved to different groups, that some groups should be split into more than one group or should be merged with another group. The reviewed 7-cluster solution did not provide complete meaningful clusters. Participants did not reach an agreement on the names for each cluster, but they did identify general constructs (categories) across the groups. For example, group 1 and 2 representing "external" constructs.

4.5 FINAL CLUSTER MAP DEVELOPING THE CONCEPT MAP

The consensus meeting did not lead to an agreement on the number and names of clusters which means that the seven-cluster solution was not the optimal solution. The concept of the statements within each group and whether they belong together or not required further examination. Therefore, an additional analysis was performed to create a more acceptable cluster set using the recommendations and notes Activity 3, and the logical and subjective analysis of each cluster (described in the next section). Based on the results from the MDS,

hierarchal cluster analysis, and the discussion in the consensus meeting, the final cluster solution was determined by applying subjective judgement on the meaning of the statements in each group.

First, I examined the lowest branches of the dendrogram where the statements that were grouped together more frequently were located. This led to producing some two-statement clusters and a one-statement cluster, and a cluster solution that exceeded the R-CMap cluster solution which is limited to 20 clusters. As the higher levels on the dendrogram were reviewed, larger groups with similar statements were formed; an example is provided in Figure 4.9. Starting from the lowest level on the dendrogram in Figure 4.9 A, seven groups were created. Going higher on the dendrogram (Figure 4.9 B, C, and D consequently) led to the number of groups becoming fewer, but each group became larger. Each group of statements was examined individually as the clustering goes bottom-up and notes were made on what unites or connects them. Recommendations and comments from the participants in Activity 3 were considered when deciding the names of the clusters.

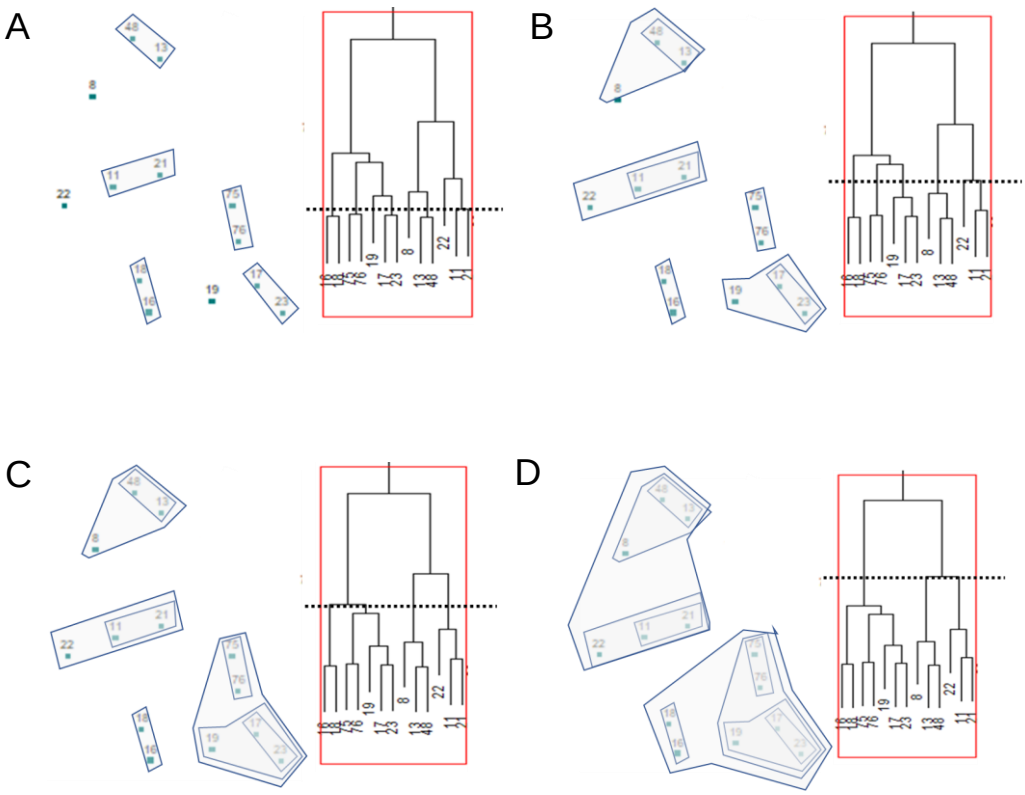


Figure 4.9 An example of examining the statements within each group
The level of branching (the black dashed line) on the dendrogram indicates the level of cluster solution. (A) The highest cluster solution shows the formation of few 2-statement groups while few statements formed their own groups. By decreasing the level of the cluster solutions (going bottom up) more statements come together and form large groups as seen in B, C, and D.

This analysis created three main clusters and 11 groups (Figure 4.10). The boundaries between the main clusters were determined by the 3-cluster solution run by R-CMap and divided the map into three clusters. These three clusters were named "*individualized experiences*" cluster, "*internal factors*" cluster, and "*external factors*" cluster.

Cluster 1 was the smallest cluster and was formed of two groups (10 statements). Cluster 2 was formed of three groups (33 statements). Cluster 3 was the largest and formed of six groups that contained 42 statements (Figure 4.10).

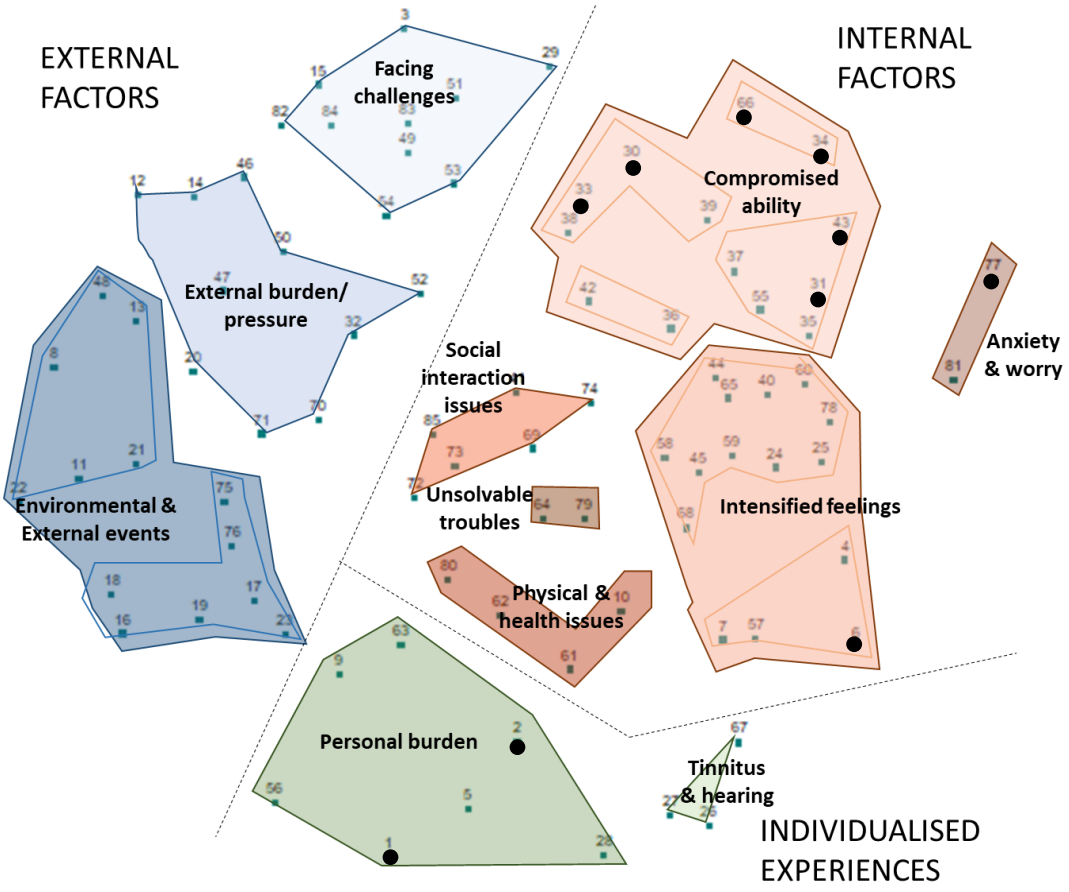


Figure 4.10 The final concept map shows the 11 groups and the three clusters.
The dashed line indicates the boundaries between the three clusters as resulted from the 3-cluster solution. Large black dots refer to the position of the 10 highest rated statements.

Table 4.9 provides a list of the groups, the mean ratings of the statements within the group (M), a description of each group, how many statements in each group, and lastly an example statement with its ID.

Table 4.9 The final 3 main clusters and 11 groups that represents how people who have tinnitus define the word "stress."

Group (M)*	Description		Number of statements in each group with examples (ID)
Cluster 1: Individualised experiences (3.307)			
Personal burden (3.383)	The individual experience during a situation.	7	(1) Stress is a significant burden to some people but has little effect on others
Disability (3.130)	A specific disability related to tinnitus and hearing impairment.	3	(26) Stress is to be aware of tinnitus day and night and the mental effort to ignore it and not being able to hear "quiet."
Cluster 2: External factors (3.172)			
Facing challenges (3.224)	Occurring of events that lead to an achievement once completed. For example, challenges at work.	10	(54) Stress is feeling (or being) pushed to your limit at home, in work, or in another external environment.
Environmental & External events (3.084)	Being in problems that affect the person emotionally or facing uncomfortable situations like waiting for someone/ something.	13	(21) Stress is experiencing upsetting events or problems requiring urgent attention that someone feels powerless to resolve.
External burden/ pressure (3.233)	Being or feeling under pressure and the presence of an external burden on the person.	10	(14) Stress means feeling (or being) under pressure.
Cluster 3: Internal factors (3.164)			
Intensified feelings (3.002)	Stress is described as "feelings" this can be intensified feelings or overwhelming emotion. The person feels vulnerable, withdrawn, socially isolated and lonely.	15	(6) Stress includes tiredness (mentally and/or Physically), worry, anxiety, tension, irritability, mental pressure, unpleasant feelings and/or unusual situations. (40) Stress is feeling (or being) not in control of a situation, thoughts, or feelings.
Unresolved troubles (2.775)	The person faces challenges that they cannot solve or overcome and prevent them from leading a normal life	2	(79) Stress is being worried about get caught in troubles that someone cannot resolve.
Physical & health issues (3.073)	Stress is physical response and its effect on health.	4	(61) Stress is having health issues (or risks) and medical symptoms (like vertigo, headache, and high blood pressure) that make the person too feel generally unwell.
Social interactions issue (2.768)	Difficulties in social interaction with people in general.	6	(41) Stress is a compromised ability to handle uncontrollable conditions and escalating situations that interfere in someone's life.
Compromised ability (3.578)	Loss of ability to relax, control over somethings, cope with difficult situation, or escape a difficult situation.	13	(31) Stress is not being able to completely relax even when completely feeling tired. (30) Stress is feeling trapped in a situation and unable to escape.
Anxiety & worry (3.455)	Increase in anxiety and overthinking about something.	2	(77) Stress means heightened anxiety and emotional strain.

**M indicates the mean of "statements rating" within each group, ID= Statement's Identification Number.*

It is important to mention that almost all statements can be allocated to more than one group or cluster. Statement 6 for example covers more than one aspect of stress. The framework that is proposed here is based on the agreement between the participants and therefore it reflects how stress is mapped onto tinnitus.

4.6 CHECKING INCLUSIVENESS OF THE CLUSTERS

Sentences that were generated by the participants in Activity 1 were examined to identify to which cluster and group each one belongs, and whether each participant generated statement was covered by the three clusters (internal factors, external factors, and individualised experiences) or not. Out 76 participants, those whose inputs answered the research question, 22 participants (28.9%) generated statements that has been allocated into one cluster only, 34 (44.7%) into two clusters, and 20 (26.4%) into three clusters.

Statements that were generated by 70 participants (92.1%) ended up forming the *internal factors* cluster. The statements list of the *Individualised experiences* and *External Factors* clusters were generated by 26 and 54 participants, respectively. Table 4.10 summarises how many participants had written statements that were assigned to each cluster and group. Figure 4.11 illustrates the percentages of statements in each cluster.

Table 4.10 Number of participants and their inputs in each cluster and group

Cluster	Participants (N)	Group	Participants (N)
Internal Factors	70	Intensified feelings	39
		compromised ability	35
		Social interactions	19
		Physical & Health	14
		Unresolved troubles	8
		Anxiety & worry	7
Individualised Experiences	26	Personal burden	15
		Disability	12
External Factors	55	Facing Challenges	23
		Environment & events	28
		External burden/ pressure	29

Data collected in Activity 1 from 85 participants. The totals do not add up as each participant could have written many statements that allocated in different groups and therefore each statement counted as one.
N= Number of the participants.

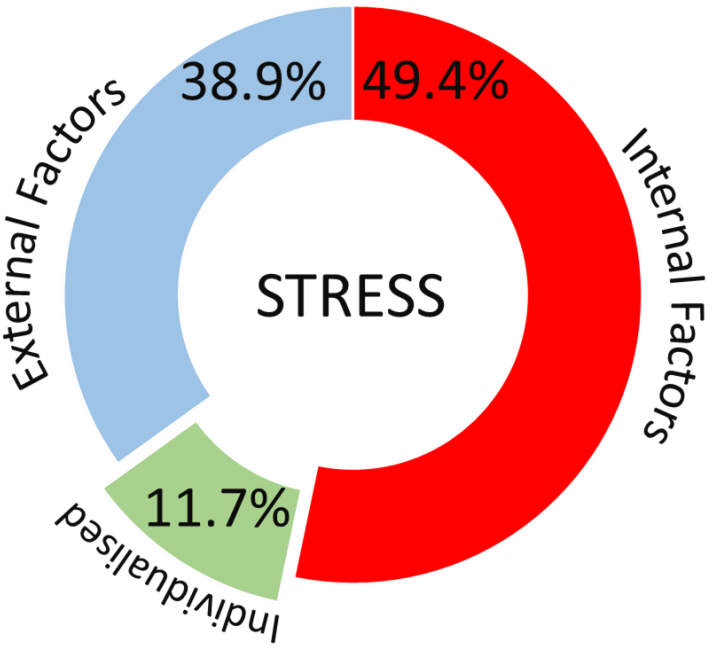


Figure 4.11 Percentages of statements in each cluster of all statements sorted in Activity 2.
Almost half of the statements were grouped under the internal factors cluster (in red). The other half of the statements were grouped under the External Factors (blue) and Individualised (green) clusters.

4.7 DISCUSSION AND CONCLUSION

The GCM method was used in this study to form clusters and groups that can be presented as a map or a list of rated statements about stress. Herein, I present the concept map of the meaning of the word "*stress*" for people who have tinnitus.

Statements generated by participants reflect how people with tinnitus understand the word stress. I presented the definitions of stress in the Chapter 1. Upon comparing statements and groups that were generated in this study, they cover the stimulus-based and the transactional model of stress. Participants did not acknowledge the response-based definition of stress. Some participants recognised that stress can be physical, behavioral, mental, psychological, or emotional response, but not a bio-physiological response. Only 20 participants generated statements that related to all three clusters. This means that not all tinnitus patients conceptualise stress in the same way. The word "*stress*" has many qualitatively distinct meanings that may affect how a cause-effect relations can be studied (Kagan, 2016). Therefore, the use of the word "*stress*" in tinnitus self-reported measurements may confuse patients in clinical settings and participants in research studies; responses to questions about stress in tinnitus may differ simply because of individual differences in understanding the concept of stress. This study also identified a cluster that was related to the participant experience with tinnitus which may indicate that presence of tinnitus is part of the stress experience.

All participants had tinnitus for more than 1 year and the majority had it for more than 5 years. This means their personal experiences have affected their opinion about this relationship. Many believed that stress is the effector. Most participants generated statements that define stress as internal. Also, eight out of ten highest rated statements are located in the internal factor cluster. The five highest rated statements belonged to the compromised ability, anxiety and worry, intensified feelings (internal factor cluster) and the personal burden groups (Figure 4.10 A). Stress is depicted as negative feelings or consequences (Crum et al., 2013), which may explain why the participants emphasise this negativity.

Tinnitus is commonly associated with hearing impairment or other audiological disorders which may cause an additional source of stress. It was not possible to perform a comparison between participants who had hearing impairment (33 participants) and those who did not (10 participants) as the number of participants in the latter group was not sufficient to produce a reliable MDS (explained in 4.3.3.1). However, the presence of other audiological disorders should be considered when assessing stress in a tinnitus population.

The consensus meeting ended without reaching a consensus about the definition of stress. One of the reasons of not reaching consensus was the broadness of the concept studied (Newton and Shaw, 2016) which seems to be true with the word “*stress*”. Also, each participant brought their own experience with tinnitus to the meeting, and this led to lengthy discussions and exchanges between the participants that were not

related to the discussion topic. Reaching an agreement in this case may occur through several meetings rather than one. It usually takes time to reach consensus especially in face-to-face meetings (Howze and Dalrymple, 2004). In retrospect, two meetings or emailing pre-meeting materials (results of Activity 2 with explanation) to read beforehand might have helped in reaching a consensus level of agreement. The concept mapping method does not give advice about overcoming this issue. ~~However,~~ I drew the concept map based on the comments and recommendation given by the participants in the meeting. This should overcome this issue and lessen its negative implications on the results of this study.

4.8 RELEVANCE FOR CLINICAL PRACTICE AND RESEARCH

This study produced statements about stress and a conceptual construct of stress developed with people who experience tinnitus. This will be informative for clinical practice and research. To explain, for people with tinnitus, the highest rated statements may represent the definition of stress, and cluster analysis may indicate which aspect of stress is more relevant to them. Within each cluster, there is a set of rated statements that can inform questionnaire or clinical interview design, or to study the relationship between tinnitus and a specific construct of stress. There is a little known about how each aspect of stress as identified in this study interacts with tinnitus. For example, is tinnitus affected by the internal factors more than the external factors or vice versa? All available questionnaires that assess tinnitus-related

stress examine stress as one entity, which limits their usefulness for detailed assessment. One example of the value of studying the effect of different aspects on tinnitus is a study conducted by Biehl and colleagues where they described the mediating effect of stress on the relationship between personality and tinnitus. They found that while worry and emotional tension (or the internal factors) mediated the relationship between personality and tinnitus-related distress, the demands (or the internal perception of external stressors assessed by the PSQ) mediated only the relationships between tinnitus-related distress on the one hand and the excitability and somatic complaints on the other (Biehl et al., 2020). Developing a new questionnaire that can distinguish between different aspects of stress may be of value in understanding which one is more relevant to tinnitus and how. This would subsequently inform future tinnitus guidelines and prioritising management according to the aspect of stress that is more problematic than the others. NICE guidelines for tinnitus research (NICE, 2020) lists the key recommendations for tinnitus research. Some of these research areas would benefit from the distinguishing between these aspects. For example, it would be possible to determine which aspect improves due to stress managements like CBT and mindfulness in tinnitus participants.

Further study is required to assess the possibility of using these statements instead of the conventional stress questionnaires that are used. Also, these statements can be used with smartphone apps to capture the real-time assessment of stress and tinnitus. With the

increased use of research that relies on apps, statements can be sent more than one time per day. The researcher can use one statements or more, which provides flexibility in monitoring the level of stress. Clinicians can use these statements as questions to assess stress during tinnitus assessment. This will help in providing better health service to people with tinnitus.

4.9 LIMITATION OF THE STUDY

Although I followed the recommendation for conducting internet-based concept mapping studies as advised by Kane and Trochim (2007), this study had some limitations. The statement list was reviewed by the research team and PPI contributors. However, there were issues with the wording and clarity of some statements. Adding a stage before the rating and clustering tasks (i.e. before activity 2) where a group of lay people revise the list is recommended to ensure that statements are understandable and possibly to reduce the list. Concept mapping methodologists advise that the number of statements should be less than 100. I managed to limit this number to 84 statements. However, participants in Activity 2 found the list to be very long and, and as a result, fewer participants completed Activity 2.

Participants did not sort all the statements into groups (Figure 4.6) as advised. However, at least 21 participants (the number of participants who sorted the last statement) had read the whole list before sorting the statements into groups, and they did not tend to sort the first statements only. According to Bar and Mentch (2017), this type of incomplete data

should not affect the analysis. The R-CMap uses a different weight for each statement that depends on the number of participants who did sort each statement instead of dividing the counts by the number of participants. Thus, the dissimilarity matrix is normalised.

Most participants in this study had completed a higher education degree. Therefore, the generated statements may have a sophisticated language that may not be suitable for everyone, or to directly inform questionnaire or clinical interview questions. It was recommended during the meeting that the wording of the statements should be revised and edited to be more accessible. Statements which stated that stress causes a change in the person's status were excluded from the analysis (see 4.4.1.2). This meant that this study ignored the potential effects of stress in favour of statements which contributed to a definition of stress. These excluded statements (n=37, 7% of total) were about the negative emotional status that stress can cause. Including these statements could have increased the number of statements within the "internal factor" cluster or they could have emerged as a separate cluster of their own.

CHAPTER 5 STRESS ASSESSMENT AND MANAGEMENT IN TINNITUS CLINICS: A SERVICE EVALUATION

The aim of this chapter is to examine how health professionals assess and manage psychological stress in tinnitus clinics.

5.1 INTRODUCTION

When asked, about half of individuals with tinnitus believed stress can be the predisposing and/or the exacerbating factor in tinnitus (Study 2, Chapter 4). Besides, clinical experts reported a relevance of stress to tinnitus (Cima et al., 2020). Therefore, clinicians ought to consider stress in history taking and patient assessment. This is recommended by NICE tinnitus guidelines (2020) and the European clinical practice guideline for tinnitus assessment (Cima et al., 2019). However, there is no clear guidance about best practice to assess stress. For example, NICE tinnitus guidelines (2020) considers that TQ or mini-TQ alongside the TFI are appropriate questionnaires to use to assess the psychological impact of tinnitus in adults when there are concerns about depression or anxiety. The decision to use these questionnaires is subjective to the clinician's opinion and thus it is important to evaluate clinician's knowledge about stress.

In many countries, tinnitus management is interdisciplinary including but not limited to audiologists, ENT surgeons, audio-vestibular physicians, psychologists, and hearing therapists (Fuller et al., 2017, Cima et al., 2020). In the United Kingdom (UK), NHS audiology departments play a

major role in offering therapy and support for patients with tinnitus (Aazh et al., 2016). The question I ask here is *how* clinical professionals who have diverse educational backgrounds and expertise assess and manage stress in tinnitus patients when there is no clear guidance in this regard, and given the complexity of stress. Health Research Authority (2017) states that a “service evaluation is designed and conducted solely to define or judge current care”, should measure current service without reference to a standard and involves an intervention in use only. In this service evaluation I evaluated how health services for tinnitus manage and assess stress and explored what challenges they are facing.

5.2 THE AIM OF THE STUDY

The main aim of this service evaluation was to determine how stress is assessed and managed in tinnitus clinics. This required determining the knowledge of clinicians regarding the meaning of stress, and the experience (facilitators and barriers) of those clinicians in assessing and managing stress.

5.3 MATERIAL AND METHODS

This service evaluation was conducted as an online survey, designed and reported according to Kelley et al. (2003).

5.3.1 Survey development

The survey was formed of 18 questions, including a screening question. Those questions were a mix of open-end and multiple-choice questions, grouped into five categories (Table 5.1).

Table 5.1 Survey categories and questions

1. Screening question: Do you ever see patients who have tinnitus (not necessary as their main complaint)? Yes/ No
General Information
2. Which country you are working in?
3a. What is your current job role? Audiologist/ ENT Surgeon/ Psychologist/ Hearing therapist/ Audio-vestibular physician/ others
3b. If others, please specify
4. Total years in current job are: <1/ 2-4/ 5-7/ 8-10/ >10
5. Do you work within: Public (example NHS)/ Private sector/ Both
6. On average, how many tinnitus patients do you see in a week? 0-1/2-5/6-10/>10
Definition of stress
*7. How would you define the word stress?
*8. What are the cues that indicates the patients is "stressed"? Words, phrases, behaviours… etc.
Stress assessment
9. Do you routinely assess whether your tinnitus patient is experiencing stress? Always/ sometimes/ never
10. Do you use a validated questionnaire to measure stress? Yes/ Sometimes/ No
11a. If yes or sometimes, which questionnaire? Perceived Stress Scale (PSS)/ Perceived Stress Questionnaire (PSQ)/ Depression Anxiety Stress Scale (DASS)/ Others.
11b. If others please specify
*12. Do you usually record whether the patient is stressed in their medical notes?
Stress management
13. Do you offer any specific management strategies for tinnitus patients who are stressed? Yes/ Sometimes/ No
*14. What management strategies do you offer for tinnitus patients who are stressed?
*15. If you do not or only sometimes offer stress managements for patients you recognise as “stressed”, can you tell us why?
*16. What do you find most difficult about managing stress in tinnitus patients?
Comment and feedback
17. Do you have any other information about stress and tinnitus that you wish us to know?
18. Any feedback?

**Open-end questions*

These categories are:

1. The first category titled General information is included five closed-end questions. It collected general information about respondents' experiences and their place of work.
2. The second category titled Definition of stress included two open-ended questions about how the respondent defined the word stress and how they subjectively identify stressed patients. It aimed to evaluate the knowledge of clinicians regarding the meaning of stress.
3. The third category, titled Stress assessment, examined how often they assess stress (closed question 9). If they answered yes or sometimes, they were asked what tool they are using (closed question 10 and 11) and whether they record the patient as stressed or not (open question 12). They were routed to the following category if they never assessed stress in tinnitus.
4. The fourth category, titled Stress management. The participants were asked if they stated that they offered stress management to tinnitus patients, they were asked to describe the strategies that they used (open question 14). But, if they stated that they do not or only sometimes offered stress management, then they were asked to identify what prevented them from offering management (open question 15). All respondents were asked to explain the difficulties that they faced when managing stress in tinnitus clinic (open question 16).

5. The fifth category titled Comment and feedback. It included two open-end questions. The respondents were given the option to provide any other comments or feedback.

The survey was developed in Jisc Online survey (previously known as Bristol Online Survey), written in English, and was titled “Stress assessment and management in tinnitus clinics”. The research team (DH, DB, and KF) reviewed and revised the questions before the launch of the survey. Figure 5.1 illustrates the design of the survey and the routing questions.

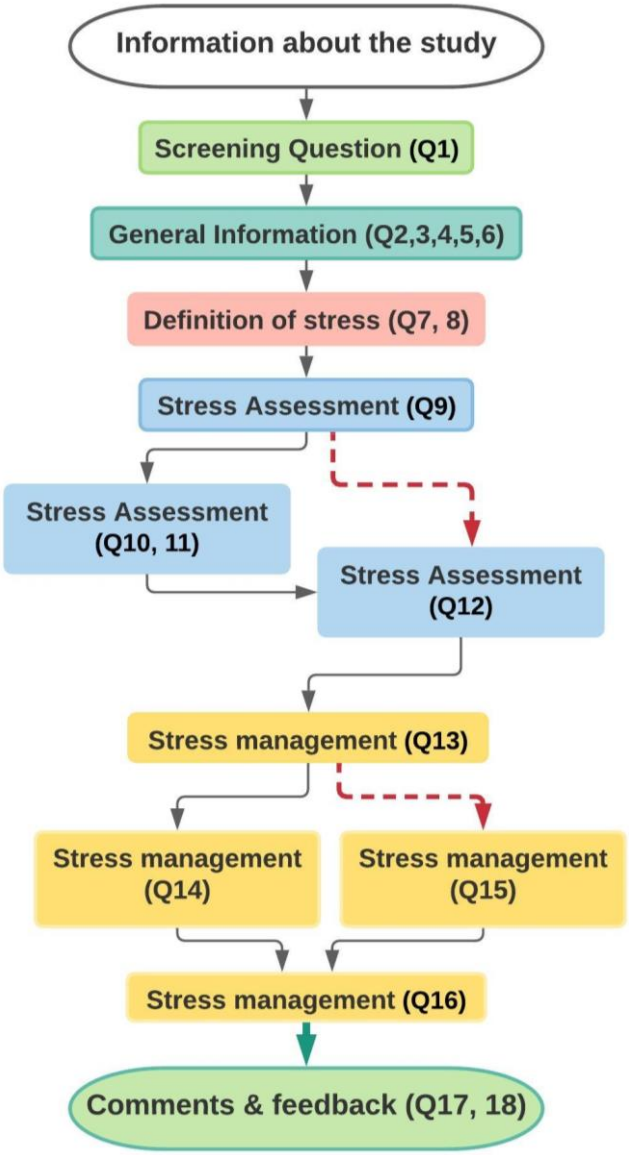


Figure 5.1 Structure and design of the survey "Stress assessment & management in tinnitus clinics."
Survey map illustrates the routing in the survey (red dashed arrows).
Q= Question

5.3.2 Survey distribution and recruitment

This internet-based survey was open to UK-based and overseas health professionals involved in tinnitus management including but not limited to audiologists, ENT surgeons, and psychologists. The link to the survey was advertised on social media platforms (Twitter, Facebook, and LinkedIn) and on the NIHR Nottingham BRC social media

accounts. It was distributed through the Nottingham University Hospitals (NUH) Audiology service email list. Flyers were distributed at scientific conferences (British Cochlear Implant Group (BCIG) meeting, March 2020). Data were collected in the period from 31 January 2020 to 31 March 2020.

5.3.3 Statistical and data analysis

5.3.3.1 Descriptive statistics

I exported data into an Excel sheet where I calculated the descriptive statistics. Those include the frequency and percentage of answers to closed questions.

5.3.3.2 Qualitative data analysis

I used thematic analysis and qualitative content analysis to examine data collected through open-ended questions. Thematic analysis is a method for identifying, analysing and reporting patterns within data (Braun and Clarke, 2006). Qualitative content analysis is the examination of the contents of narrative data to identify prominent themes and patterns among these themes (Polit, 2010). This is an accepted approach of investigating scripts and presents the result in numerical form of features of the given text (Marks and Yardley, 2004).

These two qualitative analytic methods share many principles and procedures. Both are used to identify meanings that are valid across respondents rather than identifying connections between meanings within a particular narrative (Marks and Yardley, 2004), and both can be used in either an inductive or a deductive way (Braun and Clarke, 2006,

Elo et al., 2014). Compared to content analysis, thematic analysis pays greater attention to the qualitative aspects of the material analysed, and draws attention to both the observable and latent meaning of the data (Marks and Yardley, 2004). In this study, I used inductive analysis to develop conclusions from the data.

5.3.3.2.1 Thematic analysis

Thematic analysis the data collected from three open-ended questions; item 7 “How would you define the word stress?”, item 15 “If you do not or only sometimes offer stress managements for patients you recognise as “stressed”, can you tell us why?”, and item 16 “What do you find most difficult about managing stress in tinnitus patients?”

TA has six established phases (Braun and Clarke, 2006) these are:

1. Familiarising with data: To become familiar with all aspects of the data prior to generating codes, the research team (AE, KF, and DH) read and re-read the answers to each question, wrote notes that represents the initial ideas, and marked ideas for coding.
2. Generating initial codes: We generated codes for that represents the emerging features of the data individually across the entire data set. Then, I compared the data relevant to each code.
3. Searching for themes: I sorted different codes into potential themes and sub-themes. I repeated this step twice to ensure each code belongs to one theme.
4. Reviewing themes: The research team checked whether the themes work in relation to the codes generated previously and the entire

data set to ensure that the data and codes within the theme are coherent and there is a clear distinction between each theme.

5. Defining and meaning themes: I refined the specifics of each theme, and/or sub-themes, and generated definitions and names for each one which was reviewed by the research team.
6. Producing the report: We selected compelling extract examples and related them back to the research question. This is reported in the result section.

5.3.3.2.2 Qualitative content analysis (QCA)

QCA has fewer rules to follow than TA (Bengtsson, 2016). We (AE & KF) used QCA to analyse data collected through two open-ended questions item 8 “What are the cues that indicate the patient is "stressed"?” and item 14 “What management strategies do you offer for tinnitus patients who are stressed?” It involves three main phases according to Elo et al. (2014):

1. Preparation phase: This phase consists of defining the method of data collection and sampling strategies (as described in 5.3.1 and 5.3.2). In addition, this phase includes identifying the unit of analysis that serve the purpose of the research. For item 8, I set two units of analysis. The first unit was “what are the cues of stress.” The second unit was “how they identify the patient is stressed.” Regarding Item 14, the unit of analysis was “what management strategies they offer.”
2. Organisation phase: We familiarised ourselves with the data. We generated codes individually and then I reviewed and merged the

codes. I sorted the codes into categories, and I reviewed them to detect any overlap. Next, I conducted a qualitative analysis to generate names and definitions of the categories and calculated the frequency of respondents who gave answers that fall in the categories. This represents the most commonly used cue of stress or stress management offered by the respondents.

3. Reporting phase: I reported the findings in the result section in narrative, tabulated and/or visual forms.

5.4 RESULTS

5.4.1 Respondents

Sixty-seven respondents completed the survey. The responses came from 16 countries including 36 responses (53.73%) from the UK. Twelve out of the remaining responses came from countries where English is an official language (United State of America (USA)=4, Ireland=3, South Africa= 2, Canada=3, India=1, Ghana=1), and six responses were from other European countries.

The respondents were 40 audiologists, seven ENT surgeons, five hearing therapists, four audio-vestibular physicians, and three psychologists. Other respondents were a psychotherapist, a general physician, a speech therapist, a specialised nurse, a clinical scientist, a practice education co-ordinator, and two physiotherapists.

Most respondents worked in public sector only (59.70%), had experience of more than 10 years (47.76%), and were visited by 2-10 tinnitus patients per week (Table 5.2).

Table 5.2 The frequencies and percentages of answers per each question with a comparison between UK-based and non-UK-based clinicians.

	All (67)		UK (36)		Non-UK (31)	
	Frequency	%	Frequency	%	Frequency	%
Current job role						
Audiologist	**40**	**59.70**	**25**	**69.44**	**15**	**48.39**
AVM physician	4	5.97	0	0.00	4	12.90
ENT Surgeon	7	10.45	1	2.78	6	19.35
Hearing therapist	5	7.46	5	13.89	0	0.00
Psychologist	3	4.48	2	5.56	1	3.23
Others	8	11.94	3	8.33	5	16.13
Work sector						
Both	18	26.87	8	22.22	10	32.26
Private	9	13.43	3	8.33	6	19.35
Public	**40**	**59.70**	**25**	**69.44**	**15**	**48.39**
Years of experiences in current job						
<1	2	2.99	2	5.56	0	0.00
2 - 4 years	12	17.91	6	16.67	6	19.35
5 - 7 years	12	17.91	6	16.67	6	19.35
8 - 10 years	9	13.43	3	8.33	6	19.35
>10	**32**	**47.76**	**19**	**52.78**	**13**	**41.94**
Number of tinnitus patients each week						
0 - 1	9	13.43	4	11.11	5	16.13
2 - 5	**26**	**38.81**	12	33.33	**14**	**45.16**
6 - 10	22	32.84	**13**	**36.11**	9	29.03
>10	10	14.93	7	19.44	3	9.68

The bold text indicates the highest frequencies and percentages in each category.
<1= less than one year, >10 = more than ten years.
AVM= Audio-vestibular Medicine, ENT= Ear Nose Throat.

5.4.2 General knowledge about stress

5.4.2.1 Definition of stress

TA of the data regarding the question “How would you define the word stress?” yielded four themes (Table 5.3). These were:

1. Response to stressors: Respondents defined stress as an automatic response or reaction to stressors that vary in intensity. This response is bio-physical and/or emotional based. The stressor can be a usual or unusual event, excessive demands, negative influences, and/or mental pressure.

2. Increased demands that may exceed resources: Stress is an increase in demands that require more effort, but not necessarily associated with negative effects on the person or a negative response. People may express stress as being overwhelmed, pressured, or overloaded.
3. Inability to overcome difficulties and challenges: Stress can be described as the reduced ability to manage demanding situations. This reduced ability can manifest in different forms. People may report that they are not functioning properly to complete tasks, feel a lack or loss of control over situations in daily life, loss of control over own emotions, loss of the ability to recover from a situation, feel tired and unable to relax, or are unable or have reduced capacity to cope with situations that occur in everyday life.
4. Emotional interactions: Stress can manifest as negative effects of a pressuring situation on wellbeing (Physical, behavioural, and/or emotional) and on all aspects of life (reduction in quality of life). Stress can involve intensified feelings that the person reveals without identifying a source of that feeling which may reflect their attitude toward their surroundings. The main interpretation of stress here tended to focus on the emotional aspect of stress rather than physical or psycho-social aspects.

Table 5.3 The outline of themes and example quotes of stress definition.

Theme	Example quotes	N
Response to stressors	*"An automatic, emotional response to a situation that can be deemed difficult, complex, time consuming or uncomfortable." (R9, Specialist nurse)* *"Stress is how our body reacts to any type of mental or emotional pressure." (R28, Audiologist)*	*17*
Increased demands that may exceed resources	*"A state of mind where you are overwhelmed by different pressures." (R6, Audiologist)* *"An expectation that is impossible to achieve." (R45, Audiologist)* *"The experience of being overwhelmed by circumstance." (R54, Hearing therapist)*	*22*
Inability to overcome difficulties and challenges	*"Concern that current load outweighs mental/time capacity to complete required work." (R19, Audiologist)* *"Something that can affects your ability to stay relaxed." (R26, Audiologist)* *"Stressors in excess of capacity to cope." (R17, Psychologist)* *"Stress occurs when there is a lot to do or think about where one feels one has limited control to manage the situation." (R32, Clinical Scientist)* *"Feeling like things are not within your control and that you can't cope." (R14, Audiologist)*	*20*
Emotional interactions	*"Anxiety, irritability and nervousness." (R1, ENT Surgeon)* *"Feeling of tension or discomfort, with an effect on emotional wellbeing." (R15, Audiologist)* *"When one feels overwhelmed or under pressure which can have an adverse effect of one's mood." (R36, Audiologist)*	*11*

The respondents' ID (Rn) and their professions are stated at the end of each quotes. The last column indicates the number of responses (N) that coded in each theme*. ENT= Ear Nose Throat.*

5.4.2.2 Approaches to identify stressed patients

Sixty-one respondents listed the cues that show if the patient is stressed. QCA based on "what are the cues of stress" as the unit of analysis (see 5.3.3.2) resulted in seven categories and 31 sub-categories (Table 5.4). Respondents frequently listed signs that relate to emotional status (such as worry, anger, and lack of enjoyment) and physical manifestation of stress (72 and 78 times respectively). Few respondents relied on direct patient-reported complaint during history taking, i.e. stress is mentioned by the patients or they answered that they were stressed.

Table 5.4 Categories and subcategories of the cues that are used to identify stressed patients

Categories	N	Sub-categories	N	Example phrase
Recognising the emotional status of the patient or Emotionally unsettled	72	Anxiety/worry/concern	29	*Anxiety, Worried, Nervous, Concerned*
		Despondent	12	*No hope, patient says 'what's the point', Self-blaming, Depression, feeling low, fed up*
		Anger	8	*Anger, Short fuse, Defensive, Verbally aggressive.*
		Upset	8	*Bothered, Upset, Tearful, Crying, Becoming frustrated.*
		Negative reaction	8	*Irritated, Irritating, Shouting, Irritable, Feeling negative*
		Lack of enjoyment	4	*Not enjoying things, Lack of enjoyment of things that used to be enjoyed.*
		Fear	3	*Afraid, Patient reports feeling panicked or Frightened.*
Physical manifestation of stress or Physically unsettled	78	Being agitated	22	*Agitated, Fidgeting, Trembling or shaking, Tense, Hypervigilance, Flustered.*
		Physical complaints/ symptoms	18	*Headache, Visual changes, clenched jaw, Sweating, Shortness of birth, increased HR, Muscle pain.*
		Emotional exhaustion	16	*Having no energy or power, Burnout, Fatigue, Run down, Tiredness and exhaustion.*
		Compulsive speech	14	*Talking too much and too fast, Excessive talking and movements, Racing thoughts, Excessive questions.*
		Restlessness	8	*Cannot settle or keep still, Constantly on the go.*
Changes in cognitive functions	33	Concentration and attention difficulties	13	*Difficulty to focus and/or prioritise, Poor concentration, Inability to take on information, Not thinking straight.*
		Negative appraisals	11	*Negative thinking, they feel things are getting worse, Negative vocabulary and language, Low self-esteem/ worth, Desperate-report that nothing works.*
		Disconnected	4	*Disconnected, Not engaging or over the top engagement, mistaking what people are saying, Not actively listening.*
		Focused on one problem unable to move on	5	*Always talking about the same problem, Difficulty switching off, Preoccupied. Patients repeat themselves.*

Table 5.4 Cont'd

Categories	N	Sub-categories	N	Example phrase
Behavioural manifestation	51	Sleep problems	20	*Lack of sleep, Sleeping disorders.*
		Unable to function or cope	16	*Not being able to cope, Inability to function, giving up on things, Difficult to manage.*
		Lack of control	5	*Out of control, wanting to control things, Unloading.*
		Change in healthy habits	4	*Eating disorders, Drinking or smoking too much.*
		Change in behaviour	3	*Demeanour, Emotional changes, Change in normal behaviour or mood noticeable by others.*
		Avoidance	3	*Avoiding things, they used to enjoy, Social isolated.*
External source of stress	43	Being overwhelmed	17	*Overwhelmed, very busy, "need a break", "I'm struggling with this", Not having time for things you would like to do.*
		Too many demands, unable to complete work	16	*Workload, Inability to finish tasks, Patient says "my job is demanding", Too much to do, Pressures at work, Feeling under pressure.*
		Disrupted life/ Difficult home life	8	*Difficult home life, Work life events, Disrupted daily life, Stressful situation, Life events.*
		Tinnitus	2	*Tinnitus, Patient cannot hear because of it.*
Patients reported complaints	7	Spotted through history taking or Questionnaires	4	*High HADS, THI, or other mental health questionnaires scores. Being asked directly about their stress levels.*
		Patients reported that they are stressed	3	*Patients call themselves stressed, "I'm always stressed."*
Others	17	Body language	15	*Body language (slouched/leg shaking), Poor eye contact, Staring eyes, Facial expressions, Appearance. Patient's expression: A wry smile or a nod of acknowledge when you mention stress.*
		Expressing lack of support	2	*Not taking time for themselves, Hint or admit that they do not have the support they need.*
Ambiguous			8	*Cribbing behaviours, Returning focus in language.*

Example phrases are listed in the last column. The frequency of listing the phrases (N) that belong to each category and sub-category.
HADS= Hospital Anxiety and Depression Scale, HR= Heart Rate, THI= Tinnitus Handicap Index

Four categories emerged from the QCA based on the unit of analysis “how they identify the patient is stressed” (Figure 5.2). The first was the “Subjective Identification of stress symptoms and sign” that the respondent recognised the patient as stressed when they exhibit emotional or physical signs such as anxiety, lack of control, or being agitated. The second category was “verbal/ certain words or expressions” in which stressed patients use verbal cues. In other words, when the patients say they “*feel overwhelmed*”, “*can’t sleep*” “*have a lot going on*”, or they say words like 'worried', 'concerned', or 'stressed'. Eleven respondents would identify patients who are stressed from their body language cues such as poor eye contact or facial expression. Only four respondents stated that they ask about stress and/or use questionnaires to assess it.

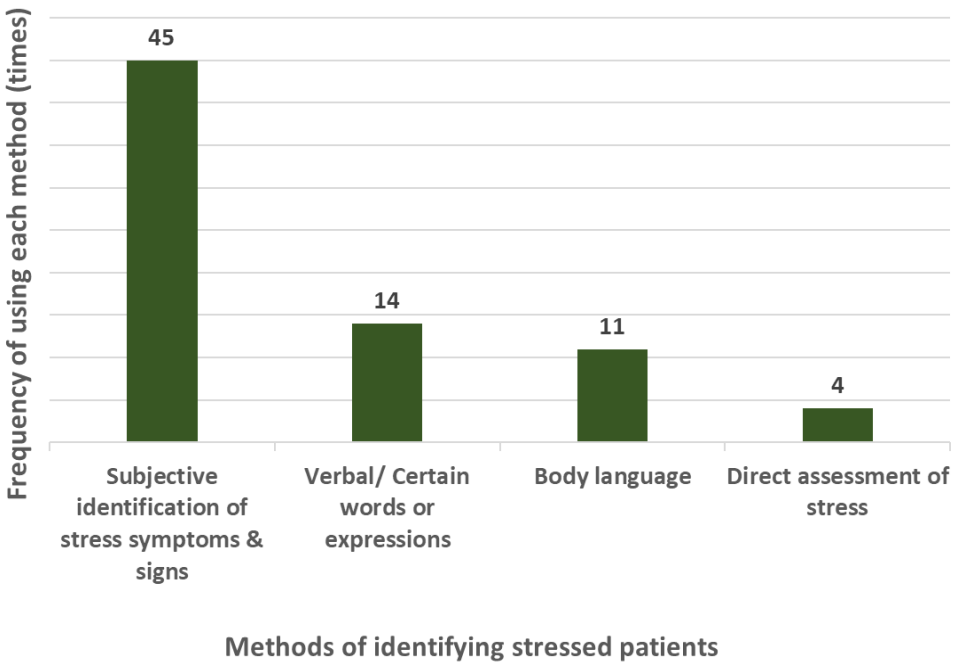


Figure 5.2 Methods of identifying stressed patients

5.4.3 Frequency of assessing stress and instruments used

Only six respondents (8.95%) said they never assess stress. Most of those were not based in the UK clinics (5 out of 6 respondents). The respondents either assessed stress always (52.24%) or sometimes (38.81%). Out of those 61 clinicians who said that they routinely assessed stress, 41 (67.2%) did not use a validated questionnaire; this represents 61.19% of all respondents. The frequencies and percentages of respondents from the UK and other countries are listed Table 5.5.

Table 5.5 Number and percentages of respondents who routinely assess stress and those who used validated questionnaires

1- Assessed stress in their clinics

	All (67)		UK (36)		Non-UK (31)	
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
Always	**35**	**52.24**	**21**	**58.33**	**14**	**45.16**
sometimes	26	38.81	14	38.89	12	38.71
Never	6	8.95	1	2.78	5	16.13

2- Have used validated questionnaires

	All (61)		UK (35)		Non-UK (26)	
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
Yes	13	21.31	10	28.57	3	11.54
Sometimes	7	11.48	2	5.71	5	19.23
No	**41**	**67.21**	**23**	**65.71**	**18**	**69.23**

The bold text indicates the highest frequencies and percentages in each category

Forty respondents (59.7%) said that they would add their findings or questionnaire score to the patient notes, and 15 would report it in the clinical notes if it was possible or relevant. Eleven respondents said they would rather not record their findings.

Twenty-six respondents (38.8%) said they used a validated questionnaire to assess stress. Only 21 respondents listed the validated questionnaires that they use in their clinics; of those 14 respondents were based in the UK. Four reported use of more than one instrument. The Hospital Depression and Anxiety Scale (HADS; Zigmond and Snaith, 1983) was used by eight clinicians (Figure 5.3).

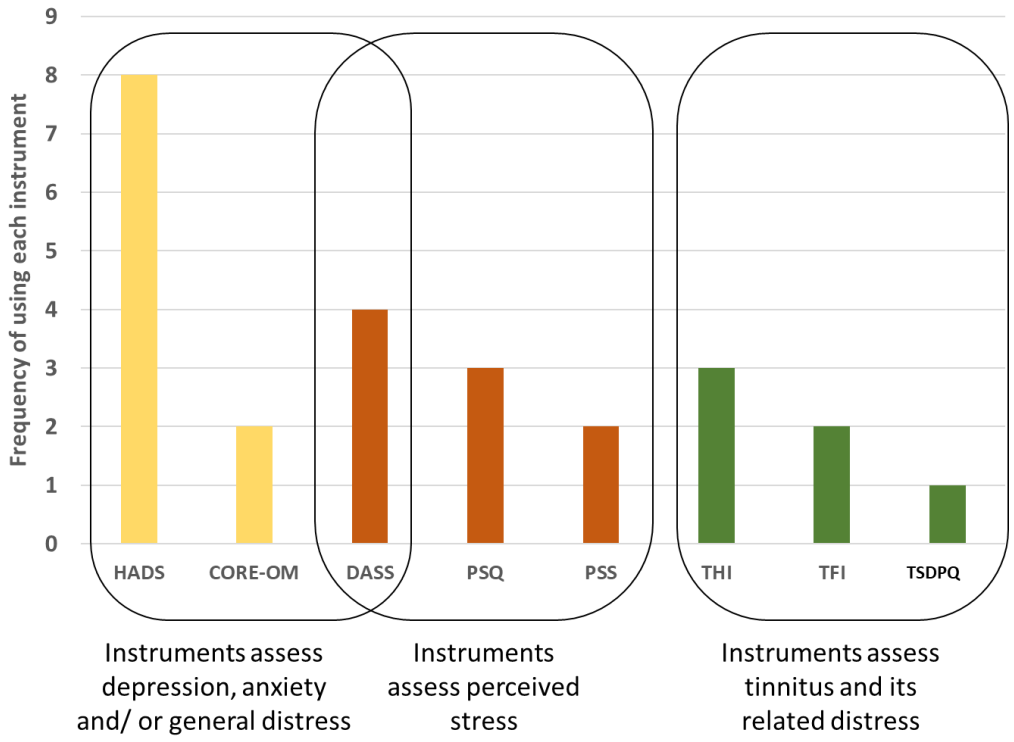


Figure 5.3 Validated questionnaires used in tinnitus clinics by survey respondents.
HADS= Hospital Anxiety & Depression Scale, CORE-OM= Clinical Outcomes in Routine Evaluation – Outcome Measure, DASS= Depression Anxiety Stress Scale, PSQ= Perceived Stress Questionnaire, PSS= Perceived Stress Scale, THI= Tinnitus Handicap Inventory, TFI= Tinnitus Functional Index, TSDPQ= Tinnitus specific distress psychosomatic questionnaire (not specified).

One respondent used narrative identification of stress only

> *"We don't use a questionnaire to assess stress, but we always ask the patient if they feel they are stressed or if they feel there is any difference in tinnitus perception when they are under stress." (R32, UK, Clinical Scientist, more than 10 years' experience).*

5.4.4 Stress management in tinnitus clinics

5.4.4.1 Management strategies offered to patients

QCA identified eight categories and 19 sub-categories that represent different approaches respondents adapted in their clinics to manage stress in tinnitus patients (Table 5.6). Besides providing management directly, respondents referred patients to other specialities or signposted them to other sources of information on stress.

Table 5.6 Categories and sub-categories of management methods.

Categories	N	Sub-categories	N
Psychological treatments	52	Psychotherapy	51
		Coping strategies	1
Relaxation Methods	29	Relaxation in general	11
		Muscular relaxation	12
		Mental relaxation	6
Targeted management	25	Tackle stress	10
		Management of tinnitus perception	10
		Management of hearing impairment	2
		Medical treatment	3
Referral to other specialities	28	Referral to clinical speciality	25
		Referral to non-clinical services	3
Signposting to resources for self-management	20	Signposting to materials	8
		Signposting to website	9
		Providing written information	3
Providing Advice to improve quality of life	18	Advice to improve physical health	12
		Advice for self-care	6
Educating patients	6	Provide information	4
		Provide explanation	2
Others	3	Acupuncture	3

5.4.4.1.1 Psychological treatments

The “psychological treatments” category has two sub-categories of treatments reported by respondents: Psychotherapy and Coping strategies (Figure 5.4).

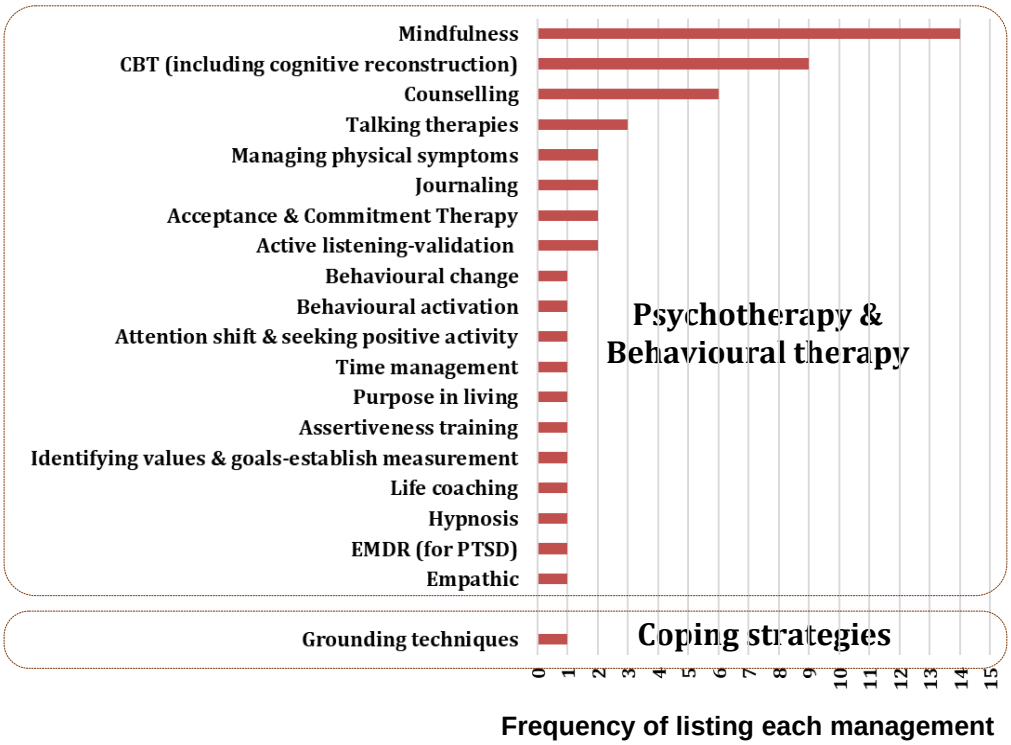


Figure 5.4 Psychological treatments listed by the participants.
The figure shows the sub-categories and the frequency of listing each management. Mindfulness was listed 14 times, which is the highest among all managements.
CBT= Cognitive Behavioural Therapy, EMDR= Eye movement desensitization and reprocessing, PTSD= Post-traumatic Stress Disorder.

The psychotherapy sub-category listed several therapeutic methods. For example, mindfulness was listed 14 times with some participants indicating that it can be administered as one-to-one or as group therapy. CBT was listed by nine respondents and counselling was listed six times. Other therapy methods, such as life coaching, identifying values, behavioural activation, and attention shift, were also reported although these can be part of other psychotherapy methods such as CBT (Fuller et al., 2020). Two respondents indicate that they use "talking therapies" to manage stress. One respondent said:

“But mainly I take the time to just speak and try to let the patient talk about it.” (R30, Audiologist)

Grounding technique, a type of coping strategy, was reported by one respondent, hence this formed a “coping strategies” sub-category.

5.4.4.1.2 Relaxation techniques

Relaxation techniques were reported 29 times (Figure 5.5). Eleven of those were not specified and the respondents mentioned “relaxation methods” or “relaxation techniques”. Therefore, the first sub-category was named “Relaxation in general”. The second sub-category “muscular relaxation” included techniques that are used to achieve relaxation through physical exercises, and these are breathing exercises (reported four times), relaxation exercises (3), progressive muscle relaxation (2), muscle loosening exercises (2), massage (1), and Yoga (2). The third sub-category “Mental relaxation” included meditation (3), and imaginal relaxation (1).

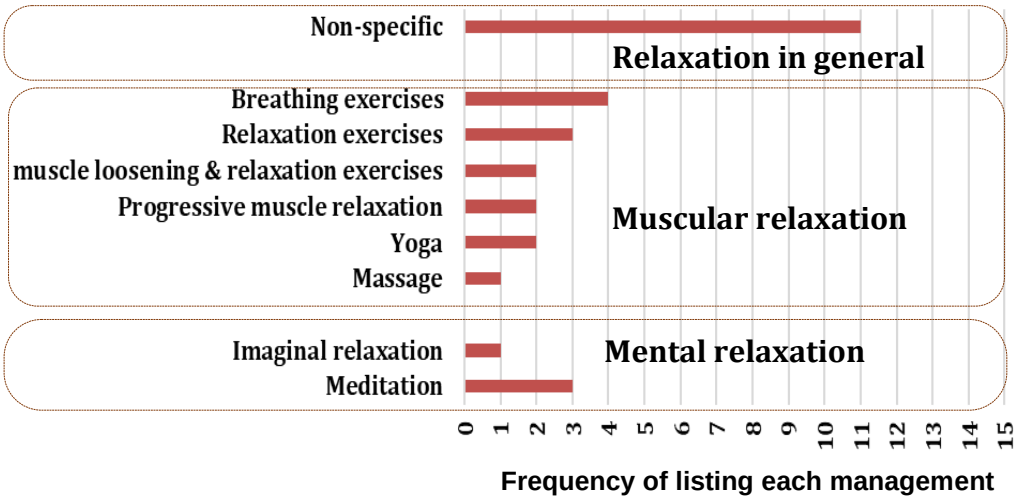


Figure 5.5 Relaxation techniques listed by the participants.
The figure shows the sub-categories and the frequency of listing each management.

5.4.4.1.3 Targeted management

Managing stress, tinnitus perception, and /or hearing impairment was reported 25 times (Figure 5.6). Sound therapy for tinnitus included the use of noise source, tinnitus maskers, or modifying the patients' sound environment. Few participants indicated the use of medical therapy; one of these was anxiolytic drugs. Tackling stress involved identifying the source of stress, and then using problem solving techniques to avoid or minimise the stress.

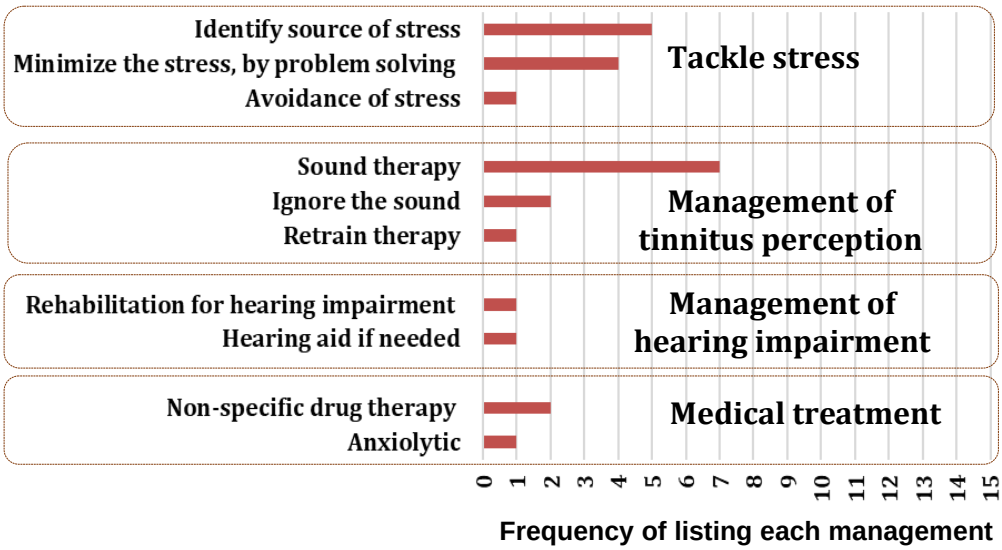


Figure 5.6 Targeted management listed by the participants.
The figure shows the sub-categories and the frequency of listing each management.

5.4.4.1.4 Referral to other specialities

Twenty-eight respondents said that they would "refer the patients to other specialities", and most to psychologists or psychiatrists for CBT. Others would refer patients to their general practitioners for counselling and stress management, to a tinnitus clinic, or to an ENT surgeon to rule out underlying ear diseases. Few respondents reported they would refer patients to non-clinical services such as local mental health services or a social worker who manage stress (Figure 5.7).

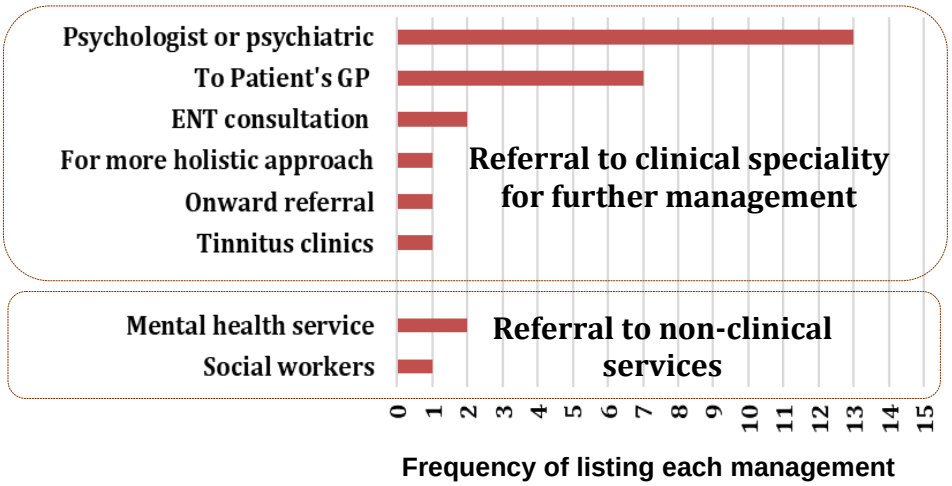


Figure 5.7 Clinical and non-clinical specialities where participants refer the patient for stress management.
The figure shows the sub-categories and the frequency of listing each management.
GP= General Practitioner, ENT= Ear Nose and Throat.

5.4.4.1.5 Signposting to resources for self-management

Respondents have signposted patients to various electronic materials such as CDs and e-books (Figure 5.8). Some smartphone applications were mentioned by respondents including the Calm App ("Calm Meditation and Sleep" is a smart phone application delivers mindfulness meditation (Huberty et al., 2019)), and applications that provide sound therapy and/ or mindfulness to tinnitus patients. Also, they signposted patients to resources such as the Improving Access to Psychological Therapies (IAPT) services and BTA websites which were the most signposted. One respondent reported referring patients to the Take on Tinnitus online course. Few respondents provided patients with written materials about stress and tinnitus to provide information for self-management.

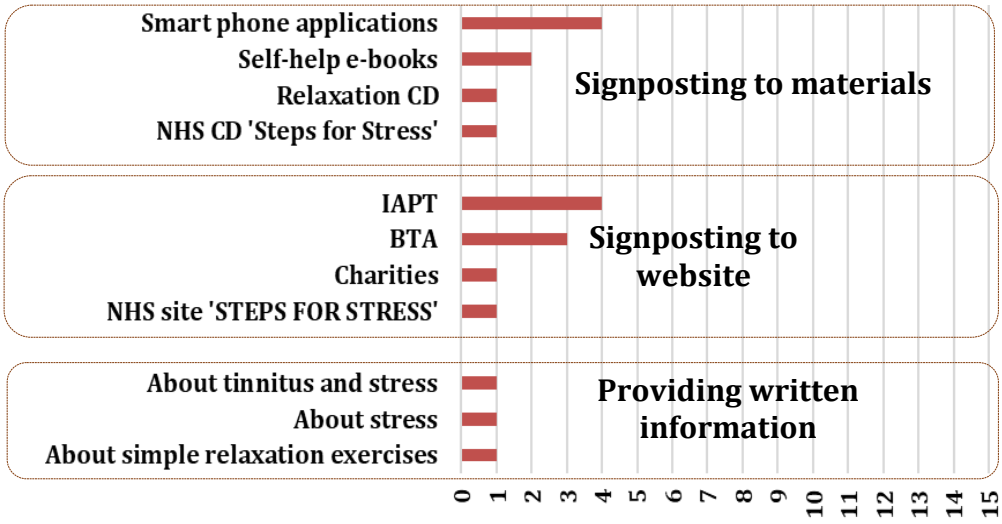


Figure 5.8 Resources for self-management as identified by the participants.
The figure shows the sub-categories and the frequency of listing each management.
CD= Compact Desk, NHS= National Health Service, IAPT= Improving Access to Psychological Therapies, BTA= British Tinnitus Association.

5.4.4.1.6 Providing advice to improve quality of life

Respondents reported that they provide advice to their patients that is not related to tinnitus and stress per se (Figure 5.9). This was classified into “Advice to improve health” and “Advice for self-care" sub-categories. The former includes advice about physical exercises, sleep management, eating habits and other standard health tips. The latter describes advice about engaging in different activities and building social connections.



Figure 5.9 Providing advice to improve quality of life
The figure shows the sub-categories and the frequency of listing each management.

5.4.4.1.7 Educating patients

This category represents spending time to educate and explain certain topics to the patient directly rather than referring them to another resource. Respondents would provide information about tinnitus and stress (4) or provide explanation about habituation (2).

5.4.4.1.8 Others

Use of acupuncture was reported by three respondents (*R16, Audiologist, Brazil; R24, Audiologist, Brazil; R52, Audiologist, USA*).

5.4.4.2 Difficulties in managing stress in tinnitus clinics

When respondents were asked to explain their reasons for not offering stress managements, four themes emerged.

5.4.4.2.1 Patient understanding and willingness to commit to stress management

This theme had four subthemes:

1. Patient's challenging thoughts/mind-set: Most respondents recognised that getting the patient to overcome certain thoughts can be challenging. Patients may fixate on tinnitus and finding a cure and therefore clinicians cannot get them to ignore tinnitus. Patients do not acknowledge stress, stress may affect tinnitus, and there is a link between tinnitus and stress. They may not accept they are stressed.
2. Patient engagement/motivation: Respondents said that it is difficult to motivate the patient to seek solutions and they are usually unwilling to reduce stressors, or struggle to engage in relaxation exercises. It is difficult to achieve compliance even when the resources available; patient do not comply once they leave the clinic. Lack of patient engagement is another difficulty in stress management.
3. Patients' lack of awareness/acceptance: Patients lack awareness of stress which makes it difficult to change attitudes toward stress management. They do not accept the occurrence of tinnitus. Counselling them that it may not go away is needed.
4. Patient's emotional state: The emotional state of the patient, such as anxiety, hopelessness, and inability to relax, may lead to difficulties in managing stress. Occasionally, talking about tinnitus may make the patient more stressed.

5.4.4.2.2 Factors that may affect clinicians' abilities tomanage stress

Two sub-themes describe the difficulties related to clinicians' knowledge and confidence to manage stress:

1. Clinician lack of skill/training: Lack of training or skill and resources for training makes the respondents unable to address stress and stressors that affect the patient.
2. Clinician knowledge about stress assessment and management: Several respondents said that they face difficulties as they lacked knowledge about managing stress and they cannot solve patient's problems. This means they are not confident to give the right advice or management, and they are uncertain about the effectiveness of the management if they offer it. They considered stress management is out of their experience and prefer to refer the patient to qualified personnel; they have an issue with deciding who needs referral for specialist care.

5.4.4.2.3 Factors related to management setting

A small number of the respondents indicated issues that arise when they conduct clinical sessions or refer patients to other speciality or to self-management.

1. Clinical referral pathway/ triage is not optimal: Respondents indicated that there is a lack of resources and efficient stress management programmes or care planning. Access to other services and specialised support is not sufficient. Onward referral of

patients to already busy clinics is associated with a long wait list which can lead to loss of follow up.

2. Conducting the clinical sessions: A small number of respondents reported specific difficulties related to tinnitus. These include managing patient's expectation during the clinical appointment, exacerbating tinnitus while discussing it, and overcoming barriers posed by hearing loss.
3. Difficulties in carrying out self-management: A few respondents reported that managing stress and managing habits outside of the clinic are patient's task and their compliance is required for self-management. Respondents identified a lack of resources to support self-help.

5.4.4.2.4 The nature of stress and its relationship with tinnitus

This theme represents difficulties that are related to the nature of stress. It is not practical to identify or avoid the stressors and stress cannot be eliminated. Each type of stressor that the patient faces require different focused management and management strategies should be patient-tailored approach. Respondents mentioned that it is difficult to understand the cause-effect relationship between tinnitus and stress, and how to break this cycle.

The themes, sub-themes, the number of participants in each sub-theme, and example quotes are listed in Table 5.7.

Table 5.7 Outline of themes and sub-themes of the difficulties that prevent the respondents from offering stress management.

Theme	Sub-theme	N	Example quote
Patient's understanding and willingness to commit in stress management	Patient's challenging thoughts/mind-set	19	"*Most often they come to the audiology clinic wanting you to give some medication that can cure the tinnitus. The therapy is not enough, they want absolute cure". (R23, Audiologist)*
	Patient engagement/motivation	16	*"Patient agreeing to take consistent time for themselves to manage it." (R35, Audiologist)*
	Patients lack awareness/acceptance.	8	*"Getting them to believe in it, committing" (R43, ENT surgeon)* *"a lot of patients don't feel stressed or don't acknowledge it as a factor even when you explain the links." (R27, Audiologist)*
	Patients emotional state	6	*"Belief there is nothing they can do" (R52, Audiologist)*
Factors that may affect clinicians' abilities to manage stress	Clinician Lack of skill/training	10	*"I Feel able to identify stress but don't feel qualified to give stress management advice." (R53, Hearing therapist)*
	Clinician knowledge about stress assessment and management	9	*"That a lot of what a patient needs is not in my scope of practice almost always necessitating a need for referral." (R47, Audiologist)*
Factors related to management setting	Clinical referral pathway/ triage is not optimal	7	*"Lack of direct support from either GP's or psychology or any other health professional who has more mental health training & awareness than I. " (R61, Audiologist)*
	Conducting the clinical sessions	3	*"The fact that talking about their tinnitus makes them aware of it and therefore more stressed." (R44, Psychotherapist)*
	Difficulties in carrying out self-management	6	*"Changing/managing habits outside of the clinic." (R6, Audiologist)*
The nature of stress and its relationship with tinnitus		9	*"It's sometimes really diffuse and you don't know what came first - tinnitus resulting in stress or the other way round." (R10, Psychologist)*
Not relevant and no answer (excluded)		10	

N represents the number of respondents with data coded at each sub-theme. The respondents ID (Rn) and their professions are stated at the end of each quotes.
ENT= Ear Nose and Throat, GP= General Practitioner.

5.4.4.3 Reasons for not offering stress management

Nine respondents reported they do not offer management for stress. Only eight explained the reasons behind this. Stress generally is not acknowledged properly and there is a limited information available about management techniques.

> *"I have limited knowledge on what to suggest, other than relaxation techniques and evaluating what might be their stress trigger." (R28, Audiologist, UK).*

Respondents said that they may lack confidence to manage stress and they are not qualified to give advice, so they prefer to refer the patient to another speciality.

> *"I do not feel qualified to do so - I am a junior member of staff and refer on people with bothersome tinnitus to specialists in the depth who will offer stress management suggestions." (R14, Audiologist, UK).*

> *"It's not part of my therapeutic approach to offer practical management - my approach is exploratory." (R44, Psychotherapist, UK).*

Lack of training or required skills is another barrier to providing management.

> *"I feel I do not have the skill set to address patient's level of stress and give appropriate management options to combat it. It is not something I have received training in." (R13, Practice Education Co-ordinator, Ireland).*

5.4.5 Discrepancies in assessing and managing stress across different professional roles and years of experiences

57.5% of the 40 audiologists reported they always assess stress, 32.5% sometimes did, and only 10% never assessed stress. This trend is similar for other professionals where 51.8% (of the 37 other professionals) assessed, 40.74% sometimes assessed, and 7.4% never assessed stress.

Regarding management of stress, 45% and 42.5% of audiologists always and sometimes offered stress management for tinnitus patients. 62.96% of other professions offered management and 25.92% sometimes did. The percentages of audiologists and other professions who did not offer stress management to tinnitus patients were 12.5% and 11.1% respectively. Figure 5.10 illustrates the breakdown of percentages across all professions.

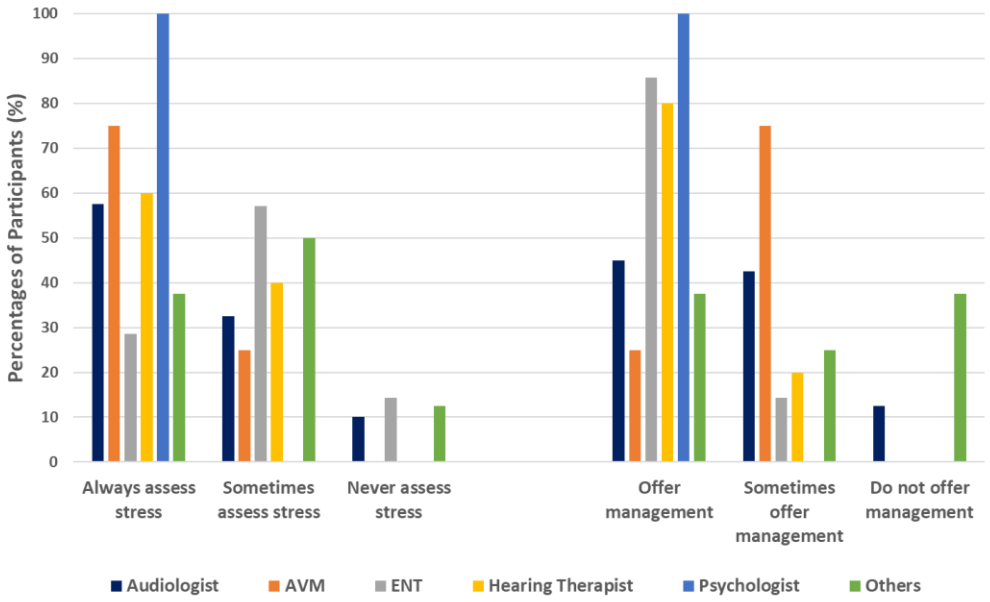


Figure 5.10 Stress assessment and management offered by different specialities.
The percentages of respondents in each professional category and their answers to the close-ended questions about performing stress assessment and providing management.
AVM= Audio-vestibular Medicine, ENT= Ear Nose Throat.

Regardless of the level of experience, most respondents would always or sometimes assess stress and offer stress management. Among those who were working in the same job role for 1-4 years, 21.4% never assessed stress and 28.57% did not offer stress management. The percentages of respondents who never assessed stress nor offered management was lower among respondents with longer experiences (as listed in Table 5.8).

Table 5.8 The frequency and percentages of assessing and managing stress

Years of experiences	1-4 years (N=14)		5-7 years (N=12)		8-10 years (N=9)		> 10 years (N=32)	
	N	%	N	%	N	%	N	%
Always assess stress	4	28.57	**7**	**58.3**	**5**	**55.56**	**19**	**59.4**
Sometimes assess stress	**7**	**50.00**	3	25.0	4	44.44	12	37.5
Never assess stress	3	21.43	2	16.7	0	0.00	1	3.1
Offer management	4	28.57	**8**	**66.7**	**6**	**66.67**	**16**	**50.0**
Sometimes offer management	**6**	**42.86**	3	25.0	2	22.22	13	40.6
Do not offer management	4	28.57	1	8.3	1	11.11	3	9.4

The bold text indicates the highest frequencies and percentages in each category

N= Number of participants.

5.4.6 Respondents' comments and feedback

Twenty-one respondents added comments and four added feedback that reflect their thoughts about stress and tinnitus. Four respondents agreed on the existence of a relationship between tinnitus and stress

"Exercise stress and Tinnitus, odd link I've seen a number of times" (R54, Hearing therapist)

"I always explain to patients how tinnitus is often an indicator of stress, and although it adds to their stress, the real target of change is often in reducing and managing stress (not reducing and managing tinnitus per se). I tie this to the habituation model and use it to motivate patients into reducing their stress, e.g. changing behaviours and practicing relaxation (as this is really hard for some people) and also see if it can give them a

sense of control over their experiences a bit more." (R34, Psychologist)

One respondent had observed changes in tinnitus levels when patients adapted stress relieving strategies

"I have a couple of patients in meditation, Ti (Tai Chi), and Yoga that feel way much better dealing with stress and that their tinnitus is now bearable." (R33, ENT Surgeon)

One respondent recognised the potential role of glucocorticoids measurement in stress assessment:

"Stress assessment by checking the corticosteroid can be useful in specific patient only. Because some pts (patient) with some ch. (chronic) disease already on Steroids." (R4, General physician).

Respondents commented on the importance of increasing patient's understanding of stress and tinnitus either by discussing the topic during tinnitus assessment or providing the clinicians with guidance about sources for written information.

"I think it is really important to talk about stress as part of a tinnitus assessment. I think it is really important for 1st line healthcare professionals such as GP's to recognise that telling patients they just need to "live with the tinnitus" increases the patients stress and anxiety." (R32, Clinical Scientist)

“I would love to have some general guidance that I can give my patients - preferably written or pointing to a website, so that they can follow it up when they are ready.” (R14, Audiologist)

Training for audiologists is also required to help them understand the link between tinnitus and stress and possible management techniques

“I feel that that there should be some form of training for all Audiologists at any level of their work to be able to recognise this connection and be able to help the patient more effectively and timely. I'm only thinking of a couple of hours or a half day training similar to that is available for suicide awareness.” (R61, Audiologist).

“Many people are managing tinnitus outside of ENT and audiology and we need better awareness about treatment and management options across all areas of healthcare.” (R9, Specialist nurse)

Alternatively, stress can be managed by other professionals. However, patients may come to audiology clinics with unmanaged stress as some patients may be reluctant to accept that they are “stressed”

“We see many patients with stress as a comorbid factor. Sometimes they are already talking to other services and GP to help manage stress but also, we see people who are living with stress unmanaged. Often this is due to a reluctance to accept the levels of stress they have and also to seek any help.” (R29, Audiologist)

Additionally, the required health services may not be available in certain countries or regions.

"In Sub-Saharan Africa there is limited or no tinnitus therapist so treating such patients is quite challenging." (R23, Audiologist)

5.5 DISCUSSION

The respondents to this survey had different professional backgrounds. The majority were audiologists and from the UK. There were no differences between those who were based in the UK and those from other countries in terms of years of experiences and number of patients per week. Although this survey was open to any professional who was involved in tinnitus care, there were no GPs or family physicians among the respondents. One respondent was specialised in general medicine which is not a usual profession that forms part of tinnitus management pathways. GPs and family physicians are very often the first clinical contact for tinnitus patients. Some of them will attend an appointment within the secondary care. For example, a survey of GPs in the UK showed that 37% of tinnitus patients were referred to secondary care (El-Shunnar et al., 2011) and 31% of tinnitus patients were referred in Ireland (Kilroy and El Refaie, 2020). In a survey of tinnitus patients in the UK, 76.6 % reported that they were referred to secondary care after one or more GP appointments (McFerran et al., 2018). Some respondents to our survey said they would refer patients to their GP for stress management. The results of this survey represent findings within the secondary care level as we could not obtain details on how stress is

assessed and managed within a primary care setting. Therefore, further research to develop guidance for tinnitus assessment in primary care is needed. This was recognised by NICE (2020) as a key area for research.

The respondents defined stress under four different themes. Stress was mostly defined as demands exceeding the resources or inability to overcome difficulties which are more related to the concept of stress as stimulus and perceived. Some respondents defined stress as a response to stressors or as emotional interactions. The definitions given by the respondents have captured the meaning of stress as defined in literature. However, none of them defined stress under the three main concepts, that are response-based, stimulus-based, and transactional-model-based definitions, collectively.

Identification of stressed patients was mainly based on a wide variety of emotional and physical signs during the clinical sessions. The respondents subjectively detect the presence of these signs. The listed signs are not specific or diagnostic for stress. For example, shortness of breath and worry are symptoms of anxiety, and lack of enjoyment occurs in depression, as specified in the Diagnostic and statistical manual of mental disorders (DSM-5®) manual book (American Psychiatric Association, 2013). Anxiety and depression are common in tinnitus patients (Belli et al., 2008, Pattyn et al., 2016) and therefore NICE tinnitus guidelines (2020) provide further and detailed steps to assess anxiety and depression by a healthcare professional competent in mental health assessment.

Most respondents assess stress during the clinical session. Yet, it seems that they do not rely on the use of validated instruments. HADS (Zigmond and Snaith, 1983), which has been found to be reliable in detecting anxiety and depression -but not stress- in a hospital and out-patients setting (Snaith, 2003), was reportedly used more frequently than other questionnaires in this study, and previously as reported by Hoare et al. (2015). This might be because most tinnitus guidelines recommend the use of HADS (Fuller et al., 2017). Few respondents said they use the Clinical Outcomes in Routine Evaluation–Outcome Measure (CORE-OM) which is not stress-specific but used to assess domains of well-being, problems/symptoms, life function, and risk that related to the psychological wellbeing (Evans et al., 2002). Few respondents reported using perceived stress instruments such as the DASS, PSS, and PSQ. Tinnitus questionnaires were listed, not including the TQ which is recommended by NICE tinnitus guidelines (2020). Tinnitus questionnaires can provide an important tool to assess the problems tinnitus patients face (Tunkel et al., 2014), in particular, if they focus on emotional and psychological effects (Kennedy et al., 2004). These includes THI (the most commonly used tinnitus questionnaire in the European countries (Cima et al., 2020)) and the THQ, both of which include questions that mention "*stress*" (as described in 4.1). These questionnaires have a higher proportions of questions relating to psychological/ emotional effects of tinnitus than the TQ (Kennedy et al., 2004). However, there is no recommendation on which instrument should be used to assess the level of stress in tinnitus

patients. The recommendations for specific questionnaires to measure psychological symptoms varied between different countries, for example, the Dutch and Swedish guidelines recommend the use of the HADS, and USA guidelines have not mentioned any tool (Fuller et al., 2017, Tunkel et al., 2014). NICE tinnitus guidelines (2020) were published after the launch of this study. Previously, NICE issued a clinical knowledge summary for tinnitus (last updated in 2017). This summary had less information about managing stress and it is no longer available online. We may see more consistent use of TQ and TFI to assess tinnitus-related distress across clinics particularly in the UK when they follow the recent NICE tinnitus guidelines.

Respondents reported different management strategies they offer patients. However, it is not clear whether the respondents will apply the management by themselves or they will refer the patient to a mental health professional. Some respondents said they would refer the patients to other clinical professionals either for further management or to explore possible pathologies underlying tinnitus. However, referral means that patients would go to a waiting list which can last for weeks or months. This was acknowledged by few respondents as a cause that lead to loss of the follow up. Some respondents would rather refer the patients to self-management resources for tinnitus and stress. The interest in electronic resources for tinnitus in terms of providing information, assessment or management has been growing recently (Kleinjung and Langguth, 2020). Self-management resources have a promising role in managing tinnitus either as a sole strategy for those

who have mild tinnitus level or between clinic visits for those who have high tinnitus level (Smith et al., 2018). However, engaging in self-management programme requires patient's compliance. Respondents identified potential patient-related barriers to managing stress such as the patients' mind-set, their willingness to engage, and their emotional status (5.4.4.2). Negative thinking patterns are related to stress, either directly or indirectly (Abbas et al., 2019) which can be a recognisable barrier in managing stress. Patient's understanding and willingness to commit to stress management can be improved by educating the patients about the nature of tinnitus and stress (Henry et al., 2010). Searchfield et al. (2020) recently proposed that a single tinnitus instruction and counselling session can show a promising result in managing tinnitus. Respondents would provide advice to improve the quality of life, or health tips, which is a non-specific management but helpful in improve individuals' resilience needed to overcome stressful situation. Therefore, educating patients about tinnitus, stress, and adopting healthy lifestyle can be integrated as part of tinnitus education programmes.

Most psychological and relaxation therapies listed by the respondents as stress management options, such as mindfulness, CBT, and muscle relaxation are also used to manage the impact of tinnitus (McFerran et al., 2018, Cima et al., 2020). The efficacy of these therapies on managing stress was subjected to systematic reviews and meta-analyses. Mindfulness positively improved the stress levels as measured by self-reported and biophysiological measurements as

reviewed by Sharma (2014), and it moderately reduced perceived stress (Burton et al., 2017, Bartlett et al., 2019). Lau et al. (2017) reviewed the efficacy of therapist-supported internet-based CBT and found that it effective in eliminating stress symptoms compared to control groups. There was no evidence on the effectiveness of relaxation on reducing stress (Ravalier et al., 2016). Therefore, it is possible to use mindfulness and CBT in managing tinnitus and stress at the same time. CBT may be the most suitable intervention that can be used to manage tinnitus impact (Brüggemann et al., 2018, Hesser et al., 2012) and stress (Granath et al., 2006, Varvogli and Darviri, 2011). It has been modified for tinnitus management and it is recommended to decrease tinnitus-related distress, fear, disability, and tinnitus-related cognitive problems (Cima et al., 2019, Fuller et al., 2020). It is highly accepted by tinnitus patients (Aazh et al., 2016), and it can be delivered online (Beukes et al., 2018).

Nevertheless, some of the 20 treatments have been listed in the category “psychological treatments.” (Figure 5.4) can be part of one other (Ong et al., 2004). For example, CBT is a form of talking therapy (Marshman and Williams, 2017), and the differentiation between these types of management requires in-depth understanding of each one. Respondents to this survey said that they lack the knowledge about stress managements and skills required to manage stress. Hence, it is essential to train and educate healthcare professionals about different strategies to manage stress that are also valid to manage tinnitus-related distress. Implementing training programmes to improve the

knowledge about stress may benefit those who have regular contact with tinnitus patients but less experience in psychology. Those include audiologists, ENT surgeons, and audio-vestibular physicians.

Targeted management was identified by the respondents as an important step to manage stress and tinnitus. They said that tackling and removing sources of stress if possible, managing hearing impairment, and sound therapy for tinnitus are some options. Tunkel et al. (2014) recommended the use of soothing sounds not only to offer distraction from tinnitus, but also to aid relaxation and stress-relief.

The nature of the relationship between tinnitus and stress is not fully understood, therefore the approach in managing both at the same time is important. Also, educating the patients and health professionals about the most valid methods to assess and manage stress is vital in improving the health service provided for tinnitus patients.

5.6 CONCLUSION

Regardless of how they defined the word “stress”, most participants in this survey have assessed and managed stress in tinnitus clinic. Besides recognising that they lack knowledge and training to provide the suitable stress management, they identified several barriers that are related to the patients, the clinical settings, and the nature of stress. These barriers can be overcome by identifying the most effective stress management that can be implemented in tinnitus clinics and primary care.

5.7 LIMITATIONS OF THE STUDY

This survey was availabe online and open access which may lead to selection bias of interested respondents that limit the generalisability of the result (Eysenbach and Wyatt, 2002). I indicated earlier that primary care level is not represented in this study as there was no responses from health care professionals who work at that level.

In addition, the responses came from different countries. Few countries had clear tinnitus guidelines before the launch of this study, mainly USA (Tunkel et al., 2014) and European countries (Cima et al., 2019). The findings of this survey did not show any differences between UK-based and overseas professionals in the frequency of assessing stress or offering management.

The response rate was not high. 1241 people accessed the first page only which includes information about the study. Forty-two people withdrew from the survey when asked to define stress. The reason of leaving the survey is not clear and it is not possible to find out the reason as the respondents could withdraw without giving one. It may be that this topic is challenging for some people or out of their expertise.

CHAPTER 6 GENERAL DISCUSSION AND CONCLUSIONS

The main aim of this thesis was to examine the relationship between tinnitus and stress. Examining such a relationship appears to be challenging mainly because of the multidimensional or heterogenous natures of both tinnitus (Cederroth et al., 2019) and stress (Simmons et al., 2020). Therefore, I followed a new approach in this thesis to explore this relationship from a range of different perspectives and methodologies. Firstly, I examined the similarities between tinnitus and stress in the literature, then using scoping review methodology, I catalogued the evidence (or lack of) for this relationship. The findings of the literature and scoping reviews directly informed the design of the longitudinal cortisol study in which I examined stress using specific measurements that assess the three different concepts of stress (stimulus-based, response-based, and the transactional model). I examined whether HCC differs between tinnitus and non-tinnitus participants, and whether it correlated with self-reported and psychoacoustic measurements of tinnitus, and whether the change in hair cortisol levels were associated with changes in tinnitus. Due to the diverse understanding of the concept of ‘stress’ and how this could influence the relationship between stress and tinnitus, I conducted a concept mapping study to explore how people who have tinnitus define the word ‘*stress*‘. I also looked at the definition of stress from the perspective of health professionals who manage tinnitus patients and evaluated how they assess and manage tinnitus-related stress.

The findings of this thesis give new insight into the relationship between tinnitus and stress which can be used to inform future studies about stress-related disorders and about tinnitus distress (i.e. stress that attributed to tinnitus). Hereafter, I summarise the key findings.

6.1 KEY FINDINGS

6.1.1 The importance of refining the methodological approach to reach a conclusion about the relationship between tinnitus and stress

The main drawback of previous studies was their methodological approach. Studies tended to assess one or two aspects stress and ignore the others. Through the review, I found that the studies mainly assessed the perceived stress associated with tinnitus level in varying degrees, depending on the questionnaire measure used in the study. For example, the strength of correlations between tinnitus level and self-reported stress levels varied according to the instrument used. Therefore, there were discrepancy reported across the findings. Additionally, I found that there was a lack in reporting the effect of stress on the psychoacoustic measurements of tinnitus. It was therefore not clear whether stress, assuming stress does affect tinnitus, changes the perception of tinnitus or not. Exploration of this idea could clarify whether the stress response would lead to neurological changes in the auditory areas. The variability in the methodologies of the reviewed studies made it difficult to draw definitive conclusions about the relationship between tinnitus and stress. Similarly, studies into the relationship between stress and other health disorders were mostly

inconclusive for the same reason. For example, Baum et al. (2011) could not characterise the relationship between stress and cancer due to the variability in methodology; most studies were retrospective, focused on stress and quality of life, or lacked uniformity in stress measures. Nevertheless, improving the methodological approach could lead to solid conclusions. For example, rigorous research about the role of early and recent life stress, genetic, and the role of different stress biomarkers in depression and cardiovascular diseases led to identification of the role of corticotropic releasing hormone (CRH) and early life stress in developing depression (Gutman and Nemeroff, 2011) and stress-eating, and cardiometabolic disorders in the relationship between stress and heart disease (Brooks et al., 2011). Moreover, it is also important to note that each type of stress measurements (stimulus-based, perceived measures, and biophysiological) relates to different underlying mechanisms, predicts different aspects of illness, and is associated with different disorders (Monroe, 2008). In a commentary from the National Institute of Mental Health (NIMH) in the United State, Simmons et al. (2020) recommended to consider the complexity of stress and to search for 'mechanistic links' between stress and mental disorders. They highlighted the importance of assessing multiple variables when studying the stress-associated risks for psychopathology. These variables can be contributing or protective factors against the impacts of stressors such as social support and cognitive function. Weckesser et al. (2019) stated that subjective and objective stress measures should ideally not be considered as fully

interchangeable instruments, as they probably assess different underlying physiological and psychological mechanisms.

Taken together, there is an emphasis on adopting a more comprehensive approach to studying the link between stress and tinnitus. In my longitudinal cortisol study, I measured stress using stimulus-based, perceived measurements of stress, and HCC to identify which of these assessment tools is more relevant to tinnitus than the other. Also, I assessed the social support as a modulating factor to cortisol and cognitive functions that may be modulated by HCC in tinnitus population.

6.1.2 Identifying the mechanistic links between stress and tinnitus

The main finding of the hair cortisol study was that there were no significant correlations between the total stress levels and the global tinnitus scores, nor with its psychoacoustic characteristics. The level of stress was not significantly different in the tinnitus population from the non-tinnitus population. This indicates that stress might not have a role in developing tinnitus. Therefore, the link between stress and tinnitus is not as clear as previously presumed. Yet, it was possible to identify some links between aspects of stress and some domains of tinnitus complaint.

6.1.2.1 The role of cortisol in tinnitus

Cortisol was the most studied stress biomarker in tinnitus in the reviewed studies, yet the review showed that the findings depended on the setting of the study and time of collecting the sample. They reported

a discrepancy in terms of the differences in cortisol levels between tinnitus and non-tinnitus participants (Table 2.4). I found no significant differences in HCC between the groups (TP vs NTP), however HCC was significantly correlated with tinnitus impact on sense of control and sleep. Although these correlations were not significant at the second visit, they had the same strength and direction. Regression analysis showed an association between HCC and tinnitus awareness when adjusted for DHS and DASS-D. Regression analysis showed that the change in TFI scores were more likely to be predicted by the preceding HCC than the following HCC.

The question whether cortisol plays a role in tinnitus can be partially answered here. Change in the long-term secretion of cortisol is associated with some tinnitus problem domains but not the global impact of tinnitus. It has been suggested that the change in cortisol secretion pattern during the day is more relevant to developing diseases (Leng et al., 2019). HCC does not assess the pattern of cortisol secretion (i.e. the circadian rhythm or the momentary pulsating of cortisol secretion). Therefore, the theory that cortisol could play a role in developing tinnitus is still possible.

6.1.2.2 Daily hassles and perceived stress

Daily hassles and perceived stress correlated significantly with tinnitus-related emotional distress (TFI-E). Previous studies also showed positive correlation between perceived stress and tinnitus when the later was assessed with questionnaires that assess tinnitus distress (e.g. TQ and THI; as seen in Table 2.3). This finding may help in

classifying tinnitus patients accordingly and in prioritising stress management in those with high TFI-E scores.

6.1.2.3 Exposure to stressful life events has no role in tinnitus levels

Contrary to the general believe about the role of exposure to stressful events in developing or exacerbating tinnitus, this thesis found no association between recent life changes and tinnitus. There are few studies that have assessed the impact of life events on tinnitus. Jackson (2019) reported negative correlation between SRLE and T-VAS severity, and Basso et al. (2020) reported tinnitus was more bothersome in those reporting traumatic or negative stressful events. In contrast, in this thesis, I found that the strength and the direction of the correlations between recent life event (measures by stimulus-based instrument the RLCQ) and TFI sub-scales changed in the second visit (i.e. the strength increased or decreased, and the direction changed from positive to negative or *vice versa*). Also, the perceived level of tinnitus impact was not significantly different between those who experienced a stressful event in the month before the first visit and those who reported no event. In line with this, Morrison and Bennett (2009) found that SRRS (the scoring of RLCQ) had only a weak association with developing diseases, and Gerber et al. (1985) reported no significant correlation between SRRS scores and the severity of tinnitus. This support the finding of this study that there is no correlation between the recent life changes and tinnitus levels. Therefore, these

results would suggest that life events do not predictably contribute to tinnitus-related stress.

6.1.3 Mapping the concept of stress

6.1.3.1 The importance of defining '*stress*'

As discussed in Chapter 1, there is no consensus definition of stress which may have led to the ambiguity of understanding around the word '*stress*' (Simmons et al., 2020, Kagan, 2016). The scoping review showed that stress was not clearly defined in many studies. This might have had an unexpected impact on the findings of the studies, especially those that assessed stress using single item measurement (e.g. S-VAS) and studied the onset of tinnitus and stress. The concept mapping study showed that people who have tinnitus have different conceptualisations of 'stress'. The variety in definitions given by participants may have resulted from their personal experiences and from the use of the word stress in varying contexts (Simmons et al., 2020, Kagan, 2016). This could have impacted on the opinion of tinnitus patients about the direction of the relationship between tinnitus and stress. As seen in Figure 4.5, more than half of the participants believed that stress is a causative or exacerbating factor for tinnitus. In contrast to participants in the concept mapping study, some clinicians, when asked to define 'stress', used the biophysiological response as a definition of stress. This reflects how personal experiences and general knowledge could affect how a person defines 'stress'. This supports the importance of using a validate questionnaire to assess stress that covers multiple concepts.

6.1.3.2 The meaning of the word ’stress’ in tinnitus

The majority of generated statements in the concept mapping study referred to internal factors that associated stress with feelings and emotion. In contrast, most generated statements by health professionals reflected increased demands or inability to overcome challenges. This shows that tinnitus patients mostly consider stress as an internal locus of feeling while health professionals externalise the concept of stress.

However, 'Compromised ability' (the inability to relax, cope, control or to escape a stressful situation) was considered an important element of stress by all groups, and sense of control was highlighted as an important domain that connects stress and tinnitus.

6.1.4 Inconsistency in assessing and managing stress

Regardless of the level of the professional experience, there was a lack of knowledge about the best stress management or a clear clinical triage. This was reflected in the variety of management options offered to patients identified as 'stressed’. Stress management options, such as CBT, are already used to manage tinnitus, and have been shown to be relative effective in managing tinnitus (Fuller et al., 2020, Landry et al., 2020) and stress (Lau et al., 2017, Hopkinson et al., 2019). In forthcoming clinical guidelines, a consensus about the management pathway, which can be used as a reference when referring stressed tinnitus patients, should be implemented.

Health professionals have demonstrated various ways to identify patients exhibiting stress, including looking for many stress signs and

symptoms. Among all tinnitus questionnaires that are regularly used in research and in clinical assessment, the TFI is the only questionnaire that assesses tinnitus impact on sense of control (Fackrell et al., 2014). TFI-SC scores, which correlated with HCC, can help in clinical assessment and in prioritising psychotherapies that improve sense of control. Additionally, stress scores (DASS-S and DHS) were found to correlate with the emotional impact of tinnitus (TFI-E subscale scores) which means the latter can be used to assess emotional stress. The TFI is recommended by NICE tinnitus guidelines (2020), evaluated in UK-based population (Fackrell et al., 2018), and is the second most commonly used questionnaire in tinnitus clinics in the UK (Hoare et al., 2015). For these reasons, it is possible to implement a clinical pathway to manage tinnitus patients based on their TFI-SC and TFI-E scores.

6.2 STRENGTHS OF THE FINDINGS

A. Using novel approaches: This is the first time that long-term cortisol production has been measured in a chronic tinnitus population and compared with cortisol levels in non-tinnitus participants. Also, the three concepts of stress were measured and examined in this thesis, which has seldomly been investigated in tinnitus and stress research. This approach seems to give better insight into the relationship between stress and diseases.

B. The relationship between stress and diseases can be affected by multiple confounders which I have controlled through the inclusion criteria and statistical analyses.

C. The longitudinal study provided a two-point assessment in the same participants which helped in identifying the unchanging correlations that could represent the links between tinnitus and stress.

D. Statements generation, rating and sorting in the concept mapping study were completed online by the participants. Web-based approach minimises the influence of the researcher on the participant's opinion (Rosas and Kane, 2012). Participants were supported and allowed to send emails if they had general enquiry about the tasks.

E. The targeted number of participants in the concept mapping study was achieved. More than 40 participants completed the sorting activity which led to generating a point map with acceptable stress index.

6.3 LIMITATIONS AND CHALLENGES

A. In the main study, I applied strict inclusion criteria and consequently most recruited participants had mild-moderate tinnitus. This might also lead to an error in the estimated association between tinnitus and stress.

B. Issues with the recruitment: None of the participants recruited had recent onset tinnitus. In 2018, McFerran et al. (2018)

surveyed people who have tinnitus and found that almost half of them reached their GPs within three months of tinnitus onset. It usually takes time to evaluate the potential underlying causes of tinnitus, which were exclusion criteria for this study. Therefore, by the time the patients reached ENT/Audiology they were no longer considered recent onset. Although we actively recruited online through advertisement on social media, the BTA and public events (see 3.3.3.3), only three people with recent onset tinnitus contacted me. However, none of them met out inclusion criteria.

C. Participants were required to attend the visit in NIHR Nottingham BRC. This led to losing potential participants who needed to travel for a long distance.

D. It was not possible to examine whether HCC can be used as an objective tool as none of the participants in the cortisol study received any new treatments before the second visit. Tinnitus patients do not find tinnitus management effective (McFerran et al., 2019) and therefore they may not comply with management offered.

E. This thesis was limited in not considering the role of attention control in tinnitus. There is evidence that attentional process is important for tinnitus habituation as tinnitus becomes more bothersome when there is a malfunctioning attentional process (Cima, 2018). Many tinnitus management techniques such as CBT and sound maskers aim to draw the person's attention from

their tinnitus (Han et al., 2009) which may lead to alteration in the attentional neuronal network and subsequently may lead to habituation of tinnitus (Shahsavarani et al., 2021). The thesis found that the level of HCC was positively correlated with the tinnitus-related sense of control. I suggested that the neuronal activity within the dACC may have a role in this association. It is believed that ACC plays a significant role in attention control (Crottaz-Herbette and Menon, 2006, Sarrias-Arrabal et al., 2022). This area showed stronger connectivity with the hippocampus after exposure to daily stress (Ren et al., 2022). It is believed that attentional process is affected by stress and therefore tinnitus is more bothersome due to exposure to stress (Cima, 2018). This suggests the importance of the attentional network in the relationship between tinnitus and stress which warrants studying in future research.

F. Although I attempted to assess factors that may influence the studied relationship, many confounders can be complex and require more sophisticated instruments to be measured. According to the transactional model of stress (Lazarus and Folkman, 1984) social support is part of the resources that can help the person to cope with the stressful situation, and therefor minimise the perceived stress. Social support can affect coping with stress and plays a part in appraisals and reappraisals of the stressors (Jacobson, 1986, Cobb, 1976). This indicates the close relationship between stress and social support and their potential

effects on health. Social support is a multifaceted concept and there is a wide variety of instruments that has been developed to measure it (Kocalevent et al., 2018, Schwarzer and Knoll, 2007). Multiple types of social support have been identified (Cyranowski et al., 2013), and are commonly mentioned by researchers in their studies. Each type refers to certain construct of social support as summarised by Östberg and Lennartsson (2007) and Finfgeld-Connett (2005) Emotional support refers to the availability of someone who can show concern and empathy so the person can talk to about problems. Instrumental support refers to help with material needs for example financial support or providing tangible goods. Meanwhile informational or appraisal support is the availability of advice or information. Companionship or the availability of reliable social network is also seen as support (ibid). These types are described as received social support in contrast to perceived social support which is the person's belief about the amount and the quality of support potentially available from their social contacts (Wang et al., 2018, Gottlieb and Bergen, 2010). The received and perceived social support measures are mildly related (Haber et al., 2007) which indicates that each has separate effect on health. The strength of the relation between received and perceived support is possibly greater when the person received the support when it mostly needed (Melrose et al., 2015), so the timing of receiving the social support is important factor in

studying its effect on health. Many studies reported that perceived social support measures are better at predicting the status of mental health than the received social support (Yu et al., 2021). Also, social support level will vary between individuals based on many factors like their social class, age, cultural differences, and working conditions (Kessler et al., 1985, Sarla et al., 2020). Nevertheless, the support can be delivered by using different methods including in-person, group meetings, and online support (Cole et al., 2017). Therefore, there are many aspects of social support that have not been covered in this thesis. I did not ask the participants if they had received any support before or during the study, so this can be considered as a limitation. .

G. As mentioned in 3.8, there are many factors that can affect stress levels as measured by self-reported instruments. These factors include sleep quality, personality, and coping. For example, bias in self-reported stress assessments can result from low self-efficacy or high neuroticism (Weckesser et al., 2019). Personality trait of neuroticism determines how the person reflect on the experienced event. They could perceive the event as highly stressful, report more stressful events in a given period, and react negatively to these events (Udayar et al., 2021). So, this could affect the daily hassles and the perceived stress measurements. Nevertheless, some factors can affect each other. Neuroticism was negatively related to domains of social

well-being and perceived social support (Udayar et al., 2020, Yu et al., 2021). Following an active coping strategies like task-centred approach and the availability of social support could buffer the effect of stressful situations (Bouteyre et al., 2007). In this thesis, the duration of tinnitus varied among the participants (see 3.6.2.4, and 4.11). The participants could have received social/medical support and learned how to cope with their tinnitus. The result of the service evaluation study in this thesis showed how stress is managed in tinnitus clinics (see 5.4.4). We can assume that the participants had received informational social support, psychological management, relaxation exercises, or another management that can indirectly improve their coping strategies with stressful situations. This might have decreased the level of perceived stress. But personality trait and sleeping quality which might have affected perceived stress were not assessed. As these factors were not assessed in this thesis, the findings of the studies should be taken with cautions.

6.4 FUTURE DIRECTIONS IN RESEARCH AND CLINICAL PRACTICE

This thesis explored the link between tinnitus and stress from different perspectives. It has determined possible biophysiological processes revealed gaps and variability in public and professional understanding of stress. Hence, the findings can inform future research on tinnitus, stress, and other stress-related disorders.

6.4.1 Exploring the findings in larger populations

The generalisability of the findings in the cortisol study is limited by its ~~one~~ small sample of tinnitus patients with certain characteristics (i.e. the majority had mild-moderate tinnitus and came from non-clinical setting). To confirm the findings, the study should be repeated in a clinical setting with less restrictive recruitment criteria, to include patients who have severe impact of tinnitus, patients with other chronic diseases, ear disease, and associated psychological disorders like depression and anxiety. This will help in recruiting a larger sample size which will help in assessing whether HCC can be used to identify a sub-type of tinnitus. Dajani et al. (2018) reported that collecting and processing hair was simpler and more tolerable than saliva collection. They conducted their study in a large population (n=727). Studies by Basso et al. (2022a, 2022b) were conducted in clinical setting and assessed HCC within tinnitus patients. They found that increased HCC was associated with tinnitus loudness but not with tinnitus-related distress measured by the TQ. Their findings support the use of hair cortisol as a biomarker of tinnitus loudness, and they advised for further research. With the current advice about using TFI in tinnitus clinics (NICE, 2020), it will be more feasible to compute the same statistical analyses conducted in this thesis. The findings of our study suggested some links between tinnitus impact and HCC. These links deserve further study considering other confounders including coping, sleep, and personality. This would help in assessing the effect of coping on HCC in tinnitus populations, and whether cortisol levels change in those who habituate to their

tinnitus. HCC would measure cortisol levels over an extended period with minimal sample collection points, which cannot be achieved by using other methods of cortisol assessment.

6.4.2 Identifying other mechanistic links between tinnitus and stress

There are plenty of opportunity to discover more mechanistic links that may explain the role of stress in tinnitus. These studies could be in different fields that include, but are not limited to, experimental, neuroimaging, genetics, and clinical studies. HPAA and SAM short-term stress biophysiological markers have not proven useful or reliable clinically, however, they have been proven valuable in research (Simmons et al., 2020). Mazurek et al. (2019) have listed possible stress biomarkers that ought to be studied in tinnitus such as TNF-α, interleukins and SAM biomarkers. These possibly are linked to different tinnitus-related patients' complaints, such as tinnitus intrusiveness or emotional distress, which require further research. Furthermore, the links identified in this thesis have underlined neurological hubs that links stress and tinnitus, namely dACC and SCN. Neuroimaging studies measuring HCC as one of the outcomes may confirm whether HCC is a suitable indicator of the neurological activities in these hubs.

6.4.3 Ecological Momentary Assessment studies

The hair cortisol study has demonstrated an association between the daily hassles and tinnitus levels. To date, assessing daily hassles has been neglected in tinnitus research. Even when Ecological Momentary Assessment (EMA) was used in tinnitus (Probst et al., 2016, Probst et

al., 2017), participants were simply asked whether they were stressed, which has been proven to be less than reliable in this thesis. Nevertheless, the EMA methods may overcome the recall bias that can affect scoring of the self-reported stress instruments (Weckesser et al., 2019). This makes EMA methods valuable to confirm the relationship between daily hassles and tinnitus or to identify other links. Statements that were highly rated and categorised by the participants in the concept mapping study might be used to avoid the effect of ambiguity in the definition of stress. Corroborating data collected by EMA and HCC of the corresponding timeframe is another approach that could be applied in future studies. Alternatively, other methods for longitudinal assessment can be used. For example, tinnitus diary can be used to collect the changes in tinnitus impact levels on daily or weekly basis.

6.4.4 Exploring the effect of tinnitus management on TFI-SC

As yet, there has not been a study that focused on evaluating the effectiveness of tinnitus management on sense of control. It is evident that changes on the TFI sense of control subscale, and possibly other TFI subscales, have an underlying biological basis, which might have a greater value in monitoring the effect of tinnitus management. It is possible to explore this hypothesis by conducting secondary research of patients' clinical records or through a systematic review of clinical trials that monitored the change in tinnitus impact by TFI.

6.4.5 Examining the effect of cortisol on attention in tinnitus population

Given the role of attention network in tinnitus and that poorer performance on task requiring attention has been reported in tinnitus participants (Malesci et al., 2021), cognitive tests that assess attention might have been more appropriate in detecting the effect of tinnitus on cognitive function and possible mediating role of cortisol. An example of cognitive tests that assess attention skills and cognitive interference and could have been used in this study is the Stroop test. Andersson et al. (2000) and Gonendik et al. (2021) found that those who have tinnitus performed worse than those who do not have tinnitus on the Stroop test. Brueggemann et al. (2021) found that tinnitus distress affected performance in the Stroop test negatively. Also, exposure to stress and change in attention network can be related to changes in cortisol levels (Broeders et al., 2021). Scheffer et al. (2019) reported a significant positive correlation between Stroop Test performance and the last month level of hair cortisol, but not with the perceived level of stress. Pulopulos et al. (2016) observed better processing speed on the Stroop test when the CAR increased. Higher magnitude of CAR is also associated with better performance of executive functions (Evans et al., 2012). Although these studies show that better performance on the Stroop test is associated with higher cortisol level and lower tinnitus distress, it is not possible to predict whether cortisol mediated this relationship without further studies.

6.4.6 Re-examining the relationship by assessing coping with stress

As mentioned in this thesis, assessing stress and its relationship with health is a broad topic and a variety of factors may affect this relationship. I considered the effect of many confounders on the studied relationship. However, stress coping strategies and their confounding effect on this relationship was not considered. Coping may alter how a person perceives a situation as stressful and they will display changes in their behaviour to overcome stressful situations. Participants in the hair cortisol study could have faced stressful situations and they had coped with it before they attended the visit. This may have affected the level of stress when assessed at the visit. Future studies could consider the mediating effect of coping on the relationship between tinnitus and stress. Also, assessing behavioural responses such as facial displays of emotion and observers' ratings of anxious nonverbal behaviour can be used to measure stress and have shown better correspondence with cortisol reactivity than self-reported instruments (Laures-Gore et al., 2010). These methods were not covered in this thesis, but they could be used in future studies.

6.4.7 Improving healthcare and tinnitus management

The findings of this thesis should not only to be used in research; they can be used to create an educational programme to inform health professionals about stress and its relationship with tinnitus. This can help overcome one of the obstacles in managing stress in tinnitus clinic, the lack of knowledge about stress. Supported by scientific findings, it

would be more feasible to educate the public about the meaning of stress how it affects tinnitus. It will help in changing the patients' challenging mind-set that has prevent them from accepting certain tinnitus managements.

References

AAZH, H., MOORE, B. C. J., LAMMAING, K. & CROPLEY, M. 2016. Tinnitus and hyperacusis therapy in a UK National Health Service audiology department: Patients' evaluations of the effectiveness of treatments. *International Journal of Audiology,* 55**,** 514-522.

ABBAS, J., AQEEL, M., JAFFAR, A., NURUNNABI, M. & BANO, S. 2019. Tinnitus perception mediates the relationship between physiological and psychological problems among patients. *Journal of Experimental Psychopathology,* 10**,** 2043808719858559.

ABBOTT, J.-A. M., KALDO, V., KLEIN, B., AUSTIN, D., HAMILTON, C., PITERMAN, L., WILLIAMS, B. & ANDERSSON, G. 2009. A cluster randomised trial of an internet-based intervention program for tinnitus distress in an industrial setting. *Cognitive behaviour therapy,* 38**,** 162-173.

ABELL, J. G., STALDER, T., FERRIE, J. E., SHIPLEY, M. J., KIRSCHBAUM, C., KIVIMÄKI, M. & KUMARI, M. 2016. Assessing cortisol from hair samples in a large observational cohort: The Whitehall II study. *Psychoneuroendocrinology,* 73**,** 148-156.

ADAM, E. K. & KUMARI, M. 2009. Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology,* 34**,** 1423-1436.

ADJAMIAN, P., HALL, D. A., PALMER, A. R., ALLAN, T. W. & LANGERS, D. R. 2014. Neuroanatomical abnormalities in chronic tinnitus in the human brain. *Neuroscience & Biobehavioral Reviews,* 45**,** 119-133.

AGUILERA, G. 2012. The hypothalamic-paitutary-adrenal axis and neuroendocrine responses to stress. *In:* FINK, G. P., D. W. ; LEVINE, J. E. (ed.) *Handbook of neuroendocrinology.* 1st ed. Amsterdam; Boston.: Academic Press/Elsevier.

AHMED, B., AMMAR AHMED, M. A., AKHTAR, T. & SALIM, S. 2017. Impact of tinnitus perception on psychological distress in male and female tinnitus patients. *Foundation University Journal of Psychology Vol. 1, No. 1, Jan 2017***,** 56.

AIGRAIN, J., SPODENKIEWICZ, M., DUBUISSON, S., DETYNIECKI, M., COHEN, D. & CHETOUANI, M. 2018. Multimodal Stress Detection from Multiple Assessments. *IEEE Transactions on Affective Computing,* 9**,** 491-506.

AKOGLU, H. 2018. User's guide to correlation coefficients. *Turkish journal of emergency medicine,* 18**,** 91-93.

AL-HARIRI, M. 2016. The pathophysiological mechanisms of diabetic otopathy. *Journal of Taibah University Medical Sciences,* 11**,** 401-403.

AL-MANA, D., CERANIC, B., DJAHANBAKHCH, O. & LUXON, L. 2008. Hormones and the auditory system: a review of physiology and pathophysiology. *Neuroscience,* 153**,** 881-900.

AL-SWIAHB, J. & PARK, S. N. 2016. Characterization of tinnitus in different age groups: A retrospective review. *Noise Health,* 18**,** 214-9.

AL-SWIAHB, J. N., HWANG, E. S., KONG, J. S., KIM, W. J., YEO, S. W. & PARK, S. N. 2016. Clinical and audiologic characteristics of patients with sensorineural tinnitus and its association with psychological aspects: an analytic retrospective study. *Eur Arch Otorhinolaryngol,* 273**,** 4161-4165.

ALDHAFEERI, F. M., MACKENZIE, I., KAY, T., ALGHAMDI, J. & SLUMING, V. 2012. Neuroanatomical correlates of tinnitus revealed by cortical thickness analysis and diffusion tensor imaging. *Neuroradiology,* 54**,** 883-892.

ALDWIN, C. M. 2007. *Stress, coping, and development [electronic resource] : an integrative perspective* New York, New York : Guilford Press.

ALESI, M., GIORDANO, G., GIACCONE, M., BASILE, M., COSTA, S. & BIANCO, A. 2020. Effects of the Enriched Sports Activities-Program on Executive Functions in Italian Children. *Journal of Functional Morphology and Kinesiology,* 5**,** 26.

ALSALMAN, O. A., TUCKER, D. & VANNESTE, S. 2016. Salivary Stress-Related Responses in Tinnitus: A Preliminary Study in Young Male Subjects with Tinnitus. *Frontiers in Neuroscience,* 10.

ALSTER, J., SHEMESH, Z., ORNAN, M. & ATTIAS, J. 1993. Sleep disturbance associated with chronic tinnitus. *Biological Psychiatry,* 34**,** 84-90.

AMERICAN PSYCHIATRIC ASSOCIATION 2013. *Diagnostic and statistical manual of mental disorders (DSM-5®)*, American Psychiatric Pub.

ANDERSON, B., WETHINGTON, E. & KAMARCK, T. W. 2011. Interview assessment of stressor exposure.

ANDERSSON, G., ERIKSSON, J., LUNDH, L. G. & LYTTKENS, L. 2000. Tinnitus and cognitive interference: a stroop paradigm study. *J Speech Lang Hear Res,* 43**,** 1168-73.

ANDERSSON, G. & MCKENNA, L. 2006. The role of cognition in tinnitus. *Acta Oto-Laryngologica,* 126**,** 39-43.

ANTONY, M. M., BIELING, P. J., COX, B. J., ENNS, M. W. & SWINSON, R. P. 1998. Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. *Psychological assessment,* 10**,** 176.

AOKI, M., WAKAOKA, Y., HAYASHI, H., KUZE, B., MIZUTA, K. & ITO, Y. 2012. Effect of Lyophilized Powder Made From Enzymolyzed Honeybee Larvae on Tinnitus-Related Symptoms, Hearing Levels, and Hypothalamus-Pituitary-Adrenal Axis-Related Hormones. *Ear and Hearing,* 33**,** 430-436.

ARKSEY, H. & O'MALLEY, L. 2005. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology,* 8**,** 19-32.

ARMSTRONG, R. A. 2019. Is there a large sample size problem? *Ophthalmic and Physiological Optics,* 39**,** 129-130.

ARTHUR, A. R. 2004. Work-related stress, the blind men and the elephant. *British Journal of Guidance & Counselling,* 32**,** 157-169.

ASCHBACHER, K., O'DONOVAN, A., WOLKOWITZ, M.;, O., DHABHAR, F. S., SU, Y. & EPEL, E. 2013. Good Stress, Bad Stress and Oxidative Stress: Insights from Anticipatory Cortisol Reactivity. *Psychoneuroendocrinology,* 38**,** 1698-1708.

ATTANASIO, G., CARTOCCI, G., COVELLI, E., AMBROSETTI, E., MARTINELLI, V., ZACCONE, M., PONZANETTI, A., GUELI, N., FILIPO, R. & CACCIAFESTA, M. 2012. The Mozart effect in patients suffering from tinnitus. *Acta Otolaryngol,* 132**,** 1172-7.

AYDIN, N. & SEARCHFIELD, G. D. 2019. Changes in tinnitus and physiological biomarkers of stress in response to short-term broadband noise and sounds of nature. *Complement Ther Med,* 46**,** 62-68.

BABIKIAN, T., BOONE, K. B., LU, P. & ARNOLD, G. 2006. Sensitivity and Specificity of Various Digit Span Scores in the Detection of Suspect Effort. *The Clinical Neuropsychologist,* 20**,** 145-159.

BAGULEY, D., MCFERRAN, D. & HALL, D. 2013. Tinnitus. *Lancet,* 382**,** 1600-7.

BAIGI, A., ODEN, A., ALMLID-LARSEN, V., BARRENAS, M. L. & HOLGERS, K. M. 2011. Tinnitus in the general population with a focus on noise and stress: a public health study. *Ear Hear,* 32**,** 787-9.

BALDO, P., DOREE, C., MOLIN, P., MCFERRAN, D. & CECCO, S. 2012. Antidepressants for patients with tinnitus. *The Cochrane database of systematic reviews***,** CD003853.

BALE, T. L. & VALE, W. W. 2004. CRF and CRF receptors: role in stress responsivity and other behaviors. *Annu. Rev. Pharmacol. Toxicol.,* 44**,** 525-557.

BALI, A. & JAGGI, A. S. 2015. Preclinical experimental stress studies: Protocols, assessment and comparison. *European Journal of Pharmacology,* 746**,** 282-292.

BALL, G., STOKES, P., RHODES, R., BOSE, S., REZEK, I., WINK, A.-M., LORD, L.-D., MEHTA, M., GRASBY, P. & TURKHEIMER, F. 2011. Executive Functions and Prefrontal Cortex: A Matter of Persistence? *Frontiers in Systems Neuroscience,* 5.

BAR, H. & MENTCH, L. 2017. R-CMap—An open-source software for concept mapping. *Evaluation and Program Planning,* 60**,** 284-292.

BARTLETT, L., MARTIN, A., NEIL, A. L., MEMISH, K., OTAHAL, P., KILPATRICK, M. & SANDERSON, K. 2019. A systematic review and meta-analysis of workplace mindfulness training randomized controlled trials. *J Occup Health Psychol,* 24**,** 108-126.

BASILE, C.-É., FOURNIER, P., HUTCHINS, S. & HÉBERT, S. 2013. Psychoacoustic assessment to improve tinnitus diagnosis. *PloS one,* 8**,** e82995.

BASSO, L., BOECKING, B., BRUEGGEMANN, P., PEDERSEN, N. L., CANLON, B., CEDERROTH, C. R. & MAZUREK, B. 2020. Gender-Specific Risk Factors and Comorbidities of Bothersome Tinnitus. *Frontiers in Neuroscience,* 14.

BASSO, L., BOECKING, B., NEFF, P., BRUEGGEMANN, P., MAZUREK, B. & PETERS, E. M. 2022a. Psychological Treatment Effects Unrelated to Hair-Cortisol and Hair-BDNF Levels in Chronic Tinnitus. *Frontiers in psychiatry,* 13.

BASSO, L., BOECKING, B., NEFF, P., BRUEGGEMANN, P., PETERS, E. M. & MAZUREK, B. 2022b. Hair-cortisol and hair-BDNF as biomarkers of tinnitus loudness and distress in chronic tinnitus. *Scientific reports,* 12**,** 1-14.

BASTOS, S. & SANCHEZ, T. 2017. Neuromodulation on Tinnitus Perception and Distress. *Otolaryngol Res Rev,* 1**,** 39-48.

BAUM, A., GAROFALO, J. P. & YALI, A. M. 1999. Socioeconomic status and chronic stress. Does stress account for SES effects on health? *Ann N Y Acad Sci,* 896**,** 131-44.

BAUM, A., TREVINO, L. A. & DOUGALL, A. L. 2011. Stress and the cancers. *The handbook of stress science: Biology, psychology, and health***,** 411-424.

BELL, S. & LEE, C. 2002. Development of the Perceived Stress Questionnaire for Young Women. *Psychology, Health & Medicine,* 7**,** 189-201.

BELLI, S., BELLI, H., BAHCEBASI, T., OZCETIN, A., ALPAY, E. & ERTEM, U. 2008. Assessment of psychopathological aspects and psychiatric comorbidities in patients affected by tinnitus. *European Archives of Oto-Rhino-Laryngology,* 265**,** 279-285.

BENCSIK, B., TAMAS, L., TRIMMEL, K. & STAUDER, A. 2015. Hungarian adaptation of the Tinnitus Handicap Inventory: reliability and validity. *Eur Arch Otorhinolaryngol,* 272**,** 2243-8.

BENGTSSON, M. 2016. How to plan and perform a qualitative study using content analysis. *NursingPlus Open,* 2**,** 8-14.

BENNETT, R. J., MEYER, C. J., EIKELBOOM, R. H. & ATLAS, M. D. 2018. Investigating the Knowledge, Skills, and Tasks Required for Hearing Aid Management: Perspectives of Clinicians and Hearing Aid Owners. *American Journal of Audiology,* 27**,** 67-84.

BETZ, L. T., MUHLBERGER, A., LANGGUTH, B. & SCHECKLMANN, M. 2017. Stress Reactivity in Chronic Tinnitus. *Scientific Reports,* 7.

BEUKES, E. W., BAGULEY, D. M., ALLEN, P. M., MANCHAIAH, V. & ANDERSSON, G. 2018. Audiologist-guided Internet-based cognitive behavior therapy for adults with tinnitus in the United Kingdom: A randomized controlled trial. *Ear and Hearing,* 39**,** 423-433.

BIEHL, R., BOECKING, B., BRUEGGEMANN, P., GROSSE, R. & MAZUREK, B. 2020. Personality Traits, Perceived Stress, and Tinnitus-Related Distress in Patients With Chronic Tinnitus: Support for a Vulnerability-Stress Model. *Frontiers in Psychology,* 10.

BINZ, T., RIETSCHEL, L., STREIT, F., HOFMANN, M., GEHRKE, J., HERDENER, M., QUEDNOW, B., MARTIN, N., RIETSCHEL, M. & KRAEMER, T. 2018. Endogenous cortisol in keratinized matrices: Systematic determination of baseline cortisol levels in hair and the influence of sex, age and hair color. *Forensic Science International,* 284**,** 33-38.

BLACKBURN, H. L. & BENTON, A. L. 1957. Revised administration and scoring of the Digit Span Test. *Journal of Consulting Psychology,* 21**,** 139-143.

BLOCH, G. J., NEELEMAN, L. & ALEAMONI, L. M. 2004. The Salient Stressor Impact Questionnaire (SSIQ) A Measurement of the Intensity and Chronicity of Stress. *Assessment,* 11**,** 342-360.

BOALS, A. & BANKS, J. B. 2012. Effects of traumatic stress and perceived stress on everyday cognitive functioning. *Cognition and Emotion,* 26**,** 1335-1343.

BORG, G. & BORG, E. 2001. A new generation of scaling methods: Level-anchored ratio scaling. *Psychologica,* 28**,** 15-45.

BORG, I. & GROENEN, P. J. 2005. *Modern multidimensional scaling: Theory and applications*, Springer Science & Business Media.

BÖRNER, D., GLAHN, C., STOYANOV, S., KALZ, M. & SPECHT, M. 2010. Expert concept mapping study on mobile learning. *Campus-Wide Information Systems*.

BOUTEYRE, E., MAUREL, M. & BERNAUD, J.-L. 2007. Daily hassles and depressive symptoms among first year psychology students in France: the role of coping and social support. *Stress and Health,* 23**,** 93-99.

BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology,* 3**,** 77-101.

BROEDERS, T. A. A., SCHOONHEIM, M. M., VINK, M., DOUW, L., GEURTS, J. J. G., VAN LEEUWEN, J. M. C. & VINKERS, C. H. 2021. Dorsal attention network centrality increases during recovery from acute stress exposure. *NeuroImage: Clinical,* 31**,** 102721.

BROOKS, L., MCCABE, P. & SCHNEIDERMAN, N. 2011. Stress and Cardiometabolic Syndrome. *The Handbook of Stress Science: Biology, Psychology, and Health,* 399.

BROWN, C. 2000. Clinical Interpretation of "A Comparison of the Allen Cognitive Level Test and the Wisconsin Card Sorting Test in Adults With Schizophrenia". *American Journal of Occupational Therapy,* 54**,** 134-136.

BROWN, G. W. & HARRIS, T. O. 1989. *Life events and illness*, Guilford Press.

BRUEGGEMANN, P., NEFF, P. K. A., MEYER, M., RIEMER, N., ROSE, M. & MAZUREK, B. 2021. Chapter 13 - On the relationship between tinnitus distress, cognitive performance and aging. *In:* LANGGUTH, B., KLEINJUNG, T., DE RIDDER, D., SCHLEE, W. & VANNESTE, S. (eds.) *Progress in Brain Research.* Elsevier.

BRÜGGEMANN, P., OTTO, J., LORENZ, N., SCHORSCH, S., SZCZEPEK, A. J., BÖCKING, B. & MAZUREK, B. 2018. Long-term changes in multimodal intensive tinnitus therapy: A 5-year follow-up. *HNO,* 66**,** 34-38.

BRUGGEMANN, P., SZCZEPEK, A. J., ROSE, M., MCKENNA, L., OLZE, H. & MAZUREK, B. 2016. Impact of multiple factors on the degree of tinnitus distress. *Frontiers in Human Neuroscience,* 10.

BURGOS, I., FEIGE, B., HORNYAK, M., HARTER, M., WESKE-HECK, G., VODERHOLZER, U. & RIEMANN, D. 2005. Chronic tinnitus and associated sleep disturbances. *Somnologie,* 9**,** 133-138.

BURTON, A., BURGESS, C., DEAN, S., KOUTSOPOULOU, G. Z. & HUGH-JONES, S. 2017. How effective are mindfulness-based interventions for reducing stress among healthcare professionals? A systematic review and meta-analysis. *Stress and Health,* 33**,** 3-13.

BURTON, H., WINELAND, A., BHATTACHARYA, M., NICKLAUS, J., GARCIA, K. S. & PICCIRILLO, J. F. 2012. Altered networks in bothersome tinnitus: a functional connectivity study. *BMC neuroscience,* 13**,** 1-15.

BUYSSE, D. J., REYNOLDS III, C. F., MONK, T. H., BERMAN, S. R. & KUPFER, D. J. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research,* 28**,** 193-213.

CANNON, W. B. 1923. *Bodily Changes in Pain, Hunger, Fear and Rage - An Account of Recent Researches Into the Function of Emotional Excitement (1927)*, Read Books Limited.

CEDERROTH, C. R., GALLUS, S., HALL, D. A., KLEINJUNG, T., LANGGUTH, B., MARUOTTI, A., MEYER, M., NORENA, A., PROBST, T. & PRYSS, R. C. 2019. Towards an Understanding of Tinnitus Heterogeneity. *Frontiers in aging neuroscience,* 11**,** 53.

CHAN, C. W. H., CHOI, K. C., SO, W. K. W. & CHAN, H. Y. L. 2012. Concept mapping in palliative medicine research. *Annals of palliative medicine,* 1**,** 179-181.

CHAN, K. C. A., LIT, L. C. W., LAW, E. L. K., TAI, M. H. L., YUNG, C. U., CHAN, M. H. M. & LAM, C. W. K. 2004. Diminished Urinary Free Cortisol Excretion in Patients with Moderate and Severe Renal Impairment. *Clinical Chemistry,* 50**,** 757-759.

CHEN, Y.-C., WANG, F., WANG, J., BO, F., XIA, W., GU, J.-P. & YIN, X. 2017a. Resting-state brain abnormalities in chronic subjective tinnitus: a meta-analysis. *Frontiers in human neuroscience,* 11**,** 22.

CHEN, Y. C., CHEN, G. D., AUERBACH, B. D., MANOHAR, S., RADZIWON, K. & SALVI, R. 2017b. Tinnitus and hyperacusis: Contributions of paraflocculus, reticular formation and stress. *Hear Res,* 349**,** 208-222.

CHO, C. G., CHI, J. H., SONG, J. J., LEE, E. K. & KIM, B. H. 2013. Evaluation of anxiety and depressive levels in tinnitus patients. *Korean J Audiol,* 17**,** 83-9.

CIANFRONE, G., MAZZEI, F., SALVIATI, M., TURCHETTA, R., ORLANDO, M. P., TESTUGINI, V., CARCHIOLO, L., CIANFRONE, F. & ALTISSIMI, G. 2015. Tinnitus Holistic Simplified Classification (THoSC): A New Assessment for Subjective Tinnitus, With Diagnostic and Therapeutic Implications. *Ann Otol Rhinol Laryngol,* 124**,** 550-60.

CIMA, R. F., KIKIDIS, D., MAZUREK, B., HAIDER, H., CEDERROTH, C. R., NORENA, A., LAPIRA, A., BIBAS, A. & HOARE, D. J. 2020. Tinnitus healthcare. *BMJ Open,* 10.

CIMA, R. F. F. 2018. Bothersome tinnitus. *HNO,* 66**,** 369-374.

CIMA, R. F. F., MAZUREK, B., HAIDER, H., KIKIDIS, D., LAPIRA, A., NOREÑA, A. & HOARE, D. J. 2019. A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. *HNO,* 67**,** 10-42.

CIRIMELE, V., KINTZ, P., DUMESTRE, V., GOULLE, J. & LUDES, B. 2000. Identification of ten corticosteroids in human hair by liquid chromatography–ionspray mass spectrometry. *Forensic science international,* 107**,** 381-388.

CLARKE, N. A., HENSHAW, H., AKEROYD, M. A., ADAMS, B. & HOARE, D. J. 2020. Associations Between Subjective Tinnitus and Cognitive Performance: Systematic Review and Meta-Analyses. *Trends in Hearing,* 24**,** 2331216520918416.

COBB, S. 1976. Social support as a moderator of life stress. *Psychosomatic medicine*.

COHEN, S., GIANAROS, P. J. & MANUCK, S. B. 2016. A Stage Model of Stress and Disease. *Perspectives on Psychological Science,* 11**,** 456-463.

COHEN, S., JANICKI-DEVERTS, DENISE; DOYLE, W. J., MILLER, G. E., FRANK, E., RABIN, B. S. & TURNER, R. B. 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences of the United States of America,* 109**,** 5995-5999.

COHEN, S., JANICKI-DEVERTS, D. & MILLER, G. E. 2007. Psychological stress and disease. *Jama,* 298**,** 1685-1687.

COHEN, S., KAMARCK, T. & MERMELSTEIN, R. 1983. A global measure of perceived stress. *Journal of Health and Social Behavior,* 24**,** 385-396.

COHEN, S., KESSLER, R. C. & GORDON, L. U. 1995. Strategies for measuring stress in studies of psychiatric and physical disorders. *Measuring stress: A guide for health and social scientists***,** 3-26.

COHEN, S., MURPHY, M. L. & PRATHER, A. A. 2019. Ten surprising facts about stressful life events and disease risk. *Annual review of psychology,* 70**,** 577-597.

COLE, D. A., NICK, E. A., ZELKOWITZ, R. L., ROEDER, K. M. & SPINELLI, T. 2017. Online social support for young people: does it recapitulate in-person social support; can it help? *Computers in human behavior,* 68**,** 456-464.

CONCEIÇÃO, S. C., SAMUEL, A. & YELICH BINIECKI, S. M. 2017. Using concept mapping as a tool for conducting research: An analysis of three approaches. *Cogent Social Sciences,* 3**,** 1404753.

CONRAD, C. D. 2011. *The handbook of stress : neuropsychological effects on the brain,* Oxford, Wiley-Blackwell.

COOPER, M. S. & STEWART, P. M. 2009. 11β-Hydroxysteroid Dehydrogenase Type 1 and Its Role in the Hypothalamus-Pituitary-Adrenal Axis, Metabolic Syndrome, and Inflammation. *The Journal of Clinical Endocrinology & Metabolism,* 94**,** 4645-4654.

COWIN, L. S., HENGSTBERGER-SIMS, C., EAGAR, S. C., GREGORY, L., ANDREW, S. & ROLLEY, J. 2008. Competency measurements: testing convergent validity for two measures. *Journal of Advanced Nursing,* 64**,** 272-277.

CRAWFORD, J. R. & HENRY, J. D. 2003. The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample. *British journal of clinical psychology,* 42**,** 111-131.

CROCETTI, A., FORTI, S., AMBROSETTI, U. & BO, L. D. 2009. Questionnaires to evaluate anxiety and depressive levels in tinnitus patients. *Otolaryngol Head Neck Surg,* 140**,** 403-5.

CRÖNLEIN, T., LANGGUTH, B., PREGLER, M., KREUZER, P. M., WETTER, T. C. & SCHECKLMANN, M. 2016. Insomnia in patients with chronic tinnitus: Cognitive and emotional distress as moderator variables. *Journal of Psychosomatic Research,* 83**,** 65-68.

CROSCHERE, J., DUPEY, L., HILLIARD, M., KOEHN, H. & MAYRA, K. 2012. The effects of time of day and practice on cognitive abilities: Forward and backward Corsi block test and digit span. *PEBL Technical Report Series*.

CROTTAZ-HERBETTE, S. & MENON, V. 2006. Where and when the anterior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. *Journal of cognitive neuroscience,* 18**,** 766-780.

CRUM, A. J., SALOVEY, P. & ACHOR, S. 2013. Rethinking stress: The role of mindsets in determining the stress response. *Journal of personality and social psychology,* 104**,** 716.

CUDA, D. & DE CARIA, A. 2008. Effectiveness of combined counseling and low-level laser stimulation in the treatment of disturbing chronic tinnitus. *International Tinnitus Journal,* 14**,** 175-180.

CYRANOWSKI, J. M., ZILL, N., BODE, R., BUTT, Z., KELLY, M. A. R., PILKONIS, P. A., SALSMAN, J. M. & CELLA, D. 2013. Assessing social support, companionship, and distress: National Institute of Health (NIH) Toolbox Adult Social Relationship Scales. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* 32**,** 293-301.

D'ANNA-HERNANDEZ, K. L., ROSS, R. G., NATVIG, C. L. & LAUDENSLAGER, M. L. 2011. Hair cortisol levels as a retrospective marker of hypothalamic-pituitary axis activity throughout pregnancy: comparison to salivary cortisol. *Physiol Behav,* 104**,** 348-53.

DADOO, S., SHARMA, R. & SHARMA, V. 2019. Oto-acoustic emissions and brainstem evoked response audiometry in patients of tinnitus with normal hearing. *The international tinnitus journal,* 23**,** 18-25.

DAGNINO-SUBIABRE, A. 2013. Effects of chronic stress on the auditory system and fear learning: an evolutionary approach. *Reviews in the neurosciences,* 24**,** 227-37.

DAJANI, R., HADFIELD, K., VAN UUM, S., GREFF, M. & PANTER-BRICK, C. 2018. Hair cortisol concentrations in war-affected adolescents: A prospective intervention trial. *Psychoneuroendocrinology,* 89**,** 138-146.

DANCEY, C. P. & REIDY, J. 2007. *Statistics without maths for psychology*, Pearson education.

DANTZER, B., FLETCHER, Q. E., BOONSTRA, R. & SHERIFF, M. J. 2014. Measures of physiological stress: a transparent or opaque window into the status, management and conservation of species? *Conservation Physiology,* 2**,** cou023-cou023.

DAWES, P., FORTNUM, H., MOORE, D. R., EMSLEY, R., NORMAN, P., CRUICKSHANKS, K., DAVIS, A., EDMONDSON-JONES, M., MCCORMACK, A., LUTMAN, M. & MUNRO, K. 2014. Hearing in middle age: a population snapshot of 40–69 year olds in the UK. *Ear and hearing,* 35**,** e44-e51.

DE KLOET, E., FITZSIMONS, C., DATSON, N., MEIJER, O. & VREUGDENHIL, E. 2009. Glucocorticoid signaling and stress-related limbic susceptibility pathway: about receptors, transcription machinery and microRNA. *Brain research,* 1293**,** 129-141.

DELONGIS, A., FOLKMAN, S. & LAZARUS, R. S. 1988. The Impact of Daily Stress on Health and Mood: Psychological and Social Resources as Mediators. *Journal of Personality and Social Psychology,* 54**,** 486-495.

DENOVAN, A. & MACASKILL, A. 2013. An interpretative phenomenological analysis of stress and coping in first year undergraduates. *British Educational Research Journal,* 39**,** 1002-1024.

DETTENBORN, L., TIETZE, A., KIRSCHBAUM, C. & STALDER, T. 2012. The assessment of cortisol in human hair: associations with sociodemographic variables and potential confounders. *Stress,* 15**,** 578-88.

DIAMOND, A. 2013. Executive functions. *Annual review of psychology,* 64**,** 135-168.

DINEEN, R., DOYLE, J. & BENCH, J. 1997. Audiological and psychological characteristics of a group of tinnitus sufferers, prior to tinnitus management training. *Br J Audiol,* 31**,** 27-38.

DINEEN, R., DOYLE, J., BENCH, J. & PERRY, A. 1999. The influence of training on tinnitus perception: an evaluation 12 months after tinnitus management training. *British journal of audiology,* 33**,** 29-51.

DOHRENWEND, B. P., RAPHAEL, K. G., SCHWARTZ, S., STUEVE, A. & SKODOL, A. 1993. The structured event probe and narrative rating method for measuring stressful life events.

DOHRENWEND, B. S., ASKENASY, A. R., KRASNOFF, L. & DOHRENWEND, B. P. 1978. Exemplification of a Method for Scaling Life Events: The PERI Life Events Scale. *Journal of Health and Social Behavior,* 19**,** 205-229.

DONNELLY, J. P. 2017. A systematic review of concept mapping dissertations. *Evaluation and Program Planning,* 60**,** 186-193.

DURAI, M. & SEARCHFIELD, G. 2016. Anxiety and depression, personality traits relevant to tinnitus: A scoping review. *Int J Audiol,* 55**,** 605-15.

DURAI, M. & SEARCHFIELD, G. D. 2017. A mixed-methods trial of broad band noise and nature sounds for tinnitus therapy: Group and individual responses modeled under the adaptation level theory of tinnitus. *Frontiers in Aging Neuroscience,* 9.

DURIC, V., CLAYTON, S., LEONG, M. L. & YUAN, L.-L. 2016. Comorbidity Factors and Brain Mechanisms Linking Chronic Stress and Systemic Illness. *Neural Plasticity,* 2016**,** 16.

EGGERMONT, J. J. & ROBERTS, L. E. 2004. The neuroscience of tinnitus. *Trends Neurosci,* 27**,** 676-82.

EL-SHUNNAR, S. K., HOARE, D. J., SMITH, S., GANDER, P. E., KANG, S., FACKRELL, K. & HALL, D. A. 2011. Primary care for tinnitus: practice and opinion among GPs in England. *Journal of evaluation in clinical practice,* 17**,** 684-692.

EL MLILI, N., AHABRACH, H. & CAULI, O. 2021. Hair Cortisol Concentration as a Biomarker of Sleep Quality and Related Disorders. *Life,* 11.

ELARBED, A., FACKRELL, K., BAGULEY, D. M. & HOARE, D. J. 2020. Tinnitus and stress in adults: a scoping review. *International Journal of Audiology***,** 1-12.

ELO, A.-L., LEPPÄNEN, A. & JAHKOLA, A. 2003. Validity of a single-item measure of stress symptoms. *Scandinavian journal of work, environment & health***,** 444-451.

ELO, S., KÄÄRIÄINEN, M., KANSTE, O., PÖLKKI, T., UTRIAINEN, K. & KYNGÄS, H. 2014. Qualitative content analysis: A focus on trustworthiness. *SAGE open,* 4**,** 2158244014522633.

ENGERT, V., BLASBERG, J. U., KÖHNE, S., STRAUSS, B. & ROSENDAHL, J. 2021. Resilience and personality as predictors of the biological stress load during the first wave of the Covid-19 pandemic in Germany. *Translational Psychiatry,* 11**,** 443.

EPEL, E. S., CROSSWELL, A. D., MAYER, S. E., PRATHER, A. A., SLAVICH, G. M., PUTERMAN, E. & MENDES, W. B. 2018. More than a feeling: A unified view of stress measurement for population science. *Frontiers in neuroendocrinology,* 49**,** 146-169.

ERICKSON, T. M., JACOBSON, S. V., BANNING, R. L., QUACH, C. M. & REAS, H. E. 2021. Big five traits and interpersonal goals during stressors as predictors of hair cortisol. *Comprehensive Psychoneuroendocrinology,* 8**,** 100084.

EVANS, C., CONNELL, J., BARKHAM, M., MARGISON, F., MCGRATH, G., MELLOR-CLARK, J. & AUDIN, K. 2002. Towards a standardised brief outcome measure: Psychometric properties and utility of the CORE–OM. *The British Journal of Psychiatry,* 180**,** 51-60.

EVANS, P., HUCKLEBRIDGE, F., LOVEDAY, C. & CLOW, A. 2012. The cortisol awakening response is related to executive function in older age. *International Journal of Psychophysiology,* 84**,** 201-204.

EYSENBACH, G. & WYATT, J. 2002. Using the Internet for Surveys and Health Research. *J Med Internet Res,* 4**,** e13.

FABBRI, M., BERACCI, A., MARTONI, M., MENEO, D., TONETTI, L. & NATALE, V. 2021. Measuring Subjective Sleep Quality: A Review. *International Journal of Environmental Research and Public Health,* 18.

FACKRELL, K., HALL, D. A., BARRY, J. & HOARE, D. J. 2014. Tools for tinnitus measurement: development and validity of questionnaires to assess handicap and treatment effects. *Tinnitus: causes, treatment and short and long-term health effects. New York: Nova Science Publishers Inc*, 13-60.

FACKRELL, K., HALL, D. A., BARRY, J. G. & HOARE, D. J. 2016. Psychometric properties of the Tinnitus Functional Index (TFI): Assessment in a UK research volunteer population. *Hear Res,* 335**,** 220-235.

FACKRELL, K., HALL, D. A., BARRY, J. G. & HOARE, D. J. 2018. Performance of the Tinnitus Functional Index as a diagnostic instrument in a UK clinical population. *Hearing Research,* 358**,** 74-85.

FAGELSON, M. A. 2007. The association between tinnitus and posttraumatic stress disorder. *American Journal of Audiology,* 16**,** 107-117.

FARAG, N., MOORE, W., LOVALLO, W., MILLS, P., KHANDRIKA, S. & EICHNER, J. 2008. Hypothalamic-Pituitary-Adrenal Axis Function: Relative Contributions of Perceived Stress and Obesity in Women. *Journal Of Womens Health,* 17**,** 1647-1655.

FARESJÖ, Å., JULLANDER, M., GÖTMALM, S. & THEODORSSON, E. 2014. Higher perceived stress and poorer health reflected in elevated cortisol concentrations measured in extracts of hair from middle-aged healthy women. *BMC Psychology,* 2**,** 1-9.

FARRELL PAGULAYAN, K., BUSCH, R. M., MEDINA, K. L., BARTOK, J. A. & KRIKORIAN, R. 2006. Developmental normative data for the Corsi Block-tapping task. *Journal of clinical and experimental neuropsychology,* 28**,** 1043-1052.

FENSKE, M. 2006. Urinary free cortisol and cortisone excretion in healthy individuals: Influence of water loading. *Steroids,* 71**,** 1014-1018.

FIELD, A. 2013. *Discovering statistics using IBM SPSS statistics*, sage.

FIELLIN, D. A., REID, M. C. & O'CONNOR, P. G. 2000. Screening for alcohol problems in primary care: a systematic review. *Archives of internal medicine,* 160**,** 1977-1989.

FIGUEROA, I. J. & YOUMANS, R. J. Failure to maintain set: A measure of distractibility or cognitive flexibility? Proceedings of the human factors and ergonomics society annual meeting, 2013. Sage Publications Sage CA: Los Angeles, CA, 828-832.

FINFGELD-CONNETT, D. 2005. Clarification of Social Support. *Journal of Nursing Scholarship,* 37**,** 4-9.

FINK, G., PFAFF, D. W. & LEVINE, J. 2012. Handbook of neuroendocrinology. *In:* FINK, G. P., D. W.; LEVINE, J. (ed.). Amsterdam; Boston: Academic Press/Elsevier.

FINNELL, J. E., LOMBARD, C. M., PADI, A. R., MOFFITT, C. M., WILSON, L. B., WOOD, C. S. & WOOD, S. K. 2017. Physical versus psychological social stress in male rats reveals distinct cardiovascular, inflammatory and behavioral consequences. *PloS one,* 12**,** e0172868-e0172868.

FIORETTI, A., EIBENSTEIN, A. & FUSETTI, M. 2011. New trends in tinnitus management. *The open neurology journal,* 5**,** 12-17.

FIORETTI, A. B., FUSETTI, M. & EIBENSTEIN, A. 2013. Association between sleep disorders, hyperacusis and tinnitus: evaluation with tinnitus questionnaires. *Noise and Health,* 15**,** 91.

FOLMER, R. L. & GRIEST, S. E. 2000. Tinnitus and insomnia. *American Journal of Otolaryngology,* 21**,** 287-293.

FOLMER, R. L., GRIEST, S. E., MEIKLE, M. B. & MARTIN, W. H. 1999. Tinnitus severity, loudness, and depression. *Otolaryngol Head Neck Surg,* 121**,** 48-51.

FORTENBAUGH, F. C., DEGUTIS, J., GERMINE, L., WILMER, J. B., GROSSO, M., RUSSO, K. & ESTERMAN, M. 2015. Sustained attention across the life span in a sample of 10,000: Dissociating ability and strategy. *Psychological science,* 26**,** 1497-1510.

FREDERIKSEN, T. W., RAMLAU-HANSEN, C. H., STOKHOLM, Z. A., GRYNDERUP, M. B., HANSEN, Å. M., LUND, S. P., KRISTIANSEN, J., VESTERGAARD, J. M., BONDE, J. P. & KOLSTAD, H. 2016. P121 Salivary cortisol and tinnitus. *Occupational and Environmental Medicine,* 73**,** A160-A160.

FRIEDLAND, N., KEINAN, G. & REGEV, Y. 1992. Controlling the uncontrollable: Effects of stress on illusory perceptions of controllability. *Journal of personality and social psychology,* 63**,** 923.

FULFORD, A. J. & HARBUZ, M. S. 2005. Chapter 1.3 - An introduction to the HPA axis. *In:* STECKLER, T., KALIN, N. H. & REUL, J. M. H. M. (eds.) *Techniques in the Behavioral and Neural Sciences.* Elsevier.

FULLER, T., CIMA, R., LANGGUTH, B., MAZUREK, B., VLAEYEN, J. W. S. & HOARE, D. J. 2020. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews*.

FULLER, T. E., HAIDER, H. F., KIKIDIS, D., LAPIRA, A., MAZUREK, B., NORENA, A., RABAU, S., LARDINOIS, R., CEDERROTH, C. R., EDVALL, N. K., BRUEGGEMANN, P. G., ROSING, S. N., KAPANDAIS, A., LUNGAARD, D., HOARE, D. J. & CIMA, R. F. F. 2017. Different Teams, Same Conclusions? A Systematic Review of Existing Clinical Guidelines for the Assessment and Treatment of Tinnitus in Adults. *Frontiers in Psychology,* 8**,** 206.

GAO, W., KIRSCHBAUM, C., GRASS, J. & STALDER, T. 2016. LC–MS based analysis of endogenous steroid hormones in human hair. *The Journal of Steroid Biochemistry and Molecular Biology,* 162**,** 92-99.

GENITSARIDI, E., PARTYKA, M., GALLUS, S., LOPEZ-ESCAMEZ, J. A., SCHECKLMANN, M., MIELCZAREK, M., TRPCHEVSKA, N., SANTACRUZ, J. L., SCHOISSWOHL, S., RIHA, C., LOURENCO, M., BISWAS, R., LIYANAGE, N., CEDERROTH, C. R., PEREZ-CARPENA, P., DEVOS, J., FULLER, T., EDVALL, N. K., HELLBERG, M. P., D'ANTONIO, A., GEREVINI, S., SEREDA, M., REIN, A., KYPRAIOS, T., HOARE, D. J., LONDERO, A., PRYSS, R., SCHLEE, W. & HALL, D. A. 2019. Standardised profiling for tinnitus research: The European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ). *Hear Res,* 377**,** 353-359.

GERBER, K. E., NEHEMKIS, A. M., CHARTER, R. A. & JONES, H. C. 1985. Is tinnitus a psychological disorder? *Int J Psychiatry Med,* 15**,** 81-7.

GERIN, W. 2011. Acute stress responses in the psychophysiological laboratory. *The handbook of stress science: biology, psychology, and health. New York: Springer***,** 501-514.

GHOSH, S., LAXMI, T. R. & CHATTARJI, S. 2013. Functional connectivity from the amygdala to the hippocampus grows stronger after stress. *Journal of Neuroscience,* 33**,** 7234-7244.

GLISKY, E. L. 2007. Changes in cognitive function in human aging. *Brain aging: Models, methods, and mechanisms,* 1.

GOLDBERG, S. B., MANLEY, A. R., SMITH, S. S., GREESON, J. M., RUSSELL, E., VAN UUM, S., KOREN, G. & DAVIS, J. M. 2014. Hair cortisol as a biomarker of stress in mindfulness training for smokers. *J Altern Complement Med,* 20**,** 630-4.

GOMAA, M., ELMAGD, M., ELBADRY, M. M. & KADER, R. 2014. Depression, Anxiety and Stress Scale in patients with tinnitus and hearing loss. *Eur Arch Otorhinolaryngol,* 271**,** 2177-84.

GONENDIK, Z. A., MUJDECI, B., KARAKURT, S. E. & DERE, H. H. 2021. Assessment of Stroop Color Word Interference Test-TBAG form performance in subjects with tinnitus. *European Archives of Oto-Rhino-Laryngology,* 278**,** 1403-1409.

GOTTLIEB, B. H. & BERGEN, A. E. 2010. Social support concepts and measures. *Journal of psychosomatic research,* 69**,** 511-520.

GOUIN, J.-P., GLASER, R., MALARKEY, W. B., BEVERSDORF, D. & KIECOLT-GLASER, J. 2012. Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology,* 31**,** 264.

GOW, R., KOREN, G., RIEDER, M. & VAN UUM, S. 2011. Hair cortisol content in patients with adrenal insufficiency on hydrocortisone replacement therapy. *Clin Endocrinol (Oxf),* 74**,** 687-93.

GRANATH, J., INGVARSSON, S., VON THIELE, U. & LUNDBERG, U. 2006. Stress management: a randomized study of cognitive behavioural therapy and yoga. *Cogn Behav Ther,* 35**,** 3-10.

GRANT, D. & BERG, E. 1948. The Wisconsin Card Sort Test: directions for administration and scoring. *Odessa: Psychological Assessment*.

GRAY, N., DHANA, A., VAN DER VYVER, L., VAN WYK, J., KHUMALO, N. & STEIN, D. 2018. Determinants of hair cortisol concentration in children: A systematic review. *Psychoneuroendocrinology,* 87**,** 204-214.

GREFF, M. J., LEVINE, J. M., ABUZGAIA, A. M., ELZAGALLAAI, A. A., RIEDER, M. J. & VAN UUM, S. H. 2019. Hair cortisol analysis: An update on methodological considerations and clinical applications. *Clinical biochemistry,* 63**,** 1-9.

GREVE, K. W. & BIANCHINI, K. J. 2002. Using the Wisconsin Card Sorting Test to Detect Malingering: An Analysis of the Specificity of Two Methods in Nonmalingering Normal and Patient Samples. *Journal of Clinical and Experimental Neuropsychology,* 24**,** 48-54.

GREVE, K. W., HEINLY, M. T., BIANCHINI, K. J. & LOVE, J. M. 2009. Malingering detection with the Wisconsin Card Sorting Test in mild traumatic brain injury. *The Clinical Neuropsychologist,* 23**,** 343-362.

GRISSOM, N. & BHATNAGAR, S. 2009. Habituation to repeated stress: get used to it. *Neurobiol Learn Mem,* 92**,** 215-24.

GROENEWEG, F. L., KARST, H., DE KLOET, E. R. & JOËLS, M. 2011. Rapid non-genomic effects of corticosteroids and their role in the central stress response. *Journal of endocrinology,* 209**,** 153-167.

GU, S., PASQUALETTI, F., CIESLAK, M., TELESFORD, Q. K., YU, A. B., KAHN, A. E., MEDAGLIA, J. D., VETTEL, J. M., MILLER, M. B., GRAFTON, S. T. & BASSETT,

D. S. 2015. Controllability of structural brain networks. *Nature Communications,* 6**,** 8414.

GUNBEY, H., GUNBEY, E., ASLAN, K., BULUT, T., UNAL, A. & INCESU, L. 2017. Limbic-auditory interactions of tinnitus: An evaluation using diffusion tensor imaging. *Clinical neuroradiology,* 27**,** 221-230.

GUTMAN, D. A. & NEMEROFF, C. B. 2011. Stress and depression. *The handbook of stress science: Biology, psychology, and health***,** 345-357.

HABER, M. G., COHEN, J. L., LUCAS, T. & BALTES, B. B. 2007. The relationship between self-reported received and perceived social support: A meta-analytic review. *American Journal of Community Psychology,* 39**,** 133-144.

HAGER, K., MACHEIN, U., KRIEGER, S., PLATT, D., SEEFRIED, G. & BAUER, J. 1994. Interleukin-6 and selected plasma proteins in healthy persons of different ages. *Neurobiology of Aging,* 15**,** 771-772.

HAIDER, H., FACKRELL, K., KENNEDY, V. & HALL, D. A. 2016. Dimensions of tinnitus-related complaints reported by patients and their significant others: protocol for a systematic review. *BMJ Open,* 6**,** e009171.

HAIDER, H. F., BOJIĆ, T., RIBEIRO, S. F., PAÇO, J., HALL, D. A. & SZCZEPEK, A. J. 2018. Pathophysiology of Subjective Tinnitus: Triggers and Maintenance. *Frontiers in Neuroscience,* 12.

HALL, D. A. 2017. Outcome measures associated with perceived stress. *Tinnitus and Stress.* Springer.

HALL, D. A., FACKRELL, K., LI, A. B., THAVAYOGAN, R., SMITH, S., KENNEDY, V., TINOCO, C., RODRIGUES, E. D., CAMPELO, P. & MARTINS, T. D. 2018. A narrative synthesis of research evidence for tinnitus-related complaints as reported by patients and their significant others. *Health and quality of life outcomes,* 16**,** 61.

HALL, D. A., MEHTA, R. L. & FACKRELL, K. 2017. How to choose between measures of tinnitus loudness for clinical research? A report on the reliability and validity of an investigator-administered test and a patient-reported measure using baseline data collected in a phase IIa drug trial. *American Journal of Audiology,* 26**,** 338-346.

HALLAM, R. S., JAKES, S. C. & HINCHCLIFFE, R. 1988. Cognitive variables in tinnitus annoyance. *Br J Clin Psychol,* 27 (Pt 3)**,** 213-22.

HAMMEN, C. 2004. Stress and Depression. *Annual Review of Clinical Psychology,* 1**,** 293-319.

HAN, B. I., LEE, H. W., KIM, T. Y., LIM, J. S. & SHIN, K. S. 2009. Tinnitus: Characteristics, Causes, Mechanisms, and Treatments. *Journal of Clinical Neurology (Seoul, Korea),* 5**,** 11-19.

HARKNESS, K. L. & MONROE, S. M. 2016. The assessment and measurement of adult life stress: Basic premises, operational principles, and design requirements. *Journal of Abnormal Psychology,* 125**,** 727-745.

HASHIMOTO, T., TAKEUCHI, H., TAKI, Y., SEKIGUCHI, A., NOUCHI, R., KOTOZAKI, Y., NAKAGAWA, S., MIYAUCHI, C. M., IIZUKA, K., YOKOYAMA, R., SHINADA, T., YAMAMOTO, Y., HANAWA, S., ARAKI, T., HASHIZUME, H., KUNITOKI, K. & KAWASHIMA, R. 2015. Neuroanatomical correlates of the sense of control: Gray and white matter volumes associated with an internal locus of control. *NeuroImage,* 119**,** 146-151.

HASSON, D., THEORELL, T., WALLÉN, M. B., LEINEWEBER, C. & CANLON, B. 2011. Stress and prevalence of hearing problems in the Swedish working population. *BMC Public Health,* 11**,** 130-130.

HAWKLEY, L. C., LAVELLE, L. A., BERNTSON, G. G. & CACIOPPO, J. T. 2011. Mediators of the relationship between socioeconomic status and allostatic load in the Chicago Health, Aging, and Social Relations Study (CHASRS). *Psychophysiology,* 48**,** 1134-1145.

HEALTH RESEARCH AUTHORITY. 2017. *Defining Research Table* [Online]. HRA. Available: http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf [Accessed 20.04.2020].

HEATON, R. K. 1981. Wisconsin card sorting test manual. *Psychological assessment resources*.

HEATON, R. K. & STAFF, P. 1993. Wisconsin card sorting test: computer version 2. *Odessa: Psychological Assessment Resources,* 4**,** 1-4.

HÉBERT, S., CANLON, B. & HASSON, D. 2012a. Emotional Exhaustion as a Predictor of Tinnitus. *Psychotherapy and Psychosomatics,* 81**,** 324-326.

HÉBERT, S., CANLON, B., HASSON, D., MAGNUSSON HANSON, L. L., WESTERLUND, H. & THEORELL, T. 2012b. Tinnitus Severity Is Reduced with Reduction of Depressive Mood – a Prospective Population Study in Sweden. *PLoS ONE,* 7**,** e37733.

HÉBERT, S. & CARRIER, J. 2007. Sleep Complaints in Elderly Tinnitus Patients: A Controlled Study. *Ear and Hearing,* 28.

HÉBERT, S., FULLUM, S. & CARRIER, J. 2011. Polysomnographic and quantitative electroencephalographic correlates of subjective sleep complaints in chronic tinnitus. *Journal of sleep research,* 20**,** 38-44.

HEBERT, S. & LUPIEN, S. J. 2007. The sound of stress: blunted cortisol reactivity to psychosocial stress in tinnitus sufferers. *Neurosci Lett,* 411**,** 138-42.

HEBERT, S. & LUPIEN, S. J. 2009. Salivary cortisol levels, subjective stress, and tinnitus intensity in tinnitus sufferers during noise exposure in the laboratory. *Int J Hyg Environ Health,* 212**,** 37-44.

HÉBERT, S., MAZUREK, B. & SZCZEPEK, A. J. 2017. Stress-Related Psychological Disorders and Tinnitus. *In:* SZCZEPEK, A. & MAZUREK, B. (eds.) *Tinnitus and Stress.* Springer.

HEBERT, S., PAIEMENT, P. & LUPIEN, S. J. 2004. A physiological correlate for the intolerance to both internal and external sounds. *Hear Res,* 190**,** 1-9.

HEINECKE, K., WEISE, C. & RIEF, W. 2009. Psychophysiological effects of biofeedback treatment in tinnitus sufferers. *British Journal of Clinical Psychology,* 48**,** 223-239.

HEINECKE, K., WEISE, C., SCHWARZ, K. & RIEF, W. 2008. Physiological and psychological stress reactivity in chronic tinnitus. *J Behav Med,* 31**,** 179-88.

HEINZE, K., LIN, A., RENIERS, R. L. & WOOD, S. J. 2016. Longer-term increased cortisol levels in young people with mental health problems. *Psychiatry Res,* 236**,** 98-104.

HELLER, M. F. & BERGMAN, M. 1953. VII Tinnitus aurium in normally hearing persons. *Annals of Otology, Rhinology & Laryngology,* 62**,** 73-83.

HELLHAMMER, D. H., WUST, S. & KUDIELKA, B. M. 2009. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology,* 34**,** 163-71.

HENLEY, P., JAHEDMOTLAGH, Z., THOMSON, S., HILL, J., DARNELL, R., JACOBS, D., JOHNSON, J., WILLIAMS, N. C., WILLIAMS, R. M., VAN UUM, S., BEND, J. R. & KOREN, G. 2013. Hair cortisol as a biomarker of stress among a first nation in Canada. *Ther Drug Monit,* 35**,** 595-9.

HENRY, J., MCMILLAN, L. & MANNING, C. 2019a. Multidisciplinary Tinnitus Care. *The Journal for Nurse Practitioners,* 15**,** 671-675.

HENRY, J., ZAUGG, T., MYERS, P. & KENDALL, C. 2010. Progressive Tinnitus Management. *Clinical Handbook for Audiologists Appendixes. Long Beach, CA: VA Employee Education System,* 59**,** 97.

HENRY, J. A. 2016. “Measurement” of Tinnitus. *Otology & Neurotology,* 37**,** e276-e285.

HENRY, J. A., JAMES, K. E., OWENS, K., ZAUGG, T., PORSOV, E. & SILASKI, G. 2009. Auditory test result characteristics of subjects with and without tinnitus. *Journal of Rehabilitation Research & Development,* 46.

HENRY, J. A., PISKOSZ, M., NORENA, A. & FOURNIER, P. 2019b. Audiologists and Tinnitus. *American journal of audiology,* 28**,** 1059-1064.

HENRY, J. A., ROBERTS, L. E., CASPARY, D. M., THEODOROFF, S. M. & SALVI, R. J. 2014. Underlying Mechanisms of Tinnitus: Review and Clinical Implications. *Journal of the American Academy of Audiology,* 25**,** 5-126.

HENRY, J. A., SCHECHTER, M. A., ZAUGG, T. L., GRIEST, S., JASTREBOFF, P. J., VERNON, J. A., KAELIN, C., MEIKLE, M. B., LYONS, K. S. & STEWART, B. J. 2006. Clinical trial to compare tinnitus masking and tinnitus retraining therapy. *Acta Oto-Laryngologica,* 126**,** 64-69.

HERANE-VIVES, A., PAPADOPOULOS, A., DE ANGEL, V., CHUA, K.-C., SOTO, L., CHALDER, T., YOUNG, A. H. & CLEARE, A. J. 2020. Cortisol levels in chronic fatigue syndrome and atypical depression measured using hair and saliva specimens. *Journal of Affective Disorders,* 267**,** 307-314.

HERMAN, J. P., MCKLVEEN, J. M., GHOSAL, S., KOPP, B., WULSIN, A., MAKINSON, R., SCHEIMANN, J. & MYERS, B. 2016. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Comprehensive Physiology.*

HESSE, G. 2016. Evidence and evidence gaps in tinnitus therapy. *GMS current topics in otorhinolaryngology, head and neck surgery,* 15.

HESSER, H., GUSTAFSSON, T., LUNDEN, C., HENRIKSON, O., FATTAHI, K., JOHNSSON, E., WESTIN, V. Z., CARLBRING, P., MAKI-TORKKO, E., KALDO, V. & ANDERSSON, G. 2012. A randomized controlled trial of internet-delivered cognitive behavior therapy and acceptance and commitment therapy in the treatment of tinnitus. *Journal of Consulting and Clinical Psychology,* 80**,** 649-661.

HILTON, M. P., ZIMMERMANN, E. F. & HUNT, W. T. 2013. Ginkgo biloba for tinnitus. *Cochrane Database of Systematic Reviews*.

HOARE, D., BROOMHEAD, E., STOCKDALE, D. & KENNEDY, V. 2015. Equity and person-centeredness in provision of tinnitus services in UK National Health Service

audiology departments. *European Journal for Person Centered Healthcare,* 3**,** 318-326.

HOARE, D. J., EDMONDSON-JONES, M., SEREDA, M., AKEROYD, M. A. & HALL, D. 2014. Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Cochrane Database of Systematic Reviews*.

HOBSON, J., CHISHOLM, E. & EL REFAIE, A. 2012. Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database of Systematic Reviews*.

HODES, A., LODISH, M. B., TIROSH, A., MEYER, J., BELYAVSKAYA, E., LYSSIKATOS, C., ROSENBERG, K., DEMIDOWICH, A., SWAN, J., JONAS, N., STRATAKIS, C. A. & ZILBERMINT, M. 2017. Hair cortisol in the evaluation of Cushing syndrome. *Endocrine,* 56**,** 164-174.

HOEKSTRA, C. E. L., RYNJA, S. P., VAN ZANTEN, G. A. & ROVERS, M. M. 2011. Anticonvulsants for tinnitus. *Cochrane Database of Systematic Reviews*.

HOLMES, T. H. & RAHE, R. H. 1967. The social readjustment rating scale. *Journal of psychosomatic research,* 11**,** 213-218.

HOMACK, S. & RICCIO, C. A. 2004. A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. *Archives of Clinical Neuropsychology,* 19**,** 725-743.

HOPKINSON, M. D., REAVELL, J., LANE, D. A. & MALLIKARJUN, P. 2019. Cognitive Behavioral Therapy for Depression, Anxiety, and Stress in Caregivers of Dementia Patients: A Systematic Review and Meta-Analysis. *The Gerontologist,* 59**,** e343-e362.

HORNER, K. C. 2003. The emotional ear in stress. *Neuroscience & Biobehavioral Reviews,* 27**,** 437-446.

HOWZE, P. C. & DALRYMPLE, C. 2004. Consensus without all the meetings: using the Delphi method to determine course content for library instruction. *Reference Services Review,* 32**,** 174-184.

HUANG, Y. & RAO, R. P. N. 2011. Predictive coding. *WIREs Cognitive Science,* 2**,** 580-593.

HUBER, G., SCHUSTER, F. & RAASCH, W. 2017. Brain renin-angiotensin system in the pathophysiology of cardiovascular diseases. *Pharmacological Research,* 125**,** 72-90.

HUBERTY, J., GREEN, J., GLISSMANN, C., LARKEY, L., PUZIA, M. & LEE, C. 2019. Efficacy of the mindfulness meditation mobile app “Calm” to reduce stress among college students: Randomized controlled trial. *JMIR mHealth and uHealth,* 7**,** e14273.

HUSAIN, F. T. 2016. Neural networks of tinnitus in humans: elucidating severity and habituation. *Hearing research,* 334**,** 37-48.

IGLESIAS, S., JACOBSEN, D., GONZALEZ, D., AZZARA, S., REPETTO, E. M., JAMARDO, J., GOMEZ, S. G., MESCH, V., BERG, G. & FABRE, B. 2015. Hair cortisol: A new tool for evaluating stress in programs of stress management. *Life Sci,* 141**,** 188-92.

IMAM, S. S. 2008. Depression anxiety stress scales (DASS): Revisited. *The Journal of Behavioral Science,* 3**,** 104-116.

INAGAKI, Y., SUZUKI, N., OISHI, N., GOTO, F., SHINDEN, S. & OGAWA, K. 2021. Personality and sleep evaluation of patients with tinnitus in Japan. *Psychiatric Quarterly,* 92**,** 249-257.

IOB, E., KIRSCHBAUM, C. & STEPTOE, A. 2018. Positive and negative social support and HPA-axis hyperactivity: Evidence from glucocorticoids in human hair. *Psychoneuroendocrinology,* 96**,** 100-108.

JACKSON, J. G. 2019. The Cortisol Awakening Response: A Feasibility Study Investigating the Use of the Area Under the Curve With Respect to Increase as an Effective Objective Measure of Tinnitus Distress. *American journal of audiology,* 28**,** 583-596.

JACKSON, R., VIJENDREN, A. & PHILLIPS, J. 2019. Objective measures of tinnitus: a systematic review. *Otology & Neurotology,* 40**,** 154-163.

JACKSON, S. E., KIRSCHBAUM, C. & STEPTOE, A. 2017. Hair cortisol and adiposity in a population-based sample of 2,527 men and women aged 54 to 87 years. *Obesity (Silver Spring),* 25**,** 539-544.

JACOBSON, D. E. 1986. Types and timing of social support. *Journal of health and Social Behavior***,** 250-264.

JASON, R. B., SARA, J. A.-K., CHRISTOPHER, L. & JOHN, P. L. 2016. The Persistence of Tinnitus after Acoustic Neuroma Surgery. *Otolaryngology-Head and Neck Surgery,* 155**,** 317-323.

JASTREBOFF, P. J. 1990. Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neuroscience Research,* 8**,** 221-254.

JASTREBOFF, P. J. & HAZELL, J. W. 2008. *Tinnitus retraining therapy: Implementing the neurophysiological model*, Cambridge University Press.

JAWORSKA, N. & CHUPETLOVSKA-ANASTASOVA, A. 2009. A review of multidimensional scaling (MDS) and its utility in various psychological domains. *Tutorials in quantitative methods for psychology,* 5**,** 1-10.

JOËLS, M. & BARAM, T. Z. 2009. The neuro-symphony of stress. *Nature reviews neuroscience,* 10**,** 459.

JOËLS, M., DE KLOET, E. R. & KARST, H. 2012. Corticosteroid Actions on Neurotransmission. *In:* FINK, G. P., D. W. ; LEVINE, J. E. (ed.) *Handbook of Neuroendocrinology.* Amsterdam; Boston.: Elsevier.

JUSTER, R.-P., MCEWEN, B. S. & LUPIEN, S. J. 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews,* 35**,** 2-16.

KABAT-ZINN, J., LIPWORTH, L., BURNEY, R. & SELLERS, W. 1987. Four-Year Follow-Up of a Meditation-Based Program for the Self-Regulation of Chronic Pain: Treatment Outcomes and Compliance. *The Clinical Journal of Pain,* 3**,** 60.

KAGAN, J. 2016. An overly permissive extension. *Perspectives on Psychological Science,* 11**,** 442-450.

KALLIOKOSKI, O., JELLESTAD, F. K. & MURISON, R. 2019. A systematic review of studies utilizing hair glucocorticoids as a measure of stress suggests the marker is more appropriate for quantifying short-term stressors. *Scientific reports,* 9**,** 1-14.

KANE, M. & TROCHIM, W., M. 2007. Concept Mapping for Planning and Evaluation. Thousand Oaks, California: SAGE Publications, Inc.

KANNER, A. D., COYNE, J. C., SCHAEFER, C. & LAZARUS, R. S. 1981. Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of behavioral medicine,* 4**,** 1-39.

KARASEK, R. A. 1981. Job socialization and job strain: The implications of two related psychosocial mechanisms for job design. *Working Life: A social science contribution to work reform (Gardell B, and Johansson G, eds.). London: Wiley*.

KARATSOREOS, I. N. 2018. Stress: Common themes toward the next frontier. *Frontiers in neuroendocrinology,* 49**,** 3-7.

KARATSOREOS, I. N. & MCEWEN, B. S. 2011. Psychobiological allostasis: resistance, resilience and vulnerability. *Trends Cogn Sci,* 15**,** 576-84.

KARLAMANGLA, A. S., SINGER, B. H., CHODOSH, J., MCEWEN, B. S. & SEEMAN, T. E. 2005. Urinary cortisol excretion as a predictor of incident cognitive impairment. *Neurobiology of Aging,* 26**,** 80-84.

KELLEY, K., CLARK, B., BROWN, V. & SITZIA, J. 2003. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care,* 15**,** 261-6.

KENNEDY, V., WILSON, C. & STEPHENS, D. 2004. Quality of life and tinnitus. *Audiological medicine,* 2**,** 29-40.

KESSELS, R. P., VAN DEN BERG, E., RUIS, C. & BRANDS, A. M. 2008. The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment,* 15**,** 426-434.

KESSELS, R. P. C., VAN ZANDVOORT, M. J. E., POSTMA, A., KAPPELLE, L. J. & DE HAAN, E. H. F. 2000. The Corsi Block-Tapping Task: Standardization and Normative Data. *Applied Neuropsychology,* 7**,** 252-258.

KESSLER, R. C., PRICE, R. H. & WORTMAN, C. B. 1985. Social Factors in Psychopathology: Stress, Social Support, and Coping Processes. *Annual Review of Psychology,* 36**,** 531-572.

KHAN, R. A. & HUSAIN, F. T. 2020. Tinnitus and cognition: Can load theory help us refine our understanding? *Laryngoscope Investigative Otolaryngology,* 5**,** 1197-1204.

KILROY, N. & EL REFAIE, A. 2020. Tinnitus management in Ireland: a pilot study of general practitioners. *Irish Journal of Medical Science (1971-)***,** 1-11.

KIM, D., CHUNG, D., BAE, S. C., PARK, K., YEO, S. & PARK, S. 2014. Diagnostic value and clinical significance of stress hormones in patients with tinnitus. *European Archives Of Oto-Rhino-Laryngology,* 271**,** 2915-2921.

KIM, H.-G., CHEON, E.-J., BAI, D.-S., LEE, Y. H. & KOO, B.-H. 2018. Stress and heart rate variability: A meta-analysis and review of the literature. *Psychiatry investigation,* 15**,** 235.

KIM, J.-I., CHOI, J.-Y., LEE, D.-H., CHOI, T.-Y., LEE, M. S. & ERNST, E. 2012. Acupuncture for the treatment of tinnitus: a systematic review of randomized clinical trials. *BMC complementary and alternative medicine,* 12**,** 97.

KINO, T. 2015. Stress, glucocorticoid hormones, and hippocampal neural progenitor cells: implications to mood disorders. *Frontiers in Physiology,* 6**,** 230.

KIRA, I. A., SHUWIEKH, H. A. M., RICE, K. G., ASHBY, J. S., ELWAKEEL, S. A., SOUS, M. S. F., ALHUWAILAH, A., BAALI, S. B. A., AZDAOU, C., OLIEMAT, E. M. & JAMIL, H. J. 2021. Measuring COVID-19 as Traumatic Stress: Initial Psychometrics and Validation. *Journal of Loss and Trauma,* 26**,** 220-237.

KIRSCH, C. A. & BLANCHARD, E. B. 1987. A multiple-baseline evaluation of the treatment of subjective tinnitus with relaxation training and biofeedback. *Biofeedback and Self-Regulation,* 12**,** 295-312.

KLEINJUNG, T. & LANGGUTH, B. 2020. Avenue for Future Tinnitus Treatments. *Otolaryngologic Clinics of North America*.

KNOPKE, S., SZCZEPEK, A. J., HÄUSSLER, S. M., GRÄBEL, S. & OLZE, H. 2017. Cochlear implantation of bilaterally deafened patients with tinnitus induces sustained decrease of tinnitus-related distress. *Frontiers in neurology,* 8**,** 158.

KOCALEVENT, R.-D., BERG, L., BEUTEL, M. E., HINZ, A., ZENGER, M., HÄRTER, M., NATER, U. & BRÄHLER, E. 2018. Social support in the general population: standardization of the Oslo social support scale (OSSS-3). *BMC Psychology,* 6**,** 31.

KÖHN, M., PERSSON LUNDHOLM, U., BRYNGELSSON, I.-L., ANDERZÉN-CARLSSON, A. & WESTERDAHL, E. 2013. Medical yoga for patients with stress-related symptoms and diagnoses in primary health care: a randomized controlled trial. *Evidence-Based Complementary and Alternative Medicine,* 2013.

KOKSOY, S., ETI, C. M., KARATAS, M. & VAYISOGLU, Y. 2017. The Effects of Yoga in Patients Suffering from Subjective Tinnitus. *International Archives of Otorhinolaryngology*.

KONADATH, S. & MANJULA, P. 2016. Auditory brainstem response and late latency response in individuals with tinnitus having normal hearing. *Intractable & Rare Diseases Research,* 5**,** 262-268.

KOOLHAAS, J. M., BARTOLOMUCCI, A., BUWALDA, B., DE BOER, S. F., FLÜGGE, G., KORTE, S. M., MEERLO, P., MURISON, R., OLIVIER, B. & PALANZA, P. 2011. Stress revisited: a critical evaluation of the stress concept. *Neuroscience & Biobehavioral Reviews,* 35**,** 1291-1301.

KOUMANTAROU MALISIOVA, E., MOURIKIS, I., DARVIRI, C., ZERVAS, I. M., PAPAGEORGIOU, C. & CHROUSOS, G. P. 2020. Hair cortisol concentrations in mental disorders: A systematic review. *Physiology & Behavior***,** 113244.

KOVACS, K. J., MILKLOS, I. H. & BALI, B. 2004. Psychological and physiological stressors. *In:* STECKLER, T. K., N.H.; REUL, J.M.H.M. (ed.) *Handbook on stress and the brain. Part 1, The neurobiology of stress.* Amsterdam: London: Elsevier.

KRAAN, G. P., DULLAART, R. P., PRATT, J. J., WOLTHERS, B. G., DRAYER, N. M. & DE BRUIN, R. 1998. The daily cortisol production reinvestigated in healthy men. The serum and urinary cortisol production rates are not significantly different. *The Journal of Clinical Endocrinology & Metabolism,* 83**,** 1247-1252.

KREUZER, P. M., VIELSMEIER, V. & LANGGUTH, B. 2013. Chronic Tinnitus: an Interdisciplinary Challenge. *Deutsches Ärzteblatt International,* 110**,** 278-284.

KRUSKAL, J. B. 1964. Multidimensional scaling by optimizing goodness of fit to a nonmetric hypothesis. *Psychometrika,* 29**,** 1-27.

KUK, F. K., TYLER, R. S., RUSSELL, D. & JORDAN, H. 1990. The psychometric properties of a tinnitus handicap questionnaire. *Ear Hear,* 11**,** 434-45.

KUMARAN, D. 2008. Short-term memory and the human hippocampus. *Journal of Neuroscience,* 28**,** 3837-3838.

LANDGREBE, M., LANGGUTH, B., ROSENGARTH, K., BRAUN, S., KOCH, A., KLEINJUNG, T., MAY, A., DE RIDDER, D. & HAJAK, G. 2009. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. *Neuroimage,* 46**,** 213-8.

LANDRY, E. C., SANDOVAL, X. C. R., SIMEONE, C. N., TIDBALL, G., LEA, J. & WESTERBERG, B. D. 2020. Systematic review and network meta-analysis of cognitive and/or behavioral therapies (CBT) for tinnitus. *Otology & Neurotology,* 41**,** 153-166.

LANFEAR, J. H., VOEGEL, C. D., BINZ, T. M. & PAUL, R. A. 2020. Hair cortisol measurement in older adults: Influence of demographic and physiological factors and correlation with perceived stress. *Steroids,* 163**,** 108712.

LANGGUTH, B., GOODEY, R., AZEVEDO, A., BJORNE, A., CACACE, A., CROCETTI, A., DEL BO, L., DE RIDDER, D., DIGES, I. & ELBERT, T. 2007. Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. *Progress in brain research,* 166**,** 525-536.

LARSSON, G., BERGLUND, A. K. & OHLSSON, A. 2016. Daily hassles, their antecedents and outcomes among professional first responders: A systematic literature review. *Scandinavian Journal of Psychology,* 57**,** 359-367.

LAU, Y., HTUN, T. P., WONG, S. N., TAM, W. S. W. & KLAININ-YOBAS, P. 2017. Therapist-supported internet-based cognitive behavior therapy for stress, anxiety, and depressive symptoms among postpartum women: a systematic review and meta-analysis. *Journal of medical Internet research,* 19**,** e138.

LAURES-GORE, J., S., DUBAY, M., F., DUFF, M., C. & BUCHANAN, T., W. 2010. Identifying Behavioral Measures of Stress in Individuals With Aphasia. *Journal of Speech, Language, and Hearing Research,* 53**,** 1394-1400.

LAZARUS, R. S. 2000. Toward better research on stress and coping.

LAZARUS, R. S. & FOLKMAN, S. 1984. *Stress, appraisal, and coping* New York, New York : Springer.

LAZARUS, R. S. & FOLKMAN, S. 1987. Transactional theory and research on emotions and coping. *European Journal of Personality,* 1**,** 141-169.

LEAVER, A., SEYDELL-GREENWALD, A., TURESKY, T., MORGAN, S., KIM, H. & RAUSCHECKER, J. 2012. Cortico-limbic morphology separates tinnitus from tinnitus distress. *Frontiers in Systems Neuroscience,* 6.

LEAVER, A. M., RENIER, L., CHEVILLET, M. A., MORGAN, S., KIM, H. J. & RAUSCHECKER, J. P. 2011. Dysregulation of limbic and auditory networks in tinnitus. *Neuron,* 69**,** 33-43.

LEBEAU, M. A., MONTGOMERY, M. A. & BREWER, J. D. 2011. The role of variations in growth rate and sample collection on interpreting results of segmental analyses of hair. *Forensic science international,* 210**,** 110-116.

LEDOUX, J. 2007. The amygdala. *Current biology,* 17**,** R868-R874.

LEE, J. H., RA, J. J. & KIM, Y. H. 2014. Adequacy of the simplified version of the Tinnitus Handicap Inventory (THI-S) to measure tinnitus handicap and relevant distress. *Korean Journal of Audiology,* 18**,** 19-27.

LEMYRE, L. & TESSIER, R. 1988. Mesure de Stress Psychologique (MSP): Se sentir stressé-e. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement,* 20**,** 302.

LENG, Y., MUSIEK, E. S., HU, K., CAPPUCCIO, F. P. & YAFFE, K. 2019. Association between circadian rhythms and neurodegenerative diseases. *The Lancet Neurology,* 18**,** 307-318.

LEONG, S. L., TCHEN, S., ROBERTSON, I. H., ALSALMAN, O., TO, W. T. & VANNESTE, S. 2020. The potential interruptive effect of tinnitus-related distress on attention. *Scientific Reports,* 10**,** 11911.

LEVAC, D., COLQUHOUN, H. & O'BRIEN, K. K. 2010. Scoping studies: advancing the methodology. *Implementation Science : IS,* 5**,** 69-69.

LEVENSTEIN, S., PRANTERA, C., VARVO, V., SCRIBANO, M., BERTO, E., LUZI, C. & ANDREOLI, A. 1993. Development of the Perceived Stress Questionnaire - A new tool for psychosomatic research. *Journal Of Psychosomatic Research,* 37**,** 19-32.

LEVINE, A., ZAGOORY-SHARON, O., FELDMAN, R., LEWIS, J. G. & WELLER, A. 2007. Measuring cortisol in human psychobiological studies. *Physiology & Behavior,* 90**,** 43-53.

LEVINE, J. E. 2012. An Introduction to Neuroendocrine System. *In:* FINK, G. P., D. W. ; LEVINE, J. E. (ed.) *Handbook of neuroendocrinology.* 1st ed. Amsterdam; Boston.: Academic Press/Elsevier.

LI, J., JIN, J., XI, S., ZHU, Q., CHEN, Y., HUANG, M. & HE, C. 2019a. Clinical efficacy of cognitive behavioral therapy for chronic subjective tinnitus. *Am J Otolaryngol,* 40**,** 253-256.

LI, Y.-L., HSU, Y.-C., LIN, C.-Y. & WU, J.-L. 2021. Sleep disturbance and psychological distress in adult patients with tinnitus. *Journal of the Formosan Medical Association*.

LI, Y., QIN, J., YAN, J., ZHANG, N., XU, Y., ZHU, Y., SHENG, L., ZHU, X. & JU, S. 2019b. Differences of physical vs. psychological stress: evidences from glucocorticoid receptor expression, hippocampal subfields injury, and behavioral abnormalities. *Brain imaging and behavior,* 13**,** 1780-1788.

LIGHTMAN, S. L. & CONWAY-CAMPBELL, B. L. 2010. The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration. *Nature Reviews Neuroscience,* 11**,** 710-718.

LIN, Y.-H., CHEN, C.-Y., HONG, W.-H. & LIN, Y.-C. 2010. Perceived job stress and health complaints at a bank call center: comparison between inbound and outbound services. *Industrial health,* 48**,** 349-356.

LINDBERG, P., LYTTKENS, L., MELIN, L. & SCOTT, B. 1984. Tinnitus-incidence and handicap. *Scandinavian Audiology,* 13**,** 287-291.

LING, J., XU, D., ROBBINS, L. B. & MEYER, J. S. 2020. Does hair cortisol really reflect perceived stress? Findings from low-income mother-preschooler dyads. *Psychoneuroendocrinology,* 111**,** 104478.

LOVIBOND, P. F. & LOVIBOND, S. H. 1995. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther,* 33**,** 335-43.

LU, T., LI, S., MA, Y., LAI, D., ZHONG, J., LI, G. & ZHENG, Y. 2020. Positive correlation between tinnitus severity and poor sleep quality prior to tinnitus onset: a retrospective study. *Psychiatric Quarterly,* 91**,** 379-388.

LUDWIG, L., PASMAN, J. A., NICHOLSON, T., AYBEK, S., DAVID, A. S., TUCK, S., KANAAN, R. A., ROELOFS, K., CARSON, A. & STONE, J. 2018. Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. *The Lancet Psychiatry,* 5**,** 307-320.

LUGO, A., EDVALL, N. K., LAZAR, A., MEHRAEI, G., LOPEZ-ESCAMEZ, J.-A., BULLA, J., UHLEN, I., CANLON, B., GALLUS, S. & CEDERROTH, C. R. 2020. Relationship between headaches and tinnitus in a Swedish study. *Scientific Reports,* 10**,** 8494.

MAES, M., LIN, A., BONACCCORSO, S., VAN HUNSEL, F., GASTEL, A. V., DELMEIRE, L., BIONDI, M., BOSMANS, E., KENIS, G. & SCHARPÉ, S. 1998. Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not h patients with fibromyalgia. *Acta Psychiatrica Scandinavica,* 98**,** 328-335.

MALESCI, R., BRIGATO, F., DI CESARE, T., DEL VECCHIO, V., LARIA, C., DE CORSO, E. & FETONI, A. R. 2021. Tinnitus and Neuropsychological Dysfunction in the Elderly: A Systematic Review on Possible Links. *Journal of Clinical Medicine,* 10.

MANENSCHIJN, L., KOPER, J. W., LAMBERTS, S. W. J. & VAN ROSSUM, E. F. C. 2011. Evaluation of a method to measure long term cortisol levels. *Steroids,* 76**,** 1032-1036.

MANENSCHIJN, L., KOPER, J. W., VAN DEN AKKER, E. L. T., DE HEIDE, L. J. M., GEERDINK, E. A. M., DE JONG, F. H., FEELDERS, R. A. & VAN ROSSUM, E. F. C. 2012. A Novel Tool in the Diagnosis and Follow-Up of (Cyclic) Cushing's Syndrome: Measurement of Long-Term Cortisol in Scalp Hair. *The Journal of Clinical Endocrinology & Metabolism,* 97**,** E1836-E1843.

MANNING, C., THIELMAN, E. J., GRUSH, L. & HENRY, J. A. 2019. Perception versus reaction: comparison of tinnitus psychoacoustic measures and Tinnitus Functional Index scores. *American journal of audiology,* 28**,** 174-180.

MARKS, D. F. & YARDLEY, L. 2004. Content and Thematic Analysis. *Research methods for clinical and health psychology.* London: Sage.

MARSHMAN, Z. & WILLIAMS, C. 2017. Cognitive Behavioural Therapy. *In:* CAMPBELL, C. (ed.) *Dental Fear and Anxiety in Pediatric Patients: Practical Strategies to Help Children Cope.* Cham: Springer International Publishing.

MARTIN, D. J., OREN, Z. & BOONE, K. 1991. Major depressives' and dysthymics' performance on the wisconsin card sorting test. *Journal of Clinical Psychology,* 47**,** 684-690.

MARTINES, F., BENTIVEGNA, D., MARTINES, E., SCIACCA, V. & MARTINCIGLIO, G. 2010. Characteristics of tinnitus with or without hearing loss: clinical observations in Sicilian tinnitus patients. *Auris Nasus Larynx,* 37**,** 685-93.

MARTINEZ-DEVESA, P., PERERA, R., THEODOULOU, M. & WADDELL, A. 2010. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews*.

MARTINEZ, C., WALLENHORST, C., MCFERRAN, D. & HALL, D. A. 2015. Incidence rates of clinically significant tinnitus: 10-year trend from a cohort study in England. *Ear Hear,* 36**,** e69-75.

MARTZ, E. 2016. Coping with tinnitus. *Journal of rehabilitation research and development,* 53**,** 729.

MAYER, E. A., NALIBOFF, B. D., CHANG, L. & COUTINHO, S. V. 2001. V. Stress and irritable bowel syndrome. *American Journal of Physiology-Gastrointestinal and Liver Physiology,* 280**,** G519-G524.

MAZUREK, B., BOECKING, B. & BRUEGGEMANN, P. 2019. Association Between Stress and Tinnitus—New Aspects. *Otology & Neurotology,* 40.

MAZUREK, B., HAUPT, H., OLZE, H. & SZCZEPEK, A. J. 2012. Stress and tinnitus—from bedside to bench and back. *Frontiers in Systems Neuroscience,* 6**,** 47.

MAZUREK, B., SZCZEPEK, A. J. & HEBERT, S. 2015. Stress and tinnitus. *HNO,* 63**,** 258-265.

MCCORMACK, A., EDMONDSON-JONES, M., SOMERSET, S. & HALL, D. 2016. A systematic review of the reporting of tinnitus prevalence and severity. *Hearing Research,* 337**,** 70-79.

MCEWEN, B. S. 1998. Protective and damaging effects of stress mediators. *New England journal of medicine,* 338**,** 171-179.

MCEWEN, B. S. 2003. Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. *Metabolism,* 52**,** 10-16.

MCEWEN, B. S. 2005. Stressed or stressed out: What is the difference? *Journal of Psychiatry and Neuroscience,* 30**,** 315-318.

MCEWEN, B. S. 2017. Neurobiological and systemic effects of chronic stress. *Chronic Stress,* 1**,** 2470547017692328.

MCEWEN, B. S. 2019. What is the confusion with cortisol? *Chronic Stress,* 3**,** 2470547019833647.

MCEWEN, B. S. & AKIL, H. 2020. Revisiting the Stress Concept: Implications for Affective Disorders. *Journal of Neuroscience,* 40**,** 12-21.

MCEWEN, B. S. & STELLAR, E. 1993. Stress and the individual: mechanisms leading to disease. *Archives of internal medicine,* 153**,** 2093-2101.

MCFERRAN, D., HOARE, D. J., CARR, S., RAY, J. & STOCKDALE, D. 2018. Tinnitus services in the United Kingdom: a survey of patient experiences. *BMC health services research,* 18**,** 110.

MCFERRAN, D. J., STOCKDALE, D. J., HOLME, R., LARGE, C. H. & BAGULEY, D. M. 2019. Why is there no cure for tinnitus? *Frontiers in neuroscience,* 13**,** 802.

MCINTOSH, C. 2005. ESTIMATING MEDIATED EFFECTS IN HEALTH AND EPIDEMIOGICAL RESEARCH. *Proceedings of Statistics Canada Symposium 2005. Methodological Challenges for Future Information Needs.* Canada: Statistics Canada.

MCKIMMIE, B. M., BUTLER, T., CHAN, E., ROGERS, A. & JIMMIESON, N. L. 2019. Reducing stress: Social support and group identification. *Group Processes & Intergroup Relations***,** 1368430218818733.

MCNEILL, C., TAVORA-VIEIRA, D., ALNAFJAN, F., SEARCHFIELD, G. & WELCH, D. 2012. Tinnitus pitch, masking, and the effectiveness of hearing aids for tinnitus therapy. *International Journal Of Audiology,* 51**,** 914-919.

MEIKLE, M. B., HENRY, J. A., GRIEST, S. E., STEWART, B. J., ABRAMS, H. B., MCARDLE, R., MYERS, P. J., NEWMAN, C. W., SANDRIDGE, S., TURK, D. C., FOLMER, R. L., FREDERICK, E. J., HOUSE, J. W., JACOBSON, G. P., KINNEY, S. E., MARTIN, W. H., NAGLER, S. M., REICH, G. E., SEARCHFIELD, G., SWEETOW, R. & VERNON, J. A. 2012. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear,* 33**,** 153-76.

MEIKLE, M. B., STEWART, B. J., GRIEST, S. E. & HENRY, J. A. 2008. Tinnitus Outcomes Assessment. *Trends in Amplification,* 12**,** 223-235.

MELROSE, K. L., BROWN, G. D. A. & WOOD, A. M. 2015. When is received social support related to perceived support and well-being? When it is needed. *Personality and Individual Differences,* 77**,** 97-105.

MENG, Z., LIU, S., ZHENG, Y. & PHILLIPS, J. S. 2011. Repetitive transcranial magnetic stimulation for tinnitus. *Cochrane Database of Systematic Reviews*.

MEWES, R., REICH, H., SKOLUDA, N., SEELE, F. & NATER, U. M. 2017. Elevated hair cortisol concentrations in recently fled asylum seekers in comparison to permanently settled immigrants and non-immigrants. *Transl Psychiatry,* 7**,** e1051.

MEYER, J. S. & NOVAK, M. A. 2012. Minireview: hair cortisol: a novel biomarker of hypothalamic-pituitary-adrenocortical activity. *Endocrinology,* 153**,** 4120-4127.

MILEROVA, J., ANDERS, M., DVORAK, T., SAND, P. G., KONIGER, S. & LANGGUTH, B. 2013. The influence of psychological factors on tinnitus severity. *Gen Hosp Psychiatry,* 35**,** 412-6.

MILLER, E. K. & COHEN, J. D. 2001. An integrative theory of prefrontal cortex function. *Annual review of neuroscience,* 24**,** 167-202.

MILLER, M. A. & RAHE, R. H. 1997. Life changes scaling for the 1990s. *Journal Of Psychosomatic Research,* 43**,** 279-292.

MILLOY, V., FOURNIER, P., BENOIT, D., NOREÑA, A. & KORAVAND, A. 2017. Auditory brainstem responses in tinnitus: a review of who, how, and what? *Frontiers in aging neuroscience,* 9**,** 237.

MIRODDI, M., BRUNO, R., GALLETTI, F., CALAPAI, F., NAVARRA, M., GANGEMI, S. & CALAPAI, G. 2015. Clinical pharmacology of melatonin in the treatment of tinnitus: a review. *European journal of clinical pharmacology,* 71**,** 263-270.

MOHAMAD, N., HOARE, D. J. & HALL, D. A. 2016. The consequences of tinnitus and tinnitus severity on cognition: A review of the behavioural evidence. *Hearing Research,* 332**,** 199-209.

MOHAMAD, W. N. 2015. *Tinnitus : priority research questions and the impact of the condition for working memory and attention / Wan Najibah Wan Mohamad.* Thesis (PhD)--University of Nottingham.

MØLLER, A. R. 2016. Sensorineural tinnitus: its pathology and probable therapies. *International journal of otolaryngology,* 2016**,** 2830157.

MONROE, S. M. 2008. Modern approaches to conceptualizing and measuring human life stress. *Annu. Rev. Clin. Psychol.,* 4**,** 33-52.

MORRISON, V. & BENNETT, P. 2009. *An introduction to health psychology,* Harlow, Harlow : Pearson.

MUELLER, S. T. & PIPER, B. J. 2014. The psychology experiment building language (PEBL) and PEBL test battery. *Journal of neuroscience methods,* 222**,** 250-259.

MULLER, K., EDVALL, N. K., IDRIZBEGOVIC, E., HUHN, R., CIMA, R., PERSSON, V., LEINEWEBER, C., WESTERLUND, H., LANGGUTH, B., SCHLEE, W., CANLON, B. & CEDERROTH, C. R. 2016. Validation of online versions of tinnitus questionnaires translated into Swedish. *Frontiers in Aging Neuroscience,* 8.

MUNN, Z., PETERS, M. D. J., STERN, C., TUFANARU, C., MCARTHUR, A. & AROMATARIS, E. 2018. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology,* 18**,** 143.

MYERS, B., MCKLVEEN, J. M. & HERMAN, J. P. 2012. Neural regulation of the stress response: the many faces of feedback. *Cellular and molecular neurobiology,* 32**,** 683-694.

NEWMAN, C. W., JACOBSON, G. P. & SPITZER, J. B. 1996. Development of the tinnitus handicap inventory. *Archives of Otolaryngology–Head & Neck Surgery,* 122**,** 143-148.

NEWTON, P. E. & SHAW, S. D. 2016. Disagreement over the best way to use the word 'validity'and options for reaching consensus. *Assessment in Education: Principles, Policy & Practice,* 23**,** 178-197.

NICE. 2020. *Tinnitus: assessment and management* [Online]. Available: https://www.nice.org.uk/guidance/ng155/resources/tinnitus-assessment-and-management [Accessed 12.03.2020].

NOPPE, G., DE RIJKE, Y. B., DORST, K., VAN DEN AKKER, E. L. T. & VAN ROSSUM, E. F. C. 2015. LC-MS/MS-based method for long-term steroid profiling in human scalp hair. *Clinical Endocrinology,* 83**,** 162-166.

NOREÑA, A. J. 2015. Revisiting the cochlear and central mechanisms of tinnitus and therapeutic approaches. *Audiology and Neurotology,* 20**,** 53-59.

NOREÑA, A. J. & FARLEY, B. J. 2013. Tinnitus-related neural activity: theories of generation, propagation, and centralization. *Hearing Research,* 295**,** 161-171.

OLSTHOORN, N. M., ANDRINGA, S. & HULSTIJN, J. H. 2012. Visual and auditory digit-span performance in native and non-native speakers. *International Journal of Bilingualism,* 18**,** 663-673.

OLZE, H., GRABEL, S., FORSTER, U., ZIRKE, N., HUHND, L. E., HAUPT, H. & MAZUREK, B. 2012. Elderly patients benefit from cochlear implantation regarding auditory rehabilitation, quality of life, tinnitus, and stress. *Laryngoscope,* 122**,** 196-203.

OLZE, H., SZCZEPEK, A. J., HAUPT, H., FORSTER, U., ZIRKE, N., GRABEL, S. & MAZUREK, B. 2011a. Cochlear implantation has a positive influence on quality of life, tinnitus, and psychological comorbidity. *Laryngoscope,* 121**,** 2220-7.

OLZE, H., SZCZEPEK, A. J., HAUPT, H., ZIRKE, N., GRAEBEL, S. & MAZUREK, B. 2011b. The impact of cochlear implantation on tinnitus, stress and quality of life in postlingually deafened patients. *Audiology and Neurotology,* 17**,** 2-11.

ONG, L., LINDEN, W. & YOUNG, S. 2004. Stress management: What is it? *Journal of Psychosomatic Research,* 56**,** 133-137.

ÖSTBERG, V. & LENNARTSSON, C. 2007. Getting by with a little help: The importance of various types of social support for health problems. *Scandinavian journal of public health,* 35**,** 197-204.

PANAGIOTOPOULOS, G., GALANAKIS, M., VARVOGLI, L., CHROUSOS, G. & DARVIRI, C. 2015. Validation of the Greek version of Mini Tinnitus Questionnaire as a Brief Screening Test for Assessment of Tinnitus-related Distress: our experience in 301 adult patients. *Clin Otolaryngol,* 40**,** 363-9.

PAPATHANASIOU, I. V., TSARAS, K., NEROLIATSIOU, A. & ROUPA, A. 2015. Stress: Concepts, theoretical models and nursing interventions. *American Journal of Nursing Science,* 4**,** 45-50.

PARK, C. L. & IACOCCA, M. O. 2014. A stress and coping perspective on health behaviors: theoretical and methodological considerations. *Anxiety, Stress, & Coping,* 27**,** 123-137.

PARK, K. H., LEE, S. H., KOO, J. W., PARK, H. Y., LEE, K. Y., CHOI, Y. S., OH, K. W., LEE, A., YANG, J. E., WOO, S. Y., KIM, S. W. & CHO, Y. S. 2014. Prevalence and associated factors of tinnitus: data from the Korean National Health and Nutrition Examination Survey 2009-2011. *J Epidemiol,* 24**,** 417-26.

PARK, S. Y., HAN, J. J., HWANG, J. H., WHANG, E. S., YEA, S. W. & PARK, S. N. 2017. Comparison of tinnitus and psychological aspects between the younger and older adult patients with tinnitus. *Auris Nasus Larynx,* 44**,** 147-151.

PATTYN, T., VAN DEN EEDE, F., VANNESTE, S., CASSIERS, L., VELTMAN, D. J., VAN DE HEYNING, P. & SABBE, B. C. G. 2016. Tinnitus and anxiety disorders: A review. *Hearing Research,* 333**,** 255-265.

PETERS, F. T., DRUMMER, O. H. & MUSSHOFF, F. 2007. Validation of new methods. *Forensic science international,* 165**,** 216-224.

PETERSEN, S. E. & POSNER, M. I. 2012. The attention system of the human brain: 20 years after. *Annual review of neuroscience,* 35**,** 73-89.

PHAM, M. T., RAJIĆ, A., GREIG, J. D., SARGEANT, J. M., PAPADOPOULOS, A. & MCEWEN, S. A. 2014. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. *Research synthesis methods,* 5**,** 371-385.

PHILIPPOT, P., NEF, F., CLAUW, L., DE ROMRÉE, M. & SEGAL, Z. 2012. A randomized controlled trial of mindfulness-based cognitive therapy for treating tinnitus. *Clinical psychology & psychotherapy,* 19**,** 411-419.

PHILLIPS, J. S. & MCFERRAN, D. 2010. Tinnitus Retraining Therapy (TRT) for tinnitus. *Cochrane Database of Systematic Reviews*.

PHILLIPS, J. S., MCFERRAN, D. J., HALL, D. A. & HOARE, D. J. 2018. The natural history of subjective tinnitus in adults: A systematic review and meta-analysis of no-intervention periods in controlled trials. *The Laryngoscope,* 128**,** 217-227.

PIENKOWSKI, M. 2019. Rationale and Efficacy of Sound Therapies for Tinnitus and Hyperacusis. *Neuroscience,* 407**,** 120-134.

PINTO, P. C. L., MARCELOS, C. M., MEZZASALMA, M. A., OSTERNE, F. J. V., DE MELO TAVARES DE LIMA, M. A. & NARDI, A. E. 2014. Tinnitus and its association with psychiatric disorders: systematic review. 128**,** 660-664.

POCHIGAEVA, K., DRUZHKOVA, T., YAKOVLEV, A., ONUFRIEV, M., GRISHKINA, M., CHEPELEV, A., GUEKHT, A. & GULYAEVA, N. 2017. Hair cortisol as a marker of

hypothalamic-pituitary-adrenal Axis activity in female patients with major depressive disorder. *Metab Brain Dis,* 32**,** 577-583.

POLIT, D. F. 2010. *Essentials of nursing research*, Wolters Kluwer Health/Lippincott Williams & Wilkins.

POTTER, G. D. M., SKENE, D. J., ARENDT, J., CADE, J. E., GRANT, P. J. & HARDIE, L. J. 2016. Circadian Rhythm and Sleep Disruption: Causes, Metabolic Consequences, and Countermeasures. *Endocrine Reviews,* 37**,** 584-608.

POWELL, D. J. & SCHLOTZ, W. 2012. Daily Life Stress and the Cortisol Awakening Response: Testing the Anticipation Hypothesis. *PLOS ONE,* 7**,** e52067.

PRADO-GASCÓ, V., DE LA BARRERA, U., SANCHO-CASTILLO, S., DE LA RUBIA-ORTÍ, J. E. & MONTOYA-CASTILLA, I. 2019. Perceived stress and reference ranges of hair cortisol in healthy adolescents. *PloS one,* 14**,** e0214856.

PROBST, T., PRYSS, R., LANGGUTH, B. & SCHLEE, W. 2016. Emotional states as mediators between tinnitus loudness and tinnitus distress in daily life: Results from the "TrackYourTinnitus" application. *Sci Rep,* 6**,** 20382.

PROBST, T., PRYSS, R. C., LANGGUTH, B., RAUSCHECKER, J. P., SCHOBEL, J., REICHERT, M., SPILIOPOULOU, M., SCHLEE, W. & ZIMMERMANN, J. 2017. Does tinnitus depend on time-of-day? An ecological momentary assessment study with the "trackyourtinnitus" application. *Frontiers in Aging Neuroscience,* 9.

PULOPULOS, M. M., HIDALGO, V., ALMELA, M., PUIG-PEREZ, S., VILLADA, C. & SALVADOR, A. 2014. Hair cortisol and cognitive performance in healthy older people. *Psychoneuroendocrinology,* 44**,** 100-111.

PULOPULOS, M. M., HIDALGO, V., PUIG-PEREZ, S. & SALVADOR, A. 2016. Cortisol awakening response and cognitive performance in hypertensive and normotensive older people. *Hormones and Behavior,* 83**,** 75-82.

PUZIANOWSKA-KUŹNICKA, M., OWCZARZ, M., WIECZOROWSKA-TOBIS, K., NADROWSKI, P., CHUDEK, J., SLUSARCZYK, P., SKALSKA, A., JONAS, M., FRANEK, E. & MOSSAKOWSKA, M. 2016. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immunity & Ageing : I & A,* 13**,** 21.

PYLYSHYN, Z. W. & STORM, R. W. 1988. Tracking multiple independent targets: Evidence for a parallel tracking mechanism. *Spatial vision,* 3**,** 179-197.

QI, X., JI, S., ZHANG, J., LU, W., SLUITER, J. K. & DENG, H. 2017. Correlation of emotional labor and cortisol concentration in hair among female kindergarten teachers. *Int Arch Occup Environ Health,* 90**,** 117-122.

QUARANTA, N., WAGSTAFF, S. & BAGULEY, D. M. 2004. Tinnitus and cochlear implantation. *International Journal of Audiology,* 43**,** 245-251.

RABAU, S., COX, T., PUNTE, A. K., WAELKENS, B., GILLES, A., WOUTERS, K., DE VAREBEKE, S. J. & VAN DE HEYNING, P. 2015. Changes over time of psychoacoustic outcome measurements are not a substitute for subjective outcome measurements in acute tinnitus. *European Archives of Oto-Rhino-Laryngology,* 272**,** 573-581.

RABIN, L. A., PAOLILLO, E. & BARR, W. B. 2016. Stability in test-usage practices of clinical neuropsychologists in the United States and Canada over a 10-year period: A follow-up survey of INS and NAN members. *Archives of Clinical Neuropsychology,* 31**,** 206-230.

RAJ-KOZIAK, D., GOS, E., SWIERNIAK, W., KARPIESZ, L., NIEDZIALEK, I., WLODARCZYK, E., SKARZYNSKI, H. & SKARZYNSKI, P. H. 2019. Relationship Between Tinnitus Loudness Measure by Visual Analogue Scale and Psychoacoustic Matching of Tinnitus Loudness. *Otology & Neurotology,* 40.

RAMAGE-MORIN, P. L., BANKS, R., PINEAULT, D. & ATRACH, M. 2019. Tinnitus in Canada. *Health reports,* 30**,** 3-11.

RAO, R. P. & BALLARD, D. H. 1999. Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature neuroscience,* 2**,** 79-87.

RAPHAEL, K. G., CLOITRE, M. & DOHRENWEND, B. P. 1991. Problems of Recall and Misclassification With Checklist Methods of Measuring Stressful Life Events. *Health Psychology,* 10**,** 62-74.

RAUL, J. S., CIRIMELE, V., LUDES, B. & KINTZ, P. 2004. Detection of physiological concentrations of cortisol and cortisone in human hair. *Clin. Biochem.,* 37**,** 1105–1111.

RAUSCHECKER, J. P., LEAVER, A. M. & MÜHLAU, M. 2010. Tuning out the noise: Limbic-auditory interactions in tinnitus. *Neuron,* 66**,** 819-826.

RAVALIER, J. M., WEGRZYNEK, P. & LAWTON, S. 2016. Systematic review: complementary therapies and employee well-being. *Occupational Medicine,* 66**,** 428-436.

RAVIKUMAR, G. & MURTHY, V. A. 2016. A Study of Brainstem Auditory Evoked Responses in Normal Hearing Patients with Tinnitus. *Indian J Otolaryngol Head Neck Surg,* 68**,** 429-433.

REDFIELD, J. & STONE, A. A. 1979. Individual viewpoints of stressful life events. *Journal of Consulting and Clinical Psychology,* 47**,** 147.

REICH, W. P., PARRELLA, D. P. & FILSTEAD, W. J. 1988. Unconfounding the Hassles Scale: External sources versus internal responses to stress. *Journal of Behavioral Medicine,* 11**,** 239-249.

REINERT, D. F. & ALLEN, J. P. 2002. The alcohol use disorders identification test (AUDIT): a review of recent research. *Alcoholism: Clinical and Experimental Research,* 26**,** 272-279.

REN, X., ZHAO, X., LI, J., LIU, Y., REN, Y., PRUESSNER, J. C. & YANG, J. 2022. The Hippocampal–Ventral Medial Prefrontal Cortex Neurocircuitry Involvement in the Association of Daily Life Stress With Acute Perceived Stress and Cortisol Responses. *Psychosomatic Medicine,* 84.

REYNOLDS, C. R. 1997. Forward and backward memory span should not be combined for clinical analysis. *Archives of Clinical Neuropsychology,* 12**,** 29-40.

RHODES, M. G. 2004. Age-Related Differences in Performance on the Wisconsin Card Sorting Test: A Meta-Analytic Review. *Psychology and aging,* 19**,** 482-494.

RICE, V. H. 2012. *Handbook of stress, coping, and health : implications for nursing research, theory, and practice. ,* Thousand Oaks, Calif., Thousand Oaks, Calif. : SAGE Publications.

RICHARDSON, J. T. E. 2007. Measures of Short-Term Memory: A Historical Review. *Cortex,* 43**,** 635-650.

RILEY, R. D., SNELL, K. I. E., ENSOR, J., BURKE, D. L., HARRELL JR, F. E., MOONS, K. G. M. & COLLINS, G. S. 2019. Minimum sample size for developing a multivariable prediction model: Part I – Continuous outcomes. *Statistics in Medicine,* 38**,** 1262-1275.

ROBERTS, L. E., MOFFAT, G., BAUMANN, M., WARD, L. M. & BOSNYAK, D. J. 2008. Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. *Journal of the Association for Research in Otolaryngology,* 9**,** 417-435.

RODGERS, J. L. 1991. Matrix and stimulus sample sizes in the weighted MDS model: Empirical metric recovery functions. *Applied psychological measurement,* 15**,** 71-77.

ROERINK, M. E., ROERINK, S. H. P. P., SKOLUDA, N., VAN DER SCHAAF, M. E., HERMUS, A. R. M. M., VAN DER MEER, J. W. M., KNOOP, H. & NATER, U. M. 2018. Hair and salivary cortisol in a cohort of women with chronic fatigue syndrome. *Hormones and Behavior,* 103**,** 1-6.

ROSAS, S. R. & KANE, M. 2012. Quality and rigor of the concept mapping methodology: a pooled study analysis. *Evaluation and program planning,* 35**,** 236-245.

ROSENBERG, M., NOONAN, S., DEGUTIS, J. & ESTERMAN, M. 2013. Sustaining visual attention in the face of distraction: a novel gradual-onset continuous performance task. *Attention, Perception, & Psychophysics,* 75**,** 426-439.

RUSSELL, E., KOREN, G., RIEDER, M. & VAN UUM, S. 2012. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. *Psychoneuroendocrinology,* 37**,** 589-601.

SAAVEDRA, J. M., SÁNCHEZ-LEMUS, E. & BENICKY, J. 2011. Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: Therapeutic implications. *Psychoneuroendocrinology,* 36**,** 1-18.

SALAHALDIN, A. H., ABDULHADI, K., NAJJAR, N. & BENER, A. 2012. Low-level laser therapy in patients with complaints of tinnitus: a clinical study. *ISRN otolaryngology,* 2012.

SALIMETRICS, L. & SALIVABIO, L. 2011. Saliva collection and handling advice. *State College, PA: Salimetrics LLC, SalivaBio LLC***,** 1-14.

SALOMON, R. E., TAN, K. R., VAUGHAN, A., ADYNSKI, H. & MUSCATELL, K. A. 2020. Minimally-invasive methods for examining biological changes in response to chronic stress: A scoping review. *International Journal of Nursing Studies,* 103**,** 103419.

SALVIATI, M., BERSANI, F. S., TERLIZZI, S., MELCORE, C., PANICO, R., ROMANO, G. F., VALERIANI, G., MACRI, F., ALTISSIMI, G., MAZZEI, F., TESTUGINI, V., LATINI, L., DELLE CHIAIE, R., BIONDI, M. & CIANFRONE, G. 2014. Tinnitus: clinical experience of the psychosomatic connection. *Neuropsychiatr Dis Treat,* 10**,** 267-75.

SALVIATI, M., MACRI, F., TERLIZZI, S., MELCORE, C., PROVENZANO, A., CAPPARELLI, E., ALTISSIMI, G. & CIANFRONE, G. 2013. The Tinnitus Handicap Inventory as a screening test for psychiatric comorbidity in patients with tinnitus. *Psychosomatics,* 54**,** 248-56.

SANDI, C. 2013. Stress and cognition. *Wiley Interdiscip Rev Cogn Sci,* 4**,** 245-261.

SANDNER, M., LOIS, G., STREIT, F., ZEIER, P., KIRSCH, P., WÜST, S. & WESSA, M. 2020. Investigating individual stress reactivity: High hair cortisol predicts lower acute stress responses. *Psychoneuroendocrinology,* 118**,** 104660.

SARASON, I. G. & JOHNSON, J. H. 1976. The life experiences survey: preliminary findings. WASHINGTON UNIV SEATTLE DEPT OF PSYCHOLOGY.

SARKAR, P. L., ZENG, L., CHEN, Y., SALVANTE, K. G. & NEPOMNASCHY, P. A. 2013. A longitudinal evaluation of the relationship between first morning urinary and salivary cortisol. *American Journal of Human Biology,* 25**,** 351-358.

SARLA, E., LAMBRINOU, E., GALANIS, P., KALOKAIRINOU, A. & SOURTZI, P. 2020. Factors That Influence the Relationship Between Social Support and Health-Related Quality of Life of Older People Living in the Community. *Gerontology & geriatric medicine,* 6**,** 2333721420911474-2333721420911474.

SARRIAS-ARRABAL, E., IZQUIERDO-AYUSO, G. & VÁZQUEZ-MARRUFO, M. 2022. Attentional networks in neurodegenerative diseases: anatomical and functional evidence from the Attention Network Test. *Neurología (English Edition)*.

SAUNDERS, J. B., AASLAND, O. G., BABOR, T. F., DE LA FUENTE, J. R. & GRANT, M. 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction,* 88**,** 791-804.

SAUVE, B., KOREN, G., WALSH, G., TOKMAKEJIAN, S. & VAN UUM, S. H. 2007. Measurement of cortisol in human hair as a biomarker of systemic exposure. *Clin Invest Med,* 30**,** E183-91.

SAVASTANO, M., AITA, M. & BARLANI, F. 2007. Psychological, neural, endocrine, and immune study of stress in tinnitus patients: any correlation between psychometric and biochemical measures? *The Annals of otology, rhinology, and laryngology,* 116**,** 100-6.

SAXENA, R. P. 1980. *Hans Selye, text book of stress / [edited by] R.P. Saxena ; sponsored by International Society for the Prevention of Stress,* Laindon, Essex, Laindon, Essex : Journal of Chronic Diseases and Therapeutics Research.

SCHAAF, H., FLOHRE, S., HESSE, G. & GIELER, U. 2014. [Chronic stress as an influencing factor in tinnitus patients]. *HNO,* 62**,** 108-114.

SCHAEFER, A., BRAVER, T. S., REYNOLDS, J. R., BURGESS, G. C., YARKONI, T. & GRAY, J. R. 2006. Individual differences in amygdala activity predict response speed during working memory. *Journal of Neuroscience,* 26**,** 10120-10128.

SCHEFFER, M., BECKER, J., DE AZEREDO, L. A., GRASSI-OLIVEIRA, R. & DE ALMEIDA, R. M. M. 2019. Subjective and physiological stress measurement in a multiple sclerosis sample and the relation with executive functions performance. *Journal of Neural Transmission,* 126**,** 613-622.

SCHMITT, C., PATAK, M. & KRONER-HERWIG, B. 2000. Stress and the onset of sudden hearing loss and tinnitus. *Int Tinnitus J,* 6**,** 41-9.

SCHNEIDER, W. R., HILK, A. & FRANZEN, U. 1994. [Social support, disability, coping with stress and personality markers in patients with subjective chronic aural tinnitus and a clinical control group]. *HNO,* 42**,** 22-27.

SCHNEIDERMAN, N., IRONSON, G. & SIEGEL, S. D. 2005. STRESS AND HEALTH: Psychological, Behavioral, and Biological Determinants. *Annual review of clinical psychology,* 1**,** 607-628.

SCHOK, M. L., KLEBER, R. J. & LENSVELT-MULDERS, G. J. 2010. A model of resilience and meaning after military deployment: Personal resources in making sense of war and peacekeeping experiences. *Aging & mental health,* 14**,** 328-338.

SCHOMMER, N. C., HELLHAMMER, D. H. & KIRSCHBAUM, C. 2003. Dissociation Between Reactivity of the Hypothalamus-Pituitary-Adrenal Axis and the Sympathetic-Adrenal-Medullary System to Repeated Psychosocial Stress. *Psychosomatic Medicine,* 65**,** 450-460.

SCHROEDER, D. H. & COSTA, P. T. 1984. Influence of life event stress on physical illness: Substantive effects or methodological flaws? *Journal of Personality and Social Psychology,* 46**,** 853-863.

SCHROEDER, R. W., TWUMASI-ANKRAH, P., BAADE, L. E. & MARSHALL, P. S. 2011. Reliable Digit Span: A Systematic Review and Cross-Validation Study. *Assessment,* 19**,** 21-30.

SCHWARZ, L. A. & LUO, L. 2015. Organization of the locus coeruleus-norepinephrine system. *Current Biology,* 2**5,** R1051-R1056.

SCHWARZER, R. & KNOLL, N. 2007. Functional roles of social support within the stress and coping process: A theoretical and empirical overview. *International journal of psychology,* 42**,** 243-252.

SCOTT, B. & LINDBERG, P. 2000. Psychological profile and somatic complaints between help-seeking and non-help-seeking tinnitus subjects. *Psychosomatics,* 41**,** 347-52.

SCOTT, K. A., TAMASHIRO, K. K. & SAKAI, R. R. 2012. Chronic Social Stress: Effects on Neuroendocrine Function. *In:* FINK, G. P., D. W. ; LEVINE, J. E. (ed.) *Handbook of Neuroendocrinology.* Amsterdam; Boston.: Elsevier.

SEARCHFIELD, G. D., BOONE, M., BENSAM, J., DURAI, M., HODGSON, S.-A., LINFORD, T. & VOGEL, D. 2020. A proof-of-concept study of the benefits of a single-session of tinnitus instruction and counselling with homework on tinnitus. *International Journal of Audiology,* 59**,** 374-382.

SEDLEY, W., FRISTON, K. J., GANDER, P. E., KUMAR, S. & GRIFFITHS, T. D. 2016. An Integrative Tinnitus Model Based on Sensory Precision. *Trends Neurosci,* 39**,** 799-812.

SELYE, H. 1936. A syndrome produced by diverse nocuous agents. *Nature,* 138**,** 32.

SELYE, H. 1956. *The stress of life,* New York, McGraw-Hill Book Company.

SEREDA, M., XIA, J., EL REFAIE, A., HALL, D. A. & HOARE, D. J. 2018. Sound therapy (using amplification devices and/or sound generators) for tinnitus. *Cochrane Database of Systematic Reviews*.

SEYDEL, C., HAUPT, H., SZCZEPEK, A. J., KLAPP, B. F. & MAZUREK, B. 2010. Long-term improvement in tinnitus after modified tinnitus retraining therapy enhanced by a variety of psychological approaches. *Audiol Neurootol,* 15**,** 69-80.

SHAHSAVARANI, S., SCHMIDT, S. A., KHAN, R. A., TAI, Y. & HUSAIN, F. T. 2021. Salience, emotion, and attention: The neural networks underlying tinnitus distress revealed using music and rest. *Brain Research,* 1755**,** 147277.

SHAN, I.-K., CHEN, Y.-S., LEE, Y.-C. & SU, T.-P. 2008. Adult normative data of the Wisconsin card sorting test in Taiwan. *Journal of the Chinese Medical Association,* 71**,** 517-522.

SHARGORODSKY, J., CURHAN, G. C. & FARWELL, W. R. 2010. Prevalence and Characteristics of Tinnitus among US Adults. *The American Journal of Medicine,* 123**,** 711-718.

SHARMA, M. 2014. Yoga as an alternative and complementary approach for stress management: a systematic review. *Journal of evidence-based complementary & alternative medicine,* 19**,** 59-67.

SHELDON, S. & LEVINE, B. 2016. The role of the hippocampus in memory and mental construction. *Annals of the New York Academy of Sciences,* 1369**,** 76-92.

SHI, L., MASER-GLUTH, C. & REMER, T. 2008. Daily urinary free cortisol and cortisone excretion is associated with urine volume in healthy children. *Steroids,* 73**,** 1446-1451.

SIMMONS, J. M., WINSKY, L., ZEHR, J. L. & GORDON, J. A. 2020. Priorities in stress research: a view from the US National institute of mental health. *Stress***,** 1-7.

SIMOENS, V. L. & HEBERT, S. 2012. Cortisol suppression and hearing thresholds in tinnitus after low-dose dexamethasone challenge. *BMC Ear, Nose and Throat Disorders,* 12**,** 4.

SIMÕES, J., SCHLEE, W., SCHECKLMANN, M., LANGGUTH, B., FARAHMAND, D. & NEFF, P. 2019. Big five personality traits are associated with tinnitus improvement over time. *Scientific Reports,* 9**,** 1-9.

SINGH, S., AICH, T. K. & BHATTARAI, R. 2017. Wisconsin Card Sorting Test performance impairment in schizophrenia: An Indian study report. *Indian journal of psychiatry,* 59**,** 88-93.

SIROIS, F. M., DAVIS, C. G. & MORGAN, M. S. 2006. " Learning to live with what you can't rise above": control beliefs, symptom control, and adjustment to tinnitus. *Health Psychology,* 25**,** 119.

SLAVICH, G. M. 2020. Psychoneuroimmunology of stress and mental health. *The Oxford handbook of stress and mental health. Oxford University Press, New York*.

SMITH, S. M. & VALE, W. W. 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin Neurosci,* 8**,** 383-95.

SMITH, S. N., BROOMHEAD, E., GREENWELL, K., WATTS, E., STOCKDALE, D. & HOARE, D. J. 2018. Promotion and views on tinnitus self-help within United Kingdom National Health Service audiology departments. *International journal of audiology,* 57**,** 906-913.

SMYTH, N., HUCKLEBRIDGE, F., THORN, L., EVANS, P. & CLOW, A. 2013. Salivary cortisol as a biomarker in social science research. *Social and Personality Psychology Compass,* 7**,** 605-625.

SNAITH, R. P. 2003. The Hospital Anxiety And Depression Scale. *Health and Quality of Life Outcomes,* 1**,** 29.

SOBELL, L. C., SOBELL, M. B., RILEY, D. M., SCHULLER, R., PAVAN, D. S., CANCILLA, A., KLAJNER, F. & LEO, G. I. 1988. The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. *Journal of studies on alcohol,* 49**,** 225-232.

SPIGA, F. & LIGHTMAN, S. L. 2020. Chapter 8 - Rhythms of stress resilience. *In:* CHEN, A. (ed.) *Stress Resilience.* Academic Press.

STALDER, T., STEUDTE-SCHMIEDGEN, S., ALEXANDER, N., KLUCKEN, T., VATER, A., WICHMANN, S., KIRSCHBAUM, C. & MILLER, R. 2017. Stress-related and basic determinants of hair cortisol in humans: A meta-analysis. *Psychoneuroendocrinology,* 77**,** 261-274.

STALDER, T., STEUDTE, S., MILLER, R., SKOLUDA, N., DETTENBORN, L. & KIRSCHBAUM, C. 2012. Intraindividual stability of hair cortisol concentrations. *Psychoneuroendocrinology,* 37**,** 602-10.

STAUFENBIEL, S. M., PENNINX, B. W., SPIJKER, A. T., ELZINGA, B. M. & VAN ROSSUM, E. F. 2013. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology,* 38**,** 1220-35.

STAUFENBIEL, S. M., PENNINX, B. W. J. H., DE RIJKE, Y. B., VAN DEN AKKER, E. L. T. & VAN ROSSUM, E. F. C. 2015. Determinants of hair cortisol and hair cortisone concentrations in adults. *Psychoneuroendocrinology,* 60**,** 182-194.

STECKLER, T., KALIN, N. H. & REUL, J. M. H. M. 2004. *Handbook on stress and the brain. Part 1, The neurobiology of stress* Amsterdam, London : Elsevier.

STENGEL, A. & TACHÉ, Y. F. 2017. Activation of Brain Somatostatin Signaling Suppresses CRF Receptor-Mediated Stress Response. *Frontiers in Neuroscience,* 11**,** 231.

STEPTOE, A. & AYERS, S. 2004. Stress, health and illness. *The Sage handbook of health psychology***,** 169-196.

STOHLER, N. A., REINAU, D., JICK, S. S., BODMER, D. & MEIER, C. R. 2019. A study on the epidemiology of tinnitus in the United Kingdom. *Clinical Epidemiology,* 11**,** 855.

STOUFFER, J. L., TYLER, R. S., KILENY, P. R. & DALZELL, L. E. 1991. Tinnitus as a function of duration and etiology: counselling implications. *Am J Otol,* 12**,** 188-94.

SUGAYA, N., IZAWA, S., OGAWA, N., SHIROTSUKI, K. & NOMURA, S. 2020. Association between hair cortisol and diurnal basal cortisol levels: A 30-day validation study. *Psychoneuroendocrinology,* 116**,** 104650.

SWANK, J. M. & MULLEN, P. R. 2017. Evaluating Evidence for Conceptually Related Constructs Using Bivariate Correlations. *Measurement and Evaluation in Counseling and Development,* 50**,** 270-274.

TAE, W.-S., YAKUNINA, N., LEE, W. H., RYU, Y.-J., HAM, H.-K., PYUN, S.-B. & NAM, E.-C. 2018. Changes in the regional shape and volume of subcortical nuclei in patients with tinnitus comorbid with mild hearing loss. *Neuroradiology,* 60**,** 1203-1211.

TAYLOR, A. E., KEEVIL, B. & HUHTANIEMI, I. T. 2015. Mass spectrometry and immunoassay: how to measure steroid hormones today and tomorrow. *Eur J Endocrinol,* 173**,** D1-D12.

TEGG-QUINN, S., BENNETT, R. J., EIKELBOOM, R. H. & BAGULEY, D. M. 2016. The impact of tinnitus upon cognition in adults: A systematic review. *International Journal of Audiology,* 55**,** 533-540.

TEISMANN, H., WOLLBRINK, A., OKAMOTO, H., SCHLAUG, G., RUDACK, C. & PANTEV, C. 2014. Combining transcranial direct current stimulation and tailor-made notched music training to decrease tinnitus-related distress--a pilot study. *PLoS One,* 9**,** e89904.

TOPAL, O., ERBEK, S. S., ERBEK, S. & OZLUOGLU, L. N. 2008. Subjective pulsatile tinnitus associated with extensive pneumatization of temporal bone. *European Archives of Oto-Rhino-Laryngology,* 265**,** 123-125.

TREVIÑO, M., ZHU, X., LU, Y. Y., SCHEUER, L. S., PASSELL, E., HUANG, G. C., GERMINE, L. T. & HOROWITZ, T. S. 2021. How do we measure attention? Using

factor analysis to establish construct validity of neuropsychological tests. *Cognitive Research: Principles and Implications,* 6**,** 51.

TREVIS, K. J., MCLACHLAN, N. M. & WILSON, S. J. 2018. A systematic review and meta-analysis of psychological functioning in chronic tinnitus. *Clinical Psychology Review,* 60**,** 62-86.

TRICCO, A. C., LILLIE, E., ZARIN, W., O'BRIEN, K. K., COLQUHOUN, H., LEVAC, D., MOHER, D., PETERS, M. D. J., HORSLEY, T., WEEKS, L., HEMPEL, S., AKL, E. A., CHANG, C., MCGOWAN, J., STEWART, L., HARTLING, L., ALDCROFT, A., WILSON, M. G., GARRITTY, C., LEWIN, S., GODFREY, C. M., MACDONALD, M. T., LANGLOIS, E. V., SOARES-WEISER, K., MORIARTY, J., CLIFFORD, T., TUNCALP, O. & STRAUS, S. E. 2018. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med,* 169**,** 467-473.

TRIPEPI, G., JAGER, K. J., DEKKER, F. W. & ZOCCALI, C. 2010. Selection bias and information bias in clinical research. *Nephron Clinical Practice,* 115**,** c94-c99.

TROCHIM, W. M. 1989. An introduction to concept mapping for planning and evaluation. *Evaluation and program planning,* 12**,** 1-16.

TROCHIM, W. M. & MCLINDEN, D. 2017. Introduction to a special issue on concept mapping. *Evaluation and Program Planning,* 60**,** 166-175.

TSANG, S., ROYSE, C. F. & TERKAWI, A. S. 2017. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. *Saudi journal of anaesthesia,* 11**,** S80-S89.

TSIGOS, C. & CHROUSOS, G. P. 2002. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research,* 53**,** 865-871.

TUCKER, D. A., PHILLIPS, S. L., RUTH, R. A., CLAYTON, W. A., ROYSTER, E. & TODD, A. D. 2005. The effect of silence on tinnitus perception. *Otolaryngology—Head and Neck Surgery,* 132**,** 20-24.

TUNKEL, D. E., BAUER, C. A., SUN, G. H., ROSENFELD, R. M., CHANDRASEKHAR, S. S., CUNNINGHAM, E. R., JR., ARCHER, S. M., BLAKLEY, B. W., CARTER, J. M., GRANIERI, E. C., HENRY, J. A., HOLLINGSWORTH, D., KHAN, F. A., MITCHELL, S., MONFARED, A., NEWMAN, C. W., OMOLE, F. S., PHILLIPS, C. D., ROBINSON, S. K., TAW, M. B., TYLER, R. S., WAGUESPACK, R. & WHAMOND, E. J. 2014. Clinical practice guideline: tinnitus. *Otolaryngol Head Neck Surg,* 151**,** S1-s40.

TURPEINEN, U. & HÄMÄLÄINEN, E. 2013. Determination of cortisol in serum, saliva and urine. *Best Practice & Research Clinical Endocrinology & Metabolism,* 27**,** 795-801.

UDAYAR, S., URBANAVICIUTE, I., MORSELLI, D., BOLLMANN, G., ROSSIER, J. & SPINI, D. 2021. The LIVES Daily Hassles Scale and Its Relation to Life Satisfaction. *Assessment***,** 10731911211047894.

UDAYAR, S., URBANAVICIUTE, I. & ROSSIER, J. 2020. Perceived Social Support and Big Five Personality Traits in Middle Adulthood: a 4-Year Cross-Lagged Path Analysis. *Applied Research in Quality of Life,* 15**,** 395-414.

VAN DEN HEUVEL, L. L., ACKER, D., DU PLESSIS, S., STALDER, T., SULIMAN, S., THORNE, M. Y., KIRSCHBAUM, C. & SEEDAT, S. 2020. Hair cortisol as a biomarker of stress and resilience in South African mixed ancestry females. *Psychoneuroendocrinology,* 113**,** 104543.

VAN DIJK, F. J. H., SOUMAN, A. M. & DE VRIES, F. F. 1987. Non-auditory effects of noise in industry - VI. A final field study in industry. *International Archives of Occupational and Environmental Health,* 59**,** 133-145.

VAN HOUDENHOVE, B. & LUYTEN, P. 2006. Stress, depression and fibromyalgia. *Acta neurologica belgica,* 106**,** 149.

VAN REETH, O., WEIBEL, L., SPIEGEL, K., LEPROULT, R., DUGOVIC, C. & MACCARI, S. 2000. Physiology of sleep (review)–interactions between stress and sleep: from basic research to clinical situations. *Sleep Medicine Reviews,* 4**,** 201-219.

VANAELST, B., HUYBRECHTS, I., BAMMANN, K., MICHELS, N., DE VRIENDT, T., VYNCKE, K., SIOEN, I., IACOVIELLO, L., GÜNTHER, K. & MOLNAR, D. 2012. Intercorrelations between serum, salivary, and hair cortisol and child-reported estimates of stress in elementary school girls. *Psychophysiology,* 49**,** 1072-1081.

VANNESTE, S., PLAZIER, M., DER LOO, E. V., DE HEYNING, P. V., CONGEDO, M. & DE RIDDER, D. 2010. The neural correlates of tinnitus-related distress. *NeuroImage,* 52**,** 470-480.

VARVOGLI, L. & DARVIRI, C. 2011. Stress Management Techniques: evidence-based procedures that reduce stress and promote health. *Health science journal,* 5**,** 74.

VASUDEVAN, H., GANAPATHY, K., PALANISWAMY, H. P., SEARCHFIELD, G. & RAJASHEKHAR, B. 2021. Systematic review and meta-analysis on the effect of continuous subjective tinnitus on attention and habituation. *PeerJ,* 9**,** e12340.

VENTURA-SILVA, A. P., BORGES, S., SOUSA, N., RODRIGUES, A. J. & PÊGO, J. M. 2020. Amygdalar corticotropin-releasing factor mediates stress-induced anxiety. *Brain Research,* 1729**,** 146622.

VOUIMBA, R. M., YANIV, D., DIAMOND, D. & RICHTER-LEVIN, G. 2004. Effects of inescapable stress on LTP in the amygdala versus the dentate gyrus of freely behaving rats. *Eur J Neurosci,* 19**,** 1887-94.

WALLHÄUSSER-FRANKE, E., BRADE, J., BALKENHOL, T., D'AMELIO, R., SEEGMÜLLER, A. & DELB, W. 2012. Tinnitus: Distinguishing between Subjectively Perceived Loudness and Tinnitus-Related Distress. *PLOS ONE,* 7**,** e34583.

WALLHÄUSSER-FRANKE, E., DELB, W., BALKENHOL, T., HILLER, W. & HÖRMANN, K. 2014. Tinnitus-Related Distress and the Personality Characteristic Resilience. *Neural Plasticity,* 2014**,** 370307.

WANG, J., MANN, F., LLOYD-EVANS, B., MA, R. & JOHNSON, S. 2018. Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. *BMC Psychiatry,* 18**,** 156.

WARDELL, J. D., CUNNINGHAM, J. A., QUILTY, L. C., CARTER, S. & HENDERSHOT, C. S. 2020. Can the AUDIT consumption items distinguish lower severity from high severity patients seeking treatment for alcohol use disorder? *Journal of Substance Abuse Treatment,* 114**,** 108001.

WEBER, C., ARCK, P., MAZUREK, B. & KLAPP, B. F. 2002. Impact of a relaxation training on psychometric and immunologic parameters in tinnitus sufferers. *J Psychosom Res,* 52**,** 29-33.

WECKESSER, L. J., DIETZ, F., SCHMIDT, K., GRASS, J., KIRSCHBAUM, C. & MILLER, R. 2019. The psychometric properties and temporal dynamics of subjective

stress, retrospectively assessed by different informants and questionnaires, and hair cortisol concentrations. *Scientific reports,* 9**,** 1-12.

WECKESSER, L. J., PLESSOW, F., PILHATSCH, M., MUEHLHAN, M., KIRSCHBAUM, C. & MILLER, R. 2014. Do venepuncture procedures induce cortisol responses? A review, study, and synthesis for stress research. *Psychoneuroendocrinology,* 46**,** 88-99.

WEISE, C., HEINECKE, K. & RIEF, W. 2008. Stability of physiological variables in chronic tinnitus sufferers. *Appl Psychophysiol Biofeedback,* 33**,** 149-59.

WESTEN, D. & ROSENTHAL, R. 2003. Quantifying construct validity: two simple measures. *Journal of personality and social psychology,* 84**,** 608.

WESTER, V. L., REINCKE, M., KOPER, J. W., VAN DEN AKKER, E. L. T., MANENSCHIJN, L., BERR, C. M., FAZEL, J., DE RIJKE, Y. B., FEELDERS, R. A. & VAN ROSSUM, E. F. C. 2017. Scalp hair cortisol for diagnosis of Cushing's syndrome. *European journal of endocrinology,* 176**,** 695-703.

WETHINGTON, E., KESSLER, R. & BROWN, G. 1993. Training manual and technical report for the structured life events inventory. *Ithaca, NY: Life Course Institute, Cornell University*.

WHO 2019. AUDIT : the Alcohol Use Disorders Identification Test : guidelines for use in primary health care. second edition ed.

WILSON, P. H., HENRY, J., BOWEN, M. & HARALAMBOUS, G. 1991. Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. *J Speech Hear Res,* 34**,** 197-201.

WOODS, D. L., KISHIYAMA, M. M., YUND, E. W., HERRON, T. J., EDWARDS, B., POLIVA, O., HINK, R. F. & REED, B. 2011. Improving digit span assessment of short-term verbal memory. *Journal of Clinical and Experimental Neuropsychology,* 33**,** 101-111.

WOSU, A. C., VALDIMARSDÓTTIR, U., SHIELDS, A. E., WILLIAMS, D. R. & WILLIAMS, M. A. 2013. Correlates of Cortisol in Human Hair: Implications for Epidemiologic Studies on Health Effects of Chronic Stress. *Annals of epidemiology,* 23**,** 797-811.e2.

WRIGHT, A. G., ASLINGER, E. N., BELLAMY, B., EDERSHILE, E. A. & WOODS, W. C. 2019. Daily stress and hassles. *The Oxford Handbook of Stress and Mental Health***,** 27.

WRIGHT, M., CREED, P. & ZIMMER-GEMBECK, M. J. 2010. The Development and Initial Validation of a Brief Daily Hassles Scale Suitable for Use with Adolescents. *European Journal of Psychological Assessment,* 26**,** 220-226.

WYNN, P. C., HAUGER, R. L., HOLMES, M. C., MILLAN, M. A., CATT, K. J. & AGUILERA, G. 1984. Brain and pituitary receptors for corticotropin releasing factor: Localization and differential regulation after adrenalectomy. *Peptides,* 5**,** 1077-1084.

XIE, Q., GAO, W., LI, J., QIAO, T., JIN, J., DENG, H. & LU, Z. 2011. Correlation of cortisol in 1-cm hair segment with salivary cortisol in human: hair cortisol as an endogenous biomarker. *Clin Chem Lab Med,* 49**,** 2013-9.

YATES, D. B., ZIBETTI, M. R., PAWLOWSKI, J., SALLES, J. F., PARENTE, M. A. D. M. P., ARGIMON, I. D. L., FONSECA, R. P. & TRENTINI, C. M. 2013. WCST and NEUPSILIN: relationships among executive functions, attention, memory and language. *Psicologia: Reflexão e Crítica,* 26**,** 506-515.

YıLDıRıM, N., AKSOY, S. & ERDOĞAN, O. 2017. Role of stressful life events as the precipitating factor for chronic tinnitus. *Journal of Hearing Science,* 7**,** 138-138.

YLIKOSKI, J., LEHTIMAKI, J., PIRVOLA, U., MAKITIE, A., AARNISALO, A., HYVARINEN, P. & YLIKOSKI, M. 2017. Non-invasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus. *Acta Oto-Laryngologica,* 137**,** 426-431.

YOUNG, E. A., ABELSON, J. & LIGHTMAN, S. L. 2004. Cortisol pulsatility and its role in stress regulation and health. *Frontiers in Neuroendocrinology,* 25**,** 69-76.

YU, Y., ZHAO, Y., LI, D., ZHANG, J. & LI, J. 2021. The Relationship Between Big Five Personality and Social Well-Being of Chinese Residents: The Mediating Effect of Social Support. *Frontiers in Psychology,* 11.

YUAN, P. & RAZ, N. 2014. Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. *Neuroscience & Biobehavioral Reviews,* 42**,** 180-192.

ZEMAN, F., KOLLER, M., SCHECKLMANN, M., LANGGUTH, B. & LANDGREBE, M. 2012. Tinnitus assessment by means of standardized self-report questionnaires: Psychometric properties of the Tinnitus Questionnaire (TQ), the Tinnitus Handicap Inventory (THI), and their short versions in an international and multi-lingual sample. *Health and Quality of Life Outcomes,* 10**,** 128-128.

ZIGMOND, A. S. & SNAITH, R. P. 1983. The hospital anxiety and depression scale. *Acta psychiatrica scandinavica,* 67**,** 361-370.

ZIMMERMANN, M. & JUCKS, R. 2018. How experts' use of medical technical jargon in different types of online health forums affects perceived information credibility: Randomized experiment with laypersons. *Journal of medical Internet research,* 20**,** e30.

ZIRKE, N., SEYDEL, C., SZCZEPEK, A. J., OLZE, H., HAUPT, H. & MAZUREK, B. 2013. Psychological comorbidity in patients with chronic tinnitus: analysis and comparison with chronic pain, asthma or atopic dermatitis patients. *Qual Life Res,* 22**,** 263-72.

Appendices

Appendix I. Peer reviewed publication

Elarbed A, Fackrell K, Baguley DM, and Hoare DJ. *Tinnitus and stress in adults: a scoping review*. International Journal of Audiology 2020: 1-12. doi.org/10.1080/14992027.2020.1827306.

Appendix II. Meeting abstracts

Tinnitus and stress.

Elarbed, A., Fackrell, K., Baguley, D.M. and Hoare, D.J.

- 11th Tinnitus Research Initiative (TRI) Meeting and TINNIT conference 2018. Regensburg, Germany. March 2018. [**Poster ID 165**].

Tinnitus and stress in adults: A scoping review.

Elarbed, A., Fackrell, K., Baguley, D.M. and Hoare, D.J.

- 55th Inner Ear Biology Workshop. Berlin, Germany. September 2018. [**Poster ID 11-8**].
- BTA conference. Birmingham, UK. September 2018 [**Poster**].

The association between tinnitus and stress evaluated using hair cortisol and self-reported measures.

Elarbed, A., Fackrell, K., Baguley, D.M. and Hoare, D.J.

- 56th Inner Ear Biology Workshop. Padua, Italy. September 2019. [**Poster ID 115**].

Tinnitus and stress in adults: The role of cortisol.

Elarbed, A., Fackrell, K., Baguley, D.M. and Hoare, D.J.

- Sue Watson oral presentation (School of Medicine, University of Nottingham). Nottingham, UK. October 2019. [**Oral presentation**].
- BOARS Autumn meeting. Sheffield, UK. November 2019. [**Oral presentation**].

The difference in stress levels between tinnitus and non-tinnitus participants.

Elarbed, A., Fackrell, K., Baguley, D.M. and Hoare, D.J.

- Research sandpit School of Medicine, Nottingham, UK. February 2020. [**Oral presentation**].

Test-retest reliability of self-reported stress measurements in tinnitus.

Elarbed, A., Fackrell, K., Baguley, D.M. and Hoare, D.J.

- British Society of Audiology (BSA) Annual e-conference 2020. Online event. October 2020. **[e-Poster 26].**

Appendix III. Recent Life Changes Questionnaire

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

NHS
National Institute for Health Research

Research Study:

Tinnitus and Stress: The Role of Cortisol

Name of Researchers:

Asma Elarbed, Dr Kathryn Fackrell, Prof David Baguley, Dr Derek Hoare

Site code:

ID code:

Date:

The information you provide in these questionnaire will be treated with utmost confidentiality. Please answer the questions as accurately as possible as this is very important to the outcome of this research.

Recent Life Changes Questionnaire (RLCQ): This questionnaire will assess the stress related to occurrence of major life events in the last six months.

Recent Life Changes Questionnaire (RLCQ)

In the last six months, which of the following events happened in your life?

Please, copy the number of Life Change Units (LCU) into the next column, and if possible indicate the month in which this event happened in the last column MMM in three letters format.

In case the event is unrelated to you, for example problems at work when you are not employee, fill in the cells with a hyphen (-).

Health	LCU		MMM
An illness or injury that kept you in bed for more than a week or sent you to the hospital	74		
An illness or injury that was less serious than above	44		
Major dental work	26		
Major change in eating habits	27		
Major change in sleeping habits	26		
Major change in your usual type and/or amount of recreation	28		
Work	**LCU**		**MMM**
Change to a new type of work	51		
Change in your work hours or conditions	35		
More work responsibilities	29		
Fewer work responsibilities	21		
A promotion	31		
A demotion	42		
A transfer	32		
Trouble with your boss	29		
Trouble with your coworkers	35		
Trouble with those you supervise	35		
Other work troubles	28		
Major business readjustment	60		
Retirement	52		
Laid off	68		
Fired	79		
Took a course to help your work	18		

Home and family	LCU		MMM
Move within same city or town	25		
Move to different town, city, or state	47		
Major change in living conditions	42		
Change in family get-togethers	25		
Major change in health or behavior of a family member	55		
Marriage	50		
Pregnancy	67		
Miscarriage or abortion	65		
Birth of a child	66		
Adoption of a child	65		
Relative moves in with you	59		
Spouse begins or stops work	46		
Child leaves home to attend college or for marriage	41		
Child leaves home for other reasons	45		
Change in arguments with spouse	50		
Problems with relatives or in-laws	38		
Parents' divorce	59		
A parent remarries	50		
Separation from spouse due to work	53		
Separation from spouse due to marital difficulties	79		
Divorce	96		
Birth of grandchild	43		
Death of spouse	119		
Death of child	123		
Death of parent	100		
Death of a brother or sister	102		
Personal and social	**LCU**		**MMM**
Change in personal habits	26		
Beginning or ending school	38		
Change of school or college	35		
Change in political beliefs	24		
Change in religious beliefs	29		
Change in social activities	27		
Vacation	24		
New, close personal relationship	37		
Engagement to marry	45		
Girlfriend or boyfriend problems	39		

Personal and social	LCU		MMM
Sexual difficulties	44		
An accident	48		
"Falling out" of a close personal relationship	47		
Minor violation of the law	20		
Being held in jail	75		
Major decision about immediate future	51		
Major personal achievement	36		
Death of a close personal friend	70		
Financial	**LCU**		**MMM**
Major loss of income	60		
Major increase in income	38		
Investment and/or credit difficulties	56		
Loss/damage to personal property	43		
Major purchase	37		
Moderate purchase	20		
Foreclosure on mortgage or loan	58		

TOTAL SCORE _____

Appendix IV. Daily Hassles Scale

Research Study:

Tinnitus and Stress: The Role of Cortisol

Name of Researchers:

Asma Elarbed, Dr Kathryn Fackrell, Prof David Baguley, Dr Derek Hoare

Site code:

ID code:

Date:

The information you provide in these questionnaire will be treated with utmost confidentiality. Please answer the questions as accurately as possible as this is very important to the outcome of this research.

Daily Hassles Scale (DHS): Daily hassles are the daily events that acts as stressor. This scale assesses the level of stress associated with the occurrence of these events.

DAILY HASSLES SCALE

Check each hassle that you are currently experiencing and circle the degree of severity using the following scale:

1 = Somewhat severe 2 = Moderately severe 3 = Extremely severe

1) Misplacing or losing things	1	2	3	61) Too many interruptions	1	2	3
2) Troublesome neighbors	1	2	3	62) Not enough money for food	1	2	3
3) Social obligations	1	2	3	63) No enough money for necessities	1	2	3
4) Inconsiderate smokers	1	2	3	64) Dislike coworkers	1	2	3
5) Troubling thoughts about your future	1	2	3	65) Dislike current work duties	1	2	3
6) Thoughts about death	1	2	3	66) Laid-off or out of work	1	2	3
7) Health of a family member	1	2	3	67) Concerns about retirement	1	2	3
8) Not enough money for clothing	1	2	3	68) Care for pets	1	2	3
9) Not enough money for housing	1	2	3	69) Concerns about job security	1	2	3
10) Concerns about owing money	1	2	3	70) Housekeeping responsibilities	1	2	3
11) Concerns about money for emergencies	1	2	3	71) Trouble making decisions	1	2	3
12) Someone owes you money	1	2	3	72) Difficult customers/clients	1	2	3
13) Financial responsibility for someone who doesn't live with you	1	2	3	73) Physical appearance	1	2	3
14) Conserving electricity, water, etc.	1	2	3	74) Difficulties getting pregnant	1	2	3
15) Smoking too much	1	2	3	75) Concerns about health in general	1	2	3
16) Use of alcohol	1	2	3	76) Social isolation	1	2	3
17) Personal use of drugs	1	2	3	77) Preparing meals	1	2	3

18) Too many responsibilities	1	2	3	78) Auto maintenance	1	2	3
19) Decisions about having children	1	2	3	79) Neighborhood deterioration	1	2	3
20) Non-family members living with you	1	2	3	80) Declining physical abilities	1	2	3
21) Planning meals	1	2	3	81) Concerns about bodily functions	1	2	3
22) Concerns about the meaning of life	1	2	3	82) Not getting enough rest	1	2	3
23) Trouble relaxing	1	2	3	83) Problems with aging parents	1	2	3
24) Problems getting along with coworkers	1	2	3	84) Problems with your lover	1	2	3
25) Concerns about medical treatment	1	2	3	85) Difficulties seeing or hearing	1	2	3
26) Fear of rejection	1	2	3	86) Too many things to do	1	2	3
27) Sexual problems due to physical causes	1	2	3	87) General job dissatisfaction	1	2	3
28) Sexual problems other than physical	1	2	3	88) Worry about changing jobs	1	2	3
29) Friends or relatives too far away	1	2	3	89) Too many meetings	1	2	3
30) Wasting time	1	2	3	90) Problems with divorce/separation	1	2	3
31) Filling out forms	1	2	3	91) Gossip	1	2	3
32) Financing children's education	1	2	3	92) Concerns about weight	1	2	3
33) Gender bias/harassment at work	1	2	3	93) Watching too much television	1	2	3
34) Being exploited	1	2	3	94) Concerns about inner conflicts	1	2	3
35) Rising prices of common goods	1	2	3	95) Feeling conflicted about what to do	1	2	3
36) Not getting enough sleep	1	2	3	96) Regrets over past decisions	1	2	3
37) Problems with your children	1	2	3	97) Menstrual problems	1	2	3
38) Problems with younger people	1	2	3	98) The weather	1	2	3
39) Problems with older people	1	2	3	99) Nightmares	1	2	3
40) Unchallenging work	1	2	3	100) Concerns about getting ahead	1	2	3

41) Concerns about meeting high standards	1	2	3	101) Hassles from boss/supervisor	1	2	3
42) Financial dealing with friends	1	2	3	102) Difficulties with friends	1	2	3
43) Trouble reading, writing, or spelling	1	2	3	103) Overload of family responsibilities	1	2	3
44) Trouble with math	1	2	3	104) Problems with employees	1	2	3
45) Legal problems	1	2	3	105) Not enough time for family	1	2	3
46) Not enough time to get things done	1	2	3	106) Transportation problems	1	2	3
47) Not enough energy	1	2	3	107) Not enough money for transportation	1	2	3
48) Side effects of medication	1	2	3	108) Not enough money for recreation	1	2	3
49) Physical illness	1	2	3	109) Shopping responsibilities	1	2	3
50) Inability to express yourself	1	2	3	110) Prejudice/discrimination from others	1	2	3
51) Silly practical mistakes	1	2	3	111) Property, investments, or taxes	1	2	3
52) Financial security	1	2	3	112) Not enough time for recreation	1	2	3
53) Fear of confrontation	1	2	3	113) Home maintenance (inside)	1	2	3
54) Not enough money for health care	1	2	3	114) Yard work/outside maintenance	1	2	3
55) Feeling lonely	1	2	3	115) Concerns about current events	1	2	3
56) Concerns about accidents	1	2	3	116) Noise	1	2	3
57) Concerns about getting a loan/credit	1	2	3	117) Crime	1	2	3
58) Having to wait in lines	1	2	3	118) Traffic	1	2	3
59) Too much time on your hands	1	2	3	119) Pollution	1	2	3
60) Unexpected company	1	2	3				

Have we missed any of your current hassles?

If so, write them below:

120) 1 2 3

121) 1 2 3

122) 1 2 3

Has there been a recent change in your life that affected how you answered this scale? What?

.....

.....

.....

.....

.....

.....

.....

.....

Total Number of Hassles_____ Total Severity Points_____

Appendix V. Depression Anxiety Stress Scale

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

NHS
National Institute for Health Research

Research Study:

Tinnitus and Stress: The Role of Cortisol

Name of Researchers:

Asma Elarbed, Dr Kathryn Fackrell, Prof David Baguley, Dr Derek Hoare

Site code:

ID code:

Date:

The information you provide in these questionnaire will be treated with utmost confidentiality. Please answer the questions as accurately as possible as this is very important to the outcome of this research.

Depression, Anxiety, Stress Scale (DASS): this scale measures the symptoms of depression, anxiety, and stress.

DEPRESSION ANXIETY STRESS SCALE-42 (DASS).

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time.

			For researcher use	
1	I found myself getting upset by quite trivial things	0 1 2 3		
2	I was aware of dryness of my mouth	0 1 2 3		
3	I couldn't seem to experience any positive feeling at all	0 1 2 3		
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0 1 2 3		
5	I just couldn't seem to get going	0 1 2 3		
6	I tended to over-react to situations	0 1 2 3		
7	I had a feeling of shakiness (eg, legs going to give way)	0 1 2 3		
8	I found it difficult to relax	0 1 2 3		
9	I found myself in situations that made me so anxious I was most relieved when they ended	0 1 2 3		
10	I felt that I had nothing to look forward to	0 1 2 3		
11	I found myself getting upset rather easily	0 1 2 3		
12	I felt that I was using a lot of nervous energy	0 1 2 3		
13	I felt sad and depressed	0 1 2 3		
14	I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)	0 1 2 3		

15	I had a feeling of faintness	0	1	2	3		
16	I felt that I had lost interest in just about everything	0	1	2	3		
17	I felt I wasn't worth much as a person	0	1	2	3		
18	I felt that I was rather touchy	0	1	2	3		
19	I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion	0	1	2	3		
20	I felt scared without any good reason	0	1	2	3		
21	I felt that life wasn't worthwhile	0	1	2	3		
22	I found it hard to wind down	0	1	2	3		
23	I had difficulty in swallowing	0	1	2	3		
24	I couldn't seem to get any enjoyment out of the things I did	0	1	2	3		
25	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3		
26	I felt down-hearted and blue	0	1	2	3		
27	I found that I was very irritable	0	1	2	3		
28	I felt I was close to panic	0	1	2	3		
29	I found it hard to calm down after something upset me	0	1	2	3		
30	I feared that I would be "thrown" by some trivial but unfamiliar task	0	1	2	3		
31	I was unable to become enthusiastic about anything	0	1	2	3		
32	I found it difficult to tolerate interruptions to what I was doing	0	1	2	3		
33	I was in a state of nervous tension	0	1	2	3		
34	I felt I was pretty worthless	0	1	2	3		
35	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3		

36	I felt terrified	0	1	2	3		
37	I could see nothing in the future to be hopeful about	0	1	2	3		
38	I felt that life was meaningless	0	1	2	3		
39	I found myself getting agitated	0	1	2	3		
40	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3		
41	I experienced trembling (eg, in the hands)	0	1	2	3		
42	I found it difficult to work up the initiative to do things	0	1	2	3		

SCORES:

Depression .....

Anxiety .....

Stress .....

Appendix VI. Tinnitus Functional Index

Research Study:

Tinnitus and Stress: The Role of Cortisol

Name of Researchers:

Asma Elarbed, Dr Kathryn Fackrell, Prof David Baguley, Dr Derek Hoare

Site code:

ID code:

Date:

The information you provide in these questionnaire will be treated with utmost confidentiality. Please answer the questions as accurately as possible as this is very important to the outcome of this research.

Tinnitus Functional Index (TFI): This questionnaire will assess the impact of your tinnitus on your everyday life.

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

NHS National Institute for Health Research

TINNITUS FUNCTIONAL INDEX

Please read each question below carefully. To answer a question, select ONE of the numbers that is listed for that question, and draw a CIRCLE around it like this: (10%) or (1.)

I	**Over the PAST WEEK...**

1. What percentage of your time awake were you consciously **AWARE OF** your tinnitus?

Never aware ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *Always aware*

2. How **STRONG** or **LOUD** was your tinnitus?

Not at all strong or loud ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely strong or loud*

3. What percentage of your time awake were you **ANNOYED** by your tinnitus?

None of the time ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *All of the time*

SC	**Over the PAST WEEK...**

4. Did you feel **IN CONTROL** in regard to your tinnitus?

Very much in control ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Never in control*

5. How easy was it for you to **COPE** with your tinnitus?

Very easy to cope ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to cope*

6. How easy was it for you to **IGNORE** your tinnitus?

Very easy to ignore ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to ignore*

C	**Over the PAST WEEK, how much did your tinnitus interfere with...**

7. Your ability to **CONCENTRATE**?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

8. Your ability to **THINK CLEARLY**?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

9. Your ability to **FOCUS ATTENTION** on other things besides your tinnitus?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

SL	**Over the PAST WEEK...**

10. How often did your tinnitus make it difficult to **FALL ASLEEP** or **STAY ASLEEP**?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

11. How often did your tinnitus cause you difficulty in getting **AS MUCH SLEEP** as you needed?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

12. How much of the time did your tinnitus keep you from **SLEEPING** as **DEEPLY** or as **PEACEFULLY** as you would have liked?

None of the time ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *All of the time*

Please read each question below carefully. To answer a question, select ONE of the numbers that is listed for that question, and draw a CIRCLE around it like this: (10) or (1)

A	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere* ▼										*Completely interfered* ▼
13.	Your ability to **HEAR CLEARLY**?	0	1	2	3	4	5	6	7	8	9	10
14.	Your ability to **UNDERSTAND PEOPLE** who are talking?	0	1	2	3	4	5	6	7	8	9	10
15.	Your ability to **FOLLOW CONVERSATIONS** in a group or at meetings?	0	1	2	3	4	5	6	7	8	9	10
R	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere* ▼										*Completely interfered* ▼
16.	Your **QUIET RESTING ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
17.	Your ability to **RELAX**?	0	1	2	3	4	5	6	7	8	9	10
18.	Your ability to enjoy "**PEACE AND QUIET**"?	0	1	2	3	4	5	6	7	8	9	10
Q	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere* ▼										*Completely interfered* ▼
19.	Your enjoyment of **SOCIAL ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
20.	Your **ENJOYMENT OF LIFE**?	0	1	2	3	4	5	6	7	8	9	10
21.	Your **RELATIONSHIPS** with family, friends and other people?	0	1	2	3	4	5	6	7	8	9	10

22. How often did your tinnitus cause you to have difficulty performing your **WORK OR OTHER TASKS**, such as home maintenance, school work, or caring for children or others?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

E	**Over the PAST WEEK...**

23. How **ANXIOUS** or **WORRIED** has your tinnitus made you feel?

Not at all anxious or worried ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely anxious or worried*

24. How **BOTHERED** or **UPSET** have you been because of your tinnitus?

Not at all bothered or upset ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely bothered or upset*

25. How **DEPRESSED** were you because of your tinnitus?

Not at all depressed ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely depressed*

Appendix VII.Tinnitus Sample Case History Questionnaire

Research Study:

Tinnitus and Stress: The Role of Cortisol

Name of Researchers:

Asma Elarbed, Dr Kathryn Fackrell, Prof David Baguley, Dr Derek Hoare

Site code:

ID code:

Date:

The information you provide in these questionnaire will be treated with utmost confidentiality. Please answer the questions as accurately as possible as this is very important to the outcome of this research.

Modified Tinnitus Sample Case History Questionnaire (TSCHQ): This is a standardized questionnaire for obtaining patient case histories, and symptoms that associated with tinnitus.

MODIFIED TINNITUS SAMPLE CASE HISTORY QUESTIONNAIRE (TSCHQ)

1. Handedness: Right / Left / Both Sides

2. Family history of tinnitus complaints

☐ YES If YES: ☐ parents ☐ siblings ☐ children ☐ NO

3. Initial onset: When did you first experience your tinnitus? _____

4. How did you perceive the beginning? ☐ Gradual ☐ Abrupt

5. Was the initial onset of your tinnitus related to:

☐ loud blast of sound ☐ whiplash ☐ change in hearing ☐ stress
☐ head trauma ☐ others _____

6. Does your tinnitus pulsate?

☐ YES with heart beat ☐ YES different from heart beat ☐ NO

7. Where do you perceive your tinnitus

☐ right ear ☐ left ear ☐ both ears, worse in left ☐ both ears, worse in right
☐ both ears, equally ☐ inside the head ☐ elsewhere

8. How does your tinnitus manifest itself over time?

☐ Intermittent ☐ constant

9. Does the LOUDNESS of the tinnitus vary from day to day?

☐ YES ☐ NO

10. Describe the *LOUDNESS* of your tinnitus using a scale from 1-100.

(1 = *VERY FAINT*; 100 = *VERY LOUD*)

_____ (1 – 100)

11. Please describe in your own words what your tinnitus usually sounds like:

_____

The following list gives examples of some possible sensations, feel free to use other terms as well: hissing, ringing, pulsing, buzzing, clicking, cracking, tonal (like a dial tone or other kinds of tones), humming, popping, roaring, rushing, typewriter, whistling, whooshing

12. Does your tinnitus more sound like a tone or more like noise:

☐ tone ☐ noise ☐ crickets ☐ other

13. Please describe the PITCH of your tinnitus:

☐ Very high frequency ☐ high frequency ☐ medium frequency ☐ low frequency

14. What percent of your total awake time, over the last month, have you been aware of your tinnitus? For example, 100% would indicate that you were aware of your tinnitus all the time, and 25% would indicate that you were aware of your tinnitus 1/4 of the time

_____ % (Please write in a single number between 1 and 100.)

15. What percent of your total awake time, over the last month, have you been annoyed, distressed, or irritated of your tinnitus?

_____ % (Please write in a single number between 1 and 100.)

16. How many different treatments have you undergone because of your tinnitus?

☐ none ☐ one ☐ several ☐ many

17. Is your tinnitus reduced by music or by certain types of environmental sounds such as the noise of a waterfall or the noise of running water when you are standing in the shower?

☐ YES ☐ NO ☐ I don't know

18. Does the presence of loud noise make your tinnitus worse?

☐ YES ☐ NO ☐ I don't know

19. Does any head and neck movement (e.g. moving the jaw forward or clenching the teeth), or having your arms/hands or head touched, affect your tinnitus?

☐ YES ☐ NO

20. Does taking a nap during the day affect your tinnitus?

☐ Worsen my tinnitus ☐ reduce my tinnitus ☐ has no effect

21. Is there any relationship between sleep at night and your tinnitus during the day?

☐ YES ☐ NO ☐ I don't know

22. Does stress influence your tinnitus?

☐ Worsen my tinnitus ☐ reduce my tinnitus ☐ has no effect

23. Does medication have an effect on your tinnitus?

Medication	Effect/ Details

24. Do you suffer from headache?

☐ YES ☐ NO

25. Do you suffer from vertigo or dizziness?

☐ YES ☐ NO

26. Do you suffer from temporomandibular disorder?

☐ YES ☐ NO

27. Do you suffer from neck pain?

☐ YES ☐ NO

28. Do you suffer from pain syndromes?

☐ YES ☐ NO

29. Are you currently under treatment for psychiatric problems?

☐ YES ☐ NO

Appendix VIII. Concept Mapping study: surveys

Registration form



Registration form

Page 1: Instructions

Tinnitus and stress concept mapping study

Before you register, please take time to read the participant information sheet [link] carefully. Talk to others (family members and friends) about registering. Contact us if there is anything that is not clear or if you would like more information.

We will ask you initially to confirm that you have had tinnitus for more than 6 months, your age is 18 or above, and you have read and understood the participant information sheet. Then, you will agree to register your interest.

We will ask to provide your name, age, and email so we can send you the link to online activities in the future. We will also collect information about where you heard about the study.

Important information:

Any personal data you provide here will be saved in a password protected file that only can be accessed by members of the research team. It will not be used in any publication (see the information sheet for more details).

The study was approved by the University of Nottingham research ethics committee, reference number: [insert number].

Page 2: Consent

I confirm that I have tinnitus for more than 6 months. * *Required*

- Yes

I confirm that I am 18 years or above. * *Required*

- Yes

I confirm that I read and understood the information sheet. * *Required*

- Yes

I agree to register my interest in the study * *Required*

- Yes

Page 3

Name * *Required*

Age (years) * *Required*

contact email * *Required*

Please enter a valid email address.

How did you hear about the study? * *Required*

- Invitation email from NIHR Nottingham BRC
- Social media- NIHR
- Social media- Others
- A website
- Poster or card handed in a public event
- Poster or card handed in BTA Expo 2019
- Through a Tinnitus Support Group
- Poster displayed in a university building
- Other

If you selected Other, please specify:

Page 4: Final page

Thank you for registering your interest in the study.

We will email you the link to the online activity once it is launched.

You can exit this survey by closing the browser.

Activity 1: Generating statements



Activity 1: Generating statements

Page 1: Instruction

Thank you for participating in *Activity 1*. Your participation will lead to generating statements that we will use in *Activity 2* of this study.

The activity will include:

- Consent to participate in the study in the form of a checklist.
- A short survey, which has only 5 questions and should take you less than 5 minutes to complete.
- Writing statements about stress. We will use these statements in *Activity 2* of this study.

Page 2: Consent

1. Please note that you may only participate in this survey if you are 18 years of age or over, you have had tinnitus for more than 6 months, and agree to participate with the understanding that the data (including any personal data) you submit will be processed accordingly. **If you have not read the Participant Information Sheet, please do so. You can access the information sheet on this [link].** Please check the relevant boxes below to get started.

	Check each box * *Required*
	yes
I confirm that I have read and understood the information sheet for the above study which is attached and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.	☐
I understand that should I withdraw, more than 7 days after the activity has taken place then the information collected so far cannot be erased and that this information may still be used in the study analysis.	☐
I understand that relevant sections of my data collected in the study may be looked at by the research group and by other responsible individuals for monitoring and audit purposes. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.	☐
I understand that information about me recorded during the study will be made anonymous before it is stored. It will be uploaded into a secure database on a computer kept in a secure place. Data will be kept for 7 years after the study has ended and then destroyed.	☐
I agree that my research data may be stored and used in possible future research during and after 7 years, and shared with other researchers including those working outside the University.	☐
I confirm that I understand and agree with the above.	☐
I certify that I am 18 years of age or over.	☐
I have tinnitus for more than 6 months.	☐
I agree to take part in the above study.	☐

Page 3: Survey

2. Which category below includes your age? * Required

- 18-20
- 21-30
- 31-40
- 41-50
- 51-60
- 61-70
- 71-80
- Above 80

3. What is your gender? * Required

- Female
- Male
- Prefer not to say

4. What is the highest degree or level of school you have completed/ received? * Required

- Higher Education & professional/vocational equivalents.
- A levels or GCSE
- Other qualifications: level unknown (including foreign qualifications).
- No qualifications.
- Prefer not to say

5. Tinnitus duration * Required

- <1 year
- 1-5 years
- 5-10 years
- 10-15 years
- 15-20 years
- >20 years

6. How did you perceived the beginning of your tinnitus? * Required

- Gradual
- Sudden
- Other

Page 4: Generating statements

Instructions: In this activity, you can write up to 20 sentences, we call them here statements. However, each sentence should contain one idea, and you have to write at least 1 sentence.

Here, we would like to ask you to write your response to the following statement.

"Stress may worsen tinnitus, and the word stress means....."

7. Statement 1 * Required

More info

Please enter a response that only contains letters.

7.a. Statement

More info

Statement 2	
Statement 3	
Statement 4	
Statement 5	
Statement 6	

Statement 7	
Statement 8	
Statement 9	
Statement 10	
Statement 11	
Statement 12	
Statement 13	
Statement 14	
Statement 15	
Statement 16	
Statement 17	
Statement 18	
Statement 19	
Statement 20	

Page 5: Final page

Thank you for completing this activity.

Your participation in this activity is now complete.

You can exit this survey by closing the browser.

Activity 2: Structuring Statements





Activity 2: Structuring Statements

Page 1: Instructions

Welcome to Activity 2 of **Tinnitus and stress concept mapping study**.

Participants in Activity 1 generated statements that represent the definition of stress for them (thank you if you were one of them). We revised those statements to make them more clear and combined similar statements whenever it was needed.

This activity will include:

- Consent to participate in the study in the form of a checklist.
- A short survey, which has only 13 questions and should take you less than 7 minutes. Some of these questions are required- marked with an asterisk (*)- and others are optional, but it will help us if you respond to all questions.
- In the first part of the activity, you will rate the statements.
- Then we will ask you to choose 10 statements and rank them.
- Lastly, you will group similar statements.

We will provide further instructions at each part of this activity.

Your participation will lead to rate and group statements that will help us to develop the concept map of stress.

Page 2: Consent

Please note that you may only participate in this survey if you are 18 years of age or over, you have had tinnitus for more than 6 months, and agree to participate with the understanding that the data (including any personal data) you submit will be processed accordingly. **If you have not read the Participant Information Sheet, please do so. You can access the information sheet on this [link].** Please check the relevant boxes below to get started.

	Check each box * *Required*
	yes
I confirm that I have read and understood the information sheet for the above study which is attached and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.	☐
I understand that should I withdraw, more than 7 days after the activity has taken place then the information collected so far cannot be erased and that this information may still be used in the study analysis.	☐
I understand that relevant sections of my data collected in the study may be looked at by the research group and by other responsible individuals for monitoring and audit purposes. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.	☐
I understand that information about me recorded during the study will be made anonymous before it is stored. It will be uploaded into a secure database on a computer kept in a secure place. Data will be kept for 7 years after the study has ended and then destroyed.	☐
I agree that my research data may be stored and used in possible future research during and after 7 years, and shared with other researchers including those working outside the University.	☐
I confirm that I understand and agree with the above.	☐
I certify that I am 18 years of age or over.	☐
I have tinnitus for more than 6 months.	☐
I agree to take part in the above study.	☐

Page 3: Survey

Which category below includes your age? * *Required*

- ○ 18- 20
- ○ 21-30
- ○ 31-40
- ○ 41-50
- ○ 51-60
- ○ 61-70
- ○ 71-80
- ○ Above 80

What is your gender? * *Required*

- ○ Female
- ○ Male
- ○ Prefer not to say

What is the highest degree or level of school you have completed/ received? * *Required*

- ○ Higher Education & professional/vocational equivalents.
- ○ A levels or GCSE
- ○ Other qualifications: level unknown (including foreign qualifications).
- ○ No qualifications.
- ○ Prefer not to say

Page 4: Survey

Tinnitus duration * *Required*

- ○ <1 year
- ○ 1-5 years
- ○ 5-10 years
- ○ 10-15 years
- ○ 15-20 years
- ○ > 20 years

How did you perceived the beginning of your tinnitus? * *Required*

- ○ Gradual
- ○ Sudden
- ○ Other

Describe the sound of tinnitus * *Required*

- ○ Tonal
- ○ Hissing
- ○ Ringing
- ○ Other

Please, rate you current Tinnitus bothersome (out of 100; where 100 mean tinnitus is the most bothersome it can be)

Please rate your current Tinnitus loudness (out of 100; where 100 mean tinnitus is the loudest it can be)

Do you

Please don't select more than 1 answer(s) per row.

	Yes	No
have hearing problems	☐	☐
have difficulty in understanding what others were saying in noisy or crowded places	☐	☐
wear hearing aids	☐	☐
wear cochlear implants	☐	☐

Stress and Tinnitus: Which statement do you most agree with * *Required*

- ☐ Stress causes tinnitus
- ☐ Stress causes and worsens tinnitus
- ☐ Stress worsens tinnitus but it is not a cause
- ☐ Tinnitus increases stress
- ☐ There is no relationship between tinnitus and stress
- ☐ I disagree with all of the above

If you disagree with all the statements in the previous question, can you tell us what you think about the relationship between tinnitus and stress

Page 5: Rating statements

We would like to ask you rate each statement according to the rating focus.

Rating focus:

'Rate each potential outcome on a five-point scale in terms of how strongly you think the statement is more representing the definition of stress, where '1' means 'Not at all' '3' means 'Moderately representing the definition,' and '5' means 'strongly representing the definition'

Rating * *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 15 answer(s).

	1 Not at all	2	3 Moderately	4	5 Strongly
Statement text	☐	☐	☐	☐	☐
Statement text	☐	☐	☐	☐	☐
Statement text	☐	☐	☐	☐	☐

Page 6: 10 Statements

Choose 10 statements and sort them in order of best representing the definition of stress.
Please, write the number of statement.

You can find the list of statements on this link [insert link]

Ranking 10 statements

	Statements' number * *Required*
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

Page 7: Statements sorting

Instructions:
- In this activity, you need to sort each statement into a cluster or a group.
- You cannot put all statements into a single group. These must be at least two groups.
- Each statement can be placed in only one group (i.e., a statement can't be placed in two groups at the same time)
- You can give each group a name.

You can find the list of statements on this link [insert link].

You are required to sort the statements for at least 2 groups which you can write them in Sorting-1 section (see below).

If you think that these statements can be grouped into more than two groups, please write them in Sorting-2 section.

Sorting-1. Required

	Suggested group name * *Required*	Statements' number Ex: 1, 5, 7, 12 * *Required*
Group 1		
Group 2		

Sorting-2: Optional

	Suggested group name	Statements' number Ex: 1, 5, 7, 12
Group 3		
Group 4		
Group 5		
Group 6		
Group 7		
Group N-1		

Page 8: Registration for Activity 3

If you would like to take part in Activity 3, please register to participate.

This meeting will take place at the NIHR Nottingham BRC (NG1 5DU).

Only registered respondents will receive invitation emails.

Would you like to register your interest in Activity 3?

- ○ Yes
- ○ No

Page 9: Final page

Thank you for completing this activity

Your participation in this activity is now complete.

You can exit this survey by closing the browser.

Appendix IX. Concept Mapping study: Original and umbrella statements

	Umbrella statements	Original sentences
ID	**General Definition**	
1	Stress is a significant burden to some people but has little effect on others	A significant burden to some people, but has little effect on others
2	Stress is a feeling which affects both your physical and mental approach in situations	a feeling which affects both your physical and mental approach in situations
3	Stress is a motivation to get something done	Stress can also be a motivation to get something done.
4	Stress is uncomfortable, irrational, uncontrollable thoughts, and behaviours	Uncomfortable, irrational, uncontrollable thoughts and behaviour.
5	Stress is something someone notes and takes action if it was severe, and not to act if it was mild	mild stress is something one notes as being present but does not need action to be taken
		severe stress is a stress which causes one to take action to try and reduce the stress
6	Stress includes tiredness (mentally and/or Physically), worry, anxiety, tension, irritability, mental pressure, unpleasant feelings and/or unusual situations	Includes tiredness (mentally and/or Physically), worry, anxiety, unusual situations
		Mental or physical strain
		Tension, Irritability, mental pressure, or Unpleasant feeling
7	Stress is undue activities that cause the mind to overthink and feelings of wanting to shut down and unhappiness	Stress is undue activities that causes the mind to overthink and feelings of wanting to shut down.
		a mental condition, caused by an outside influence and which causes unhappiness
	Response	
8	Stress is an emotional response to outside influences	Stress is an emotional response to outside influences.
		A potential of becoming more emotional.
9	Stress is any physical, mental, or emotional stimulus which tends to alter routine functioning or one's behaviour pattern	A potential for change in your behaviour pattern.
		any physical, mental, or emotional stimulus which tends to alter routine or basic functioning
10	Stress is mental, physical, emotional, and psychological responses to things rather than rational, objective responses (losing the sense of reasoning)	Mental, physical, emotional, and psychological responses to things rather than rational, objective responses.
		A potential of making wrong decisions.
		Stress is difficult to control by reasoning
		Stress is the potential of losing sense of reasoning.
11	Stress is pressure (from outside sources or self-generating) causing a physical reaction	Pressure (from outside sources or self generating) causing a physical reaction
	Pressure (general)	
12	Stress means enduring pressure, often without being consciously aware	Enduring pressure, often without being consciously aware
13	Stress is feeling under pressure to stay normal and calm	Feeling under pressure to stay normal and calm
14	Stress means feeling (or being) under pressure	Feeling under pressure
		Feeling under pressure
		Feeling under pressure
		Feeling under pressure
		Feeling under pressure
		Pressure
		Feeling pressured.
		Mental pressure
		Emotional pressure
		Being under pressure
		Under pressure
		Pressure
		Stress means feeling under pressure
		Pressure on yourself
15	Stress means feeling under pressure to do something.	Feeling pressured to do something.
		my kids wanting things done NOW.
		Feeling under pressure in some area of my life.
		Struggling with the pressure of what you have to do.
46	Stress is too much pressure	Too much pressure
		Too much pressure
		It is a lot worse than pressure ..which most people experience
47	Stress is experiencing an unusual or additional pressure from external factors	Unusual pressure from external factors
		Extra emotional pressure
		Additional pressures on you
		Negative environment
		Stress is feeling weighted down by external factors or pressures

48	Stress is having financial pressure or money issues	Having financial pressures.
		Money pressures
49	Stress is feeling pressure to perform at a higher level of competence than the usual level	Feeling under pressure to perform well
		Being pressurised to perform at a higher level of competence than normal
	Pressure (time)	
50	Stress is being time-pressured	Being time pressured
		Time constraints
		Time pressures
51	Stress is having (or feeling) too much to do when there is not enough time (too short time)	Not enough time to get things done
		too much to do and not enough time to do it in.
		Having too much to do and not enough time
		having too much to do and not enough time.
		Feeling like I've got too much to do, in too short a space of time.
		Feeling like there is too much to do in too little time
52	Stress is not having (or feeling) enough time to achieve all the daily tasks	the feeling of too many tasks to undertake in one day
		Not enough time in the day
		feeling there is not enough time to achieve tasks of the day
53	Stress is feeling unable or fear of failing to meet the approaching deadline or being late for important scheduled events	hitting a deadline
		Approach of an upcoming demanding task.
		Fear of failing to meet deadlines
		Feeling like things need to be done quickly.
		Being extra rushed at work
		feeling unable to meet deadlines.
		Anything that makes me late
		Running late for appointments
		Being late for something, such as a form of public transport
		Being late might cause stress
	Pressure (from other people)	
54	Stress is feeling (or being) pushed to your limit at home, in work, or in another external environment	peer pressure.
		Being pushed to your limit at home, in work or another external environment.
69	Stress is feeling worried (or fear) of letting someone down and do not reach their expectations	Feeling of letting people down and worrying about this
		Fear of letting somebody down.
		Difficulty in managing expectations.
		a feeling of not reaching other persons expectations of you.
70	Stress is trying to do too much for others and not being able to say no	Not being able to say no
		Trying to do too much for others
	Relationship issue	
71	Stress is being caught in a middle of problems or arguments brought by family members or other people which increase impatience	increased impatience with others usually family members
		Family arguments
		Family problems
		Stress can be put on you by other people.
		Brought on by being with others , concentration!
		problems in relationship
		Brexit discussions / arguments / divisions caused
		Arguments with people
72	Stress is feeling let down by others when you rely on them	Asking someone to do something and they don't.
		unable to rely on others
73	Stress is feeling that you have upset someone by what you have said or done	When I have upset someone by what I have said or done
74	Stress means increased anxiety (worrying) especially about relationships with people in general	Stress means increased anxiety(worrying) Especially about relationships with people in general
75	Stress is feeling upset or harmed by being verbally bullied by members of the close circle at work	When someone has upset me by what they have said or done
		people intending to harm me
		being bullied by work colleagues.
		verbal abuse
	Anxiety and worry	
76	Stress is being worried or anxious about something or someone (like health-related issues, money-related issues, or others)	Stress means feeling worried or anxious
		feeling worried
		Feeling anxious
		feeling anxious
		Feeling anxious
		Feeling anxious
		I feel anxious under stress.
		Worried about something
		being worried about something
		If a person is worried about something
		Being worried about your health
		Being worried about the health of a family member or a

		friend
		Being worried about money
		Money worries can cause stress
		Stress means increased anxiety(worrying) Especially about relationships with people in general
		worrying about my children
		worrying about what other people might do
77	Stress means heightened anxiety and emotional strain	Anxiety, emotional strain
		anxiety
		Stress means heightened anxiety
		increased anxiety
78	Stress is being over-worried (that appears to be unnecessary) about minor details and small incidents	worrying about minor details
		Worrying over a small incident, of no real value and to no benefit
		Overworrying
		unnecessary worry
79	Stress is being worried about get caught in troubles that someone cannot resolve	being worried about being in trouble
		feeling anxious, pressurised and no immediate way out of the situation
		Worry that you can't resolve
80	Stress is being worried that someone will not be able to carry on doing what they can do (possibly because of health issues)	the worry of not being able to carry on doing what I do
		Fear of health issues interfering with ability to perform
	Overthinking	
81	Stress is overthinking about something	Thinking unnecessarily about something
		Excessive thinking
		overthinking
	workload, overwhelmed	
82	Stress is being (or feeling) constantly having excessive workload	Work
		Overworked
		having too much to do
		Too much work
		Stress means overworked
		a feeling of work over-load.
		Constantly being too busy
83	Stress is feeling conflicted by too many things that need attention	Feeling conflicted by multiple demands on time
		Too many issues that need my attention
84	Stress is working hard to keep on top of things	being an unhealthy perfectionist (not knowing when something is good enough to stop working on it). thankfully I overcame this problem
		working hard to keep on top of things.
85	Stress is feeling overwhelmed by what is happening around the world	Feeling overwhelmed
		Feeling overwhelmed
		Feeling overwhelmed
		Feeling overwhelmed.
		overwhelmed and trapped
		Feeling overwhelmed by what is happening around the world
29	Stress is feeling overwhelmed and pressured with even minor tasks or requests at work/ home	feeling overwhelmed with even minor tasks or requests at work/ home
		Feeling overwhelmed by work pressures
30	Stress is feeling trapped in a situation and unable to escape	No escape
		Feeling I can't escape.
		No escape 24/7
		Feeling trapped in a situation could make one feel stressed
		Feeling trapped in a situation
	Difficulties with relaxation and sleep	
31	Stress is not being able to completely relax even when completely feeling tired	not being relaxed
		Tired out - unable to find ways of standing , sitting to alleviate it
		the inability to completely relax.
		I am unable to settle when stressed.
32	Stress is not having space or enough time to rest and/or relax	Not having space to chill and relax
		not having enough time to rest
33	Stress is feeling tense and opposite of calm and relaxed	Feeling very Tense
		tenseness
		feeling extremely tense
		Stress means feeling tense
		Feeling the opposite of calm and relaxed.
34	Stress is having difficulty getting to sleep, lack of sleep, or not sleeping well	Not sleeping..
		not sleeping
		Feeling like I just want to go to sleep, but can't get to sleep.

		Having difficulty getting to sleep
		Lack of sleep
		Lack of sleep
		not sleeping well
35	Stress is feeling frustrated as a result of not got enough sleep and overthinking	feeling frustrated because I have not got enough sleep because I have too much going on in my head
36	Stress is being (or feeling) very tired (fatigue), even when there are things to do	Tired
		Extreme fatigue
		Feeling very Tired
		being tired when there are things to do.
		Being tired mentally
		Being tired physically
		When I am mentally tired
		When I am physically tired
	Coping	
37	Stress is being (or feeling) unable to cope with situations	Feeling unable to cope
		Feeling like I'm not coping.
		Feeling as if you are not able to cope with a situation
		Inability to cope
		Unable to cope
		Unable to cope
38	Stress is struggling to cope with different situations	Feeling like I'm struggling to cope
		Being less able to cope with things most would take in their stride
		everything feeling too much to cope with
		Struggling to cope
		coping with group situations
		having difficulty coping with or prioritising several things that require attention.
	Sense of control	
39	Stress is feeling out of control over everything	Feeling out of control
		Feeling out of control over everything
40	Stress is feeling (or being) not in control of a situation, thoughts, or feelings	When I have a feeling that I cannot control a situation
		Not feeling in control of a situations.
		Not being in control of a situation.
		Not feeling in control
		a feeling of not being in control.
		There is a sense of not being in control.
		not in control
		Not in control of feelings
		Thoughts and feelings which seem out of my control
		Not being in control of my time
41	Stress is a compromised ability to handle uncontrollable conditions and escalating situations that interfere in someone's life	Compromised ability to handle situations
		Stress to me is feeling out of control of a situation that I am not comfortable with
		Things outside my control that interfere in my life
		An emotional state associated with difficulty controlling events
		situations that happen around me that I can't control
		Uncontrollable conditions
		feeling under severe pressure and not able to control whatever is causing that
		concerns with issues beyond your control with a fear they may escalate.
55	Stress is feeling unable to put the thoughts in order, to prioritize simple tasks, or to start tackling the important tasks	feeling I unable to order my thinking/ prioritize simple tasks
		not knowing what to do first.
		Unable to organise and control workload or things happening around you
		Unable to organise and control your workload
		being unable to prioritise matters in order of importance.
		having difficulty coping with or prioritising several things that require attention.
		Feeling like I don't know where/how to start tackling whatever is in front of me.
	Environment and events	
56	Stress is being in a noisy atmosphere (continuous, loud, or low-level noise)	noise
		noise
		A noisy atmosphere
		Noisy atmospheres/places
		Continuos noise.
		Being subjected to loud noises
		there being too much noise

		Excessive noise
		very loud noise.
		Some music played in shops, relaxing music or quiet would be better.
		Loud noise including concerts or a loud bang
		Extreme noise upsets my hearing and temper and is stressful
		irritating low level noise like the hum of neon or LED lighting.
		If someone, maybe a child for instance shouts or squeals near to your ear
16	Stress is living in potential disaster or troubled areas	Living in a potential disaster area e.g. flood plain
		Living in an area with a high level of small-time crime e.g. burglary, mugging
17	Stress is events or circumstances which make someone feels uncomfortable, annoyed, or frustrated	events or circumstances which bring pressure
		to be put in an uncomfortable position.
		Public speaking
		Public speaking
		Discovering that you don't have your wallet with you, wondering if it's at home or lost.
		Trying to repair / resolve an intermittent fault (equipment)
		Waiting for the result of a test.
		waiting endlessly for a company customer services rep to answer your call.
		Persistent telesales agents refusing to accept that I do not want or need their product
		Completing an online purchase having provided credit card details then seeing the message "a fault has occurred"
		Situations that may annoy or frustrate
18	Stress is being in uncomfortable situations, like being in a crowded place, visiting the dentist or doctor, driving and dealing with inconsiderate drivers, dealing with pet issues, or getting ready for a holiday	Uncomfortable situations can cause stress
		Having to read a menu / document when you have left your spectacles at home.
		Dealing with authority
		Standing too long in supermarket checkout queues when you're in pain.
		crowds.
		Crowds of people.
		Visiting the dentist or doctor might make one feel stressed
		Waiting too long for hospital appointments.
		Driving lessons
		Driving test
		inconsiderate drivers
		Inconsiderate / irresponsible drivers who treat the motorway as a dogem track.
		Road rage
		Some driving situations.
		Being caught up in a traffic jam (whilst driving)
		Pet issues
		Getting ready to go on holiday.
		Preparing to go on holiday
19	Stress is waiting for someone who did not turn up on time, or waiting for something which did not arrive on the scheduled time	Waiting for a train / bus / plane which has not arrived on time.
		people not turning up for appointments on time.
20	Stress is facing work-related difficulties and situations like interviews and meetings, dealing with clients, having the plans disturbed at short notice, difficulties in participating meaningfully in meetings, and/ or having to concentrate to process information in groups	Having my plans disrupted at short notice
		Clients at work
		Important meetings
		Interviews
		A job interview might make one feel stressed
		After having to concentrate to process information in groups
		great difficulty in participating meaningfully in meetings. charitable work
21	Stress is experiencing upsetting events or problems requiring urgent attention that someone feels powerless to resolve	Experiencing events requiring urgent attention that someone feels powerless to resolve
		When confronted by upsetting situations
		When I have a problem which is difficult to solve
22	Stress is external factors or new situations that intrude in someone's life	When in a new situation
		Intrusion into normal living
		Experiencing physical, mental or emotional situation at a level above what one would consider the norm
		a condition which I believe I may never have experienced
		External forces
23	Stress is the problems that arising gradually	Problems arising gradually
	Negative feelings	

24	Stress is feeling uncomfortable and restless	Feeling uncomfortable and restless
		Feeling very uncomfortable
25	Stress is feeling scared or having uncontrollable panic	feeling scared frightened
		Panic
		Uncontrollable panic
		Facing personal phobia.
42	Stress means lacking concentration and focus	Concentrating ones focus
		lack of concentration
		Lack of concentration
		Feeling unable to concentrate
43	Stress means having the likelihood of becoming more aggressive, irritable, agitated, annoyed, edgy, tense, and loss empathy with others	Having the likelihood of becoming more aggressive.
		agression
		Becoming irritable.
		Irritability
		Feeling agitated
		Feeling annoyed
		feeling angry
		Being uptight
		tinnitus worsens stress. Stress means feeling uptight about everyday activities.
		Edgy and tense
		less empathy with others
44	Stress means feeling vulnerable or upset	Stress means feeling vulnerable
		When I am emotionally upset
		Anything that upsets me
		Upset routine
		feeling underwhelmed
		getting worked up about things.
45	Stress is feeling withdrawn from situations and problems	feeling withdrawn
		walking away from problems.
57	Stress is withdrawn from social interactions	Fear - meeting people for the first time
		Unable to intrract
		finding it difficult to make friends.
		Afraid to participate
		Feeling like I want people to leave me alone.
		Other people when I don't want to be around other people
58	Stress is feeling alone and isolated from people and there is no one to talk with	Feeling alone
		On ones own one has to find good trades men
		Feeling isolated from people around you.
		Feeling isolated.
		Insular
		Being alone and lacking human Company is stressful for me
		Stress builds up with long periods of loneliness (No social contact)
		Not having someone to talk to
		Feeling like nobody else understands.
		No help found anywhere
59	Stress is the unpleasant feelings which encompass a person's life. These feelings prevent them from seeing any positivity in life and make them believe that the future is dark	It can be a dark feeling which encompasses everything you do.
		Stop finding any positives in life
		Believing the future is dark and negative
		thinking about death/self harm
		Focusing on negative emotions and feelings
		Unpleasant feeling
60	Stress means feeling useless and having low self-esteem, lacking confidence, feeling helpless and hopeless, feeling lost, and/or in a low mood	Stress is increased by low self esteem
		lacking confidence when you know you should be able to achieve something
		Never feeling quite good enough
		thinking I'm doing damage
		Feeling useless to be able to do anything
		feeling completely useless
		feeling helpless
		a sense of hopelessness
		Feeling hopeless.
		Feeling lost
		Worry and low mood
	Health/physical related	
61	Stress is having health issues (or risks) and medical symptoms (like vertigo, headache, high blood pressure) that make the person too feel generally unwell	Having Health issues
		Medical symptoms
		Generally feeling less well
		Illness

		Feeling body is not functioning at its optimum
		Feeling unwell eg. vertigo.
		Vertigo
		Injury
		Having a higher risk of serious health issues.
		Anything that is likely to increase blood pressure
		Pressure in head
		biting my finger nails
62	Stress is feeling pain (continuous, uncontrollable, or unbearable)	Unbearable pain
		Uncontrollable pain
		Continuos pain.
		Stress is painful, skin feels sore, ragged
		Stress is taut body, stiff neck and shoulders
	Other	
63	Stress is being out of one's comfort zone	Being out of ones comfort zone is stressful
		Being out of your comfort zone.
64	Stress means finding life-changing and difficult which prevent the person from leading a normal life or progress in their career. In particular when they can work out a solution or a way out	finding it difficualt to progress in your career.
		Being able to manage the difficulties in life
		finding life difficult
		Uncertainty in the correct solution or path
		Feeling of no clear path to a solution
		Not being able to live a normal life.
		Life changing when nothing works
65	Stress is Lower tolerance of regular things like thoughts and experiences	Lower tolerance of regular things like thoughts and experiences
	Tinnitus/ hearing loss	
66	Stress means feeling overwhelmed by circumstances and usually when overtired and at those times tinnitus seems louder	Stress for me means feeling overwhelmed by circumstances and usually when overtired and at those times my tinnitus seems louder.
67	Stress is inability to hear other people, to join conversations, and to enjoy entertainment	Unable to hear
		asking my wife to repeat herself very frequently
		Finding it hard to make out what is being said
		Not being able to hear conversations
		trying to lipread more than one person at a time
		Being deaf
		unable to make or receive telephone calls.
		Having difficulty in hearing a softly spoken person in a noisy environment.
		Group conversations
		unable to enjoy tv even using subtitles
		the inability to enjoy music.
26	Stress is to be aware of tinnitus day and night and the mental effort to ignore it and not being able to hear "quiet"	Having to listen to the different noises during the day and night
		the mental effort of ignoring my tinnitus.
		not being able to hear 'quiet.'
27	Stress is having severe interfering tinnitus that prevents the person from multitasking	Severe tinnitus.
		the inability to multi task because I have to concentrate so hard to stop tinnitus interfering
28	Stress is knowing that someone has an invisible disability (continuous noise in the head) that no one understands and there is no cure for it	People don't understand continuous noise in head
		knowing there is no cure
		knowing you have an invisible disability
68	Stress is being in a very quiet space that makes someone thinks deeply and worry	If you are in a room where it is very quiet
		Extreme silence means I think deeply and worry for example waiting to go to sleep.

Appendix X. Concept Mapping study surveys: Statements rating

ID	Statement	M	SD
1	Stress is a significant burden to some people but has little effect on others	3.74	1.07
2	Stress is a feeling which affects both your physical and mental approach in situations	4.07	1.1
3	Stress is a motivation to get something done	2.77	1.17
4	Stress is uncomfortable, irrational, uncontrollable thoughts and behaviours	3.12	1.25
5	Stress is something someone notes and takes action if it was severe, and not to act if it was mild	2.72	1.18
6	Stress includes tiredness (mentally and/or Physically), worry, anxiety, tension, irritability, mental pressure, unpleasant feelings and/or unusual situations	4.4	0.79
7	Stress is undue activities that cause the mind to overthink and feelings of wanting to shut down and unhappiness	3.17	1.27
8	Stress is an emotional response to outside influences	3.7	0.96
9	Stress is any physical, mental, or emotional stimulus which tends to alter routine functioning or one's behaviour pattern	3.4	1.26
10	Stress is mental, physical, emotional and psychological responses to things rather than rational, objective responses (losing the sense of reasoning)	3.38	1.23
11	Stress is pressure (from outside sources or self-generating) causing a physical reaction	3.51	1.08
12	Stress means enduring pressure, often without being consciously aware	3.57	1.11
13	Stress is feeling under pressure to stay normal and calm	2.65	1.09
14	Stress means feeling (or being) under pressure	3.65	0.95
15	Stress means feeling under pressure to do something.	3.16	1.23
16	Stress is living in potential disaster or troubled areas	3.17	1.28
17	Stress is events or circumstances which make someone feels uncomfortable, annoyed, or frustrated	3.28	1.22
18	Stress is being in uncomfortable situations, like being in a crowded place, visiting the dentist or doctor, driving and dealing with inconsiderate drivers, dealing with pet issues, or getting ready for a holiday	2.95	1.13
19	Stress is waiting for someone who did not turn up on time, or waiting for something which did not arrive on the scheduled time	2.3	0.91
20	Stress is facing work-related difficulties and situations like interviews and meetings, dealing with clients, having the plans disturbed at short notice, difficulties in participating meaningfully in meetings, and/ or having to concentrate to process information in groups	2.91	1.04
21	Stress is experiencing upsetting events or problems requiring urgent attention that someone feels powerless to resolve	3.63	1.02
22	Stress is external factors or new situations that intrude in someone's life	3.02	0.99
23	Stress is the problems that arising gradually	2.33	0.89
24	Stress is feeling uncomfortable and restless	2.93	1.08
25	Stress is feeling scared or having uncontrollable panic	3.3	1.21
26	Stress is to be aware of tinnitus day and night and the mental effort to ignore it and not being able to hear "quiet"	3.37	1.36
27	Stress is having severe interfering tinnitus that prevents the person from multitasking	3.28	1.3
28	Stress is knowing that someone has an invisible disability (continuous noise in the head) that no one understands and there is no cure for it	3.3	1.21
29	Stress is feeling overwhelmed and pressured with even minor tasks or requests at work/ home	3.42	1.12
30	Stress is feeling trapped in a situation and unable to escape	3.86	1.01
31	Stress is not being able to completely relax even when completely feeling tired	3.98	1.03
32	Stress is not having space or enough time to rest and/or relax	3.42	1.12
33	Stress is feeling tense and opposite of calm and relaxed	3.88	1.03
34	Stress is having difficulty getting to sleep, lack of sleep, or not sleeping well	3.77	1.04
35	Stress is feeling frustrated as a result of not got enough sleep and overthinking	3.39	1.22
36	Stress is being (or feeling) very tired (fatigue), even when there are things to do	3.12	1.2
37	Stress is being (or feeling) unable to cope with situations	3.72	1.14
38	Stress is struggling to cope with different situations	3.42	1.12
39	Stress is feeling out of control over everything	3.56	1.37
40	Stress is feeling (or being) not in control of a situation, thoughts, or feelings	3.63	1.23
41	Stress is a compromised ability to handle uncontrollable conditions and escalating situations that interfere in someone's life	3.3	1.19
42	Stress means lacking concentration and focus	2.93	1.26
43	Stress means having the likelihood of becoming more aggressive, irritable, agitated, annoyed, edgy, tense, and loss empathy with others	3.84	1.04
44	Stress means feeling vulnerable or upset	3.3	0.96
45	Stress is feeling withdrawn from situations and problems	2.6	1.22
46	Stress is too much pressure	3.44	1.01
47	Stress is experiencing an unusual or additional pressure from external factors	3.35	1.02
48	Stress is having financial pressure or money issues	3.42	0.98
49	Stress is feeling pressure to perform at a higher level of competence than the usual level	3.33	1.05
50	Stress is being time-pressured	3.31	1.09
51	Stress is having (or feeling) too much to do when there is not enough time (too short time)	3.49	1.16
52	Stress is not having (or feeling) enough time to achieve all the daily tasks	3.14	1.21
53	Stress is feeling unable or fear of failing to meet the approaching deadline or being late for important scheduled events	3.28	1.05
54	Stress is feeling (or being) pushed to your limit at home, in work, or in another external environment	3.56	1.12
55	Stress is feeling unable to put the thoughts in order, to prioritize simple tasks, or to start tackling the important tasks	3.23	1.25
56	Stress is being in a noisy atmosphere (continuous, loud, or low-level noise)	3.33	1.21
57	Stress is withdrawn from social interactions	2.4	1.15
58	Stress is feeling alone and isolated from people and there is no one to talk with	2.62	1.23
59	Stress is the unpleasant feelings which encompass a person's life. These feelings prevent them from seeing any	2.77	1.21

	positivity in life and make them believe that the future is dark		
60	Stress means feeling useless and having low self-esteem, lacking confidence, feeling helpless and hopeless, feeling lost, and/or in a low mood	2.6	1.14
61	Stress is having health issues (or risks) and medical symptoms (like vertigo, headache, high blood pressure) that make the person too feel generally unwell	3.07	1.22
62	Stress is feeling pain (continuous, uncontrollable, or unbearable)	2.93	1.33
63	Stress is being out of one's comfort zone	3.12	1.26
64	Stress means finding life-changing and difficult which prevent the person from leading a normal life or progress in their career. In particular when they can work out a solution or a way out	2.76	1.11
65	Stress is Lower tolerance of regular things like thoughts and experiences	3	1.05
66	Stress means feeling overwhelmed by circumstances and usually when overtired and at those times tinnitus seems louder	3.81	1.24
67	Stress is inability to hear other people, to join conversations, and to enjoy entertainment	2.74	1.24
68	Stress is being in a very quiet space that makes someone thinks deeply and worry	2.12	1.22
69	Stress is feeling worried (or fear) of letting someone down and do not reach their expectations	2.64	1.03
70	Stress is trying to do too much for others and not being able to say no	2.7	1.15
71	Stress is being caught in a middle of problems or arguments brought by family members or other people which increase impatience	2.84	1.17
72	Stress is feeling let down by others when you rely on them	2.3	0.89
73	Stress is feeling that you have upset someone by what you have said or done	2.84	1.09
74	Stress means increased anxiety (worrying) especially about relationships with people in general	2.86	1.06
75	Stress is feeling upset or harmed by being verbally bullied by members of the close circle at work	2.88	1.26
76	Stress is being worried or anxious about something or someone (like health-related issues, money-related issues, or others)	3.26	1.11
77	Stress means heightened anxiety and emotional strain	3.93	1.14
78	Stress is being over-worried (that appears to be unnecessary) about minor details and small incidents	3.07	1.32
79	Stress is being worried about get caught in troubles that someone cannot resolve	2.79	1.21
80	Stress is being worried that someone will not be able to carry on doing what they can do (possibly because of health issues)	2.91	1.17
81	Stress is overthinking about something	2.98	1.35
82	Stress is being (or feeling) constantly having excessive workload	3.26	1.26
83	Stress is feeling conflicted by too many things that need attention	3.3	1.24
84	Stress is working hard to keep on top of things	2.67	1.29
85	Stress is feeling overwhelmed by what is happening around the world	2.67	1.17

Appendix XI. Concept Mapping study surveys: cluster rating map and point rating map

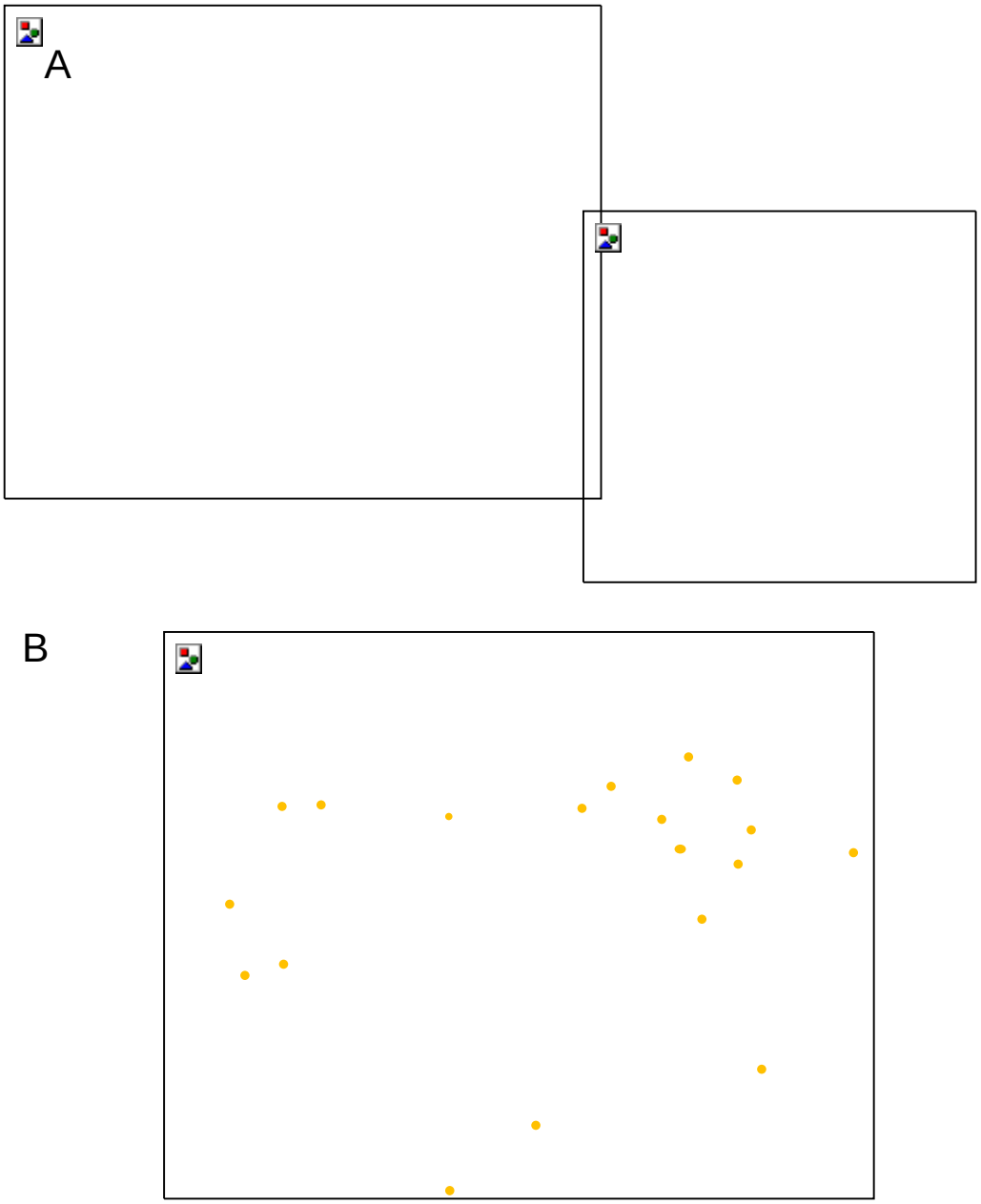


Figure X.1 Visual product of GCM of this study.
(A) Cluster rating map. The table shows the mean (M) and standard deviation (SD) of each group. (B) Point rating map. The yellow dots indicate the statements that rated more than 3.5 as listed in Table 4.5.