EPIDEMIOLOGICAL INVESTIGATIONS OF TINNITUS

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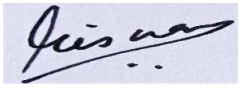
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ABSTRACT

Subjective tinnitus is defined as the conscious perception of an auditory sensation in the absence of a corresponding external stimulus. Severe tinnitus can significantly affect physical and mental well-being while incurring substantial social and financial costs on the individual and society. Nonetheless, tinnitus research and financial investment are substantially lower than other comparable conditions. Adequate assessment of tinnitus prevalence and investigating tinnitus-related risk factors could help recognise the burden of tinnitus and the need for adequate resource allocation. Understanding the epidemiology of tinnitus is crucial for addressing the population-level questions and identifying and quantifying exposures that predispose an individual to tinnitus.

The objectives of this PhD was to address two major aspects of tinnitus epidemiology: (i) estimating the Pan-European prevalence of tinnitus and (ii) identifying tinnitus-related risk factors and quantifying their association with tinnitus, particularly modifiable lifestyle-related risk factors.

A cross-sectional study using standardised assessment questions across 12 European countries estimated 15% prevalence for any, 6% for bothersome, and 1% for severe tinnitus. Eastern European countries showed a consistently higher prevalence compared to the rest of Europe. A literature search for tinnitus-related risk factors was conducted. Evidence from high-quality analytical studies reported an increased risk of tinnitus in the presence of hearing loss, occupational noise exposure, temporomandibular joint disorders, head injury, and ototoxic medications, and decreased risk in people with diabetes. Meta-analyses conducted mostly on cross-sectional studies, reported significantly increased tinnitus risk for smokers and the obese, but no effect of alcohol consumption. Analysing a real-world prospective cohort dataset, moderate alcohol consumption was observed to reduce the risk of incident tinnitus. Adherence to healthy dietary patterns, namely Dietary Approaches to Stop Hypertension (DASH) pattern and Alternative Mediterranean diet (AMED) diet, increased tinnitus risk. Obesity was observed to have no effect on incident tinnitus.

Around 65 million in the EU28 (including UK) report any tinnitus, 26 million report bothersome tinnitus and 4.4 million report severe tinnitus. Not much is known about

the causal risk factors for tinnitus since most data are derived from cross-sectional studies. A meta-analysis on modifiable lifestyle-related risk factors found smoking to be related to tinnitus. In women, healthy diet increased the risk of developing tinnitus, while alcohol consumption in moderation was protective. Obesity did not affect tinnitus risk in women.

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Publications

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Oral Presentations

Epidemiology of tinnitus: risk factors and findings from a Pan-European survey. Tinnitus Research Initiative (TRI) Conference on May 2019, Taiwan.

Assessment of Pan-European prevalence of tinnitus using a standardised set of questions across countries. Basic Auditory Science meeting in September, 2019 in UK.

Poster Presentations

Adapting and Translating Questions for Estimating Tinnitus Prevalence and Severity, Hearing Loss and Usage of Healthcare Resources in 12 European Languages. Runner-up award at the annual British Tinnitus Association (BTA) Conference on September 2018 in UK.

Prevalence estimates for tinnitus, severe tinnitus, healthcare resource use for tinnitus, and hearing difficulty, across 12 European countries. Best paper award at the Tinnitus Research Initiative (TRI) Conference on May 2019 in Taiwan.

A study of the Pan-European prevalence of tinnitus and hearing difficulty using a standardized set of questions. Association of Research in Otolaryngology (ARO) Midwinter Meeting January 2020 in San Jose, California.

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LIST OF ABBREVIATIONS

AMED	Alternative Mediterranean Diet
AT	Any Tinnitus
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMHS	Blue Mountain Hearing Study
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence Interval
CINAHL	Cumulated Index to Nursing and Allied Health Literature
CPRD	Clinical Practice Research Datalink
CT	Computed Tomography
DASH	Dietary Approaches to Stop Hypertension
EFAS	European Federation of Audiology Society
ENT	Ear, Nose and Throat
EHLS	Epidemiology of Hearing Loss Study
ESIT	European School for Interdisciplinary Tinnitus Research
ETS	European Tinnitus Survey
EU	European Union
GDP	Gross Domestic Product
GP	General Practitioner
HES	Hospital Episode Statistics
HL	Hearing Loss
HR	Hazards Ratio
HRQOL	Health-related Quality of Life
IRFMN	Istituto di Ricerche Farmacologiche Mario Negri
KNHANES	Korean National Health and Nutrition Examination Survey
MSCA	Marie Skłodowska-Curie Actions
MeSH	Medical Subjects Headings
MET	Metabolic Equivalent of Task
MOS	Medical Outcomes Study

MRI	Magnetic Resonance Imaging
NHIRD	National Health Insurance Research Database
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
NOS	Newcastle Ottawa Scale
OR	Odds Ratio
PR	Prevalence Ratio
PTA	Pure Tone Audiometry
QOL	Quality of Life
RCT	Randomised Control Trials
RR	Relative Risk
Ref/ref	Reference category
SES	Socioeconomic Status
SF-36	Short Form Health Survey
SFFQ	Semi-quantitative Food Frequency Questionnaire
SNHL	Sensorineural Hearing Loss
SCL-90-R	Symptom Check list-90 Revised questionnaire
TackSHS	Tackling Second-Hand Tobacco Smoke and e-cigarette emission
TRI	Tinnitus Research Initiative
TRT	Tinnitus Retraining Therapy
UK	United Kingdom
UN	United Nations
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization
WHO-QOL	World Health Organization- Quality of Life

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Chapter 1 . Introduction

Tinnitus is a common symptom of clinically heterogeneous pathologies and is defined as the conscious perception of an auditory sensation in the absence of a corresponding external stimulus (Baguley et al., 2013). Subjective tinnitus is experienced by an individual, while objective tinnitus can be heard by an observer. Pulsatile tinnitus is a rhythmic or pulsatile sound that can be synchronous with the heartbeat or asynchronous. For the context of this thesis, the focus will be on subjective tinnitus. It is a self-reported condition with widespread global variability in prevalence estimates. Most available data show prevalence estimates between 10% and 15%, making it a relatively common symptom (Baguley et al., 2013). In the last few decades, there has been substantial progress in tinnitus research with regards to mechanism and treatment options, with an abundance of published literature (Cederroth et al., 2019). However, pathophysiological mechanisms of tinnitus are still mostly hypotheses and conjectures, diagnostic methods lack an objective measure, and treatment options are focused on clinical management, without any definite cure.

1.1 Pathophysiology

Despite an increase in research in the last decade, the precise mechanism of tinnitus pathophysiology remains unclear. Animal models on hearing loss (HL) and tinnitus largely inform our current understanding (Eggermont and Roberts, 2004; Norena, 2011). However, caution is warranted when applying the results from animal models to humans (Adjamian et al., 2009). The lack of a standardised animal model of tinnitus is an important disadvantage (Haider et al., 2018). Moreover, a major conceptual challenge in predicting human findings based on animal models is the difference in measurement techniques. The events from animal models, which are at the subcellular neuronal level, are translated to interpret results from brain activity patterns in people with tinnitus (Adjamian et al., 2009). In animal models, tinnitus is typically considered a consequence of an acute peripheral lesion, while human neuroimaging studies tend to emphasise the role of the the central auditory system in maintaining tinnitus (Eggermont, 2016; Brozoski and Bauer, 2016). Hence, there remain multiple challenges in using animal models to understand the neural correlates of tinnitus.

Given its association with high frequency HL, in humans, tinnitus is considered the product of maladaptive neuroplastic response to sensory deprivation (Eggermont and Roberts, 2004; Shore et al., 2016). In the peripheral auditory system, tinnitus onset is precipitated by noise exposure or age-related HL, which can damage the cochlea. In the auditory system, tones of similar frequency are processed in topologically neighbouring regions, and this systematic spatial arrangement is referred to as a tonotopic organisation. Any damage to the cochlear hair cells can lead to imbalanced firing patterns in this tonotopic array. However, the firing pattern imbalance of the damaged cochlea cannot sufficiently explain the mechanism of tinnitus because the auditory component is maintained in the brain even when input from the ear is eradicated by dissecting the auditory nerve (Haider et al., 2018; House and Brackmann, 1981). Therefore, while cochlear damage can initiate tinnitus, maintenance of the condition is more likely dependent on changes in the central auditory system (Baguley et al., 2013).

There could be a few potential mechanisms for this neural component for tinnitus. For example, it is proposed that hyperexcitability within the central auditory system occurs through the downregulation of inhibitory cortical processes. This downregulation results from reduced activity of the peripheral auditory region due to damage of the cochlear nerve (Norena and Eggermont, 2003). Another potential mechanism is temporal synchrony in spontaneous firing patterns of neurons in the auditory cortex. This pattern increases post noise exposure, particularly in the affected part of the tonotopic arrangement (Norena and Eggermont, 2003). Studies have linked tonotopic re-organisation due to HL, with tinnitus. However, psychoacoustic findings suggest that the dominant tinnitus pitch falls within the range of HL and not at the edge of HL. Therefore, the neural temporal dynamics are more likely to explain the neural correlate of tinnitus rather than expansion of the tonotopic map at the audiometric edge. Clinical research also suggests an analogy between phantom pain and phantom sound, i.e., tinnitus. A proposed model is that the phantom perception of sound (tinnitus) results from multiple parallel overlapping brain networks. This explanation is supported by evidence from human neuroimaging data, which suggests the involvement of the central auditory system as well as non-auditory brain areas in tinnitus (De Ridder et al., 2014; Langguth et al., 2012).

The pathophysiology of tinnitus exhibits heterogeneity. A thorough understanding of the underlying pathophysiology is vital to improve the clinical management of tinnitus, particularly to personalise tinnitus treatment based on individual symptoms.

1.2 Diagnosis

As of yet, there is no available objective measure for tinnitus. It is a self-reported condition, and careful history taking and assessment of the effects of tinnitus on an individual's life form the basis of tinnitus diagnosis and management. Tinnitus can co-exist with multiple comorbidities and can be a symptom of various underlying pathologies, including life-threatening conditions like carotid stenosis and vestibular schwannoma. Moreover, tinnitus in its debilitating form can lead to psychological conditions like depression and even suicidal tendencies. Therefore, a multidisciplinary approach to tinnitus diagnosis is desirable to understand any underlying pathology and examine any co-existing factors, and then manage accordingly (Baguley et al., 2013; Langguth et al., 2013). Langguth et al. (2007) proposed a stepwise diagnostic approach including the following steps: (i) detailed case history; (ii) assessment of severity using questionnaires; (iii) clinical examination of the ear; and (iv) audiological assessment.

The case history should include information on the onset, duration, location, and character of tinnitus - mainly whether there is a pulsatile component, modifying factors, and related conditions (Baguley et al., 2013; Langguth et al., 2007). There are standardised tools available for history taking. For example, the Tinnitus Sample Case History Questionnaire is a case history instrument developed by the Tinnitus Research Initiative (TRI) for the standardised collection of information about the tinnitus characteristics and is used in some clinics (Langguth et al., 2007). The more recently published European School for Interdisciplinary Tinnitus Research-Screening Questionnaire is another comprehensive case history instrument that can be used in both people with and without tinnitus and collects data on risk factors for tinnitus along with tinnitus characteristics (Genitsaridi et al., 2019).

It is also vital to assess tinnitus severity and the consequences of tinnitus symptoms on an individual's life (Baguley et al., 2013). Many questionnaires are currently available that allow individuals to rate the tinnitus-related distress, addressing different domains such as health, impact on lifestyle, psychological and emotional abilities,

sleep, and tinnitus-specific effects (Kennedy et al., 2004). The Tinnitus Questionnaire, Tinnitus Handicap Questionnaire, Tinnitus Handicap Inventory, Tinnitus Functional Index, and Tinnitus Reaction Questionnaire are examples of instruments that clinicians use to assess tinnitus symptom severity and changes over time (Fackrell and Hoare, 2017; Meikle et al., 2007).

Thorough clinical examination is necessary to identify possible underlying physical causes like abnormalities of the cochleo-vestibular system or in the head and neck region. An otoscopy and oto-microscopy are commonly conducted to examine the external auditory canal, assess the integrity of the tympanic membrane, and check for infection/abnormalities in the external and middle ear (Langguth et al., 2011). Laboratory tests can be ordered, depending on preliminary history and neck examination (Chari and Limb, 2018). Head and neck examinations are critical in pulsatile tinnitus, given its association with neurovascular and cardiovascular conditions and because it can sometimes be detected objectively through auscultation (Baguley et al., 2013).

HL is a major risk factor, and most individuals with tinnitus show some degree of HL. Pure tone audiometry (PTA) is, therefore, commonly done. However, tinnitus is mainly associated with sensorineural HL (SNHL) in higher frequencies, which cannot be detected using a regular PTA. Although pitch and loudness matching is sometimes done, they are difficult to perform and usually neither serve to predict the patients' distress nor contribute much to the subsequent management plan (Langguth et al., 2013).

Among neuroimaging methods, Magnetic Resonance Imaging (MRI) is the preferred choice to further investigate the presence of asymmetric tinnitus, asymmetric hearing on PTA, or other associated neurological symptoms or signs, like headache, space-occupying lesions, benign intracranial hypertension, etc. More complex investigational algorithms are chosen in synchronous pulsatile tinnitus that can include ultrasonography, Computed tomography (CT), MRI, CT angiography, MR angiography, or conventional angiography (Baguley et al., 2013). Co-existing psychiatric conditions, like depression, anxiety, and insomnia, need specific investigation and treatment as they aggravate the impact of tinnitus on quality of life

(Langguth et al., 2013). Hyperacusis and phonophobia often co-occur with tinnitus, and it is useful to assess such symptoms (Baguley et al., 2013).

1.3 Management

Tinnitus has no definite cure. Unclear understanding of the pathophysiology, heterogeneous subtypes requiring different or personalised treatments, lack of objective outcome measures, the large placebo effect, and small size of clinical trials are some of the impediments in the pathway to tinnitus cure (McFerran et al., 2019). Only when an exact underlying cause for tinnitus is detected (for example, impacted cerumen) can adequate treatment eliminate the auditory sensation (Baguley et al., 2013). Tinnitus treatment is directed towards reducing the impact and not eliminating the percept (McFerran et al., 2019). Most of the time, it is impossible to find a clinical condition causing the phantom perception, so a specific treatment might not be possible. Considering the heterogeneity in most aspects of tinnitus, various treatment modalities are proposed using a multidisciplinary approach, although with limited success (McFerran et al., 2019). In the absence of a treatable underlying pathology, explanation of cause, sound therapy, i.e., providing hearing aids or sound generators, and counselling for tinnitus-related distress using relaxation therapy and cognitive behavioural therapy are standard treatments (Baguley et al., 2013).

Hearing aids are commonly used for individuals with tinnitus along with HL. By compensating for the deprivation of input caused by HL, hearing aids increase the level of ambient noise perceived by an individual. This distracts them from the tinnitus perception, thereby partially masking it and making it less intrusive and less annoying (Del Bo and Ambrosetti, 2007; Hoare et al., 2014). Sound generators produce environmental sounds, like sea waves, rain, or white noise to mask the tinnitus, either totally or partially. Custom sound generators produce a wide band sound, with adjustable frequency composition and loudness (Langguth et al., 2013). However, a review of the effectiveness of sound therapy for tinnitus found no data comparing sound therapy to placebo or information/education and no device. Moreover, there is also insufficient evidence to favour any one type of sound therapy over another (Sereda et al., 2018).

Relaxation therapy and cognitive behavioural therapy have shown effective results in decreasing the impact of tinnitus by reducing emotional symptoms and improving

quality of life without affecting tinnitus loudness (Hesser et al., 2011; Martinez-Devesa et al., 2007; Weise et al., 2008). These treatments have mainly shown benefits for severely distressed patients needing professional psychological counselling (McFerran and Baguley, 2009). Tinnitus retraining therapy (TRT), which includes sound therapy and counselling, aims to reach a stage in which the patients' awareness of their tinnitus is low enough to no longer interfere with day-to-day life (Jastreboff, 2007). Even though TRT seems to be a popular choice for tinnitus treatment, a Cochrane review found that the quality of research on TRT is poor (Phillips and McFerran, 2010).

Neuromodulatory treatments by using brain stimulation have been applied to tinnitus, and some of them have shown promising results (Smit et al., 2016). Auditory cortex stimulation, direct electrical stimulation, transcranial magnetic stimulation, and deep brain stimulation are some brain stimulation methods. Pharmacologic treatments have also been tested, although there is still no licensed drug therapy for tinnitus in either Europe or the United States (Baguley et al., 2013). Often the drug therapy alleviates an associated symptom or comorbidity instead of directly treating tinnitus. For example, antidepressants, particularly selective serotonin reuptake inhibitors, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors commonly prescribed for tinnitus, are indicated for anxiety and depression, and not specifically for tinnitus (Belli et al., 2012; Langguth et al., 2013; Robinson, 2007). Similarly, melatonin prescribed in tinnitus and sleep disturbance mainly helps by treating the latter (Miroddi et al., 2015). Several other drugs like diuretics, anticonvulsants, and vasodilators have been tried for tinnitus treatment with little to no success (Baguley et al., 2013).

There is a clear gap for evidence-based practice in tinnitus management that prevents linking assessment and diagnostic measures to the most effective management strategies. Moreover, assessment and management strategies lack consensus across tinnitus types, healthcare providers, and countries (Hoare and Hall, 2011). Pharmacological treatments are preferred in acute subjective tinnitus, while audiological and psychological approaches are often the treatment modalities in chronic cases (Baguley et al., 2013). A recent review on tinnitus therapies across Europe reported wide variability across countries and European regions in terms of

treatment of choice, referral pathways, the involvement of multidisciplinary teams, and availability of tinnitus specialist clinics (Cima et al., 2020). Given this lack of standard practice, treatment choice depends on many factors, including physician preference, available resources, and local and patient preferences (Baguley et al., 2013; Hall et al., 2011).

1.4 Epidemiology

Tinnitus is a clinical enigma. Heterogeneity is apparent in all aspects of tinnitus, from its manifestation to underlying pathophysiology, making any cure elusive (Cederroth et al., 2019; McFerran et al., 2019). There are several unmet needs in tinnitus research. For example, there is a lack of clear understanding of the proportion of the global population affected by tinnitus and what makes one population group more vulnerable than others. Knowledge and understanding of the epidemiology of tinnitus are of key importance in addressing these population-level questions as well as in identifying and quantifying various exposures that predispose individuals to tinnitus.

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems (Last, 2001). Some key terms in this definition reflect the main concepts of epidemiology. It is a data-driven scientific discipline that uses systematic and unbiased methods to collect, analyse, and interpret data. Measures of frequency like prevalence and incidence are used to determine the distribution of a health condition and identify the pattern of a condition, i.e., whether the number of affected individuals is increasing or declining over time in a specified population. Determinants include risk factors and concomitant diseases, conditions, behaviours, or lifestyles that predispose an individual to a health condition (Centers for Disease Control (CDC), 2012). Epidemiology does not just include identifying the determinants but also quantifying them using various measures of effects like relative risk (RR), odds ratio (OR), and hazards ratio (HR).

In the following section, a literature review is provided for tinnitus epidemiology along with explanations of epidemiological concepts using examples from tinnitus literature. Some of these sections are adapted from an invited book chapter titled “Prevalence, Incidence, and Risk Factors for Tinnitus” (Biswas and Hall, 2020).

1.4.1 Prevalence

Prevalence is the proportion of persons in a population who have a particular disease or health condition at a specified point in time or over a specified period of time. For example, if in a sample of 100,000 people, 5,000 report tinnitus, the percent prevalence is five (5%). Prevalence values are influenced by the number of new cases (incidence) and the duration of the condition. Higher prevalence can be attributed either to an increased number of new cases or an increased survival of cases without any cure or both. The latter is crucial for conditions like tinnitus, where there is no cure, and due to the chronic, insidious nature, the exact time of onset is hard to recognise. Prevalence is often used as a frequency measure for quantifying the distribution of chronic conditions like tinnitus.

1.4.1.1 Heterogeneity in tinnitus prevalence

Systematic reviews indicate widespread global variability in tinnitus prevalence estimates. For example, McCormack et al. (2016) reviewed 35 studies and reported prevalence estimates ranging from 5% to 43% (Gibrin et al., 2013; Quaranta et al., 1996). Major contributors to this variability included the lack of an agreed assessment question, heterogeneous reporting measures, differences in population demographics (for example, studies conducted on different age groups), and geographic location bias in prevalence studies (Gallus et al., 2015; McCormack et al., 2016). The lack of standardisation hinders pooling estimates across countries to measure the global prevalence of tinnitus and makes comparisons between countries or world regions difficult. It is possible that the assessment questions, used for deciding whether or not a person has tinnitus, introduce variability because population-based prevalence and incidence studies rely on self-report.

In spite of a straightforward clinical definition, there is no consensus on the assessment question or research definition used in tinnitus prevalence studies. In their systematic review, McCormack et al. (2016) found eight different assessment questions for tinnitus. Approximately 34% (12/35) of studies in this review, included the phrase ‘tinnitus lasting for more than five minutes at a time’, which is the most commonly used phrase in tinnitus assessment questions . However, using the common phrase did not necessarily guarantee uniformity in measured estimates. For

example, a study by Hannula et al. (2011) used the assessment question “Nowadays, do you ever get noises in your head or ears (tinnitus) which usually last longer than five minutes?”. Another study by McCormack et al. (2014a) used the UK Biobank question “Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time?” . The two aforementioned questions both included the “lasting for five minutes” phrase and were apparently similar. However, there was a key difference. While one of them defined a time frame “nowadays”, the other did not. The term “nowadays” is slightly ambiguous as it could have been interpreted as now, or in the last few days, or even in the last month. On the other hand, the inclusion of the “do you get or have you had” phrase in the close-ended UK biobank question with binary response options (yes or no), broadened the scope of the question and could have been interpreted as tinnitus symptoms at present or in the recent past or maybe even one odd event in a person’s lifetime.

Approximately 26% percent (9/35) of studies included the second most commonly used phrase “experiencing tinnitus in the last year” (McCormack et al., 2016). In the studies by Nondahl et al. (2002) and Spankovich et al. (2017), subjects were asked about tinnitus in the last year (for example, “In the past year have you had buzzing, ringing or noise in your ears?”) . On the other hand, Xu et al. (2011) in China and Bhatt et al. (2016) in the US used questions that assessed tinnitus over the last year and lasting for five minutes (example “In the past year have you had noises in your ears or head which lasted longer than 5 minutes?”). While both questions included a time frame of one year, one specified tinnitus duration, and the other did not. From the above examples, it is evident that studies with broadly similar assessment questions often included or omitted key terms that address crucial information relating to an individual’s tinnitus symptoms.

Many epidemiological studies seeking information on tinnitus prevalence have also sought information about the severity or bothersomeness of tinnitus symptoms (McCormack et al., 2014; Nondahl et al., 2011). This is a reasonable approach considering a mild tinnitus experience is arguably different from a “clinically significant” tinnitus where the condition hampers an individual’s quality of life enough to seek medical help (Hoekstra et al., 2014). Severe tinnitus can be debilitating, significantly

affecting an individual's health and emotional well-being and incurring substantial social and financial costs on the individual and the society at large (Hall et al., 2018a; Maes et al., 2013; Stockdale et al., 2017). Severe tinnitus is different from any tinnitus (which does not distinguish the severity of symptoms) in terms of effect, assessment, and reporting of symptoms. However, "severe tinnitus" definitions are also plagued by inconsistencies.

Eight out of the 13 studies (62%) reporting tinnitus severity, that McCormack et al. (2016) included in their review, defined severity or bothersomeness of tinnitus symptoms in terms of how bothered, annoyed, or worried it made the individual. Not all severity assessment questions uniformly included all three emotional descriptors. For example, Jun et al. (2015) and Welch and Dawes (2008) both used the term "annoy" to assess the effect of tinnitus severity, although the latter also included the term "upset" ("How annoying or upsetting is it?") . On the other hand, the severity question from the UK Biobank used three emotional descriptors ("How much do these noises worry, annoy or upset you when they are at their worst?"), while the Swedish Longitudinal Occupational Survey of Health replaced annoy with the term "bother" ("How much do you feel that the tinnitus sounds worry, bother or upset you?") (Hasson et al., 2010; McCormack et al., 2014). These emotional descriptors have subtle underlying differences in their meanings. Since severity is a self-reported perception, even these subtle nuances can affect the findings of a study.

The severity of tinnitus symptoms is also expressed in terms of its effect on sleep and concentration, or an individual's ability to lead a normal life. McCormack et al. (2016) reported that three out of eight studies in the systematic review assessed severity in terms of its impact on sleep, concentration, while two out of eight studies in terms of an individual's ability to lead a normal life . The three assessment questions for tinnitus symptom severity addressed different constructs, and it is not possible to either pool or compare results from studies that measure and report findings from such conceptually different elements.

Tinnitus frequency, measured by "how often the tinnitus happens", is another component that has been assessed in some studies to distinguish constant or persistent tinnitus from occasional occurrences (Bhatt et al., 2016; Degeest et al., 2017; Folmer et al., 2011; Shargorodsky et al., 2010; Spankovich et al., 2017). This

component suffers from the same lack of consensus across the tinnitus research community. Interestingly though, this heterogeneity is related more to how constant or persistent tinnitus is defined in the response options rather than how the frequency question is phrased. Shargorodsky et al. (2010) defined frequent tinnitus as occurring "almost always or at least once a day" . Folmer et al. (2011) defined constant tinnitus as occurring "almost always," while Spankovich et al. (2017) defined persistent or constant tinnitus as tinnitus occurring "at least once a month or more". In another study, Degeest et al. (2017) defined constant tinnitus as lasting for more than 72 hours. Bhatt et al. (2016) included "nearly constant" as a response option in their study.

1.4.1.2 Prevalence estimates for tinnitus

Prevalence studies use diverse assessment questions and often lack explicit statements to describe the time frame for tinnitus symptoms. Therefore, the results capture point, period, or lifetime prevalence estimates, which is a potential cause for the heterogeneous results. A call to meet this challenge of developing standardised assessment questions has been raised by several authors (Gallus et al., 2015; McCormack et al., 2016).

Point prevalence refers to the number of cases of a condition at a specific time point. In chronic conditions like tinnitus, it is useful for capturing individuals who experience the symptoms most of the time or all the time. Ideally, point prevalence would be data collected at one specific point in time. However, it is usually difficult to assess the prevalence of a condition in the entire sample population at one instant, and some amount of flexibility is acceptable in defining time. For all practical purposes, a point in time can be defined as an event rather than a precise calendar date. In a population-based cross-sectional study conducted on adults aged 18 years and above living in the city of Sao Paulo, Brazil between April and October 2012, tinnitus affected individuals included participants who responded "yes" to the question "Do you have ringing in your ears?" with binary response options (yes or no). (Oiticica and Bittar, 2015). Since the question was not bound by a defined time frame and asked about the presence of the symptom in the current context, it can be assumed that the prevalence thus measured was an estimate of point prevalence. In this study, the prevalence of tinnitus was 22% (Oiticica and Bittar, 2015). The authors acknowledged that the prevalence rate was higher than that reported by some other studies and cited

the lack of a defined time frame, pattern, and severity in their assessment method as some possible causes. In this regard, it is essential to note that the waxing and waning nature of chronic symptoms can bias the estimates for point prevalence. The unrestricted time frame of the question used, along with the simplified response options, might lead to the inclusion of individuals having an acute, rare and transient episode of tinnitus following some recent exposure like loud noise, thereby causing overestimation. Alternatively, people with chronic intermittent tinnitus who are experiencing a tinnitus free phase (i.e., intermittent tinnitus) respond “no,” thereby underestimating the findings. In the above study, a follow-up question found that two-thirds of the affected population had intermittent tinnitus (Oiticica and Bittar, 2015). Therefore, caution should be exercised when relying on point prevalence estimates.

In the research definitions of tinnitus, the distinction between point and period prevalence is often not made clear by authors. Perhaps the reason is the practical difficulty in assessing all cases simultaneously, since surveys tend to have a data collection period spanning over weeks, months, or even years. Period prevalence is conceptually similar to point prevalence except that it considers a broader time range. While point prevalence provides a single snapshot of burden, period prevalence paints a picture over a longer time frame. For example, this could be measured using a survey asking individuals if they have experienced tinnitus during the past 12 months. Another difference is that, when calculating period prevalence, the denominator is the average or the mid-interval population, as against point prevalence where the denominator is the population at the same point in time. Bhatt et al. (2016) conducted a cross-sectional study on nationally representative population-based data from the 2007 US National Health Interview Survey (NHIS) to assess tinnitus prevalence. They measured tinnitus prevalence in the preceding 12 months on adults aged 18 years and above and reported a prevalence estimate of 9.6% (question: “In the past 12 months, have you been bothered by ringing, roaring, or buzzing in your ears or head that lasts for 5 minutes or more?”) (Bhatt et al., 2016). Given that a considerably more extended period (e.g., 12 months) is considered, people with intermittent episodes of tinnitus are less likely to be missed. However, overestimation is a potential risk as individuals having had a single acute incident of transient tinnitus in the last 12 months may respond affirmatively, leading to a mixed estimate of acute and chronic tinnitus.

Lifetime prevalence refers to the number of cases of tinnitus over an individual's lifetime. Because tinnitus (in most cases) is chronic in nature, one might expect lifetime and period prevalence to yield similar estimates. Lifetime prevalence could be measured using a survey asking individuals if they have ever experienced tinnitus. For tinnitus, the chronic debilitating form presents the main public health concern. A survey question about ever having tinnitus would yield a mixed estimate of acute, transient, and chronic symptoms and would not necessarily be a true reflection of the burden of tinnitus. No tinnitus prevalence study specifically assesses lifetime prevalence. Although the result from the analysis of the UK Biobank data collected between 2006 and 2010 might include a mix of point and lifetime prevalence (McCormack et al., 2014a). The UK Biobank question on current tinnitus was "Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time?" with the response option "yes" or "no." The question is ambiguously phrased by including both "do you" and "have you had" and can be positively responded to by individuals experiencing acute or transient or chronic symptoms, potentially leading to over-estimation of percent prevalence. Therefore, in the absence of a clearly defined time frame, the tinnitus assessment questions do not necessarily measure appropriate and comparable estimates.

To pool, compare, and meaningfully interpret findings across studies, prevalence estimates for any tinnitus must be reliable. With regards to reliability, two statistical concepts are vital: accuracy and precision. Accuracy is the degree to which a measurement, or an estimate based on measurements, represents the real value of the measured attribute. Precision is defined as the inverse of the variance of a measurement or estimate (Last, 1988). In other words, accuracy determines how close the estimate is to the true value, while precision determines how close the repeated estimates are to each other after successive measurements (Figure 1.1). Accuracy and precision do not always concur. The median range of tinnitus prevalence estimates in Western Europe and America is between 10% and 15% (Baguley et al., 2013). An accurate and precise estimate of tinnitus prevalence would therefore ideally be around this benchmark for these world regions.

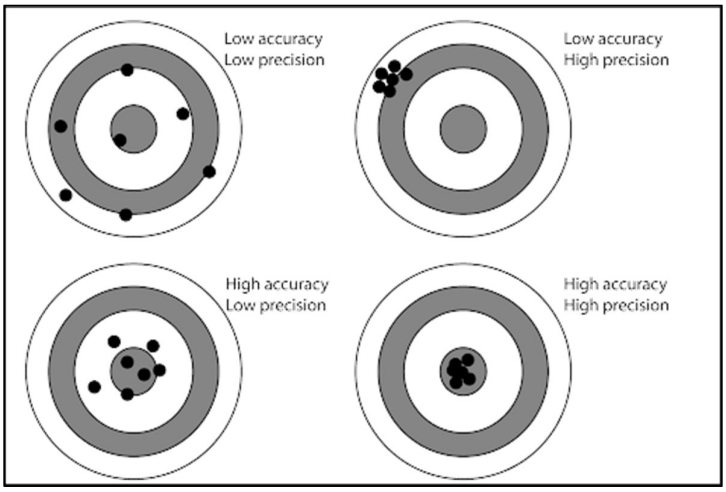


Figure 1.1 Graphical illustration of accuracy and precision

1.4.1.3 Effect of demographics and geographical location

Population demographics and the vulnerability of specific population groups often influence the prevalence estimates, thereby skewing the results. Literature shows that tinnitus prevalence and reported severity increases with increasing age. Bhatt et al. (2016) conducted their analysis on nationally representative data in the US and found that the group reporting tinnitus symptoms was older than the group without symptoms, with a mean difference of 8 years. They also reported a direct positive correlation between age and tinnitus prevalence (r=0.08) .

Gallus et al. (2015) conducted a prevalence study in a nationally representative population in Italy, finding that the prevalence of any tinnitus was 6% higher in individuals older than 45-years (9% prevalence) compared to individuals younger than 45 years (prevalence was 3%). They also reported that 97% of study participants reporting severe tinnitus symptoms were older than 45 years (Gallus et al., 2015). McCormack et al. (2014a) also reported a trend for bothersome tinnitus in both men and women with increasing age in a study conducted on UK Biobank data. Given the age-dependent increase of tinnitus, when pooling data from various studies or comparing prevalence in different populations, one must be careful of the age range.

There is no clear consensus on sex differences in tinnitus prevalence. Bhatt et al. (2016) found tinnitus to be 2% more prevalent in men than in women, but with no difference in severity. On the other hand, Nondahl et al. (2002) reported that female

sex increased tinnitus risk in a prospective cohort dataset. Gallus et al. (2015) reported no significant difference in the prevalence of any tinnitus between men and women, but double the prevalence of severe tinnitus symptoms in women (1.6%) compared to men (0.8%). McCormack et al. (2014a) found current tinnitus to be 4% more common in men than women and reported women to have a slightly higher prevalence of bothersome tinnitus (4.1% in women and 3.5% in men). Park and Moon (2014) analysed data from the Korean National Health and Nutrition Examination Survey (KNHANES) to report women having an increased likelihood of any tinnitus than men, although the likelihood of annoying tinnitus did not differ across the two sexes. A potential cause for study-specific differences in sex distribution could be attributable to differences in the socio-cultural and behavioural structures across countries. While plausible, this explanation seems unlikely because studies conducted in the same countries often report contradictory findings regarding sex differences (Bhatt et al., 2016; Nondahl et al., 2002).

Another crucial issue in epidemiological research in tinnitus is that it has been predominantly restricted to Western Europe, the US, and Australia (McCormack et al., 2016). In recent years, there have been some prevalence studies conducted in other parts of the world, including parts of South-East Asia, the Middle East, and Africa (Jalessi et al., 2013; Park et al., 2014; Baek et al., 2016; Manche et al., 2016; Shih et al., 2017), but still many fewer. Consequently, any attempt to derive a global estimate from available studies would bias the results towards specific world regions where more research is conducted.

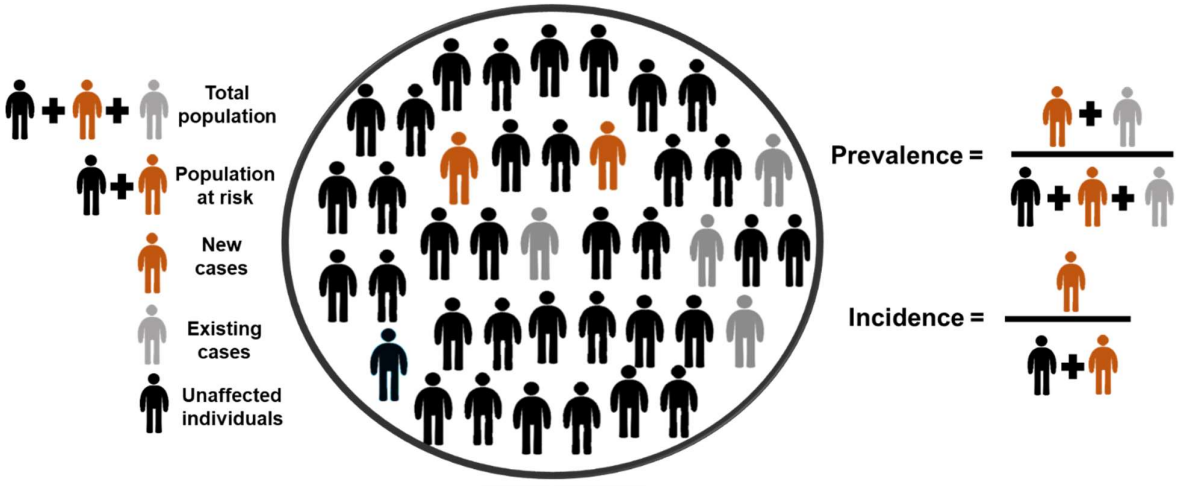


Figure 1.2 Graphical representation of prevalence and incidence in a population (adapted from Biswas and Hall,2020)

1.4.2 Incidence

The incidence rate is calculated by dividing the number of new cases over a specified period either by the average population (usually mid-period, which is the population half-way through the period being evaluated), or person-time (which is a measure of the number of persons at risk and the time they were at risk). It is a measure of the frequency with which new tinnitus events occur over a particular time frame (e.g., the number of new cases per year). Incidence is assessed using longitudinal study designs, which involve observing people without tinnitus in a non-controlled environment without interfering or manipulating other aspects of the study. Not many longitudinal studies are available in tinnitus research, and therefore, incidence data is scarce (Baguley et al., 2013).

The Epidemiology of Hearing Loss Study (EHLS) is a prospective population-based survey that followed tinnitus-free individuals in the baseline period (1993 to 1995) for ten years. Among the 4,541 individuals eligible to participate in this study, 83% (n=3,753) participated at baseline, and of these, 3,429 were tinnitus-free. This is the subset at risk of developing tinnitus. Four follow-up surveys were conducted between 1995 and 2005 (1995–1997, 1998–2000, 2000–2002, and 2003–2005). Over this period, 2,922 individuals aged 48 to 92 years provided information on their tinnitus

status at least once and up to four times. Results indicated that the cumulative incidence of tinnitus was 13% (Nondahl et al., 2010).

Martinez et al. (2015) retrospectively collected data from anonymised patient records sourced from two National Health Service databases: The United Kingdom Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) to measure incident cases of clinically significant tinnitus. Clinically significant tinnitus was defined in several different ways in an attempt to capture all cases. For example, it could be a patient discharged from hospital with a primary discharge diagnosis of tinnitus (e.g., formally defined with ICD-10 code H931), or a patient having a recording of tinnitus by the family doctor and having either a specific diagnosis or a relevant onward referral. The observation period (i.e., when a patient from the study population was at-risk for developing clinically significant tinnitus) was from 2002 to 2011. This study calculated the incidence rate given by the number of new cases of clinically significant tinnitus divided by the total person-years at-risk of the study population and reported the incidence rate as 5.4 new cases of clinically significant tinnitus per 10,000 person-years (Martinez et al., 2015).

The former was a prospective study, while the latter was a retrospective population-based study that reviewed existing health records. Section 1.4.4 shows more details on the definitions, advantages, and disadvantages of various study designs. However, one thing that can be noted is that incident reporting by Martinez et al. (2015) is dependent on medical help-seeking behaviour. A majority of individuals suffering from tinnitus are not affected enough by the symptoms to seek medical advice, while a comparatively fewer proportion of individuals who report bothersome tinnitus require some form of clinical intervention (Dobie, 2004; Henry et al., 2015). This means incidence estimates for tinnitus from a retrospective analysis of health records are not directly comparable with results from a prospective survey on the general population, such as EHLS. Therefore, incidence estimates for tinnitus are not only rare but also plagued by heterogeneous assessment methods.

1.4.3 Risk factors

Tinnitus is a neuro-otological condition precipitated by changes in the auditory pathway, altered somatosensory inputs, and abnormal activities in the central nervous

system, and is multifactorial in most cases (Langguth et al., 2013; Kreuzer et al., 2012). It is difficult to pinpoint a specific cause of tinnitus. Conditions that lead to cochlear damage like sudden HL, loud noise exposure, presbycusis and ototoxic medications often result in tinnitus.

Tinnitus is not a disease but a symptom associated with a number of communicable and non-communicable diseases. It has been reported in presence of otological diseases, like otosclerosis, Ménière's disease, and vestibular schwannoma (acoustic neuroma). Hyperacusis (decreased sound tolerance) is noted in 40% of patients with tinnitus, and up to 86% of patients reporting hyperacusis also report tinnitus (Baguley et al., 2013). Tinnitus onset is often associated with emotional stressors and occurs as a comorbidity with conditions like anxiety and depression (Langguth et al., 2013). Other conditions like cardiovascular diseases, neuro-degenerative conditions, arthritis and temporomandibular joint disorders have been suggested as possible risk factors (Baguley et al., 2013; Nondahl et al., 2010).

As an adverse effect, certain medications can cause damage to the inner ear or auditory nerve, i.e., ototoxicity, which is characterised by degeneration of cochlear or vestibular tissue leading to their dysfunction. Such damage can lead to the perception of tinnitus (Cianfrone et al., 2011; Ganesan et al., 2018). Additionally, tinnitus is hypothesised to be associated with behavioural and lifestyle-related factors like smoking, alcohol consumption, obesity (which can be determined by body mass index (BMI)) caffeine intake (Baguley et al., 2013; Biswas and Hall, 2020). Recent studies have alluded to the genetic predisposition for tinnitus, although evidence supporting this is sparse and calls for more research (Lopez-Escamez et al., 2016; Vona et al., 2017).

Tinnitus perception can develop post-exposure to a diverse set of underlying conditions and risk factors (Baguley et al., 2013; Biswas and Hall, 2020). Implementing appropriate preventive measures to reduce the impact of these risk factors can substantially reduce the burden of tinnitus. Nonetheless, developing effective preventive strategies is not always a straightforward process. The type of risk factor and the nature of its association with tinnitus play a crucial role.

Table 1.1 Potential tinnitus-related risk factors

Category	Examples
Otological	HL, Noise exposure, Infections, Neoplasms, Meniere's disease,
Neurological	Meningitis, Migraine, Epilepsy
Traumatic	Head and neck injury, Blast injury
Other medical comorbidities	Hypertension, Diabetes, Rheumatoid Arthritis
Psychological	Anxiety, Depression
Lifestyle	Smoking, Alcohol consumption, Obesity (BMI), Caffeine intake
Ototoxic medications	Antibiotics, Anti-neoplastic drugs, Non-steroidal anti-inflammatory drugs

For example, HL is regarded as the most critical risk factor for tinnitus (Baguley et al., 2013; Davis and Rafaie, 2000; Michikawa et al., 2010; Sindhusake et al., 2004). However, the relationship between tinnitus and HL is not straight forward, and the underlying mechanism of the relationship is complicated and still quite unclear. HL and tinnitus do not always co-exist, and an abnormal audiogram is not found in all individuals with tinnitus (Curti et al., 2019a; Ramage-Morin et al., 2019).

Another primary concern in tinnitus risk factor analyses is the considerable gaps in knowledge in the cause and effect relationship between potential risk factors and tinnitus (Biswas and Hall, 2020). Most information for tinnitus-related risk factors is derived from cross-sectional studies, sufficient to generate hypotheses but not sufficient to establish causality. For example, a recent systematic review and meta-analysis by Veile et al. (2018) based on 20 studies related to the association between smoking and tinnitus reported that both current and former smokers had significantly increased risk of having tinnitus. However, a causal association could not be concluded because most of these data came from cross-sectional studies (Veile et al., 2018).

1.4.4 Study designs

Selecting an appropriate study design is crucial to the quality, execution, and interpretability of healthcare research (Aschengrau and Seage, 2013; Rothman et al., 2008). The research question of interest is the most important deciding factor in choosing a study design (Checkoway et al., 2007; Thiese, 2014). Other feasibility

constraints that have a role include prior research, participant availability, funding, and time constraints (Thiese, 2014). Research can be either primary or secondary research. Data is gathered from original studies in primary research, particularly for that specific research purpose or to address a specific research question (Ahrens and Pigeot, 2014; Rothman et al., 2008).

Figure 1.3 illustrates a common scheme for categorising primary research based on researchers' role (observational versus interventional) and the research purpose (descriptive versus analytical).

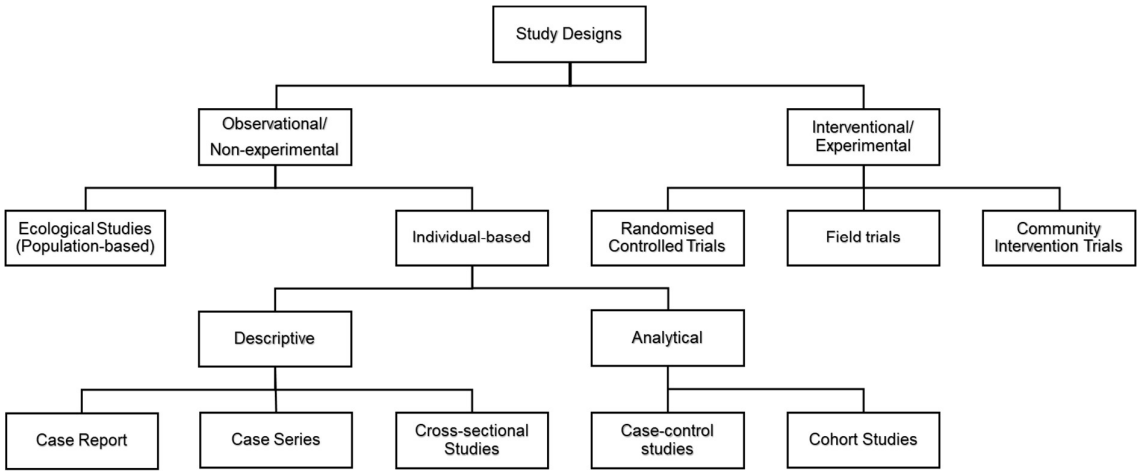


Figure 1.3 Schematic classification of research study designs

In observational study designs, investigators observe each study participant's exposure and disease status in a non-controlled environment. In experimental study designs, the investigators introduce a treatment or prevention strategy (exposure) and then, through a controlled process, track individuals or communities over time to detect the effects of the exposure. In tinnitus, depending on the research question, both types of study designs are implemented. Observational studies measure tinnitus prevalence and are also used to generate and test hypotheses about the cause (Sackett, 2000). Interventional studies, particularly randomised controlled trials (RCT), are used to assess the efficacy of treatment and management options for tinnitus. Table 1.2

illustrates some commonly used study designs and their application in tinnitus research, advantages, and disadvantages.

Not all study designs report equal strength of evidence: In scientific literature, the hierarchy of evidence is represented by a pyramid (Figure 1.4A). With each increasing step of the pyramid, bias is reduced, and reliability increases. A major deciding factor for the strength of evidence is the ability to suggest causation (Thiese, 2014). Hill's criteria are commonly used to establish causation, and demonstrating the cause preceding outcome is mandatory for suggesting temporality (Hill, 1965).

Descriptive observational studies are useful for measuring frequency (prevalence and incidence) and generating causal hypotheses but do not demonstrate temporality. Therefore, they cannot provide causal conclusions. Further evidence from analytical studies is required to establish causality. For testing causal hypotheses, prospective studies that follow study participants forward over time (prospective cohort studies) and interventional studies are more suited and rank higher in the general hierarchy of evidence.

Observational study designs have often been criticised for confounding variables. Confounding occurs when the straightforward relationship between a risk factor and an outcome is distorted by the effect of a third variable, i.e., the confounder. Nonetheless, well-conducted observational studies, which adjust for all potential confounding effects, can yield qualitatively comparable results to intervention studies such as RCTs (Benson and Hartz, 2000; Concato et al., 2000).

Table 1.2 Study design descriptions, their use in tinnitus research, advantages and disadvantages

Study design	Description	Use in tinnitus research (measure of effect)	Advantages	Disadvantages
Ecological studies	Studies the relationship between exposures and outcomes in populations rather than in individuals.	Hypothesis generator for causes and treatments (correlation coefficient)	• Easy to conduct; relatively inexpensive • Important to generate hypotheses at population level	• Based on aggregate data. Therefore, not possible to exclude confounding • Ecological fallacy present
Case reports	Description about a single patient's clinical manifestations, clinical course or prognosis of a medical condition.	Hypothesis generation for causes and treatments	• Easy, and quick to conduct; relatively inexpensive • First report of new trends or disease (helps in identifying them) • Good for rare diseases or rare manifestations	• No comparator group • Less generalisability • Cannot prove causality
Case series	Collection of case reports i.e., descriptions about clinical manifestations, clinical course or prognosis of a medical condition in a group of patients.	Hypothesis generation for causes and treatments	• First report of hypothesis generation for causes and treatments	• No comparator group • Cannot provide quantitative health indicators like prevalence, incidence or risk estimates
Cross-sectional study	Evaluates the prevalence of a disease or condition at a definite point or period in time, and describes the relationship between a potential risk factor and outcome by assessing them at the same point in time.	• Frequency measures (prevalence) • Hypothesis generation by identifying relationship (Relative risk)	• Easy, and quick to conduct; relatively inexpensive • Ethically safe • Representative cross-sectional studies are best suited for assessing prevalence estimates	• Cannot provide incidence • Cannot establish causality: Exposure and outcome are assessed at the same time. Therefore, cannot establish temporality i.e., exposure preceding outcome. • Susceptible to recall bias and confounding

Table 1.2 Study design descriptions, their use in tinnitus research, advantages and disadvantages

Study design	Description	Use in tinnitus research (measure of effect)	Advantages	Disadvantages
Case-control study	Compare cases, i.e., subjects with the outcome of interest, with controls, i.e., those without outcome of interest. Participants are selected based on outcome status.	Hypothesis testing by comparing groups (Odds ratio)	• Compared to cohort, quick and relatively inexpensive • Most suited for rare outcomes and conditions with long latency • Initial study to establish association	• Relies on records (retrospective) • Only relative risks can be estimated • Difficulty in control group selection • Susceptible to biases (recall bias, observer bias, selection bias) • Difficulty in eliminating confounders
Cohort study	Group of individuals are followed over time to investigate how the exposures affect their outcome. Outcome free participants are selected based on exposure status: exposed and unexposed groups. Prospective: individuals are followed over time, and data is collected about them. Retrospective: individuals are sampled and information is collected about their past exposures, either through interviews or through administrative data (like hospital records).	• Frequency measures (incidence) • Causal hypotheses analyses (Relative risk) • Efficacy of treatments (Relative risk)	• Cheaper and simpler than RCTs • Representative population sample (less selection bias) • Only study that can determine incidence (i.e., absolute risk) • Can overcome recall (prospective study) and observer biases • Multiple outcomes can be studied • Can establish the sequence of events i.e., exposure and outcome, deriving causal inference	• Resource-consuming and complex • Feasible for common diseases • Cannot exclude unknown confounders • Cause-effect only possible for few factors (determined at the start)

Table 1.2 Study design descriptions, their use in tinnitus research, advantages and disadvantages

Study design	Description	Use in tinnitus research (measure of effect)	Advantages	Disadvantages
Randomised controlled trial (RCT)	Participants are randomly assigned either to an intervention or control group, and followed-up until the end of the study period to compare the occurrence of outcome of interest.	Efficacy of treatments (Relative risk)	• Randomisation minimizes risk of bias • Best suited to investigate the treatment efficacy • Rigorous evaluation of single variable • Most powerful statistical evidence	• Needs more resources, time consuming • Ethical issues • Because of the strict eligibility criteria and controlled setting, results may not always mimic real life treatment situations • Possibility of selection (volunteer), observer and hidden bias
Field trial	The outcome of an intervention is studied “on the ground” or “on the field”, in disease-free subjects of the population who are not in hospitals/institutions.	Efficacy of interventions or treatments in the field	• Less selection, confounding and measurement bias • Greater generalisability • Evaluate single variable in precisely defined group	• Needs more resources, time consuming • Difficulty in recruiting subjects • Ethical issues and practical feasibility
Community intervention trial	Extension of field trials where the outcome of the intervention in studied with a community as the unit of assignment.	Efficacy of interventions in a community	• Can evaluate a public health intervention in natural, non-controlled circumstances.	• Selection bias due to allocation by community. • People in control community may receive the intervention under study by themselves as it is difficult to maintain a tight control, as in controlled settings

In the pyramid of evidence, systematic reviews and meta-analyses, which are types of secondary research, are considered most trustworthy. In secondary research, results from single or multiple data sources should be collated to derive inferences (Sutton et al., 2000). Systematic reviews, meta-analyses, critical appraisals, and best practice guidelines for treatments are common secondary research methods.

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. Explicit and systematic methods planned to minimise bias are used to provide more reliable findings from which conclusions can be drawn and decisions made. Systematic reviews are analysed using meta-analyses, if possible, or the data are synthesised qualitatively. Meta-analytic approaches use statistical methods to summarise the results from multiple independent studies. By combining data from all relevant studies, meta-analyses provide more precise estimates of the effects of exposure on an outcome than those derived from individual studies (Green et al. 2008).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group developed a framework in which certainty in evidence considered numerous factors and not just study design, thereby challenging the pyramid concept. According to this framework, the study design is insufficient as a surrogate for risk of bias. Methodological limitations of a study, like imprecision, inconsistency, and indirectness, are factors that are independent of study design but can lower the quality of evidence. On the other hand, factors like large effect size and calculation of dose-response effect can improve the quality of evidence (Balshem et al., 2011; Murad et al., 2016). The pyramid of evidence was recommended to be re-designed with wavy lines reflecting the GRADE approach of rating high and low based on all domains of evidence quality (Figure 1.4B).

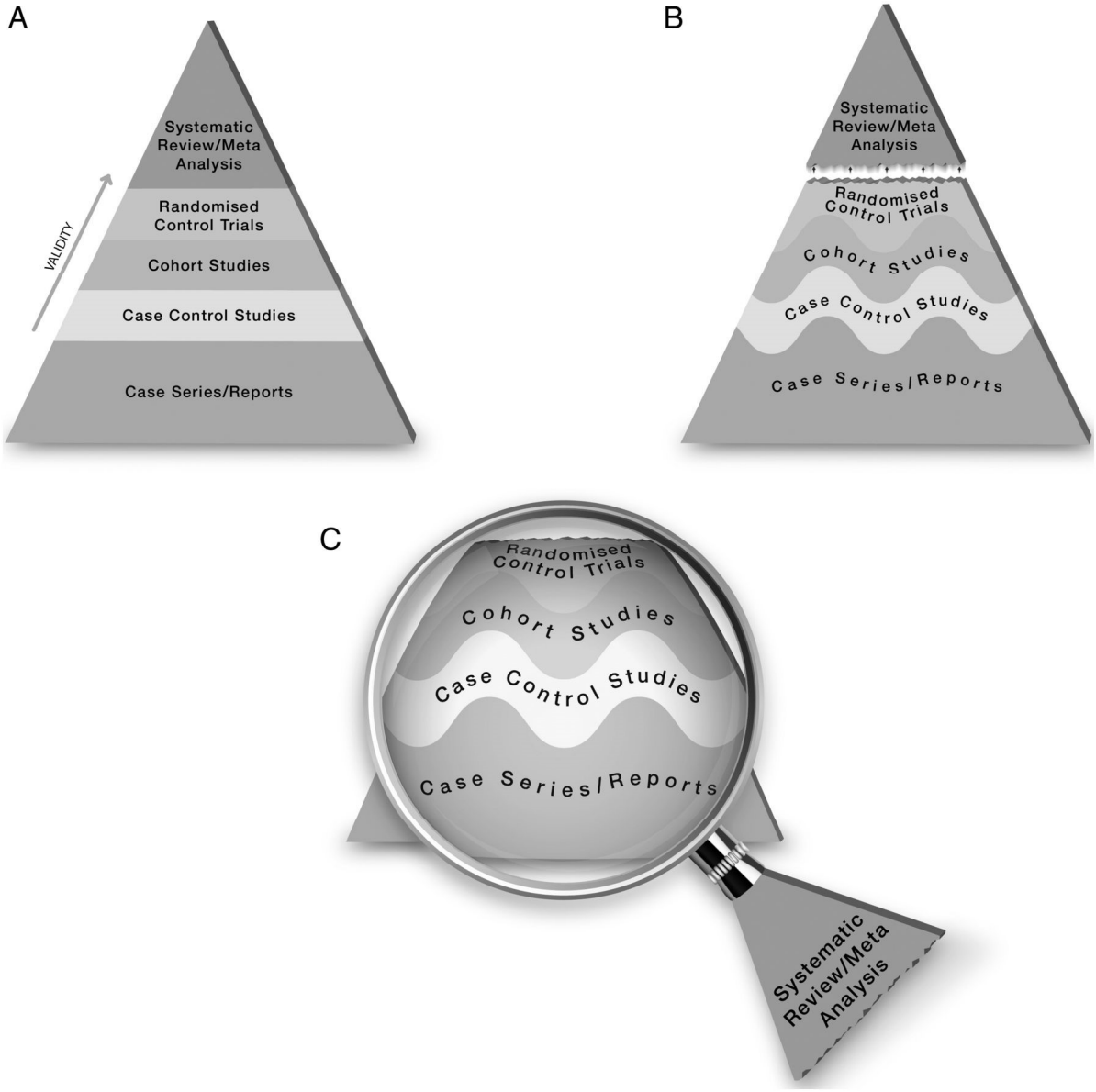


Figure 1.4(A) The traditional pyramid. (B) Evidence pyramid revised: wavy separating lines and systematic review and meta-analysis cut from rest of study design. (C) Systematic review and meta-analysis as lens. (Murad et al., 2016)

Additionally, it is recommended not to place systematic reviews and meta-analyses at the top of the pyramid (Murad et al., 2016). This is because a meta-analysis collating data from low-quality observational studies cannot be considered to be more reliable than a large, well-conducted RCT. Moreover, it is not desirable to equate a meta-analysis of well-conducted RCTs with a low risk of bias to a meta-analysis of observational studies with a higher risk of bias. To avoid these unequal comparisons,

at first, the credibility of the process of a systematic review needs to be evaluated (comprehensive literature search, rigorous study selection process, etc.). If the systematic review is sufficiently credible, then the quality of evidence should be evaluated (Murad et al., 2016). Limitations in the original studies can introduce bias in a meta-analysis. Hence, it is desirable to evaluate the quality of the original studies included in the systematic review (Sanderson et al., 2007). An appropriate approach is to use systematic reviews and meta-analyses as an instrument to observe other studies rather than as the best quality evidence (Murad et al., 2016).

1.4.5 Measures of effect

Various measures of effect are used to quantify the strength of association between an exposure and an outcome, and the type of measure varies by the study design used to examine this relationship (Table 1.2). A comparison is made between the proportion of affected individuals exposed to a potential risk factor (exposure) with the proportion of affected individuals who are unexposed. Either the ratio or the difference in the frequency measures between the two groups is utilised to calculate measures of effect. The resultant value is the risk estimate and provides an assessment of the increase or decrease in risk of developing any health condition in the exposed population compared to the unexposed. In this section, a brief explanation is provided for some commonly used measures of effect.

Relative Risk (RR) defines the likelihood of developing a condition or disease linked to the exposure (such as age, sex, noise exposure, etc.). RR is calculated by the ratio of the probability of the outcome occurring in the exposed group compared to the probability of the outcome occurring in the non-exposed group. If RR is greater than 1 for the exposed group, then the exposed individuals are more likely to develop the outcome than unexposed individuals, and when it is less than 1, the exposed group is less likely to develop the outcome than the unexposed. RR = 1 indicates that the outcome is no different in the exposed and unexposed groups. If the 95% Confidence Interval (CI) for the relative risk includes the value of 1.0, then there is no statistically significant difference in the exposed and unexposed groups.

Hazards Ratio (HR) is another measure used for dichotomous variables and is calculated as the hazard in the exposed groups divided by the hazard in the

unexposed groups. In cohort studies, Cox's proportional hazards model is commonly used to calculate HR. A single estimate of HR summarises the experience from the entire follow-up period. In practice, HR is the commonly used measure of effect reported by epidemiological studies, and it is interpreted in the same way as RR.

A third commonly used measure of effect is the Odds Ratio (OR). It is a statistic to quantify the strength of association between the outcome of interest (e.g., tinnitus), given a particular exposure. In a case-control study, the odds ratio is interpreted as the ratio of the likelihood of the odds of exposure in one group (i.e., cases) relative to another group (i.e., controls). An OR with a value of 1.0 means that exposure is no different between the cases and controls. If the CI spans the value of 1.0, then the association between the exposure and outcome is not statistically significant.

In subsequent chapters, these measures of effect have been used to quantify the relationship between tinnitus and various exposures.

1.5 Research objectives

The overarching aim of this PhD work was to understand the epidemiology of tinnitus, with a particular emphasis on Europe, by answering the following three research questions:

i. How many people in Europe are affected by any, bothersome and severe tinnitus?
ii. What information is available on tinnitus-related risk factors?
iii. Do selected modifiable lifestyle-related factors (smoking, diet, alcohol consumption, obesity, caffeine intake) influence the risk of having tinnitus?

The project objectives address the key elements of epidemiological research in tinnitus (measure of frequency and measure of effect):

(i) Estimating Pan-European prevalence of tinnitus and making inter-country comparisons

(ii) Identifying all tinnitus-related risk factors

(iii) Quantifying the association between specific factors and tinnitus, particularly modifiable lifestyle-related factors Rationale

Health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organization (WHO), 1948). Therefore, any condition that adversely affects any of these three domains of well-being harms the individual's overall health. Tinnitus, in its debilitating form, negatively impacts all three domains of well-being. It is a physical perception that impacts many factors relevant to emotional health and social well-being (Hall et al., 2018a). It could precipitate psychological distress severe enough to cause physical harm, such as self-harm and suicidal ideations, to the affected individual (Aazh and Moore, 2018; Lugo et al., 2019). Several epidemiological studies have shown a negative relationship between tinnitus and quality of life; the latter worsening with increased tinnitus symptom severity (Nondahl et al., 2007; Zeman et al., 2014). Individual and societal costs for tinnitus are positively related to tinnitus symptom severity (Hall et al., 2018a; Hoekstra et al., 2014; Maes et al., 2013; Stockdale et al., 2017). Given its impact on individuals and the overall population, it becomes crucial to take adequate preventive measures and health interventions.

Prevalence estimates provide information on how common a condition is. Tinnitus prevalence estimates show wide variability. Methodological drawbacks, including lack of a universal research definition and appropriate phrasing of epidemiological questions, are apparent in tinnitus prevalence studies. Most prevalence studies report estimates between 10% and 15%, although these results are predominantly derived from studies conducted in Western Europe and the US, thereby exhibiting an evident geographical bias (Baguley et al., 2013; McCormack et al., 2016).

Moreover, tinnitus being a subjective condition, its impact depends on an individual's perception of its effect on their life, i.e., on the subjective severity of the condition. Therefore, "severe" tinnitus symptoms are a better predictor for the emotional, societal and financial burden of tinnitus than is "any" tinnitus (Maes et al., 2013; Stockdale et al., 2017). Consequently, distinguishing severe tinnitus from any tinnitus seems reasonable. While epidemiological studies have tried to measure any and severe tinnitus separately, both these concepts are troubled by heterogeneity in definitions and assessment methods.

Knowledge of the prevalence of a condition helps understand the magnitude of its impact on the population and inform decisions regarding resource allocation and

implementation of appropriate interventions and policies. Tinnitus research and financial investment are substantially lower than other comparable conditions like depression, chronic pain, anxiety, and HL. An imprecise understanding of prevalence estimates is a major hindrance affecting resource allocation for tinnitus research (McFerran et al., 2019).

Tinnitus is a complex chronic condition. Multiple causal risk factors and related comorbidities are among the main dimensions of tinnitus heterogeneity (Cederroth et al., 2019). Synthesising available information on risk factors could potentially shed some light on causal factors for tinnitus. Additionally, it would help identify gaps in knowledge and provide insights for future research directions. Moreover, there is no specific way to cure the condition despite there being quite a few therapies for tinnitus. Knowledge of risk factors will help in directing preventive strategies in the right direction.

1.6 Overview of experimental chapters

Three research projects were undertaken to fulfil the overall PhD objectives. For ease of narration, each research project has been presented in one or two experimental chapters. The following section provides an overview of each research project and a summary of the contents of the corresponding chapter(s).

Project#1: Pan-European assessment of the prevalence of tinnitus using the European Tinnitus Survey (ETS)

This project was conducted to evaluate the Pan-European prevalence of tinnitus and tinnitus severity using a set of standardised questions and making inter-country comparisons. I am doing my PhD as a part of the ESIT (European School of Interdisciplinary Tinnitus Research) consortium, which is funded by the European Union's (EU) Horizon 2020 plan, and I am jointly hosted by the University of Nottingham and Istituto di Ricerche Farmacologiche Mario Negri (IRFMN), Milan, Italy. This prevalence study was a part of the ESIT project "A coherent epidemiological survey of tinnitus." I collaborated with my supervisory team and other members from the IRFMN laboratory for this project. This project is described in Chapters 2 and 3. An overview of their contents are as follows:

Chapter 2

For this project, it was first necessary to create a translated set of questions and response options (collectively referred to as items) from English into different European languages and confirm their cross-cultural equivalence with the source. The European Tinnitus Survey (ETS) is a set of four questions and response options in12 European languages: Bulgarian, English, French, German, Greek, Italian, Latvian, Polish, Portuguese, Romanian, Russian, and Spanish. The four items were adapted from existing survey questionnaires in English by a panel of experts in tinnitus and hearing research (my supervisors, Professors Hall and Akeroyd, were part of this panel).

In Chapter 2, I report the process of selecting the source question and response options in English, and translating them into 11 European languages. This translation process was published as a technical note in Hearing Research (reference provided in "List of Publications arising from this thesis"). My primary contribution in this translation process was to develop the field testing survey, recruit the field testing participants, cross-checking the item summaries with the original English version, and summarising the final recommendations.

Chapter 3

The ETS questions and response options were then implemented for data collection. The data collection fieldwork was conducted by an Italian market research company called DOXA and their partners in various countries (henceforth referred to as DOXA partners). Approximately 1000 adults aged 18 years and above, from each of the following 12 countries: Bulgaria, England, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania, and Spain, were recruited for the study. Chapter 3 reports the overall prevalence for three working definitions of tinnitus (any, bothersome and severe), along with country-specific prevalence estimates. The latter was used to make between-country comparisons. Apart from prevalence, the relationship of tinnitus with hearing difficulty and other demographic variables were examined.

I led this project by developing the statistical analysis plan, managing the data, and analysing the datasets using SAS 9.4 (SAS Institute; Cary, North Carolina, USA).

Project #2: Systematic Review and Meta-analyses of Prevalence and Risk factors for tinnitus

An extensive systematic review was conducted with the objectives to provide the most updated and comprehensive evidence of risk factors for tinnitus. The protocol for this review has been registered in PROSPERO (registration number CRD42018095610). The overall project was subdivided into the following two segments illustrated in Chapters 4 and 5.

Chapter 4

Chapter 4 describes the work to identify and extract information from high quality analytical (case-control and cohort) studies on tinnitus-related risk factors. The risk factors thus identified were grouped into categories. For risk factors with evidence from multiple studies, meta-analyses were conducted using R 3.5.2., when possible.

I led this project, which is in collaboration with ESIT colleagues from IRFMN, Karolinska Institute, University of Nottingham, and the University of Regensburg. I project managed this multi-centre study and led the work on identifying the articles, screening, data extraction, and quality assessment, as well as evidence synthesis using meta-analysis and narrative synthesis, where appropriate.

Chapter 5

Chapter 5 describes four systematic reviews on the relationship between tinnitus and modifiable lifestyle-related risk factors, namely, smoking, alcohol, BMI, and caffeine intake. Separate meta-analyses were conducted for each risk factor. Additionally, within each risk factor category, meta-analyses were conducted for each type of study design, when possible. This systematic review and meta-analyses have been accepted for publication in a Special Issue for Tinnitus in Progress in Brain Research.

This second part was part of my PhD. I systematically reviewed the included articles and developed a statistical analyses plan with the IRFMN team based on previous meta-analyses methods used in previous projects. Where possible, I conducted the meta-analyses using R 3.5.2 software.

Project #3: Dietary pattern, alcohol consumption, obesity, and risk of incident tinnitus

This project aimed to examine the relationship between tinnitus and selected modifiable risk factors that have been hypothesised to be associated with tinnitus, using a real-world dataset. There is evidence that tinnitus may be associated with some modifiable lifestyle factors, including alcohol consumption, obesity, and diet (Baguley et al., 2013; Hoffman and Reed 2004). The role of diet in tinnitus has been identified as a research priority by both patients and clinicians (Hall et al., 2013).

Chapter 6

Due to Covid 19 related travel disruption, my secondment to Karolinska Institute, Sweden, and a planned project on the Stockholm Public Health Cohort dataset was cancelled. I reached out to Professors Gary and Sharon Curhan from Harvard University, USA, and collaborated with them to analyse the Nurses' Health Study II (NHSII) dataset and investigate the effect of diet, alcohol consumption, and obesity on tinnitus.

Chapter 6 reports the relationship between dietary patterns, namely the Dietary Approaches to Stop Hypertension (DASH) and Alternate Mediterranean diet (AMED), alcohol consumption, BMI, and the risk of developing tinnitus among participants of NHSII, a prospective cohort dataset. For this project, I was involved in developing the research proposal and the statistical analysis plan. The analyses were run on SAS 9.4 by a biostatistician from Channing Laboratory at Harvard University.

Chapter 2 . Specifications and translation of epidemiological questions for addressing prevalence of tinnitus, tinnitus severity, healthcare use in people with tinnitus, and hearing difficulty

[Some parts of the Introduction section of this chapter have been published as a book chapter named "Prevalence, Incidence and Risk factors for Tinnitus" in Current Topics in Behavioral Neuroscience (Biswas and Hall, 2020). A summary of this project has been published in Hearing Research as a technical note named "Standardized questions in English for estimating tinnitus prevalence and severity, hearing difficulty and usage of healthcare resources, and their translation into 11 European languages" (Biswas et al., 2019).]

2.1 Introduction

Hearing health professionals use an array of tools and diagnosis protocols to evaluate and assess subjective tinnitus. However, there is no defined objective test to measure tinnitus, and assessment is predominantly dependent on self-report of the subjects (Baguley et al., 2013). Similarly, when estimating the burden of tinnitus, researchers also depend on self-reported estimates. In research, there are no standard unambiguously phrased assessment questions that are used consistently across studies (McCormack et al., 2016). This produces a wide distribution of tinnitus prevalence estimates and poses a problem in understanding the disease burden at a population level. Considering the impact of tinnitus on an individual's everyday life and its socio-economic implications, from a public health standpoint, implementation of adequate prevention and intervention strategies become crucial (Hall et al., 2018a, Maes et al., 2013; Stockdale et al., 2017). For that, it is essential to know how much of the overall population is affected by tinnitus. In other words, it is important to understand the burden of tinnitus at a population-level.

2.1.1 Effect of heterogeneous definition on prevalence estimates

Systematic reviews on tinnitus prevalence indicate large variability in estimates (Gallus et al., 2015; McCormack et al., 2016). Lack of an agreed assessment question, heterogeneous reporting measures, an evident geographical bias, and differences in population demographics of the study are some crucial issues in tinnitus epidemiological research (Gallus et al., 2015, McCormack et al., 2016). Because of the lack of standardisation when estimating tinnitus prevalence, it is impossible to pool estimates across countries or examine differences between countries or world regions. These inherent methodological issues prevent data synthesis from various prevalence studies to derive a global prevalence estimate. Given that tinnitus is self-reported, inconsistent assessment methods constitute a substantial challenge (Gallus et al., 2015; McCormack et al., 2016). Section 1.4.1 provides detailed information on heterogeneous reporting measures and methodological issues that plague tinnitus prevalence studies.

The Blue Mountain Hearing Study (BMHS) and the EHLS are population-based surveys conducted in Australia and the US, respectively, to evaluate HL characteristics in older adults (Cruickshanks e al., 1998; Sindhusake et al., 2001). The study populations of BMHS and EHLS are similar in terms of age, sex, marital status, pure tone average, ethnicity, occupational history, and cardiovascular profile. Nondahl et al. (2002) analysed the EHLS data from 1993 to a follow up of 5 years and reported the prevalence of "significant tinnitus" as 8.2%. They defined "significant" tinnitus as "buzzing, ringing, or noise" in the ears in the past year that was at least moderate in severity or that caused problems getting to sleep (Nondahl et al., 2002). The BMHS study reported a tinnitus prevalence of 30% between 1997 and 1999. In BMHS, tinnitus was reported as "any prolonged ringing or buzzing in the ears or head within the past one year…...lasting for five minutes or longer" (Sindhusake et al., 2003).

Despite the relatively similar socio-demographics, the two studies showed wide variability in prevalence. In a comment to the article by Sindhusake et al. (2003), Nondahl et al. (2004) attributed this difference to the different reporting measures used in these two studies. Unlike the BMHS definition, the EHLS tinnitus definition from the article by Nondahl et al. (2002) did not include the "five minutes" duration component. In their five-year follow-up analysis, EHLS added the duration component to the

reporting measure for tinnitus ("buzzing, ringing or noise in your ears in the past year that usually lasts longer than five minutes"). This addition increased the prevalence value for tinnitus to 17.9% in the EHLS population (Nondahl et al., 2004). Although the value was still lower than the BMHS estimates, it can be noted that the alignment in definitions brought the two prevalence values closer. Both Sindhusake et al. (2003) and Nondahl et al. (2004) recognised that diverse tinnitus assessment questions contributed to differences in prevalence estimates beyond what is expected due to demographic differences.

The role of reporting measures in the variability of tinnitus prevalence can be further illustrated from two studies conducted in similar age groups in the US. The only difference in the tinnitus assessment question used by the two studies by Bhatt et al. (2016) and Spankovich et al. (2017) was the inclusion of the phrase "lasting for more than 5 minutes" in the former. However, the prevalence estimates reported by Bhatt et al. (2016) was of around 10% and while Spankovich et al. (2017) reported a prevalence of 21%.

Interestingly, adding the "lasting for five minutes" duration component to the tinnitus assessment question did not have a consistent effect on the prevalence values. The prevalence of tinnitus in EHLS reported by Nondahl et al. (2004) increased after introducing this phrase. However, it had the exact opposite effect on the findings from the two US-based studies, with Bhatt et al. (2016) reporting a lower prevalence value. This differential effect of the duration component further points towards potential variability due to various reporting measures.

Recently conducted studies that used both the time frame of 12 months and tinnitus duration of 5 minutes seem to give more comparable and consistent prevalence estimates, with values ranging between 6% and 15% (Bhatt et al., 2016; Gallus et al., 2015; Xu et al., 2011). On the other hand, studies that did not use the duration component reported 20% and 21% prevalence, respectively (Choi et al., 2017, Spankovich et al., 2017). Therefore, using only the time frame in the tinnitus assessment question, the range of prevalence estimates became narrow, although the reported value became much higher than expected. Studies that included only the duration component ("lasting for five minutes") and "nowadays" to describe the time frame reported prevalence between 18% and 31% (Gilles et al. 2017, Lohi et al.,

2017). Therefore, when the time frame is omitted, the values for prevalence become quite widespread. Given the small number of studies that use each assessment question, it is difficult to conclude the best way to measure prevalence. However, the numbers hover around the median when both time frame and duration are taken into consideration. Thus, it can be assumed that tinnitus assessment questions addressing both of these commonly-used concepts might be a good measure for estimating prevalence.

2.1.2 Any tinnitus versus severe tinnitus

Many epidemiological studies seeking information on tinnitus prevalence also seek information about the severity or bothersomeness of tinnitus symptoms. In its severe debilitating form, tinnitus can significantly affect an individual's overall health and emotional well-being, and can incur substantial social and financial costs on the individual and society. Studies have shown an inverse relationship between tinnitus severity and quality of life (Nondahl et al., 2007; Zeman et al., 2014). Nondahl et al. (2007) used the Medical Outcomes Study Short Form Health Survey (SF-36) to assess the relationship between tinnitus severity and quality of life (QOL). They analysed data from the EHLS to assess severity. Patients who reported having "ringing or buzzing or noise" in their ears over the last year were asked to rate their severity as "Mild / Moderate /Severe / Unknown" (question asked: "How severe is this noise in its worst form?"). In SF-36, function, well-being, and self-evaluation of physical and mental health are assessed using questions on eight domains related to physical and mental health. These eight domains are further summarised into two component scales: the Physical Component Summary Scale and the Mental Component Summary Scale. Increased tinnitus symptom severity was associated with decreased scores for all eight domains and both the component scales (Nondahl et al., 2007).

Zeman et al. (2014) examined the relationship between subjective perception of tinnitus severity and QOL, using the case reports from TRI database, which is an international database having standardised information in German, Dutch, Portuguese and Spanish. They used a simple tinnitus severity question, "How much of a problem is your tinnitus?" with the corresponding response options of "no problem/ a small problem/ a moderate problem/ a big problem/ a very big problem." To assess QOL, they used 24 out of the 26 items in the World Health Organization-Quality of Life

questionnaire (WHO QOL). These items assess the domains of physical health, psychological health, social relationships, and environment. This study also reported a strong negative correlation between tinnitus severity and QOL (Zeman et al., 2014).

Additionally, severe tinnitus symptoms have important socio-economic implications. Increased severity of tinnitus leads to a rise in healthcare costs per patient. In a study conducted in Netherlands, mean annual costs per patient were €767 for people reporting mild tinnitus symptoms, €1,329 for moderate tinnitus, and €2,218 for severe tinnitus (Maes et al., 2013). Therefore, a person with severe tinnitus has thrice as much expenditure as a person with mild tinnitus. A similar pattern of increasing costs with increased tinnitus symptom severity was noted in a US-based study (Goldstein et al., 2015). The increased expenses resulted from a combination of increased doctors' appointments including specialist appointment, cost of therapy, loss of productivity, travel to and from clinics, and other associated expenses like headphones, ear protection, and alternative therapy (Maes et al., 2013; Goldstein et al., 2015; Stockdale et al., 2017).

Severe tinnitus is phenomenologically different from non-severe tinnitus. Population-based studies that have looked at prevalence estimates of both "any" and "severe" tinnitus have reported differences between the two estimates. Bhatt et al. (2016) reported a tinnitus prevalence of 10% in the US population, although only 7.2% reported that their tinnitus was a big or very big problem. A more substantial gap was noted in the prevalence of severe tinnitus and any tinnitus in a study conducted on the Italian population (Gallus et al., 2015). While 6% of the population reported tinnitus, only 1% complained of severe tinnitus. Both these studies assessed any tinnitus as "ringing or buzzing lasting for five minutes in the past year," while severity was assessed by how much it bothered or annoyed the individual (Bhatt et al., 2016; Gallus et al., 2015).

McCormack et al. (2014a) analysed the UK Biobank data for tinnitus prevalence estimates. Any tinnitus was found to be 16% prevalent. The UK Biobank also measured tinnitus by annoyance or bothersomeness ("How much do these noises worry, annoy or upset you when they are at their worst?"). The authors combined the moderate and severe responses for the severity question and reported the prevalence of bothersome tinnitus as 4%. Nondahl et al. (2011) reported any tinnitus as "buzzing,

ringing, or noise" in the ears in the past year that was at least moderate in severity or that caused problems getting to sleep"; and severe tinnitus was assessed by the question "How severe is this noise in its worst form?". Here the prevalence of any tinnitus was 10.6%, and that of severe tinnitus was 1%.

Knowing the burden of a disease or condition helps understand the magnitude of its impact on the population and the importance of allocation of resources and implementing interventions. There is a substantial difference in effect, assessment, and reporting of any and severe tinnitus. Therefore, it is pivotal to distinguish severe from non-severe tinnitus to get the overall picture of tinnitus-related burden.

2.1.3 Tinnitus and healthcare resource use

Individuals suffering from severe tinnitus are more likely to seek healthcare resources. Therefore, they impose more obvious personnel and financial resource burden on the healthcare system, compared to any tinnitus (Maes et al., 2013; Goldstein et al., 2015: Stockdale et al., 2017). However, irrespective of severity, data from multiple countries suggest that individuals experiencing tinnitus impose a substantially high economic burden on the system. Studies conducted in the UK, the US, and the Netherlands reported average annual health care costs per tinnitus patient being £717, $2,110, and €1,544, respectively (Goldstein et al., 2015; Maes et al., 2013; Stockdale et al., 2017). The average annual healthcare costs include the direct costs incurred, that is, healthcare professional appointments and medicines. Since all healthcare systems do not have a definite tinnitus treatment pathway, tinnitus-affected individuals seek medical advice from various sources (Maes et al., 2013; Stockdale et al., 2017). The lack of a definite and efficient tinnitus pathway in healthcare systems can often cause patients to make repeated appointments, creating a ‘revolving door’ pattern of healthcare (McFerran et al., 2018). This makes multiple clinic appointments a crucial factor contributing to increased tinnitus-related expenditure, and the number of visits can reportedly be as high as 21.1 per patient (Goldstein et al., 2015, Maes et al., 2013).

Apart from the direct healthcare costs, there are other expenditures like productivity costs and societal costs. In the Dutch study by Maes et al. (2013), individuals were absent for 15.4 days annually for tinnitus leading to an annual productivity cost of €3,702 per patient. As per the findings by Goldstein et al. (2015), in 2013, in the US,

the productivity costs for chronic tinnitus was $5,065 per patient. A large part of the total mean societal costs for tinnitus, which amounted to €6.8 billion in the Dutch study, was not related to healthcare (Maes et al., 2013). In the UK, 0.6% of the total public sector spending in healthcare was for tinnitus-related healthcare services (Stockdale et al., 2017). Therefore, to truly understand the burden of tinnitus as a health condition, it seems relevant to assess the tinnitus-related use of healthcare in population-based surveys since this gives a comprehensive insight into the socio-economic impact of tinnitus.

2.1.4 Tinnitus and hearing difficulty

Hearing difficulty has been reported to be a major risk factor for tinnitus (Davis and Refaiae, 2000; Sindhusake et al., 2003, Sindhusake et al., 2004; Michikawa et al.., 2010, Baguley et al., 2013). Nondahl et al. (2003) reported an 83% increased risk of developing tinnitus in HL patients in the EHLS data. An internet-based study by Moore et al. (2017) found that 41% of those subjects who responded positively to at least a slight self-reported hearing difficulty also reported tinnitus symptoms. In a cross-sectional study on German teachers conducted to assess the prevalence of hearing disorders (including tinnitus), most subjects were found to suffer from more than one hearing disorder simultaneously (Meuer and Hiller, 2015). Thus, the presence of HL or hearing difficulty not only increases the risk of having tinnitus but often co-occur in an individual.

According to WHO estimates of 2012, approximately 15% of the global adult population has some degree of HL (WHO, 2012). Globally about 6.8% of the population suffers from disabling HL, defined as HL of >40 dB in the better hearing ear (Global Burden of Diseases (GBD) study, 2016; Wilson et al., 2017). It is thus evident that HL is a common condition affecting a sizeable part of the global population. On the other hand, despite the widespread scatter in tinnitus prevalence, most studies report a prevalence estimate between 10% and 15% (Baguley et al., 2013). Thus, both-tinnitus and HL are common mutually-related medical conditions (Ratnayake et al., 2009; Nondahl et al., 2011; Moore et al., 2017). Despite the suggested relationship, not many population-based surveys have looked at tinnitus prevalence in populations with hearing difficulty, nor is there much information on the co-existence of these two conditions. Hence, given the strong correlate reported in published literature, to get a

complete picture of the burden of tinnitus, it would be worthwhile to know the prevalence of tinnitus in HL-affected population.

2.1.5 Measured hearing loss versus self-reported hearing difficulty

Prevalence estimates for HL are affected by the reporting measure used. The WHO defines HL as a mean hearing threshold of >25 dB HL measured at 0.5, 1, 2, and 4 kHz in the better ear (WHO, 2015). Audiometric clinical recordings give an objective measurement of HL. PTA is the gold-standard for measuring HL, and some population-based studies are sufficiently well-resourced to define HL in this way. However, population-based surveys or large cohort studies predominantly rely on self-reported hearing difficulty because of cost-effectiveness and ease of administration.

The self-reported hearing difficulty is measured by a single question about the hearing status or a set of questions to quantify an individual's hearing ability. For example, Choi et al. (2016) reported findings from the US National Health and Nutrition Examination Survey (NHANES) data, where the participants were asked a single question on hearing difficulty, "Which statement best describes your hearing (without a hearing aid)? Would you say your hearing is excellent, good, that you have a little trouble, moderate trouble, a lot of trouble, or are you deaf?". The same question was used by Kim et al. (2017) in a Korean population. Other studies included a single straightforward question for hearing difficulty ("'Do you feel you have a hearing loss?") (Sindhusake et al., 2001, Torre et al., 2006). A German cross-sectional study assessed self-reported hearing ability by measuring "understanding speech in quiet" and "listening effort" (von Gablenz et al., 2018). Another US-based study used the Hearing Handicap Inventory for self-report, which included a set of four questions that asked about understanding speech in a noisy background, when multiple people are talking, hearing co-workers, and hearing conversation in a restaurant (Tremblay et al., 2015). Therefore, like tinnitus, self-reported hearing difficulty is also measured by using diverse assessment questions.

Since PTA is an objective measure of HL, multiple studies have compared prevalence estimates for self-reported hearing difficulty with prevalence estimates for audiometric HL. Two studies found that 10% of people with normal audiometric threshold have self-reported hearing difficulty (Tremblay et al., 2015; Spankovich et al., 2017). Three

studies found that the concordance in HL and hearing difficulty estimates increased with the presence of tinnitus as a co-existing condition (Bishop et al., 2019; Choi et al., 2016; Kim et al., 2017). Few studies found that a single question ("Do you feel you have hearing loss?") for self-reported hearing difficulty had sensitivity and specificity of around 70% to 80% when evaluated against PTA. The questions did particularly well in the presence of moderate hearing impairment (Nondahl et al., 1998; Sindhusake et al., 2001; Torre et al., 2006).

Given the level of sensitivity and ease of administration, a single question on self-reported hearing difficulty is recommended for use in population-based or large cohort studies to measure the burden of HL (Nondahl et al., 1998; Sindhusake et al., 2001; Torre et al., 2006). However, the question used should keep in mind practical constraints like time, budget, and personnel (Nondahl et al., 1998). Considering the co-occurrence of tinnitus and HL and the lack of discrepancy between hearing measured by self-report and audiometry (especially in the presence of tinnitus), using a single assessment question for hearing difficulty in population-based tinnitus surveys seems reasonable as well as pragmatic.

2.1.6 Need for standardised assessment questions

This PhD project aims to report the Pan-European prevalence of tinnitus and tinnitus symptom severity, and compare those estimates across countries. Informed by previously published literature, it was essential to collect data from different countries using the same assessment questions. This approach would minimise inter-country variability caused by heterogeneous reporting measures. Moreover, this would also ensure that data from different countries are comparable.

However, there was no such standardised set of questions translated into multiple European languages following the good practice guidelines (Hall et al., 2018b). To tackle this issue, as a preliminary step, a set of questions and response options (collectively referred to as items) were adapted from existing population-based tinnitus surveys in English to develop the European Tinnitus Survey (ETS) by a panel of four hearing experts (details in Section 2.2.1). The ETS was translated to 11 strategically selected European languages, such that there was cross-cultural equivalence of the translations to the English language source. The questions included in this survey

addressed four domains (tinnitus prevalence, tinnitus symptom severity, healthcare resource use for tinnitus, and prevalence of hearing difficulty). The two latter questions were added to make the survey more informative and better understand the burden of tinnitus in Europe. This chapter provides details of the rationale for selecting and adapting the questions, the step by step translation process, and the final translated versions produced.

2.2 Methods

The ETS comprises a set of four items. The original English language items were translated to culturally appropriate versions in 11 European languages, namely Bulgarian, French, German, Greek, Italian, Latvian, Polish, Portuguese, Romanian, Russian, and Spanish. This section provides the details of the complex methodology that was used to develop and translate the items included in this population-based survey.

2.2.1 Development of tinnitus survey in English

The original English language questions and response options included in the survey items were adapted from existing survey questionnaires by a panel of four with subject matter expertise in tinnitus and hearing research (Professors Hall and Akeroyd were part of this panel). The survey included instruction to the participants and interviewer, the survey questions, and corresponding response options.

2.2.2 Provenance of questions and selection process

The panel of experts shortlisted eight candidate questions (with the corresponding response options) that could be used to understand the epidemiology of tinnitus. These were informed from previously published tinnitus and hearing-related questionnaires, namely the UK Biobank, UK Medical Research Council (MRC) Centenary project 2013, MRC study of hearing difficulties, and National Study of Hearing (UK Biobank, 2011; Moore et al., 2017). Of these questions and response options, four were included in the final selection, as they provided the most comprehensive information on tinnitus while using the least number of questions. Moreover, most of the information gathered from the excluded candidate questions

was already captured by the four questions included. As much as possible, the phrasing of the English language items was informed by previously published work.

Prevalence of tinnitus: The UK Biobank is a published population-based survey. Question H11 of the UK Biobank informed the ETS question on the prevalence of tinnitus: "Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time?" (UK Biobank, 2011). It was modified slightly by adding "over the past year" time frame. The resulting question, therefore, incorporated the two most commonly used concepts in tinnitus definition, i.e., "tinnitus lasting for more than five minutes at a time" and "experiencing in the last one year" (McCormack et al.,2016). Response options were mostly the same as the UK Biobank, with one slight modification. One response option in the UK Biobank was "Yes, but not now, but have in the past." Because the ETS question already included the qualifier "over the past year," this UK Biobank response option no longer made sense. Instead, an alternative option, "No, not in the past year," was included. By specifying the "one year" fixed period, the risk of recall bias was reduced considerably. Moreover, subjects with one occasional episode, occurring more than a year earlier, were excluded from the tinnitus affected group.

Tinnitus Severity: The severity question was also adapted from the UK Biobank (question H11a: "How much do these noises worry, annoy or upset you when they are at their worst?", UK Biobank. 2011). This question was also modified to include the time frame- "over the past year." The response options were identical to the UK Biobank. By asking about the emotional descriptors, this question aims to assess the distress (handicap) caused by tinnitus. Also, according to the systematic review on tinnitus prevalence by McCormack et al. (2016), in available population-based studies this was the commonest way of assessing tinnitus symptom severity.

Use of healthcare resources: Despite the difference between tinnitus requiring and not requiring medical attention, there has been no published population-based survey asking participants a question on the use of healthcare resources for tinnitus. Hence for this question, an unpublished relevant question from the MRC study of hearing difficulties was included. The MRC study of hearing difficulties has been partly published (Noble et al., 2012), but this does not include the following healthcare resource use question "Have you ever been to your family doctor or hospital about

problems with noises in your ears?". The response options were "No / Yes visited doctor (GP) only / Yes, visited GP and been referred to hospital" (GP referred to general practitioner). The question was modified for the ETS to include the one-year recall period. The wording of the question was also revised to include healthcare professionals at a clinic or hospital. The MRC study of hearing difficulties is UK based. This revision made the question applicable to countries where the distinction between GP and hospital is not as well-defined as in the UK. When assessing population-based health care costs for tinnitus, studies often consider the number of tinnitus-related clinic visits as a parameter for estimating the financial burden on healthcare resources. Therefore, the response options to the ETS question on healthcare resource use included the number of clinic visits.

Hearing difficulty: The question about hearing difficulty was adapted from a public science experiment by Moore et al. (2017). The original question "Do you currently have any difficulty with your hearing?" was revised to include the qualifying phrase "listening to speech in a noisy situation." Listening to speech in noise is a common complaint in everyday situations (Vas et al., 2017), and the prevalence of serious hearing difficulty increases with increased hearing trouble in the presence of background noise (Li et al., 2018). Hence, adding the qualifying phrase made the question more informative. Response options used were the same as the original.

2.2.3 Rationale for language selection

The languages for translation were strategically chosen. The rationale for choosing these languages was the varied cultural and socio-economic characteristics of their countries, despite the reasonably constrained geography. The translated questions were used for data collection in the following 12 European Union (EU) member states: Bulgaria, England, France, German, Greek, Ireland, Italy, Latvia, Poland, Portugal, Romania, and Spain. The total population of these countries contributes to about two-thirds of the EU population. Therefore, an estimate for tinnitus prevalence in the sample population derived from these countries would be a good approximation for Pan-European prevalence.

2.2.4 Guidelines for questionnaire translation

The translation process for each language was carried out in a step-by-step approach aligned with the good practice guidelines for survey questionnaire translation, as described by Hall et al. (2018b). These guidelines were informed by common elements reported in other existing guidelines (Acquadro et al., 2008; Beaton et al., 2000; Guillemin et al., 1993; Wild et al., 2005; Wild et al., 2009). The objective was not to create a verbatim translation of the English language source but to develop culturally adapted "world-for-world" translated versions. Cross-cultural equivalence between the original questionnaire and the translated version includes equivalence in the following aspects (Herdman et al., 1998):

- Conceptual- similarity in the concept of items and the same meaning in both cultures
- Item- acceptability of the question in the culture
- Semantic- similarity in sentence structure to ensure the meaning is preserved
- Operational- similarity in format, instructions, and administration (Hall et al., 2018b)

Therefore, the main idea was not just to provide the same information but to ensure that the information is interpreted similarly across all audiences.

Another key concept in the translation process was maintaining colloquialism in the wording and phrasing of each item for easy understanding of the target audience (Hall et al., 2018b). Thus, the final translated versions aimed at being easily comprehensible by the target population while preserving the meaning of the original version and adequately reflecting any nuances of the source or target languages.

2.2.5 Steps of translation

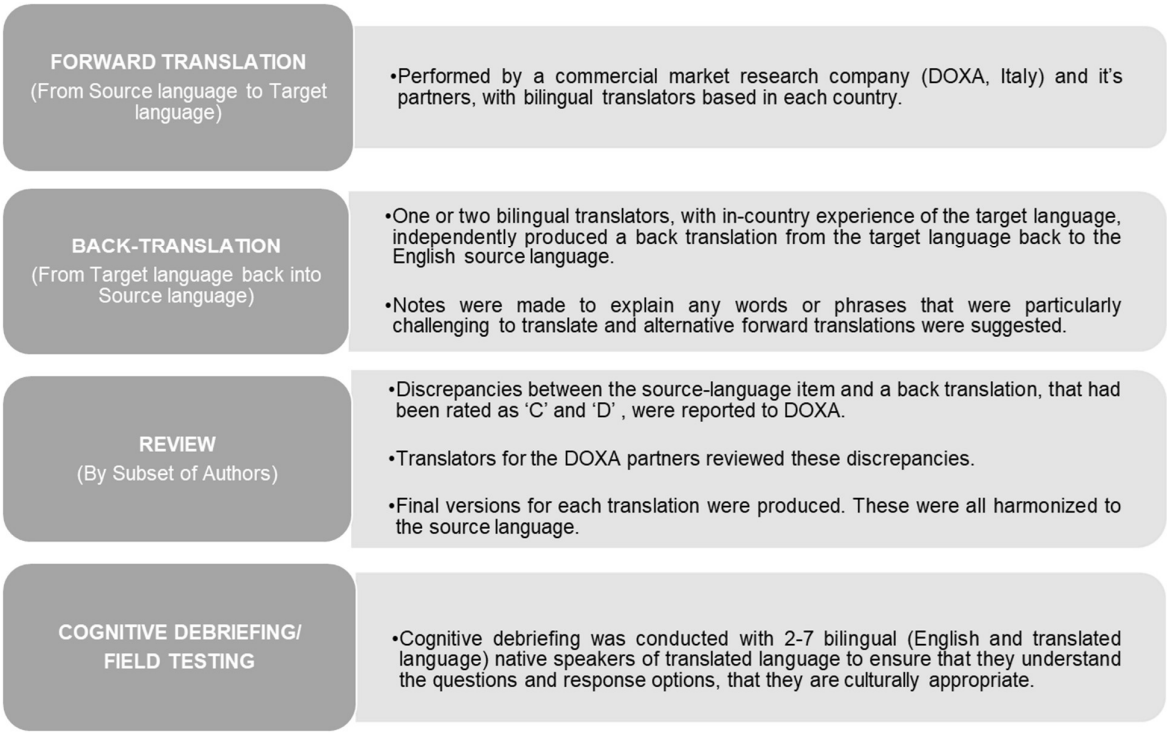


Figure 2.1 Steps of the Translation Process: The following scheme shows the order of the translation steps (Biswas et al., 2019)

Figure 2.1 is a step-wise description of the translation process (Biswas et al., 2019). In the following sections, details of the steps of the translation process are reported. In each step it was taken care that the various features of the translation guidelines were addressed appropriately. The first step of the good practice guidelines, as described by Hall et al. (2018b), involves requesting approval for translation from the relevant authorities. In this survey, novel questions were developed. Hence, the approval-seeking step was not relevant.

2.2.6 Forward translations into 11 European languages

The first step of this translation process was developing the first translated version (i.e., the forward translation) of the survey items into the 11 European languages. For this purpose, a market research group, DOXA Italia, and its partners across other target countries (henceforth referred to as DOXA partners) were approached. The DOXA partners have the required in-house expertise to translate survey items to the

respective languages. The original English language version was provided to the DOXA partners.

2.2.7 Concept definitions

For the ease of translation, a member of the research team (Prof Hall) developed the concept definitions for each of the translation items. This step is particularly crucial for the back translation (details in the following section). The back translators approached for the next step were not necessarily experts in tinnitus or hearing. Concept definitions were intended to explain the accurate meaning of each item in plain language, make the translator aware of the information the question intended to seek, and the possible expected responses. This approach would ensure that when translating back to the source language (back-translation), the back translators would focus not on the word for word translation but also the correct interpretation of the items. Certain nuances are specific to each language, which would not generate culturally equivalent translations if not captured in the translation process.

Table 2.1 Concept definitions (Biswas et al., 2019)

	Introduction	Tinnitus occurrence	Tinnitus severity	Tinnitus diagnosis	Hearing Difficulty
Concept Definitions	*These are the words to be spoken to the participant by the interviewer:* "I'll ask you some questions about hearing problems and about tinnitus. Tinnitus is when you experience a noise in your head or in your ears"	*[This is an instruction to the interviewer, to ask these questions to all adults aged 18 or over]* Thinking back over the past 12 months, the participant's experience of any episode(s) of tinnitus, which has lasted longer than 5 minutes, is to be selected from the following 6 response options: Response options 1-3 record those who have experienced tinnitus with varying degrees of frequency. 1. almost constantly 2. a lot of the time but not constantly 3. some of the time. Response options 4-5 record those who have not experienced tinnitus either 4. in the past 12 months 5. Never. Option 6. is for those who cannot remember or who do not want to respond	*[This is an instruction to the interviewer, to ask these questions only to those who have experienced tinnitus in the past year]* Thinking back over the past 12 months, the perceived severity of the tinnitus is to be selected from the following 5 response option. Severity can be judged according to a range of emotional impacts Response options 1-4 record the degree of distress. 1. Severe emotional distress 2. Moderate level of emotional distress 3. Slight distress 4. Not distressing at all. Option 5. is for those who cannot remember or who do not want to respond	*[This is an instruction to the interviewer, to ask these questions only to those who have experienced tinnitus in the past year]* Thinking back over the past 12 months, the perceived severity of the tinnitus is to be selected from the following 5 response options. Response options 1-3 record the frequency of medical appointments in the past year because of the tinnitus. 1. 5 or more appointments 2. between 2 and 4 appointments 3. only one appointment 4. No appointments at all. Option 5. is for those who cannot remember or who do not want to respond	*[This is an instruction to the interviewer, to ask these questions to all adults aged 18 or over]* Thinking about the present moment in time, the degree of hearing difficulty is to be selected from the following 6 response options. 'Degree of hearing difficulty' can mean the amount of difficulty or the frequency of difficult experiences, or a combination of the two. Response options 1-5 record the amount of difficulty (or frequency of difficulty). 1. Hearing difficulty which prevents communicating in noisy situations (or always interferes) 2. Hearing difficulty that significantly interferes with communicating in noisy situations (or often interferes) 3. Hearing difficulty that moderately interferes with communicating in noisy situations (or sometimes interferes) 4. Hearing difficulty that slightly interferes with communicating in noisy situations (or only occasionally interferes) 5. No hearing difficulty. Option 6. is for those who cannot remember or who do not want to respond

2.2.8 Back translations into English

One or two bi-lingual (English and target language) translators with in-country experience in the target language were recruited for each language. The good practice guideline for questionnaire translation recommends at least one back translator as a minimum standard (Hall et al., 2018b). The back translators were not necessarily hearing experts. Therefore, they were briefed on tinnitus and HL. They were also provided with the concept definitions of all items and the forward translations. Each translator provided a written translation of the items from the target language to English.

The process was blinded in the sense that the back-translators had no access to the original English version. Moreover, when two back-translators were recruited, they worked independently and did not have access to other translations. All back-translators were recommended to use the same terminology across questionnaire items in order to maintain consistency. They were also asked to note any specific words or phrases that were challenging and asked to provide alternative wording if necessary. These notes were maintained to facilitate discussion and reconciliation in case of discrepancies between the original and translated versions.

Owing to the difficulty in finding bilingual (Latvian-English) speakers, Google translate was used for the Latvian back translation step. Some of the resulting translations were rated “D” (rated to have no agreement with the original English items). However, on cross-checking, one native Latvian speaker opined that the original forward translation was understandable in Latvian and did not require any further changes.

In any translation process, the back-translation step serves as an assessment tool to ensure the accuracy of the translated version (Epstein et al., 2015). This step highlights the subtleties that could be missed if a simple one-step forward translation was used to develop the translated version.

2.2.9 Committee review and reconciliation to develop translated version

A review committee comprising a subset of project team members went over unit-by-unit each item of the back-translations against the English version. Any discrepancies

in words or phrases were scored in a defined scoring system (A-D) (e.g., Badia and Alonso, 1994; Sanchez-Moreno et al., 2008).

According to this scheme:
A = items show perfect conceptual equivalence and good literal and semantic parallels between the back-translated and source version
B = items show satisfactory conceptual equivalence but have used one or two different words
C = items preserve the meaning of the original, but without a satisfactory conceptual equivalence
D = items have no agreement

The items that were classified as C or D by the committee were deemed as needing further action. The committee discussed the discrepancies with the back-translators and accordingly provided recommendations and suggestions to change the translated version. Post committee review, the proposed changes were sent to DOXA for either incorporating the suggested wording or re-phrasing the translations to convey the intended meaning. The final translated versions were used in a Pan-European population based prevalence study.

2.2.10 Field Testing/Cognitive Debriefing on small test group

The cognitive debriefing step aims to qualitatively test the cultural equivalence and acceptability of the translated version. It ensures that the translated questions and response options are interpreted by the target population in the same way as the English language version and adequately reflect any nuances of the target language (Hall et al., 2018b). For the ETS translation, this step was conducted as a field testing endeavour on a small group of bilingual speakers (comprising three to seven volunteers) of the target language and English. The volunteers could participate, provided they were native speakers of the target language and were not involved in the back-translation step.

Hall et al. (2018b) recommended the cognitive debriefing step as a final pre-testing assessment for questionnaire translation (Hall et al., 2018b). However, the ETS questions were already used to collect data on tinnitus and hearing difficulty in 12 countries. Therefore, for this project, the field testing was more of a confirmation

process to ensure that the final translated versions were culturally acceptable and easily interpreted by native speakers.

Although there is no consensus in the published literature on the minimum number of volunteers needed for field testing, one recommendation is five to eight (Antunes et al., 2012). In this study, the recruitment of the recommended number of volunteers was not always possible due to time and resource constraints. For most languages, purposive sampling was used to recruit three to seven bilingual speakers. It was particularly challenging to recruit Latvian and Romanian bilingual speakers, and despite repeated attempts, no bilingual speakers could be recruited for these two languages.

The volunteers were recruited from the research team's network of colleagues and collaborators and their social and professional contacts. The European Federation of Audiology Society (EFAS) country chiefs were also contacted to help with the field testing or direct to potential participants. The final field testing volunteers were a mix of hearing researchers and non-hearing researchers, clinicians, and the general public. Each participant was provided with the four translated questions and response options, along with the link to a structured short online survey created in the Survey monkey platform. For each of the four items on the ETS, the online survey included the following questions:

- In order to let us understand how you interpret the question, please try to summarize Question#X (Items 1 to 4) and the corresponding response options in your own words (in English)
- Question#X and the corresponding response options: Would the wording of the question and response options be difficult to interpret to a member of the general public? (Yes/No). If yes, please explain.
- Question#X and the corresponding response options: Might any words or phrases sound a bit awkward according to everyday language? (Yes/No). If yes, please explain.
- Question#X and the corresponding response options: Would you propose any changes to the wording to make it clearer or more acceptable to a member of the general public? (Yes/No). If yes, please explain.

The participants were also asked to rate the overall translation on a visual analogue scale (VAS) from 0 to 100. All questions on the online survey were mandatory and could not be skipped. Since the survey was non-anonymised, the volunteers could be tracked. As a result, the distribution of hearing researchers and the general public could be ascertained. It was also possible to refer back to the field testing participants if there were any questions regarding the feedback or recommendations. The participants' version of the questions summary was cross-checked with the original English version to look for discrepancies. Notes were made on the difficult sounding or awkward wordings that the participants pointed out. Since these were followed by suggestions, explanations, and sometimes potential alternative words or phrases, there was an opportunity to determine if a major or minor correction was recommended. The median score was calculated for the overall VAS rating to understand the quality and accuracy of the final translated versions.

2.3 Results

2.3.1 Source language version of ETS

The original English survey included a general introduction for the participant about the survey content, specifically about tinnitus, instructions for the interviewer, and the four adapted questions and response options. The questions on the presence of tinnitus and hearing difficulty were asked to all participants, while the questions on severity and healthcare use were asked only to participants who answered "Yes," that is, selected response option 1 to 3 (Table 2.2) for the presence of tinnitus question. Therefore, the instruction for the interviewer was necessary for efficient survey administration. The details of the English version are provided in Table 2.2, which is taken from the article by Biswas et al. (Biswas et al., 2019).

Table 2.2 Standardised survey instructions, questions and response options in English (Biswas et al., 2019)

General instruction to participants	**"Now we ask you a few questions on hearing problems and on the sensation of noise in head or in one or both ears, which is a symptom that medical doctors call "tinnitus"**		
	Question-specific instruction to the interviewer	**Question**	**Response options**
Presence of tinnitus	To all adults (i.e., aged ≥ 18 years)	Over the past year, have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time?	• Yes, most or all of time • Yes, a lot of the time • Yes, some of the time • No, not in the past year • No, never • Do not know/ Prefer not to answer
Tinnitus severity	To participants with current tinnitus	Over the past year, how much do these noises in your head or ears worry, annoy or upset you when they are at their worst?	• Severely • Moderately • Slightly • Not at all • Do not know/ Prefer not to answer
Use of healthcare resources for tinnitus	To participants with current tinnitus	Over the past year, have you seen your family doctor, or seen a healthcare professional at a clinic or hospital about problems with noises in your head or ears?	• Yes, 5 or more visits • Yes, from 2 to 4 visits • Yes, just one visit • Not at all • Do not know/ Prefer not to answer
Presence of hearing difficulty	To all adults (i.e., aged ≥ 18 years)	Do you currently have any other difficulty with your hearing, such as listening to speech in a noisy situation?	• Yes, cannot hear at all • Yes, severe difficulty • Yes, moderate difficulty • Yes, slight difficulty • No difficulty • Do not know/ Prefer not to answer

2.3.2 Translation of survey items and cross-cultural equivalence

From the English version, DOXA developed the forward translations of the general introduction and each item. Since DOXA designed the final survey for a computer-assisted personal interview, questions were programmed to be skipped automatically depending on an individual's response. Hence, the question-specific instruction to the interviewer was not translated to the target languages. The back translators evaluated the forward translations, and provided back-translated versions (in English) along with ratings and recommendations for each item. The equivalence between the translated and the source version was determined based on the comparison between the back translations and the original English-language version.

- The introductory sentence: nine out of the 11 translations were rated A or B.
- The item on the presence of tinnitus: eight out of 11 translated questions and 10 out of 11 translated response options were rated A or B.
- The item on tinnitus severity: five out of 11 translated questions and 10 out of the 11 translated response options were rated A or B.
- The item on healthcare resource use for tinnitus: 10 out of 11 questions and all (11) response options were rated A or B.
- The item on hearing difficulty: six out of 11 translated questions and 10 out of 11 response options were rated A or B.

The items that appeared to have discrepancies between the source and target language versions (i.e., C or D ratings) were reviewed. The review committee evaluated each item against the corresponding back-translator suggestion and accordingly decided to accept or reject those suggestions to create the final translated versions.

A key element in the translation process was having satisfactory conceptual equivalence across languages. It was noted that most discrepancies resulted from difficulties in striking a balance between preserving the meaning of the original English words and capturing the nuances of the target language. The items on tinnitus severity and hearing difficulty had the maximum C and D ratings (for both questions, three translations were rated D) and required further edits in the translated versions for seven and six languages, respectively (Appendix IV, V, VII, and VIII). For example, three emotional descriptors have been used to assess tinnitus distress in the tinnitus

severity question: “worry, annoy or upset.” These three emotions have subtly different meanings in English. A major point of discrepancy was conveying the same emotion in the translated versions so that the interpretation remained consistent across languages. For the question on hearing difficulty, a key concept was listening and understanding speech against merely hearing it. Therefore, an important concern was maintaining conceptual alignment without deviating excessively from the original phrasing and structure.

2.3.3 Final translated version of survey items

The review committee decided which back-translator changes needed to be incorporated in the final translated versions. For example, the back translators rated the French version of the tinnitus prevalence question "C." They recommended replacing the phrase "ce type de bruits" (meaning: this type of noise) with "un acouphène" (meaning: a tinnitus). Since the original English version question did not have the term 'tinnitus' in it, the review committee decided the forward translation was good enough, and the term “un acouphène” was not used in the final version (Appendix II).

The Greek back translators also rated the tinnitus prevalence question "C." In the back translation, the translator used the phrase "last year", which did not capture the duration of the condition. They recommended changing this phrase in the Greek version so that the final translated version can adequately stress the period over which participants should consider their response. The review committee agreed and accepted the recommended changes (Appendix II). Appendix I to VIII report the forward translation, discrepancy rating (i.e., C or D ratings), corresponding suggestions by the back translators, and rationale behind accepting or rejecting a recommendation. The final translated versions of the items are provided in Appendix IX.

2.3.4 Field testing of final versions

The field testing step was used to evaluate the ease of interpretation of the translated versions and the cross-cultural equivalence while maintaining the same meaning as the source language version. The scores shown in Table 2.3 are a measure of the

understandability and language level of the translations. Although the numbers by themselves are not easy to interpret, it can be assumed that overall there is a general inter-rater agreement regarding the quality of the translations. The median rating scores were relatively high at 70 or higher.

Table 2.3 Evaluation scores of field testing. Scores are between 0 and 100 (Biswas et al., 2019)

Languages	Number of individual field testers	Median score	Score range	
			Minimum	Maximum
Bulgarian	3	100	90	100
French	3	80	75	99
German	7	85	70	100
Greek	5	94	75	97
Italian	5	90	85	100
Latvian	0	✘	✘	✘
Polish	3	85	60	90
Portuguese	4	77.5	25	98
Romanian	0	✘	✘	✘
Russian	5	70	60	100
Spanish	5	89	70	89

✘= Field testing was not done.

However, for some languages, the field testing volunteers showed a vast difference in opinions, with some Polish, Portuguese and Russian volunteers rating the translations at 60 or less. Since data collection (for estimating prevalence) had already started for some countries using the translated questions, no edits were made to the final translations post the field testing step. However, the field testing volunteers had the option of providing free-text comments. Given the mixed opinions for Polish, Portuguese and Russian, the open comments, as summarised in the following segments, could be informative for further refinement of the translations and for future research.

[*Some parts of the field testing comments narrated in the following paragraphs, have been published in the article by Biswas et al. (2019).]*

Polish: Three native Polish speakers, bilingual in English and Polish, volunteered to evaluate the Polish language version. None of them were hearing researchers. For the presence of tinnitus response options, two volunteers suggested removing the

comma after "Nie" in the option "Nie, w ciągu ostatniego roku". This corresponds in English to the response option "No, not in the past year".

Two volunteers found that the syntax of the question on healthcare resource use does not flow smoothly. One of them summarised the question as: "If patient seek medical attention (general practitioner, specialist in clinic/hospital) in one-year period because of unpleasant feeling in head or ears", and pointed out that in the Polish context, a specialist could be available in ambulatory care as well, and not necessarily in hospital or clinic. This makes accurate interpretation slightly difficult. The second volunteer suggested changing the word order from "W ciągu ostatniego roku czy był/a" to "Czy w ciągu ostatniego roku był/a", for conveying the "over the last one year" period. For the hearing difficulty question, all three suggested changing the word "problem" to its plural form "problemy". Two volunteers also noted that the Polish version of the question was not clear on whether difficulty in hearing in general or specifically in a loud environment was being assessed.

Portuguese: Four bilingual hearing experts evaluated the Portuguese language version. One of them noted that the translations needed modifications based on whether they were being addressed to the Portuguese population in Portugal or South American countries such as Brazil since the translations were a mix of both forms. For example, for the tinnitus prevalence question, "ringing or buzzing" was translated as "toques ou zumbidos". According to a field testing volunteer, "toques" did not necessarily translate to "rings". It could also mean "touches". For the response option "not at all" in the healthcare resource use item, two volunteers suggested changing "Nada" (meaning nothing) to "Nenhuma vez" (meaning not a single time). One volunteer commented about the hearing difficulty question: "a person may hear but not understand. If you want to focus on understanding in noise, rephrasing is important".

Russian: Five bilingual speakers, with native language Russian, evaluated the translated items. Four of them were hearing experts. The phrasing of the questions on tinnitus prevalence and tinnitus severity in Russian did not sound natural to three volunteers. They gave alternative versions for the questions or recommended changing parts of them. For the prevalence question: three suggestions were as follows:

- “В течение последнего года ощущали ли Вы в голове, одном или обоих ушах шум, напоминающий звон или свист, продолжительностью более пяти минут? (meaning “During the past year, did you feel a noise resembling a ringing or whistling in the head, one or both ears, lasting more than five minutes?”)
- “В течении последнего года ощущали ли Вы такие звуки, как шум или свист в голове, в одном или в обоих ушах, которые длились более 5 минут?” (meaning “During the past year, did you feel such sounds as noise or whistling in your head, in one or both ears that lasted more than 5 minutes?”)
- “В течение последнего года возникали ли у Вас в голове или в ухе (или в обоих ушах) шумы, похожие, например, на звон или свист, которые длились более пяти минут?” (meaning “During the past year, did you have noises in your head or in your ear (or both ears), similar to, for example, ringing or whistling, which lasted more than five minutes?”)

For the tinnitus severity question, four suggestions were as follows:

- “В течении последнего года насколько сильно эти звуки Вас беспокоили, волновали, раздражали в тот момент, когда они были наиболее ярко выражены?” (meaning: Over the past year, how much did these sounds bother you, excite, annoy you at the moment when they were most pronounced?)
- “Насколько сильно в течение последнего года эти шумы (в тот момент, когда они были наиболее интенсивными) Вас беспокоили, раздражали, огорчали?” (meaning: How much over the past year have these noises (at the moment when they were the most intense) bothered, annoyed, upset you?). The volunteer suggested that the descriptor "worried" translates better to "беспокоили" instead of "волновали".
- One of the volunteers suggested changing the phrase "когда они были наиболее яркими" to "Когда они были наиболее выражены" which better explains the concept "when they are at their worst".
- “Насколько сильно в течение последнего года этот шум в ситуациях, когда он был наиболее выраженным, беспокоил, раздражал и расстраивал Вас?” (meaning: How much over the past year has this noise in situations where it was most pronounced, bothered, annoyed and upset you?)

In general, ratings for the Russian questions were not low. However, even for the other two questions, which sounded more acceptable to the field testing volunteers, the common opinion was that sometimes the Russian syntax was slightly awkward.

The ratings given for the other language translations were relatively high and had a broad general agreement on quality. Nonetheless, there did remain some informative comments that could potentially improve the ease of interpretation. They are summarised as follows:

Bulgarian: Three bilingual speakers, of whom one was a hearing expert, evaluated the Bulgarian version. For the question on healthcare resource use, the Bulgarian hearing expert said: "I would change the phrasing "problems in your head and ears - (проблемите ви в главата или ушите) with problems concerning your tinnitus or ringing in the ears (проблеми свързани със шума в ушите или главата)".

French: Three bilingual speakers evaluated the French language version. Two of them were hearing experts. The main comments the French volunteers had was regarding the question on hearing difficulty. The hearing experts queried if the intention was to assess hearing in general or listening and understanding a conversation. They suggested rephrasing the question in order to make it more straightforward. One of them commented: "the word "écouter" refers to hearing a conversation, if you want to assess if they can understand you should use the term "comprendre".

German: Seven bilingual speakers, including four hearing experts, evaluated the German language version. The comments and feedback were mainly on the question on healthcare resource use and its response options. Four out of the seven field testing volunteers indicated that the phrase "der Hörprobleme "meaning "hearing problems" appear rather abruptly in this question. There had been no reference to hearing problems. One participant mentioned, "I think 'Hörprobleme' comes a bit out of the blue... maybe I would leave that out". Another participant commented, "the phrase "...wegen der Hörprobleme (engl. the Hearing Problem)" it suggests that people have already admitted that they have hearing problems but the only the next question is about hearing problems".

Greek: Overall, there was general agreement on the Greek language version among the five bilingual speakers, including two hearing experts, who evaluated the Greek

version. The only comment was on the final response option, which was "Do not know/Prefer not to answer": the abbreviation- "ΔΞ / ΔΑ", was used in the Greek version. Three participants recommended using the full form instead.

Italian: The Italian language version was evaluated by five bilingual speakers, including one hearing expert. For the question on the severity of tinnitus symptoms, the phrase "at their worst" was translated as "al loro peggio". Three participants suggested using a different translation for this phrase. However, there was no consensus on the alternative phrasing. The three suggested replacements were "nella loro fase piu intensa", "nella fase più acuta", and "al loro massimo grado di severità".

Spanish: Five bilingual speakers, including four hearing experts, evaluated the Spanish language version. For the tinnitus prevalence question, four out of five participants suggested changing "como sonar o zumbar" (meaning "like sound or buzz") to the plural form "como sonidos o zumbidos" (meaning "like sounds or buzzing"). The question on hearing difficulty translated well for three participants. However, two of the hearing experts raised a similar query to the Polish and French field test to clarify whether hearing or understanding was being assessed. The following statement by one of the participants summarises well the essence of the concern and a potential solution: "The main problem in patients with HL is not the ability to hear in noisy environment but to understand in noisy environment. In Spanish "hear" is "oir" and "understand" is "entender".

There was general concurrence among the field testing participants about the cross-cultural acceptability of the translations. Nevertheless, the constructive feedback identifies further revisions for further refinement of the translated versions.

2.4 Discussion

In this project, a set of four standardised questions and response options were developed in 12 European languages for use in population-based surveys of tinnitus. This was a novel attempt to create an international standard by translating survey items from English to 11 other European languages following the good practice guidelines for cross-cultural adaptation (Hall et al., 2018b). The aim was to achieve equivalence across different languages and populations (Hall et al., 2018b). Therefore, a key element in the translation process was to achieve a contextual translation instead of verbatim translations. The general agreement of opinion among the field testing volunteers and the relatively high evaluation scores indicate the cross-cultural appropriateness and functional equivalence of the survey items. Therefore, this work can be assumed to have generated a reliable assessment measure to gather comparable results across countries.

2.4.1 Contribution to the project and critical appraisal

I got involved in the project after the back translation step. The question selection, adaptation, forward and backward translation and translator selection had already been completed. I cross-checked if the updates from the back translation were accurately added to the data collection items. My main contribution was in the field testing step. I was involved in developing the field testing survey, recruiting the field testing participants, cross-checking their item summaries with the original English version, and summarising the final recommendations. The following two sections provide a critical appraisal of the project, highlighting its main strengths and limitations.

2.4.1.1 Strengths of the project

A team of hearing experts adapted the four survey items from existing questions and response options. Since the question selection was conducted by subject matter experts, one can be confident about the utility and importance of the questions asked. Moreover, being adapted from existing questionnaires, it can be expected that the findings obtained by using these items should be roughly comparable to existing published study results. For example, Bhatt et al. (2016) and Masterson et al. (2016) examined tinnitus prevalence in the US population aged 18 years and above, using

the NHIS question. The NHIS question is identical to the tinnitus prevalence question from the ETS project.

Spankovich et al. (2017) also studied the prevalence of tinnitus in the US population using NHANES data from 1999-2002. NHANES has two questions on the presence and frequency of tinnitus ("In the past 12 months, have you ever had ringing, roaring, or buzzing in your ears?" and "How often did this happen?"), which could be broadly approximated to the information derived from the item on tinnitus prevalence in this project. The question on tinnitus severity from NHIS data US in 2007 had only one of the emotional descriptors that this project uses, namely, "bothered". Overall, the two study questions are very similar, including the use of the "in the last 12 months" time frame (Bhatt et al., 2016). In the EuroTrak Survey carried out across Germany, France, and the UK from 2009 to 2015, "trouble hearing conversations in a noisy background" was used to determine the degree of HL (Bisgaard and Ruf, 2017). The conceptual alignment and consequent ease of comparison with other population-based studies are particular strengths of this work.

This work's main strength lies in the fact that it extended beyond a simple forward translation and closely followed the good practice guidelines recommended by Hall et al. (2018b). The translation process ensured that the same assessment tool was used across countries (Hall et al., 2018b). Thus, preventing the assessment-related heterogeneity, which is a major concern that plagues epidemiological research on tinnitus prevalence (McCormack et al., 2016). Authors have indicated the need to develop standardised research definitions for tinnitus and their implementation in population surveys (Gallus et al., 2015; McCormack et al., 2016). The ETS survey achieves both of these requirements. Each step included in the process, namely defining the key concepts in each question, back translation, rating equivalence, revising the target language translations, and field testing by native speakers, refined the translated versions. The focus of this project was on creating culturally appropriate and easily comprehensible translations. To maintain transparency in reporting, details of comments and revisions made at each stage, and the timing of the field testing (after survey implementation) was acknowledged in a technical note on this project. The number of translators and volunteers involved in each stage were also clearly noted (Biswas et al., 2019). Since the field testing indicated that some of the

translations could be further improved (for example, Portuguese and Russian), maintaining this transparency in reporting should provide a basis for other investigators to build on.

2.4.1.2 Limitations of the project

In multiple languages (French, Polish, and Spanish), there were some confusions about the interpretation of the question on hearing difficulty. The English language question was: "Do you currently have any other difficulty with your hearing, such as listening to speech in a noisy situation?". Based on the field testing comments, the source version was re-evaluated, which indicated that possibly the uncertainty arose at the phrasing of the source language question itself. There is a possibility that the target audience might interpret that the question seeks information only about listening to speech in a noisy situation. However, the question on hearing difficulty was not designed to be specific to hearing in noise. The intention was to ask about general hearing ability and the 'such as listening to speech in a noisy situation' statement meant to serve as an example, since this is a common complaint. There was also some confusion about whether the question was meant to assess simply "listening to speech", or "understanding speech"-since the two things are not the same. In hindsight, further adaptation and rephrasing of the question was probably needed to make it clearer to the general audience.

The main limitation of this work arose from the difficulty in connecting with bilingual speakers for various languages. For the Latvian back translation, initially, Google translate was used, and most items were rated "D". Later, a native Latvian speaker was consulted. Based on his opinion, the revised ratings were "A" and "B". The difficulty in recruiting bilingual speakers became more pronounced in the field testing stage. The good practice guidelines by Hall et al. (2018b) recommended at least eight native speakers and up to 20 native speakers for countries where there is regional variation. Due to time constraints and limited resources, the recommended field testing participant numbers were not attained for any of the 11 languages.

Despite targeting a widespread international network of professional and personal connections, no Romanian or Latvian speakers could be recruited for field testing. Nonetheless, each translated item was thoroughly scrutinised and reviewed by

multiple persons (the authors and bilingual speakers) in more than one step of the translation process (namely the back translation and the field testing steps). This group included hearing researchers with extensive knowledge and subject matter expertise. The translation process was very detailed, and at every stage, close correspondence to the good practice guidelines were attempted.

However, the survey items were implemented for data collection before the field testing step. As a result, some useful insights and suggestions provided by the field testing volunteers (Section 2.3.4), could not be incorporated into the final version for data collection. The field testing volunteers suggested only minor improvements and were in general agreement about the good quality of translated versions. The feedback on the final versions produced relatively high evaluation scores. Although some of the final translated versions could have benefitted from additional adjustments, for the most part, it can be safely concluded that the resultant final versions produced from this endeavour are reasonably well adapted and culturally acceptable translations. Nonetheless, in order to be confident that the comments of the bilingual speakers are acceptable, it is advisable to conduct more extensive field testing on a reasonably large proportion of the relevant target audience, especially for Latvian and Romanian, before any substantial revisions are made to the phrasing and syntax of the translated versions.

2.4.2 Future directions

There is general agreement in all the 12 versions of the survey items. Nonetheless, there is some scope for modifying the translations, as indicated by the various comments and feedback. Future investigators using these survey items could consider extending the field testing stage to have a bigger sample size and a better understanding of the general agreement on the translated versions. Alternatively, the suggested recommendations by the field testing participants of this study could be incorporated, and then participants' interpretation could be reassessed using a more extensive field testing sample.

The translated languages include some of the most spoken languages worldwide. Spanish, English, Portuguese and Russian are all included in the top ten most spoken languages globally and account for more than 1 billion speakers (e.g., English= 378

million speakers, Spanish = 442 million speakers, and Portuguese = 223 million speakers, Russian= 154 million speakers). The 12 languages combined account for 1.5 billion first-language speakers worldwide (Simons and Fennig, 2018). Since this translation was part of an EU funded project, the development and further steps were restricted to the continent of Europe. Some of these translated languages are widely spoken in other parts of the world, albeit with subtle nuances and intricacies typical to the country and culture. For example, English is widely spoken in the US and Australia, Spanish and Portuguese are widely spoken in the Americas, and French in Africa. Therefore, the translated versions in these languages could be used in other populations as long as additional field testing is conducted before implementation. Such a step would determine if there are requirements for any modifications to the existing translations to account for national dialects or social and cultural differences. In particular, Spanish and Portuguese as spoken in the Americas differs from those spoken in mainland Europe. Thus, this initiative has the potential for cultural adaptation for use in countries beyond mainland Europe.

2.4.3 Concluding remarks

This project illustrates a careful development of standardised survey items in 12 different languages intended to reduce variability across data collection in multi-national studies of tinnitus epidemiology. The translation process of the questions and response options with acceptable evaluation scores indicate the acceptable quality of the translated versions. Overall, this is an innovative endeavour on tinnitus and hearing difficulty prevalence. The final translated versions produced in this survey have already been implemented for data collection across 12 EU countries. The following chapter reports the findings from the analysis of this collected data and estimates a Pan-European prevalence and inter-country differences.

Chapter 3 . A Pan European assessment of the prevalence of tinnitus

3.1 Introduction

Knowledge about the prevalence of a condition is crucial for implementing adequate preventive measures and policy interventions and appropriate resource allocation (Moller, 2014). Epidemiological research, particularly population-based studies, are useful for providing up-to-date information on global prevalence. The available literature shows wide variability in tinnitus prevalence estimates (Baguley et al., 2013; McCormack et al., 2016). Inherent methodological drawbacks and between-study differences hinder deriving a global estimate by pooling data from studies conducted in different countries and world regions (Baguley et al., 2013, Gallus et al., 2015, McCormack et al., 2016). Therefore, uncertainties with regards to the true prevalence of tinnitus remain. A potential solution to address this concern would be to design and conduct a multi-national study on tinnitus prevalence, recruiting sample populations from each country such that it represents the actual country population, and using uniform methods for data collection and analysis.

3.1.1 Methodological issues in epidemiological research on tinnitus

3.1.1.1 Location bias

Epidemiological research on tinnitus has an evident location bias, focusing on Western Europe, the US, and Australia (McCormack et al., 2016). In recent years, prevalence studies have been conducted in other parts of the world, including South-East Asia and the Middle East (Jalessi et al., 2013; Park et al., 2014; Baek et al., 2016; Manche et al., 2016; Shih et al., 2017). However, such studies are far fewer in number. There is hardly any data available from the developing world, particularly from African countries. An attempt to pool available data on tinnitus prevalence would lead to specific populations being grossly underrepresented and an evident location bias with results being skewed towards some geographic regions of the world.

Prevalence studies are often conducted on sample populations restricted within some geographic regions within a country. For example, the EHLS, a very well-conducted population-based cohort study, provides valuable information on hearing-related

conditions, including tinnitus, in older adults aged 43 to 84. However, the study population is limited to participants who are residents of the township of Beaver Dam, Wisconsin, USA (Cruickshanks et al., 1998). The BMHS is another population-based study conducted in Australia on participants of the Blue Mountain Eye study cohort, who were residents of two suburban postcode areas in Sydney, Australia (Sindhusake et al., 2001). Given the demographic and geographical specifics of the study populations, the generalisability of results become questionable (Westriech et al., 2019). Despite providing valuable data, they might overrepresent or underrepsresent some population groups due to the restricted demographics and geography.

3.1.1.2 Specific demographics of study population

The UK Biobank is a useful resource of population-based data on 500,000 UK individuals where recruitment is based on voluntary participation (Fry et al., 2017; Keyes and Westreich, 2019). Compared to national estimates, the biobank sample includes more women, older people, and people living in better socio-economic areas. The data also has a healthy volunteer bias as it comprises individuals with relatively fewer health concerns (Fry et al., 2017). Despite a large sample size, proportions of individuals in different socio-demographic groups in a population-based dataset are not always representative of the country's population distribution. This limits the generalisability of estimates from such datasets.

Tinnitus prevalence studies often focus on population samples with particular socio-demographic characteristics. For example, both the BMHS and EHLS analyse hearing-related concerns in older adults (Cruickshanks e al., 1998; Sindhusake et al., 2001). Analysis of the UK Biobank data for tinnitus prevalence by McCormack et al. (2014) focused on adults aged 40 to 69 (McCormack et al., 2014). Such studies cannot be extrapolated to an entire country population that contains a mix of various age groups. The effect of age on tinnitus prevalence can be observed from the mixed results obtained by analysing the NHANES, a nationally representative dataset, for different age groups. For example, Loprinzi et al. (2013) analysed NHANES data for the population aged 12 to 19 and 70 to 85-year olds and reported prevalence estimates of 8.9% and 25.3%, respectively (Loprinzi et al., 2013). Shargorodsky et al. (2010) reported a 25.3% tinnitus prevalence for adults aged 20 years and above from the same dataset (Shargorodsky et al., 2010). Spankovich et al. (2017) reported a

prevalence of 21.1% for adults aged 20 to 69 years of age (Spankovich et al., 2017). Therefore, it is not surprising that the diverse age profiles of study populations are an essential contributing factor to heterogeneous estimates across tinnitus prevalence studies.

3.1.1.3 Diverse assessment criteria

Studies with broadly similar tinnitus assessment questions and conducted in populations with similar socio-demographics often differ by inclusion or omission of key concepts that address crucial information. Additionally, most studies do not justify their choice of wordings while framing the assessment questions (McCormack et al., 2016). These differences in assessment methods lead to widely variable prevalence estimates beyond what is expected due to the noticeable demographic variations between different populations.

Nondahl et al. (2004) raised this concern when comparing the BMHS and EHLS (Sindhusake et al., 2003). The study populations of BMHS and EHLS were similar in terms of age, sex, marital status, PTA, ethnicity, occupational history, and cardiovascular profile (Cruickshanks et al., 1998; Nondahl et al., 2004). The EHLS data from 1993 to a follow up of 5 years reported an 8.2% prevalence of significant tinnitus, which was defined as "buzzing, ringing, or noise" in the ears in the past year that was at least moderate in severity or that caused problems getting to sleep (Nondahl et al., 2002). Sindhusake et al. (2003) reported a tinnitus prevalence of 30% from BMHS data between 1997 and 1999. In BMHS, tinnitus was defined as "any prolonged ringing or buzzing in the ears or head within the past one year…...lasting for five minutes or longer". Despite the relatively similar socio-demographic characteristics, there was considerable variability in prevalence, which Nondahl et al. (2004) attributed to the different reporting measures used in these two studies. The details of the reporting measures used in these two studies are provided in section 2.1.1.

3.1.2 Individual and population level factors affecting prevalence estimates

3.1.2.1 Role of individual socio-demographics in prevalence

Published literature supports an increase in tinnitus prevalence and subjective severity with increasing age (Bhatt et al., 2016; Gallus et al., 2015; Nondahl et al., 2011). Given the increased life expectancy and lack of a cure for tinnitus, we can assume that the overall burden of tinnitus will rise in the future (Kontis et al., 2017; Mathers et al., 2015). Shargorodsky et al. (2010) reported a peak prevalence of tinnitus in the 60 to 69 years' age group. In their review, McCormack et al. (2016) also noted an increase in tinnitus prevalence up to 70 years of age and then a decline (McCormack et al., 2016). Therefore, in pooling prevalence data across populations, it is vital to note the age range of the study population. Studies conducted on different age groups have inherent differences that would pose a problem if one attempts to combine their results.

Shargorodsky et al. (2010) analysed the NHANES data to report a tinnitus prevalence of 25.3% in the US with an increased prevalence based on ethnicity. The white non-Hispanic population had the highest prevalence compared to populations of other ethnic groups (black non-Hispanic, Hispanic, and other) (Shargorodsky et al., 2010). However, in a more recent study on the African American population, House et al. (2018) reported a tinnitus prevalence of 29.5%, which is higher than the national average (House et al., 2018; Shargorodsky et al., 2010). These results are somewhat surprising, considering that African Americans report a relatively lower prevalence of tinnitus in the nationally representative sample, and warrant further exploration of the interactions between race and ethnicity and tinnitus.

However, these results reinforce the importance of recruiting representative samples in population-based studies. To have generalisable results, study populations should reflect a country's racial and ethnic population distribution. Again, large sample sizes do not necessarily ensure representativeness. For example, in the UK biobank, 94.6% of participants were white. Although nationally representative for the same age population according to the 2001 UK Census (94.5%), these proportions were somewhat higher than the numbers reported in the 2011 Census (91.3%) (Fry et al.,

2017). Therefore, dynamic population changes need to be remembered when generalising study results to the entire population and making between country comparisons. Pooling non-representative data from multiple countries in order to report global prevalence would lead to biased estimates. Moreover, representative population data helps in ascertaining the real impact of tinnitus in specific socio-demographic groups. In order to restrict the increasing prevalence of tinnitus, it is vital to identify vulnerable populations for targeted preventive interventions and resource allocation.

3.1.2.2 Country specific characteristics and prevalence

Health systems and policies are mostly country-specific. The socio-demographic and economic profile of a country often lead to variations in awareness, prevention initiatives, and availability of care, leading to variations in estimates of prevalence and incidence. To tailor health policies to population-specific challenges, it is crucial to consider the variations resulting from the factors above. In multinational studies of some conditions, variation in prevalence estimates was noted based on the country's overall economic, environmental, and health profile and geographic region (Dafni et al., 2019; Gomez-Lopera et al., 2019; Haynes-Maslow and Leone, 2015). Gross domestic product (GDP) per capita is a commonly used measure for a country's economy and has been reported to impact the epidemiology of health conditions. For example, breast cancer statistics in the EU showed that countries with high GDP per capita had higher incidence and survival of breast cancer (Dafni et al., 2019). Similarly, for diabetes mellitus, countries with higher GDP were reported to have increased incidence (Gassasse et al., 2017). Another study that looked at the Peruvian population found increased hypertension with decreased GDP (Gomez-Lopera et al., 2019). There is no real evidence from tinnitus research on the role of GDP in prevalence. Perhaps the lack of multinational studies using standardised tinnitus assessment methods prevents exploration of the relationship between a country's economy and tinnitus prevalence. Tinnitus-related studies have shown variations in prevalence based on an individual's socioeconomic status (Hasson et al., 2010; Martinez et al., 2015). Given the considerable economic influence of tinnitus on healthcare systems (Stockdale et al., 2017), it would be informative to determine the effect of GDP per capita on tinnitus prevalence in multinational studies.

In certain other conditions like breast cancer, the EU statistics reported that increased incidence could be attributed to the higher prevalence of lifestyle risk factors, while higher survival was attributed to better access to health care. This same study showed high incidence and survival in Western European countries compared to Southern European countries (Gomez-Lopera et al., 2019). Given the heterogeneity in tinnitus prevalence estimates and the impact of country-level factors on the prevalence of other chronic non-communicable conditions, it would be interesting to examine how much of the inter-country variation in tinnitus prevalence can be attributed to country-level characteristics.

3.2 Rationale

3.2.1 Impact of tinnitus on mental health and well-being

WHO defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (WHO, 1948). Any condition that affects any one of these three domains, i.e., physical, mental, or social well-being, would adversely affect health as a whole. As shown in Figure 3.1, tinnitus has an all-encompassing effect on physical health and mental health and well-being (Hall et al., 2018a).

In a study conducted on the national population of the US, 25% of people with tinnitus had self-reported depression in the preceding 12 months, while 26% had self-reported anxiety. Both anxiety and depression were significantly higher in individuals with tinnitus than individuals without tinnitus (Bhatt et al., 2017). Another study where the Hospital Anxiety and Depression Scale was administered to the Swedish population reported an increased prevalence of anxiety (25%) and depression (17%) among individuals with tinnitus (Andersson et al., 2003). Since mostly cross-sectional studies investigated the comorbidity of psychological symptoms and tinnitus, it is not easy to make firm conclusions on the direction of this association. However, a systematic review suggested a potentially bidirectional association between tinnitus symptom severity and depression, forming a vicious cycle where severe tinnitus leads to depressive symptoms, which in turn causes poor adaptation to tinnitus and increasing severity (Geocze et al., 2013).

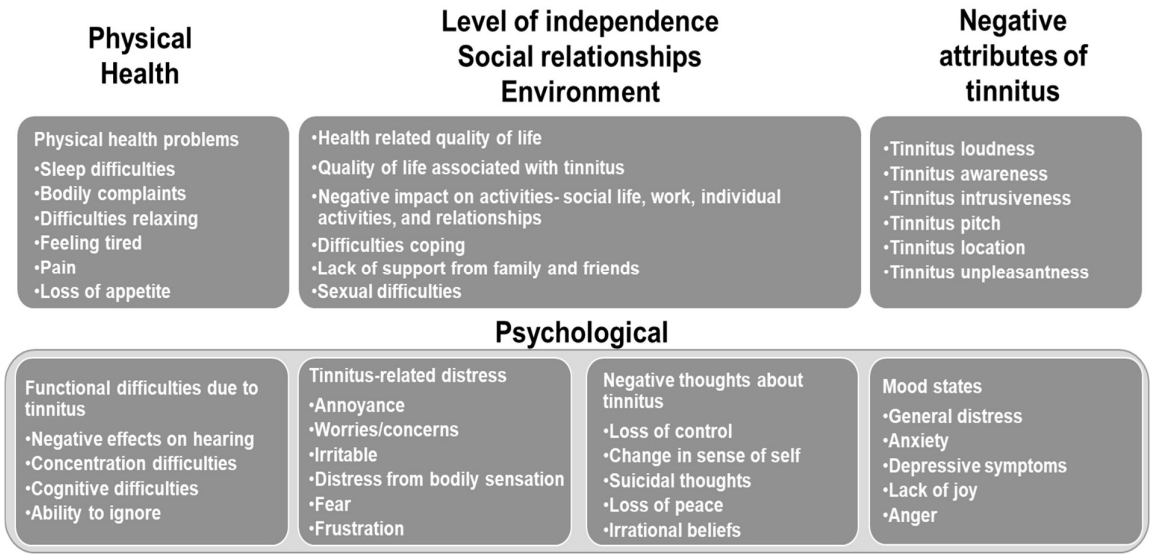


Figure 3.1 Overview of adverse effects of tinnitus in various domains of health and well-being

Not only are self-reported psychological symptoms commonly observed in people with tinnitus, but clinically diagnosed psychiatric comorbidities are also reported. Belli et al. (2008) conducted a study of tinnitus cases and controls using the Structured Clinical Interviews for Diagnostic and Statistical Manual of Mental Disorders-III-R, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Symptom Check list-90 Revised questionnaire (SCL-90-R). The authors investigated the co-existence of psychiatric comorbidities and tinnitus (Beck et al., 1961; Beck and Steer, 1988; Spitzer et al., 1992; van der Laan et al., 1999; Williams et al., 1992). People with tinnitus had significantly higher scores on SCL-90-R subscales, BAI and BDI. They also found that 26.70% of individuals with tinnitus had at least one psychiatric diagnosis, which was significantly higher than the control group. These findings concluded that symptoms of anxiety and depression in tinnitus cases should prompt clinicians to check for chronic psychiatric comorbidities (Belli et al., 2008). A study by Jacques et al. (2013) also reported that 28% of tinnitus patients having a major depressive disorder and 22.5% suffering from an anxiety disorder.

Besides, self-harm and suicidal ideations are relevant concerns in people with tinnitus, especially women, and the propensity for self-harm increases with the presence of

depression as a comorbidity (Aazh and Moore, 2018). In a nationally representative study on premenopausal women in Korea, the prevalence of perceived stress and suicidal ideation was significantly higher in women with tinnitus than in those without (Lee et al., 2017). Analysis of Stockholm Public Health Cohort dataset showed increased suicide attempts in study participants with tinnitus and a statistically significant association between suicide attempts and clinically diagnosed tinnitus in women (Lugo et al., 2019).

In summary, the impact of tinnitus on emotional well-being and mental health is a serious concern that could severely harm an individual, both psychologically and physically. Identifying vulnerable populations is essential to initiate adequate strategies to prevent tinnitus and address the specific healthcare needs of existing tinnitus cases.

3.2.2 Impact of tinnitus on quality of life

Quality of life (QOL) is a broad multidimensional concept. According to WHO, QOL is defined "as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHOQOL, 1997). Health is one of the key domains of overall QOL, along with other socio-economic and cultural domains (HRQOL concepts, CDC, 2000). The Center for Disease Control and Prevention (CDC) in the US defines the health-related quality of life (HRQOL) as "an individual's or group's perceived physical and mental health over time" (Moriarty et al., 2003).

Since tinnitus is a subjective phenomenon, its overall impact on an individual's life is the combined result of an individual's perception of the effect of tinnitus on their life, the perceived severity of the sensation, and the individual's coping ability. Published literature shows that QOL is adversely affected by tinnitus, and the impact is further aggravated with increased tinnitus symptom severity. Nondahl et al. (2007) used the Medical Outcomes Study (MOS) Short Form Health Survey (SF-36) to assess the relationship between tinnitus severity and QOL among participants of the EHLS. Study participants who reported "ringing or buzzing or noise" in their ears over the last year were asked the question "How severe is this noise in its worst form?" and had to rate the severity of their symptoms as "mild / moderate /severe / unknown". The SF-36

assesses function, well-being, and self-evaluation of physical and mental health, using questions on eight domains related to physical and mental health. These eight domains are further summarised into two component scales - the Physical Component Summary Scale and the Mental Component Summary Scale. Nondahl et al. (2007) reported that increased tinnitus symptom severity was associated with decreased scores in all eight domains, and the two-component scales of SF-36. Zeman et al. (2014) examined the relationship between subjective perception of tinnitus severity and QOL, using the case reports from the TRI database. They used a simple tinnitus severity question, "How much of a problem is your tinnitus?" with the corresponding response options of "no problem/ a small problem/ a moderate problem/ a big problem/ a very big problem". To assess QOL, they used 24 out of the 26 items in the WHO QOL (WHOQOL, 1997). These items assess the domains of physical health, psychological health, social relationships, and environment. This study also reported a strong correlation between tinnitus severity and QOL (Zeman et al., 2014). In a systematic review on tinnitus and HRQOL, Hall et al. (2018a) noted that apart from HRQOL, studies identified another tinnitus-related domain, namely the negative impact on activities. This domain encompassed the negative impact on all spheres of life, including social activities, work activities, individual activities, and relationships.

Tinnitus exerts a considerable burden on HRQOL. Knowledge of prevalence would help identify the relative proportion of people with tinnitus in different subgroups of the study population. This is required to assess the unmet needs for policies and legislation, allocate resources based on these unmet needs, and guide the development of strategic plans, to improve the existing situations and avert further deterioration in the health and HRQOL of people with tinnitus.

3.2.3 Financial impact of tinnitus

Tinnitus that leads an individual to seek medical advice has important economic implications. Studies conducted in different countries on healthcare resource use by people with tinnitus showed a substantially high economic burden, and this was directly related to the severity of the tinnitus symptoms (Maes et al., 2013; Goldstein et al., 2015). Details of tinnitus and healthcare resource use have been discussed in section 2.1.3.

Individuals seek medical advice from different healthcare professionals for their tinnitus symptoms (Maes et al., 2013; Stockdale et al., 2017). A multinational survey on healthcare professionals reported that while general physicians and Ear, Nose, and Throat (ENT) physicians were almost always involved in tinnitus referral and management in varying degrees, at times, a more multi-disciplinary team was involved. However, depending on the country, the specialist teams varied. For example, neurologists were engaged in tinnitus treatment in Germany, Italy, and Spain, whereas audiologists were included in the UK and the US (Hall et al., 2011). There is a lack of a definite tinnitus treatment pathway in most healthcare systems leading to repeated appointments for people with tinnitus (McFerran et al., 2018). Repeated appointments are particularly prevalent among individuals with chronic subjective tinnitus (Hall et al., 2011). Despite not being a predictor for patient satisfaction, the number of clinic visits is indeed a major factor contributing to increased tinnitus-related expenditure (Goldstein et al., 2015; Maes et al., 2013).

Further increments in tinnitus-related expenditure are caused by a lack of productivity and loss of work hours due to tinnitus symptoms. Maes et al. (2013) reported that people with tinnitus lost as many as 15.41 days of paid work, equivalent to a loss of €3704 per person (Maes et al., 2013). Therefore, tinnitus can be a costly clinical condition where massive expenditure does not necessarily ensure relief of symptoms or better health status.

3.3 Study objectives

The overarching aim of this project was to report the prevalence of tinnitus in Europe. Studying the population distribution of a condition is a critical element in understanding its epidemiology, and therefore, determining the prevalence estimate becomes particularly important. For this project, 12 countries were strategically chosen to represent the diverse socio-economic and cultural characteristics over a relatively constrained geographical area. The countries were Bulgaria, England, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania, and Spain. The overall prevalence estimate from these countries would provide a comprehensive understanding of the Pan-European prevalence of tinnitus.

The primary objective of this study was to estimate the overall and country-specific prevalence of any tinnitus, bothersome tinnitus, and severe tinnitus in the 12 aforementioned European countries.

The study data were also analysed to fulfil the following secondary objectives:

- To examine inter-country differences in the prevalence of tinnitus by making the following comparisons:
    - Comparing prevalence estimates in countries with relatively low versus high GDP per capita
    - Comparing prevalence estimates in countries within different European regions, i.e., Northern, Southern, Eastern, and Western
- To understand the effect of sex, age, socio-economic variables, BMI, and marital status on the overall prevalence of tinnitus
- To understand the effect of hearing difficulty on tinnitus and to disentangle the effects of hearing difficulty and the effects of age on tinnitus prevalence
- To explore the effect of tinnitus severity on the use of healthcare resource for tinnitus

3.4 Materials and methods

The tinnitus assessment questions and response options are provided in Chapter 2. The resultant survey, called the ETS, comprises a set of four assessment questions and response options (collectively referred to as items) on tinnitus prevalence, tinnitus severity, healthcare use in people with tinnitus, and hearing difficulty in 12 European languages. The following section illustrates the data collection and analysis methods used for this prevalence study.

3.4.1 Survey design and data collection instrument

This study was a cross-sectional population-based survey conducted between June 2017 and October 2018. The survey questions were implemented for data collection across 12 countries. An Italian market research company, DOXA, and their partners across different parts of Europe (henceforth, referred to as DOXA partners), was commissioned to carry out the data collection fieldwork (http://doxapharma.it/en/).

The four tinnitus-related items from ETS were administered with a parent survey for the TackSHS (Tackling Second-Hand Tobacco Smoke and e-cigarette emission) project (http://tackshs.eu/). The TACKSHS project was funded under the EU's Horizon 2020 research and innovation grant to improve knowledge of second-hand tobacco smoke and e-cigarette emissions and find ways to tackle the health burden caused by their exposure. At the end of the TackSHS survey, the ETS items were added as a separate section. All adults aged 18 years and above, who participated in TackSHS, were invited to participate in the ETS section and consented accordingly. Although administered concurrently, the ETS and TackSHS were managed as separate studies, but with a single joint lead (Dr. Gallus). The socio-demographic section was common to both surveys, and for this section, the same questions and response options were used for both ETS and TackSHS.

The socio-demographic section included information on sex, age, education, income, profession, height, and weight. Countries often have their unique system of classifying information related to income, education, and profession. Standard questions and responses reflecting the country-specific classification system are commonly used in population-based surveys for collecting this information. For example, Germany's standard response options for collecting data on profession, are different from the rest of the European countries. DOXA partners used country-specific survey questions and response options to collect such socio-demographic data.

3.4.2 Study population and sampling method

The target was to recruit 1000 individuals from each country, aged 18 years and above, representing the national population. The sample size for each country was calculated such that prevalence estimates with a maximum standard error lower than ±1.6% would be obtained. This sample size would give stable prevalence estimates (with a relatively small 95% confidence interval), for both overall and country-specific estimates for any tinnitus. Various sampling methods were used to derive sample populations representative of the country-specific age, sex, and habitat (geographic area, and urban/rural) distribution, as provided by the national statistical institutes or census data (Table 3.1). Although the multi-stage sampling method was preferred other methods, such as cluster, quota or stratified sampling methods, were also accepted. This was because the study was large and multiple countries were included.

Hence, sometimes it was not possible to conduct a multistage random sampling due to resource and time constraints. Table 3.2 describes the data collection details, including the dates of study and demographic data available.

Table 3.1 Sampling methods for each country

Country name(s)	Sampling method	Process of sampling
England	Cluster sampling	This involves dividing the population into subgroups, each of which have similar characteristics to the whole sample. Here instead of sampling individuals from each subgroup, entire subgroups are randomly selected.
France	Quota method	A quota of subjects of a specified type are recruited. Ideally the quotas selected proportionally represent the characteristics of the target population.
Germany, Portugal, Spain, Ireland	Stratified sampling	This involves dividing a population into smaller groups known as strata, comprising individuals with shared attributes (e.g. sex). A random sample from each stratum is taken in a number proportional to the stratum's size when compared to the population.
Bulgaria, Greece, Italy, Latvia, Poland, Romania	Multistage sampling	Multistage sampling divides large populations into stages and uses a combination of stratified sampling or cluster sampling. Simple random sampling is usually used.

Table 3.2 ETS socio-demographic data availability, response rates and sample sizes

Country	Data collected on	Response rates	Sample size	Age range (years)	Age	Sex	Schooling years	Education level	Income	Profession	Height and weight	Marital status
Bulgaria	Oct-17	65%	1007	≥18	✓	✓	✓	✓	✓	✓	✓	✓
England	Jan-18 -Feb-18	✘	1007	≥18	✓	✓	✓	✓	✓	✓	✓	✓
France	Nov-17 -Dec-17	✘	971	≥18	✓	✓	✓	✓	✓	✓	✓	✓
Germany	Jun-18	✘	912	≥18	✓	✓	✘	✓	✘	✓	✓	✓
Greece	Jun-18 -Jul-18	✘	945	18-64	✓	✓	✓	✓	✓	✓	✓	✓
Ireland	Nov-17	✘	941	≥18	✓	✓	✓	✓	✓	✓	✓	✓
Italy	Nov-17	✘	979	≥18	✓	✓	✓	✓	✓	✓	✓	✓
Latvia	Oct-18	✘	957	18-74	✓	✓	✓	✓	✓	✓	✓	✓
Poland	Sep-18	✘	766	≥18	✓	✓	✓	✓	✓	✓	✓	✓
Portugal	Nov-17 -Dec-17	59%	958	≥18	✓	✓	✓	✓	✓	✓	✓	✓
Romania	Jun-17 -Jul-17	✘	984	≥18	✓	✓	✓	✓	✓	✓	✓	✓
Spain	Oct-17	80%	1000	≥18	✓	✓	✓	✓	✓	✓	✓	✓

✘=No data provided by DOXA; ✓=data available

3.4.3 Definition of exposure variables and covariates used in the analysis

The explanatory variables in this dataset can be grouped into two categories: country level and individual level.

3.4.3.1 Exposure variables and covariates: Country level

- ***Country***

For all study participants, the country information was available. This information was used to estimate the country-specific prevalence and make inter-country comparisons.

- ***Gross domestic product (GDP) per capita***

For each country, information on GDP per capita (in Euros) was derived from the Eurostat data, 2018 (Eurostat, 2018). Most of the EU nations included in this study belonged to high income categories as per the World Bank income groups (The World Bank Group, 2020). There is no standard method available to stratify high income countries into relatively higher and lower income groups. For this analysis to derive the GDP categories, the countries were categorised into high and low GDP per capita groups relative to the median GDP per capita for the 12 countries. Here, inclusion into the low and high GDP per capita categories depended on whether the country's GDP per capita was higher or lower than the median for all 12 countries (Table 3.3).

- ***European region***

Over the years, throughout its history, the EU has expanded by the accession of new member states to the Union (EU Countries.,2020). The EU member states have been categorised into regional groups based on the classification by United Nations (UN) regional groups and geoscheme (UN regional groups, 2020; UNSD-Methodology, M49 standard, 1999): The four descriptive subgroups for European regions are represented in Table 3.3. In most cases, the UN geoscheme and UN regional groups are consistent. However, according to the UN geoscheme of Europe, Latvia is included in Northern Europe, but according to the UN regional groups, it is in Eastern Europe. Based on the socio-cultural similarities between Latvia and other Eastern European countries, Latvia was considered part of Eastern Europe for this analysis (Table 3.3).

Table 3.3 Table showing European region, GDP per capita and EU accession year for the 12 European countries

Region	Country	GDP per capita (in Euros)[a]	EU accession year
Northern	England	32,440	1973
	Ireland	57,960	1973
Southern	Greece	17,790	1981
	Italy	26,760	1957
	Portugal	18,110	1986
	Spain	24,880	1986
Eastern	Bulgaria	6,500	2007
	Latvia	12,190	2004
	Poland	12,430	2004
	Romania	8,700	2007
Western	France	32,830	1957
	Germany	35,860	1957

[a]The median GDP per capita was €21,495 (rounded to €21,500 for categorising countries by GDP per capita)).

3.4.3.2 Exposure variables and covariates: Individual level

- ***Sex***

The response options were: men and women. Men were used as the reference category for all analyses.

- ***Age***

The age range for the overall population was 18 years to 99 years and classified into descriptive subgroups. In epidemiological studies, the preferred method of age group distribution is either in 5-year bands or in mid-decade to mid-decade, 10-year age groups (United Nations (UN), 1982). In previously published studies on tinnitus prevalence, age has been distributed into 10-year age groups. Hence, the mid-decade to mid-decade age distribution was chosen for the descriptive statistics of the study data, with the following age categories (in years): 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, >/=75. Different countries have different population distributions, and it is expected that there would be an age difference in the population in the 12 selected countries. Since the sample population represents each country's actual population in terms of age, the age-related heterogeneity should be reflected in the sample. Given

the relationship of tinnitus with age, the between-country difference in age distribution could skew the prevalence estimates. A country with the higher number of older people could potentially show a greater prevalence of tinnitus, which could be an artifact of the country-specific age pattern. To check if heterogeneous age distribution is a potential contributing factor to these prevalence estimates, the proportion of younger (less than 35 years) and older (65 years or older) in the overall sample population was compared to that of the countries showing extreme values. Overall the two lower age categories (18-24 and 25-34) included very few individuals with tinnitus. Therefore, in the regression models, these two groups were combined and considered the reference category for this analysis.

- ***Socio-economic status (SES) variables***

Level of education: For the level of education, the response options for all countries except Italy were as follows: no school, primary, lower secondary, upper secondary school, and university. Since country-specific standard data collection methods for socio-demographic information were used, education levels were categorised differently for Italy.

Years of education: The participants were asked to enter the number of schooling years in integers. This information was available for all countries except Germany. For Germany, the school years were derived from the level of education data (each level was assumed to correspond to a specific number of schooling years).

Household income: Income was reported as a self-assessment of how the participants compared their household income to the country's average. The response options for household income were as follows: much lower than average, quite lower than average, on average in your country, quite higher than average, and much higher than average.

Profession: In most countries, a consistent method was used to categorise and report professions except Germany, where the country-specific profession categories were different.

There were some discrepancies in the socio-economic data available for different countries. Although the level of education categories was different for Italy, mapping them to the categorisation used by other countries was relatively straightforward.

Income information was not available for Germany, and it was not straightforward to map the data on the profession to mirror the standard categorisation used by other countries. The overall effect of income and profession on tinnitus was challenging to analyse because of incomplete and non-uniform data.

The information related to education was complete and relatively homogeneous. SES was used mainly used as a covariate for the statistical models. The ETS dataset was explored to check if either education-related variables (level of education and schooling years) could be used as a proxy of SES. The descriptive statistics for each country's level of education were explored to observe the number of participants in each of the education categories, namely no school, primary, lower secondary, upper secondary school, university (Table 3.4).

Table 3.4 Participants in each education level split by country

Country	No School (%)*	Primary (%)*	Lower Secondary (%)*	Upper Secondary (%)*	University (%)*	Total (%)
Bulgaria	1 (0.1)	6 (0.6)	81 (8.0)	525 (52.0)	394 (39.0)	**1007 (100)**
England	1 (0.1)	2 (0.2)	228 (22.5)	569 (56.4)	207 (20.6)	**1007 (100)**
France	21 (2.2)	48 (4.8)	263 (27.1)	255 (26.3)	384 (39.4)	**971 (100)**
Germany	33 (3.5)	320 (35.1)	385 (42.1)	106 (11.5)	68 (7.4)	**912 (100)**
Greece	0	61 (6.5)	186 (19.7)	319 (33.7)	377 (40.0)	**945 (100)**
Ireland	0	76 (8.1)	168 (17.8)	376 (40.0)	321 (34.0)	**941 (100)**
Italy	1 (0.1)	113 (11.5)	249 (25.4)	464 (47.5)	152 (15.5)	**979 (100)**
Latvia	2 (0.2)	68 (7.1)	107 (11.2)	476 (49.7)	304 (31.8)	**957 (100)**
Poland	0	100 (13.0)	223 (29.0)	289 (37.7)	154 (20.1)	**766 (100)**
Portugal	29 (3.0)	239 (24.9)	280 (29.2)	271 (28.3)	139 (14.5)	**958 (100)**
Romania	31 (3.2)	119 (12.1)	205 (20.8)	445 (45.1)	179 (18.2)	**984 (100)**
Spain	31 (0.3)	66 (0.7)	334 (33.4)	409 (40.9)	158 (15.8)	**1000 (100)**
Total	**150 (1.3)**	**1218 (10.6)**	**2709 (23.6)**	**4504 (39.3)**	**2837 (24.7)**	**11427 (100)**

*Row percentages are provided in parenthesis

An ideal distribution would be one where there were reasonably balanced numbers across all categories. Table 3.4 shows a skewed population distribution. For example, there are 320 people in Germany and 239 people in Portugal with primary school education, while there are six people in Bulgaria and two in England at the same level. This unequal distribution and small sample size in some cells (cell sizes) made comparisons difficult and would affect the precision of the results (Biau et al., 2008).

The population distribution for schooling years (categorised by using the same upper and lower cut-offs across all countries) was more or less similar to the population distribution for education level. Categorising schooling years' data into tertiles (any two points that divide an ordered distribution into three equal parts) provided uniform cell sizes. Other authors have adopted this data-driven solution to define categories where the population distribution of data is skewed and yields non-uniform and small cell sizes. In a previously published paper by Gallus et al. (2015), this same method of representing data as tertiles was used to describe income. For the convenience of analysis, this approach was adopted, and the data for schooling years were distributed into three categories, such that each category included approximately a third of the population sample size for the country, thereby forming three tertiles. For analysis, the first tertile was used as a reference. Schooling years was chosen as a proxy for SES.

- ***BMI***

BMI was derived from the height (in meters) and weight (in kilograms) responses in the dataset.

$$\text{BMI} = \text{Weight (in kg)} / (\text{Height in meters})^2$$

For all analyses, individual BMI values were interpreted based on the WHO classification for BMI as follows: underweight (BMI less than 18.5), normal weight (BMI between 18.5 and less than 25, overweight (BMI between 25 to less than 30) and obese (BMI equal to or greater than 30) (WHO, 2000). BMI for normal weight was the reference category.

- ***Marital status***

The categories include: married/live-in partner, divorced/separated, widowed, single. For all analyses, married was the reference category.

- ***Hearing difficulty***

Hearing difficulty was assessed using a modified version of the question from Moore et al. (2017): 'Do you currently have any difficulty with your hearing?' with the qualifying phrase 'listening to speech in a noisy situation' (details in Chapter 2 Table 2.2). Participants who responded "no difficulty" to the question "Do you currently have any other difficulty with your hearing, such as listening to speech in a noisy situation?" were included in the no hearing difficulty group, which was the reference category. Participants who chose the "yes, slight difficulty" response option were classified as having slight hearing difficulty. Participants who responded, "cannot hear at all, moderate or severe difficulty," were collectively included in the bothersome hearing difficulty group.

3.4.3.3 Outcome variables

Epidemiological studies on tinnitus commonly seek information on the prevalence of any tinnitus as well as on the prevalence of bothersome or severe tinnitus, given that the impact of mild tinnitus on an individual's life differs substantially from severe tinnitus. The ETS data included information on both tinnitus symptoms and their severity. Therefore, in this study, prevalence estimates for three different working definitions of tinnitus were estimated.

- ***Any tinnitus***

Any tinnitus prevalence was assessed using the question "Over the past year, have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time?" (see section 2.2.2). For this analysis, "any" tinnitus included the following responses to the above question "Yes, most or all of time/ Yes, a lot of the time/ Yes, some of the time," and the reference category of no tinnitus was determined by the responses to "No, not in the past year/ No, never". This same question was used in the NHIS in the US to examine tinnitus prevalence in adults

above 18 years. However, this survey used binary response options (yes/no) to estimate tinnitus prevalence (Bhatt et al., 2016; Masterson et al., 2016). Gallus et al. (2015) also used the same question and binary response options (yes/no) to estimate tinnitus prevalence in the Italian population. The ETS data's response options were grouped accordingly to make the overall and country-specific results comparable to existing literature.

- ***Bothersome tinnitus***

Bothersome tinnitus prevalence was estimated as the proportion of the sample population who responded "moderately" or "severely" to the question "Over the past year, how much do these noises in your head or ears worry, annoy or upset you when they are at their worst?". This item was adapted from the UK Biobank (see section 2.2.2). McCormack et al. (2014a) used the UK biobank question for their analysis and defined bothersome tinnitus as people who responded moderately or severely to the severity question. Dawes et al. (2014a) also used the same method to categorise the response options. Informed by previously published literature, the ETS data for bothersome tinnitus were grouped to make the overall and country-specific results comparable to existing literature.

- ***Severe tinnitus***

Severe tinnitus prevalence was estimated as the proportion of the sample population who responded severely to the question "Over the past year, how much do these noises in your head or ears worry, annoy or upset you when they are at their worst?" (see section 2.2.2). In their analysis of the NHIS data from the US in 2007, Bhatt et al. (2016) used a slightly different question where they had only bothered as an emotional descriptor (not worry or annoy). Nevertheless, the study used the "in the last 12 months" time frame. The response options for this study were: "not a problem/a small problem/moderate problem/big problem/very big problem". They grouped "big problem/very big problem" together for severity (Bhatt et al., 2016). Informed by previously published literature, severe tinnitus has been defined for the ETS analysis.

- ***Healthcare resource use for tinnitus***

No published study using a similar question and response options were available as a guide (see section 2.2.2). Therefore, the results for this variable were reported by presenting the response options in the most logical and relevant manner. People with tinnitus who responded as having one or more than one clinical visits were coded as responding "yes" for this variable. (Question: "Over the past year, have you seen your family doctor, or seen a healthcare professional at a clinic or hospital about problems with noises in your head or ears?").

3.4.4 Statistical analyses

All data exploration, management, and analyses were performed using SAS software, Version 9 of the SAS Institute Inc., Cary, North Carolina, US.

3.4.4.1 Missing data

Before carrying out the analysis, the data was explored to look for missing data and inter-country variation in data. In the final dataset, for most of the variables (except SES; see section 3.4.3.2), there was equivalence in the way data was collected in different countries. Response options "do not know/prefer not to answer" along with skipped, invalid, and missing responses were classified as missing data. Since the total percentage of missing data was less than 10%, it was well within an acceptable range to not affect the final results (Bennett, 2001). Therefore, no additional statistical method was used to address this issue.

3.4.4.2 Statistical weights

Since this data had individual and country-level components, it was important that the sample population was representative of the country demographics and that the different population sizes of the included countries were taken into account. Hence two types of statistical weights were used for the analysis.

It is ideal to have representative samples that reflect the target population's demographics for calculating prevalence estimates. Although in this study, the intention was to have a sample representative of the country-specific demographics in terms of sex, age, and geographic area, sometimes it was not possible to include in each

category exactly similar proportions of individuals as the target population. The DOXA partners provided individual statistical weights for survey participants when there was a difference between the sample population and target country population to maintain the representativeness of the sample. Thus, the final prevalence estimates obtained were not affected by this issue.

Additionally, since this is a multinational analysis, country populations needed to be represented in proportion to their actual population size aged 18 years and above. Without this weighting, there would be the risk of over-representation of countries with smaller population sizes or under-representation of countries with a larger population. Therefore, an additional country-specific statistical weight was introduced when analysing the overall data for all countries. For each country, the country weights were computed by multiplying the inverse of country-specific sampling probability to the proportion of the total target population contributed by the specific country's sample. The country population was derived from Eurostat, 2017 data (Eurostat, 2017).

3.4.4.3 Data analysis plan

Descriptive statistics were reported as absolute numbers and proportions. Weighted prevalence estimates were calculated using individual and country weights and reported for any, bothersome and severe tinnitus. Weighted percentages were also estimated for socio-demographic characteristics, country characteristics, healthcare resource use, and hearing difficulty in subjects with tinnitus. The 12 EU countries included in this study represented the socio-demographic, geographical, legislative and cultural variations within the EU. Moreover, the selection included the seven most populated EU member states (Germany, Spain, France, Italy, United Kingdom, Poland, Romania), and, among less populated countries, middle-income countries were prioritized (Bulgaria, Romania). Overall, the 12 selected countries represented approximately 80% of the EU28 population. Hence the prevalence results from this study could provide reasonable estimates of Pan-European prevalence and the results were extrapolated on to the overall EU population to derive the Pan-European prevalence.

Since the dataset has two data levels, namely the individual and country-level, a multilevel logistic regression model was first tested (Model 1). In model 1, ORs and the

corresponding 95% CIs were estimated using random-effects models considering the heterogeneity between the 12 countries. Country effects were considered as random intercepts and sex, age, and education level as adjusting variables. Note that the GDP and geographic region data were determined from the UN and World bank sites, using the country information available. Consequently, having the country as a random intercept in the multilevel model could arguably mask the effect of GDP and geographic region.

Given that the number of countries was less and the within country sample size not very large (approximately 1000), an unconditional multiple logistic regression model was also tested (Model 2) to check if there was a difference in results between the two models. In model 2, country, GDP, and geographic region were kept in the same analysis level as the individual-level variables. The two models provided very similar results. Therefore, it was assumed that using the complex multilevel model (model 1) did not provide any additional benefits. Model 2, the unconditional multivariate logistic regression model, was chosen as the final model adjusting for sex, age, and level of education. Given the inter-relationship between age, hearing difficulty, and tinnitus, the final model, was modified to include hearing difficulty as a covariate to examine the effect of age on tinnitus when adjusted for hearing difficulty.

3.5 Results and interpretations

This section presents the ETS results and compares it to findings from published literature, where information is available.

3.5.1 Primary objective: To assess the overall and country specific prevalence of any tinnitus, bothersome tinnitus, and severe tinnitus

3.5.1.1 Any tinnitus

The overall prevalence of any tinnitus was 14.7% across Europe. This prevalence estimate (14.7%) falls within the expected 10% to 15% range (Baguley et al., 2013). When this prevalence estimate was plotted along with previous epidemiological studies, it corresponded approximately to the median value of the published estimates (Figure 3.2). Moreover, the studies that used the same question for estimating any tinnitus (“Over the past year, have you had noises (such as ringing or buzzing) in your

head or in one or both ears that lasts for more than five minutes at a time?") had reasonably similar results to the ETS (Bhatt et al., 2016; Xu et al., 2011). The slight difference in prevalence estimates seems to be within reasonable limits and potentially a reflection of inherent differences in population characteristics of various countries. The studies that used the one-year time frame but did not include the "lasting for 5 minutes" qualifier for tinnitus showed similar estimates to each other, although this was much above the median for most published data and the ETS estimate (Kim et al., 2015; Spankovich et al., 2017).

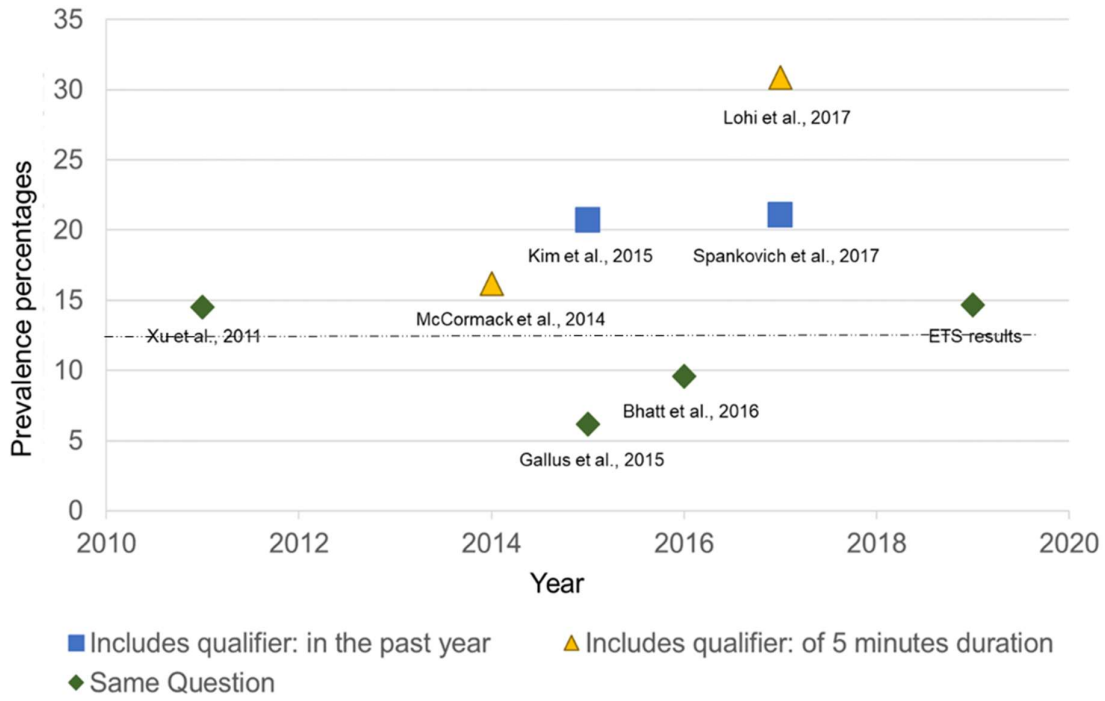


Figure 3.2 Comparison with previous studies using similar research definition for any tinnitus. Dotted line implies median of the expected 10% to 15% prevalence.

On the other hand, the studies that did not use the time frame of the last one year but included the "lasting for 5 minutes" qualifier for tinnitus showed wide variability in prevalence estimates (McCormack et al., 2014; Lohi et al., 2017) (Figure 3.2). Tinnitus assessment questions including both the time-period, i.e., "over the last one year" and duration, i.e., "lasting for 5 minutes", reported results that were within the predicted range (10% to 15%), confirming the accuracy and with consistent findings on repeated measurements across various studies, confirming the precision. Therefore, this

research definition for tinnitus seems to produce relatively accurate and precise prevalence estimates.

Figure 3.3 (A) shows a colour gradient map for the country-specific prevalence of any tinnitus, where gradually increasing colour darkness represents increasing tinnitus prevalence. The prevalence estimates ranged from 8.7% in Ireland to 28.3% in Bulgaria. This study is the first attempt to analyse multinational data to estimate Pan-European tinnitus prevalence, and so there is no comparable evidence in published literature. Nonetheless, some country-specific prevalence estimates are available of any tinnitus from studies conducted in nationally representative populations.

The MRC National Study of Hearing, which analysed data from England, Scotland, and Wales, used three working definitions for tinnitus. Tinnitus was assessed in the National Study of Hearing using the question “Nowadays do you get noises in your head or ears” and was further qualified by asking whether it lasted for five minutes and whether or not preceded by a loud noise. Prolonged spontaneous tinnitus, defined as tinnitus lasting for 5 minutes and not only preceded by loud noise, was reported to have a prevalence of 10.1%. In indeterminate tinnitus type individuals had tinnitus but did not respond to the two other qualifiers, and the rest, classified as having non- prolonged spontaneous tinnitus, had a mean prevalence of 26% (Akeroyd et al., 2019). In the ETS dataset, the prevalence of any tinnitus in England was 15.3%. Given that the National Study of Hearing inquired if the respondents had tinnitus nowadays, they could estimate point prevalence while ETS measured period prevalence. Like most chronic conditions, tinnitus symptoms are often intermittent with some tinnitus-free intervals. Therefore, point prevalence estimates could potentially fail to capture the affected individuals having a symptom-free interval phase. This could be a possible explanation of the lower prevalence estimates for prolonged spontaneous tinnitus as described in the National Study of Hearing compared to the ETS estimates.

On the other hand, given the definition, the non-prolonged spontaneous tinnitus estimates could include tinnitus lasting for less than 5 minutes (excluding “the lasting for 5 minutes” component) or respondents having tinnitus only after exposure to loud noise. This might explain the higher prevalence of non-prolonged spontaneous tinnitus in the National Study of Hearing analyses than ETS. As per ETS, the prevalence estimate for any tinnitus in England lies between the two prevalence estimates given

by the National Study of Hearing. There is an acceptable explanation of how the two definitions in the National Study of Hearing capture more and fewer individuals with tinnitus than ETS. The UK Biobank question on tinnitus prevalence was the provenance for the ETS tinnitus prevalence question and response options. McCormack et al. (2014a) analysed the UK Biobank data and reported tinnitus prevalence to be 16% among 45 to 60-year-olds in the UK. Although these results are very close to the ETS prevalence estimates, given the specific age range for the UK Biobank data, it is not ideal to compare the two results.

Gallus et al. (2015) estimated the prevalence of any tinnitus in Italy to be 6.4% using the same question as ETS . This value is almost half the prevalence for Italy, as estimated by analysing the ETS data (13.6%). A potential cause of this large difference could be a misinterpretation of the meaning of tinnitus. The ETS survey questions were preceded by an explanation for the definition of tinnitus, which was not provided in the Gallus et al. (2015) study. Defining the condition could potentially help the participants understand the question and response options, therefore, providing a more accurate estimation of prevalence.

For understanding how the country of origin affects the risk of having tinnitus, Italy has been used as the reference for calculating the country-specific OR, using unconditional multiple logistic regression models, adjusting for sex, age, and years of education. As shown in Table 3.5, for all three definitions of tinnitus, the percent prevalence in Italy was somewhat in the middle of the range. The reference was chosen to recognise the countries showing extreme values and for better data visualisation. Eastern European countries like Bulgaria, Latvia, Poland, and Romania had significantly higher odds ratios, while Ireland had the lowest odds ratios. However, despite a similar geographical location to Ireland, England had higher odds for any tinnitus (Table 3.5).

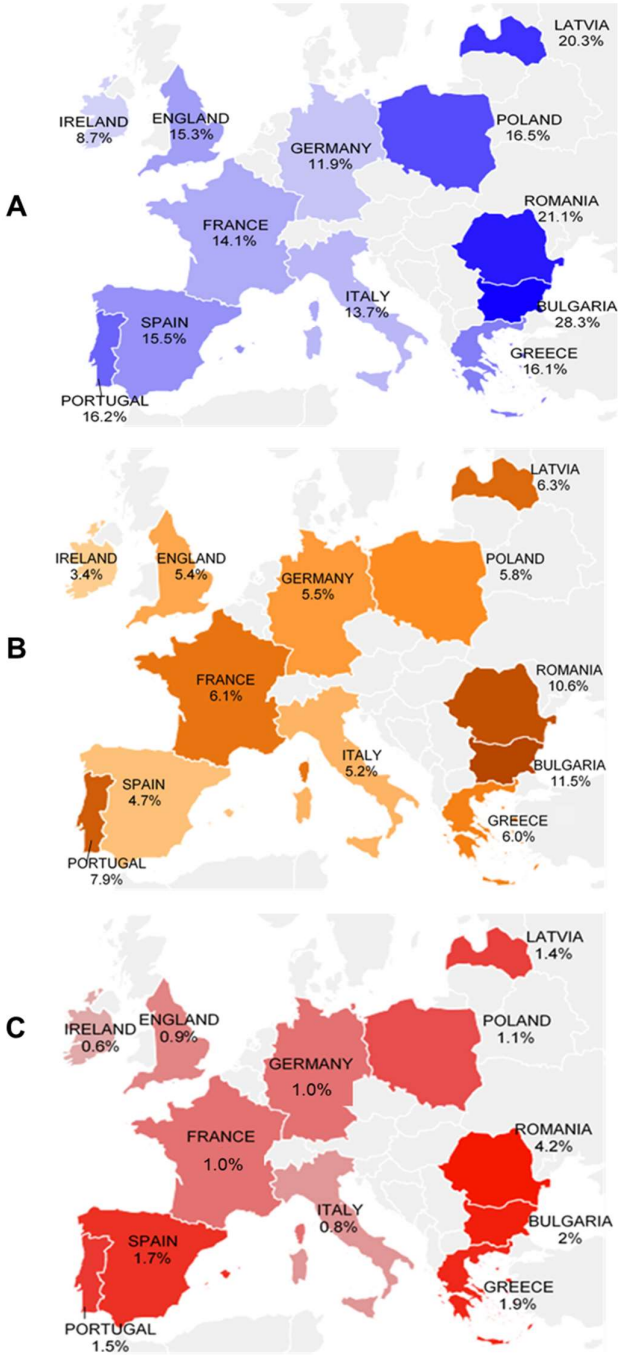


Figure 3.3 Colour gradient map of prevalence of "any" (A), "bothersome" (B) and "severe" (C) tinnitus across 12 European countries. Darker colour implies higher prevalence.

Table 3.5 Country-specific ORs of any tinnitus, bothersome tinnitus, and severe tinnitus

Country	Total sample size of population	Any Tinnitus OR (95% CI)[a]	Bothersome Tinnitus OR (95% CI)[a]	Severe Tinnitus OR (95% CI)[a]
Bulgaria	1007	**2.9(2.0-4.1)**	**2.8 (1.7-4.6)**	**3.0 (1.02-9.4)**
England	1007	**1.5(1.2-1.8)**	**1.4 (1.1-2.0)**	1.6 (0.8-3.3)
France	971	1.2 (1.0-1.5)	**1.4 (1.1-1.9)**	1.5 (0.8-3.2)
Germany	912	0.9 (0.7-1.0)	1.1 (0.8-1.5)	1.3 (0.6-2.5)
Greece*	945	1.3 (0.9-1.9)	**2.0 (1.2-3.5)**	3.1 (1.0-9.5)
Ireland	941	0.7 (0.4-1.4)	0.9 (0.3-2.5)	1.1 (0.1-11.8)
Italy	979	Ref	Ref	Ref
Latvia§	957	2.0 (1.0-4.1)	1.5 (0.5-4.9)	2.4 (0.2-26.2)
Poland	766	**1.5 (1.2-1.9)**	1.3 (0.9-1.9)	1.8 (0.8-4.0)
Portugal	958	1.3 (0.9-1.8)	1.6 (1.0-2.6)	2.0 (0.6-5.9)
Romania	984	**1.9 (1.4-2.4)**	**2.4 (1.7-3.5)**	**6.5 (3.3-13.1)**
Spain	1000	1.3 (1.0-1.6)	1.0 (0.7-1.4)	**2.2 (1.1-4.6)**

Ref=Reference category
[a]ORs and the corresponding 95% CIs were estimated using unconditional multiple logistic regression adjusting for sex, age and level of education.
Statistically significant ORs are in bold.

3.5.1.2 Bothersome tinnitus

Bothersome tinnitus was found in 6.0% of the overall population. The highest country-specific prevalence of bothersome tinnitus was 11.5% in Bulgaria, and the least prevalence was 3.4% in Ireland (Figure 3.3 B). There are no available data on the Pan-European prevalence of bothersome tinnitus, and among the 12 European countries included in this analysis, previously published information on bothersome tinnitus is available only for the UK. McCormack et al. (2014a) used the UK biobank question for their analysis and defined bothersome tinnitus as people who responded moderately or severely to the severity question. The prevalence of bothersome tinnitus in the UK Biobank was 3.8%, while in the ETS data, it was 5.4%. There could be a couple of factors responsible for this difference:

- The question itself was slightly different considering, unlike the UK biobank, the ETS included “last 12 months” as a qualifying time frame.
- The UK Biobank includes participants between 45 to 60 years of age.

- In the UK biobank, the severity question was asked to participants who responded yes to the question “Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that lasts for more than five minutes at a time?”, and also categorised their symptoms as current tinnitus by selecting any of the following response options “Yes, now most or all of the time’, ‘Yes, now a lot of the time’ or ‘Yes, now some of the time”.

Given that the UK biobank first asked if the respondents had tinnitus now, they could estimate point prevalence. Point prevalence estimates could fail to capture people with tinnitus who have a symptom-free interval phase, leading to underestimation. On the other hand, ETS measured period prevalence by including the phrase over the past year in the question, and therefore also included people currently in a tinnitus-free interval phase.

The country-specific ORs (Table 3.5) showed Eastern European countries like Bulgaria, Latvia, Poland, and Romania had significantly higher OR, while Ireland had the lowest OR. Even for bothersome tinnitus, England had higher OR compared to Ireland, despite similar geographical regions. The Southern European countries, i.e., Greece, Portugal, and Spain, had relatively similar estimates to Italy. A higher OR indicates an increased likelihood of tinnitus. For example, the population from Bulgaria has a 2.8 times more likelihood of having bothersome tinnitus than the population from Italy. Despite individual country-specific variations, the overall pattern indicates that Eastern European countries have an increased likelihood of having bothersome tinnitus than other European regions.

3.5.1.3 Severe tinnitus

Overall severe tinnitus was found in 1.2% of participants, which is five times fewer than bothersome tinnitus and 12 times fewer than any tinnitus (Figure 3.3 C). Since no studies report Pan-European prevalence of severe tinnitus, the only available option was to compare country-specific prevalence estimates to published data and assess the differences or similarities in results.

As shown in Figure 3.3C, the prevalence of severe tinnitus ranged from 0.6% in Ireland to 4.2% in Romania. This was the only variable for which Bulgaria did not have the highest prevalence. However, Eastern European countries still showed much higher

estimates than the rest of Europe. Gallus et al. (2015) estimated the prevalence of severe tinnitus in Italy using the same question and response options as ETS and reported it to be 1%. Unlike the prevalence estimate for any tinnitus, the ETS 0.8% prevalence of severe tinnitus in Italy was very close to the prevalence reported by Gallus et al. (2015). A possible explanation for the consistency in results could be the use of the same assessment question. However, this explanation does not hold in case of any tinnitus prevalence. Therefore, even though it is reassuring to have results similar to that found in published literature, it is difficult to explain why Italy's prevalence estimates do not remain consistently aligned between ETS and a published study using the same question.

As reported in Table 3.5, the ORs for countries were adjusted for age, sex, and level of education, and Italy was the reference category. Romania, having the highest prevalence, had the highest OR for severe tinnitus (OR=6.4; 95% CI 3.3,13.1), and the OR was significant, meaning the odds are significantly higher than the reference prevalence estimates. Interestingly, Spain had significantly higher OR (OR= 2.2, 95% CI 1.1,4.6) than Italy, despite the similar socio-demographic and regional characteristics of Southern European countries and the relatively similar prevalence of any tinnitus. Although Latvia had an OR of 2.4, it was not significant as the 95% CI ranged from 0.2 to 26.2 (the CI included 1). This wide range of 95% CI reduces the precision of the OR.

The overall population in the EU is 514 million with approximately 85% aged 18 years and above (Eurostat, 2021). This means approximately 65 million in the EU28 (including UK) report any tinnitus, 26 million report bothersome tinnitus and 4.4 million report severe tinnitus. There are substantial numbers of people affected by tinnitus. The likelihood of having tinnitus is similar in seven out of the 12 countries, given that six of the countries and the reference level Italy did not have significantly different prevalence estimates. However, some countries, namely Bulgaria, Romania, and England, had a significantly higher likelihood of tinnitus than the reference level.

While the overall prevalence of tinnitus is within the expected range, there are vast inter-country differences. It was noted that some countries like Bulgaria and Romania had consistently higher prevalence across all estimates when compared to the rest of the countries, while Ireland had a much lower prevalence percentage. This difference

in estimates could not be attributed to country-specific population distribution of younger or older people, since the proportion of people in the highest and lowest age brackets in countries with extreme values was similar to the overall population (Table 3.6).

For some countries, the results from ETS analyses were comparable to previously published data. However, for other countries like Bulgaria, Romania, and Latvia with a very high prevalence of tinnitus, no previous epidemiological prevalence studies were available. Therefore, there was no way to compare and validate the results of this analysis.

Table 3.6 Age distribution in overall population and countries with highest and lowest prevalence estimates

		Age groups in years (number (N) and proportions (%))					
		18-34		35-64		>/=65	
		N	%	N	%	N	%
Highest prevalence	Bulgaria	483	47.96	353	35.05	171	16.98
	Romania	463	47.05	369	37.50	152	15.45
Lowest prevalence	Ireland	420	44.63	359	38.15	162	17.22
Overall Population distribution by age		5130	44.89	4267	37.34	2030	17.76

3.5.2 Secondary objectives

3.5.2.1 To understand the inter-country differences in tinnitus prevalence of tinnitus by investigating the effect of GDP per capita and European region

Comparing country groups by GDP per capita, it was found that lower GDP per capita was associated with significantly increased odds and prevalence for all three definitions of tinnitus (Table 3.7). This means that countries with higher GDP per capita are at a lesser risk for tinnitus than countries with lower GDP per capita. Several factors could be responsible for this. Countries with higher GDP per capita are usually the higher income countries and spend more on healthcare than ones with lower GDP per capita. Thus it can be assumed that higher GDP per capita could lead to better access to care, better treatment options, and thereby prevent aggravation of tinnitus symptoms. For

example, England and France are two countries with a high GDP per capita, and those values are quite close. They also show a relatively similar percentage in healthcare resource use for tinnitus (see later, Figure 3.5) and comparatively lower prevalence estimates than countries like Bulgaria, which have lower GDP per capita (Figure 3.3).

Exposure to occupational health hazards like industrial noise exposure increases tinnitus risk. Europe has always had a vital role in the field of occupational health and safety. The EU policy framework directive on occupational health and safety has positively impacted the assessment and management of occupational risk factors and has set common standards across the EU (Gagliardi et al., 2012). Eastern European countries with lower GDP per capita were accessed to the EU much later, in the 2000s (EU 2020). Consequently, they came under the EU legislation, including those for occupational safety, much later. It is possible that the regulations in these countries were not as strict and regularised before EU accession, resulting in exposures that predisposed their nationals to tinnitus.

There is not much evidence to explain why GDP per capita of a country might affect the prevalence of tinnitus and little corroborating evidence. More studies are needed to explore the relationship between tinnitus prevalence in a country and its GDP per capita to strengthen this evidence.

Table 3.7. Percent prevalence, and OR and 95% CIs of any tinnitus, bothersome tinnitus, and severe tinnitus based on country level variables

	Number of subjects	Any tinnitus (%)[a]	Any tinnitus (OR[d] and 95% CI)	Bothersome tinnitus (%)[a]	Bothersome tinnitus (OR[d] and 95% CI)	Severe tinnitus (%)[a]	Severe tinnitus (OR[d] and 95% CI)
Based on GDP per capita[b]							
Higher than median	5617	13.5	Ref	5.4	Ref	0.9	Ref
Lower than median	5810	17.1	**1.38 (1.23-1.54)**	6.6	**1.26 (1.06-1.48)**	1.8	**2.07 (1.48-2.90)**
Based on Geographic region[c]							
Eastern	3714	19.2	1.22 (0.88-1.68)	8.8	1.27 (0.82-1.98)	2.4	1.88 (0.82-4.33)
Western	1883	12.5	**0.69 (0.52-0.92)**	5.7	0.88 (0.60-1.31)	1.1	0.93 (0.43-2.01)
Northern	1948	15.3	Ref	5.4	Ref	0.9	Ref
Southern	3882	14.3	0.79 (0.59-1.05)	5.2	0.80 (0.54-1.20)	1.3	1.08 (0.50-2.35)

Ref=Reference category

[a] Country weight was applied, which combines individual weight with an additional weighting factor, with each country contributing in proportion to its population aged 18 years and above.

[b]GDP per capita in Euros was used from Eurostat data 2018. Low and high GDP per capita imply if GDP per capita is higher or lower than the median for the 12 European countries.

[c]The European country regions were based on the classification by UN regional groups.

[d] ORs and the corresponding 95% CIs were estimated using unconditional multiple logistic regression adjusting for sex, age and level of education.

Statistically significant ORs are in bold.

This study is the first of its kind that looked at multinational prevalence estimates of tinnitus using the same set of standardised questions. Although some individual country-specific differences in prevalence estimates were noted, there was no significant difference in the tinnitus prevalence in different geographic regions in Europe, except forthe Western European countries that had less prevalence of any tinnitus compared to Northern Europe. This could be attributed to the relatively low prevalence estimates in France and Germany compared to the other European countries. In summary, the country-specific estimates of tinnitus prevalence in the EU are diverse, with the Eastern European countries having a relatively higher prevalence than the rest of the EU.

3.5.2.2 To understand the effect of sex, age, SES, BMI and marital status on tinnitus prevalence

Table 3.8 reports the descriptive characteristics of the study population, including the distribution of hearing difficulty. The OR, adjusted for sex, age, and years of education, of the socio-demographic variables, are reported in Table 3.9.

- ***Effect of sex***

The overall prevalence of any tinnitus in men was 14.0% and in women at 15.2%. For bothersome tinnitus, it was 5.1% in men and 6.8% in women, and for severe tinnitus, it was 1.1% in men and 1.6% in women (Table 3.8). Difference between prevalence in men and women were noted for all three definitions of tinnitus. However, the difference was significant only for bothersome tinnitus with an OR of 1.26 (95% CI: 1.07-1.48) in women compared to men (Table 3.9). Therefore, the results show inconsistent sex differences across the three definitions of tinnitus.

- ***Effect of age***

With increasing age, the prevalence of any, bothersome and severe tinnitus increased. The p for trends was highly significant. The percent prevalence was approximately six times higher in the oldest age group (≥ 75 years) compared to the youngest (18-24 years) for any tinnitus, 13 times higher for bothersome tinnitus, and 20 times higher for severe tinnitus (Table 3.8). The OR for almost all age groups was significantly higher

than the reference category, which included the two lowest age categories (18-34 years). The only exception was severe tinnitus, where the 35-44 years' age group (OR: 2.04; 95% CI: 0.90-4.65) did not have significantly different odds compared to the reference category (Table 3.9).

ETS results were similar to the published literature where an increase in tinnitus prevalence and subjective severity is reported with an increase in age (Bhatt et al., 2016; Gallus et al., 2015; Nondahl et al., 2011). However, Shargorodsky et al. (2010) showed a peak prevalence of tinnitus in the 60 to 69 years' age group. In this analysis, the prevalence of tinnitus showed an increasing trend with age. Even the OR adjusted for sex and level of education followed the same increasing pattern. The increase was quite steep across all variables. For example, for any tinnitus OR was 1.48 in 35 to 44-year-olds and 5.68 in 75 years and older-when compared to 18 to 34-year-olds; for bothersome tinnitus OR was 2.04 in 35-44 years and 9.20 in 75 years and older individuals, and for severe tinnitus OR was 2.04 in 35 to 44-year-olds and 11.86 in 75-year-olds and older.

- ***Effect of education***

The level of education was categorised as tertiles. Individuals in the first tertile (low level of education) for the level of education reported a 19.5% prevalence of any tinnitus; for the second (intermediate level of education) tertile, the prevalence was 11.4% and 12.0% for the third tertile (high level of education). The prevalence of bothersome tinnitus was 9.8% in the first tertile and 3.7% in the second tertile and the third tertile. The prevalence of severe tinnitus was 1.8% in the first tertile and 1.0% in the second tertile and the third tertile (Table 3.8). The p for trends was <0.001, which indicates that more schooling years (which meant inclusion in a higher tertile for the level of education) showed lesser prevalence of any, bothersome and severe tinnitus. The odds of having any and bothersome tinnitus significantly decreased in the second and third tertile, compared to the first tertile, i.e., the reference category. For severe tinnitus, the level of education did not show any significant change in prevalence (Table 3.9).

Table 3.8 Prevalence estimates for any tinnitus, bothersome tinnitus, and severe tinnitus overall and according to selected individual-level and country-specific characteristics. Europe, 2017-2018

	Number of subjects	Any tinnitus (%)[a]	Bothersome tinnitus (%)[a]	Severe tinnitus (%)[a]
Total	11427	14.7	6.0	1.2
Sex				
Men	5404	14.0	5.0	1.0
Women	6023	15.2	6.6	1.4
Age groups				
18-24	1050	5.3	1.3	0.2
25-34	1885	8.5	2.0	0.4
35-44	2195	10.0	3.7	0.7
45-54	2275	13.3	5.8	1.4
55-64	1992	18.1	7.0	1.3
65-74	1482	26.3	11.8	2.7
>=75	548	30.4	16.7	4.0
Education				
Low level	4036	19.5	9.8	1.8
Intermediate level	4184	11.4	3.7	1.0
High level	3204	12.0	3.7	1.0
Missing	3			
BMI				
Underweight	277	10.2	2.1	0.1
Normal	4947	12.4	5.0	1.1
Overweight	3810	16.7	6.8	1.3
Obese	1597	18.2	8.3	2.3
Missing	796			
Marital status				
Married or cohabitant	6499	14.5	5.7	1.0
Divorced	1483	16.3	7.4	1.8
Widowed	861	26.6	15.4	4.4
Single	2584	10.2	3.0	0.8

[a]Country weight was applied, which combines individual weight with an additional weighting factor, with each country contributing in proportion to its population aged 18 years and above.

The level of education (given by the number of schooling years) was used as a proxy for SES, and the primary purpose was using it as a covariate in regression models. In the published literature, evidence for the effect of SES on tinnitus is inconsistent. Shargorodsky et al. (2010) reported higher education associated with lower tinnitus prevalence. Martinez et al. (2015) reported that the higher SES population also had a greater incidence of clinically significant tinnitus, defined as tinnitus with a diagnosed ICD 10 code, and would require more access to care. The ETS results reported contradictory trends to Martinez et al. (2015). Several factors like increased awareness, less occupational exposure to noise due to the job profile and better healthcare access could be potential causes.

- ***Effect of BMI***

The percent prevalence of any tinnitus was 12.4%, bothersome tinnitus 5.0%, and severe tinnitus 1.1% in individuals with normal BMI. This prevalence estimate was higher than underweight individuals who had 10.2%, 2.1%, and 0.1% prevalence of any, bothersome and severe tinnitus, respectively. Overweight individuals reported prevalence of 16.7%, 6.8%, and 1.3%, and obese individuals reported 18.2%, 8.3%, and 2.3% prevalence of any, bothersome and severe tinnitus, respectively (Table 3.8). The p for trends were also significant for all three definitions of tinnitus. The ORs were borderline significant for overweight (OR: 1.17; 95% CI: 1.03-1.32) and obese (OR: 1.17; 95% CI: 0.98-1.38) individuals for any tinnitus. However, despite the increasing trends, the odds of having tinnitus was not significantly different between the different BMI categories.

- ***Effect of marital status***

Widows had the highest percent prevalence of any (26.6%), bothersome (15.4%), and severe (4.4%) tinnitus. On the other hand, single individuals had the lowest percent prevalence, with 10.2% reporting any, 3.0% bothersome, and 0.8% severe tinnitus (Table 3.8). Despite varying prevalence percentages, once adjusted for age, sex, and years of education, there was no difference in prevalence depending on marital status. There was no significant relationship of marital status with tinnitus, except for widows who reported having significantly greater odds of severe tinnitus (OR: 2.18; 95% CI: 1.32-3.59) compared to the married individuals- the reference category (Table 3.9).

This could be due to the underlying relationship between age and marital status. Older people are more likely to be widowed and are also more likely to have tinnitus. On the other hand, younger people are more likely to be single and less likely to have tinnitus. The higher prevalence in widows could be due to higher age, which is taken into account in the adjusted estimates.

Nonetheless, widows did show an increased prevalence of severe tinnitus. A possible explanation could be stress related to marital status. Stress levels and depression are often related to tinnitus (Zeman et al., 2014; Probst et al., 2016). These stressors could be related to the widowed status, which is not a choice unlike other marital groups, and therefore, could predispose to tinnitus. However, the ETS dataset did not have enough information to form conclusive opinions in this regard.

3.5.2.3 To understand the effect of hearing difficulty on tinnitus and to disentangle the effect of age and effect of hearing difficulty

- ***Hearing difficulty and tinnitus***

The prevalence for any tinnitus was 6.5% in individuals with no hearing difficulty, which increased almost ten-fold for individuals with at least moderate hearing difficulty (58.7% individuals with moderate hearing difficulty had tinnitus). For both bothersome and severe tinnitus, the prevalence increased over twenty times in individuals with moderate hearing difficulty than those with no hearing difficulty (Table 3.10).

For regression models, individuals in moderate, severe, and cannot hear at all categories were considered together as having bothersome hearing difficulty. The odds for any, bothersome and severe tinnitus variables significantly increased with increased hearing difficulty (Table 3.11). The likelihood of having any tinnitus was 7.7 times more in those with slight hearing difficulty and 18.5 times more in those with bothersome hearing difficulty than the reference category, i.e., no hearing difficulty. For bothersome tinnitus, the likelihood was 6.3 times more in those with slight hearing difficulty and 33.2 times more in those with bothersome hearing difficulty than the reference category. Therefore, an increasing trend was noted for increasing hearing difficulty associated with a higher reported prevalence of tinnitus, noted for all tinnitus definitions ($p<0.001$) (Table 3.11).

Table 3.9 Odd ratios and corresponding 95% CIs for tinnitus according to selected individual-level characteristics. Europe 2017-2018.

	Numbers	Any tinnitus OR[a] (95% CI)	Bothersome tinnitus OR[a] (95% CI)	Severe tinnitus OR[a] (95% CI)
Sex				
Men	5404	Ref	Ref	Ref
Women	6023	1.03 (0.93-1.15)	**1.26 (1.07-1.48)**	1.36 (0.97-1.92)
Age groups				
18-34	2935	Ref	Ref	Ref
35-44	2195	**1.42 (1.17-1.74)**	**2.22 (1.54-3.21)**	2.04 (0.90-4.65)
45-54	2275	**2.05 (1.70-2.47)**	**3.62 (2.58-5.08)**	**4.26 (2.05-8.86)**
55-64	1992	**2.74 (2.28-3.31)**	**3.85 (2.73-5.42)**	**3.73 (1.74-7.99)**
65-74	1482	**4.57 (3.77-5.54)**	**6.83 (4.87-9.58)**	**7.49 (3.59-15.63)**
>=75	548	**5.68 (4.53-7.11)**	**9.20 (6.40-13.23)**	**11.86 (5.48-25.67)**
p for trend		**<0.001**	**<0.001**	**<0.001**
Education[o]				
First tertile	4036	Ref	Ref	Ref
Second tertile	4184	**0.80 (0.70-0.91)**	**0.53 (0.43-0.65)**	0.91 (0.60-1.39)
Third tertile	3204	**0.81 (0.70-0.94)**	**0.57 (0.46-0.72)**	0.82 (0.51-1.32)
p for trend		**<0.001**	**<0.001**	**<0.001**
BMI[o]				
Underweight	277	0.93 (0.63-1.37)	0.51 (0.23-1.14)	0.11 (0.00-4.12)
Normal	4947	Ref	Ref	Ref
Overweight	3810	1.17 (1.03-1.32)	1.09 (0.91-1.32)	0.95 (0.64-1.40)
Obese	1597	1.17 (0.98-1.38)	1.20 (0.95-1.53)	1.44 (0.91-2.29)
p for trend		**<0.001**	**<0.001**	**0.02**
Marital status				
Married or cohabitant	6499	Ref	Ref	Ref
Divorced	1483	0.88 (0.75-1.04)	0.98 (0.78-1.24)	1.30 (0.80-2.11)
Widowed	861	1.07 (0.87-1.31)	1.28 (0.98-1.66)	**2.18 (1.32-3.59)**
Single	2584	0.97 (0.83-1.15)	0.81 (0.62-1.06)	1.35 (0.78-2.31)

Ref= Reference category
[a]ORs and the corresponding 95% Cis were estimated using unconditional multiple logistic regression adjusting for sex, age and level of education.
Statistically significant ORs are in bold.

The results from ETS analysis corroborates with the previous finding from other studies. Multiple studies have reported hearing difficulty to be a major risk factor for tinnitus (Davis and Rafaie, 2000; Sindhusake et al., 2003, Sindhusake et al., 2004; Michikawa et al., 2010, Baguley et al., 2013). Moore et al. (2017) used a very similar question and response options to ETS, which was: "Do you currently have any difficulty with your hearing?" with response options being "no difficulty/slight difficulty/ moderate difficulty/ great difficulty/ cannot hear at all". They found a strong positive correlation (r=0.3) between tinnitus and hearing difficulty.

Table 3.10 Prevalence estimates for any tinnitus, bothersome tinnitus, and severe tinnitus overall and according to hearing difficulty categories. Europe, 2017-2018

	Number of subjects	Any tinnitus[b] (%)	Bothersome Tinnitus[b] (%)	Severe Tinnitus[b] (%)
Total	11427	14.7	6.0	1.2
Hearing difficulty[a]				
No difficulty	8839	6.5	1.7	0.3
Slight difficulty	1451	39.0	12.1	2.1
Moderate	725	58.7	38.6	7.7
Severe difficulty	190	67.3	50.5	16.9
Cannot hear at all	16	55.2	49.0	43.3

[a]The numbers for hearing difficulty do not add up to the total because of missing values.
[b]Country weight was applied, which combines individual weight with an additional weighting factor, with each country contributing in proportion to its population aged 18 years and above.

- ***Age, hearing difficulty and tinnitus***

Hearing difficulty is known to increase as people age, so these two variables are strongly correlated (Cruickshanks et al., 1998; Davis et al., 2016; Lin et al., 2011). Hearing difficulty is also a well-established risk factor for tinnitus (Nondahl et al., 2010). The results from the ETS analyses corroborate these findings and show that tinnitus increases both with increasing age and increasing hearing difficulty (Table 3.8 and Table 3.10). Therefore, to disentangle the relationship between age, hearing difficulty, and tinnitus, it would be worthwhile to examine the effect of age on tinnitus after adjusting for hearing difficulty.

Table 3.9 reports the effect of age on tinnitus and shows increasing odds of tinnitus with increasing age when adjusted for sex and level of education. After adjusting for hearing difficulty in the regression models for any, bothersome and severe tinnitus, the ORs for age groups are reported in Appendix X.

In Figure 3.4, the ORs for any, bothersome and severe tinnitus at each age group are plotted-both adjusted and unadjusted for hearing difficulty. The two sets of plots consistently show the same pattern. Age is strongly associated with a rise in tinnitus prevalence. However, once the variance associated with hearing difficulty is accounted for in the model, the effect of age is much diminished, i.e., the difference in the bars' height becomes a lot less, effectively countering the apparent effect of age. Therefore, the effect of age on tinnitus is more pronounced when hearing difficulty is not accounted for in the model. Even though this interaction is expected, it highlights the need for careful interpretation of the data so that the effect of age is not exaggerated, and the effect of hearing difficulty is not overlooked.

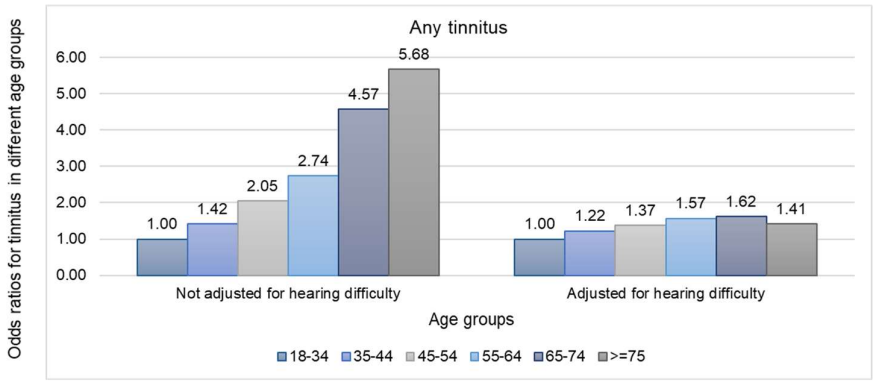
Table 3.11 Odd ratios and corresponding 95% CIs for tinnitus according to hearing difficulty categories. Europe 2017-2018.

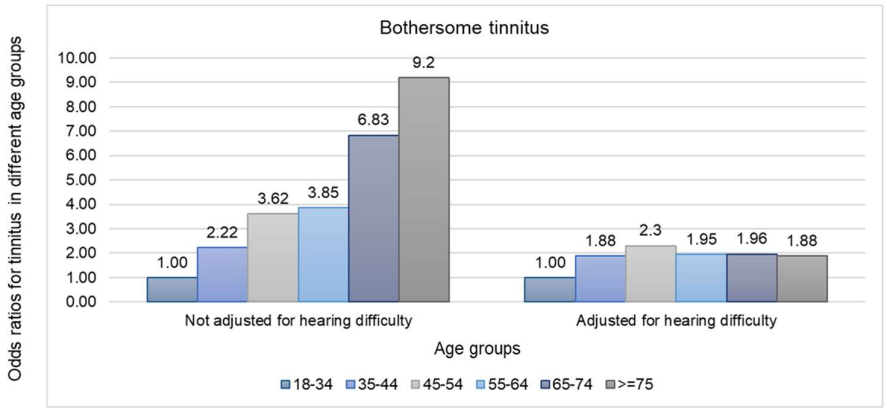
	N	Any tinnitus OR[a] (95% CI)	Bothersome Tinnitus OR[a] (95% CI)	Severe Tinnitus OR[a] (95% CI)
Hearing difficulty[o]				
No difficulty	8839	Ref	Ref	Ref
Slight difficulty	1451	**7.77 (6.72-8.99)**	**6.27 (4.94-7.96)**	**5.41 (3.14-9.33)**
Bothersome hearing difficulty	931	**18.53 (15.55-22.08)**	**33.21 (26.37-41.82)**	**30.03 (18.77-48.04)**
p for trend		**<0.001**	**<0.001**	**<0.001**

N= Number of subjects; Ref= Reference category

[a] ORs and the corresponding 95% Cis were estimated using unconditional multiple logistic regression adjusting for sex, age and level of education. Statistically significant ORs are in bold.

For any tinnitus, the unadjusted (for hearing difficulty) OR showed a monotonic increasing trend with age. Once adjusted for hearing difficulty, the OR increase showed a non-monotonic pattern with a decline after the 65-74 years' age group. While this pattern was not repeated for bothersome and severe tinnitus, the pattern for any tinnitus is consistent with some previous findings (McCormack et al., 2016).





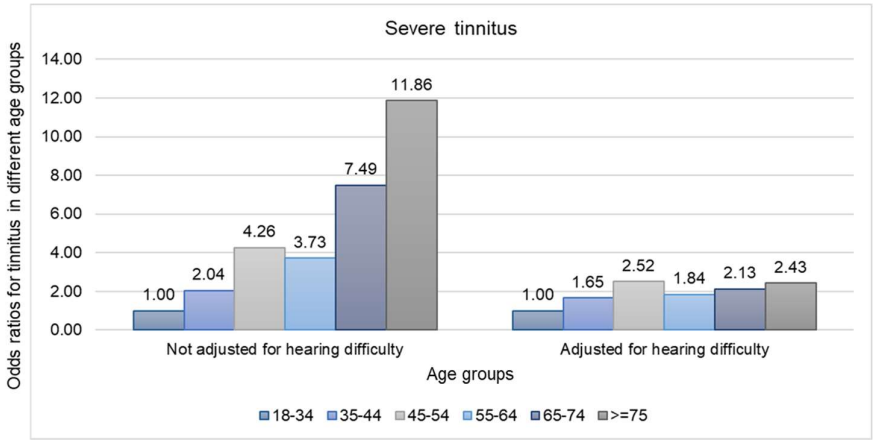


Figure 3.4 Trends in odds ratios for any, bothersome and severe tinnitus (sex and level of education adjusted) with increase in age adjusting and not adjusting for hearing difficulty

This exploratory analysis suggests adjusting for hearing difficulty risks over-adjusting the model by introducing an extra covariate and leading to an underestimation of the effect of age on tinnitus. On the other hand, given the high rates of reported hearing difficulty in the population, not adjusting for this factor risks an overestimation of the role of age in tinnitus prevalence. While we cannot completely negate the possibility that this reduction in the effect of age on tinnitus in the presence of hearing difficulty is an artifact, the importance of considering the inter-relationship between age, tinnitus, and hearing difficulty during analyses cannot be neglected.

3.5.2.4 Healthcare resource use for tinnitus

The overall percentage of individuals reporting at least one clinical visit for tinnitus was 6.8%, with the highest values for Bulgaria at 13.4% and the least for Greece at 4.1%.

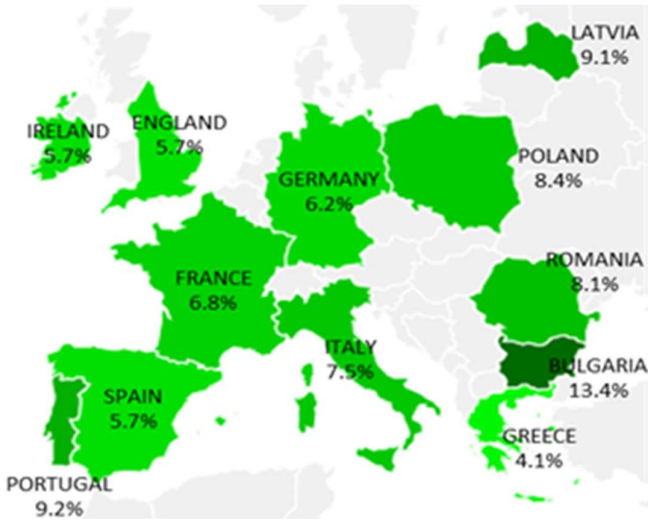


Figure 3.5 Colour gradient map of prevalence of healthcare resource use for tinnitus across 12 European countries

The two Northern European countries (England and Ireland) had the same prevalence of healthcare resource use for tinnitus. Similar patterns were noted for Western European countries (Table 3.12). Except for Bulgaria, the three other Eastern European countries had similar estimates. This was expected since Bulgaria has much higher prevalence estimates for tinnitus. Therefore, it is likely that the healthcare resource use will also be higher (Table 3.12). However, the Southern European

countries had quite variable prevalence estimates ranging from 4.1% population using healthcare resources for tinnitus in Greece to 9.2% in Portugal.

Table 3.12 Overall and country-specific prevalence estimates and odds ratios for healthcare resource use. Europe, 2017-2018

Country	Healthcare resource use for tinnitus (%)	Country-specific OR[a] (95% CI)
Eastern Europe	8.9	
Bulgaria	13.4	**3.1 (1.9-5.2)**
Latvia	9.1	1.2 (0.3-4.8)
Poland	8.4	**2.7 (2.0-3.7)**
Romania	8.1	1.5 (1.0-2.2)
Western Europe	6.2	
France	6.8	**1.9 (1.4-2.5)**
Germany	6.2	1.3 (1.0-1.7)
Northern Europe	5.7	
England	5.7	**1.9 (1.4-2.6)**
Ireland	5.7	2.0 (0.9-4.2)
Southern Europe	6.7	
Greece*	4.1	1.6 (0.8-3.0)
Italy	7.5	Ref
Portugal	9.2	**4.3 (2.9-6.4)**
Spain	5.7	**1.8 (1.3-2.4)**
Total	6.7	

Ref=Reference category
[a]ORs and the corresponding 95% Cis were estimated using unconditional multiple logistic regression adjusting for sex, age and level of education

The country-specific ORs for healthcare resource use for tinnitus after adjusting for age, sex, and education level (with Italy as the reference category) are reported in Table 3.12. Portugal had significantly higher odds of people using healthcare resources for tinnitus than Italy, and this OR was the highest among all countries. All Eastern European countries had high ORs for healthcare resource use except Latvia. England and France had similar ORs for healthcare resource use. The similarities in GDP per capita, which impacts healthcare resource use, could explain the similar ORs in England and France.

- **To explore the effect of tinnitus severity on healthcare resource use for tinnitus**

Over 80% of individuals with not bothered by clinical symptoms had no visit (Figure 3.6). This is expected given that people who are not bothered by their tinnitus symptoms, once assured that the symptoms do not result from some serious underlying medical condition, make no demands on the healthcare system (Henry et al., 2015). The ETS findings show that tinnitus symptom severity has the greatest impact on healthcare resource use. The steepest rise in the number of 5 or more clinic visits is observed from the moderately affected category. It can be noted that with the increase in tinnitus symptom severity, more people opt to seek medical advice, which means more burden on the healthcare system and increased expenditure.

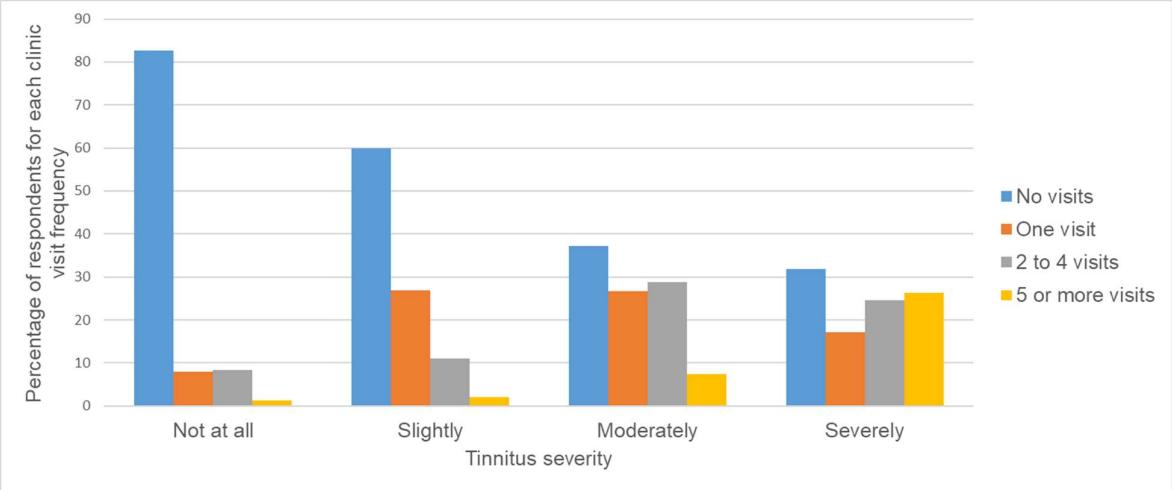


Figure 3.6 Relationship between tinnitus severity and healthcare resource use

3.6 Discussion

A summary of the principal findings is as follows: The ETS data showed an overall prevalence of any tinnitus of 14.7%, which is within the expected 10-15% range (Baguley et al., 2013). The prevalence for bothersome tinnitus was less than half for any tinnitus at 6.0%, and that of severe tinnitus was 1.2%, which is approximately 12 times less than the prevalence of any tinnitus. The inter-country difference was widespread with the Eastern European countries like Bulgaria, Latvia, Romania, and

Poland, showing consistently higher prevalence for all three working definitions of tinnitus. Age and hearing difficulty were positively associated with tinnitus prevalence. Healthcare resource use varied between countries, and a higher prevalence of tinnitus and higher GDP per capita resulted in more resource use.

Nonetheless, by far, the most crucial factor determining tinnitus-related healthcare resource use was tinnitus symptom severity. GDP per capita was negatively associated with tinnitus prevalence, and among SES variables, higher education level showed lower tinnitus prevalence. Sex differences and the effect of marital status were inconsistent. Although trends were observed for an increased likelihood of tinnitus with higher BMI, no significant association was found.

3.6.1 Inter-country differences

The inter-country differences in prevalence estimates were substantial. In the published literature, heterogeneous assessment methods and different age groups of the study population are among the most important causes of variability in tinnitus prevalence. Since culturally adapted questions and response options were used for this survey, variability due to diverse assessment methods can be excluded. Tinnitus prevalence increases with increasing age, and so it is expected that a population with older people would report a higher prevalence of tinnitus. The demographics of the 12 selected countries vary, and the sample population for each country was age representative for the country population. However, it was noted that in the ETS dataset, the proportions of younger (less than 35 years) and older (65 years or older) individuals in the countries with extreme prevalence values were similar to that of the overall sample population. Therefore, the inter-country variability in prevalence had some underlying cause and was not attributed to country-specific variations in the age distribution.

The published literature on tinnitus focuses on Western European countries. No previous studies have investigated tinnitus prevalence in Eastern European countries like Bulgaria, Romania, and Latvia. The ETS data provides the first prevalence information on these countries. Given the high prevalence estimates in Eastern Europe, future research to examine socio-demographic, lifestyle and behavioural factors that make one population group more vulnerable than another could be useful.

The ETS was a multinational study. Therefore, it was possible to look at the effect of country-specific GDP per capita and European regional differences in tinnitus prevalence. No other study had looked at these variables for tinnitus, and therefore, it was not possible to compare the ETS results with existing evidence. However, countries with higher GDP per capita are known to allocate more resources to health and safety (WHO, 2016). Hence, more healthcare resources could be accessible for people with tinnitus along with the availability of more protective measures, leading to reduced prevalence. Although this rationale sufficiently explains the reported lower prevalence of tinnitus in countries with higher GDP, more research is needed to confirm these conclusions.

Gallus et al. (2015) hypothesised the potential role of diet in tinnitus prevalence and indicated that the Mediterranean diet, as followed in Southern Europe, could be protective. The Alternate Mediterranean diet has also been reported to reduce the risk of HL (Curhan et al., 2018). Dawes et al. (2020) analysed the UK biobank data and reported that a healthy dietary pattern including more fruits, vegetables, and meat, and low in fat, have a protective effect and reduce the likelihood of tinnitus (Dawes et al., 2020). Countries and regions often influence food habits. There were no significant regional differences in tinnitus prevalence across the EU, except for the significantly lower prevalence of any tinnitus in Western Europe than in Northern Europe. In this regard, it should be noted that the Western European countries, namely France and Germany, also have the highest GDP per capita among the 12 countries included in ETS (International Monetary Fund, 2020). With the available information in the ETS dataset, it is hard to tell what caused the European regional difference in tinnitus prevalence. Future research exploring the effect of European regional differences, GDP per capita, socio-cultural habits, and dietary patterns on tinnitus prevalence could provide vital insights on causes and risk factors for tinnitus.

3.6.2 Risk factors worthy of further study

Inconsistent sex differences for tinnitus prevalence were observed. These findings are in alignment with the available literature. For any and severe tinnitus, there were no significant differences between men and women. In contrast, bothersome tinnitus had a significantly higher prevalence in women. In men, a tendency of downplaying or denying the severity of symptoms has been noted, leading to underreporting (Tudiver

and Talbot, 1999). For a self-reported condition like tinnitus, this behavioural difference could skew the prevalence data in favour of women. Moreover, the difference was significant only for bothersome tinnitus and not for any or severe tinnitus. Hence it cannot be said with certainty whether the sex difference in prevalence estimates of bothersome tinnitus were real or the result of the difference in attitude and perception between men and women.

With an increasing global trend, HL is one of the top five causes of overall disease burden in multiple European countries (Shield, 2019). Disability weight (a number between 0 and 1, with 0 implying a state of full health 1 implying a state equivalent to death) represents the severity of a condition compared with other conditions. Studies report that the disability weight of HL increases in the presence of tinnitus (Salomon et al., 2012; 2015). Increased life expectancy, increased leisure noise exposure in younger people, and early detection of health conditions are responsible for the increased prevalence of HL, and age-related HL is a major contributor to the overall prevalence (Shield, 2019). The burden of HL is increased with associated tinnitus symptoms. Age is related to both tinnitus and HL. Given the interrelationship between these three factors, it is complicated to tease apart the effects of age and HL on tinnitus. In the ETS data, after adjusting for hearing difficulty, it was noted that the effect of age on tinnitus prevalence and severity was altered considerably. There was still an increasing trend of tinnitus prevalence with increasing age, although the increase was markedly reduced. Therefore, it seems crucial to adjust hearing difficulty when examining the effect of age on tinnitus prevalence, to avoid biased estimates.

The healthcare resource-related findings from ETS analyses align with the multilevel tinnitus pyramid that explains how people are affected by different severities of tinnitus. According to the pyramid, the majority of the individuals (~80%) experience non-bothersome tinnitus. A relatively fewer proportion of individuals report bothersome tinnitus that requires some clinical intervention, and even fewer numbers experience severe debilitating tinnitus (Dobie, 2004; Henry et al., 2015). Tinnitus exerts a substantial financial burden on the healthcare system (Stockdale et al., 2017). Studies typically use the number of tinnitus-related GP visits or hospital visits to estimate tinnitus-related expenditure (Maes et al., 2013). The present study reported that increased severity of tinnitus symptoms leads to an increased number of clinical visits.

This means that more severe tinnitus requires more financial and personnel involvement and poses an additional burden on healthcare resources. Therefore, despite any tinnitus affecting more people, perhaps the severe form is more of a concern given the burden it imposes on global and national healthcare systems.

3.6.3 Contribution to the project and critical evaluation

My main contribution to this project was data input from the 12 textual data files (one for each country) into 12 corresponding SAS datasets, and then creating a unique final dataset in SAS. Data checking for coherence, data cleaning and data management. I also formulated the data analysis plan, analysed the data and interpreted the findings. The data collection was already underway when I joined the project. The survey questions were implemented before field testing (Section 2.4.1). Although the survey questions generally seemed well-adapted, there was some scope of improvement (Section 2.4.1). Field testing provides an opportunity to examine the wording of the questions and response items. For ETS, the field testing questions also asked if some words or phrases were particularly difficult and therefore, illustrated the potential difficulty in understanding the survey items. Field testing is recommended before using the translated questions and reponse options in real population research in the good practice guideline (Hall et al., 2018b). For this study, had the field testing been done before data collection, assessment and consequently the findings would be more reliable.

Although the aim was to use multistage random sampling in all countries, due to time and resurce constraints it was not possible. Moreover, a mix of quota, random, and cluster sampling was used for selecting the sample population. There is potential for sampling bias due to different characteristics for selecting quota, cluster, or strata. In this study, the use of consistent characteristics for representativeness had plausibly reduced the risk of bias to some extent. Nonetheless, there is some potential risk of bias inherent to the diverse sampling methods used. Although the resultant is always representative of the country population, there could be minor inter-country differences in sample selection.

For example, the quota method is a non-probability sampling method, where the selected sample represents only those characteristics that were considered when

defining the quota. Although cluster and stratified sampling are superficially similar, the key difference lies in the fact that while selected clusters are studied in the former, random samples are drawn from each stratum in the latter. Therefore, in cluster sampling, if the selected clusters are not representative of the population, there is a risk of sampling error. For stratified sampling, if the stratifying characteristics are not appropriate, there could be a risk of bias. In this study, the sampling bias while selecting quota, cluster or strata, had been considerably reduced by deciding to have representativeness regarding some specific attributes (sex, age, and habitat) for all samples. However, the selection of sampling methods often depends on the availability of information about the population, heterogeneity of population distribution, and other non-controllable factors like time constraints and accessibility of population. Therefore, it is not always possible to choose homogeneous sampling methods, especially in a large multinational study. Hence, there is some potential risk of bias inherent to the diverse sampling methods used.

The study protocol was not pre-registered. In line with open science practices, ensuring registration prior to the study increases the quality of research. Keeping this in mind, the study protocol has been submitted to clinicaltrials.gov retrospectively before manuscript submission to a journal. Although a prospective registration would be ideal, registration prevents the non-publication of potentially valuable research. Moreover, the transparent inclusion of the date of registration in the published article would be clear indication in the study registry that it was registered retrospectively, and will increase transparency and ensure that readers are aware. The following two sections provide a critical appraisal of the project, highlighting its main strengths and limitations.

3.6.4 Strengths of the study

The ETS dataset is a novel approach at collecting multinational data using the same standardised survey questions and response options. For every country, the study sample was representative of the sex, age, and geographic habitat: this prevented sample selection bias and improved generalisability of the data. Moreover, the face-to-face interview using a computer-assisted personal interview method minimises measurement bias that could be introduced using handwritten or self-administered surveys.

Additionally, the 12 countries included in this survey represent the different socio-economic and cultural variability of the EU countries. There are 28 countries in the EU. Collecting data from all of them to ascertain Pan-European prevalence would be quite expensive, time-consuming, and have feasibility issues. Therefore, the strategic selection of countries is a reasonable approach to measure the Pan-European prevalence of tinnitus.

3.6.5 Limitations of the study

One limitation of this study is recruiting a population up to age 65 years for Greece and up to age 75 years for Latvia. Since age is related to tinnitus, the prevalence in these two countries might have been underestimated. A possible solution could have been to impute data using linear regression or age standardisation. However, when the weighted overall and country-specific estimates were calculated, Greece and Latvia showed similar results to neighbouring countries. Moreover, the confidence intervals for ORs derived from the regression models were precise with narrow confidence intervals. Therefore, the overall accuracy was only hampered slightly since the prevalence estimate for any tinnitus was within the expected range.

Additionally, the country-specific sample sizes were relatively limited. The prevalence of any tinnitus is likely to be stable given its relative commonality. But for severe tinnitus, which is a rarer condition, a larger sample size would have provided more stable prevalence estimates. The other limitations are inherent to the study design and sampling methods used. Since it was a cross-sectional study, it was impossible to infer causal association or temporality of tinnitus and various determinants.

3.6.6 Future directions

The study results indicate that one in seven adults in the EU suffers from any tinnitus, one in 17 from bothersome tinnitus, and one in 100 from severe tinnitus. These numbers are concerning because they show that tinnitus, which has no cure, is a relatively common condition. This calls for adequate interventions and the implementation of preventive measures to reduce the prevalence. Elderly individuals and people with hearing difficulties are at high-risk. Therefore, policy interventions need to focus more on these vulnerable groups. Certain countries are at higher risk

than others. It is worthwhile to look for potential factors that could lead to vast inter-country differences in prevalence. Since the higher values are concentrated more towards some geographic locations (for example Eastern Europe), it could be interesting to look at potential genetic and environmental factors. Similarities between statistical maps of genetic variation and geographic maps of population location have been reported in recent studies and are particularly prominent within Europe, where there is a strong correlation between genetic and geographic distance (Lao et al., 2008; Novembre et al., 2008; Wang et al., 2012). Environmental factors like occupational noise exposure, protective hearing devices, noise control regulations, and attitude towards noise also play crucial roles in hearing functions. Occupational noise exposure is the second most common risk factor in workplaces (WHO, 2018). In the US, from NHANES dataset, 22% of workplace-related health issues are due to noise exposure (Tak et al., 2009).

Studies have found that occupational noise exposure directly results in HL (Safe Work Australia, 2010; Mahboubi et al., 2013). There is a strong correlation between noise-induced HL and tinnitus, and the severity of tinnitus is influenced by the degree of noise-induced HL (Henderson et al., 2011; Mazurek et al., 2010). A large multinational European study has found a difference in the levels of occupational noise-induced HL in Europe, with some countries showing worsening levels and some showing significant improvements over time (Stocks et al., 2015). Future research is needed to assess if the heterogeneous occupational noise-induced HL levels could play a role in the inter-country variations in tinnitus prevalence. Moreover, occupational health safety correlates with GDP per capita. High income countries invest more in occupational safety (WHO, 2018), leading to a lesser prevalence of workplace related health accidents and injuries, including HL. Type of profession and education level (skilled versus unskilled job) may also influence the probability of exposure to noise and awareness about using protective devices, which could explain the reduction in tinnitus prevalence with higher levels of education.

Gallus et al. (2015) had suggested a potential protective role of the Mediterranean diet in tinnitus prevalence and provided the example of Italy, where the prevalence is relatively low. Dawes et al. (2020) found that the lack of specific vitamins in the diet predisposes individuals to tinnitus. Therefore, it might be interesting to examine if there

are substantial dietary variations across countries that impact tinnitus prevalence. However, apart from measurable determinants, other factors like cultural effect and attitude towards a condition could give rise to differences but are challenging to assess and control in a research setting.

3.6.7 Concluding remarks

This study is a novel attempt at gaining a multinational perspective on the epidemiology of tinnitus. From the results, it can be concluded that tinnitus is a common condition, with some countries and regions having a substantially more number of affected individuals. Resource allocation, policy interventions, stricter regulations, and creating awareness are necessary to reduce new cases and the worsening of existing symptoms. Nonetheless, there are lots of gaps in knowledge that warrant the need for future research in this direction to explore various aspects of tinnitus research and bridge the knowledge gap.

Chapter 4 . A systematic review on risk factors for tinnitus and summary of evidence from high-quality studies

4.1 Introduction

One in seven adults in the EU are affected by any tinnitus, and one in 100 are severely affected. There is no specific aetiology for tinnitus, and causal factor knowledge suffers from inadequate information and heterogeneity (Cederroth et al., 2019). Peripheral auditory lesions are responsible for tinnitus onset leading to changes in the central auditory system (Eggermont and Roberts, 2004; Shore et al., 2016). Additionally, while changes in the auditory network cause the percept, changes in the brain's non-auditory regions are hypothesised to be involved in the emotional aspect of tinnitus perception (Elgoyhen et al.,2015; Moller 2011; Jastreboff and Hazell, 1993). Tinnitus heterogeneity regarding perception, distress caused, and aetiology makes it challenging to demonstrate the reproducible clinical benefit of anyone specific therapy (Cederroth et al., 2019; Hall et al., 2016; Hall et al., 2019).

Recent years have seen remarkable progress in tinnitus research. Nonetheless, the triggering factors for tinnitus onset and the mechanism of tinnitus generation and maintenance are not entirely unravelled and are one of the major roadblocks in the pathway to tinnitus cure (Baguley et al., 2013; Henry et al., 2014; McFerran et al., 2019). Identifying and quantifying the relationship between tinnitus and potential risk factors could shed some light on underlying pathophysiology, improve management strategies, and inform preventive interventions.

4.1.1 What are risk factors?

An individual's health and well-being are affected by multiple physiological, environmental, behavioural, lifestyle-related, demographic, and genetic factors. Many aspects of personal behaviour or lifestyle, environmental exposures, or a hereditary characteristic can be associated with an increase in the occurrence of a particular disease, injury, or other health condition (Principle of Epidemiology CDC, 2012). Risk factors are behaviours, exposures, or characteristics that increase the likelihood of an adverse health outcome.

It is essential to distinguish a risk factor from a correlate (Offord and Kraemer, 2000). In both cases, one variable provides some information about the other. However, in correlation, two variables (exposure and outcome) are related, and one causes an increasing or decreasing trend in the other but is not causative. Causation is when the exposure explicitly causes the outcome (Altman and Krzywinski, 2015). A concomitant correlate can be measured simultaneously as the outcome, and if measured after the outcome, then the correlate is a consequence. Risk factors are specific types of correlate that have to occur before the outcome of interest. Another defining characteristic of a risk factor is the ability to subgroup the population into high and low risk. The high-risk group must have a greater probability of the outcome than the low-risk group (Offord and Kraemer, 2000). Statistical analysis methods are used to assess the strength of association between a risk factor and its outcome while investigating the biological mechanism to establish causality. Therefore, a better understanding of risk factors could shed light on any health condition's aetiology and pathophysiology.

Risk factors play a pivotal role in formulating policies for preventive interventions. The success of preventive strategies depends on the type of risk factors and the nature of their association with an outcome. Some risk factors cannot be changed and are termed as fixed markers. Age, sex, and ethnicity are some examples. Risk factors that change spontaneously or in response to some intervention are termed a variable risk factor. Manipulating some variable risk factors changes the probability of the outcome, and they are called causal risk factors. In contrast, variable markers are those variable risk factors controlling which do not change the outcome's likelihood (Offord and Kraemer, 2000). In this regard, it is to be noted that causality does not imply that this specific exposure is the only cause of the outcome. More often, a health condition is multifactorial, i.e., the outcome of a multitude of factors.

It is crucial to distinguish between different types of risk factors to implement adequate intervention strategies and plan useful prevention studies. If the aim is to reduce the incidence of new cases, interventions should target causal risk factors. Whereas manipulating a correlate and variable risk marker might modify the outcome's overall impact, the incidence would not be affected. Fixed markers like age are unique because they cannot be changed. Hence it is not practicable to consider modifying

them. However, such risk factors are crucial to identify vulnerable population groups at a greater risk of developing an outcome of interest.

4.1.2 Tinnitus-related risk factors

Tinnitus is a complex chronic disorder related to environmental and genetic factors (Cederroth et al., 2019). It can be a symptom of various communicable and non-communicable diseases and can have multiple potential risk factors. The most widely reported risk factor for tinnitus is HL (Baguley et al., 2013; Davis and Rafaie, 2000; Michikawa et al., 2010; Sindhusake et al., 2004). Environmental influences that damage the auditory system and lead to HL, like exposure to loud noise and ototoxic medications, can also trigger tinnitus (Eggermont, 2015). Other causal factors for tinnitus include whiplash and neck trauma, blast-injury and traumatic brain injury, vestibular schwannoma, and Ménière's disease, stress, and temporomandibular joint disorder (Eggermont, 2015; Haider et al., 2017). Neurological conditions like migraine or tension-type headaches, psychological conditions like depression and distress, and audiological conditions like hyperacusis are related to tinnitus (Langguth et al., 2015; Pattyn et al., 2016; Schecklmann et al., 2013; Schecklmann et al., 2014). Apart from other comorbidities and neuro-otological disorders, socio-demographic and behavioural factors like diet, smoking, alcohol consumption, hypertension, and obesity have also been hypothesised to be related to tinnitus (Biswas and Hall, 2020; Baguley et al., 2013; Figueiredo et al., 2014). Additionally, tinnitus causality could also have a genetic component. For example, in men, the heritability of bilateral tinnitus was estimated as 0.68, while that of unilateral tinnitus was 0.27 (Cederroth et al.; Maas et al., 2017). A summary of known risk factors for tinnitus has been illustrated in section 1.4.3.

There is not enough evidence for most of these risk factors to infer whether the relationship between the risk factor and tinnitus is correlational or causal. The underlying biological mechanism is complicated and often unclear. For example, the relationship between HL and tinnitus is plagued by knowledge gaps and methodological challenges. The first challenge stems from diverse reporting measures for hearing impairment. PTA is a very commonly used hearing test with several advantages including highly accurate results and diagnostic usefulness as it identifies heaing loss, laterality, type and severity. Even though PTA is regarded as the gold

standard for measuring HL, population-based surveys often rely on self-reported hearing difficulty to assess hearing impairment. Studies have found people with normal audiometric threshold having self-reported hearing difficulty and people with audiometric evidence of HL reporting good hearing (Curti et al., 2019b; Ramage-Morin et al., 2019; Tremblay & Backer, 2016). HL and hearing difficulty are separate concepts, often showing a lack of agreement. Moreover, laboratory assessments of hearing do not provide a definitive diagnosis of whether or not there is damage to the hearing system. This is particularly true for high-frequency HL (> 8 kHz), which cannot be detected by standard clinical audiometric assessment. Schaette and McAlpine (2011) suggested that some individuals with no audiometric HL can have cochlear neuropathy related to perceptual dysfunction. This alludes to the concept of hidden HL in which individuals with cochlear damage have hearing impairment, but on a sub-clinical level, which cannot be diagnosed using current psychometric tests (Prendergast 2017a; 2017b). Apart from reporting biases and challenges with audiometric assessments, it should also be noted that tinnitus and hearing impairment do not always go hand in hand. Many people with tinnitus do not have HL and vice versa. Even when input from the ear is eradicated by dissecting the auditory nerve, tinnitus can persist (Baguley et al., 2013). The relationship is also predisposed to confounding effects by factors like age and noise exposure, which affect both tinnitus and hearing impairment. These complexities make it challenging to tease apart the inter-relationships and find a straightforward association.

Multiple related comorbidities further complicate this picture (Cederroth et al., 2019). Tinnitus can be significantly related to generalised anxiety disorder, depression, and sleep disturbance (Gopinath et al., 2010a; Khedr et al., 2010; Shargorodsky et al., 2010; Sclecklmann et al., 2015). In a study conducted on a national population in the US, 25% of people with tinnitus reported problems with depression, and 26% reported problems with anxiety, which was significantly higher than people without tinnitus (Bhatt et al., 2017). Similar results were also found for anxiety (25%) and depression (17%) in a study that used the HADS on tinnitus patients (Andersson et al., 2003). A systematic review on tinnitus and depression suggested three possible associations between depression and tinnitus: depression as a factor affecting tinnitus, tinnitus as a predisposing factor for depression, and tinnitus and depression as comorbidities. However, the mechanisms of interaction remained unclear, and since evidence

predominantly came from cross-sectional studies, the cause-and-effect association between depression and tinnitus could not be established (Geocze et al., 2013).

Lack of analytical observational studies is another hindrance in establishing risk factors' causality (Baguley et al., 2013; Biswas and Hall, 2020). With most information from cross-sectional studies, understanding of tinnitus-risk factors is still mainly hypotheses and conjectures. Most reported risk factor studies were conducted in specific population groups such as patients attending hearing or tinnitus clinics or specific geographical areas or demographic characteristics. For example, the EHLS provides valuable risk factor information on HL and tinnitus. However, the study population is limited to older adults aged 43 to 84 years who are residents of the township of Beaver Dam, Wisconsin, US (Cruickshanks e al., 1998; Nondahl et al., 2010). Similarly, the BMHS was conducted on residents of two suburban postcode areas in Sydney, Australia (Sindhusake et al., 2001). It is essential to use caution when generalising risk factor information from such studies with specific characteristics, as risk factors do not necessarily affect all population groups in the same manner (Offord and Kraemer, 2000; Westriech et al., 2019). Especially for a condition like tinnitus with ageing as a known risk factor, risks in comparatively older adults might not be comparable to risks in the general population, which usually has a sizeable younger population. More comprehensive knowledge of tinnitus risk factors from representative populations and using appropriate study designs could help distinguish correlation and causation, as well as clarify biological mechanisms, improve management, and implement precautionary measures for tinnitus.

4.1.3 Quality of evidence

When exploring evidence-based information on risk factors, the aim should be to select the highest level of evidence. There is a hierarchy of evidence determined by the methodological quality of the study designs, their validity, and their applicability in research. A detailed discussion on the pyramid of evidence and its modification in the last two decades, including adopting the GRADE framework, has been reported in section 1.4.4.

Quality of evidence is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation (Guyatt et al., 2008a). GRADE is

a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations (Guyatt et al., 2008a, 2008b). RCTs are located higher up in the pyramid of evidence, and therefore, they provide high-quality evidence. Observational study designs are the mainstay of evidence for studies on prevalence, incidence, diagnostic accuracy, risk factors, and aetiology. However, the navigation guide of the GRADE framework, designed for epidemiological research on environmental health factors, regards observational studies as only moderate quality evidence, with prospective cohort studies providing the strongest evidence (Woodruff and Sutton, 2014). It is not always possible to obtain the highest level of evidence because of various ethical (or feasibility) constraints, particularly for lifestyle, behavioural, and environmental risk factors. For example, to assess smoking as a risk factor, controlled intervention would be unethical.

Additionally, the quality of evidence may be downgraded in the presence of limitations in study design or implementation, imprecision of estimates (wide confidence intervals), variability in results, indirectness of evidence, or publication bias. Whereas quality may be upgraded when there is a large effect size, a dose-response gradient, and if all apparent biases would reduce an apparent effect (Guyatt et al., 2008a). Therefore, critical appraisal of evidence is crucial, and methodological quality assessment of studies included in reviews and meta-analyses is necessary.

The Cochrane Collaboration Risk of Bias Tool, introduced in 2008 and edited on March 20, 2011, was proposed by the Cochrane Collaboration Group to evaluate RCTs in meta-analyses and reviews. This is the recommended tool to assess an RCTs (Higgins et al., 2011; Higgins et al., 2019; Ma et al., 2020). No such recommended tool is available to evaluate the external and internal validity of observational studies. Multiple systematic reviews have been conducted to enumerate the tools available to assess analytical observational studies (Deeks et al., 2003; Sanderson et al., 2007; Shamliyan et al., 2010). However, none of them have been identified as the gold standard for quality assessment. Deeks et al. (2003) recommended the Newcastle-Ottawa scale (NOS) as the most useful tool for quality assessment of observational studies (Deeks et al., 2003). It was also recommended by the Cochrane collaboration (2011) for non-randomised studies (Higgins et al., 2011). Owing to its design and

content, the NOS is an easy-to-use tool that has been used to assist the interpretation of meta-analytic results (Wells et al., 2019; Deeks et al., 2013). Developed as an ongoing collaboration between the Universities of Newcastle, Australia, and Ottawa, Canada, the authors of the scale report that while the content validity and inter-rater reliability of NOS have been established, the criterion validity is still being examined (Wells et al., 2019). Nonetheless, systematic reviews and meta-analyses that have used this scale have identified it as reliable and valid (Li et al., 2008; Stang, 2010).

The NOS comprises eight items defined across three broad perspectives: the selection of study groups, the comparability of the groups, and assessment of the outcome in cohort studies, or exposure in case-control studies. Each of these items comes with a series of response options, and semi-quantitative evaluation of study quality can be conducted using a 'star-system' (Wells et al., 2019; Stang, 2010). Items can be awarded up to a maximum of one star, except the item on the comparability of groups that can have up to two stars, and the total stars awarded to the study can be between zero and nine (Stang, 2010). When assessing risk factors for tinnitus or any other health condition, it is pertinent to identify and quantify the evidence, but there is also the need to judge the evidence quality.

4.2 Study objectives

The overall project on the systematic review and meta-analyses on tinnitus-related risk factors had two parts. This chapter describes the first part of the project, which was in collaboration with ESIT colleagues from IRFMN, Karolinska Institute, University of Nottingham, and the University of Regensburg. I led and managed this work, which aimed to identify tinnitus-related risk factors reported in high-quality studies and identify the gaps in knowledge.

The study objectives were as follows:

1. To provide the most comprehensive evidence of the risk factors for tinnitus
2. To identify and quantify risk factors for which high-quality evidence is available, as well as to identify the gaps in knowledge for known risk factors for tinnitus

The second part of this project was a systematic review and meta-analyses on selected modifiable lifestyle-related risk factors (described in Chapter 5), accepted for publication in a Special Issue on Tinnitus in Progress in Brain Research. Some parts

of this chapter's methods section are based on work that has been accepted for publication.

4.3 Methods

A comprehensive literature review was conducted to identify all publications providing information on the relationship between tinnitus and potential risk factors, along with publications providing information on tinnitus prevalence. The review protocol has been registered on the international prospective register of systematic reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO), under the registration number CRD42018095610. To identify high-quality studies on tinnitus-related risk factors, quality assessment was conducted following the full-text screening. Specific criteria were agreed upon, which were needed to be fulfilled by the study to be considered high-quality.

4.3.1 Search strategy

The initial search string was developed for Medline using a combination of Medical Subjects Headings (MeSH) and text words related to tinnitus, related risk factors, and prevalence. The common terminologies were identified by reviewing MeSH terms and keywords used in MEDLINE to describe a pre-defined set of 12 key publications already known to the authors. Different versions of this syntax were piloted to find the final search string that successfully recovered all 12 pre-defined articles. The final Medline search string was adapted accordingly to fit the other medical/ healthcare databases used in our search, namely Embase, Cochrane Database of Systematic Reviews (CDSR), and Cumulated Index to Nursing and Allied Health Literature (CINAHL) (Table 4.1). A literature search was conducted to identify all original studies published on tinnitus and potential risk factors on 29/11/2017 and updated on 06/11/2019. No restriction was applied on the start date.

Table 4.1 Search strings used in various databases

Name of database	Search string used
MEDLINE (Pubmed)	("tinnitus"[MeSH Terms] OR "tinnitus"[All Fields]) AND ("prevalence"[MeSH Terms] OR "incidence"[MeSH Terms] OR prevalence[OT] OR incidence[OT] OR "risk factors"[MeSH Terms] OR "risk factors"[All fields] OR "case-control"[Tiab] OR "cohort"[Tiab] OR "cohort"[OT] OR "cross-sectional"[Tiab] OR "cross-sectional"[OT] OR meta-analysis[tiab] OR pooled-analysis[tiab] OR survey[tiab] OR representative[tiab] OR longitudinal[tiab])
Embase	Tinnitus:ti,ab,kw AND (prevalence:kw OR incidence:kw OR “risk factors” OR case-control:ti,ab OR cohort,ti:ab,kw OR cross-sectional:ti,ab,kw OR meta-analysis:ti,ab OR pooled-analysis:ti,ab OR survey:ti,ab OR representative:ti,ab OR longitudinal:ti,ab) AND [embase]/lim NOT [MEDLINE]/lim AND ('article'/it OR 'article in press'/it OR 'review'/it)
CINAHL	MH tinnitus AND "risk factor**" OR epidemiol* OR cohort OR "case control" OR "cross sectional" OR survey* OR longitudinal OR "pooled analysis" OR "meta analysis" OR representative*
CDSR	tinnitus:ti (among Cochrane Reviews)

4.3.2 Eligibility criteria

Studies were included in the present review if they satisfied the eligibility criteria mentioned in the following sections.

4.3.2.1 Study population

Observational studies conducted on human subjects providing data on tinnitus (including pulsatile tinnitus) and associated risk factors, and population-based surveys providing data on tinnitus prevalence in various subpopulations, were included in this review. No age restriction was applied. Animal studies were excluded. Since the aim was to retrieve all information on tinnitus-related risk factors, including social and environmental factors, no restrictions in settings were applied. However, since the objective was risk factor analyses for causal inference studies, including people experiencing tinnitus without a clear comparator group, were excluded. The aim was to identify exposures and quantify the effect comparing exposed to unexposed.

Assessing a dose-effect on tinnitus per unit change of a risk factor was beyond the scope of this review.

4.3.2.2 Exposures

All studies providing data on tinnitus and the role of potential risk factors, such as socio-economic characteristics (e.g., level of education), lifestyle habits (including tobacco smoking, alcohol drinking, dietary patterns, obesity, physical activity, mobile use), comorbidities (including depression, anxiety, vertigo, selected cardiovascular diseases, history of trauma), any medications (e.g., aspirin, ototoxic drugs), and otological conditions (e.g., HL), were included. Studies assessing treatment efficacy for tinnitus therapies and known concomitant medical conditions like Meniere's Disease were excluded.

4.3.2.3 Comparators/controls

Subjects not exposed to tinnitus-associated risk factors were treated as comparators. RR, HR, and OR were used as the measures of effect to ascertain the excess risk of tinnitus incidence/prevalence for subjects exposed to specific risk factors as compared to those who were not exposed.

4.3.2.4 Outcomes

All studies reported information on either tinnitus incidence or prevalence, or some measure quantifying effect of various exposures on tinnitus, such as, RR, HR, OR, or prevalence ratio (PR) with 95% CI, or included sufficient information to compute crude estimates of RR for tinnitus-related risk factors.

4.3.2.5 Study design

Eligible study designs included cross-sectional (including population-based surveys on specific sub-populations), case-control, cohort studies, meta-analyses, pooled-analyses, and systematic reviews. Case reports, case series, letters to the editor, book chapters, conference proceedings, dissertations, and thesis were excluded.

4.3.3 Screening of articles

An EndNote library was populated with all articles retrieved after searching various electronic databases. Duplicate records were deleted. After running the updated search, the library was updated to include additional results. The stepwise screening methods are elaborated in the following sections.

4.3.3.1 Title and abstract screening

After excluding duplicate publications, the literature search identified 2389 publications, titles, and abstracts, which were independently screened for eligibility by two reviewers (one other reviewer and me). The publications were scored on a scale of 1-5 where:1=Publication not pertinent or of limited interest for the review; 2=Publication probably not pertinent or of limited interest; 3=Not possible to evaluate on the basis of title/abstract/keywords, only; 4=Publication probably pertinent or of interest; 5=Publication pertinent or of clear interest for the review. The two reviewer scores were merged to give total scores ranging between 2 and 10. Inclusion of articles for full text (second) screening depended on the total scores derived by adding the independent scores of the two reviewers from the first screening. Publications with combined scores of 5 or more were considered for the next screening step.

4.3.3.2 Full text screening and data extraction

The full text of potentially eligible studies was retrieved, and each article was again independently assessed for eligibility by a group of three reviewers (two other reviewers and me). Each eligible article was independently assessed for eligibility by two out of three reviewers. There was in general agreement (~75%) between the reviewers and the few discrepancies were resolved by discussion and a majority decision. No study was excluded a priori for the weakness of design or data quality.

An initial data extraction template in Excel was created to extract the following information: first author, year of publication, type of study (i.e., cross-sectional, case-control, cohort, meta-analysis, pooled-analysis, or systematic review), the measure of association (RR, OR, PR or numbers to get the crude estimates), presence of incidence and/or prevalence data, and type/category of risk factor assessed.

4.3.4 Risk factor categorisation

There is no recommended classification system for tinnitus-related risk factors. Although Baguley et al. (2013) provided a risk factor categorisation for tinnitus, it primarily focused on ototoxic medications and other comorbidities related to tinnitus. This categorisation was expanded to include other tinnitus-related risk factors such as demographics, socio-economic characteristics, lifestyle habits including tobacco smoking, alcohol drinking, dietary patterns, obesity, physical activity, mobile use, comorbidities, otologic conditions, and medications used. The initial data extraction template was updated and coded to align with the more detailed risk factor categories.

4.3.5 Quality assessment

In the first and second screening steps, none of the publications were excluded for the weakness of design or data quality. Quality assessment was conducted following full text screening. For this review, the following three criteria were required to be considered as high quality:

- Analytical observational study designs: case-control and cohort studies
- The measure of effect reported as risk ratios (RR, HR, OR, PR)
- Quality assessment scores measured using the NOS

4.3.5.1 Assessment of study design

Evidence from analytical observational study designs was regarded as high quality because they are useful for deriving conclusions on the degree of association and establishing causality.

4.3.5.2 Assessment of measure of effect

Studies that reported measures of effect (RR, OR, HR, or PR) adjusted for relevant covariates were given higher rank in the hierarchy of evidence. Although crude estimates of risk ratios can be calculated from studies providing raw data (numbers and proportions), this does not give an accurate picture because the risk for confounding remains. For this review, high-quality studies comprised those publications where measures of effect were reported as risk ratios, namely, RR, OR, HR or PR.

4.3.5.3 Scoring of articles: Newcastle Ottawa Scale (NOS)

The third step for the quality assessment process involved a quality appraisal of the original studies using a scoring scale. The NOS was selected as the quality assessment scale of choice for this review. The total number of stars awarded to an individual study was between zero and nine. NOS is not a validated or standardised tool, and there is no explicitly mentioned cut-off to separate high and low quality observational studies. This quality appraisal step was not conducted to identify high-quality studies. The purpose was to evaluate the studies that were identified as high-quality in the previous two steps, using a consistent scale. Moreover, a scoring system is preferable for the ease of reporting.

4.3.6 Strategy for data synthesis

Very few risk factors had high-quality information from multiple studies. Risk factors with evidence from two or more high-quality studies were identified. Data on the definitions of exposures and outcomes and risk estimates were extracted in a pre-defined template. For each of those tinnitus-associated risk factors, meta-analyses were conducted to quantify the increase in risk in individuals exposed to the risk factor compared to the unexposed group. When the same study results were published in more than one original article, data published in the most recent or complete article was used. Heterogeneity between studies was assessed using the Q and I^2 tests. The pooled RRs from random-effects models using the DerSimonian and Laird moment estimator of the between-study variance component was evaluated.

4.4 Results

4.4.1 Selection of eligible articles

Of the 847 articles eligible for full-text screening, 392 were excluded because they did not fit the eligibility criteria or had no relevant information. For 15 publications out of 392, the full text was not found. Four hundred fifty-five (455) articles were relevant to this review, of which 374 reported information on risk factors, and 81 had data only on the prevalence or incidence of tinnitus. Of these 374 studies, 49 were analytical observational (seven case-control and 42 cohorts), 301 were cross-sectional, and 24 reviews (Figure 4.1).

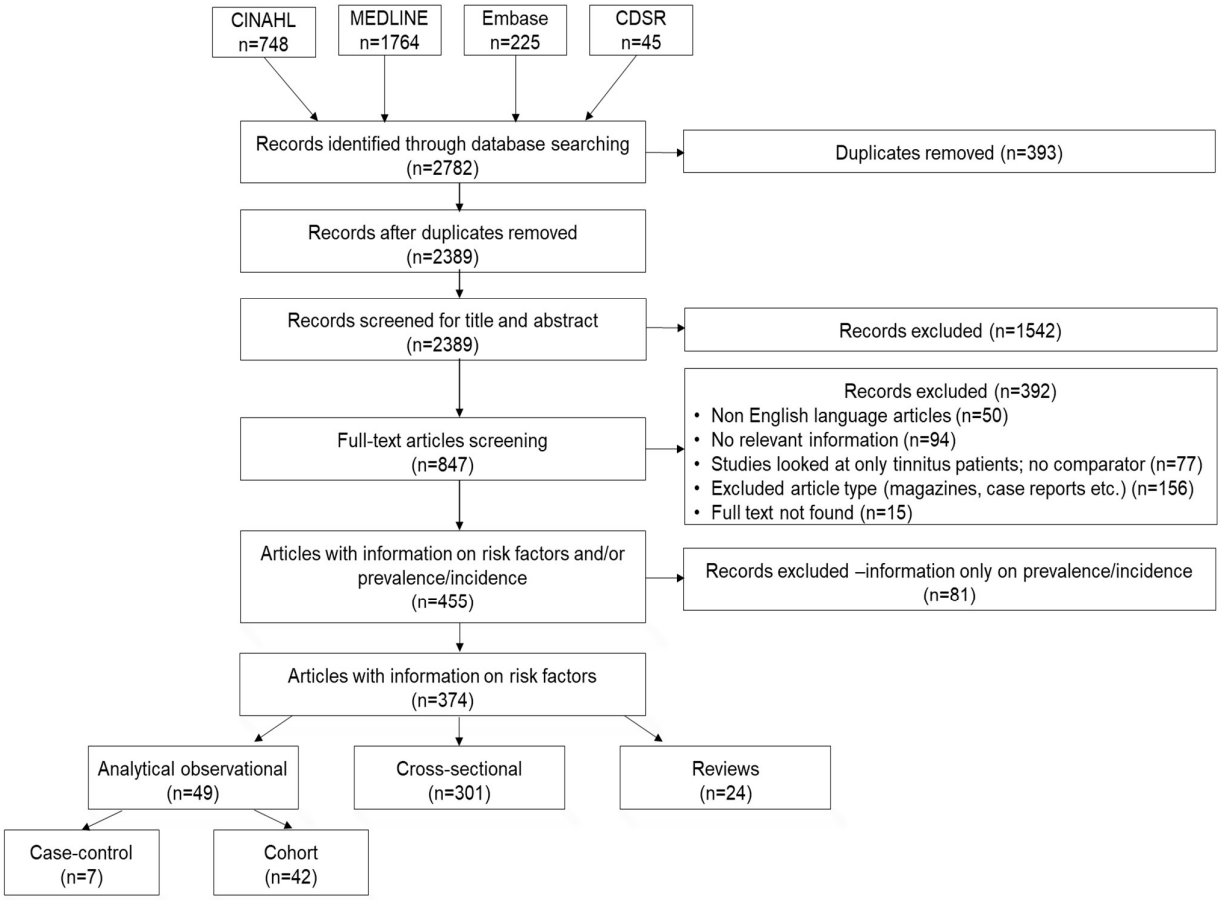


Figure 4.1 PRISMA flow diagram for the systematic review

4.4.2 Risk factor categorisation

The risk factors were broadly categorised into six primary domains: hearing function-related factors, lifestyle-related factors, socio-demographic factors, specific diseases or conditions, treatments, and other factors. Under the same domain, many diverse risk factors could be included. For example, exposures and substance use are both lifestyle-related risk factors. Similarly, it makes sense to group the specific diseases or conditions related to tinnitus depending on the body system it affects. Hence, the risk factor domains were subcategorised further.

Table 4.2 Risk factor categorisation

Category	Sub-category	Examples
Hearing Function-Related Factors		
Types of measurement	Clinically measured	Unspecified HL, SNHL
	Self-reported	Hearing difficulty, Hyperacusis
Lifestyle-Related Factors		
Exposures	Chemical	Chemical solvents
	Noise	Non-occupational: phone use, leisure music
		Occupational: military, musician
	Physical/Other	Computer use, electromagnetic field, solid waste
Nutrition	Anthropometric	BMI, Waist to hip ratio
	Diet and nutrition	Dietary patterns, deficiency
	Physical activity	Hours of exercise
Substance Use	Alcohol	Drinking status , amount of consumption
	Coffee	Drinking status
	Drug Addictions	Drug abuse
	Smoking	Smoking behaviour, Second-hand smoke
Socio-Demographic Factors		
Age		
Family History		
Marital Status		
Race/Ethnicity		
Region		Geographic region, Urbanization level
Socioeconomic	Education	School years, Education level
	Employment Status	
	Income	Yearly income, Income Level
	Deprivation Score	Deprivation index
Sex		
Social Environment		Family or school situation, Working conditions
Other Demographics	Benefits	Disability benefits, Health insurance
Specific Diseases or Conditions		
Cardiovascular		Heart Failure, Hypertension, Peripheral Vascular Disease
Endocrine and Metabolic		Diabetes, Hyperlipidaemia, Thyroid Disorders
ENT, Other	Nasal Disorders	Rhinitis, Sinusitis

Table 4.2 Risk factor categorisation

Category	Sub-category	Examples
Hepatological		Transplant, Cirrhosis, Hepatitis B
Immune-Mediated		Systemic lupus erythematosus
Infections (systemic)		Human immunodeficiency virus, Human T-cell lymphotropic virus type 1
Musculoskeletal		Osteoporosis
Neurological		Stroke, Meningitis, Migraine, Tension-type headache
Non-Otological Neoplastic		Childhood Cancer, Cancer Survivors
Orofacial	Dental Conditions	Teeth Grinding, Clenching
	Musculoskeletal	Temporomandibular Joint Disorder
Otologic	Infectious	Otitis media, otitis externa
	Labyrinthine	Cochlear Implants, Vertigo, Vestibular dysfunction
	Neoplastic	Acoustic neuroma, Schwannoma
	Other	Cerumen, Otosclerosis, Presbycusis
Mental and Behavioural		Anxiety, Dementia, Depression, Stress, Suicidal ideation
Renal		Chronic kidney disease
Respiratory		Chronic Obstructive Pulmonary Disease
Rheumatological		Rheumatoid arthritis
Sleep Disorder		Sleep apnoea, Hypersomnia, Insomnia
Traumatic	Ear Injury	External ear Injury, Tympanic membrane perforation
	Head And Neck Injury	Head Injury, Traumatic Brain Injury, Whiplash injury
	Other Bodily Injury	Bodily Injury Score
Other Systemic conditions		Chronic illness, Disability, Allergy, Menstruation, Pregnancy
Treatments		
Ototoxic Medications	Antibiotics	Erythromycin, Macrolides, Anti-tuberculosis Drugs
	Anti-Neoplastic	Platinum-Based Therapy
	Other Drugs	Aspirin, Nonsteroidal Anti-Inflammatory Drugs, Diuretics
Radiotherapy		Radiation (gamma)
Other Factors		
Genetics		Genotype, Specific alleles
Other		

Clinically measured HL and self-reported hearing difficulty are conceptually different. Diet and physical activity are related to nutritional epidemiology but address different risk factors. In the same way, alcohol consumption and smoking are examples of substance use. In such cases, the risk factors within the same categories were too different to be grouped. On the other hand, for some variables, it was not necessary to create a sub-category. For example, socio-demographic factors like age and sex, or diseases arising from a specific system like cardiovascular or renal, did not need to be further categorised to accommodate the risk factors. Hence, depending on the risk factor category, sub-categories were sometimes created to illustrate a more comprehensive picture of the risk factor profile for tinnitus. Table 4.2 illustrates a detailed view of the domains, categories, and sub-categories of risk factors along with examples within each category and sub-category.

4.4.3 High-quality studies

The details of the high-quality studies along with the country they were conducted in, sample characteristics, and factors assessed has been reported in Table 4.3. 25 out of 49 articles on analytical studies fit the high-quality criteria. Three of them analysed data from case-control studies, whereas 22 analysed data from cohort studies. Among the cohort studies, nine included data from prospective cohorts and 13 from retrospective cohort databases . Most studies were conducted in Australia, Western and Northern Europe, North America (the US and Canada), and only one Asian from Taiwan. The Taiwan data (one case-control and six cohorts) came from the Taiwan National Health Insurance Resource Database (NHIRD). In Taiwan, a single-payer National Health Insurance program was launched on March 1, 1995, and as of 2014, it covers 99.9% of Taiwan's population[1]. The articles were published after 2014 and constituted retrospective analyses of the NHIRD. Hence, a large number of studies were available from Taiwan.

Among case-control studies, one included cases and matched controls from an outpatient ENT clinic (Hutter et al., 2010). Another case-control study used medical

1 National Health Insurance Administration, Ministry of Health and Welfare, Taiwan, R.O.C. (2014). National Health Insurance Annual Report 2014-2015.

records from CPRD, an anonymised database created in 1987 having ongoing medical records from over 11 million patients provided by approximately 700 GP practices throughout the UK (Stohler et al., 2019).

One study conducted in the UK used hearing-related information from participants of the Oxford-Family Planning Association contraceptive study- a prospective cohort study. This prospective cohort database had data from 17,000 women recruited at 17 clinics in England and Scotland between 1968 and 1974. The authors included 26 years of follow-up information for their study (Vessey and Painter, 2001). The EHLS was a population-based study designed to evaluate epidemiological data for HL in adults aged 48-92 years, residing in Beaver Dam, Wisconsin. Two articles used 5-year and 10-year follow-up information from the EHLS (Nondahl et al., 2002; Nondahl et al., 2010). Two studies included data from the BMHS, a population-based survey of age-related HL in 55-99-year-olds residing in two postcodes of Sydney, Australia. Baseline recruitment was conducted during the period 1997 to 1999, and individuals in this prospective cohort were followed for 5-years (Gopinath et al., 2010a; Gopinath et al., 2010b). Data for the article from Bernhardt et al. (2011) was derived from the Study of Health in Pomerania, a population-based prospective cohort study conducted in Germany to assess the prevalence and incidence of common risk factors, subclinical disorders, and clinical diseases, and to investigate associations and interactions between them. One US-based study included tinnitus data from NHSII, a prospective cohort study on 25 to 42-year-old nurses from 14 US States to study conditions and risk factors related to women's health (Glicksman et al., 2014). The School Hearing Investigation in Nord-Trøndelag was carried out yearly from 1954 to 1986, and the second wave of the Nord-Trøndelag Health Study was conducted from 1995 to 1997. The same study participants recruited at 7, 10 or 13 years during the School Hearing Investigation in Nord-Trøndelag were between 20 and 56 years old during Nord-Trøndelag Health Study, a general health screening study for the adult population in Nord- Trøndelag County. The Nord-Trøndelag Hearing Loss Study was conducted in Norway from 1996 to 1998 as part of the Nord-Trøndelag Health Study. Aarhus et al. (2015 and 2019) used these datasets to study risk factors (Table 4.3).

Among the retrospective cohort studies, two used the Childhood Cancer Survivor Study dataset – a North American multi-institutional collaborative retrospective study

of individuals who survived at least five years after diagnosis of cancer during childhood or adolescence, and a cohort of their sibling not affected by cancer (King et al., 2017; Whelan et al., 2011). Two US-based studies conducted retrospective analyses of health records of military personnel from military hospital-based databases (Dougherty et al., 2013; Eick-Cost et al., 2017). All six articles from Taiwan and one article from Germany by Schink et al. (2014) used medical health insurance data for retrospective analyses (Chen et al., 2018; Chen et al., 2019; Hwang et al., 2018; Lee et al., 2016; Schink et al., 2014; Shih et al., 2017; Yang et al., 2015). One study retrospectively analysed a mobile phone subscriber database (Auvinen et al., 2019). Another study's authors sent a recall questionnaire to primary school teachers and a sex and age-matched cohort from the general population to collect tinnitus-related data retrospectively (Table 4.3).

Table 4.3 High-quality studies along with country, sample characteristics, and risk factors assessed

Author and year	Country	Sample characteristics	Risk factors
Case-control studies			
Hutter et al., 2010	Austria	ENT clinic cases and matched controls	Noise exposure
Hwang et al., 2017	Taiwan	Taiwan NHIRD data	Hearing function, Sleep disorder
Stohler et al., 2019	UK	CPRD data	Hearing function, lifestyle-related, Specific diseases or conditions
Prospective cohort studies			
Vessey and Painter, 2001	UK	Oxford-Family Planning Association contraceptive study	Treatment (Ototoxic medications)
Nondahl et al., 2002	USA	EHLS data	Hearing function Specific diseases or conditions
Gopinath et al., 2010a	Australia	BMHS data	Hearing function
Gopinath et al., 2010b	Australia	BMHS	Hearing function, Specific diseases or conditions
Nondahl et al., 2010	USA	Adults aged 48 to 92 from the EHLS	Hearing function, lifestyle-related, Specific diseases or conditions, Socio-demographic
Bernhardt et al., 2011	Germany	Study of Health in Pomerania, Germany.	Specific diseases or conditions
Glicksman et al., 2014	USA	NHSII data	Lifestyle-related (Caffeine)
Aarhus et al., 2015	Norway	School Hearing Investigation in Nord-Trøndelag, and Nord-Trøndelag Hearing Loss Study	Hearing function, Specific diseases or conditions
Aarhus et al., 2019	Norway	School Hearing Investigation in Nord-Trøndelag, and Nord-Trøndelag Hearing Loss Study	Specific diseases or conditions

Table 4.3 High-quality studies along with country, sample characteristics, and risk factors assessed

Author and year	Country	Sample characteristics	Risk factors
Retrospective cohort studies			
Whelan et al., 2011	USA and Canada	Childhood Cancer Survivor Study and a sibling cohort	Specific diseases or conditions, Treatment
Dougherty et al., 2013	USA	Expeditionary Medical Support System data	Noise exposure; Traumatic
Schink et al., 2014	Germany	Health insurance database	Noise exposure, Socio-demographic
Yang et al., 2015	Taiwan	NHIRD data	Specific diseases or conditions, Treatment
Lee et al., 2016	Taiwan	NHIRD data	Hearing function, Socio-demographic, Specific diseases or conditions
Eick-Cost et al., 2017	USA	Defense Medical Surveillance System, Pharmacy Data Transaction Service, Theater Medical Data Store .	Treatment
King et al., 2017	USA and Canada	Childhood Cancer Survivor Study data	Specific diseases or conditions, Treatment
Shih et al., 2017	Taiwan	NHIRD data	Socio-economic status, Specific diseases or conditions, Treatment
Chen et al., 2018	Taiwan	NHIRD data	Hearing function, Socio-economic status, Specific diseases or conditions, Treatment
Hwang et al., 2018	Taiwan	NHIRD data	Neurological
Auvinen et al., 2019	Finland	Databases of mobile phone operators.	Noise exposure
Chen et al., 2019	Taiwan	NHIRD data	Neurological
Fredriksson et al., 2019	Sweden	Pre-school teachers and a matched cohort population	Noise exposure

4.4.4 Risk factors and quality of evidence

Table 4.4 illustrates the list of risk factors for which more than one high-quality publications reported a relationship with tinnitus. In some cases, the publications reported results derived from the same study during the same period. For example, six high-quality publications reported data on HL. These included two articles on EHLS- one 5-year and one 10-year follow-up. Since the individuals followed-up for 5-years were included in the 10-year analyses, the most updated information was used for the meta-analysis. Among the four other studies, two were analyses on the BMHS dataset and two on NHIRD, from the same study period. Among the three articles on SNHL, two reported data from NHIRD and were of the same study period and, therefore, the one with the complete information, Hwang et al., 2018, was used. Risk factor information for hypertension, diabetes, and stroke were available from NHIRD for the same study period from Shih et al. (2017) and Chen et al. (2018) . Since Chen et al. analysed information for women and Shih et al. for both sexes, the latter results were used for meta-analyses.

One study was excluded from the meta-analyses on occupational noise exposure since it compared different levels of exposure in individuals (Dougherty et al., 2015). The two other studies compared professionals exposed to the occupational noise and unexposed population (Friedricksson et al., 2019; Schink et al., 2014). For SNHL, the two case-control studies compared tinnitus in individuals with SNHL to those without SNHL. (Hwang et al., 2017; Stohler et al., 2019). Another cohort study by Aarhus et al. (2015) used childhood HL as the reference group and was excluded from the meta-analyses for SNHL. Two articles by Aarhus et al. (2015 and 2019) were excluded from the meta-analyses on otitis media as the reference group was normal childhood hearing. Two other studies by Gopinath et al. (2010) and Stohler et al. (2019) compared individuals with otitis media to those without were included in the meta-analyses .

In the high-quality studies, two working definitions of tinnitus were used- any tinnitus(self-reported) and clinically significant tinnitus. Given the lack of analytical studies, the variability in tinnitus definition was not a restriction criterion when pooling data for meta-analysis of high-quality studies. No causal inferences were interpreted from the meta-analyses results. They were conducted mainly to summarise risk factor

data and inform association. It was noted that the average quality assessment scores from NOS, i.e., the number of stars received, were relatively high (7 and above out of 9) for all risk factors examined in the high-quality studies.

Table 4.4 Risk factors analysed using meta-analytic approach along with number of high-quality studies and quality assessment scores

Risk factor	Analytical study design used		Total studies	Average quality assessment score from NOS
	Case-control	Cohort		
HL (unspecified)	0	6[a]	6[a]	8
SNHL	2	1	3[c]	8
Non-occupational Noise Exposure	1	1	2	8
Occupational Noise exposure	1	2	3[b]	7
Obesity	1	1	2	8
Alcohol consumption	1	1	2	8
Smoking (current)	1	1	2	8
Sex	0	4	4	9
Heart Failure	1	1	2	8
Hypertension	1	3	4[a]	8
Diabetes	2	1	3[a]	8
Hyperlipidaemia	1	1	2	8
Depression	1	1	2	8
Migraine	1	1	2	8
Stroke	1	2	3[a]	8
Temporomandibular disorder	1	1	2	8
Otitis media	2	2	4[c]	7
Chronic Obstructive Pulmonary Disease	1	1	2	8
Rheumatoid arthritis	1	1	2	8
Head Injury	1	3	4	8
Whiplash	1	1	2	7
Platinum	0	4	4	7

[a]Data from all articles were not included in the meta-analyses because more than one original article reported results of the same study (data published in the most recent and/or complete article was included). Three studies were excluded from the meta-analysis for HL, one excluded for SNHL, one for diabetes, one for hypertension, one for stroke.
[b]One study was excluded from the meta-analyses because it compared individuals with different levels of exposure; while the other studies compared exposed and unexposed population.
[c]Study was excluded from the meta-analyses as the reference group was different from the other studies
Risk factors in bold are related to tinnitus.

Table 4.5 reports the list of factors for which evidence was pooled from more than one high-quality studies. Risk factors affecting the auditory system, such as depression, HL, SNHL, Temporo-mandibular disorder, otitis media, and occupational noise exposure, showed a positive association with tinnitus. However, non-occupational noise exposure showed no association. Among comorbidities, only diabetes showed a negative association with tinnitus. No association was found for lifestyle-related factors (obesity, alcohol consumption, smoking), sex, neurological conditions like migraine and stroke, and other comorbidities (Appendix XI)Given an evident scarcity of high-quality studies, most meta-analyses were conducted on results from two or three sources, thereby compromising the results' reliability.

Table 4.5 Evidence from high quality studies on tinnitus-related risk factors

Positive association
Depression
Head Injury
HL
Occupational noise exposure
Otitis media
Platinum therapy
SNHL
Temporomandibular disorder

Negative association
Diabetes

Null association
Alcohol consumption
Chronic Obstructive Pulmonary Disease
Heart Failure
Hypertension
Hyperlipidaemia
Migraine
Non-occupational noise exposure
Obesity
Rheumatoid arthritis
Sex
Smoking
Stroke
Whiplash

4.4.5 Risk factors with gaps in knowledge

For some risk factors, no information was available from high-quality studies. For example, there was one high-quality case-control study with information on otosclerosis (Nondahl et al., 2002). Two studies with information on cerumen were available, but data could not be compared as they used diverse reference categories (Aarhus et al., 2015; Stohler et al., 2019). Among immune-mediated conditions, only one high-quality study has analysed the relationship between tinnitus and systemic

lupus erythematosus. Psychological conditions like anxiety disorders are hypothesised to be associated with tinnitus, although only one high-quality study analysed the relationship (Stohler et al., 2019). Besides platinum therapy in cancer patients, other ototoxic medications had information either from analytical or low-quality studies. In this regard, it should be noted that two original articles, Stohler et al. (2019) and Shih et al. (2017), analysed a case-control and a cohort database, respectively, and reported the association between tinnitus and multiple risk factors. Two potential neurological risk factors for tinnitus, meningitis, and epilepsy, have no analytical observational study results. Similarly, factors like diet and physical activity, known to affect the risk for multiple communicable conditions, were studied only in cross-sectional datasets.

4.5 Discussion

In this systematic literature search, 374 articles had risk factor information on tinnitus. A diverse and comprehensive categorisation had to be developed to accommodate all the risk factors hypothesised to be associated with tinnitus. Only 13% of articles reported information from analytical observational, i.e., case-control and cohort studies and about half of them fit the high-quality criteria defined for this review. Most of these studies provided evidence for ear and hearing-related risk factors for tinnitus. Little or no evidence was available for several tinnitus-related risk factors, including those hypothesised as potential risk factors in previously published literature (such as anxiety) or identified as a research priority (such as diet).

4.5.1 Heterogeneous risk factors

Many risk factors related to tinnitus have been reviewed, both related and unrelated to hearing function and the auditory system. These risk factors included socio-demographic characteristics, lifestyle-related factors, and diseases related to other systemic conditions. Some studies also found genetic factors related to tinnitus. Such findings establish that tinnitus can be related to multiple risk factors and comorbidities, giving rise to heterogeneous causality and creating a complex clinical picture (Baguley et al., 2013; Cederroth et al., 2019). Tinnitus research has many unresolved questions, and there is a need to employ a multidisciplinary approach to address the challenges and diversity in all aspects of tinnitus research (Cederroth et al., 2019; Cima et al., 2019; Langguth et al., 2013).

Moreover, although considered separately, risk factors often co-exist. Investigating multiple risk factors simultaneously might provide new insights regarding their combination and interplay in causing tinnitus symptoms. Additionally, the same risk factor might be related to more than one health condition. Therefore, using a multidisciplinary approach in tinnitus-related risk factor analysis might provide new perspectives about the pathophysiology, management, and prevention measures.

4.5.2 Study design and analyses issues

A lack of information from analytical studies, particularly prospective cohorts, was evident. Systematic reviews for tinnitus-related risk factors have so far relied on cross-sectional evidence, consequently showing correlation and not causation (Figuerido et al., 2015; Veile et al., 2018). For example, a systematic review on smoking and tinnitus found sufficient evidence of an association between smoking and tinnitus, but the lack of analytical studies hindered concluding on causal associations and weakened the strength of evidence (Veile et al., 2018). Similarly, another systematic review of tinnitus and hypertension showed a positive relationship but could not report a cause and effect relationship (Figueiredo et al., 2015). Hence there is a clear need for analytical observational studies in risk factor analyses for tinnitus.

Systematic reviews are a useful way of combining data from multiple studies and increasing the breadth of information. However, the interpretation of results from systematic reviews depends on the quality of evidence and the risk of bias (van Dalen et al., 2007). Observational studies are generally most appropriate to study aetiology and risk factors (Woodruff and Sutton, 2007). The degree of reliability of observational studies can be from excellent to very poor and depends on the registry's design from which data is collected, methods used for analysis, and, most importantly, the quality of the data recorded (Dreyer et al., 2014). The latter point is a critical issue in observational studies as it forms the basis of evidence quality and can introduce sources of a bias-this phenomenon is illustrated by the acronym 'GIGO' (Garbage In, Garbage Out) (Mitchell, 1985; Schiele, 2017). About half of the analytical studies found in this review fit the high-quality criteria. There is an apparent need for well-conducted analytical observational studies, such that there is confidence in the results, irrespective of whether studies are considered individually or as a part of a systematic review.

NOS is not a validated tool. Hence, in this review, NOS could not be used to identify high-quality studies but was a quality appraisal tool for the studies identified as high-quality. Notably, the 25 publications identified as high-quality using the other two steps, i.e., the analytical studies that reported measures of effect, scored very well in NOS. Nonetheless, a validated instrument that considers the inherent issues that downgrade the quality of evidence from observational studies is needed.

4.5.3 Lack of evidence

Tinnitus being a neuro-otological condition, studies commonly explore the associations between the ear and hearing-related risk factors and tinnitus. This systematic review observed that most high-quality data examined conditions that affect the auditory system. Some other factors, such as lifestyle-related risk factors, cardiovascular, endocrine, renal, and rheumatological comorbidities, were also analysed in high-quality studies. Only diabetes showed a negative association with tinnitus. However, most of these meta-analyses included findings from two to three publications, and so the evidence, although sufficient to establish a correlation, warrants caution when making causal inferences.

There are two critical issues in risk factor analyses for tinnitus. Firstly, most data are derived from cross-sectional studies, which is vital for generating hypotheses, but not for establishing causality. Consequently, risk factor information is still mostly conjectured, awaiting conclusive evidence from well-conducted analytical observational studies. Secondly, the few high-quality studies available explore selected risk factors with a clear preference for auditory conditions. As a result, some relevant associated conditions have not been investigated adequately, and gaps in knowledge continue to prevail. Anxiety disorders have been consistently hypothesised to be related to tinnitus (Baguley et al., 2013; Langguth et al., 2013). Treating anxiety disorders have been shown to reduce the impact of tinnitus (Langguth et al., 2013). An apparent interest lies in the tinnitus research community to further explore this relationship. However, available data is mostly cross-sectional, with only one case-control study reporting a positive association.

4.5.4 Heterogeneous assessment methods

In Chapters 2 and 3, the variability in tinnitus assessment was discussed in the context of prevalence studies. Variability in tinnitus definition was also noted in risk factor analyses. Both self-reported “any” tinnitus and “clinically significant” tinnitus have been measured as outcomes of interest. Population-based studies such as EHLS and BMHS relied on tinnitus self-report. On the other hand, hospital-based case-control studies or retrospective cohorts based on electronic health records like the CPRD, or insurance databases such as the NHIRD, used medically diagnosed tinnitus as the outcome of interest. Tinnitus requiring medical attention is fundamentally different from any tinnitus that is self-reported in the general population. These differences are elaborated in detail in section 2.1.3.

Additionally, a heterogeneous pattern was evident for some measures of risk factors. Either different assessment methods or diverse reference groups were used for comparison. For example, among the high-quality studies, the article by Aarhus et al. (2015) used a reference group (normal childhood hearing), and this was different from all other articles on SNHL. As a result, the Aarhus et al. (2015) study could not be included in the meta-analyses leading to loss of information when pooling data (Aarhus et al., 2015).

4.5.5 Modifiable risk factors

An unhealthy diet and physical inactivity along with tobacco use and the harmful use of alcohol are four lifestyle-related factors prioritised by the WHO to increase the risk of many communicable diseases, including those with similar risk factor profile to tinnitus (like cardiovascular conditions). (Djoussé et al., 2009; Hemmert et al., 2019; WHO, 2012; Zhang et al., 2011). Knowledge of the association of these risk factors with tinnitus could help clarify pathophysiology and initiate adequate strategies to reduce new cases. The lack of a cure makes preventive measures essential for tinnitus. Incidentally, due to their commonality, some of these risk factors already have prevention strategies in place. Therefore, exploring these relationships could support cost-effective means of tinnitus prevention.

Diet is a potential area for tinnitus research prioritised by clinicians and patients (Hall et al., 2013). However, very few cross-sectional studies have analysed this risk factor, and different assessment methods have been used to quantify diet. For example, to assess diet, Spankovich et al. (2017) used dietary patterns, while McCormack et al. (2014) measured food types (McCormack et al., 2014; Spnakovich et al., 2017). In six articles, four different assessment methods were used for diet. For physical activity as well, different measures of assessment were used such as binary (yes or no) response to a defined amount of daily exercise, measuring cardiorespiratory fitness while walking on a treadmill, accelerometer measured exercise, and energy expenditure from activity calculated in metabolic equivalent units (Fujii et al., Loprinzi et al., 2013; Nondahl et al., 2011).

4.5.6 Strengths of the study

The main strength of this review is its comprehensiveness. The initial search string was further refined using keywords from known high impact studies on tinnitus prevalence and risk factors, thereby ensuring the identification of maximum publications. Additionally, the registration of the review protocol on PROSPERO was a good practice in open research that ensured transparency, and prevented publication bias and duplication of study. Moreover, the quality assessment step was conducted at a much later stage of the review, and was not a restriction or exclusion criteria. This made the search more comprehensive and better elicited the multifactorial structure of tinnitus and the evident gaps in knowledge.

No study was excluded a priori for the weakness of design or quality of evidence. As a result, the heterogeneity of causal factors for tinnitus was evident, and the risk factor categories were expanded to accomodate all risk factors. The detailed quality assessment process was useful in identifying high-quality data and highlighted gaps in knowledge. Since data on the cohorts was extracted, it was possible to identify existing sources of risk factor information. Some examples include the EHLS, BMHS, Beaver Dam offspring study, Jackson Heart Study, Nurses' Health Study (I and II), Conservation of Hearing Study (CHEARS), and the UK Biobank (Cruickshanks et al., 1998; Glicksman et al., 2014; House et al., 2018; McCormack et al., 2014; Nondahl et al., 2011; Sindhusake et al., 2004). Some of these explored cohorts dedicatedly collected information on hearing-related conditions, such as EHLS and BMHS.

However, other cohorts on general health conditions (like NHSII) that included an assessment question for tinnitus have also been explored to study risk factors. An advantage of cohort studies is that multiple outcomes of the same risk factor(s) can be analysed simultaneously.

4.5.7 Limitations of the study

Where possible, meta-analyses on high-quality articles were conducted for specific risk factors. In most cases, data was pooled from one or two articles. This information was not sufficient to draw causal inferences on the relationships between tinnitus and the risk factor even though data was from high-quality studies. Consequently, while the challenges and gaps in knowledge could be highlighted, no conclusive deductions could be made on the risk factor associations. Also, only English language articles were used for this review. Given the paucity of high-quality data, expanding the review to include non-English literature might have increased volume of information and more confidence in the study results.

4.5.8 Future directions

The two most striking gaps highlighted in this review include the lack of analytical observational studies and gaps in knowledge about some known risk factors. Due to the lack of analytical studies, it is impossible to elicit the cause and effect relationship between potential risk factors and tinnitus. It is possible to conduct hospital-based case-control studies from ENT clinics or population-based case-control studies from existing healthcare or health insurance databases by selecting tinnitus cases and tinnitus-free controls matched for index dates. However, to obtain accurate results, in both instances, reliable coding of tinnitus is essential. In tinnitus research, there are very few examples of such case-control studies (Hutter et al., 2010; Hwang et al., 2017; Stohler et al., 2019).

Moreover, medical health records and insurance databases can be used to conduct retrospective cohort studies. For example, Martinez et al. (2015) conducted a retrospective cohort study using a healthcare record (CPRD – HES data from the UK) data . Data from such studies cannot be used to make firm conclusions.

Nonetheless, this can be convenient to generate hypothesis and quantify some degrees of association between a risk factor and tinnitus.

Prospective cohort studies provide the strongest evidence in risk factor analysis. Some large population-based prospective cohorts have explored the relationship between tinnitus and various risk factors. Conducting new, large, and well-designed prospective cohort studies would be ideal. Nonetheless, it would also be worthwhile and resource-friendly to explore the existing databases to look for associations between tinnitus and risk factors illustrated in Table 4.2. This perspective motivated me to collaborate with the Harvard University team, who had previously analysed the NHSII dataset for some hearing and tinnitus-related risk factors. We investigated the effect of diet, alcohol, and obesity on incident tinnitus in women participating in NHSII. The details of the study are provided in Chapter 6.

4.5.9 Concluding remarks

Data identification, synthesis, and reporting have emerged as necessary steps in disseminating and translating raw data into clinical practice and policy decisions. High-quality primary data acquisition is a pre-requisite for high-quality data synthesis. For risk factors analysis, this implies conducting well-designed analytical observational studies to provide stronger evidence. Findings from this review show that tinnitus is related to multiple exposures or risk factors. However, for most of them, there is insufficient data to conclude a causal relationship. The knowledge of risk factors is not just crucial for understanding tinnitus aetiology. It could also provide insights for pathophysiological mechanisms, contribute to improved tinnitus management, and individualise treatments based on the underlying condition instead of alleviating the tinnitus percept alone.

Chapter 5 . Systematic review of modifiable lifestyle-related factors for tinnitus

5.1 Introduction

For chronic debilitating conditions like tinnitus, risk factor prevention could prove a useful public health strategy to reduce incidence. In chapter 4, various categories of tinnitus-related risk factors were enumerated. For some lifestyle-related risk factors, it is feasible to implement preventive interventions. Since most lifestyle-related risk factors affect multiple non-communicable conditions and diseases, population-level preventive strategies are already in place for some of them. By establishing the impact of such lifestyle-related risk factors on tinnitus, it might be possible to reinforce existing prevention strategies as cost-effective means to prevent the incidence and consequently, reduce tinnitus burden at both individual and population levels.

5.1.1 Modifiable lifestyle-related risk factors

Modifiable risk factors can be reduced or controlled by appropriate interventions, reducing the probability of a disease or health condition. Lifestyle choices or behaviours can be adapted by creating awareness and initiating preventive measures. WHO prioritises four behavioural risk factors common to most non-communicable chronic diseases or conditions. These are tobacco use, physical inactivity, unhealthy diet, and the harmful use of alcohol. They are crucial since they result in four fundamental metabolic changes-raised blood pressure, overweight/obesity, raised blood glucose, and raised cholesterol (WHO, 2012).

As mentioned in section 4.5.5, data on the relationship of diet and physical activity with tinnitus are scarce and lack consistency in assessment measures. Both of these methodological issues contributed to the inability to pool data from multiple studies and conduct the meta-analyses. However, obesity is related to unhealthy diet and physical inactivity (Balhareth et al., 2019; Bradbury et al., 2017; Fogelholm et al., 2012) and has been hypothesised to be related to tinnitus (Baguley et al., 2013). Among the priority risk factors, comparatively more studies investigated the relationship between tobacco use

(smoking) and alcohol consumption and tinnitus, using relatively standard assessment measures for the exposures. Coffee consumption or caffeine intake have been explored concerning chronic diseases with similar concurrent risk factors (such as cardiovascular conditions) showing beneficial effects (Floegel et al., 2012; Ranheim and Halvorsen, 2005). Smoking, alcohol consumption, obesity, and caffeine intake/ coffee drinking (henceforth referred to as caffeine intake) are risk factors hypothesised to be related to tinnitus (Baguley et al., 2013, Figueiredo et al., 2014). However, chapter 4 revealed that there is no clear consensus on their impact on tinnitus. In this chapter, the relationships between tinnitus and these four modifiable lifestyle-related risk factors have been reviewed.

Risk factors- although presented individually, in practice, they often co-exist. Therefore, the eventual effect produced is not the effect of a single risk factor, but results from their interaction with one another. For example, studies have found smoking and drinking to be closely related (Schlecht et al., 1999; Shiffman and Balabanis, 1996). Again, gene-alcohol interactions have been found to moderate the effect of genes on BMI (Liao et al., 2016). Hence, some studies have investigated the role of these risk factors in developing chronic conditions simultaneously. This is particularly true for cardiovascular conditions where the multifactorial impact significantly increases the risk of chronic heart diseases (Djoussé et al., 2009; Hemmert et al., 2019; Merry et al., 2011). Since tinnitus and cardiovascular diseases have a shared risk profile, it seems logical to use the same approach to assess the effect of these modifiable risk factors on tinnitus (Zhang et al., 2011).

5.1.2 Preventive strategies for modifiable risk factors

In general, health risk behaviours tend to cluster within individuals (Boyle et al., 2000; Institute of Medicine, 2001). Targeted interventions towards risk factors can change people's lifestyle and risk behaviour and reduce new cases and the overall burden of a health condition. There are challenges and barriers in addressing lifestyle-related health risk factors, both singly or in combination. Nonetheless, there is an urgent need to address health risk behaviours (Pronk et al., 2004).

There are at least four specific benefits in addressing health risk behaviours or lifestyle-related factors in a unified manner. Firstly, many individuals present with numerous lifestyle-related risk factors. Therefore, the integrated approach to risk assessment and intervention would perhaps be more personalised, holistic, and generate greater satisfaction for affected individuals. Secondly, individuals are more likely to adhere to lifestyle modifications, which they are already contemplating to change. Therefore, an integrated approach with flexibility allowing individuals to prioritise lifestyle habits to work on, might be more effective. Thirdly, there are similarities in the interventional strategies, principles, and infrastructure for modifying these cluster of factors. It should ideally become unnecessary to reinvent the flow of the process for each lifestyle-related factor and behaviour. Finally, an integrated approach to prevention would potentially be time-efficient and resource-friendly for both healthcare and personnel resources (Pronk et al., 2004).

For the integrated prevention approach to work, it is crucial to understand which modifiable lifestyle-related risk factor affects an outcome of interest and how it affects the outcome. For conditions like cardiovascular diseases and cancer, with existing unified prevention strategies, the associations with modifiable lifestyle-related risk factors are known, or at least there is some assessment of the trends. As elaborated in Chapter 4, there are evidence gaps for tinnitus, except for smoking. Nevertheless, there are two reasons for including smoking in this review. Firstly, to evaluate any new work published on this topic since the review by Veile et al., 2018, and secondly to consider smoking alongside other modifiable factors using a consistent search and analysis methodology.

Tinnitus could benefit from both isolated and unified approaches at preventing modifiable risk factors, particularly the latter since the lifestyle-related exposures often co-occur. Most lifestyle-related risk factors, mainly the four explored in this review, underlie multiple outcomes. Therefore, interventions are already in place that have to be disseminated and circulated in the context of tinnitus.

5.2 Study objectives

The objective of this review was to provide an overview of how smoking, alcohol consumption, obesity, and caffeine intake affect tinnitus risk. Careful identification of all relevant published literature and analysing them through the lens of meta-analyses are the most logical approach to formally evaluate this body of published literature. This project is a novel attempt to assess the effect of alcohol consumption, obesity, and caffeine intake on the risk of developing tinnitus.

5.3 Methods

This work built on the systematic review described in Chapter 4.

5.3.1 Search strategy

Details of the search strategy and search strings are provided in section 4.3.1.

5.3.2 Eligibility criteria and screening

The eligibility criteria and screening steps are described in sections 4.3.2 and 4.3.3, respectively.

5.3.3 Identification of articles on selected modifiable risk factors

The data extraction reported in Chapter 4 was re-evaluated to identify data relevant to the main questions of interest. Risk factor information was used to identify eligible articles reporting information on the modifiable lifestyle-related risk factors of interest, namely smoking, alcohol, BMI, and caffeine intake. Reference lists of meta-analyses, systematic reviews, and selected works were also checked to identify additional papers. Only smoking had a previous systematic review and meta-analysis, and from that two articles (a book chapter and a conference proceeding) were identified. However, these were excluded because they did not meet the eligibility criteria.

Ideally, systematic reviews conducted for risk factor analyses should exclude cross-sectional studies. However, there is a known paucity in published literature for analytical studies (i.e., case-control and cohort studies) on tinnitus-related risk factors. Therefore,

to have a robust search result and some understanding of potential risk factors, cross-sectional studies were also considered in this review.

This review investigated the population-level effect of risk factors on tinnitus. Population surveys mostly rely on self-reported tinnitus. Tinnitus for which an individual seeks medical help is inherently different from tinnitus not requiring medical help. In Chapter 3, it has been reported that individuals with tinnitus who are not bothered by their symptoms often do not seek care. Since the aim was to assess effect of exposures on general population and their risk for tinnitus, for this review only studies on self-reported tinnitus were included, and not those which reported information on tinnitus diagnosed by a healthcare provider. No study was excluded for the weakness of design or data quality. Information about the publication, including first author, year of publication, study design, the measure of association, and type of risk factor assessed, was extracted using a pre-defined template. The included publications reported either some measure of risk estimate like RR, HR, OR, PR, or sufficient information to derive crude estimates of RR.

5.3.4 Data extraction

A pre-defined Excel template was used for data extraction from all potentially eligible studies to enable the planned data synthesis and meta-analysis. A separate template was used for each of the four risk factors of interest. The template included information on the publication (including first author, year of publication, journal name), study characteristics (including country of study, study name, study period, study design, outcomes, and sample size), statistical model (the list of covariates accounted for in the model), and, for individual exposures the various exposure categories, the relative risk (RR) estimates (with the corresponding 95% confidence interval, CI) for each category, and when available, the number of cases and controls (or subjects at risk/person-years, for cohort studies). The final review included studies providing information on the specific risk factor addressed, i.e., smoking, alcohol consumption, BMI, or caffeine intake, and reporting findings expressed as estimates of RR, OR or HR along with the corresponding 95% CIs or providing sufficient information to compute them.

5.3.5 Statistical analysis

For analysis, when the same study results were published in more than one original article, data published in the most recent or complete article was considered. The pooled estimates of the RR, HR, and OR were assessed in the following categories for the presence of tinnitus:

- Current, former, and ever smokers versus never smokers (three meta-analyses)
- Alcohol drinkers versus non-drinkers
- Overweight (BMI≥25 kg/m^2) versus normal/underweight (BMI<25 kg/m^2) individuals, and obese (BMI≥30 kg/m^2) versus non-obese (BMI<30 kg/m^2) individuals;
- Caffeine intake versus no caffeine intake

The method described by Hamling et al. (2008) was used for pooling non-independent estimates and for changing the reference category or combining the RRs of two or more categories, as and when needed..

Random-effects meta-analytic models were used, given the heterogeneity of risk estimates. Heterogeneity between studies was assessed using the χ^2 test, and inconsistency was measured using the I^2 statistic, representing the proportion of total variation attributable to between-study variance. When available, the risk estimates adjusted for selected confounders were considered. Alternatively, the crude (unadjusted) RRs were computed from the raw data reported in the publications. RRs and 95% CIs were computed for all studies included and also stratifying by study designs. Forest plots were used to display the results of the meta-analyses. To evaluate the publication bias, the funnel plots were examined, and Egger's test was applied to assess funnel plot asymmetry. The funnel plots are scatter plots where each study is represented as a dot. The RRs (effect estimate) were plotted on the x-axis and the standard error on the y-axis. In the absence of publication bias, the shape of the scatter plot should resemble a symmetrical inverted funnel with a broad base (consisting of small studies with large effect estimate variability) and a narrow top (consisting of large studies with small effect

estimate variability). All statistical analyses were performed using the R-software version 3.5.2 (R Development Core Team, 2018), particularly the meta-package.

5.4 Results

Of the 384 eligible studies, 45 were relevant to this review, with 38 of them providing information on smoking, 20 providing information on alcohol consumption, 21 providing information on BMI, and three studies on caffeine intake (Figure 5.1).

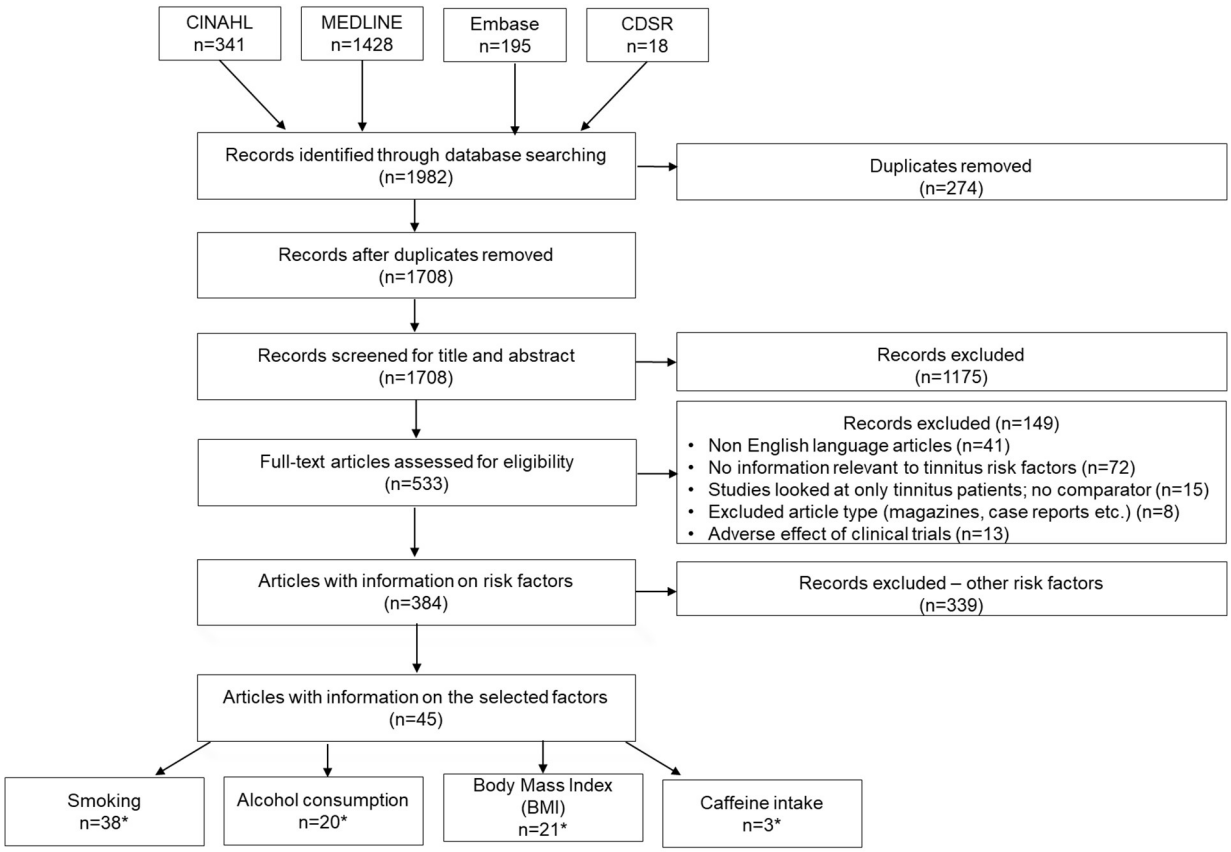


Figure 5.1 PRISMA flow diagram of study selection for modifiable lifestyle-related risk factors and tinnitus.
**Since some studies had information on more than one risk factors, these add up to greater than 45. (CDSR: Cochrane Database of Systematic Reviews; CINAHL: Cumulative Index of Nursing and Allied Health Literature)*

Appendix XII has the complete list of the 45 studies included in the final review with information on the risk factor/s assesses, the study characteristics including population examined, the definition used for tinnitus, and reported incidence or prevalence estimates. Two studies were limited to clinically diagnosed tinnitus cases and were, therefore, excluded from all analyses (Martinez et al., 2015; Swan et al., 2017). Multiple articles analysed data from 2009 to 2012 from the KNHANES dataset. The last or most complete article was included for analyses (Park et al., 2014a; Park et al., 2014b, Joo et al., 2015, Kim et al., 2015, Lee et al., 2017; Park and Moon, 2014). Additionally, some other articles were excluded from the meta-analyses for specific risk factors. Explanations for excluding such study data are given in the relevant results sections for each risk factor.

5.4.1 Smoking

Eleven studies (Rubak et al., 2009; Paschoal and de Azevedo., 2008; Brydoy et al., 2009; Sogebi, 2013; Degirmenci et al., 2014; Martines et al., 2015; Masterson et al., 2016; Degeest et al., 2017; Mofateh et al., 2017; Bhatt, 2018; Tan et al., 2018) were found in this review that were not included in the previous meta-analysis on smoking (Veile et al., 2018).

Meta-analyses were conducted to examine the relationship between tinnitus and the three smoking status (current, former, and ever smokers) versus never smokers. Studies on clinically diagnosed tinnitus and subsequent updated publications on the same dataset were excluded (Joo et al., 2015, Lee et al., 2017, Martinez et al., 2015; Park et al., 2014b; Park and Moon, 2014, Swan et al., 2017). Both articles by Nondahl et al. (2002 and 2010) reporting data on the same participant cohort were included in the analysis as one article (2002) provided baseline (cross-sectional) information, while the other provided the 10-year follow-up information (cohort). The article by Sindhusake et al. (2004) was excluded as Sindhusake et al. (2003) provided complete information for the same dataset. Loprinzi et al. (2013) was excluded because of insufficient data. Amani and Yarmohammadi (2015) was excluded as it provided data on parental smoking and childhood otitis media. Among the 38 studies providing information on the relation between smoking and tinnitus, nine were excluded (Appendix XII). Two studies had insufficient numerical data in the

original article (Marmut et al., 2014; Sindhusake et al., 2003). The review on smoking by Veile et al. (2018) contained more detailed numerical information on these articles, and so those information was used for the meta-analyses (Veile et al., 2018).

For current smoking habits, twenty-six studies (25 cross-sectional and one cohort) provided information. Considering all 26 studies, the overall pooled RR for current versus never smokers was 1.27 (95% CI: 1.12, 1.43). The RR was 1.34 (95% CI: 0.93, 1.93) for the only cohort study available. For the 25 cross-sectional studies included, the RR was 1.26, with a 95% CI of 1.11, 1.43. For all pooled estimates, there was significant between-study heterogeneity (Figure 5.2).

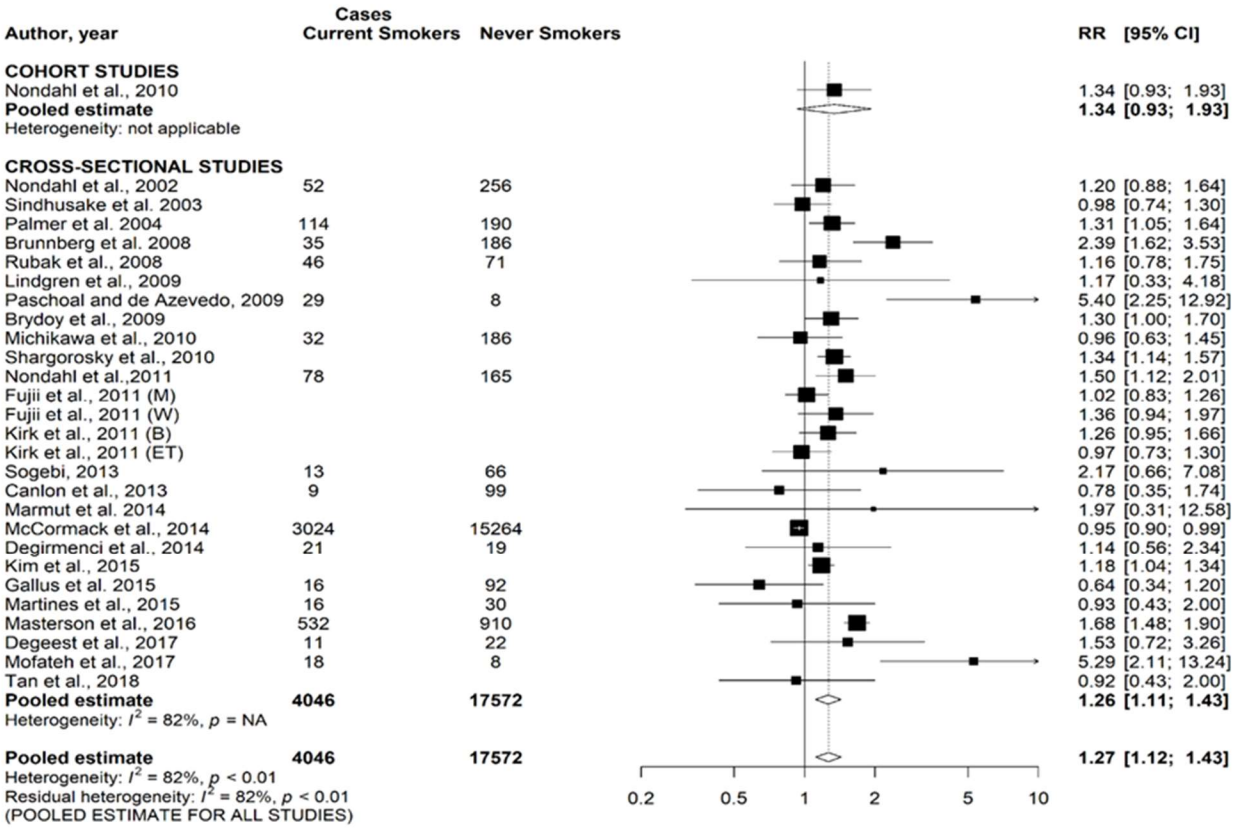


Figure 5.2 Forest plot for tinnitus in current vs never smokers

The pooled estimate for cross-sectional studies is statistically significant with RR of 1.26 and 95% CI: 1.11,1.43. The overall pooled estimate is statistically significant with RR of 1.27 and 95% CI: 1.12,1.43.

For former smokers, 12 studies (11 cross-sectional and one cohort studies) provided information. Considering all 12 studies, the overall pooled RR for former smokers versus never smoked was 1.21 (95% CI: 1.07, 1.37). The RR was 1.43 (95% CI: 1.16, 1.76) for the only cohort study available. For the 11 cross-sectional studies included, the RR was 1.19 (95% CI:1.05, 1.35). For all pooled estimates, there was significant between-study heterogeneity (Figure 5.3).

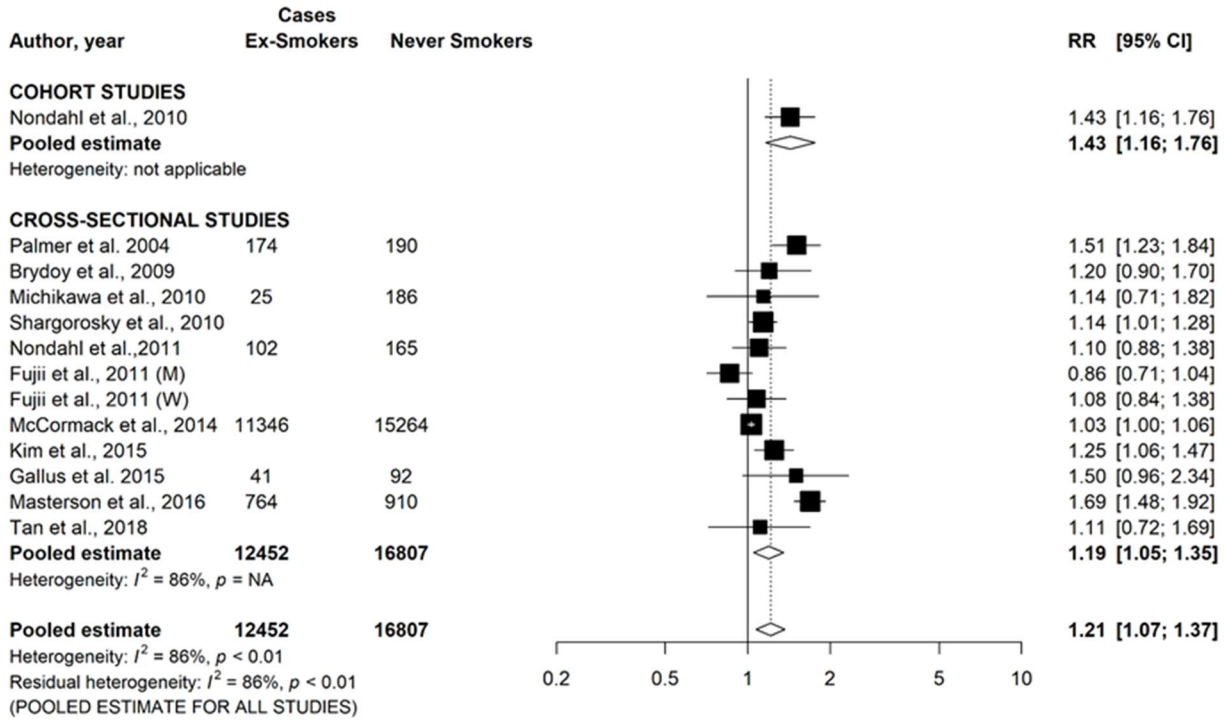


Figure 5.3 Forest plot for tinnitus in former smokers versus never smokers
The pooled estimate for cross-sectional studies is borderline significant with RR of 1.19 and 95% CI: 1.05,1.35. The overall pooled estimate is borderline significant with RR of 1.21 and 95% CI: 1.07,1.37. (M: Men; W: Women)

For ever smokers (former smokers plus current smokers),16 studies (15 cross-sectional and one cohort) provided information. Considering all 16 studies, the overall pooled RR for ever smoker versus never smoker was 1.21 (95% CI: 1.09, 1.34). The RR was 1.40 (95% CI: 1.10, 1.79) for the only cohort study available. For the 15 cross-sectional studies included, the RR was 1.20 (95% CI: 1.07, 1.33). For all pooled estimates, there was significant between-study heterogeneity (Figure 5.4).

Therefore, while cross-sectional data showed an increased risk of tinnitus in current, ever, and former smokers, data from the single cohort study available did not support the increased risk in current smokers. However, it did show an increased risk of developing tinnitus in ever and former smokers.

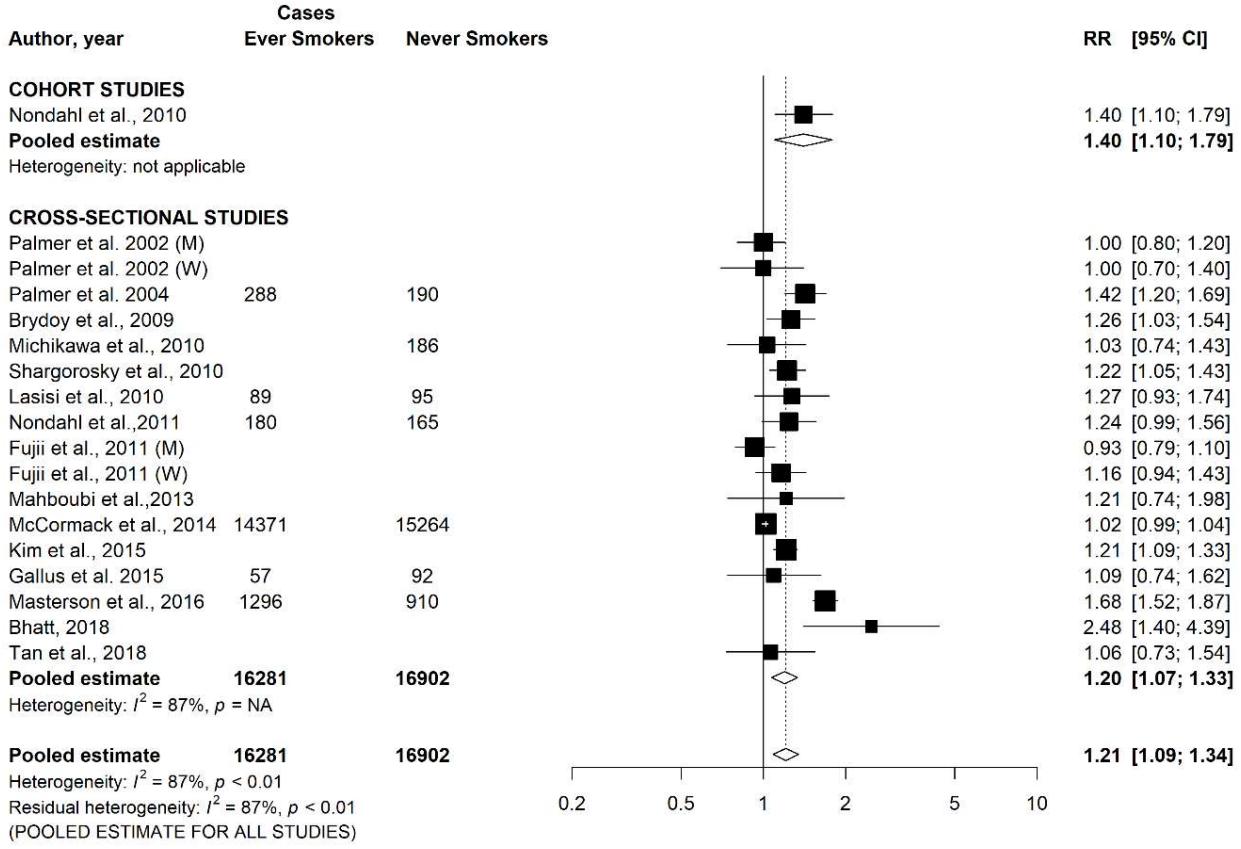


Figure 5.4 Forest plot for tinnitus in ever smoker versus never smokers
The pooled estimate for cross-sectional studies is borderline significant with RR of 1.20 and 95% CI: 1.07,1.33. The overall pooled estimate is borderline significant with RR of 1.21 and 95% CI: 1.09,1.34. (M: Men; W: Women)

5.4.2 Alcohol consumption

Among the 20 studies providing information on the relation between alcohol consumption and tinnitus, nine were excluded from this analysis for the following reasons (details in Appendix XIV): Study data for clinically diagnosed tinnitus as the outcome of interest and updated information on the same dataset were excluded (Martinez et al., 2015; Park et

al., 2014b; Park and Moon, 2014). Data assessing heavy and non-heavy drinking or a dose-response was excluded as it was not straightforward to estimate ORs for drinkers versus non-drinkers (Joo et al., 2015, Lee et al., 2017, Nondahl et al., 2002, Nondahl et al., 2010). Bhatt et al. (2017) reported data on the mean days of alcohol consumption, and it was not possible to calculate ORs in drinkers versus non-drinker. Bellé et al. (2007) only informed on affiliation to alcoholics anonymous . Data from these two publications could not be used for the meta-analyses.

All of the 11 remaining studies included in the meta-analyses were cross-sectional in design. The overall pooled RR for alcohol drinkers versus non-drinkers was 1.03 (95% CI: 0,87, 1.23). For all pooled estimates, there was a statistically significant between-study heterogeneity (Figure 5.5). Overall, alcohol consumption was found not to affect the risk of developing tinnitus.

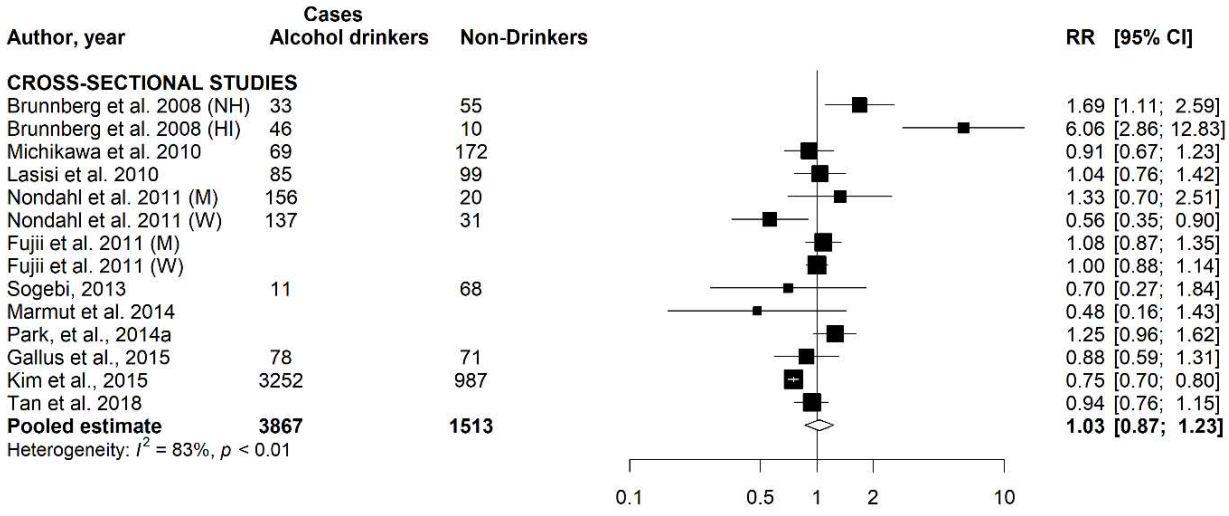


Figure 5.5 Forest plot for any tinnitus in alcohol drinkers vs non-drinkers
The overall pooled estimate (only cross-sectional studies available) is not statistically significant, with RR of 1.03 and 95% CI: 0.87,1.23. (NH: Normal hearing; HI: Hearing impaired; M: Men; W: Women)

5.4.3 Body mass index

Two meta-analyses were conducted to assess the relationship for BMI: one for overweight versus normal and underweight individuals and another between obese and non-obese individuals. Among 21 studies providing data on tinnitus and BMI, two studies, including information only on clinically diagnosed tinnitus, were excluded (Martinez et al., 2015; Swan et al., 2017). For the publications on KNHANES datasets, the one with completed or most updated information was retained for analyses, and the rest were excluded (Lee et al., 2017; Park et al., 2014a; Park et al., 2014b; Park and Moon, 2014). Articles that treated BMI as a continuous variable were excluded from the analyses as it was not possible to compute respective ORs for obese and/ or overweight (Kim et al., 2015, McCormack et al., 2014b, Park et al., 2014a). Data from one article was excluded because of insufficient information (Kim et al., 2012). The article by Fujii et al. (2011) was excluded as their reported BMI categories were different from other included articles and could not be pooled. After exclusion, 11 out of the 21 studies could be included in the meta-analyses. (Appendix XV).

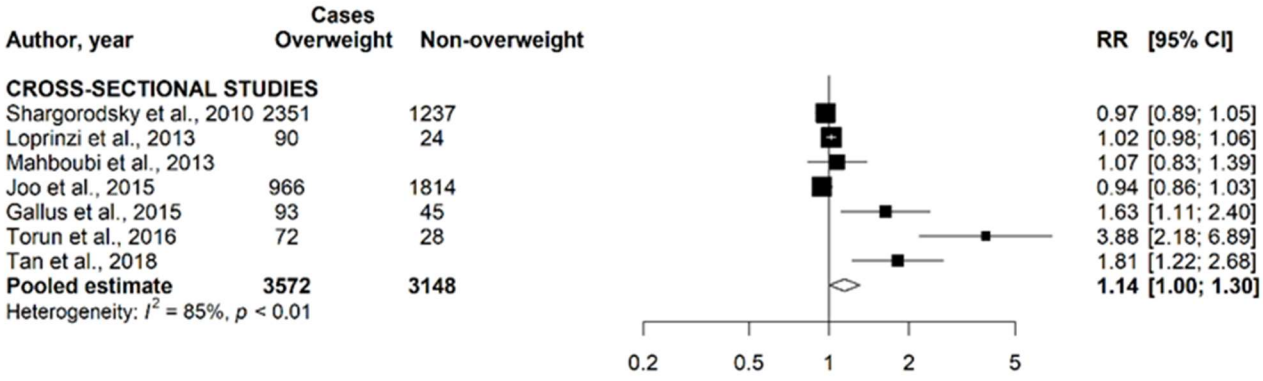


Figure 5.6 Forest plot for tinnitus in overweight versus normal and underweight
The overall pooled estimate (only cross-sectional data available) is not significant, with RR of 1.14 and 95% CI: 1.00, 1.30. (M: Men; W: Women)

Seven (all cross-sectional studies) provided information for overweight versus normal/underweight individuals. Taking all seven studies into consideration, the pooled RR was 1.14 (95% CI: 1.00, 1.30) for overweight individuals. For all pooled estimates, there was a statistically significant between-study heterogeneity (Figure 5.6).

Seven studies (six cross-sectional and one cohort studies) provided information on obese versus non-obese individuals. Considering all seven studies, for obese versus non-obese, the pooled RR was 1.69 (95% CI: 1.14, 2.50), with RR equal to 0.77 (95% CI: 0.40, 1.50) for the only cohort study available. For the six cross-sectional studies included, the RR was 2.46 (95% CI: 1.50, 4.03). For all pooled estimates, there was a statistically significant between-study heterogeneity (Figure 5.7). Therefore, cross-sectional data showed no effect of overweight on the risk of developing tinnitus, although an increased risk was found for the obese. The single cohort study available found no effect of obesity on the risk of developing tinnitus. However, given the scarcity of analytical evidence, caution is warranted when making causal assumptions from these findings.

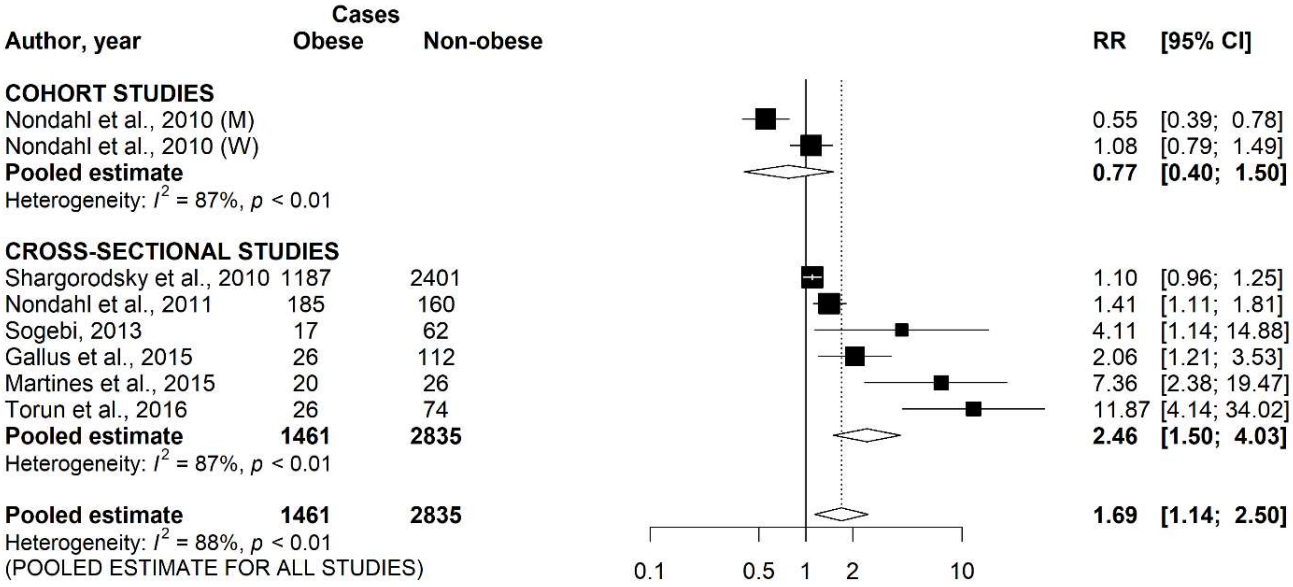


Figure 5.7 Forest plot for any tinnitus in obese versus non-obese individuals
The pooled estimate for cohort studies is not significant with RR of 0.77 and 95% CI: 0.40,1.50. The pooled estimate for cross-sectional studies is statistically significant with RR of 2.46 and 95% CI: 1.50,4.03. The overall pooled estimate is statistically significant with RR of 1.69 and 95% CI: 1.14, 2.50. (M: Men; W: Women)

5.4.4 Caffeine intake

Only three (two cross-sectional and one cohort) studies provided data on tinnitus and caffeine intake. One study provided information on caffeine avoidance as a strategy to reduce tinnitus in affected individuals (Witsell et al., 2011). One study provided data on

caffeine intake in secondary school boys and found no significant association (OR=3.15; 95% CI: 0.56, 17.71) (Marmut et al., 2014). The cohort study evaluated tinnitus in relation to different amounts of caffeine intake with the reference level at 0 to 149 mg of caffeine/ day. Although it was not possible to estimate ORs for caffeine intake and no intake, they reported that higher caffeine intake was related to a lower tinnitus risk in women (Glicksman et al., 2014) (Appendix XVI). The cohort data came from NHSII, a very well-conducted longitudinal study with a very large sample size. The evidence is, therefore, robust. Nonetheless, it is not ideal for establishing causality based on evidence from a single dataset. Considering that the studies assessed different aspects of the risk factor, a meta-analysis was not possible.

5.4.5 Publication bias

No evidence of publication bias emerged for the current, former, and ever smokers either from the visual inspection of the funnel plots or from the Egger's test with p= 0.18, p=0.84, and p=0.59 for current, former, and ever smokers, respectively. No evidence of publication bias emerged for alcohol drinkers (p=0.28 from the Eggers test). Possible publication biases existed for both the BMI related measures-overweight and obese with a p-value for the Egger's test <0.001 in both, and asymmetric funnel plots seen on visual inspection (Appendix XVII). However, given the small number of studies and inherent methodological issues, the p-values do not necessarily imply a publication bias.

5.5 Discussion

This review summarises the findings from all available data on the relationship between tinnitus and selected modifiable lifestyle-related risk factors. This review is a novel attempt to derive pooled estimates for the relationship between tinnitus and alcohol consumption, BMI, and caffeine intake. Current, previous (ex-smokers) and ever smoking, all three significantly increased the risk of tinnitus. One cohort study reported findings on the effect of all three working definitions of smoking on tinnitus (Nondahl et al., 2010). The rest of the data was derived from cross-sectional studies for the meta-analyses on smoking. Alcohol consumption showed no effect on tinnitus development. Only cross-sectional studies were included in the meta-analyses. Being overweight was not associated with

tinnitus, whereas obesity was related to significantly increased risk. Nondahl et al. (2010) reported data on obesity from a cohort study. The rest of the information was derived from cross-sectional studies. All information on being overweight and the risk of developing tinnitus was from cross-sectional studies. In the following sections, these main findings are examined, and the physiological links between each risk factor and tinnitus are discussed.

5.5.1 Smoking

A 27% relative increase in the risk of tinnitus in current smokers and 21% in former and ever smokers was estimated compared to never smokers. These results align with what has been previously reported by Veile et al. (2018), and the pooled estimates of relative risk have relatively similar values. An interesting observation is the reasonably close relative risk estimates in current, former, and ever smokers. Smoking cessation has long-term benefits on cardiovascular and cancer risk (Mons et al., 2015). Cardiovascular disease history is often related to tinnitus, and these two conditions share common risk factors (Nondahl et al., 2011, Nondahl et al., 2002; Park et al., 2014b, Tan et al., 2018). Therefore, similar trends in smoking cessation effect should have been expected for tinnitus as well. A potential cause of this could be misclassification bias resulting from former smokers having quantitatively smoked more than current smokers. Although sensible in the current context, this rationale has not been explored thoroughly.

Had smoking been causally linked to tinnitus, the risk in current smokers should have been higher than in former smokers. The pooled estimates that are slightly higher for current (RR=1.27) than for former (RR=1.21) smokers fit this hypothesis. Another potential strategy to support a causal hypothesis would be an established dose-response relationship. Very few studies have looked at this aspect and inconsistent results (Davis et al., 1992; Nondahl et al., 2011; Nondahl et al., 2010; Hoffman and Reed, 2004).

5.5.2 Alcohol consumption

This meta-analysis did not find any significant relationship between alcohol consumption and tinnitus. Most studies were cross-sectional, and causality could not be determined

since exposure and outcome were assessed simultaneously. It is possible once affected by tinnitus, individuals might choose to opt for a healthier lifestyle and alter their drinking habits. Moreover, investigating the dose-response relationship between alcohol consumption and tinnitus could be useful. Moderate alcohol consumption has a protective role in cardiovascular diseases (Bell et al., 2017; Djoussé et al., 2009). Two studies on tinnitus that looked at a dose-related effect of alcohol consumption, found moderate drinking to be protective (Nondahl et al., 2011; Nondahl et al., 2010). Given the similar risk profile for cardiovascular disease and tinnitus, and data from available cohort studies, it seems worthwhile to examine this aspect in future research.

5.5.3 Body mass index

According to the results, overweight individuals (≥ 25 kg/m^2) had a similar risk compared to normal (and underweight) individuals, while obese people (≥ 30 kg/m^2) had a 69% increased risk of tinnitus. Obesity is a global epidemic that leads to an increase in the risk of mortality and morbidity due to chronic conditions, including cardiovascular diseases and diabetes (Hurt et al., 2011; Visscher and Seidell, 2001). It is a modifiable preventable condition that is on the rise globally (Visscher and Seidell, 2001; Rubenstein, 2005). Obesity strains the body's circulatory system leading to higher blood pressure, lower circulation, and poor oxygenation of cells, including hair cells in the ear, causing tinnitus (Hwang et al., 2013, Salvi et al., 2017). Therefore, besides looking at weight categories, it would be worthwhile to examine BMI as a continuous variable and assess how a unit change of BMI affects tinnitus. This type of analysis has been considered in the cross-sectional analysis of the KNHANES dataset by Kim et al. (2015) and Park et al. (2014b) . Interestingly, the findings mirrored the results from studies on the same dataset that treated BMI as a categorical variable, and found no significant relationship with tinnitus (Kim et al., 2015; Park et al., 2014b, Joo et al., 2015).

5.5.4 Caffeine intake

While Glicksman et al. (2014) provided a dose-response relationship, Marmut et al. (2014) compared coffee consumption habits, i.e., drinkers versus non-drinkers . The third study investigated coffee avoidance as a strategy that helped reduce tinnitus symptoms

in affected individuals (Witsell et al., 2011). Therefore, the studies assessed different aspects of the risk factor, and consequently, a meta-analysis was impossible. The trends observed were also inconclusive since one study showed increased risk, and the other showed a decreased risk of tinnitus. Another potential issue in pooling the data is the specificity of the study populations. While Glicksman et al. (2014) assessed women nurses and Marmut et al. (2014) assessed secondary school boys .

5.5.5 Consistency of findings across study designs

Most available data on tinnitus-related risk factors are derived from cross-sectional studies. Since cross-sectional designs assess exposure and outcome simultaneously, they provide the weakest evidence for assessing risk factor and tinnitus relationships. Case-control study designs are comparatively more effective in establishing the association between tinnitus and lifestyle, although cohort study designs, particularly prospective cohorts, provide the most substantial evidence among observational studies and establish causality most conclusively. In this review, for each risk factor RRs were estimated across all study designs and also RRs for articles with specific study designs, i.e., separately for cross-sectional and cohort studies, to compare study design specific measures of effect. It is to be noted that no case-control studies were found that provided RRs or sufficient data to calculate RRs with regards to tinnitus and modifiable lifestyle-related risk factors.

Study design specific RR estimates provide an opportunity to compare the inconsistencies in measures of risk depending on study design. For example, the risk of developing tinnitus from smoking was consistent across cross-sectional and cohort studies. These findings agree with another systematic review of smoking and tinnitus by Veile et al. (2018). Therefore, although primarily based on cross-sectional data, this relationship seems reasonably well established. For obesity, on the other hand, the cross-sectional studies showed increased risk while the cohort study showed no relationship. Despite cohort studies providing the strongest evidence, given the diverse findings and the paucity of cohort studies (only one for obesity), further investigations by case-control and cohort studies are warranted. From the available cross-sectional data, no relationship

was found between tinnitus and alcohol consumption. However, considering that this finding has not yet been investigated using case-control and cohort study designs, no clear conclusions can be made. The trends imply a protective effect for caffeine intake, although this evidence is based on one cohort study. However, this study was large and very well conducted. Therefore, this inverse association found by Glicksman et al. (2014) should be confirmed by future longitudinal studies despite being based on evidence from one single study .

5.5.6 Heterogeneity between studies

There was statistically significant heterogeneity between the studies included in the meta-analyses. This heterogeneity can either be attributed to random error or could be true heterogeneous effects. One of the major issues in epidemiological research is the lack of a standardised research definition for tinnitus. Many authors have highlighted this issue and the need for cross-culturally adapted survey questions instead of verbatim translations (Gallus et al., 2015; McCormack et al., 2016). While this is crucial for pooling prevalence and incidence estimates across studies, this could lead to heterogeneity when pooling data for risk factor analyses. This inherent challenge in tinnitus assessment methodology and the low number of studies for each risk factor could be responsible for the asymmetric funnel plots for overweight and obesity. A second cause of the between-study heterogeneity is inherent to the diverse study groups and demographics of the sample population. Thirdly, there is the possibility of confounding with other factors when there is a multi-causal effect of risk factors on tinnitus.

5.5.7 Knowledge gaps

The major drawback of risk factor analysis for tinnitus is that the body of literature is primarily limited to cross-sectional studies where causality cannot be determined. Additionally, there is substantial heterogeneity between studies in terms of assessment methods of risk factors. Data on modifiable lifestyle-related risk factors for tinnitus is plagued by these two issues as well. Smoking is the only factor that can probably be deemed a risk factor for tinnitus, since the finding is consistent in cross-sectional and cohort studies and has been found in another meta-analysis. Obesity is potentially a risk

factor, but this awaits confirmation by future case-control and cohort studies. Nothing conclusive can be said about alcohol consumption since the evidence is cross-sectional. On the other hand, caffeine intake has one study showing reduced risk, although the quality of evidence is robust. However, both these risk factors need to be examined further with analytical observational studies.

5.5.8 Future directions

Due to the limited evidence currently available, one hesitates to make firm conclusions about the role of lifestyle-related factors on tinnitus development. There are some notable trends in the association between tinnitus and the four modifiable lifestyle-related risk factors explored in this review. However, these associations need to be established by well-conducted analytical studies, particularly prospective cohort studies showing a temporal sequence of events. Therefore, conducting new, extensive, well-designed prospective cohort studies is needed.

The role of a biological gradient, i.e., dose-response relationship, in establishing causality is debated in epidemiological literature, with studies suggesting that such results may arise from confounding (Lucas and McMichael, 2005; Rothman et al., 1998). Nonetheless, such information might be useful in indicating some cut-off above which risk increases and inform public health practice and policy guidelines. Smoking, unhealthy alcohol consumption, unhealthy diet, and physical inactivity are the four most common modifiable risk factors for chronic non-communicable conditions (WHO, 2012). Additionally, lifestyle-factors often co-exist in clusters. This is particularly true for the four most common modifiable risk factors for chronic non-communicable conditions (Poortinga, 2007; Schuit et al., 2002). There is also a substantial correlation between some of these risk factors (Balhareth et al., 2019; Bradbury et al., 2017; Fogelholm et al., 2012). Therefore, while analysing isolated risk factors is relevant for addressing the more specific knowledge gaps, perhaps investigating clusters of risk behaviours is more useful from a policy and public health point of view. In recent years, using an integrated approach to address multiple health risk behaviours has been identified by multiple stakeholders,

such as patients, employers, health systems, and policymakers, for being more efficient in terms of time, effort, and resources (Orleans, 2004; Pronk et al., 2004).

5.5.9 Concluding remarks

Longer life expectancy and an ageing population, along with the lack of a definite cure, contribute to the increasing burden of tinnitus. Additionally, tinnitus exerts a substantial burden on healthcare and personnel resources. Knowledge of unhealthy lifestyle choices that lead to tinnitus development can help in developing promotional activities towards tackling these risk factors. Timely interventions are cost-effective measures that might reduce tinnitus incidence and, consequently, minimize the rising burden on healthcare systems. Even though the results from this review on modifiable risk factors do not provide conclusive causal evidence, yet from a policy perspective, it would be beneficial to educate the general public on the likely effect of a lifestyle on tinnitus and to implement adequate measures to encourage positive health behaviour change.

Chapter 6 . Investigating the effect of dietary patterns, alcohol consumption and obesity on the risk of incident tinnitus using a prospective cohort dataset

6.1 Introduction

There is evidence that tinnitus is related to modifiable lifestyle-related factors, thereby offering possibilities for implementing adequate preventive measures. Chapters 4 and 5 review the current information on tinnitus-related risk factors. In Chapter 5, meta-analytic approaches were used to examine the relationship between tinnitus and selected modifiable risk factors, including alcohol and obesity, related to other non-communicable conditions. Although some trends were seen from the meta-analyses, no conclusive statements could be made about the associations given the lack of prospective study results. Diet is another essential lifestyle-related factor hypothesised to be related to tinnitus, but knowledge gaps are apparent (Spankovich, 2015).

In tinnitus research, a major underlying factor for the gaps in knowledge is the lack of longitudinal studies. The need for longitudinal, i.e., prospective studies to examine risk factors has been highlighted, and the same was evident from the literature reviews described in the previous chapters (Baguley et al., 2013; Gallus et al., 2015). Another option is to investigate existing prospective datasets with information on tinnitus and potential risk factors (Biswas and Hall, 2020). In this study, an existing population-based dataset was analysed to investigate the relationships between tinnitus and modifiable lifestyle-related factors such as diet, alcohol consumption, and obesity.

6.1.1 Diet and tinnitus

Diet has been reported to have important implications for hearing status. Healthy dietary patterns have been associated with a reduced risk of hearing impairment, while a diet high in lipids, carbohydrates, and sugars has been associated with poor hearing (Curhan et al., 2018; Dawes et al., 2020). Given that tinnitus is more common in people with hearing impairment, analysis of prospectively collected data would provide new insights into the association between dietary patterns and tinnitus. However, there has been limited research in this area, and the lack of consensus on the available evidence is apparent.

In a survey by Hall et al. (2013), both patients and clinicians have identified the role of diet in tinnitus as a research priority. In section 4.5.6, the paucity and inconsistencies in the published literature on the relationship between diet and tinnitus were discussed. Some anecdotal evidence is available regarding the role of specific foods, single nutrients, and dietary supplements in worsening or reducing tinnitus perception in individuals (British Tinnitus Association, 2018; Seidman and Babu, 2003; Patterson and Balough, 2006). Reduction in tinnitus in people with hyperinsulinemia following a low fat, low-calorie diabetic diet was reported by two controlled studies (Basut et al., 2003; Lavinsky et al., 2004). Some population-level data are also available for diet and tinnitus. McCormack et al. (2014b) analysed the UK Biobank, a cross-sectional dataset, and reported inconsistent associations between dietary information and persistent, bothersome, or transient tinnitus. To assess diet, they used a non-validated food frequency questionnaire. High intake of fruits and vegetables, bread, fish, and egg, increased the likelihood of persistent tinnitus, while dairy products and caffeine reduced the likelihood. Bothersome tinnitus that resulted in moderate to severe handicap was reported to have increased likelihood with wholemeal/wholegrain bread intake (McCormack et al., 2014b).

In contrast, the intake of brown bread and reduced dairy products, and caffeine was related to a reduced likelihood of transient tinnitus (McCormack et al., 2014b). Spankovich et al. (2017) analysed the cross-sectional NHANES dataset and reported a healthy diet comprising a high intake of fruits and vegetables and wholegrains reduced the likelihood of tinnitus. The dietary information for this study was indexed by the Healthy Eating Index scores developed by the United States Department of Agriculture (1995) (Spankovich et al., 2017). The results from the study by Spankovich et al. (2017) contradicted the results from McCormack et al. (2014b). Another population-based cross-sectional study in a Korean population sample (from KNHANES) used a non-validated semi-quantitative food frequency and reported lower intakes of vitamin B2 and B3 and water increased the likelihood of tinnitus perception and related annoyance estimated (Lee and Kim, 2018). Longitudinal associations between healthy dietary patterns and tinnitus have not been evaluated previously.

6.1.2 Alcohol consumption and tinnitus

Research on the question of whether alcohol intake affects tinnitus has not yet been resolved on an answer. There are inconsistencies in many of the details, and why it does (if it does) remains obscure. For example, moderate alcohol intake links to reduced risk for tinnitus, whereas heavy drinking may have no relationship (Gallus et al., 2015). Moderate alcohol consumption has been reported to have a protective effect on hearing impairment (Popelka et al., 2000; Fransen et al., 2008). The meta-analysis on alcohol (drinkers versus non-drinkers) and tinnitus described in Chapter 5 reported that alcohol does not affect the risk of tinnitus. However, most of the included studies were cross-sectional, and therefore, nothing could be said conclusively about the relationship. Additionally, while there could be a dose-dependent relationship between tinnitus and alcohol consumption, very few studies have looked at this aspect and with inconsistent findings (Nondahl et al., 2010; Nondahl et al., 2011, Hoffman and Reed, 2004).

6.1.3 Obesity and tinnitus

The information on the role of obesity on the risk of developing tinnitus is also inconsistent (Gallus et al., 2015, Kim et al., 2015, Nondahl et al., 2010, Shargorodsky et al., 2010). The meta-analysis on obesity and tinnitus described in Chapter 5 reported that obese individuals have a greater risk of tinnitus. However, considering that this finding is based mainly on cross-sectional studies (the meta-analysis included only one cohort study), further evaluation is warranted, especially using prospectively collected data.

Risk factors, particularly lifestyle-related risk factors, usually coexist, and eventual effects often result from a combination of individual effects and mutual interaction. In section 5.1.2, the rationale behind studying risk factors as clusters have been described. This unified approach is particularly relevant for obesity. Obesity is intrinsically related to other important lifestyle factors such as an unhealthy diet.

6.2 Study objectives

This study is a novel attempt to examine the association between dietary patterns (namely DASH and AMED) and incident tinnitus in adult women participating in NHSII.

Additionally, the associations between alcohol consumption and obesity with incident tinnitus are also investigated in the same cohort.

The three main objectives and research questions addressed in this study are as follows:

1. To determine the association between dietary patterns and incident tinnitus

i. Is greater adherence to healthy dietary patterns, indicated by the DASH and AMED scores, associated with lower risk of incident tinnitus?

2. To determine the association between alcohol consumption and incident tinnitus in adult women, and to assess whether there is a dose-dependent relationship

ii. Is higher alcohol consumption associated with higher risk of incident tinnitus? Is the magnitude of the elevated risk dose-dependent?

3. To determine the association between obesity and tinnitus in adult women

iii. Is obesity, specifically greater BMI and larger waist circumference, associated with higher risk of incident tinnitus?

By including the analysis for different levels of alcohol consumption (i.e., low versus moderate intake) in prospectively collected data from the NHSII study, it might be possible to provide new insights rather than repeat previous findings. Should an effect be found, a plausible rationale is that it is related to alcohol-related damage to blood vessels, which are crucial to proper cochlear function. Moreover, in this analysis, obesity is measured using BMI and waist circumference to better predict the association with the risk of developing tinnitus.

6.3 Methods

6.3.1 Study design and population

The Nurses' Health Study (NHS) and the NHSII are among the most extensive prospective cohort studies investigating the risk factors for chronic health conditions in adult women (Bao et al., 2016). The NHS, established in 1976 and funded by the National Institutes of Health, focussed initially on research related to contraception, smoking, cancer, and cardiovascular disease, but later expanded to include many other lifestyle factors and behaviours. The NHS II was established in 1989 and is funded by the National Institutes of Health since then. In NHSII, a population younger

than the original NHS cohort was recruited. The study's primary motivation was to investigate the potential long-term consequences of oral contraceptives, which were being prescribed to hundreds of millions of women since adolescence. Information was also collected on diet, physical activity, and lifestyle risk factors. The NHS II is an ongoing prospective cohort study of 116,430 female registered nurses who were aged 25 to 42 years and lived in 14 US states at the time of enrolment to the cohort in 1989 (Bao et al., 2016).

Participants have been followed up by biennially mailed questionnaires that collect information on diseases and health conditions and various health-related topics, including smoking, hormone use, pregnancy history, and menopausal status. Participant response rates to NHSII is about 85-90% for each two-year cycle. Given that diet and nutrition might play vital roles in chronic disease, since 1991, a food-frequency questionnaire is administered every four years. QOL questions were first included in 1993 and continue to be administered every four years. Additionally, various supplemental questionnaires have been sent to selected participants to collect data for specific research questions and better describe reported diseases and health outcomes. Previous studies on this dataset have explored the effect of smoking, alcohol consumption, diet, obesity, physical activity, oral contraceptives, and post-menopausal therapy on cancer, cardiovascular diseases, fracture, and eye diseases. Studies have also explored the relationship between diet, alcohol consumption, and physical activity on cognitive functions and hearing difficulty. One study also addressed the relationship between caffeine intake and tinnitus.

In the NHSII questionnaires, the presence of tinnitus was assessed using the question: "In the 12 months, have you had ringing, roaring or buzzing in your ears?". Question regarding the age of onset of tinnitus symptoms was asked only in the 2009 long-form questionnaire (https://www.nurseshealthstudy.org/participants/questionnaires) ("At what age did this first begin?"; response options: "<30", "30-39", "40-49", "50-59", "60+"). Therefore, for this study, participants included women who answered the tinnitus question on the 2009 long-form questionnaire. Women who did not respond to the tinnitus questions in the 2009 questionnaire, but responded to the 2013 and 2017 questionnaires, were also included in this study. In both these questionnaires, participants were asked about tinnitus symptoms and not about the age of onset.

Therefore, women who responded as having no tinnitus in 2013 but reported tinnitus symptoms in 2017 were included as new onset cases (incident cases) of tinnitus.

Women reporting tinnitus before study baseline (1991), with a history of cancer other than non-melanoma skin cancer (due to possible exposure to ototoxic chemotherapeutic agents), and those who did not answer the 1991 baseline diet questionnaire (Semi-quantitative food frequency questionnaire (SFFQ)) were excluded from the analysis. In the analysis, the total follow-up period was 1,321,968 person-years and included 67997 women. The NHSII cohort is managed by the Brigham and Women's, Hospital, Harvard Medical School, and Harvard T.H. Chan School of Public Health. The Institutional Review Board of the Brigham and Women's Hospital approved the protocol for this specific project.

6.3.2 Assessment of exposures

Since this was a prospective cohort study, all exposure information was collected before the onset of tinnitus. Although the NHSII cohort study started in 1989, since dietary information was first collected in 1991, the latter is regarded as the baseline for this study.

6.3.2.1 Diet

In the NHSII, the semi-quantitative food frequency questionnaire (SFFQ) developed by Willett et al. (1985) was administered once every four years to ascertain the usual diet. The SFFQ is a validated dietary data collection method that has been used extensively worldwide to examine relations between diet and numerous health outcomes (Rimm et al.1992; Willet et al.1985; Willet et al., 1988). It includes more than 130 foods, more than 20 beverages, and vitamin/mineral supplement use, accounting for over 90% of the measured nutrient intake (Willet et al., 1985). To assess the reproducibility and validity of the SFFQ, previous validation studies were conducted among members of the NHS. Good correlations were reported between nutrients assessed by the questionnaire and multiple weeks of diet records completed over the preceding year. This means that the results from the SFFQ closely correspond to the results from the weekly diet records. Moreover, a high degree of reproducibility was reported for dietary intake assessed by SFFQs administered one-year apart (Willett, 1988; Yuan et al., 2017).

In the SFFQ, a commonly used unit or portion size is specified for each food. Participants are asked how often, on average, they consumed each type of food or beverage during the previous year. Nine possible response options range from “never or less than 1 per month” to “6 or more times per day”. Nutrient intake was calculated by multiplying the portion size of a single serving of each food by its reported frequency of intake, multiplying the total amount consumed by the nutrient content of the food, and then summing the nutrient contributions of all food items, with the use of USDA food composition data (Mangels et al., 1993; Nutrient Data laboratory, 1999). Information on the use of multiple vitamins (specific brand and the usual number of tablets taken per week) and specific supplements was used to assess supplement use. Estimates of energy and nutrient consumption were derived from the frequency of consumption of foods and beverages and an overall estimate of the usual portion size obtained from the SFFQ (Willet et al., 1988). The information obtained on each SFFQ, i.e., every four years, was used to calculate the cumulative average DASH and AMED scores that measured adherence to the healthy dietary patterns.

The DASH diet has been designed to reduce blood pressure. In cases where the diet has been followed, it has been associated with a lower risk of hypertension, cardiovascular disease, diabetes, and cognitive decline (Appel et al., 2006; Ard et al., 2004; Fung et al., 2008). The National Heart, Lung, and Blood Institute of the US provides sample plans based on 1600, 2000, or 2600 calorie intake per day. These plans include specific serving sizes for the following food components: grains or grain products (preferable whole-grain), fruits, vegetables, low-fat dairy food, fats and oils, lean meat, poultry or fish, nuts, seeds or dry beans, and sweets and food with added sugars. In DASH, lowering sodium intake, sweets (in drinks and foods), and red meat is recommended. Reduced intake of saturated and trans-saturated fat and increased intake of potassium, magnesium, protein, and fibre are recommended (van Horn et al., 2016).

For this project, a DASH score was created based on the individual consumption of these foods and nutrients recommended in the DASH diet. The component score was measured as the participants’ quintile rankings. For food where a relatively high intake is recommended, such as fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains, quintile 1 was assigned 1 point, and quintile 5 was assigned 5 points. For food where a relatively low intake is recommended, such as sodium, red and

processed meats, sugar, and sweetened beverages, quintile 1 was assigned 5 points, and quintile 5 was assigned 1 point. The component scores were summed to obtain an overall DASH score, with a minimum of 8 indicating poor adherence to the DASH diet and a maximum of 40 indicating perfect adherence (Fung et al., 2008; Karanja et al., 1999).

The Mediterranean diet reflects the typical diet consumed in Mediterranean countries (e.g., Greece, Italy). In cases where the diet has been followed, it has been reported to be associated with a lower risk of many chronic diseases, including coronary heart disease, stroke, cognitive disorders, and some cancers, in clinical and epidemiological studies worldwide (Bamia et al., 2013; Fung et al., 2009; Feart and Barberger-Gateau, 2015; Praud et al., 2014; Sofi et al., 2010; Willet et al., 1995). In this project, an AMED score was created based on the individual consumption of those foods that are desirable items within the Mediterranean diet. The AMED score comprises the following nine food items: vegetables (except potatoes), fruits, nuts, legumes, whole grains, monounsaturated-to-saturated fat ratio, fish, red/processed meats, and alcohol (Fung et al., 2009). For red/processed meats, 1 point was given when intake was less than the median intake. For alcohol, 1 point was given for intakes within the range of 5–15 g/day (14 grams of pure alcohol is regarded as one standard drink per US guidelines). For the remaining items, 1 point was given for each desirable component if the participant's intake of that item was greater than the median; otherwise, no point was assigned. The total AMED score ranged from 0 to 9. Since alcohol consumption was a specific research question, two variants of AMED diet were used as exposure variables: one including alcohol as a component and one without alcohol.

Dietary exposure information was updated every four years when the participants filled out the SFFQ. Person-months of follow-up were allocated according to exposure status at the start of each follow-up period. In the absence of complete dietary information at the beginning of a time period, the participant was skipped from the associated time period. For all dietary patterns, the diet scores were categorised into quintiles based on the distribution of the entire analytic cohort. The cumulative average of the diet scores from all available SFFQs up to the start of each follow-up interval period was used as the exposure, and the use of repeated SFFQs was optimised. Tinnitus incidence in the interval between each SFFQs was related to the cumulative average intake from all preceding measures. For example, the DASH score in 1991

was used to predict tinnitus occurrence from 1991 to 1995, and the mean score from 1991 and 1995 was used to predict tinnitus risk from 1995 to 1999. For all dietary patterns examined, the lowest quintile served as the reference group,

Even though the two dietary patterns evaluated in the study, DASH and AMED, have some common components, there are still several differences, particularly regarding the derivation of scores and the components they incorporate. The DASH diet incorporates a high intake of some specific food components, and there are specified recommendations for the level of intake; such as 4 to 5 daily servings of fruits, 4 to 5 daily servings of vegetables, 7 to 8 servings per day of whole grains, 2 to 3 daily servings of low-fat or non-fat dairy, ≤2 servings per day of fish and poultry, 4 to 5 servings per week of nuts, seeds, and dry beans, and two servings per day of fats and oils. Limited intake of red meat, sweets, and sugary drinks is recommended in the DASH diet pattern (Fung et al., 2008; Karanja et al., 1999). In the AMED dietary pattern, extra virgin olive oil, whole, and minimally processed grains, legumes, vegetables (except potatoes), fruit, nuts, fish, and regular but modest alcohol intake are recommended. The main difference between the two dietary patterns is that, unlike DASH, in AMED, food components are grouped hierarchically, and no specified amounts for each food group are recommended. For example, in AMED, vegetables, fruits, nuts, whole grains, and vegetable oils, particularly olive oil, are at the base of the diet, followed by fish in the second tier, with ≥2 servings per week recommended. Poultry and dairy are recommended in moderate amounts, while meats and sweets are advised to be consumed “less often.” A key point of difference is that in DASH, alcohol intake is not included, while in AMED, it is recommended in moderation (Appel et al., 2006; Fung et al., 2009).

6.3.2.2 Alcohol consumption

The SFFQ asked separate questions about the consumption of regular beer (1 glass, bottle, can), light beer (1 glass, bottle, can), red wine (4 oz. (120 mL) glass), white wine (4 oz. (20 mL) glass), and liquor (for example, whiskey, gin) (1 drink or shot). Response options were “never or less than once/month”, “1 to 3/month”, “1/week”, “2-4/week”, “5-6/week”, “1/day”, “2-3/day”, “4-5/day”, and “6 or more/day”. Regular beer was considered to contain 13 g of alcohol per serving, light beer 11 g, wine 11 g per 4 oz serving, and spirits 14 g per serving. Total grams per day of alcohol were calculated

by summing the frequency of consumption multiplied by the alcohol content of the reported beverages. This method of calculating alcohol consumption was validated in a similar cohort of women by collecting information on two SFFQs administered one year apart and four one-week diet records collected three months apart over a period of one year. The correlation for alcohol consumption between questionnaires and dietary records was r = 0.90 (Giovannucci et al., 1991). This means that results from the SFFQ correspond closely to the results from the weekly diet records. The categories of alcohol consumption are provided in table 6.1.

For alcohol consumption, a cumulative average of total intake over the follow-up period was used to evaluate the relation of long-term exposure to alcohol and tinnitus. For alcohol consumption, no drinking was the reference category. Tinnitus incidence in the interval between each SFFQs was related to the cumulative average intake from all preceding measures.

Table 6.1 Primary exposures of interest and corresponding categories

Exposure	Measure	Categorisation
DASH score	Cumulative average DASH score	Quintiles
AMED score	Cumulative average AMED score	Quintiles
Alcohol consumption	Cumulative average alcohol intake (grams/day)	0 (reference) 0.1 to 4.9, 5 to 14.9, 15 to 29.9 30 to 34.9 35-39.9 40-44.9 45+ grams/day
BMI	Weight (kg) / height^2(m^2)	<18.5 (Underweight) 18.5-24.9 (Normal weight reference) 25–29.9 (Overweight) 30-34.9 (Class I Obesity) 35-39.9 (Class II Obesity) ≥40 (Class III Obesity)
Waist circumference	Waist (cm)	≤70 (reference) 71–79 80–87 ≥88

BMI, Body Mass Index; DASH, Dietary Approaches to Stop Hypertension; AMED, Alternate Mediterranean Diet

6.3.2.3 Obesity

BMI is the most widely used measure of obesity (Ghesmaty Sangachin et al., 2018; WHO, 1995). However, it has certain limitations. It does not reflect body shape and can be misleading as it does not account for factors like a high proportion of lean muscle mass. Waist circumference is the measure for the distribution of body fat and is more strongly associated with obesity-related health risks (Brown, 2009; Janssen et al., 2004; Seidell, 2010). Moreover, evidence indicates that waist circumference, coupled with BMI, predicts health risk better than BMI alone (Ardern et al., 2003; Janssen et al., 2002; Rexrode et al., 1998). Therefore, in this analysis, waist

circumference and BMI, both exposure variables were used to examine the risk of obesity for incident tinnitus.

BMI was measured in kg/m^2 and calculated at each two-year cycle from the current weight, and the height reported on the baseline questionnaire. BMI was categorised following the WHO categories (Table 6.1). Waist circumference was measured in centimetres. It was self-reported and assessed at two time points, i.e.,1993 and 2005, when participants were sent a measuring tape and asked to report their waist circumference to the nearest one-fourth inch (categories in Table 6.1). There is no specific categorisation for waist circumference, unlike BMI. Based on gender, the cut-offs for waist circumference are different. Moreover, people from different ethnicities have different body builds and proportions—hence different waist circumference cut-off points. For example, Asians have a naturally petite frame, and therefore the cut-off for Japanese, Chinese, and South Asian people is lower than for Caucasians. However, as a general guide, increased health risks are associated with a waist circumference greater than or equal to 94 cm in men and 80 cm in women. For white adult females, a waist circumference greater than 88 cm denotes a high waist circumference (Ross et al., 2020). For BMI, normal weight individuals were the reference group, and for waist circumference, the lowest category, i.e., equal to or less than 70 cm, served as the reference group (Table 6.1).

6.3.2.4 Tinnitus as the outcome of interest

The primary outcome of interest was tinnitus. In the 2009 long-form questionnaire for NHSII, two questions were asked on tinnitus. The first question was, “In the 12 months, have you had ringing, roaring or buzzing in your ears?” with response options “never”, “one/week or less”, “a few days/week”, and “daily”. Except for those who responded “never”, participants were then asked, “At what age did this first begin?” with response options “<30”, “30-39”, “40-49”, “50-59”, and “60+”. This data was used to identify the incident cases of tinnitus, and all exposure information was calculated before the onset of tinnitus symptoms. In this study, participants did not report a particular date of onset of tinnitus symptoms. Instead, they reported an age category when tinnitus symptoms were first noticed. For this study, the date of reported tinnitus was considered the midpoint of the reported age category when tinnitus symptoms were first noticed. This information was used as the “age of onset” of tinnitus. In the 2013 and 2017

questionnaires, participants were asked the same question ("In the 12 months, have you had ringing, roaring or buzzing in your ears?"), but with slightly different response options (i.e. "never", "one/month or less", "2-3 times/month", "about once per week", "several times per week", and "almost everyday").

Tinnitus cases were defined as those participants who (i) reported tinnitus occurring several times per week or more (response options: "a few days per weeks" and "daily") on the 2009 questionnaire, or (ii) responded "never" on the 2013 questionnaire and then several days per week or more (i.e., response options: "several times/week", "almost everyday", or "everyday") on the 2017 questionnaire. Reference cases were those participants who responded "never" to the tinnitus question. Those who responded "once/week" and "about once/week" on the 2009 questionnaire were skipped for that specific questionnaire cycle but were allowed to re-enter in later cycles if they become cases, i.e., reported tinnitus occurring "several times/week", "almost everyday", or "everyday".

6.3.2.5 Accounting for known expected confounders

Covariates that could be potential confounders were considered in the multivariable analyses. These included age (Bhatt et al., 2016; Gallus et al., 2015; Nondahl et al., 2011), race (House et al., 2018; Shargorodsky et al., 2010), smoking status (Veile et al., 2018), physical activity (Fujii et al.,2011; Loprinzi et al., 2013; Nondahl et al., 2011), history of hypertension (Yang et al., 2015), history of diabetes (Kaźmierczak and Doroszewska, 2001), history of depression (Andersson et al., 2003; Geocze et al., 2013)., ototoxic medication use (aspirin, ibuprofen, tylenol) (Baguley et al., 2013), and hearing difficulty. In chapters Chapters 4 and 5, the relationship between the confounders mentioned above and tinnitus has been addressed. Both exposure and covariate information were collected before tinnitus onset.

The Andersen-Gill counting process was used with a new data record being created for each biennial questionnaire to handle time varying covariates. It is formulated in terms of increments in the number of events along the time line. Here, it is a suitable model since we are interested in the outcome since exposure until an event occurs, i.e. time since study entry, The Andersen-Gill model assumes conditional uncorrelation for the given covariate, i.e. the correlation between event times for an individual can be explained by past events. Time dependent covariates apply for each questionnaire

cycle i.e., from the start of an interval and events occur at the end of an interval. During the analysis process, a new dataset is created with a new row for each questionnaire cycle. Each row of the resulting data set represents a time interval (time1, time2). Covariate values for each row are the covariate values that apply over that interval. The event variable for each row is 1 if the time interval ends with an event and 0 otherwise (Andersen and Gill, 1982). To control potential confounding by age, calendar time, and possible two-way interactions between these two time scales, the analysis was stratified simultaneously by age in months at the start of follow-up and calendar year of the current associated questionnaire cycle. The time scale for the analysis was measured as months since the start of the questionnaire cycle, equivalent to age in months.

The race was taken from the response given on the baseline questionnaire in 1991. Smoking status was based on the most up-to-date self-reported smoking status on the biennial questionnaires; and categorised as never smoker, past smoker, current smoker. Total physical activity was measured as energy expenditure in metabolic-equivalent tasks (METs) in hours/week and assessed from the physical activity grid completed by the participants in each questionnaire cycle Table 6.2. It was reported as average time spent per week in the previous year in a variety of recreational activities (for example, walking for exercise, walking to work, hiking outdoors, jogging, lower-intensity exercise such as yoga or stretching, vigorous activities such as weight training, flights of stairs climbed daily, etc.). Total physical activity was calculated as energy expenditure in METs in hours/week using the Ainsworth classification and was categorised in quintiles according to total METS expended per day (Ainsworth et al., 2011).

Histories of hypertension and diabetes were categorised as binary response options (“yes” or “no”), depending on participant report of whether a clinician had made a new diagnosis of the condition during the preceding two years. History of depression was categorised into binary response options (yes or no) depending on participant report of whether a clinician had made a new diagnosis of the condition during the preceding two years and/or if the participant had used anti-depressants in the past two years. Data on the history of depression was only available for the questionnaire administered in the year 2003.

Ototoxic medication information was available for aspirin, acetaminophen, and ibuprofen only from the 1995 questionnaire. Study participants were asked about regular medication use with response options categorised in days/week, as follows: None, 1 day/week, 2–3 days/week, 4–5 days/week, and ≥6 days/week.

Hearing difficulty was self-reported and assessed using the question "Which best describes your hearing?" with the following response options "excellent," "good," "a little hearing trouble," "moderate hearing trouble," and "deaf." Hearing difficulty was categorised as: no, mild, and moderate, or worse.

Details of covariate categories are provided in Table 6.2. Updated covariate information was obtained from biennial questionnaires. Covariates included in the multivariable models were age (continuous), race (5 categories), total physical activity (5 categories), smoking status (3 categories), hypertension (yes/no), diabetes (yes/no), depression (yes/no), ototoxic medication (aspirin, acetaminophen, ibuprofen) (5 categories), and hearing difficulty status (3 categories) (Table 6.2).

Table 6.2 Covariate measures and corresponding categories

Covariates	Measures	Categories
Age	In years	Continuous
Race/Ethnicity	Self-reported from baseline questionnaires	White Black Asian Hispanic Other ancestry
Physical activity	Total physical activity measured in METs in hours/week	Quintiles
Smoking	Do you currently smoke cigarettes?	Never (reference) Past[a] Current
Hypertension	Have you ever had any of these clinician-diagnosed illnesses?	No (reference) Yes
Diabetes	Have you ever had any of these clinician-diagnosed illnesses?	No (reference) Yes
Depression	Have you ever had any of these clinician-diagnosed illnesses? Or Use of anti-depressants in past two years	No (reference) Yes
Ototoxic medications • Aspirin • Ibuprofen • Tylenol	Regular use of medication	None (reference) 1 day/week 2–3 days/week 4–5 days/week ≥6 days/week.
Hearing difficulty	Response to: Which best describes your hearing? (self-reported)	No= Excellent/good (reference) Mild= A little hearing trouble Moderate or worse = Moderate hearing trouble/ a lot of hearing trouble/ deaf

[a]The prospectively collected information was updated every questionnaire cycle; therefore, if an individual answered "yes" to smoking in a previous questionnaire cycle and answered "no" in the subsequent cycle-they were categorised as "past smokers"

6.3.3 Statistical analysis

The study design was prospective, with information collected before the onset of tinnitus symptoms. Person-time of follow-up was calculated starting from the date of return of the 1991 questionnaire until the date of self-reported tinnitus onset, date of

onset of cancer (other than non-melanoma skin cancer), or end of follow-up in 2017. Relative risk (RR) was used to measure the association between the exposures and the outcome (i.e., tinnitus).

Cox proportional hazards regression models were used to estimate RRs and 95% CIs in age-adjusted and multivariate analyses (Cox, 1972). Since mutiple primary exposures were examined (DASH diet score, AMED diet score (with alcohol in the score), AMED-no alcohol diet score (the AMED without alcohol), alcohol consumption, BMI, and waist circumference, and many known confounders were taken into account, the following set of models were run for each of the exposures.

- Models only adjusted for age for each of the five primary exposures, i.e., separate age-adjusted models for DASH score, AMED, AMED no alcohol, alcohol, BMI, and waist circumference.
- Since hearing status and tinnitus are very closely related, two independent multivariate models were specified for each exposure variable, with and without adjusting for hearing status, to assess confounding.
    - The first version of multivariate models for each of the primary exposure adjusted for all covariates except for hearing status, i.e., adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use).
    - The second version of multivariate models for each of the primary exposure adjusted for all covariates including hearing status, i.e., adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
- Full multivariate models included exposures for dietary pattern, alcohol intake and obesity, and the covariates, as follows:
    - Age, DASH score, Alcohol intake, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.

- Age, AMED score, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is in the AMED score, it was not included as a covariate in the model)
- Age, AMED score no alcohol, alcohol intake, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is not in the dietary score it was included as a covariate in the model)

In this analysis, covariate selection was based on biological plausibility and information previous studies. Covariates selected had some prior information of being related to tinnitus. For example, since tinnitus occurs more frequently in elderly patients and people with hearing difficulty, both were included as covariates. An alternative approach to variable selection for confounding control could have been made based on statistical grounds. Data mining is the process of exploring a dataset and allowing the patterns in the sample to suggest the correct model rather than being guided by theory. Numerous combinations of all available independent variables can be tested to uncover statistically significant relationships. Tests can investigate whether controlling for a covariate changes an estimate by more than 10%, or by forward and backward selection of variables, or by automated model building procedures such as stepwise or best subset regression or more contemporary machine learning methods.

However, using statistical analysis for making decisions about covariate selection is not always adequate. The NHSII dataset includes information on many independent variables as the purpose was to examine various chronic health conditions (see Section 6.3.1). Therefore, the data was not collected with tinnitus as the sole outcome to be investigated, and not all independent variables in the dataset are related to tinnitus. Adding only statistically significant variables would give a seemingly improved model. Nonetheless, variable selection based only on significance thresholds can lead to exclusion of non significant variables even though the relationship is known and has a biological basis. Using statistical methods for covariate selection could use a set of randomly generated covariates and find statistically significant correlations to explain

most of the variation in any randomly generated dependent variable, including tinnitus. As a result, we could see chance patterns in the sample data that are probably not present in the population.

Instead in this analysis substantive knowledge from available literature was used to make decisions as to what variables might potentially be considered a confounder before adding them to the final model (Section 6.3.2.5). The disadvantage of the approach used is the possibility of residual confounding due to unknown confounding variables. However, given the lack of information on causal factors for tinnitus, this approach to covariate selection was decided on.

All P values were two-tailed and considered statistically significant at $P < 0.05$. Statistical tests were performed with SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC).

6.4 Results

6.4.1 Descriptive statistics

According to DASH and AMED dietary pattern categories, baseline characteristics of the study participants are provided in Table 6.3. The population was relatively young, with the mean age in all quintiles for both dietary patterns around 36 years. The population was predominantly composed of young, healthy (less than 10% had hypertension and diabetes, and around 12% had depression), non-smoking Caucasian women with the majority having no hearing difficulty. Since the baseline distribution tables looked relatively similar, the characteristics according to quintiles of AMED score without alcohol, categories of alcohol intake, BMI, and waist circumference are reported in Appendix XVIII to XX. It is relevant to note that there were very few participants in the higher alcohol intake categories with 237 women in the 30-34.9 grams of alcohol/day category, 160 women in the 35-39.9 grams/day category, 69 women in the 40-44.9 grams/day category and 142 women in the 45+ grams/day category (Appendix XIX).

During 1,321,968 person-years of follow-up on 67,997 participants, there were 11,024 cases of incident tinnitus. The results of the modelling for each exposure of interest are discussed in turn.

6.4.2 Diet and tinnitus

According to the different quintiles of DASH, AMED diet scores, and AMED score without alcohol, the age- and multivariate-adjusted RRs for tinnitus are reported in Tables 6.4A, 6.4 B, and 6.4C. For the DASH diet: In the age-adjusted and the first version of the multivariate models, no significant association was observed between DASH diet and tinnitus. Adjusting for hearing status (multivariate model second version), the two highest DASH quintiles (i.e., with maximum adherence to the DASH dietary pattern) were associated with a higher tinnitus risk compared to the reference category. The observed pattern was maintained even with the full multivariate model, i.e. adjusting for all exposure variables and covariates. For example, in the full model, women in the highest DASH quintile had multivariate RR 1.10 (95% CI 1.03,1.18) compared to women in the lowest quintile (Table 6.4A). This finding suggests that after adjusting for all potential confounders, greater adherence to DASH dietary pattern increased incident tinnitus risk.

For the AMED diet: In the age-adjusted analysis, no significant association was observed between the AMED diet and tinnitus. In the multivariate model first version, higher AMED quintiles (i.e., greater adherence to the AMED dietary pattern) were associated with a higher risk of tinnitus compared to the reference group. Adding hearing status to the multivariate model, made little difference to the observed pattern. This observed pattern was maintained even with the full multivariate model, i.e., adjusting for all exposures and covariates. For example, in the full model, women in the highest AMED quintile had a multivariate RR 1.14 (95% CI 1.07, 1.21) compared to women in the lowest quintile (Table 6.4B). This finding suggests that greater adherence to AMED dietary pattern increased the risk of incident tinnitus after adjusting for all potential confounders. For the AMED diet scores without alcohol, the same patterns were observed (Table 6.4C). Overall, the findings for diet suggest that women with the highest adherence to the DASH and AMED diets had approximately 7-15% increased risk of tinnitus than women with the lowest adherence scores.

Table 6.3 Age adjusted baseline characteristics of women in 1991 by quintile of cumulative-averaged DASH and AMED scores

	DASH Diet Score					AMED diet score				
	Q1 (n=12070)	Q2 (n=11385)	Q3 (n=12571)	Q4 (n=10685)	Q5 (n=10128)	Q1 (n=13196)	Q2 (n=10335)	Q3 (n=10818)	Q4 (n=9661)	Q5 (n=12829)
Age, years*	36.1 (4.7)	36.3 (4.7)	36.3 (4.7)	36.4 (4.6)	36.5 (4.5)	35.9 (4.8)	36.1 (4.7)	36.3 (4.7)	36.4 (4.5)	36.8 (4.5)
Race, Caucasian, %	94.4	94.1	94.3	94.8	94.1	94.8	94.4	94.6	94.1	93.8
Smoking status										
Never, %	63.1	67.2	67.8	68.9	67.7	66.3	67.9	67.0	67.5	66.0
Past, %	18.5	20.4	22.5	23.6	26.0	19.1	20.0	22.2	23.3	25.7
Current, %	18.3	12.2	9.5	7.3	6.2	14.5	12.0	10.7	9.1	8.1
Physical activity, METs	14.5 (19.9)	17.4 (22.7)	20.4 (24.6)	23.6 (28.3)	30.2 (33.6)	15.7 (21.2)	18.5 (23.8)	20.6 (25.7)	22.6 (27.7)	27.1 (31.3)
History of hypertension, %	6.6	5.9	5.7	5.8	5.1	6.5	5.6	6.1	5.7	5.4
History of diabetes, %	3.5	3.8	4.1	4.0	4.0	3.6	3.8	4.1	4.3	3.7
Depression, 2003, %	12.5	12.0	12.1	12.2	12.4	12.6	12.1	12.2	12.1	12.0
Aspirin use, 1995										
none, %	73.9	74.5	74.3	74.5	75.0	75.3	74.7	74.4	74.7	72.9
1 day/week, %	14.5	14.5	14.8	15.1	14.8	13.5	14.7	14.5	14.6	16.4
2-3 days/week, %	4.4	4.5	4.2	4.1	4.0	4.1	4.1	4.6	4.3	4.2
4-5 days/week, %	1.3	1.3	1.2	1.3	1.0	1.2	1.3	1.2	1.2	1.2
6+ days/week, %	3.2	2.9	3.1	2.9	3.2	3.4	2.9	3.1	2.8	3.1
Ibuprofen use, 1995										
none, %	33.4	32.9	32.1	32.9	34.4	33.4	33.3	32.8	32.7	33.1
1 day/week, %	37.8	39.0	40.5	39.7	40.6	38.3	39.5	39.4	40.2	40.3
2-3 days/week,%	16.5	16.9	16.0	16.5	15.1	16.1	16.0	16.4	16.3	16.2
4-5 days/week,%	3.5	3.3	3.3	3.3	2.9	3.3	3.4	3.3	2.9	3.3
6+ days/week, %	5.0	4.6	4.6	4.6	4.2	5.2	4.8	4.7	4.4	4.1

Table 6.3 Age adjusted baseline characteristics of women in 1991 by quintile of cumulative-averaged DASH and AMED scores

	DASH Diet Score					AMED diet score				
	Q1 (n=12070)	Q2 (n=11385)	Q3 (n=12571)	Q4 (n=10685)	Q5 (n=10128)	Q1 (n=13196)	Q2 (n=10335)	Q3 (n=10818)	Q4 (n=9661)	Q5 (n=12829)
Acetaminophen use, 1995										
none, %	42.3	42.4	43.3	45.2	47.5	42.3	43.8	44.1	42.7	46.8
1 day/week, %	39.6	40.9	40.9	39.4	39.2	40.3	39.6	39.8	41.5	39.1
2-3 days/week, %	10.5	10.3	9.7	9.5	8.2	10.1	10.1	9.9	9.5	8.8
4-5 days/week, %	2.0	1.9	1.7	1.8	1.3	2.0	1.8	1.8	1.7	1.4
6+ days/week,%	2.0	1.5	1.5	1.4	1.2	2.0	1.7	1.6	1.4	1.1
Hearing difficulty										
none, %	97.4	97.4	97.3	97.3	97.5	97.4	97.5	97.2	97.4	97.5
mild, %	1.6	1.7	1.7	1.8	1.6	1.7	1.5	1.8	1.6	1.6
moderate or worse, %	1.0	0.9	1.0	0.9	0.9	0.8	1.0	1.0	1.0	0.9

Values are means(SD) or medians (Q25, Q75) for continuous variables; percentages or numbers or both for categorical variables, and are standardised to the age distribution of the study population; Values of polytomous variables may not sum to 100% due to rounding.

* Value is not age adjusted

Table 6.4 Dietary patterns and risk of incident tinnitus in women in the NHSII

Table 6.4A. DASH and risk of incident tinnitus in women in the NHSII

Diet score	Quintile1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Person-years	245886	269032	260219	272206	274625
Cases	1891	2220	2229	2348	2336
Age-adjusted RR^	1.00 (ref)	1.04 (0.98, 1.11)	1.02 (0.96, 1.08)	1.04 (0.98, 1.11)	1.01 (0.95, 1.08)
Multivariate adjusted RR[a]	1.00 (ref)	1.05 (0.99, 1.12)	1.04 (0.98, 1.11)	1.07 (1.01, 1.14)	1.07 (1.00, 1.14)
Multivariate adjusted RR[b]	1.00 (ref)	1.06 (0.99, 1.12)	1.06 (0.99, 1.12)	1.09 (1.03, 1.16)	1.10 (1.03, 1.17)
Multivariate adjusted RR[º]	1.00 (ref)	1.06 (1.00, 1.13)	1.06 (1.00, 1.13)	1.10 (1.03, 1.17)	1.10 (1.03, 1.18)

Table 6.4B. AMED and risk of incident tinnitus in women in the NHSII

Diet score	Quintile1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Person-years	262665	264083	277310	247553	270357
Cases	1858	2275	2338	2176	2377
Age-adjusted RR^	1.00 (ref)	1.09 (1.02, 1.16)	1.03 (0.97, 1.10)	1.06 (0.99, 1.13)	1.06 (1.00, 1.13)
Multivariate adjusted RR[b]	1.00 (ref)	1.10 (1.03, 1.17)	1.05 (0.99, 1.11)	1.09 (1.02, 1.16)	1.11 (1.04, 1.18)
Multivariate adjusted RR[b]	1.00 (ref)	1.10 (1.04, 1.18)	1.06 (0.99, 1.13)	1.11 (1.04, 1.18)	1.14 (1.07, 1.21)
Multivariate adjusted RR[§]	1.00 (ref)	1.10 (1.04, 1.17)	1.06 (0.99, 1.13)	1.11 (1.04, 1.18)	1.14 (1.07, 1.21)

Table 6.4 Dietary patterns and risk of incident tinnitus in women in the NHSII

Table 6.4C. AMED with no alcohol and risk of incident tinnitus in women in the NHSII

Diet score	Quintile1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Person-years	255080	262933	282281	258182	263492
Cases	1889	2175	2413	2259	2288
Age-adjusted RR^	1.00 (ref)	1.09 (1.02, 1.16)	1.05 (0.98, 1.11)	1.07 (1.00, 1.13)	1.06 (1.00, 1.13)
Multivariate adjusted RR[a]	1.00 (ref)	1.10 (1.03, 1.17)	1.06 (1.00, 1.13)	1.10 (1.03, 1.17)	1.12 (1.05, 1.19)
Multivariate adjusted RR[b]	1.00 (ref)	1.11 (1.04, 1.18)	1.08 (1.01, 1.14)	1.12 (1.05, 1.19)	1.15 (1.08, 1.22)
Multivariate adjusted RR[ŧ]	1.00 (ref)	1.11 (1.04, 1.18)	1.08 (1.02, 1.15)	1.12 (1.05, 1.19)	1.16 (1.09, 1.23)

ref= Reference category
^Only adjusted for age
a: Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use).
b: Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
º Adjusted for age, alcohol intake, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
§ Adjusted for age, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is in the AMED score it was not included as a covariate in the model)
ŧAdjusted for age, alcohol intake, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is not in the dietary score it was included as a covariate in the model)

6.4.3 Alcohol consumption and tinnitus

The analyses result for cumulative alcohol consumption are provided in Table 6.5. In the age-adjusted analysis, a significantly reduced risk of incident tinnitus was observed in the 15-29.9 grams/day alcohol intake category compared to non-drinkers. No significant association was observed for the other categories. In the multivariate model first version, i.e., including all covariates except hearing status, significantly reduced risk of incident tinnitus was observed in the 5-14.9 grams/day and 15-29.9 grams/day alcohol intake category when compared to non-drinkers. Adding hearing status as a covariate to this model, i.e., using the second version of the multivariate model, made little difference to the observed pattern. The observed pattern was also maintained with the full multivariate model, i.e., when the other exposure variables, namely, dietary patterns (DASH or AMED without alcohol), BMI, waist circumference, and all covariates were included in the model. Compared with women who were non-drinkers, for women who drank 5 to 14.9 grams of alcohol per day, multivariate-adjusted RR was 0.93 (95% CI: 0.88, 0.99), and for women who drank 15 to 29.9 grams of alcohol per day, the multivariate-adjusted RR was 0.87 (95% CI: 0.80, 0.96). This finding indicates that women who drink 5 to 29.9 grams of alcohol per day have a reduced risk of incident tinnitus than women who drink little (1 to 4.9 grams/day) or no alcohol.

Few women in the cohort were in the 30+ grams per day of alcohol intake category, and therefore, the number of incident tinnitus cases in these categories were also low. For example, women who consumed 30-34.9 grams of alcohol/day contributed 6193 person-years, and the number of incident cases was 57. Women who consumed 35-39.9 grams/day contributed 3610 person-years and incidence was 24, drinkers of 40-44.9 grams/day contributed 1959 person-years and incidence was 18, while drinkers of 45+ grams/day of alcohol contributed 3015 person-years and incidence was 26 (not in table). Hence there was not enough data to reliably evaluate the effect of a higher amount of alcohol use on tinnitus incidence. Since alcohol intake is a primary exposure of interest, combining the higher categories would result in some loss of information and might not have given an accurate picture of the risk of incident tinnitus with high levels of alcohol consumption.

Table 6.5 Alcohol consumption and risk of incident tinnitus in women in the NHSII

	Alcohol consumption (grams/day)			
	Non-drinkers	**1-4.9 grams/day**	**5-14.9 grams/day**	**15-29.9 grams/day**
Person-years	368615	619331	260462	58784
Cases	2547	5384	2390	578
Age-adjusted RR^	1.00 (ref)	1.00 (0.96, 1.05)	0.94 (0.89, 1.00)	0.91 (0.83, 0.99)
Multivariate adjusted RR[a]	1.00 (ref)	0.99 (0.94, 1.03)	0.93 (0.87, 0.98)	0.88 (0.80, 0.96)
Multivariate adjusted RR[b]	1.00 (ref)	0.99 (0.94, 1.04)	0.94 (0.88, 0.99)	0.88 (0.80, 0.97)
Multivariate adjusted RR[o]	1.00 (ref)	0.99 (0.94, 1.03)	0.93 (0.88, 0.99)	0.88 (0.80, 0.97)
Multivariate adjusted RR[ŧ]	1.00 (ref)	0.98 (0.94, 1.03)	0.93 (0.88, 0.99)	0.87 (0.80, 0.96)

ref=Reference category
^Only adjusted for age
[a]Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use).
[b]Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
[o] Adjusted for age, DASH score, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
[ŧ]Adjusted for age, AMED score no alcohol, BMI, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is not in the dietary score it was included as a covariate in the model)

6.4.4 Obesity and tinnitus

The age- and multivariate-adjusted RRs of tinnitus according to the categories of BMI and waist circumference are provided in Table 6.6 and 6.7, respectively. BMI is a predictor of morbidity and mortality related to numerous chronic diseases. Additionally, abdominal obesity, assessed by waist circumference, predicts obesity-related health risks (Janssen et al., 2004; NIH, 1998; Rexrode et al., 1998; WHO, 2000). Waist circumference, coupled with BMI, predicts a greater variance in health risk than BMI

alone (Ardern et al., 2003; Janssen et al., 2002; Rexrode et al., 1998). The National Heart, Lung, and Blood Institute of the National Institutes of Health recognises the importance of BMI and waist circumference in predicting health risk, and NIH guidelines indicate a graded increase in health risk moving from normal through obese BMI categories. Also, within each BMI category for both men and women with high waist circumference are at a greater health risk than are those with normal values (NIH, 1998). Therefore, it would be relevant to assess the independent effect of BMI and waist circumference on tinnitus risk, as well as examine the effect of BMI and waist circumference in the same model.

For BMI: After adjusting for age, underweight, i.e., BMI ≤ 18 kg/m^2 was significantly associated with reduced risk of incident tinnitus, while BMI ≥ 30 kg/m^2 (class I or higher obesity) was significantly associated with an increased risk of incident tinnitus, compared to normal weight women. The risk pattern for underweight individuals was consistent across all multivariate models. For example, in the full multivariate model (including DASH diet, alcohol intake, and all covariates), compared to normal weight women, underweight women had an RR of 0.81 (95% CI: 0.67,0.99). However, for higher BMI categories (BMI ≥ 30 kg/m^2), when all other exposure and covariates were included in the model (full multivariate models), the initial association between higher BMI and tinnitus incidence did not maintain significance (Table 6.6).

For waist circumference, any initially observed pattern was not robust across models. The age-adjusted RRs of tinnitus showed an increased risk of incident tinnitus due to an increase in waist circumference compared to the reference group (≤70 cm). In the first version of the multivariate model adjusted for covariates (except hearing status), the same pattern of increasing risk remained, although only the two highest categories of waist circumference reached statistical significance, with RRs 1.11 (95% CI: 1.01,1.21) and 1.13 (95% CI: 1.14,1.34), respectively. However, after adding the hearing status to the model, only the highest waist circumference category remained statistically significant (RR of 1.10 (95% CI 1.01-1.19). No association was noted in the full multivariate model (with diet, alcohol intake, BMI, and all covariates) (Table 6.7). Therefore, once adjusted for all covariates, BMI, and waist circumference showed no effect on the risk of incident tinnitus. Comparing the modelling results for BMI and waist circumference, the overall evidence indicates no significant association between obesity and tinnitus.

Table 6.6 Body mass index (BMI) and risk of incident tinnitus in women in the NHSII

	BMI categories (kg/m$^{2)}$					
	<18.5	**18.5-24.9**	**25-29.9**	**30-34.9**	**35-39.9**	**≥ 40**
Person-years	18993	618460	333971	159347	71453	46253
Cases	105	4401	3044	1668	785	508
Age-adjusted RR^	0.79 (0.65, 0.96)	1.00 (ref)	1.04 (0.99, 1.09)	1.13 (1.07, 1.20)	1.20 (1.11, 1.29)	1.22 (1.12, 1.34)
Multivariate adjusted RR[a]	0.80 (0.66, 0.97)	1.00 (ref)	1.01 (0.96, 1.06)	1.06 (1.00, 1.13)	1.10 (1.01, 1.19)	1.09 (0.98, 1.20)
Multivariate adjusted RR[b]	0.81 (0.67, 0.98)	1.00 (ref)	1.00 (0.96, 1.05)	1.05 (0.99, 1.12)	1.09 (1.01, 1.18)	1.06 (0.96, 1.17)
Multivariate adjusted RR[º]	0.81 (0.67, 0.99)	1.00 (ref)	1.00 (0.95, 1.05)	1.05 (0.99, 1.13)	1.09 (1.00, 1.19)	1.06 (0.96, 1.18)
Multivariate adjusted RR[§]	0.82 (0.67, 0.99)	1.00 (ref)	1.01 (0.96, 1.06)	1.07 (1.00, 1.14)	1.11 (1.02, 1.21)	1.08 (0.98, 1.20)

ref=Reference category
^Only adjusted for age
a: Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use).
b: Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
º Adjusted for age, DASH score, Alcohol intake, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
§ Adjusted for age, AMED score, waist circumference, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is in the AMED score it was not included as a covariate in the model)

Table 6.7 Waist circumference and risk of incident tinnitus in women in the NHSII

	Waist circumference (in cm)			
	≤70	**71-79**	**80-88**	**>88**
Person-years	130099	250090	146634	238251
Cases	757	2009	1567	3132
Age-adjusted RR^	1.00 (ref)	1.09 (1.00, 1.19)	1.15 (1.05, 1.25)	1.24 (1.14, 1.34)
Multivariate adjusted RR[a]	1.00 (ref)	1.07 (0.99, 1.17)	1.11 (1.01, 1.21)	1.13 (1.04, 1.23)
Multivariate adjusted RR[b]	1.00 (ref)	1.06 (0.98, 1.15)	1.08 (0.99, 1.18)	1.10 (1.01, 1.19)
Multivariate adjusted RR[º]	1.00 (ref)	1.05 (0.96, 1.14)	1.06 (0.97, 1.17)	1.05 (0.96, 1.15)
Multivariate adjusted RR[§]	1.00 (ref)	1.05 (0.96, 1.14)	1.06 (0.97, 1.16)	1.05 (0.96, 1.15)

ref=Reference category
^Only adjusted for age
a: Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use).
b: Adjusted for age, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
º Adjusted for age, DASH score, Alcohol intake, BMI, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status.
§ Adjusted for age, AMED score, BMI, race, physical activity, smoking, hypertension, diabetes, depression, ototoxic medication use (aspirin use, acetaminophen use, ibuprofen use), hearing status (since alcohol is in the AMED score it was not included as a covariate in the model)

6.5 Discussion

Using a prospective cohort dataset among 67,997 US women nurses, this study aimed to determine the association between dietary patterns, alcohol consumption, and obesity and the risk of incident tinnitus. These study findings are important to the field because this is the first longitudinal study of the long-term relationship between modifiable lifestyle risk factors and incident tinnitus. All other evidence to date comes from cross-sectional datasets, which cannot confirm any causal relationship between the risk factors of interest and tinnitus. The main findings were as follows:

- After adjusting for potential confounders, greater adherence to a healthy dietary pattern appeared to be associated with a small (7-15%) increased risk of incident tinnitus, no matter whether the diet conformed to the dietary pattern to reduce blood pressure (DASH) or Mediterranean diet (AMED). These effects

seemed independent of hearing status because an adjustment in the model for this covariate made very little difference in RRs.

- Concerning alcohol, women who were modest drinkers seemed to have a lower risk of incident tinnitus than non-drinkers, after adjusting for covariates. There was somewhat of a dose-dependent relationship with women in the 15 to 29.9 grams of alcohol/ day categories having lower risk than those in the 5-14.9 grams of alcohol/ day category. The latter had a lower risk than women in the 1-4.9 grams of alcohol/day category. However, not enough data was available for women who drank more than 30 grams of alcohol/day, and hence, firm conclusions cannot be made about the dose-dependent relationship between alcohol intake and tinnitus.
- After adjusting for covariates, neither measures of obesity, i.e., BMI and waist circumference, appeared to be associated with incident tinnitus to a reliable degree.

6.5.1 Association between diet and incident tinnitus in adult women

Despite their differences, both DASH and AMED recommend a higher intake of fruits, vegetables, and wholegrain, and moderate to low intake of dairy products. Therefore, based on the evaluation of the different weightings in the diet scores and the modelling results, it can be concluded that a higher intake of fruits, vegetables, wholegrain, and fish increased the risk of developing tinnitus. In comparison, higher dairy intake decreased the risk of developing tinnitus. These results confirm the predictions made in a previous cross-sectional study (McCormack et al., 2014b). Examining a large representative dataset on UK adults aged 40 to 69 years, these authors reported that the likelihood of experiencing tinnitus was associated with higher fruit and vegetable, bread, fish, and egg intake. Similarly, dairy intake was associated with a reduced likelihood of persistent tinnitus (McCormack et al., 2014b). A more recent study on the same UK biobank dataset by the same research team reported that a diet with high fruit and vegetables and wholegrain intake (i.e., prudent diet) was not linked to the likelihood of having tinnitus symptoms, while a high protein diet was (Dawes et al., 2020). A food component analysis was also conducted in the latter study. High intake of calcium, iron, and fat, increased the odds, whereas high protein, vitamin B2, and B3, vitamin B12 were associated with a lower likelihood of having tinnitus (Dawes et

al., 2020). The authors noted some inconsistencies between their two reports. For example, in the former study, egg intake, a rich source of vitamin B12, was linked with an increased likelihood of tinnitus, while in the latter, vitamin B12 was linked to reduced likelihood. However, in the former study, dairy intake was linked with a reduced likelihood of tinnitus; and dairy is a source of vitamin B12. The authors acknowledged this discrepancy and identified their latter analysis to improve their former analysis (Dawes et al., 2020). In this study on NHSII, dietary patterns were analysed and not nutrients. Perhaps it would be worthwhile to explore the nutrient composition of the dietary patterns and quantify the amounts of particular nutrients that have been reported in the published literature to affect tinnitus or hearing status.

For example, abnormalities in the calcium signalling pathway in outer hair cells have previously been linked to tinnitus (Zenner & Ernst, 1993; Sziklai 2004). Moreover, calcium channel blockers have been prescribed for managing tinnitus (Davies et al., 1994). In auditory hair cells, calcium influx activates complex intracellular enzymatic reactions resulting in neurotransmitter release. Excessive calcium entry into sensory cells, including those of the inner ear, is responsible for over-activation of enzymes causing membrane damage and even cellular death when the cytoplasmic buffering capacity is overcome. Calcium channel blockers are suggested to be a useful measure for cochlear and vestibular dysfunctions (Monzani et al., 2015). The DASH diet is high in fibre, potassium, calcium, magnesium; and low in sodium (Fung et al., 2008; Karanja et al., 1999). Therefore, it could be possible that the association between greater adherence to DASH and increased tinnitus risk could be related to calcium levels.

Few epidemiologic studies have shown a protective effect of magnesium on HL (Attias et al., 1994; Spankovich et al., 2011). Le Prell et al. (2007a) suggested that inhibition of free radical formation is the most effective strategy to prevent HL. The free radical formation is triggered by aging, noise, and auditory trauma, leading to cell death and consequently vasoconstriction and a rebound of cochlear blood flow (Henderson et al., 2006; Le Prell et al., 2007b). Magnesium is known to reduce this noise-induced vasoconstriction (Altura et al., 1992; Haupt et al., 2002; Le Prell et al., 2007b). Since cochlear damage can lead to tinnitus, conceivably high intake of magnesium should have a protective effect on tinnitus. However, the increased tinnitus risk with greater adherence to DASH seems contradictory to the explanation described above. Since

the DASH diet includes high magnesium intake, it is difficult to say whether nutrient analysis could provide better insights into the association between diet and tinnitus.

Hearing difficulty and tinnitus are closely related outcomes, and so it is relevant to understand the impact of dietary patterns on reported hearing difficulty. A previous analysis of the NHSII dataset found that greater adherence to a healthy (either DASH or AMED) diet lowered the risk of hearing difficulty (Curhan et al., 2018). The authors also reported that overall dietary patterns were stronger predictors of hearing difficulty than the individual component nutrients of each of these dietary scores. No particular component was observed to contribute more substantially to the associations than others (Curhan et al., 2018). This is contradictory to the findings from Dawes et al. (2020). However, in this case, it is essential to remember that Curhan et al. (2018) did not assess tinnitus as an outcome. Despite being very similar conditions, tinnitus and hearing difficulty do not always co-occur nor do they always have the same risk profile (Baguley et al., 2013; Dawes et al., 2020).

In the present dataset and modelling, the association between dietary patterns and incident tinnitus did not change much after adding hearing status as a covariate in the model, suggesting that the effects might be independent of hearing difficulty. In the UK Biobank study by Dawes et al., the same pattern was noted where hearing difficulty did not influence the relationship between diet and tinnitus (Dawes et al., 2020).

The results from this study show modest associations between dietary patterns and tinnitus. While the findings provide important insights, more research is warranted before indicating potential mechanisms. There needs to be more substantive evidence before recommending dietary behaviour changes whereby all tinnitus patients are suggested to add or remove certain food groups from their diet. Separate analyses for the individual food groups included in the dietary patterns, such as fish, fruits, wholegrains, etc., might help in better understanding the impact of modifying dietary behaviour, if there is one. Until then this study offers some background for clinicians managing tinnitus patients to include dietary advice in the management protocol. It might be worthwhile to carefully monitor the diet of individual tinnitus patients to identify food groups that aggravate or reduce their tinnitus symptoms.

6.5.2 Association between alcohol consumption and incident tinnitus in adult women, and dose-dependence

In this study, modest alcohol intake (from 5 grams/day to 29.9 grams/day) was found to lower the risk of incident tinnitus. These findings concur with previously published evidence from a well-conducted prospective study by Nondahl et al. (2010) that reported moderate drinking to have a protective effect on tinnitus whereas heavy drinking had no relationship. The plausible biological rationale of this protective effect might be related to the antioxidants and vasorelaxant properties found in alcohol (Fuchs, 2005; Piano, 2017). On the other hand, high alcohol intake can cause alcohol-related damage to blood vessels, which are crucial to proper cochlear function (Piano, 2017).

Additionally, alcohol consumption has been suggested to be protective in low doses and detrimental in high doses for cognition (Brennan et al., 2020) and longevity (van den Brandt and Brandts, 2020). Dawes et al. (2014b) analysed the UK Biobank dataset to report that alcohol drinkers were approximately 40% less likely to have a hearing loss than non-drinkers. The inverse association was similar across three levels of alcohol intake (from 1–118.4 g/week, 118.4–196.8 g/week, and 196.8 g/week or more) being protective in hearing loss. In the current study, alcohol in moderate doses was found to be protective for tinnitus. However, given the lack of data on women who were consuming more than 30 grams of alcohol per day, nothing conclusive could be inferred about the effect of high doses of alcohol on incident tinnitus. It would be worthwhile to explore a study population with a reasonable number of participants in the higher drinking categories and examine if the effect of alcohol intake on tinnitus is similar to its effect on cognition and hearing loss. Since the variable information was updated every questionnaire cycle, this study reports a the cumulative alcohol intake over the study period. So a non-drinker would be an individual who did not drink alcohol at all in the follow-up period. For all other categories it was the cumulative average long term alcohol intake over the study period. It was beyond the scope of this study to assess whether binge drinking had an effect on tinnitus risk.

6.5.3 Association between obesity and tinnitus in adult women

In the NHSII dataset, obesity was assessed in terms of both BMI and waist circumference. For both these variables, no significant association was observed with the risk of tinnitus. These results concur with the findings from another cohort study by Nondahl et al. (2010), where no association was noted in women between obesity and tinnitus. In the latter study, BMI was used as a measure to assess obesity. While it remains questionable how obesity affects tinnitus in men, probably in women, there is no association.

Healthy blood flow and oxygen supply are essential for the adequate functioning of cochlear hair cells. Excess body weight makes it difficult for the heart to pump blood throughout the body. Obesity can be a defining risk factor in the proper functioning of hair cells, as it also puts a strain on the auditory microvasculature impeding efficient oxygen supply to the hair cells. From a biological standpoint, ideally, obesity should increase the risk of tinnitus. However, this is not reflected in the findings of this study. Interestingly though, underweight women with BMI <18.5 had a reduced risk of incident tinnitus. Less strain on the heart and better blood flow to auditory microvasculature could be potential explanations. Nonetheless, it is difficult to simultaneously explain the associations between underweight and obesity with risk of tinnitus using the circulatory pathway mechanism.

6.5.4 Strengths of the study

The two major strengths of this study are its prospective design and large sample size. For deriving causal associations between modifiable lifestyle-related risk factors and tinnitus where interventions are not always feasible, such study designs provide the most substantial evidence—a large sample size, which increases the power of the study.

For exploring the relationship between diet and tinnitus, Spankovich et al. (2017b) recommended further analysis based on food and nutrient intake and dietary patterns (Spankovich et al., 2017b). Single-nutrient based analyses are less susceptible to confounding than food-based analyses since many foods can have the same nutrient. However, single nutrient-based analyses do not take into account the complex interactions among nutrients. As reported in this study, dietary patterns provide a

complementary approach and demonstrate a more comprehensive and informative picture of the effect of diet on tinnitus risk as it incorporates the combined effect of all nutrients consumed (Hu, 2002).

Tinnitus has a shared risk profile to cardiovascular diseases, where a dose-response effect of alcohol consumption is evident. Consequently, in section 5.5.2, the value of examining this aspect in future tinnitus research was mentioned. This study attempts to address the dose-response relationship between alcohol consumption and tinnitus. A pattern is noted with the protective effect of alcohol intake on tinnitus risk increasing in moderate drinkers compared to no or little drinking. Additionally, in this study, both BMI and waist circumference are assessed, and both of them together are known to better predictor risk than each individually (Ardern et al., 2003; Janssen et al., 2002; Rexrode et al., 1998).

6.5.5 Limitations of the study

Information on all exposures was self-reported. Therefore, there may be measurement error in the assessment of exposures. However, multiple assessments of diet, alcohol intake and weight were averaged, which reduces random measurement error (Willett et al., 1998). Tinnitus onset is mostly insidious (Han et al., 2009). Therefore, there is a possibility for imprecision in the assessment of the date of onset. (Genitsaridi et al., 2019).

Moreover, while tinnitus onset was assessed based on participant reports in 2009, 2013, and 2017, information on exposures and covariates was collected before tinnitus onset; therefore, associations were examined prospectively. NHSII being an observational study, residual confounding could have influenced the results. However, in the analyses, selected known confounding variables, i.e., the covariates, were adjusted carefully, and many of them have been demonstrated to be well-reported in this cohort. For example, a good correlation was found for the estimates of physical activity obtained using the short physical activity questionnaire used in NHSII, past week activity recalls, and 7-day activity diaries measurement methods. Furthermore, the women being nurses, the health information validity was enhanced, and variability of demographics like education and socio-economic status were reduced. However, we cannot exclude the possibility of residual confounding by other potential or unknown risk factors (Al-Delaimy et al., 2002; Wolf et al., 1994). For example, stress

levels are associated with tinnitus (Baigi et al., 2011; Kim et al., 2015). However, the stress level was not included as a covariate in this analysis as information on stress levels was not available. Using statistical approach along with prior knowledge for covariate selection (Section 6.3.3) might have been useful in identifying and controlling for residual confounding by unknown variables.

Furthermore, the study population included women of a specific age range and, therefore, lacks generalisability. Although there is no consensus on the gender-specific differences for tinnitus prevalence, in patients with chronic tinnitus, gender differences in symptomatology and tinnitus-related distress have been found, with women being more annoyed by tinnitus than men (Niemann et al., 2020; Seydel et al., 2013).

6.5.6 Concluding remarks

This study is the first attempt at analysing a prospective cohort dataset to examine the association between dietary patterns and tinnitus. This novel approach of assessing multiple inter-related modifiable risk factors like diet, alcohol, and obesity provides a holistic picture. The increased risk of tinnitus when adhering to a healthy diet is an unexpected finding that needs further exploration to understand the underlying mechanism. The association between alcohol and tinnitus has important public health implications as the findings concur with previous prospective cohort data and provide valuable insights.

Chapter 7 . Conclusions and Recommendations

This project presents a comprehensive picture of tinnitus epidemiology, having addressed both distribution and determinants of tinnitus at a population-level. The overall aim was to measure the prevalence of tinnitus in Europe, collate available information on tinnitus-related risk factors, and examine if modifiable lifestyle-related factors had some effect on tinnitus. The lack of standardised assessment methods, non-uniform prevalence results, and insufficient risk factor knowledge are three crucial issues in tinnitus epidemiological research. This project finds a balance between critically evaluating existing information in the reviews, conducting new research to assess the prevalence, and examining unexplored existing datasets for the prospective cohort study to successfully address all three of these issues.

The studies undertaken as part of the PhD project can broadly be classified into i) prevalence-related (Chapters 2 and 3) and ii) risk factor related (Chapters 4, 5 and 6). Table 7.1 reports a summary of main findings from all studies undertaken as a part of this PhD. This work provides solutions, new insights, and exciting new directions for future research in tinnitus through these studies.

7.1 Prevalence

The ETS is a set of four questions and response options conceptually and culturally adapted from their original English version into 11 European languages. The provenance for the English version of these questions and response options were pre-existing population-based survey questionnaires, which were modified such that the most accurate data could be collected. The translation process was rigorous and followed the good practice guidelines specific to surveys. The result was a culturally adapted set of questions for use in population-based research studies. When implemented at a population level across 12 European countries, the overall prevalence of any bothersome and severe tinnitus was found to vary considerably, with estimates being 14.7%, 6.0%, and 1.2%, respectively (Table 7.1).

The prevalence of any tinnitus demonstrates the health condition's distribution, while the bothersome and severe tinnitus estimates reflect the burden of tinnitus. One in 100 adults' experience severe tinnitus. This is concerning given the impact of severe tinnitus on an individual's well-being. Despite using uniform assessment methods, vast

inter-country differences in prevalence estimates were noted. Tinnitus symptom severity was a key determinant of healthcare resource use. High tinnitus prevalence in a country was positively associated with healthcare resource use. The country's GDP per capita was negatively associated with tinnitus prevalence and positively associated with healthcare resource use for tinnitus. Sex differences were inconsistent. Age and hearing impairment were both positively related to tinnitus prevalence.

Table 7.1 Summary of findings from all studies

Tinnitus prevalence study
• Prevalence of any tinnitus was 14.7%, bothersome tinnitus was 6.0% and severe tinnitus was 1.2% • Wide inter-country variability • Age, hearing difficulty, and lower GDP per capita increased likelihood of tinnitus • Health care resource use was variable and dependent on tinnitus symptom severity and country's GDP per capita
Systematic review on high quality studies
• 25 out of 49 articles on case-control and cohort data fit the high-quality criteria • Most information was available on hearing and ear related conditions
Systematic review on modifiable factors
• Smoking o Overall: Increased likelihood of tinnitus in current, former and ever smokers o Cohort study: No association in current smokers, increased risk in former and ever smokers o Cross-sectional studies: Increased likelihood in current, former and ever smokers • Alcohol consumption o Only cross-sectional data: No relationship with tinnitus • Obesity o Overall: Increased likelihood of tinnitus in obese compared to non-obese o Cohort study: No association with tinnitus o Cross-sectional studies: Increased likelihood of tinnitus in obese
Prospective cohort study analysis
• Dietary patterns: Increased tinnitus risk when adhering to healthy dietary patterns • Alcohol consumption: Reduced tinnitus risk in moderate alcohol drinkers compared to non-drinkers • Obesity: No association with tinnitus

7.2 Risk factors

The wide diversity in prevalence estimates despite uniform assessment methods implies that specific populations are more vulnerable than others. This heterogeneity and the relatively high prevalence warrants research towards understanding the determinants of tinnitus, i.e., risk factor analysis. A comprehensive review of existing literature on tinnitus-related risk factors illustrated the lack of high-quality evidence and analytical studies establishing the temporality between exposure, i.e., risk factors, and the outcome, i.e., tinnitus (Table 7.1). Furthermore, most high-quality research is restricted to ear, and hearing-related conditions, which is obvious since tinnitus is an otological condition. Nonetheless, despite the emotional and psychological impact of tinnitus and potential inter-relationship with comorbidities like anxiety and depression, not enough high-quality data are available to infer the magnitude and direction of the associations.

Another group of risk factors, modifiable lifestyle-related (such as smoking, diet), also exhibit a paucity in available data, especially high-quality data. Tinnitus is quite prevalent at a population level, and being age-related will only increase with increasing life expectancy. The vital feature of modifiable lifestyle-related risk factors is that they can be changed with external manipulation, provided there is enough information on the interrelationship with tinnitus. A review of existing literature and analyses of selected factors (namely smoking, alcohol consumption, obesity, and caffeine intake) reported an association with obesity and smoking and no association with alcohol consumption and caffeine intake. These pieces of evidence, although indicative, were not sufficient to make causal conclusions as they were derived primarily from cross-sectional studies.

An existing well-conducted prospective cohort study on women nurses was analysed to assess some potential lifestyle-related risk factors, namely diet, alcohol consumption, and obesity, to add substantial-high-quality evidence on modifiable risk factors and address the gaps in risk factor knowledge. In the long term, healthy dietary patterns (DASH and AMED) were found to slightly increase the risk of developing tinnitus. Moderate alcohol consumption had a protective effect. Underweight women had a reduced risk of tinnitus, whereas obesity was not associated with tinnitus risk.

7.3 Comparison with previous research

The lack of a standardised research definition is one of the crucial reasons for which prevalence estimates across different population groups cannot be pooled to find a global prevalence. (McCormack et al., 2016). Standardisation of assessment methods ensure data comparability between different studies and populations (Henry et al., 2020). In epidemiological research, neither a standardised set of research questions and response options for tinnitus assessment is available, nor are there culturally adapted translated versions of the same that can be used across population-based studies in different countries. The ETS questions and response options, described in Chapter 2, are a proposed solution to address the need for standardisation in assessment methods.

The Pan-European prevalence study was the first of its kind in multinational data collection and analysis. For some investigations conducted in this study, there was no previous literature to compare. For example, this was the first attempt to assess tinnitus prevalence in some countries at a population level, such as Bulgaria, Latvia, and Romania. Notably, all these countries are Eastern European and showed the highest prevalence for tinnitus. GDP per capita of a country, European regions, and accession to the EU were some population-level factors that affected tinnitus prevalence. However, there was no pre-existing information to reconcile such findings.

The prevalence estimates for tinnitus lie between 10% and 15% in the Western World (Baguley et al., 2013). That the prevalence for any tinnitus measured in this project was within this range supports that the assessment questions are efficient in reporting accurate estimates. Variability in estimates due to heterogeneous assessment methods was prevented by using the same set questions and response options across countries. Still, there remained substantial variability between the prevalence estimates in Eastern European countries like Bulgaria and Northern Europe like Ireland. Such findings call for further exploration into the determinants that make specific populations more vulnerable to develop tinnitus. Additionally, this warrants being cautious about the geographical bias in tinnitus research.

Previous studies on healthcare resource use and tinnitus reported that the burden is directly related to the severity of the tinnitus symptoms, with increased healthcare costs in people with severe tinnitus (Goldstein et al., 2015; Maes et al., 2013). In the

Pan-European study, tinnitus severity symptoms were the critical factor in determining healthcare resource use for tinnitus. Like the published literature, this study observed no clear consensus on the association between sex and tinnitus. It varied by country and by the working definition of tinnitus. The results showed age and hearing difficulty to be related to tinnitus, which was in alignment with currently available literature (Baguley et al., 2013; Bhatt et al., 2016; Davis and Rafaie, 2000; Gallus et al., 2015; McCormack et al., 2014a; Michikawa et al., 2010; Sindhusake et al., 2004).

Gaps and heterogeneity in the knowledge of tinnitus epidemiology and lack of longitudinal data in tinnitus research have been highlighted by multiple authors (Baguley et al., 2013; Cederroth et al., 2019). In the comprehensive systematic review, these gaps were noted with a paucity of information, no information, and heterogeneous information on several risk factors. Some important lifestyle-related risk factors like diet had minimal information, despite being identified as a research priority by both clinicians and the general public (Hall et al., 2013), Tinnitus is a symptom of Meniere's disease, and dietary modifications are widely used in Meniere's treatment without any high-quality evidence to support it. Even for Meniere's disease, the role of dietary modification in treatment is identified as a research priority (JLA, 2011). Nonetheless, a systematic review aimed to identify any RCTs investigating the role of dietary modification in the treatment of Ménière's disease or syndrome found no data on dietary modifications (Hussain et al., 2018).

Additionally, apart from heterogeneous tinnitus assessment, non-uniform assessment methods for risk factors were also noted. Meta-analytic approaches can summarise risk factor information accurately when the exposure and outcome assessment methods are reasonably uniform. For example, alcohol consumption can be assessed in terms of drinking status (drinkers versus non-drinkers) and different alcohol intake units (e.g., grams/day, times/week, etc.). Studies using these two measures can be pooled together only when the latter can be reorganised to report drinking status. In Chapters 4 and 5, it was noted that a meta-analysis on the relationship between diet and tinnitus could not be conducted because dietary assessments in different available studies were too heterogeneous to be pooled together. Therefore, standardisation is necessary not just for tinnitus assessment but also for risk factor measurement.

Most data on tinnitus-related risk factors come from cross-sectional studies. Hence, systematic reviews and meta-analyses on risk factors often fail to draw firm conclusions on causal associations (Figueiredo et al., 2015; Veile et al., 2018). In the systematic review on modifiable lifestyle-related risk factors, four meta-analyses were conducted and most (sometimes all) studies included were cross-sectional. Since the results from the meta-analysis on smoking were aligned with the review and meta-analysis by Veile et al. (2018), there was more confidence in the findings (Veile et al., 2018). Another review article that looked at the role of caffeine in the causation or aggravation of otolaryngology conditions, including Ménière's, failed to identify any evidence to infer on this association (Trinidade et al., 2014). Lack of information also prevented drawing any conclusions on the relationship between caffeine intake and tinnitus in Chapter 5.

7.4 Implications of findings

The questions and response options of ETS were translated into some of the most widely spoken languages globally. Although this project's scope was restricted to the EU, the translated versions with minor adaptations can be used in various other parts of the world. Moreover, the translation process can be used to develop versions in any different language. Despite this being an EU project, the implications are relatively global. The ETS was implemented on representative populations from each EU member state included. The ETS was a novel attempt at conducting a multinational study to assess Pan-European tinnitus prevalence. The selected countries represented a well-balanced picture of the socio-cultural and financial structure of the EU. When extrapolated onto the overall EU population, the results showed that 77 million adults in the EU experience tinnitus, of whom 31million people experience bothersome tinnitus and 6.2 million experience severe tinnitus. The actual numbers give a clearer picture of the magnitude of tinnitus prevalence.

There was wide variability between inter-country estimates of prevalence. Exploring the underlying causes of such variability would mean studying the individual-level characteristics and country-specific features, i.e., the population level risk factors. For example, occupational noise exposure is a significant risk factor for tinnitus. Countries that have mandatory legislation and regulations meant to protect workers from such occupational hazards will potentially have less risk of occupational noise-induced tinnitus.

The importance of population-level approaches has been emphasised in the epidemiology of chronic pain, which is similar to tinnitus. Both are sensory-perceptual disorders that negatively affect health and well-being. Additionally, a vague understanding of the real burden and the increased prevalence in the ageing population are common in chronic pain and tinnitus (Rauschecker et al., 2015). For chronic pain, both individual-level and population-level risk factors exist for the onset or persistence of pain symptoms suggesting opportunities for multi-level intervention (Blyth, 2008). However, risk factor studies on tinnitus mostly focus on individual-level characteristics. Given the heterogeneity in tinnitus characteristics, it makes sense to identify high-risk individuals and focus on personalised assessment and management techniques. Nonetheless, ignoring population-level factors could limit the options for executing more widespread preventive strategies and reduce the overall community burden of tinnitus. In Chapter 3, a novel attempt has been made to explore some population-level aspects. More epidemiological research is needed to assess population-level factors and explore tinnitus at a community level as a public health problem.

In chronic pain epidemiology, studies that estimate the population burden either focus on pain or survey general health, where chronic pain is investigated among other health conditions. While the former provides insights on the risk factors, natural history, and pain burden within specified populations (e.g., geographical areas, age subgroups, or occupational subgroups), the latter provides general information on chronic pain relative to other conditions (van Hecke et al., 2013). A similar approach in tinnitus research would establish its place in the general health of a community relative to other chronic conditions and find exposures that concurrently impact the risk of developing tinnitus and other chronic conditions.

When assessing exposures and risk factors for tinnitus, observational studies often give the best evidence because interventional research would not be feasible. The comprehensive review of high-quality observational data on tinnitus-related risk factors did not find many new causal associations. However, it elicited many gaps in tinnitus research. The lack of analytical observational studies (case-control and cohort) and high-quality data availability restricted to specific risk factors were vital issues. In addition to that, there was even a lack of cross-sectional information for some known risk factors.

In this regard, it might be worthwhile to consider the funding available in tinnitus research. McFerran et al. (2019) demonstrated the relatively lower interest in tinnitus research by comparing clinical trials and resulting publications for tinnitus to those for other neurological or neuropsychiatric disorders, namely, depression, anxiety, chronic pain, and HL/deafness . In the US, between 2009 and 2011, average annual funding for diabetes by the National Institutes of Health was $913 million compared to $214 million for hearing disorders, and of that, only $5 million was allocated to tinnitus research. During this period, funding by the Framework Programme 7 in the EU resulted in annual funding of approximately $60 million for diabetes, compared to $3.3 million for hearing disorders with no funding for tinnitus research (Cederroth et al., 2013). Despite recent evidence by the Global Burden of Disease (GBD) study that HL is the 4th leading cause of years lived with disability, in the US, the funding allocated to hearing-related condition remains relatively low (Blustein, 2019; Wilson et al., 2017). Nonetheless, funding in Europe has improved recently with Marie Skłodowska-Curie Actions (MSCA) grants being awarded through the European Commission's Horizon 2020 funding programme, including this PhD project, which was supported by the European School for Interdisciplinary Tinnitus Research (ESIT) (Schlee et al., 2018). However, compared to other conditions like diabetes, these funding initiatives are still less, with MSCA grants allocated to 405 projects related to diabetes, 75 related to deafness or HL, and only nine related to tinnitus (McFerran et al., 2019). This apparent lack of research interest and funding for tinnitus sheds some light on the underlying cause for the gaps in knowledge of tinnitus-related risk factors.

The available risk factor information showed wide heterogeneity, and risk factor categories included hearing-related conditions, comorbidities, socio-demographic factors, lifestyle-related factors, treatment, adverse effects, and genetics. Tinnitus research is known to be multidisciplinary, and the vast array of risk factors concur the same. These risk factors included a mix of non-modifiable (fixed) and modifiable conditions. Recognising the former helps identify vulnerable population groups and inform a targeted approach to tinnitus assessment and management. On the other hand, knowledge of modifiable risk factors helps identify the population at risk and guide prevention strategies accordingly. For example, some risk factors studied in this PhD project, namely smoking, alcohol, diet, and obesity, are priority risk factors for communicable conditions like cardiovascular diseases and cancer. Therefore, in some

cases, instead of formulating new methods, existing prevention strategies for other common communicable diseases can be implemented in the context of tinnitus.

7.5 Limitations of the study

Each of the research projects has its own set of limitations described in the respective chapters. Some general limitations exist regarding the overall project. The study's first objective was to assess Pan-European tinnitus prevalence and make inter-country comparisons of estimates. Both of these were successfully done in this PhD project. However, there was not enough information to understand why there existed a wide variability in prevalence estimates. It was possible to explore some country and individual-level data, but while the difference in estimates was elicited, the underlying cause remained obscure.

Apart from the English language, tinnitus research has been conducted in various other languages. In the systematic review, all non-English literature was excluded. Some loss of information is, therefore, inevitable. Thus, it is plausible that the gaps in knowledge highlighted in the systematic review exaggerate the actual gap. However, since the gaps in knowledge were also alluded to in other previously published literature, one can be assured that the knowledge gaps are only slightly exaggerated in these project findings.

Furthermore, the prospective cohort data predominantly included white women nurses in a specific age range. In Chapter 3, the relationship between representative data and generalisability has been explained when discussing the prevalence study. The restricted population profile hinders the generalisability of the findings from the cohort analysis.

7.6 Future directions

7.6.1 Extensions of the research projects

In the overall systematic review, study and risk factor information was extracted for numerous risk factors. However, further exploration and meta-analyses was conducted for only four modifiable lifestyle-related risk factors. These meta-analyses provide useful insights. A logical extension of this project would be to examine the extracted risk factor data and conduct meta-analyses or qualitative synthesis of information for other important risk factors, if feasible. The prospective cohort dataset,

component nutrient analysis, and other dietary models could be another project where a potential extension is possible.

7.6.2 Issues that need to be addressed in future work

The geographical bias in tinnitus research is evident with paucity in prevalence data from some parts of Asia and Africa (McCormack et al., 2016). Even within limited geographical boundaries, the inter-country prevalence differences were substantial. Therefore, it is reasonable to assume that globally the data would be equally or even more widespread. To prevent skewed results when estimating global prevalence, it is crucial to know how many people are affected in those underrepresented countries. This endeavour would also help identify vulnerable populations and risk factors, particularly the country-level or population-level risk factors.

In the risk factor analysis of tinnitus, there is a need to address the lack of analytical observational studies, i.e., case-control and cohort studies. Case-control studies are relatively easier to conduct. Hospital-based case-control studies can be conducted in ENT clinics, while existing healthcare or insurance databases can be used for population-based case-control studies by selecting tinnitus cases and tinnitus-free controls matched for index dates. For example, in tinnitus research, some Taiwan studies have used data from the national insurance database for such population-based case-control studies (Hutter et al., 2010; Koo and Hwang, 2017). Stohler et al. (2019) used the CPRD dataset in the UK to identify tinnitus cases and matched tinnitus-free controls, and investigate several risk factors (Stohler et al., 2019). A dedicated and appropriate coding system for tinnitus cases is crucial for identifying them from health records (Biswas and Hall, 2020).

The healthcare databases could also be used for retrospective cohort analyses. For example, Martinez et al. (2015) and Stohler et al. (2019) conducted retrospective cohort studies using healthcare records (CPRD – HES data from the UK) data . Utilising and exhausting data from existing large population-based prospective cohorts where the relationship between tinnitus and various risk factors have been explored could be an economical solution. Ideally, new, large, well-designed, prospective cohort studies should be conducted. However, the gaps in risk factor information could initially be addressed by analyses of existing cohort databases, if possible. These findings

could then decide which risk factor associations are strong enough to warrant the implementation of prospective cohorts.

Cohort studies, particularly prospective cohort studies, provide the most robust evidence in risk factor analysis. However, conducting them is time and resource consuming. McFerran et al. (2019) demonstrated the relative lack of funding in tinnitus research compared to HL, a closely related condition. It is possible that the impact of HL, as reported in the GBD study, played a crucial role in encouraging interest in research on HL in recent years. The GBD project provides a framework to analyse the comparative global burden of all diseases and health conditions allowing appropriate health resource allocation. Through GBD projects, non-communicable such as cardiovascular conditions, cancer, and trauma, have been recognised to have a considerable impact on global health. Measuring the contributions of hearing-related conditions allow quantification of the magnitude of associated health loss and disability. Tinnitus severity increases the HL-associated disability weight, i.e., the severity of health loss associated with an HL (Saunders et al., 2018). However, tinnitus information is not yet available in the GBD database. McFerran et al. (2019) recommended its inclusion in GBD as a measure to demonstrate the need for tinnitus research to both research funders and healthcare organisations.

7.6.3 Practical impact of the findings

It is vital to establish the size of the burden of tinnitus to ensure adequate scientific and policy response. McFerran et al. (2019) identified the lack of an agreed prevalence estimate as one of the most crucial hindrances to engaging the pharmaceutical industry in searching for a tinnitus cure. In this PhD project, any tinnitus was reported to affect one in seven adults in the EU, depicting the commonality of the symptom. Furthermore, the actual burden was depicted by the prevalence of bothersome tinnitus in one in 15 adults and severe tinnitus in one in 100 adults. These numbers are relatively high, and individuals who experience severe symptoms burden both financial and personnel resources in the healthcare system. These estimates measured in a Pan-European study demonstrate the size of the problem. They could guide resource allocation for implementing effective measures and attract various stakeholders, including research funders, industrial and healthcare organizations, to engage in needful endeavours for tackling tinnitus.

Risk factor information guide the implementation of preventive strategies to curtail the growth in the number of new cases and prevent the aggravation of symptoms. Knowledge of risk factors helps identify high-risk populations and modify management and prevention strategies to fit their needs. Additionally, exploring the relationship between priority risk factors for communicable diseases (as per WHO) and tinnitus aid visibility of the health condition by linking tinnitus to existing, better-funded health priority areas such as smoking, unhealthy alcohol consumption, obesity, and healthy ageing.

7.7 Concluding remarks

A vital feature of this PhD project is its global perspective on tinnitus. The various translated versions of ETS cover languages spoken in different parts of the world, and the lack of geographical restriction in the systematic review provides a global perspective. While the cross-sectional prevalence study is EU-based, the prospective cohort dataset explores risk factors in women in the US. The ETS study is the first multi-national survey that assessed tinnitus prevalence in 12 EU member states and found a Pan-European tinnitus prevalence of about 15%. Given the lack of standardised tinnitus prevalence questions and a global prevalence estimate, this study provides both standard assessment measures and an estimate of how prevalent tinnitus symptoms are. The comprehensive literature review found gaps in risk factor related knowledge, pointed out the lack of analytical data and the lack of standardisation affecting risk factor assessment. The analysis of NHSII is the first attempt at analysing prospective data to investigate the relationship between diet and tinnitus. Healthy dietary patterns were found to increase tinnitus risk. Further exploration of the biological basis of such a finding could provide exciting insights into tinnitus pathophysiology. Given the alignment of findings with a previously conducted review and the consistent results from cross-sectional and cohort studies, it can be concluded that smoking increases the risk of tinnitus. On the other hand, the prospective cohort data reported modest drinking to reduce tinnitus risk. Considering its relatively high prevalence and the likely effect of modifiable risk factors on tinnitus, it is recommended to encourage positive health behaviour change by implementing adequate public health strategies to prevent tinnitus cases and eventually reduce the burden of tinnitus.

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Appendix I. Discrepancies in general introduction statement

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
BULGARIAN	Сега ще ви задам няколко въпроса за проблеми със слуха и усещане за шум в главата, в едното или двете уши, което е симптом, който лекарите наричат “Шум в ушите”.	C	Adding the word tinnitus at the end of the instruction, and substituting the Bulgarian term for 'symptom' with 'condition'.	Yes	The original English version says “Now we ask you a few questions on hearing problems and on the sensation of noise in head or in one or both ears, which is a symptom that medical doctors call “tinnitus”. Suggested change by translators was to add the word tinnitus: " “Шум в ушите” или тинитус".
POLISH	Teraz zadamy Pani/ Panu parę pytań dotyczących problemów ze słuchem i przykrych doznań dźwiękowych w głowie lub w uchu/ obu uszach, które są symptomem szumów usznych (nazwa medyczna).	D	This statement needs to be translated again by DOXA.	Yes	The original English version says “Now we ask you a few questions on hearing problems and on the sensation of noise in head or in one or both ears, which is a symptom that medical doctors call “tinnitus”. The Polish forward translation meant: "Now we ask you some questions about hearing problems and unpleasant sound percepts in your head, one or both ears which are a symptom of ear noises (tinnitus)". This is very different conceptually from the English version.

Appendix II. Discrepancies in question on tinnitus prevalence

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
FRENCH	Au cours de l'année passée, avez-vous expérimenté ce type de bruits (sonneries ou bourdonnements) dans votre tête, du côté d'une oreille ou des deux oreilles, qui durent plus de cinq minutes à chaque fois ?	C	Recommend changing 'ce type de bruits' to 'un acouphène'	No	Since the original English version question (B1) did not have the term 'tinnitus' in it, the researchers believed the forward translation was good enough. The term 'un acouphène' was not used.
GREEK	Κατά το περασμένο έτος, αισθανόσασταν θορύβους (όπως κουδούνισμα ή βουητό) στο κεφάλι σας ή σε ένα ή και στα δύο αυτιά που διήρκησε για περισσότερο από πέντε λεπτά τη φορά;	C	Last year does not adequately stress the period of time over which participants should consider their response.	Yes	Over the last year implies the time frame. In the back translation, the translator used the term'last year' which does not capture the duration of the condition. Hence the final version was updated. (The field testing participants translated this question as 'over the last/past year')
PORTUGUESE	No último ano, ouviu ruídos (como campainhas ou zumbidos) dentro da cabeça, ou em um, ou nos dois ouvidos que tenham durado mais de 5 minutos de cada vez?	C	Ringing seems substituted for buzzers	Yes	The back-translator translated "[…](como campainhas ou zumbidos)"as "[…](such as buzzers or buzzing)]. This is slightly different from the original English word "ringing". So it was checked if there was acloser term in Portugese.

Appendix III. Discrepancies in response options for tinnitus prevalence question

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
ITALIAN	1. Sì, quasi sempre o sempre 2. Sì, buona parte del tempo 3. Sì, qualche 4. No, non nell'ultimo anno 5. No, mai 6. Non so/Preferisco non rispondere	C	"Most or all of time" in Italian should be "La maggior parte del tempo o tutto il tempo". The researchers preferred to translate it in B1 with "quasi sempre o sempre" which means "almost always or always", since this is more comprehensible. The third option in Italian is actually different… in the last version of the questionnaire, it is "Si, qualche volta".	Yes	It was a typo where some part of the sentence was missed.

Appendix IV. Discrepancies in question on tinnitus severity

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
BULGARIAN	През изминалата година, доколко тези шумове в главата или ушите ви притесняваха, дразнеха или тревожеха, когато бяха най-силни?	C	Worried/bothered in Bulgarian mean the same thing.	Yes	The English version refers to how much these noises in your head or ears “worry, annoy or upset you”. These are three different emotions which are subtly different from one another in English. Our two back-translators translated “upset” in different ways. One translator suggested that the best fitting word for ‘upset’ might be 'разтроен' (which is to do with being emotional and sad almost to the point of crying; literally 'upset').
FRENCH	Au cours de l’année passée, dans quelle mesure ces bruits dans votre tête ou vos oreilles vous ont-ils inquiété, ennuyé ou obsédé quand ils sont à leur maximum ?	D	The back translator highlighted that the French translation for the term “upset” (i.e., obsédé) did not perfectly catch the concept.	Yes	Based on the response options provided in english, the translator felt the french question as formulated is not well adapted.
POLISH	W ciągu ostatniego roku jak bardzo ten dźwięk w Pana/i głowie lub uszach martwił, irytował Pana/ ą, kiedy osiągnął najgorsze stadium?	D	one of the emotional descriptors was missing from the Back translation	Yes	The descriptor 'upset you' was missing in the Polish translation. This was added in the final version.

Appendix IV. Discrepancies in question on tinnitus severity

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
PORTUGUESE	Durante o último ano, quanto é que esses ruídos o preocuparam, incomodaram, ou aborreceram quando estavam a afetá-lo/a?	D	Portuguese-English translation does not convey the first emotional descriptor, nor does it qualify the statement 'when the noises are at their worst'.	Yes	A different translation was used that expressed the meaning same as that of the original version.
ROMANIAN	În ultimul an, cât de mult vă îngrijorează, deranjează și supără aceste sunete când sunt în cea mai rea manifestare?	C	The back translation from Romanian was not exactly the same as the English version.	No	The researchers decided that Forward translation is conceptually similar to the original English version.
SPANISH	Durante el año pasado, ¿Le ha preocupado, molestado o trastocado ese ruido en su cabeza u oídos cuando ha estado en su peor momento?	C	The back translator highlighted that the Spanish translation for the term “upset” (i.e., trastocado) did not perfectly catch the concept.	Yes	The term "trastocado" was changed to "trastornado" to keep the conceptual meaning in alignment with the English version.

Appendix V. Discrepancies in response options to question on tinnitus severity

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
PORTUGUESE	1. Muito 2. Moderadamente 3. Ligeiramente 4. Nada 5. Não sabe/Não responde	C	Portuguese version indicates 'do not respond' instead of 'prefer not to respond' which means something slightly different	No	The same response option was categorised as "B" for other questions. So no changes were made as the researchers assumed that's the convention in Portuguese.

Appendix VI. Discrepancies in healthcare resource use question

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
POLISH	W ciągu ostatniego roku czy był/a Pan/i na wizycie u swojego lekarza rodzinnego lub specjalisty w klinice/ szpitalu w sprawie swojego problemu z przykrymi doznaniami słuchowymi w Pana/i głowie lub uszach?	C	The phrase "in a clinic or hospital"was omitted in the forward translation.	Yes	In the final version this was added since we only considered hospital/clinic visits with the doctor in the question.

Appendix VII: Discrepancies in question on hearing difficulty

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
BULGARIAN	В последно време имате ли други проблеми със слуха, като нечуване на говорящ в шумна среда?	D	The back translation doesn't have the same meaning as the forward translation or the concept definition. An important aspect of the source language English version is that the example given explicitly describes 'listening to a talker who is speaking in a situation that has background noise". A key concept is that the listener is trying to understand what the speaker is saying. It is more than simply 'hearing' the talker. The sentence also describes a specific listening scenario which is when there is loud background noise such as in a restaurant or bar. In English, simply saying "listening in a loud situation" does not discriminate whether its the speech or the background noise which is loud.	Yes	A second forward translation from English to Bulgarian was required to incorporate the key concept of trying to listen and understand speech.
GREEK	Αντιμετωπίζετε αυτή την περίοδο οποιαδήποτε άλλη δυσκολία με την ακοή σας, όπως η ακρόαση της ομιλίας σε θορυβώδη κατάσταση?	C	Environment instead of situation Is better in Greek.	Yes	The translation and reccomendations suggested by the back translator was accepted since it was conceptually equivalent to the English version.

Appendix VII: Discrepancies in question on hearing difficulty

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
POLISH	E4. Czy ma Pan/ Pani inne problem za słuchem, takie jak trudności ze słuchaniem czyjejś wypowiedzi w hałasie?	C	There is slight conceptual difference between the Polish and English versions. The Polish version say "understanding in noise" which is not exactly the same as "noisy situation".	No	This was a very minor change in concept and was thus, not included in the final version. Moreover, one of the field testing participants interpreted this as "noisy situation".
ROMANIAN	În prezent, aveți oricare alte probleme cu auzul, cum ar fi auzitul atunci când e zgomot	D	The forward translation doesn't match the concept definition.	Yes	A key concept of this question in English is that the listener is trying to understand what the speaker is saying when there is loud background noise. It is more than simply 'hearing' the speaker", and in English relates more to being able to detect sound. The back-translators translated the Romanian version of the question with "At present, do you experience any other hearing problems like hearing when there is background noise". A second forward translation from English to Romanian was required to incorporate the key concept of trying to listen and understand speech.

Appendix VII: Discrepancies in question on hearing difficulty

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
SPANISH	¿Tiene usted actualmente alguna otra dificultad con su audición, como oír en una situación ruidosa?	C	The back translator's suggested to clarify that 'not hearing well in a noisy situation' corresponds to the 'difficulty' being asked about, rather than simply describing the situation (i.e. 'hearing in a noisy situation').	No	The query and the changes were not sent to DOXA. The researchers believed that since the original English version did not have the phrase "not able to hear" (specifically the word "not" was absent in the original version); "como oir" is a more appropriate translation than "como no air bien".While the suggestion make it a bit easier for the lay person to understand, it does take the Spanish translation a bit further away from the original English on conceptual grounds.

Appendix VIII. Discrepancies in response options to hearing difficulty question

Language of translation	Forward translation	Rating based on discrepancy	Changes recommended	Changes resolved	Reasoning
GERMAN	1. Ja, ich kann überhaupt nichts verstehen 2. Ja, starke Schwierigkeiten 3. Ja, mäßige Schwierigkeiten 4. Ja, geringe Schwierigkeiten 5. Nein, keine Schwierigkeiten· Weiß nicht/ keine Angabe	D	The back translator's reccommended using 'Ja, ich kann überhaupt nichts hören/verstehen' for option 1 or revise response options (2-5) to clarify that we want to know about difficulties with following conversations.	Yes	Option 1 'Ja, ich kann überhaupt nichts verstehen' translated to 'Yes, I cannot understand anything'. The other options (2-5) says 'Schwierigkeiten'- which refers to difficulties in general. Hence option 1 was changed to 'Ja, ich kann überhaupt nichts hören' to align it with the original English version.

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Bulgarian	Сега ще ви задам няколко въпроса за проблеми със слуха и усещане за шум в главата, в едното или двете уши, което е симптом, който лекарите наричат “Шум в ушите” или тинитус	*[Към всички респонденти на възраст 18+]* През изминалата година, усещахте ли шум (звънене или бучене) в главата или в едното или двете уши, който шум продължаваше повече от пет минути? Да, през повечето или цялото време Да, често Да, понякога Не, не и през изминалата година Не, никога Не знам/ Предпочитам да не отговоря	*[Към респондентите, които имат шум в ушите]* През изминалата година, доколко тези шумове в главата или ушите ви притесняваха, дразнеха или разстройваха, когато бяха най-силни? Силно Умерено Леко Никак Не знам/ Предпочитам да не отговоря	*[Към респондентите, които имат шум в ушите]* През изминалата година, посещавали ли сте вашия Общопрактикуващ лекар или специалист в клиника или болница за проблемите ви в главата или ушите? Да, 5 или повече пъти Да, между 2 и 4 пъти Да, веднъж Не Не знам/ Предпочитам да не отговоря	*[Към всички респонденти на възраст 18+]* В последно време имате ли други затруднения с вашия слух, като например опитване да чуете и разберете реч в шумна среда? Да, не чувам изобщо Да, силно затруднение Да, умерено затруднение Да, леко затруднение Без затруднение Не знам/ Предпочитам да не отговоря

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
French	Nous allons maintenant vous poser quelques questions sur les problèmes d'audition et la sensation de bruit dans la tête ou dans une oreille ou dans des deux oreilles, qui est un symptôme que les médecins appellent «acouphènes	*[A tous les adultes de 18 ans et +]* Au cours de l'année passée, avez-vous expérimenté ce type de bruits (sonneries ou bourdonnements) dans votre tête, du côté d'une oreille ou des deux oreilles, qui durent plus de cinq minutes à chaque fois? Oui la plupart du temps ou tout le temps Oui, souvent Oui, parfois Non, pas au cours de l'année passée Non, jamais Ne sait pas/ Préfère ne pas répondre	*[Aux participants qui ont des acouphènes actuellement]* Au cours de l'année passée, dans quelle mesure ces bruits dans votre tête ou vos oreilles vous ont-ils inquiété, ennuyé ou agacé quand ils sont à leur maximum? Gravement Modérément Légèrement Pas du tout Ne sait pas/ Préfère ne pas répondre	*[Aux participants qui ont des acouphènes actuellement]* Au cours de l'année passée, avez-vous vu votre médecin généraliste, ou vu un professionnel de santé en clinique ou à l'hôpital au sujet des problèmes de bruits dans votre tête ou vos oreilles? Oui, 5 visites ou plus Oui, de 2 à 4 visites Oui, seulement une visite Pas du tout Ne sait pas / Préfère ne pas répondre	*[A tous les adultes de 18 ans et +]* Avez-vous actuellement d'autres difficultés d'audition, par exemple avez-vous du mal à écouter un discours quand il y a du bruit autour de vous? Oui, ne peut rien entendre du tout Oui, une grande difficulté Oui, une difficulté moyenne Oui, un peu de difficulté Aucune difficulté Ne sait pas/ Préfère ne pas répondre

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
German	Der Interviewer bestätigt, dass das Teilnehmer-Informationsblatt übergeben wurde und vom Befragten gelesen wurde, und dieser zustimmt an dieser Studie teilzunehmen.	*[An alle Befragten, die 18 Jahre und älter sind]* Haben Sie im Laufe des letzten Jahres Geräusche, auch ein Klingeln oder Summen, in Ihrem Kopf oder in einem oder beiden Ohren bemerkt, die jeweils länger als fünf Minuten andauerten? Ja, sehr häufig oder ständig Ja, häufig Ja, gelegentlich Nein, nicht im Laufe des letzten Jahres Nein, noch nie Weiß nicht/ keine Angabe	*[An Befragte mit einem Tinnitus]* Wie sehr haben Sie diese Geräusche in Ihrem Kopf oder in Ihren Ohren im Laufe des letzten Jahres beunruhigt, gestört oder geärgert, wenn diese besonders stark auftraten? Stark Mäßig Gering Überhaupt nicht Weiß nicht/ keine Angabe	*[An Befragte mit einem Tinnitus]* Haben Sie im Laufe des letzten Jahres Ihren Hausarzt oder einen Gesundheits-Experten in einer Klinik oder in einem Krankenhaus wegen der Hörprobleme, bzw. der Geräusche in Ihrem Kopf oder in Ihren Ohren aufgesucht? Ja, und dort 5 oder mehr Besuche Ja, und dort 2 bis 4 Besuche Ja, und 1 Besuch Nein, überhaupt kein Besuch Weiß nicht/ keine Angabe	*[An alle Befragten, die 18 Jahre und älter]* Haben Sie momentan überhaupt Schwierigkeiten mit dem Hören, wie beispielsweise beim Zuhören bei einer Rede oder beim Hören in einer geräuschvollen Umgebung? Ja, ich kann überhaupt nichts hören Ja, starke Schwierigkeiten Ja, mäßige Schwierigkeiten Ja, geringe Schwierigkeiten Nein, keine Schwierigkeiten Weiß nicht/ keine Angabe

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Greek	Τώρα θα σας κάνω μερικές ερωτήσεις σχετικά με προβλήματα ακοής και για την αίσθηση του θορύβου (βουητού) στο κεφάλι στο ένα ή και στα δύο αυτιά, το οποίο είναι ένα σύμπτωμα που οι γιατροί αποκαλούν «εμβοή»	*[Όλοι οι ενήλικες 18+]* Μέσα στον τελευταίο χρόνο, αισθανόσασταν θορύβους (όπως κουδούνισμα ή βουητό) στο κεφάλι σας ή σε ένα ή και στα δύο αυτιά που διήρκησε για περισσότερο από πέντε λεπτά τη φορά; Ναι, τον περισσότερο καιρό ή όλο το χρόνο Ναι, πολλές φορές Ναι, μερικές φορές Όχι, όχι κατά το τελευταίο έτος Όχι, ποτέ ΔΞ/ΔΑ	*[Για συμμετέχοντες με τρέχουσες εμβοές - κωδικός]* Μέσα στον τελευταίο χρόνο, πόσο αυτοί οι θόρυβοι στο κεφάλι ή τα αυτιά σας ανησύχησαν, ενόχλησαν ή αναστάτωσαν όταν ήταν στα χειρότερά τους; Σοβαρά Μέτρια Ελάχιστα Καθόλου ΔΞ/ΔΑ	*[Για συμμετέχοντες με τρέχουσες εμβοές - κωδικός]* Μέσα στον τελευταίο χρόνο, έχετε επισκεφτεί τον οικογενειακό γιατρό σας, ή έναν επαγγελματία του τομέα της υγείας σε μια κλινική ή νοσοκομείο για τα προβλήματα με τους θορύβους στο κεφάλι ή τα αυτιά σας; Ναι, 5 ή περισσότερες επισκέψεις Ναι, από 2 έως 4 επισκέψεις Ναι, απλά μία επίσκεψη Καθόλου ΔΞ/ΔΑ	*[Όλοι οι ενήλικες 18+]* Αντιμετωπίζετε αυτή την περίοδο οποιαδήποτε άλλη δυσκολία με την ακοή σας, όπως η ακρόαση μιας ομιλίας σε θορυβώδες περιβάλλον; -Ναι, δεν μπορώ να ακούσω καθόλου Ναι, έχω σοβαρή δυσκολία να ακούσω Ναι, μέτρια δυσκολία Ναι, ελαφριά δυσκολία Καμία δυσκολία ΔΞ/ΔΑ

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Italian	Ora le faremo alcune domande sui problemi di udito e sulla sensazione di suoni in testa o in una o entrambe le orecchie. Si tratta di un sintomo che i medici chiamano "acufene" o "tinnito"	*[A tutti gli adulti (età ≥ 18 anni)]* Nel corso dell'ultimo anno, ha sentito dei suoni (come fischi o ronzii) in testa o in una o entrambe le orecchie che durassero per più di 5 minuti? Sì, quasi sempre o sempre Sì, buona parte del tempo Sì, qualche volta No, non nell'ultimo anno No, mai Non so/Preferisco non rispondere	*[Solo ai partecipanti che attualmente hanno l'acufene]* Nel corso dell'ultimo anno, quanto questi suoni in testa o nelle orecchie la preoccupano, infastidiscono o disturbano quando sono nella loro fase più intensa? Fortemente Abbastanza Leggermente Per niente Non so/Preferisco non rispondere	*[Solo ai partecipanti che attualmente hanno l'acufene]* Nel corso dell'ultimo anno, si è rivolto al suo medico di famiglia, o a un professionista sanitario presso una clinica o un ospedale, per i problemi legati a questi suoni in testa o nelle orecchie? Sì, per un totale di 5 o più visite Sì, per un totale di 2-4 visite Sì, solo una volta No, mai Non so/Preferisco non rispondere	*[A tutti gli adulti (età ≥ 18 anni)]* Ha attualmente qualche altro disturbo di udito, come ad esempio difficoltà ad ascoltare chi parla in un ambiente rumoroso? Sì, non sento niente Sì, una notevole difficoltà Sì, una media difficoltà Sì, una lieve difficoltà Nessuna difficoltà Non so/Preferisco non rispondere

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Latvian	Tagad Jums tiks uzdoti daži jautājumi par dzirdes problēmām un trokšņu sajūtām galvā vai vienā vai abās ausīs. Medicīnā šādus simptomus dēvē par „*tinnitus*".	*Uzdot visiem pieaugušajiem (18+)* Vai pēdējā gada laikā Jūs esat dzirdējis/-usi trokšņus, tādus, kā zvanīšana vai sīkšana, savā galvā vai vienā vai abās ausīs, kas ilgst vairāk nekā piecas minūtes vienā reizē? Viena atbilde Jā, ļoti bieži vai visu laiku Jā, diezgan bieži Jā, dažkārt Nē, ne pēdējā gada laikā Nē, nekad Nezinu/ Nevēlos atbildēt	*E2 un E 3 uzdot* Cik ļoti, pēdējā gada laikā, šie trokšņi ir Jūs uztraukuši, kaitinājuši, apbēdinājuši, kad tie ir bijuši visizteiktākie? Ļoti stipri uztrauca Drīzāk uztrauca Nedaudz uztrauca It nemaz neuztrauca Nezinu/ Nevēlos atbildēt	*E2 un E 3 uzdot* Vai pēdējā gada laikā Jūs esat vērsies/-usies pie ģimenes ārsta vai sertificēta speciālista kādā no veselības aprūpes iestādēm ar trokšņiem galvā vai ausīs? Jā, apmeklēju 5 un vairāk reizes Jā, apmeklēju no divām līdz četrām reizēm Jā, apmeklēju tikai vienu reizi Neapmeklēju nevienu reizi Nezinu/ Nevēlos atbildēt	*Uzdot visiem pieaugušajiem (18+)* Vai Jums pašreiz ir dzirdes problēmas, piemēram, sadzirdēt teikto trokšņainā situācijā? Viena atbilde Jā, nevaru neko sadzirdēt Jā, smagas problēmas Jā, mērenas problēmas Jā, nelielas problēmas Nav problēmu Nezinu/ Nevēlos atbildēt

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Polish	Teraz zadamy Pani/ Panu parę pytań dotyczących problemów ze słuchem i wrażeniu słyszenia dźwięku w głowie lub w uchu/ obu uszach, co jest symptomem tego co lekarze nazywają szumami usznymi.	*[To all adults 18+]* Czy w ciągu ostatniego roku miał/a Pan/i przykre doznania dźwiękowe (np. dzwonienie/ bzyczenie) w głowie lub w uchu/ obu uszach, które trwało więcej niż 5 minut? Tak, prawie cały czas Tak, bardzo często Tak, czasami Nie, w ciągu ostatniego roku Nie, nigdy Nie wiem/ Wolę nie odpowiadać	*[To participants with current tinnitus - code 1-3 at E1]* W ciągu ostatniego roku jak bardzo ten dźwięk w Pana/i głowie lub uszach martwił, irytował albo niepokoił Pana/ią, kiedy osiągnął najgorsze stadium? Bardzo mocno Umiarkowanie Trochę W ogóle Nie wiem/ Wolę nie odpowiadać	*[To participants with current tinnitus - code 1-3 at E1]* W ciągu ostatniego roku czy był/a Pan/i na wizycie u swojego lekarza rodzinnego lub specjalisty w klinice/ szpitalu w sprawie swojego problemu z przykrymi doznaniami słuchowymi w Pana/i głowie lub uszach? Tak, byłem/ am na 5 lub więcej wizytach Tak byłem/am na 2 – 4 wizytach Tak, byłem/ am na jednej wizycie Nie, nie byłem/ am na żadnej wizycie Nie wiem/ Wolę nie odpowiadać	*[To all adults 18+]* Czy ma Pan/ Pani inne problem za słuchem, takie jak trudności ze słuchaniem czyjejś wypowiedzi w hałasie? Tak, w ogóle nic nie słyszę Tak, mam duże problemy Tak, mam umiarkowane problemy Tak, mam małe problemy Nie mam żadnych problemów Nie wiem/ Wolę nie odpowiadać

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Portuguese	Algumas perguntas sobre problemas de audição e uma sensação de ruído na cabeça, ou em um, ou nos dois ouvidos, sintoma de uma doença conhecida clinicamente como "tinnitus"	*[Para todos os adultos (18+)]* No último ano, teve ruídos (como toques ou zumbidos) na cabeça, em um ou nos dois ouvidos, que tenham durado mais de 5 minutos de cada vez?] Sim, sempre ou na maior parte do tempo Sim, muitas vezes Sim, algumas vezes Não, não no último ano Não, nunca Não sabe/Não responde	*[Para participantes com sintomas atuais de tinnitus]* Durante o último ano, quanto é que esses ruídos o deixaram tenso, incomodaram, ou o aborreceram quando estavam a afetá-lo/a mais? Muito Moderadamente Ligeiramente Nada Não sabe/Não responde	*[Para participantes com sintomas atuais de tinnitus]* No último ano, consultou o seu médico de família ou outro profissional de saúde acerca desses ruídos na cabeça ou ouvidos? Sim, 5 ou mais consultas Sim, de 2 a 4 consultas Sim, apenas 1 consulta Nada Não sabe/Não responde	*[Para todos os adultos (18+)]* Presentemente, sente algum outro problema na sua audição, tal como dificuldade em ouvir alguém a falar num ambiente ruidoso? Sim, não consigo ouvir de todo Sim, muita dificuldade Sim, dificuldade moderada Sim, sem grande dificuldade Sem dificuldade alguma Não sabe/Não responde

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Romanian	Acum urmează câteva întrebări despre probleme de auz și despre senzația de zgomot în cap ori în una sau ambele urechi, care este un simptom medical pe care doctorii îl numesc ''tinitus"	*[Pentru toți adulții]* În ultimul an ați auzit zgomote, cum ar fi sunete sau bâzâit, în cap ori în una sau ambele urechi, care să dureze mai mult de 5 minute de fiecare dată? Da, aproape mereu sau tot timpul Da, în mare parte a timpului Da, uneori Nu în ultimul an Nu, niciodată Nu ştiu/Nu răspund	*[Pentru toți participanții cu tinitus]* În ultimul an, cât de mult vă îngrijorează, deranjează și supără aceste sunete când sunt în cea mai rea manifestare? Grav Moderat Puțin Deloc Nu ştiu/Nu răspund	*[Pentru toți participanții cu tinitus]* În ultimul an, v-ați vizitat doctorul de familie sau un alt medic la o clinică sau spital despre problemele cu sunetele din cap sau urechi? Da, 5 sau mai multe vizite Da, 2-4 vizite Da, o singură vizită Deloc Nu ştiu/Nu răspund	*[Pentru toți adulții]* În prezent, aveți probleme cu auzul, cum ar fi dificultăți în urmărirea unui discurs atunci când este zgomot? Da, nu aud deloc Da, probleme grave Da, probleme medii Da, probleme ușoare Nicio problemă Nu ştiu/Nu răspund

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Russian	Теперь Вам будут заданы несколько вопросов о проблемах слуха и шумах в голове или в одном или обоих ушах. В медицине эти симптомы, известные как *"тиннитус".*	*Задавать всем взрослым (18+)* В течение последнего года Вы слышали шумы, такие как звон или свист, в своей голове или в одном или обоих ушах, который длится более пяти минут за один раз? *Один ответ* Да, очень часто или постоянно Да, довольно часто Да, иногда Нет, не в течение последнего года Нет, никогда Не знаю/ не желаю отвечать	*E2 и E 3 задать* Насколько сильно, в течение последнего года, эти шумы Вас волновали, раздражали, огорчали, когда они были наиболее яркими.? Очень сильно волновали Скорее волновалиНемного волновали Совсем не волновали Не знаю/ не желаю отвечать	*E2 и E 3 задать* В течение последнего года Вы обращался к семейному врачу или к сертифицированному специалисту в одним из учреждений здравоохранения с шумами в голове или ушах? Да, посетил/-а 5 или более раз Да, посетил/-а от двух до четырех раз Да, посетил/-а только один раз Не посетил/-а ни одного раза Не знаю/ не желаю отвечать	*Задавать всем взрослым (18+)* У Вас в настоящее время есть проблемы со слухом, например, услышать сказанное в шумной ситуации?Один ответ Да, ничего не слышу Да, тяжелые проблемы Да, умеренные проблемы Да, небольшие проблемы Нет проблем Не знаю/ не желаю отвечать

Appendix IX. Standardised survey instructions, questions and response options in the target languages (Biswas et al., 2019)

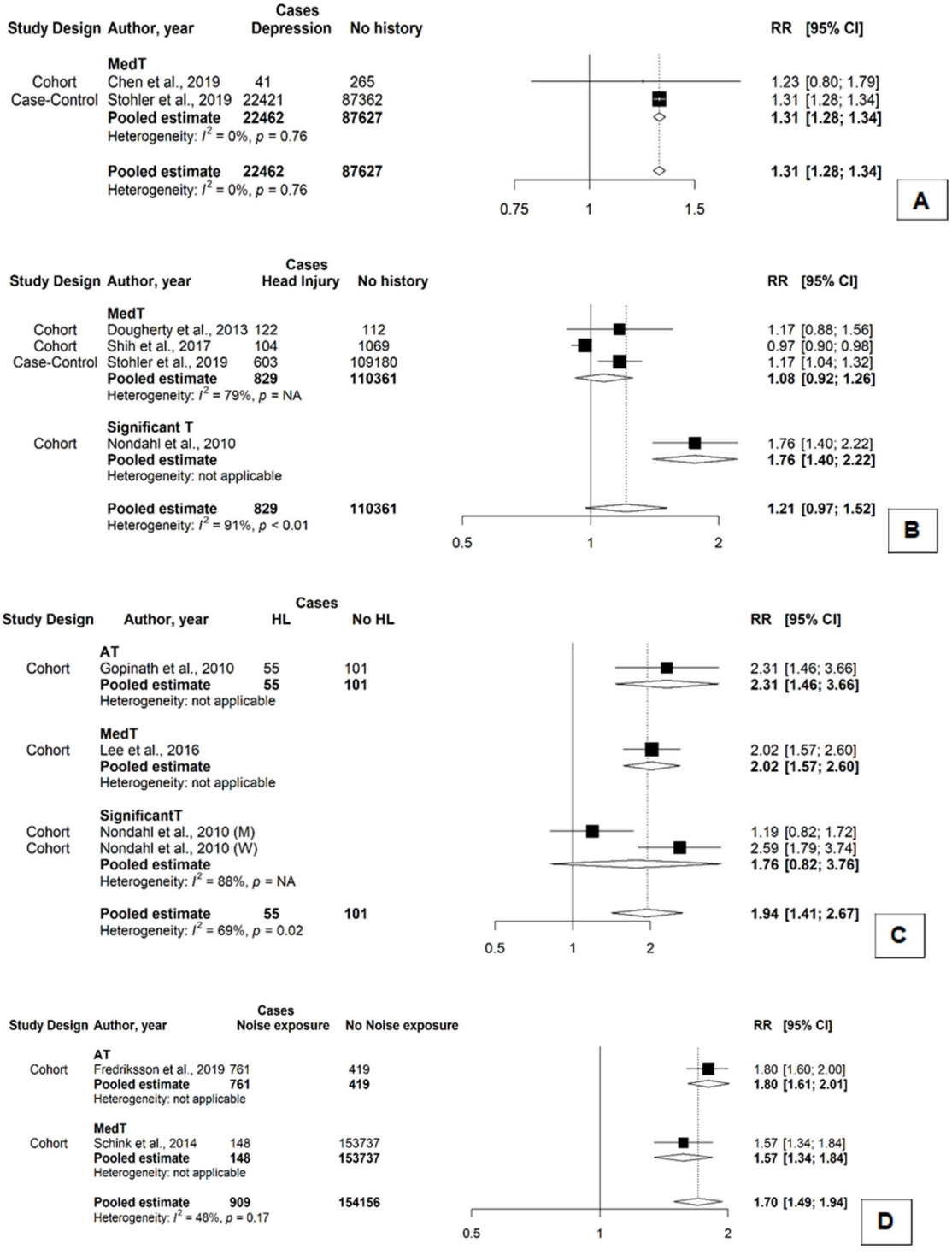
	General instruction to participants	Presence of tinnitus	Tinnitus severity	Use of healthcare resources for tinnitus	Presence of hearing difficulty
Spanish	Ahora le hacemos algunas preguntas sobre problemas auditivos y sobre la sensación de ruido en la cabeza, en uno o ambos oídos, que es un síntoma que los médicos llaman "tinnitus"	*[Base: todos pero +18 años]* Durante el año pasado, ¿usted ha tenido ruidos (como sonar o zumbar) en su cabeza o en uno o ambos oídos que ha durado más de cinco minutos seguidos? Sí, la mayoría del tiempo Sí, muchas veces Sí, algunas veces No, no en el último año No, nunca NS/NC	*[Base: Si cod. 1-3 en E1]* Durante el año pasado, ¿Le ha preocupado, molestado o trastornado ese ruido en su oídos o cabeza cuando ha estado en su peor momento? Mucho Moderadamente Ligeramente En absoluto NS/NC	*[Base: Si cod. 1-3 en E1]* Durante el año pasado, ¿usted ha visitado a su médico de cabecera o ha visto a un profesional de la salud en una clínica u hospital por sus problemas de ruidos en la cabeza o en los oídos? Sí, 5 o más visitas Sí, de 2 a 4 visitas Sí, solo una visita En absoluto NS/NC	*[Base: todos pero +18 años]* ¿Tiene usted actualmente alguna otra dificultad con su audición, como oír en una situación ruidosa? Sí, no puedo oír nada Sí, dificultad severa Sí, dificultad moderada Sí, una ligera dificultad Sin dificultad NS/NC

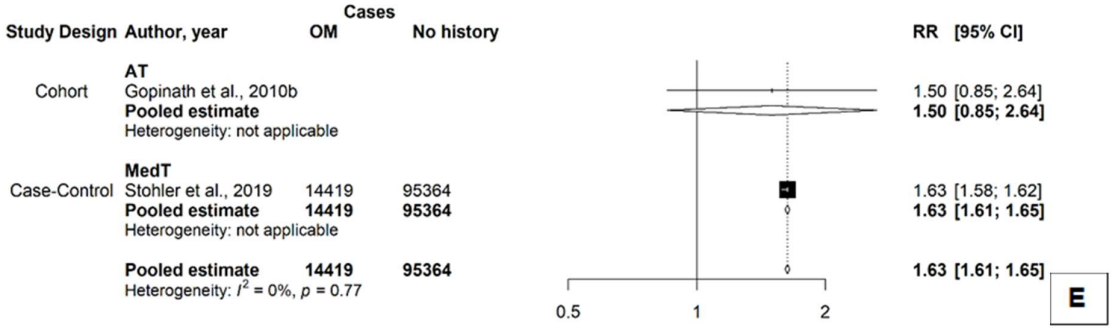
Appendix X. Odd ratios (OR) and corresponding 95% confidence intervals (CI) for tinnitus according to age group adjusting for sex, level of education and hearing difficulty. Europe 2017-2018.

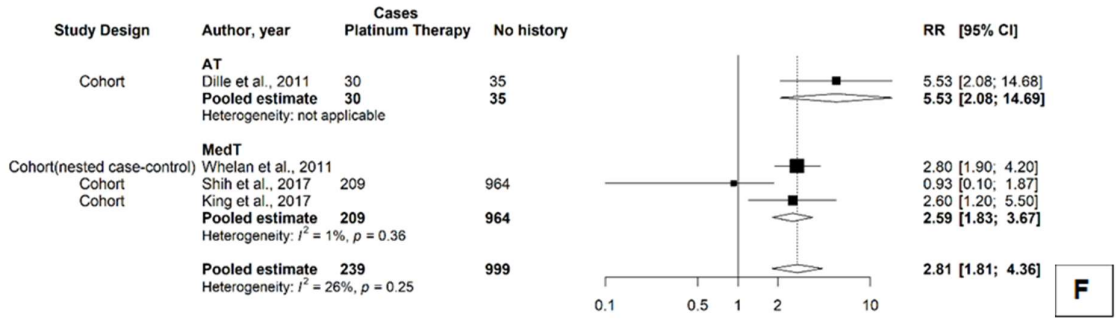
Age groups	Numbers	Any tinnitus	Bothersome tinnitus	Severe tinnitus
18-34	2935	Ref	Ref	Ref
35-44	2195	**1.22 (0.98-1.51)**	**1.88 (1.27-2.77)**	**1.65 (0.72-3.81)**
45-54	2275	**1.37 (1.12-1.68)**	**2.30 (1.60-3.30)**	**2.52 (1.19-5.34)**
55-64	1992	**1.57 (1.28-1.93)**	**1.95 (1.35-2.82)**	**1.84 (0.84-4.05)**
65-74	1482	**1.62 (1.30-2.01)**	**1.96 (1.36-2.83)**	**2.13 (0.99-4.60)**
>=75	548	**1.41 (1.09-1.82)**	**1.88 (1.26-2.80)**	**2.43 (1.08-5.4)**
p for trend		**<0.001**	**<0.001**	**<0.001**

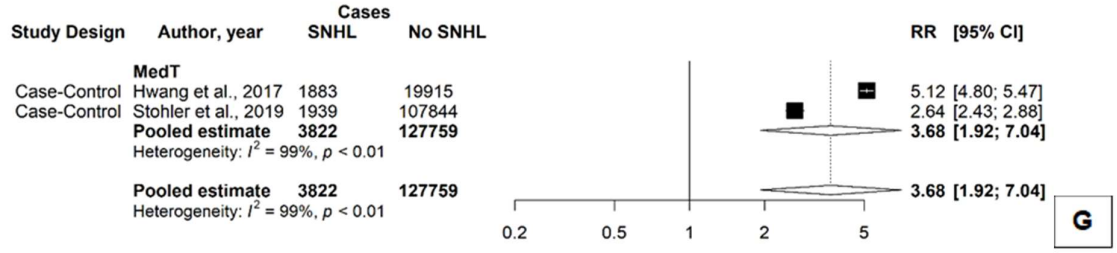
Ref=Reference category
ORs in bold are statistically significant

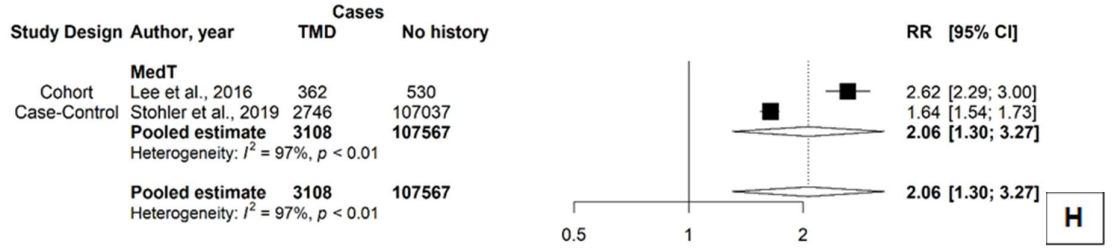
Appendix XIA Forest plots for factors with data from high-quality studies showing a positive association with tinnitus







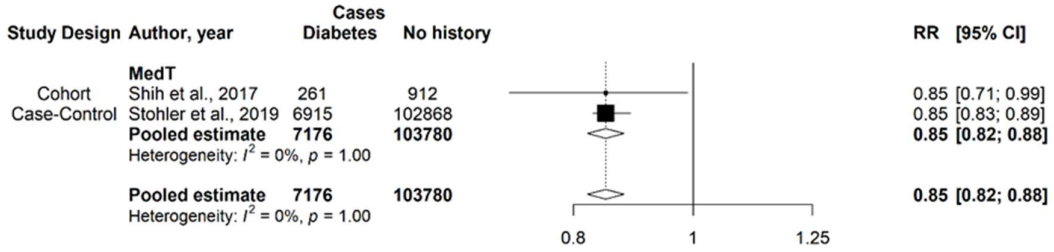




AT, Any Tinnitus; HL, Hearing Loss, MedT, Clinically-diagnosed Tinnitus; OM, Otitis Media, SNHL, Sensori-neural Hearing Loss; TMD, Temporo-mandibular Disorder

Forest plots for A: Depression; B: Head injury; C: Hearing Loss; D: Occupational Noise Exposure; E: Otitis Media; F: Platinum Therapy; G: Sensori-neural Hearing Loss; H: Temporo-mandibular Disorder

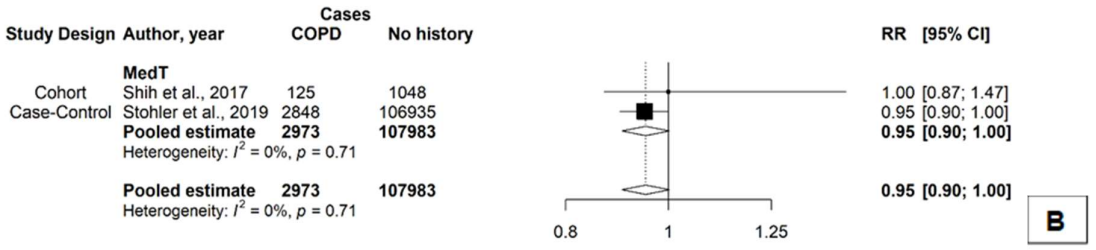
Appendix XIB Forest plots for factors with data from high-quality studies showing a negative association with tinnitus

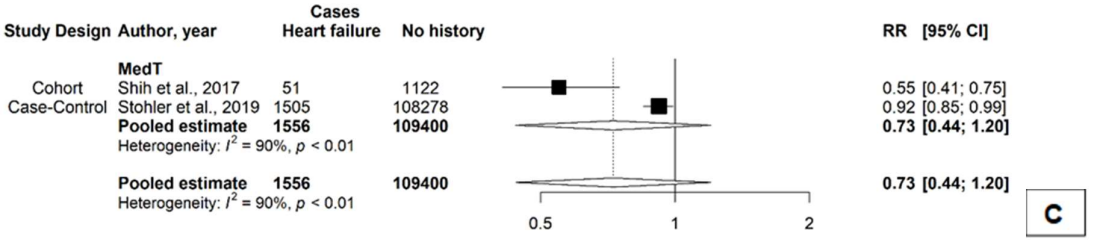


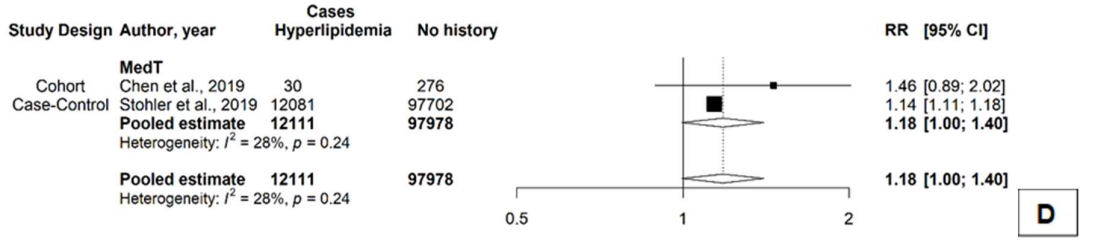
Forest plot for Diabetes
MedT, Clinically-diagnosed Tinnitus

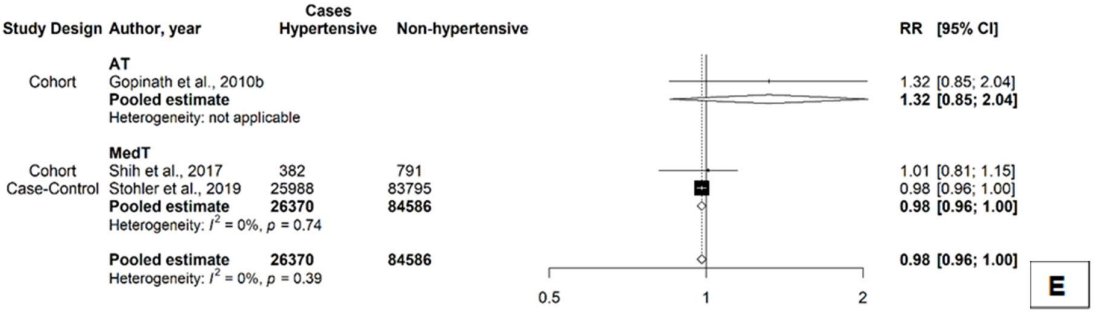
Appendix XIC Forest plots for factors with data from high-quality studies showing a null association with tinnitus

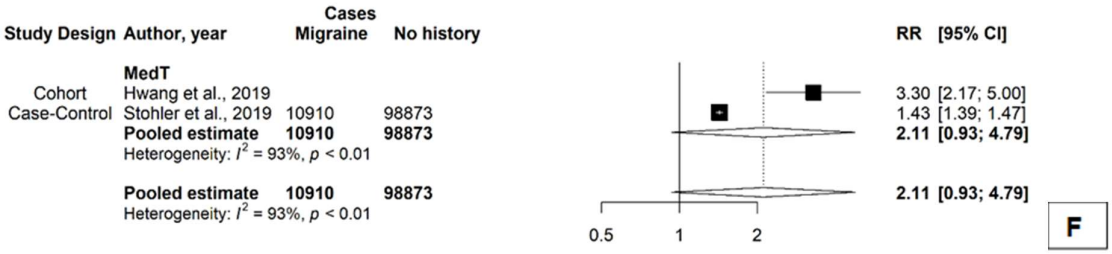


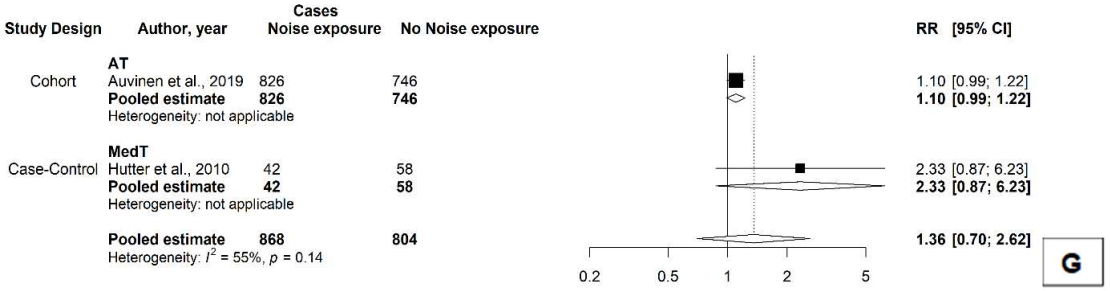


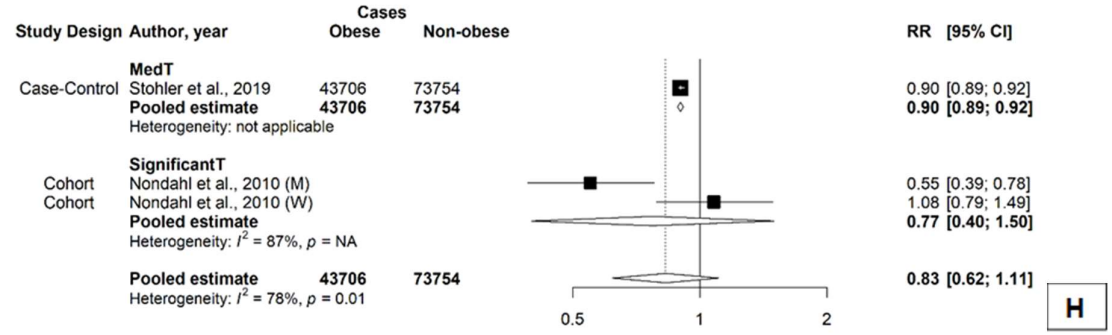


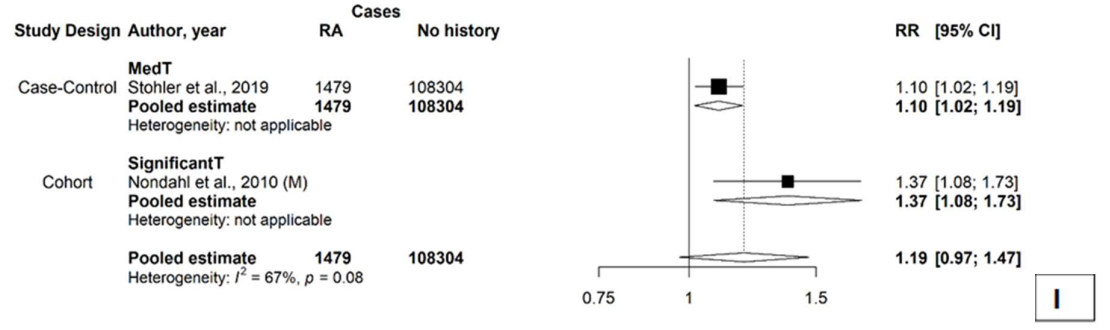


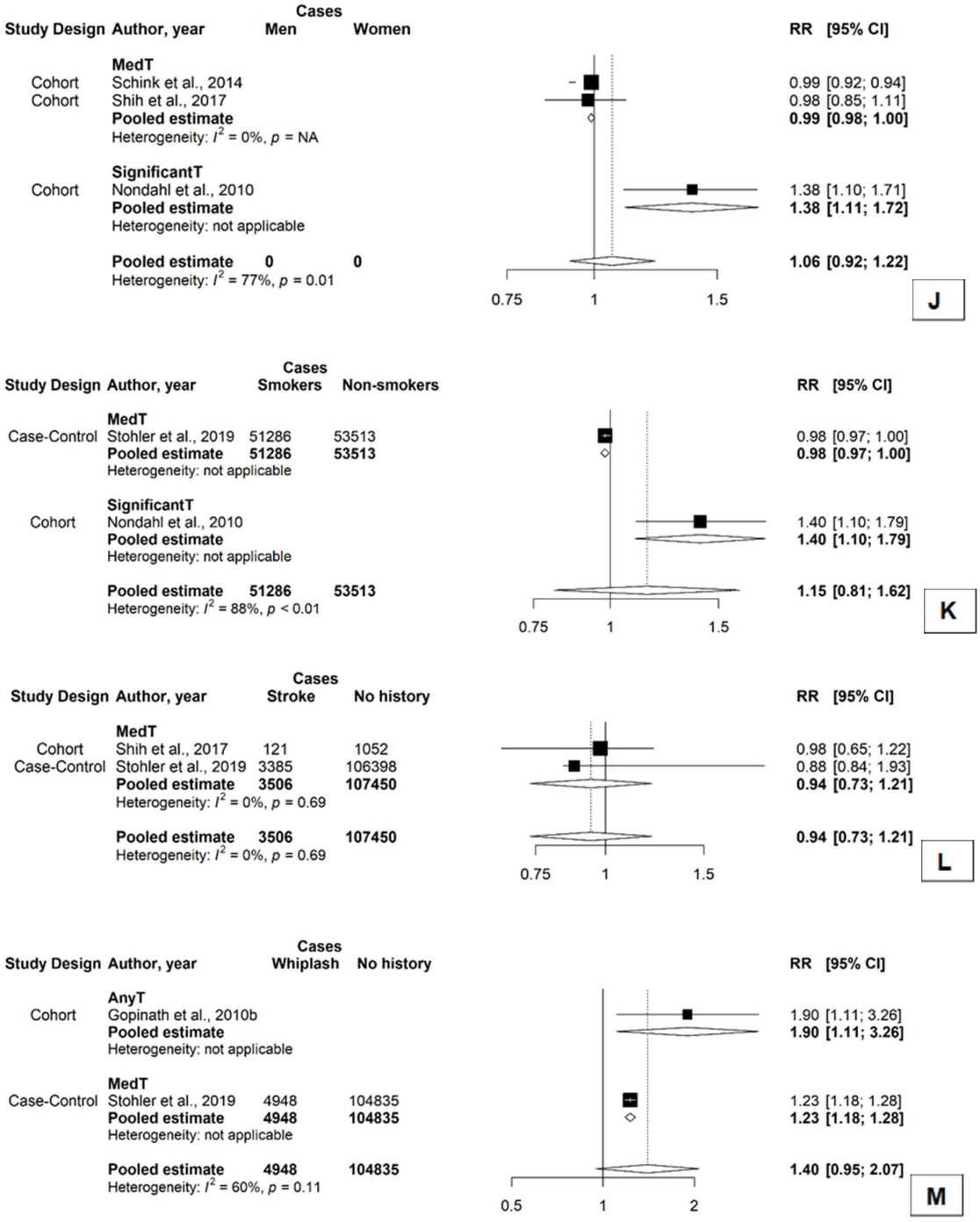



Cases
Study Design Author, year Migraine No history
RR [95% CI]
MedT
Cohort Hwang et al., 2019 3.30 [2.17; 5.00]
Case-Control Stohler et al., 2019 10910 98873 1.43 [1.39; 1.47]
Pooled estimate 10910 98873 2.11 [0.93; 4.79]
Heterogeneity: I^2 = 93%, p < 0.01
Pooled estimate 10910 98873 2.11 [0.93; 4.79]
Heterogeneity: I^2 = 93%, p < 0.01
0.5
1
2
F


Cases
Study Design Author, year Noise exposure No Noise exposure
RR [95% CI]
AT
Cohort Auvinen et al., 2019 826 746 1.10 [0.99; 1.22]
Pooled estimate 826 746 1.10 [0.99; 1.22]
Heterogeneity: not applicable
MedT
Case-Control Hutter et al., 2010 42 58 2.33 [0.87; 6.23]
Pooled estimate 42 58 2.33 [0.87; 6.23]
Heterogeneity: not applicable
Pooled estimate 868 804 1.36 [0.70; 2.62]
Heterogeneity: I^2 = 55%, p = 0.14
0.2
0.5
1
2
5
G


Cases
Study Design Author, year Obese Non-obese
RR [95% CI]
MedT
Case-Control Stohler et al., 2019 43706 73754 0.90 [0.89; 0.92]
Pooled estimate 43706 73754 0.90 [0.89; 0.92]
Heterogeneity: not applicable
SignificantT
Cohort Nondahl et al., 2010 (M) 0.55 [0.39; 0.78]
Cohort Nondahl et al., 2010 (W) 1.08 [0.79; 1.49]
Pooled estimate 0.77 [0.40; 1.50]
Heterogeneity: I^2 = 87%, p = NA
Pooled estimate 43706 73754 0.83 [0.62; 1.11]
Heterogeneity: I^2 = 78%, p = 0.01
0.5
1
2
H


Cases
Study Design Author, year RA No history
RR [95% CI]
MedT
Case-Control Stohler et al., 2019 1479 108304 1.10 [1.02; 1.19]
Pooled estimate 1479 108304 1.10 [1.02; 1.19]
Heterogeneity: not applicable
SignificantT
Cohort Nondahl et al., 2010 (M) 1.37 [1.08; 1.73]
Pooled estimate 1.37 [1.08; 1.73]
Heterogeneity: not applicable
Pooled estimate 1479 108304 1.19 [0.97; 1.47]
Heterogeneity: I^2 = 67%, p = 0.08
0.75
1
1.5
I



AT, Any Tinnitus; COPD, Chronic Obstructive Pulmonary Disease; MedT, Clinically-diagnosed Tinnitus; RA, Rheumatoid Arthritis; SigT, Significant Tinnitus

Forest plots for A: Alcohol; B: COPD; C: Heart Failure; D: Hyperlipidaemia; E: Hypertension; F: Migraine; G: Noise exposure (Non-Occupational); H: Obesity; I: Rheumatoid Arthritis; J: Sex; K: Smoking; L: Stroke; M: Whiplash

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
NORTH AMERICA						
Nondahl et al., 2002; USA	Smoking, Alcohol	Cohort study; EHLS; 1993-1995 (follow-up 1998-2000)	3737 subjects (had tinnitus data) in 1992-1995; Both sexes, 48-92 years; 2513 subjects with information at follow up	"In the past year have you had buzzing, ringing or noise in your ears?" (yes) and "How severe is this noise in its worst form?" (moderate/severe) and/or "Does this cause you to have problems getting to sleep?" (yes)	5-years cumulative incidence: AT: 5.7%	Significant tinnitus, has been considered as AT in our analysis.
Nondahl et al., 2010; USA	Smoking, Alcohol , BMI	Cohort study; EHLS; 1993-1995 (follow-up: 2003-2005)	2922 subjects; Both sexes; 48-92 years with information at follow-up	Same question as Nondahl et al., 2002	10-years cumulative incidence: AT: 12.7%	
Shargorodsky et al., 2010; USA	Smoking, BMI	Cross-sectional study; NHANES; 1999-2004	14178 subjects; Both sexes; ≥20 years	"In the past 12 months, have you ever had ringing, roaring, or buzzing in your ears?" (yes)	Prevalence AT: 25.3%	
Nondahl et al., 2011; USA	Smoking, Alcohol , BMI	Cross-sectional study; BOSS; 2005-2008	3267 subjects; Both sexes; 21-84 years	Same question as Nondahl et al., 2002	Prevalence AT:10.6%	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Witsell et al., 2011; USA	Caffeine intake	Cross-sectional study; CHEER; March 2010 to November 2010	440 responded to tinnitus questions; Both sexes; ≥ 18 years	Tinnitus began >6 months ago (Yes)	Prevalence AT: 68%;	
Loprinzi et al., 2013; USA	Smoking, BMI	Cross-sectional; NHANES; 2005-2006	1436 subjects; Both sexes; 12-19 years: n=963; 70-85 years: n=473	"In the last 12 months, have you been bothered by ringing or buzzing in your ears or head that lasted for 5 min or more?" (yes)	Prevalence 12-19: AT: 8.9% 70-85: AT: 25.3%	
Mahboubi et al., 2013; USA	Smoking, BMI	Cross-sectional; NHANES; 2005-2008	3520 subjects; Both sexes; 12-19 years	Same question as Loprinzi et al., 2013	Prevalence AT: 7.5%	
Glicksman et al., 2014; USA	Caffeine intake	Cohort study; NHSII; 1991 (follow up till 2009)	65,085 subjects; Women; 30-42 years at baseline	Any tinnitus (AT): “In the past 12 months, have you had ringing, roaring, or buzzing in your ears?” (never/ once per week or less/ a few days per week/ daily)	Incidence rate AT: 475 per 100,000 person-years	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Masterson et al., 2016; USA	Smoking	Cross-sectional study; NHIS; 2007	23393 subjects; Both sexes; ≥18 years	AT: "In the last 12 months, have you been bothered by ringing or buzzing in your ears or head that lasted for 5 min or more? (yes)	Prevalence AT: 9.59%	
Bhatt et al., 2017; USA	Alcohol	Cross-sectional study; NHIS; 2007	Both sexes; ≥18 years	AT: "In the last 12 months, have you been bothered by ringing or buzzing in your ears or head that lasted for 5 min or more? (yes)		No data on the number of participants and prevalence of tinnitus
Swan et al., 2017; USA	Smoking, BMI	Cross-sectional study; Veterans; 2002-2014	570248 subjects; Both sexes (87.14% M); ≥18 years	AT: ICD-9-CM (388.3x) diagnosed by an ENT specialist at two separate visits	Prevalence AT: 11.61%	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Bhatt, 2018; USA	Smoking	Cross-sectional study; Students; 2016	678 subjects; Both sexes; 18-30 years	AT: "In the past 12 months, have you been bothered by ringing, roaring, or buzzing in your ears or head that lasts for 5 minutes or more?" (yes) or "Have you ever experienced ringing, roaring or buzzing in your ears or head?" (yes)	Prevalence AT: 59.3% AT in the last 12 months: 21.4%	
EUROPE						
Palmer et al., 2002; UK	Smoking	Cross-sectional study; Patients and members of armed forces; 1997-1998	12 907 subjects; Both sexes; 16-64 years, Tinnitus prevalence was available for 7537	AT: "During the last 12 months have you had noises in your head or ears (such as ringing, buzzing or whistling) which lasted longer than five minutes?" (yes, most of the time + yes, all the time)	Prevalence AT: 5.84%	We calculated the prevalence through a weighted mean of values between subjects aged 35-64 years.

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Palmer et al., 2004; UK	Smoking	Cross-sectional study; Patients and members of armed forces; 1997-1998	12907 subjects; Both sexes; 16-64 years. Prevalence data available for 10418 subjects	Same as Palmer et al., 2002	Prevalence AT: 5.1%	
Brunnberg et al., 2008; Sweden	Smoking, Alcohol	Cross-sectional study, Young people; 2005;	2871 subjects; Both sexes; 15-16 years	AT: "Have you experienced tinnitus during the last three months?" (always + often)	AT Prevalence: 18.9%	We calculated overall prevalence from data on prevalence in subgroups
Rubak et al., 2008; Denmark	Smoking	Cross-sectional study; Employed workers; 2001-2002	752 subjects; Both sexes (76.6% M)	AT: “Have you had ringing or sounds in the ears, or tinnitus at least once every month?” (yes)	Prevalence AT: 15.6%	
Brydøy et al., 2009; Norway	Smoking	Cross-sectional study; Testicular cancer patients; 1998-2002	1409 subjects; M; 18-75 years	AT: “Are you troubled by ringing in your ears?” (yes)		
Lindgren et al., 2009; Sweden	Smoking	Cross-sectional study; Pilots; 2007	460 subjects; Both sexes (91% M); 32-63 years;	AT: “Have you experienced tinnitus for more than 5 minutes during the previous year?” (yes)	Prevalence AT: 40%	
Canlon et al., 2013; Sweden	Smoking	Cross-sectional study; Subgroup of SLOSH	348 subjects; Both sexes	Not clearly stated	Prevalence AT: 31%	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Marmut et al., 2014; Serbia	Smoking, Alcohol , Caffeine intake	Cross-sectional study; Serbian secondary school student; 2005	771 subjects; 35.9% M (277), 64.1% F (494); 14-20 years	AT: "Do you feel occasional or permanent buzzing or ringing in your ears?"	Prevalence AT: 12.8%	
McCormack et al., 2014; UK	Smoking, BMI	Cross-sectional data; UK Biobank; 2006-2010	171,722 subjects Both sexes; 40-69 years	AT: “Do you get or have you had noises (such as ringing or buzzing) in your head or in one or both ears that last for more than five minutes a time?"	Prevalence AT: 17.25%	AT sum of transient and persistent
Gallus et al., 2015; Italy	Smoking, Alcohol, BMI	Cross-sectional study; 2014	2952 subjects; Both sexes; ≥18 years	AT: "In the last 12 months, have you been bothered by ringing or buzzing in your ears or head that lasted for 5 min or more?"	Prevalence: ≥18 years: AT: 6.2%; ≥45 years: AT: 8.7%;	
Martines et al., 2015; Italy	Smoking, BMI	Cross-sectional data; Palermo University	120 subjects; Both sexes; 14-85 years	AT: Definition of tinnitus not clearly stated		

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Martinez et al., 2015; UK	Smoking, Alcohol , BMI	Cohort study; Data from CPRD and HES; Baseline in 2002 end of study 2011	4 703 226 subjects (26,500,000 persons/years); Both sexes; <85 years	SigT: primary hospital discharge diagnosis for tinnitus defined with ICD-10 code H931 2 primary care record for tinnitus followed by one of the fallowing within 28 days specific diagnosis or referral	Incidence 14303 incident cases; 5.4 new AT cases per 10000 person-years	
Degeest et al., 2017; Belgium	Smoking	Cross-sectional study; Group of young adults from Flanders	517 subjects; Both sexes; 18-30 years	AT: presence of tinnitus lasting more than 72h after leisure noise exposure	Prevalence AT: 6.4%	
OCEANIA						
Sindhusake et al. 2003; Australia	Smoking	Cross-sectional study; BMHS; 1997-1999	2015 subjects; Both sexes; >54 years	AT: “Have you experienced any prolonged ringing, buzzing, or other sounds in your ears or head within the past year that is, lasting for 5 minutes or longer?”	Prevalence AT: 30%	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Sindhusake et al., 2004; Australia	Smoking	Cross-sectional study; BMHS; 1997-1999	2015 subjects; Both sexes; >54 years	Same as Sindhusake et al., 2003	Prevalence AT: 30%	The sample from this article and Sindhusake et al. 2003 is the same.
Kirk et al., 2011; Australia	Smoking	Cross-sectional data; Defense personnel-deployed	5986 subjects	AT: “Have you suffered of ringing in the ears in the last month?" (yes) and severity (moderate + severe).	Prevalence Bougainville; AT: 16% East Timor; AT: 17%	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Tan et al., 2018; Australia	Smoking, Alcohol , BMI	Cross-sectional; Busselton Healthy Ageing study; 2010-2015	4877; Both sexes; 45-69 years	AT: "Do you experience tinnitus (sound in your ears and head) for longer than 5 minutes which does not have an obvious cause?" (yes) and "How does tinnitus affect your daily life and activities?" (frequently+ constantly)	Prevalence AT: 2.0%	
ASIA						
Michikawa et al., 2010; Japan	Smoking, Alcohol	Cross-sectional study; Residents of Kurabuchi Town; 2006	1320 subjects; Both sexes; ≥65 years	AT: "In the past year have you experienced any ringing, buzzing or other sounds (tinnitus) in your ears?"	Prevalence AT: 18.6%	
Fujii et al., 2011; Japan	Smoking, Alcohol , BMI	Cross-sectional study; Takayama Study; 2002	14423 subjects; Both sexes; 45-79 years	AT: "Have you ever had tinnitus lasting longer than 5 minutes? Do not include when this happened immediately after very loud sounds".	Prevalence AT: 11.9%	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Kim et al, 2012; South Korea	BMI	Cross-sectional study; Elementary school in Seoul	928 subjects; Both sexes; 10-12 years	AT: Definition of tinnitus not clearly stated	Prevalence AT: 46.9%	
Degirmenci et al., 2014; Turkey	Smoking	Cross-sectional data; patients of Mengucek Dazi Hospital	160 subjects (80 cases and 80 controls); Both sexes	AT: assessed by an ENT specialist		
Park and Moon, 2014: South Korea	Smoking, Alcohol, BMI	Cross-sectional study; KNHANES; 2010-2011	10061 subjects; Both sexes; 20-97 years	AT: "In the past year have you ever had ringing, roaring or buzzing in your ears?"	Prevalence AT: 21.4%	
Park et al., 2014a; South Korea	Alcohol, BMI	Cross-sectional study; KNHANES; 2008-2011	3047 subjects; Both sexes (47.6% W, 52.4 % M); 12-19 years	Same as Kim et al., 2015	Prevalence AT: 17.7%	
Park et al., 2014b; South Korea	Smoking, Alcohol , BMI	Cross-sectional study; KNHANES; 2009-2011	21893; Both sexes; ≥12 years	Same as Kim et al., 2015	Prevalence AT: 19.7%	
Joo et al., 2015; South Korea	Smoking, Alcohol , BMI	Cross-sectional study; KNHANES; 2010-2012	11266 subjects; Both sexes; ≥19 years	Same as Kim et al., 2015	Prevalence AT: 32.76 %	

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Kim et al., 2015; South Korea	Smoking, Alcohol, BMI	Cross-sectional study; KNHANES; 2009-2012	19290; Both sexes; 20-98 years	AT: "Have you heard any ringing, buzzing, roaring or hissing sounds without an external acoustic source in the past year?"	Prevalence AT: 20.7%	
Torun et al. 2016 Turkey	BMI	Cross-sectional data; ENT department of Erzican University	213 subjects (100 cases, 113 controls); Both sexes (55.3 % W, 44.7% M) ; 18-84 years	Tinnitus was not defined		
Lee et al., 2017; South Korea	Smoking, Alcohol, BMI	Cross-sectional study; KNHANES; 2010-2012	2736; W;19-65 years	Same as Kim et al., 2015	Prevalence AT: 22.2%	
Mofateh et al., 2017; Iran	Smoking	Cross-sectional study; Factory's Male workers; 2013	150 subjects; M	AT: Definition of tinnitus not clearly stated	Prevalence AT: 17.3%	
SOUTH AMERICA						
Bellé et al., 2007; Brazil	Alcohol	Cross-sectional study	74 subjects; Both sexes; 33-70 years	AT: complaint of tinnitus	Prevalence AT 41.9%	
Paschoal and de Azevedo 2009; Brazil	Smoking	Cross-sectional study; College students in Sao Paulo	144 subjects; Both sexes; 20-31 years	AT: Definition of tinnitus not clearly stated		
AFRICA						

Appendix XII. Main characteristics of publications providing information on the relationship between tinnitus and modifiable lifestyle-related risk factors

Publication (author, year; journal)	Risk factor/s examined	Study characteristics (design; name; period)	Study population (sample size; age range, sex)	Tinnitus definition	Tinnitus prevalence/ incidence	Comment
Lasisi et al., 2010; Nigeria	Smoking, Alcohol	Cross-sectional study; Ibadan Study of ageing; baseline 2003, follow-up 2008	1302 subjects; Both sexes; ≥65 years	AT: "Have you had a perception of ringing, swishing, humming or other type of noise in the ear or head without an external source of sound?"	Prevalence AT: 14.1%	
Sogebi, 2013; Nigeria	Smoking, Alcohol, BMI	Cross-sectional study; ENT clinic teaching hospital, Nigeria; 2007-2011	543 subjects; Both sexes; >40 years	AT: experiencing tinnitus (yes)	Prevalence AT: 14.5%	

AT: any tinnitus SigT: Significant Tinnitus; M: Men; W: Women; BMI: Body mass index; BOSS: Beaver Dam Offspring Study; BMHS: Blue Mountain Hearing Study; CPRD: Clinical practice research datalink; EHLS: Epidemiology of Hearing Loss Study; HES: Hospital episode statistics; KNHANES: Korea National Health and Nutrition Examination Survey; NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey; SLOSH: Swedish Longitudinal Occupation Survey of Health

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
NORTH AMERICA					
Nondahl et al., 2002 USA	No measure of association reported	3737 subjects at baseline	2513 subjects at follow-up		As the participants at 5-yrs follow up are the same as Nondahl et al., 2010 (which, instead, provides a 10-yrs follow-up), we considered just baseline data. Through these data we estimated the crude OR for CS: 1.20 (0.88-1.64)
Nondahl et al., 2010 USA	HR of CS, ES, and ExS (divided in period since quit) Ref: Never smokers	2922 subjects	Overall AT ES:HR: 1.40 (1.10-1.79) CS:HR: 1.34 (0.93-1.93) AT, ExS; time since quit 1-9 years: HR: 1.75 (1.21-2.49) 10-19 years: HR: 1.65 (1.13-2.41) 20-29 years: HR: 1.31 (0.87-1.96) 30-39 years: HR: 1.12 (0.67-1.86) 40+ years: HR: 0.90 (0.45-1.82)	Age and sex for ES; Age, sex, arthritis, alcohol, head injury, HL, obesity for CS.	In the paper HR are not reported for ExS, but just showed in a figure. We estimated HR on this basis. OR: 1.43 (1.16-1.76)

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Shargorodsky et al., 2010 USA	OR for CS and ExS Ref: NS	14178 subjects	Overall AT ExS: OR: 1.14 (1.01-1.28) CS: OR: 1.34 (1.14-1.57)	Age, sex, ethnicity, education level, BMI, smoking, cardiovascular factors and noise exposures	We estimated OR for ES from ExS and CS: AT OR: 1.22 (1.05-1.43)
Nondahl et al., 2011 USA	OR for ES and CS OR for categories of years since smoking cessation Ref: never smokers	3267 subjects	Overall AT ES: OR: 1.24 (0.99-1.56) CS: OR: 1.50 (1.12-2.01) Overall AT; years since smoking cessation 30+: OR: 0.86 (0.50-1.46) 20-29: OR: 1.25 (0.83-1.90) 10-19: OR: 1.00 (0.63-1.58) 1-9: OR: 1.23 (0.80-1.89)	Age and sex	For the meta-analysis, we pooled data divided in categories for years since cessation, to find just one OR for ExS: 1.10 (0.88-1.38)
Loprinzi et al., 2013 USA	Adjusted Wald tests applied to the weighted mean of serum cotinine (ng/mL)	12-19 years: 963 subjects 70-85 years 473 subjects	12-19 years: Cotinine levels: Subjects with tinnitus: 35.9 Without tinnitus: 10.4 (p=0.16) 70-85 years: Cotinine levels: Subjects with tinnitus: 10.4 Without tinnitus: 21.6 (p=0.06)		The younger group not included as it includes adolescents. In older group: insufficient data to estimate RR. This study was not included in the meta-analysis.
Mahboubi et al., 2013 USA	OR for ES Ref: NS	3115 subjects for ES; 12-19 years	Overall AT ES: OR: 1.21 (0.74-1.98)	Age, sex, ethnicity, income, BMI, HL and others.	

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Masterson et al., 2016 USA	Weighted adjusted PR for CS and ExS Ref: NS	22990 subjects	Overall AT ExS: PR: 1.69 (1.48-1.92) CS: PR: 1.68 (1.48-1.90)	Age, sex, race, work status, geographical region	We estimated OR for ES from ExS and CS: OR: 1.68 (1.52-1.87)
Swan et al., 2017 USA	OR for nicotine dependent subjects Ref: non nicotine dependent and non-Tinnitus non-HL subjects	570248 subjects	Tinnitus only subjects Nicotine dependent: OR: 0.94 (0.91-0.96) Tinnitus and HL subjects Nicotine dependent: OR: 1.05 (1.03-1.08)	All demographic and military characteristics and conditions	Since ICD 9 codes were used to define tinnitus, the study was excluded from the analysis.
Bhatt 2018 USA	OR for ES Ref: NS	678 subjects	Overall AT ES: OR: 2.48 (1.40-4.39)	Sex, ethnicity, HL,	
EUROPE					
Palmer et al., 2002 UK	PR for ES Ref: NS	7537 subjects (35-64 years)	35-64 years: M: AT ES: PR: 1.00 (0.8-1.2) 35-64 years: W: AT ES: PR: 1.00 (0.7-1.4)	Age, years worked in noisy job, frequent headaches, frequent tiredness	

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Palmer et al. 2004 UK	PR for NS, ExS and CS, divided by years spent in noisy job Ref: NS, never worked in noisy job	6947 subjects	AT; never worked in noisy job ExS: PR: 1.0 (0.7-1.4) CS: PR: 0.9 (0.6-1.3) AT: upto 5 years in noisy job NS: PR: 1.9 (1.4-2.7) ExS: PR: 2.4 (1.7-3.3) CS: PR: 2.1 (1.4-3.0) AT; 5+ years in noisy job NS: PR: 3.0 (2.2-4.1) ExS: PR: 3.8 (2.8-5.0) CS: PR: 3.6 (2.5-4.9)	Age, sex, report of tiredness, stress and headaches.	As data provided were divided according to years spent in noisy job, we merged these data to obtain a single OR for ExS and CS. ExS: OR: 1.51 (1.23-1.84) CS: OR: 1.31 (1.05-1.64) We estimated OR for ES from ExS and CS: OR: 1.42 (1.20-1.69)
Brunnberg et al., 2008 Sweden	Chi square on differences of prevalence of CS in different groups (HL & Tinnitus, Just Tinnitus, Just HL, none)	2878 subjects	Overall AT No Tinnitus/No HL: 7% Just HL: 16% Just Tinnitus: 13% Tinnitus & HL: 23% (p<0.001)	None	Authors provided prevalence of CS and NonS in these 4 groups. We merged these data and then we estimated a crude OR for CS: 2.39 (1.62-3.53)
Rubak et al., 2008 Denmark	No measure of association provided	752 subjects			Authors provided prevalence for CS and NonS. With these data we estimated the crude OR for CS: 1.26 (1.03-1.54)
Brydøy et al., 2009 Norway	OR for CS and ExS Ref: NS	1409 subjects	Overall AT CS: OR: 1.3 (1.0-1.7) ExS: OR: 1.2 (0.9-1.7)	Not specified	We estimated OR for ES from ExS and CS OR: 1.26 (1.03-1.54)

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Lindgren et al., 2009 Sweden	OR for CS Ref: NonS	388 subjects		Age, gender, military pilot, noise, employment years, types of aircraft	
Canlon et al., 2013 Sweden	Chi square on differences of prevalence of Tinnitus between CS and NonS	348 subjects	Overall AT CS: 26.5% NonS: 31.5% (p=0.55)	None	We estimated a crude OR from prevalence of CS and NonS. OR: 0.78 (0.35-1.74)
Marmut et al., 2014 Serbia	OR for reported CS Ref: NonS	277 subjects(M) 771 subjects (M+W)	M; AT CS: OR: 2.78 (0.23-33.73)	Behavioral and habits variables	Paper provided estimates for boys. Review by Veile et al. provides a lower OR, and therefore we assume they contacted the authors and merged the data from boys and girls. We decided to keep the value from Veile et al. Overall AT CS: OR: 1.97 (0.31-12.58)

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
McCormack et al., 2014 UK	OR for NS and ExS Ref: CS	170963 subjects	Overall "Transient" Tinnitus ExS: OR: 1.01 (0.95-1.07) NS: OR: 1.00 (0.94- 1.06) Overall "Persistent" Tinnitus ExS: OR: 1.18 (1.11-1.26) NS: OR: 1.12 (1.05-1.20)	Age, sex, HL, BMI and others.	As the reference was CS, we reverted the ORs considering as reference NS. Transient and Persistent Tinnitus, were merged. Risk estimates provided are: Overall AT CS: 0.95 (0.90-0.99) ExS: 1.03 (1.00-1.06) We estimated OR for ES from ExS and CS: OR: 1.02 (0.99-1.04)
Gallus et al., 2015 Italy	OR for CS and ExS Ref: NS	1723 subjects (45+ yrs)	45+; AT CS: OR: 0.64 (0.34-1.20) ExS: OR: 1.50 (0.96-2.34).	Age, sex, education, geographic area, alcohol, BMI	We estimated OR for ES from ExS and CS OR: 1.09 (0.74-1.62)
Martines et al., 2015 Italy	OR for CS Ref: NonS	46 cases 74 controls	Overall AT CS: OR: 0.93 (0.43-2.00)		
Martinez et al., 2015 UK	No measure of association provided	2968856 subjects			Excluded as clinically diagnosed tinnitus was assessed.

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Degeest et al., 2017 Belgium	Measure of association were provided but definition of Tinnitus different from other articles.	517 subjects			To align with definition of tinnitus used in most studies, we considered tinnitus lasting more than 72h as AT, and temporary Tinnitus as no tinnitus. We estimated the crude OR for CS: 1.53 (0.72-3.26)
OCEANIA					
Sindhusake et al., 2003 Australia					Received no response from authors. Used values from the review by Veile et al.: Overall AT. OR for CS: 0.98 (0.74:1.30)
Sindhusake et al., 2004 Australia					Excluded: provided same information as Sindhusake et al (2003)
Kirk et al., 2011 Australia	OR for smoking during deployment Ref: Non-smokers during deployment	Bougainville: 1869 subjects East Timor: 1 541 subjects	Bougainville; Deployed; AT Smokers during deployment OR: 1.26 (0.95-1.66) East Timor; Deployed; AT Smokers during deployment OR: 0.97 (0.73-1.30)	Age, sex, service, rank, aggregate count of number of daily exposures to potential ototoxic factors	Participants were asked about their smoking status during deployment; in order to plot these data, we considered participants as CS.
Tan et al., 2018 Australia	OR for ExS and CS Ref: NS	4877 subjects	Overall AT ExS: OR: 1.11 (0.72-1.69) CS: OR: 0.92 (0.43-2.00)	Age, sex, family history of HL	

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
ASIA					
Michikawa et al., 2010 Japan	Chi square on differences of prevalence of Tinnitus between CS, ExS and NS	1311 subjects	Overall AT NS: 18.4% ExS: 20.5% CS: 17.8% (p=0.825)		Estimated the crude ORs. ExS: OR: 1.14 (0.71-1.82) CS: OR: 0.96 (0.62-1.45) We estimated OR for ES from ExS and CS OR: 1.03 (0.74-1.43)
Fujii et al., 2011 Japan	OR for ExS and CS Ref: NS	14423 subjects	M: ExS: OR: 0.86 (0.71-1.04) CS: OR: 1.02 (0.83-1.25) W: ExS: OR: 1.08 (0.84-1.38) CS:OR: 1.36 (0.94-1.97)	Age	Estimated OR for ES from ExS and CS M: OR: 0.93 (0.79-1.10) W: OR: 1.16 (0.94-1.43)
Degirmenci et al., 2014 Turkey	No measure of association reported	80 cases 80 controls			Authors reported the prevalence of CS between subjects with and without Tinnitus. We estimated the crude OR for CS to have Tinnitus: 1.53 (0.72-3.26)
Park and Moon, 2014 South Korea	OR for CS Ref: NonS	10061 subjects	Overall AT CS: OR 0.99 (0.86-1.14)	Sex, age, alcohol, BMI, noise exposure, HL, others	Excluded from the meta-analysis as the sample is a subgroup of the one analysed by Kim et al., 2015
Park et al, 2014b South Korea	OR for CS Ref= NonS OR for ES Ref= NS	AT: 5 140 subjects (40+yrs)	40+ AT: CS: OR: 0.94 (0.76-1.16) ES: OR: 0.98 (0.83-1.16)		Excluded from the meta-analysis as the sample is a subgroup of the one analysed by Kim et al., 2015

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Joo et al., 2015 Korea	Chi square on differences of prevalence of CS in different groups	11266 subjects	Overall AT No Tinnitus/No HL: 20.9% Just HL: 22% Just Tinnitus: 19.9% Tinnitus & HL: 19.7% (p=0.8288)		Excluded from the meta-analysis as the sample is a subgroup of the one analysed by Kim et al., 2015
Kim et al.; 2015 South Korea	OR for various categories of exposure to smoke Ref: NS	19190 subjects	Overall AT; ExS: OR: 1.25 (1.06-1.47) CS (not every day): OR: 1.12 (0.90-1.40) CS (everyday): OR: 1.21 (1.04-1.41)	Covariates selected by backward selection	
Lee et al., 2017 South Korea	Chi square on differences of prevalence of CS	2736 subjects	Overall AT Tinnitus: 4.6% No Tinnitus: 5.9% (p=0.364)		Excluded: sample is a subgroup of the one analysed by Kim et al., 2015
Mofateh et al., 2017 Iran	Chi square on differences of tinnitus prevalence in CS and NonS	150 subjects	Overall AT CS: 32.7% NonS: 8.4% (p=0.07)		Estimated the crude OR from tinnitus prevalence in CS and NonS for CS: 5.29 (2.11-13.24)
SOUTH AMERICA					
Paschoal and de Azevedo 2009 Brasil	Student's t-test on differences of prevalence of Tinnitus between CS and NonS	144 subjects	Overall AT CS: 40.3% NonS: 11.1% (p<0.001)		Authors reported the prevalence of Tinnitus between CS and NonS. We estimated the crude OR for CS: 5.40 (2.25-12.92)

Appendix XIII. Estimates on the relationship between smoking habits and tinnitus

Publication (author, year; journal)	Measure of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
AFRICA					
Lasisi 2010 Nigeria	Chi square on differences of prevalence of ES between subjects with and without Tinnitus	1302 subjects	Overall AT Tinnitus: 51.6% No Tinnitus: 42.4% (p=0.84)		Prevalence of CS between subjects with and without tinnitus. Estimated the crude OR for ES to have Tinnitus: 1.25 (1.12-1.40)
Sogebi, 2013 Nigeria	Chi square on differences of prevalence of CS between subjects with and without Tinnitus	127 subjects	Overall AT Tinnitus: 16.5% No Tinnitus: 8.3% (p=0.179)		Authors reported the prevalence of CS between subjects with and without Tinnitus. We estimated the crude OR for CS to have Tinnitus: 2.17 (0.66-7.08)

OR: Odds ratio; HR: Hazards ratio; PR: Prevalence ratio; Ref: Reference; AT: Any tinnitus; Men; W: Women; CS: current smokers; NS: never smokers; ES: ever smokers; NonS: Non-smokers; ExS: Ex-smokers (same as Former smokers); RA: rheumatoid arthritis; HL: Hearing Loss; BMI: Body Mass Index

Appendix XIV. Estimates on the relationship between alcohol consumption and tinnitus

Publication (author, year, country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
NORTH AMERICA					
Nondahl et al., 2002 USA	t-test on differences in average alcohol consumption (grams/week) between subjects with and without tinnitus	Baseline 3737 subjects; follow-up 2513 subjects	Baseline: Tinnitus prevalent cases: 43.9 No tinnitus: 43.9 (p NS) Follow-up: Tinnitus incident cases: 33.9 No tinnitus: 46.2 (p < 0.05)		This study was not included in our meta-analysis as it was not possible to estimate ORs for drinkers vs non-drinkers
Nondahl et al., 2010 USA	HR of various categories of ethanol consumption (grams/week); Ref: >0 to <15 grams/week	2922 subjects	Overall AT None: HR: 0.85 (0.62-1.16) <15 (Ref):HR: 1.00; 15-74: HR: 0.91 (0.66-1.26) 75-140:HR: 0.82 (0.55-1.22) > 141:HR: 0.63 (0.41-0.96)	Age and sex	This study was not included in our meta-analysis as it was not possible to estimate ORs for drinkers vs non-drinkers
Nondahl et al., 2011 USA	ORs for current alcohol drinking (yes/no) and history of heavy drinking (4 + drinks/day – yes/no) Ref: No	3267 subjects	Current alcohol consumption (AT): M: OR: 1.33 (0.70-2.51) W: OR: 0.56 (0.35-0.90)	Age and sex	Only ORs for current alcohol drinking were included in our meta-analysis
Bhatt et al, 2017 USA	t-test on differences in mean days of alcohol consumption per year between subjects with and without tinnitus	Not available	Tinnitus 64.35 (59.44-63.77) No tinnitus 61.61 (57.61-71.09; p = 0.431)		No RR estimate was reported; insufficient data to estimate it. This study was not included in our meta-analysis
EUROPE					
Brunnberg et al., 2008 Sweden	OR for categories of alcohol drinking (times/month) Ref (NH and AT): No tinnitus/No HI	2730 NH subjects; 148 HI subjects	NH and AT: Never: OR: 0.59 (0.37-0.91) HI and AT: Never: OR: 0.31 (0.13-0.77)	Background, physical and mental health symptoms, school,	We estimated the OR for alcohol drinkers vs non-drinkers: NH: OR: 1.69 (1.11-2.59) HI: OR: 6.06 (2.86-12.83)

Appendix XIV. Estimates on the relationship between alcohol consumption and tinnitus

Publication (author, year, country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
	Ref (HI and AT): Just HI		≥ 6 twice a month: OR: 3.3 (1.3-8.4)	tobacco smoking and drugs	
Marmut et al., 2014 Serbia	OR for current alcohol drinking (yes/no) Ref: No	277 M	AT: OR: 0.48 (0.16-1.43)	Behavioral and health habits	The paper does not provide the OR for girls as it was reported as non-significant
Gallus et al., 2015 Italy	OR for different categories of alcohol drinking, sum of the number of drinks/week (around 12 g of alcohol) of 4 different types of alcoholic beverages Ref: 0	1710 subjects (> 45 years)	AT 0 (ref) OR: 1.00 < 7 OR: 0.59 (0.36-0.98) ≥ 7 OR: 1.38 (0.87-2.21)	Age, sex, education, geographic area, smoking, BMI	We estimated the OR for alcohol drinkers vs. non-drinkers: AT OR: 0.88 (0.59-1.31)
Martinez et al., 2015 UK	No measure of association reported	2621050 subjects			Excluded as clinically diagnosed tinnitus was assessed.
OCEANIA					
Tan et al., 2018 Australia	OR for current alcohol drinking (yes/no) Ref: No	4877 subjects	AT: OR: 0.94 (0.76-1.15)	Age, sex, family history of HL	
ASIA					
Michikawa et al., 2010 Japan	No measure of association reported	1300 subjects			Authors provided data on AT prevalence by alcohol consumption. With these data, we estimated the crude OR for alcohol drinkers vs non-drinkers OR: 0.91 (0.67-1.23)

Appendix XIV. Estimates on the relationship between alcohol consumption and tinnitus

Publication (author, year, country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Fujii et al., 2011 Japan	OR for various categories of alcohol consumption (ml/day); Ref=0	14423 subjects	AT: M: 0 (ref) OR:1.00 > 0 and < 38.5 OR: 1.12 (0.82-1.53) ≥ 38.5 OR: 1.04 (0.76-1.42) W:0 (ref) OR:1.00 > 0 and < 3.7 OR: 1.00 (0.83-1.19) ≥ 3.7 OR: 1.00 (0.84-1.20)	Age	We estimated ORs for alcohol drinkers vs. non-drinkers: M: OR: 1.08 (0.87-1.35) W: OR: 1.00 (0.88-1.14)
Park and Moon 2014 South Korea	OR for current alcohol drinking (yes vs no) Ref: No	10061 subjects	AT OR: 0.95 (0.84-107)	Sex, age, smoking status, BMI, noise exposure, hearing impairment and others	This study was not included in our meta-analysis as its sample (KHNANES) overlaps with the one in Kim et al., 2015
Park, et al., 2014a South Korea	OR for various categories of alcohol consumption (times/month); Ref - Nil	3047 subjects	AT: Nil (ref) OR:1.00 < 1 OR: 1.31 (0.94-1.84) 1 OR: 1.72 (1.06-2.75) 2-4 OR: 0.89 (0.54-1.46) ≥ 8 OR: 1.07 (0.55-2.09)	Multivariate analysis	We estimated ORs for alcohol drinkers vs. non-drinkers: OR: 1.25 (0.96-1.62)
Park, et al., 2014b South Korea	OR for current alcohol drinking (yes vs no) Ref: No	5140 subjects	AT: OR: 1.09 (0.90-1.31)	Multivariate analysis	This study was excluded as its sample (KHNANES) overlaps with the one in Kim et al., 2015
Joo et al., 2015 South Korea	No measure of association reported	11266 subjects			This study was excluded as it was not possible to estimate ORs

Appendix XIV. Estimates on the relationship between alcohol consumption and tinnitus

Publication (author, year, country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Kim et al., 2015 South Korea	OR for various categories of alcohol consumption (times/month); Ref = Nil	19290 subjects	AT: Nil (ref) OR:1.00 < 1 OR: 0.82 (0.72-0.93) 1 OR: 0.74 (0.63-0.87) 2-4 OR: 0.68 (0.60-0.77) 8-12 OR: 0.76 (0.66-0.87) ≥ 16 OR: 0.78 (0.65-0.93)	Simple logistic regression analysis	Estimated ORs for alcohol drinkers vs. non- drinkers: OR: 0.75 (0.70-0.80)
Lee et al., 2017 South Korea	No measure of association reported	2736 (W)			This study was excluded in the meta-analysis as ORs could not be calculated.
SOUTH AMERICA					
Bellé et al., 2007 Brazil	No measure of association reported	74 subjects			Data provided on AT based on affiliation with anonymous alcoholics. This study was excluded.
AFRICA					
Lasisi et al., 2010 Nigeria	No measure of association reported	1302 subjects			Estimated the crude OR for alcohol drinkers vs non-drinkers. OR: 1.04 (0.76-1.42)
Sogebi, 2013 Nigeria	No measure of association reported	127 subjects			Estimated the crude OR for alcohol drinkers vs non-drinkers. OR: 0.70 (0.27-1.84)

OR: Odds ratio; HR: Hazards ratio; Ref: Reference; AT: Any tinnitus; M: Men; W: Women; NH: Normal hearing; HI: Hearing impaired; HL: Hearing Loss; BMI: Body Mass Index

Appendix XV. Estimates on the relationship between BMI and tinnitus

Publication (author, year; country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
NORTH AMERICA					
Nondahl et al., 2010 USA	HR for Obesity Ref: non obese = BMI <30 (UW+NW+OW)	2922 subjects	AT: Obesity M: HR: 0.55 (0.39-0.78) W: HR: 1.08 (0.79-1.49)	Age and sex	
Shargorodsky et al., 2010 USA	OR for BMI Ref: BMI <25 (UW+NW)	14178 subjects	AT BMI 25-29 OR: 0.94 (0.86-1.03) BMI ≥30 OR: 1.08 (0.94-1.23)	Age, sex, ethnicity, education level, smoking, cardiovascular factors, noise exposure	Estimated OR for OW (BMI ≥ 25vs BMI <25): OR: 0.97 (0.89,1.05) OR for OB ((BMI ≥ 30 vs BMI <30): 1.10 (0.96,1.25)
Nondahl et al., 2011 USA	OR for Obesity Ref: non obese = BMI <30 (UW+NW+OW)	3267 subjects	AT: Obesity OR: 1.41 (1.11-1.81)	Age and sex.	
Loprinzi et al., 2013 USA	Prevalence and 95% CI were calculated for OW and OB. OR for overweight and obese Ref: BMI <25	12-19 years: 963 subjects 70-85 years 473 subjects	AT: 70-85 years OW+OB: OR: 1.02 (0.98-1.06)	Gender, poverty ratio score, race/ethnicity, smoking, age, marital status and blood pressure status.	For adolescents: OW and OB was defined as ≥ 85th percentiles for age and gender. For older adults, OW was defined as BMI ≥ 25.
Mahboubi et al., 2013 USA	OR for BMI Ref: BMI < 25	3371 subjects	AT: BMI ≥ 25: OR: 1.07 (0.83-1.39)	Age, gender, ethnicity, income, cigarette smoking, passive smoking, other factors	
Swan et al. 2017 USA	OR for Obesity Ref: BMI <30	570248 subjects	AT: Obesity: OR: 1.09 (1.06-1.12)	Demographic and military characteristics	Since tinnitus was defined ICD 9 codes, the article was excluded.

Appendix XV. Estimates on the relationship between BMI and tinnitus

Publication (author, year; country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
EUROPE					
McCormack et al., 2014 UK	OR for BMI	167550 subjects	TT: BMI: OR: 1.00 (0.99-1.01) PT: BMI: OR: 0.99 (0.98-1.00)	Smoking status, age, sex, hearing difficulty, noise exposure, body fat percentage, cardiovascular factors	Excluded in the analyses because BMI was considered as a continuous variable.
Gallus et al., 2015 Italy	OR for OW (25 ≤ BMI < 30) and Obesity (BMI ≥ 30) Ref: BMI < 25	1558 subjects	AT OW: OR: 1.49 (0.99-2.25) Obesity: OR: 2.14 (1.25-3.67).	Sex, age, level of education, geographic area, smoking status, alcohol consumption.	1558 subjects completed the questionnaire about BMI. Estimated OR for OW (BMI ≥ 25vs BMI <25): OR: 1.63 (1.11,2.40) OR for OB ((BMI ≥ 30 vs BMI <30): 2.06 (1.21, 3.53)
Martines et al., 2015 Italy	OR for BMI Ref: BMI < 30	120 subjects (46 cases, 74 controls)	AT BMI ≥ 30: OR: 7.36 (2.38-19.47)		
Martinez et al., 2015 UK	No measure of association provided	4703226 subjects			Article defined tinnitus using ICD 10 code it was excluded in the analysis
OCEANIA					
Tan et al., 2018 Australia	OR for OW, OB and severe OB Ref: BMI <25	4 77 subjects	Tinnitus: BMI 25-29.9 OR: 1.55 (0.84-2.86) BMI 30- 34.9: OR: 2.03 (1.05-3.93) BMI≥35: OR: 1.99 (0.87-4.54)	Age, sex, family history of HL	Severe obesity used (BMI ≥ 35) as a different class in the statistical analysis. Estimated OR for OW ((BMI ≥ 25vs BMI <25): OR: 1.81 (1.22, 2.68)
ASIA					

Appendix XV. Estimates on the relationship between BMI and tinnitus

Publication (author, year; country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Fujii et al., 2011 Japan	OR for BMI between 20-22, BMI between 22.1-24 and BMI >24 Ref: BMI<20	14423 subjects	Tinnitus (M) BMI 20-22: OR: 0.99 (0.79-1.25) BMI 22.1-24: OR: 0.98 (0.78-1.22) BMI >24: OR: 1.02 (0.82-1.28) Tinnitus (W) BMI 20-22: OR: 0.83 (0.67-1.02) BMI 22.1-24: OR: 1.01 (0.83-1.23) BMI >24: OR: 0.90 (0.73-1.11)	Age	Excluded from the analyses, because categories are different from other studies.
Kim et al., 2012 South Korea	No measure of association was provided	928 subjects			BMI not analysed with quantitative variable. Excluded from analyses.
Park and Moon, 2014 South Korea	OR for BMI 25-30 and BMI >30 Ref: BMI <25	10061 subjects	AT BMI 25-29.9: OR: 0.97 (0.87-1.09) BMI ≥ 30: OR: 0.91 (0.69-1.18)	Age, smoking status, drinking status,noiseexposure, hearing impairment,	Excluded -data already analysed in Joo et al., 2015
Park et al., 2014a South Korea	OR for BMI	3047 subjects	BMI: OR: 1.004 (0.973-1.036)		BMI was analysed as a continuous variable. Excluded.
Park et al., 2014b South Korea	OR for Obesity (defined as BMI>25) Ref: BMI ≤ 25	5140 subjects	AT: Obesity: OR: 0.96 (0.80-1.14)		Excluded -data already analysed in Joo et al., 2015
Joo et al., 2015 South Korea	Prevalence for BMI ≥ 25 calculated for different groups (NH and T, HL and T). Ref: BMI <25	11266 subjects	NH and T: BMI ≥25 (%) 35.0±1.2 HL and T: BMI ≥ 25 (%) 33.4±3.1	Not adjusted	OR for BMI ≥25 for AT (NH+T and HL+T) OR: 0.94 (95% CI: 0.86-1.03)

Appendix XV. Estimates on the relationship between BMI and tinnitus

Publication (author, year; country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments	Comments
Kim et al., 2015 South Korea	OR for BMI in kg/m2 Ref: Not specified	19290 subjects	Overall AT: OR: 0.99 (0.98-1.00)	Covariates selected by backward elimination	BMI continuous variable. Excluded from the analyses.
Torun et al., 2016 Turkey	Percentage of subjects in each BMI category Ref: BMI <25	213 subjects (100 cases, 113 controls).	Cases: BMI ≤ 24.9: 28% BMI 25-29.9: 46% Obese 30-34.9: 23% Morbidly Obese≥35: 3% Controls: BMI ≤ 24.9 60.2% BMI 25-29.9 35.4% Obese 30-34.9 4.4% Morbidly Obese ≥35 0%	Not adjusted	OR calculated OR for BMI 25-29.9: 3.88 (2.18-6.89) OR for BMI >30: 11.87 (4.14-34.02)
Lee et al., 2017 South Korea	Prevalence and 95% CI of obesity between subjects with and without tinnitus. Ref: BMI < 25	2736 subjects	Tinnitus: 31.4% ±2.2% No Tinnitus: 39.1% ±1.3% p value 0.004	Not adjusted	Excluded from the analyses because data already analysed in Joo et al., 2015
AFRICA					
Sogebi, 2012 Nigeria	Prevalence between subjects with tinnitus and subjects without was calculated. Ref: BMI ≤ 30	127 subjects	Tinnitus: 21.5% No Tinnitus: 6.3% p value 0.024	Not adjusted	OR calculated: 4.11 (1.14-14.88)

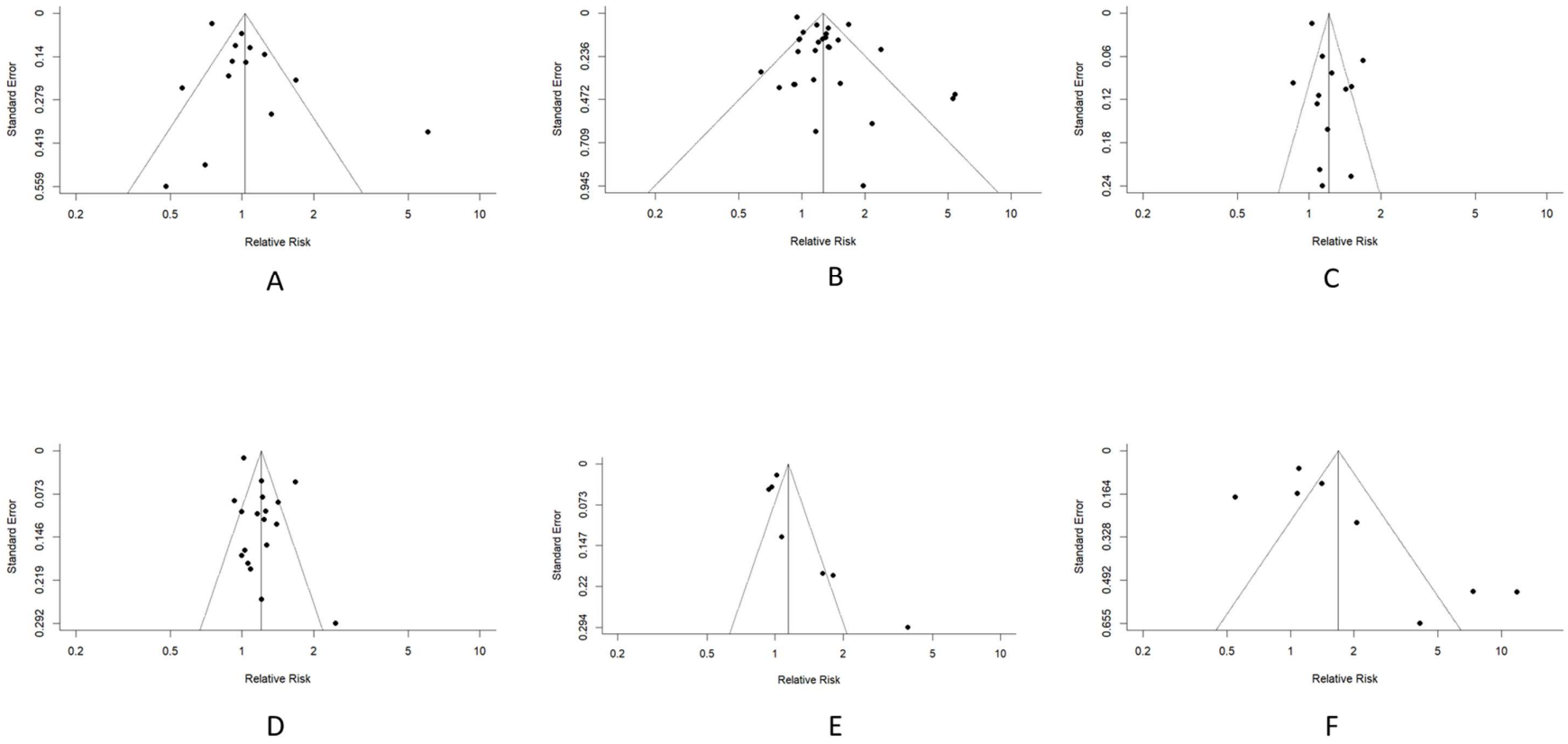
OR: Odds ratio; HR: Hazards ratio; Ref: Reference; AT: Any tinnitus; M: Men; W: Women; NH: Normal hearing; HL: Hearing loss; TT: Transient tinnitus; PT: Persistent tinnitus; BMI: Body mass index; UW: underweight; NW: normal weight; OW: overweight; OB: obesity

Appendix XVI Estimates on the relationship between risk caffeine intake (coffee drinking) and tinnitus§

Publication (author, year; country)	Measures of association; Reference category	Numbers	Estimates (95% CI)	Adjustments
Witsell et al., 2011 USA	No measure of association provided			
Marmut et al., 2014 Serbia	OR: Ref: Coffee consumption (No)	277 subjects (M)	Caffeine intake: 3.155 (0.562-17.702) only in Males	
Glicksman et al., 2014 USA	HR for caffeine intake in mg/day Ref: Caffeine intake 0-149 mg/day	65085 subjects (W)	Caffeine intake 150-299 mg/day: HR: 0.94 (0.88-1.00) Caffeine intake 300-449 mg/day: HR: 0.91 (0.84-0.98) Caffeine intake 450-599 mg/day: HR: 0.85 (0.76-0.95) Caffeine intake ≥600 mg/day: HR: 0.79 (0.68-0.91)	Age, hearing loss, smoking status, comorbid conditions, medications used (analgesics, diuretics, and antidepressants), BMI and smoking status

OR: Odds ratio; HR: Hazards ratio; Ref: Reference; AT: Any tinnitus; M: Men; W: Women; BMI: Body mass index.
§Meta-analyses was not conducted for caffeine intake

Appendix XVII. Funnel plots for all risk factors



Funnel plots for current (A), former (B) and ever (C) smokers; alcohol drinkers (D); overweight (E) and obese (F)

Appendix XVIII Baseline characteristics of women in 1991 by quintile of cumulative-averaged AMED (without alcohol) score

	AMED Diet Score (without alcohol)				
	Q1 (n=14281)	**Q2 (n=10808)**	**Q3 (n=10956)**	**Q4 (n=9579)**	**Q5 (n=11215)**
Age, years*	35.9 (4.8)	36.1 (4.7)	36.3 (4.6)	36.4 (4.5)	36.8 (4.5)
Race, Caucasian, %	94.8	94.6	94.6	93.9	93.5
Smoking Status					
-Never, %	65.3	67.2	66.9	67.9	67.6
-Past, %	19.7	20.7	22.7	23.1	24.8
-Current, %	14.8	11.9	10.3	8.8	7.4
Physical activity, METs	16 (21.5)	18.8 (24.2)	20.9 (26.1)	23 (27.7)	27.3 (31.7)
History of hypertension, %	6.4	5.6	6.0	5.8	5.5
History of diabetes, %	3.5	3.7	4.1	4.4	3.8
Depression, 2003, %	12.4	12.4	12.1	12.1	12.1
Aspirin use, 1995					
-none, %	75.0	74.6	74.5	74.3	73.5
-1 day/week, %	13.7	14.9	14.3	15.1	16.1
-2-3 days/week, %	4.2	4.3	4.6	4.0	4.2
-4-5 days/week, %	1.3	1.3	1.2	1.2	1.1
-6+ days/week, %	3.4	2.8	3.0	2.9	3.0
Ibuprofen use, 1995					
-none, %	33.3	32.8	32.8	32.8	33.5
-1 day/week, %	38.4	39.9	39.1	40.3	40.2
-2-3 days/week, %	16.2	16.2	16.5	16.3	15.9
-4-5 days/week, %	3.4	3.3	3.3	3.1	3.2
-6+ days/week, %	5.1	4.7	4.7	4.2	4.3
Acetaminophen use, 1995					
-none, %	42.7	44.1	43.7	43.1	46.7
-1 day/week, %	40.0	39.4	40.1	41.3	39.4
-2-3 days/week, %	10.1	10.1	9.9	9.4	8.7
-4-5 days/week, %	1.9	1.8	1.9	1.6	1.4
-6+ days/week, %	1.9	1.7	1.5	1.4	1.1
Hearing difficulty					
-none, %	97.5	97.4	97.2	97.3	97.5
-mild, %	1.7	1.5	1.8	1.7	1.6
-moderate or worse, %	0.8	1.1	1.0	1.0	0.9

Values are means(SD) or medians (Q25, Q75) for continuous variables; percentagesor numbers or both for categorical variables, and are standardised to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding

* Value is not age adjusted

Appendix XIX. Baseline characteristics of women in 1991 by category of cumulative-average alcohol intake

	Alcohol intake, grams/day							
	none (n=23622)	**1-4.9 (n=22282)**	**5-14.9 (n=8749)**	**15-29.9 (n=1578)**	**30-34.9 (n=237)**	**35-39.9 (n=160)**	**40-44.9 (n=69)**	**45+ (n=142)**
Age, years*	36.4 (4.7)	36.1 (4.6)	36.3 (4.7)	37.2 (4.6)	37.1 (4.5)	38.5 (4.3)	37.6 (4.3)	37.6 (4)
Race, Caucasian, %	92.6	95.4	96.0	95.8	97.2	95.7	96.6	96.3
Smoking Status								
-Never, %	75.9	65.1	53.7	42.0	30.3	39.1	32.6	29.3
-Past, %	15.9	23.6	31.6	36.4	33.7	28.9	29.3	29.5
-Current, %	8.0	11.1	14.6	21.6	36.0	32.0	38.1	41.2
Physical activity, METs	18.6 (25.2)	21.6 (26.4)	24.4 (28.9)	25.3 (28.7)	23.2 (30.2)	22.2 (25.4)	19 (19)	20.6 (30)
History of hypertension, %	6.7	5.2	4.9	6.8	8.6	8.2	3.9	7.5
History of diabetes, %	4.7	3.7	2.4	2.3	1.3	3.2	1.1	2.3
Depression, 2003, %	12.4	11.9	12.0	13.5	20.1	20.2	20.3	10.4
Aspirin use, 1995								
-none, %	76.8	74.4	70.4	64.9	60.4	67.3	67.6	63.4
-1 day/week, %	12.6	15.3	17.7	20.5	22.6	23.2	13.5	16.6
-2-3 days/week, %	3.9	3.9	5.3	6.4	8.1	6.9	11.2	6.0
-4-5 days/week, %	1.1	1.2	1.4	2.4	2.9	0.7	0.0	4.0
-6+ days/week, %	3.2	2.9	3.0	3.1	4.3	1.4	6.1	6.6
Ibuprofen use, 1995								
-none, %	36.3	31.2	29.9	28.2	33.4	27.4	32.0	30.6
-1 day/week, %	37.5	41.0	40.9	40.1	34.0	41.4	37.4	42.2
-2-3 days/week, %	14.8	16.6	18.5	19.2	20.2	17.2	12.0	12.1
-4-5 days/week, %	3.0	3.3	3.6	3.7	4.5	4.1	7.3	1.3
-6+ days/week, %	5.0	4.4	4.0	4.5	6.1	7.8	9.6	7.1
Acetaminophen use, 1995								
-none, %	42.5	43.6	47.8	48.5	50.7	45.9	49.7	55.9
-1 day/week, %	40.7	40.8	37.3	37.5	31.5	38.3	34.0	27.4
-2-3 days/week, %	9.9	9.7	9.3	7.0	11.1	13.5	7.9	6.0
-4-5 days/week, %	1.9	1.6	1.5	1.8	1.2	0.4	2.2	4.4
-6+ days/week, %	1.9	1.3	1.3	1.5	3.4	0.4	4.5	2.1

Appendix XIX. Baseline characteristics of women in 1991 by category of cumulative-average alcohol intake

	Alcohol intake, grams/day							
	none (n=23622)	**1-4.9 (n=22282)**	**5-14.9 (n=8749)**	**15-29.9 (n=1578)**	**30-34.9 (n=237)**	**35-39.9 (n=160)**	**40-44.9 (n=69)**	**45+ (n=142)**
Hearing difficulty								
-none, %	97.4	97.3	97.7	97.0	94.1	95.4	100.0	99.4
-mild, %	1.7	1.7	1.3	1.8	3.8	2.1	0.0	0.6
-moderate or worse, %	0.9	1.0	0.9	1.1	2.1	2.5	0.0	0.0

Values are means(SD) or medians (Q25, Q75) for continuous variables; percentages or ns or both for categorical variables, and are standardised to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding

* Value is not age adjusted

Appendix XX. Baseline characteristics of women in 1991 by categories of BMI and waist circumference

	Body mass index, kg/m²						Waist circumference in cm			
	<18.5 (n=1515)	**18.5-24.9 (n=35816)**	**25-29.9 (n=11067)**	**30-34.9 (n=4179)**	**35-39.9 (n=1770)**	**40+ (n=993)**	**<71 (n=8382)**	**71-79 (n=11441)**	**80-88 (n=4522)**	**89+ (n=5267)**
Age, years*	34.9 (4.6)	36 (4.6)	36.7 (4.7)	37.2 (4.6)	37.2 (4.5)	37.5 (4.2)	35.9 (4.6)	36.4 (4.6)	36.9 (4.6)	37.3 (4.5)
Race, Caucasian, %	94.9	94.8	93.8	93.1	93.8	93.4	95.0	94.7	94.3	93.8
Smoking Status										
-Never, %	69.7	67.3	65.7	67.1	66.2	65.9	69.4	67.1	66.8	66.3
-Past, %	16.6	22.0	22.6	21.6	22.6	23.2	20.5	22.8	22.0	21.6
-Current, %	13.5	10.5	11.6	11.2	11.1	10.7	9.9	10.0	11.1	11.9
Physical activity, METs	24.9 (33.5)	22.8 (27.8)	18.6 (23.5)	15.1 (19.9)	12.7 (19.1)	11.3 (16.2)	27.3 (32)	21.8 (25.9)	18.2 (22.4)	16.1 (23)
History of hypertension, %	2.2	3.1	7.0	14.0	21.3	30.2	2.5	3.6	5.7	11.6
History of diabetes, %	2.0	3.0	4.9	6.1	8.5	8.7	2.5	3.4	4.4	5.8
Depression, 2003, %	9.6	11.0	12.8	16.2	19.7	22.0	10.3	11.3	13.0	17.6
Aspirin use, 1995										
-none, %	77.4	74.5	74.1	73.3	75.2	70.8	75.7	74.8	74.2	73.4
-1 day/week, %	13.1	15.2	14.4	13.8	13.3	12.6	16.3	16.6	16.5	15.8
-2-3 days/week, %	3.8	4.2	4.4	4.5	4.3	6.1	4.0	4.5	4.9	5.0
-4-5 days/week, %	1.0	1.2	1.4	1.5	0.8	2.2	1.0	1.3	1.4	1.6
-6+ days/week, %	2.6	2.8	3.2	3.7	4.5	5.2	2.9	2.9	2.9	4.2
Ibuprofen use, 1995										
-none, %	39.9	34.5	30.5	29.4	26.3	24.2	36.1	33.3	31.4	29.4
-1 day/week, %	40.3	40.9	38.4	35.2	34.0	31.0	43.0	42.5	41.5	37.4
-2-3 days/week, %	12.2	15.5	17.8	18.9	18.7	19.0	14.9	16.6	17.3	19.0
-4-5 days/week, %	1.9	2.7	3.8	4.2	6.6	7.0	2.2	3.0	3.6	4.9
-6+ days/week, %	2.4	3.3	6.0	7.5	11.1	13.3	3.0	3.8	5.3	8.1

Appendix XX. Baseline characteristics of women in 1991 by categories of BMI and waist circumference

	Body mass index, kg/m²						Waist circumference in cm			
	<18.5 (n=1515)	**18.5-24.9 (n=35816)**	**25-29.9 (n=11067)**	**30-34.9 (n=4179)**	**35-39.9 (n=1770)**	**40+ (n=993)**	**<71 (n=8382)**	**71-79 (n=11441)**	**80-88 (n=4522)**	**89+ (n=5267)**
Acetaminophen use, 1995										
-none, %	46.6	45.1	42.0	41.5	40.4	39.0	48.6	46.2	43.9	41.4
-1 day/week, %	39.1	40.4	40.4	38.4	38.2	35.8	40.3	41.0	43.1	40.9
-2-3 days/week, %	8.2	9.1	10.6	11.2	12.4	13.1	8.1	9.1	9.2	12.1
-4-5 days/week, %	1.3	1.5	1.9	2.5	3.4	3.5	1.4	1.7	1.8	2.6
-6+ days/week, %	1.9	1.2	1.9	2.2	2.6	4.3	1.1	1.4	1.6	2.3
Hearing difficulty										
-none, %	97.4	97.6	97.2	97.3	96.9	95.7	97.5	97.4	96.7	96.8
-mild, %	1.5	1.6	1.7	1.8	1.9	3.0	1.7	1.7	2.0	2.0
-moderate or worse, %	1.1	0.9	1.1	0.9	1.3	1.2	0.9	0.8	1.3	1.2

Values are means(SD) or medians (Q25, Q75) for continuous variables; percentages or ns or both for categorical variables, and are standardised to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding

* Value is not age adjusted