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EARLY IDENTIFICATION AND MONITORING OF COCHLEAR DAMAGE USING EXTENDED HIGH-FREQUENCY AUDIOMETRY: A SYSTEMATIC REVIEW

By

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DECLARATION OF ORIGINALITY

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Declaration:

I, Nadia Troskie declare that this dissertation is my own work and has not been previously submitted.

Where secondary material has been used, it has been carefully acknowledged and reference in accordance with the University of Pretoria's requirements. I am aware and understand the University of Pretoria's policies and implications regarding plagiarism.

Signature

25 October 2021

Date

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Contents

LIST OF ABBREVIATIONS

ANSI	American national standard institute's
DPOAE	Distortion product otoacoustic emission
DSR	Distiller Systematic review
DM	Diabetes Mellitus
CG	Control group
SNHL	Sensorineural hearing loss
SG	Study group
EHF	Extended high frequency
EHFs	Extended high frequencies
MDR-TB	Multidrug-resistant tuberculosis
NIHL	Noise induced hearing loss
NOS	Newcastle-Ottawa scale
PRISMA-P	Preferred reporting items for systematic review and meta-analysis protocols
WHO	World Health Organization

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FORMATTING

APA 7th edition manuscript format and referencing style was utilised in this dissertation

ABSTRACT

Extended-high frequency (EHF) audiometry has been recommended for early identification and monitoring of cochlear damage. The main reason is that cochlear damage occurs at frequencies higher than 8000 Hz before the thresholds at conventional frequencies (250 Hz to 8000 Hz) are affected. Furthermore, hair cell damage at the frequencies higher than 8000 Hz cannot be detected using conventional audiometry. Thus, it is important that cochlear damage be detected earlier to reduce the progression of hearing loss. However, utilizing EHF audiometry for monitoring individuals at risk of developing cochlear damage is at present an inconsistent procedure, as it is not well established in standard clinical care. As the interest in EHF audiometry is increasing, it is important to determine to what extent EHF audiometry may be used for the early identification and monitoring of cochlear damage, as the clinical value of the procedure still has to be determined. The present systematic review was conducted to investigate existing evidence regarding the potential value of EHF audiometry for the early identification and monitoring of cochlear damage.

A systematic review was conducted using peer-reviewed literature in order to identify a large number of relevant publications that would assist in answering the research question. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P) checklist was used as a guideline. Four electronic databases were utilised in this study to search for the relevant publications, namely Academic Search Complete (Ebscohost), Medline (Ebscohost), Scopus, and PubMed. A manual secondary search was conducted using the reference list of relevant reports already identified during the primary search. Reports were selected according to predefined inclusion and exclusion criteria and selection was followed by data extraction.

A total of 502 articles were identified and screened. Only 16 of the articles were compatible with the criteria and therefore included in the systematic review. These 16 articles included cross-sectional and cohort studies, which were evaluated using the Newcastle-Ottawa scale (NOS) for quality assessment. A factor that influenced the conclusions of the systematic review, is that all the studies were heterogeneous in nature. These differences had an influence on the practicability of comparing these studies. Due to a variety of equipment used to measure EHFs, no conclusion could be

reached on preferred equipment. It is suggested that individuals should be tested with the same equipment over time for intra-monitoring of the EHFs to increase test-retest reliability. Despite the variations, the use of EHF audiometry was considered to be a valuable procedure for the early identification of cochlear damage by seven studies (43.75%). The other studies included in the systematic review suggested that the procedure would be useful when combined with conventional audiometry (six studies – 37.5%) or distortion product otoacoustic emission (DPOAE) testing (two studies – 12.5%), or both methods (one study – 6.25%).

Comparing EHF audiometry to conventional audiometry and DPOAE testing, the majority of the studies included in the systematic review (10 studies - 62.5%) found that EHF audiometry was the most sensitive procedure to identify cochlear damage. Many studies reported that the entire EHF threshold range was deteriorating in participants at risk for developing cochlear damage. The majority (seven) of the studies included, however, determined that 14 000 Hz and/or 16 000 Hz were the most sensitive to cochlear damage, especially in participants with NIHL. In conclusion, the systematic review demonstrated that EHF audiometry may be beneficial in the clinical assessment of cochlear damage both for early identification and for monitoring purposes. Including this procedure in clinical practice will allow practitioners to identify cochlear damage earlier and possibly preserve the hearing of these individuals at risk.

Keywords: Extended-high frequencies, Extended-high frequency audiometry, cochlear damage, early identification, monitoring

1. INTRODUCTION

Chapter aim: *The aim of the chapter is to provide background on the present research available regarding the potential benefits of EHF audiometry in early identification and monitoring of cochlear damage. The chapter focuses on the gaps in and lack of knowledge regarding the potential value EHF audiometry may add to an assessment. The chapter concludes with a rationale answering the need of a systematic review as well as a research question.*

According to the World Health Organisation (WHO), approximately 466 million people around the world have some type of disabling hearing loss (WHO, 2020). Sensorineural with hearing loss (SNHL) is the most common type of hearing loss. It is reported to be the cause of more than 90% of hearing loss in adults (Eyvazzadeh, 2020). SNHL due to cochlear damage may result from various factors, including genetic anomalies, excessive or persistent noise exposure, aging, and exposure to ototoxic drugs (Wagner & Shin, 2019). This cochlear damage is revealed in a high-frequency hearing loss that steadily progresses towards the lower frequencies (Campbell & Le Prell, 2018; Mehrparvar et al., 2014; Vlaming et al., 2014). The damage caused to both the inner hair cells and the outer hair cells is permanent, since hair cells within the cochlea cannot be regenerated. Once the hair cells are damaged, individuals will suffer from an irreversible hearing loss (Wagner & Shin, 2019). Treatment options for SNHL are limited and these individuals are primarily fitted amplification devices, which are not able to restore the damage to the cochlea (Baiduc et al., 2013).

It is difficult to identify cochlear damage at the early stages of destruction. The reason for this is that the average individual is born with approximately 16 000 hair cells, and 30 to 50% of these hair cells may be destroyed before any noticeable symptoms of a hearing loss is reported (Daniel, 2007). Individuals typically do not report any noticeable symptoms during the early stages of cochlear damage, as their perception of hearing is dominated by low-frequency hearing (Vlaming et al., 2014). However, the more severe the degree of high-frequency SNHL, the greater the effect will be on

speech recognition abilities. These individuals typically complain of struggling to understand speech, especially in background noise (Li et al., 2017). Although some persons may already experience communication difficulties, they often delay seeking assistance (Vlaming et al., 2014). Thus, it is important that cochlear damage be detected as soon as possible, and appropriate measures be taken to reduce the progression of hearing loss (Macca et al., 2015; Valiente et al., 2016).

The gold standard for assessing hearing sensitivity is pure-tone audiometry conducted at frequencies from 250 Hz to 8000 Hz, including 3000 Hz and 6000 Hz (Baiduc et al., 2013; Mehrparvar et al., 2014). In order to obtain reliable audiometric test results, a controlled test environment as specified by legislation should be used. Testing should be conducted in a controlled environment with ambient noise levels adhering to the American National Standard Institute (ANSI S3.1-1999) specific maximum permissible levels (Frank, 2000). This may be achieved by audiometric test booths and sound-treated rooms that provide sound-isolated testing environments (Maclennan-Smith et al., 2013). Although reliable thresholds will be obtained, it is argued that cochlear damage occurs before the thresholds at conventional frequencies (125 Hz to 8000 Hz) are affected (Ahmed et al., 2001).

Hair cell damage affecting hearing thresholds at frequencies higher than 8000 Hz may not be detected by conventional audiometry (Ahmed et al., 2001). Therefore, additional equipment and procedures are needed to identify deterioration of thresholds at an earlier stage. The human auditory range extends to approximately 20 000 Hz (Le Prell et al., 2013). One recommended procedure for the early detection and monitoring of individuals at risk for cochlear damage is through extended high-frequencies (EHF) audiometry (Valiente et al., 2016). EHF audiometry or ultra-audiometry refers to the assessment of high frequency hearing that ranges from 10 000 to 20 000 Hz (Le Prell et al., 2013). Audiometers that deliver sounds at adequate sound pressure levels to EHFs can be used as a tool for measuring EHF thresholds (Bornman et al., 2018). It is hypothesised that EHF audiometry may be used as an early indicator for cochlear damage if a deterioration in the thresholds of frequencies higher than 8000 Hz is detected, prior to evident deterioration in the thresholds at standard frequencies (Ahmed et al., 2001; Valiente et al., 2016).

Research investigating the use of EHF audiometry for the early identification and monitoring of cochlear damage has recently extended to include various populations. The value of using EHF audiometry as a monitoring tool in clinical practice has been reported in individuals exposed to ototoxicity, as it is more sensitive and reliable in detecting initial ototoxic damage than conventional audiometry (Jacobs et al., 2012; Knight et al., 2007). The focus is mainly on medication-induced ototoxic damage as a primary cause of auditory and vestibular dysfunction (Hammill & Campbell, 2018). The most frequently used medications that may cause ototoxicity are platinum-based chemotherapeutic agents, aminoglycoside antibiotics, loop diuretics, macrolide antibiotics, anti-malaria drugs, and nonsteroidal anti-inflammatory drugs (Lord, 2019). Early detection of ototoxicity can lead to early intervention, which may halt the progression of hearing loss (Campbell & Le Prell, 2018). However, monitoring of individuals exposed to ototoxicity using EHF audiometry is at present a non-standardised procedure, and one not well established in standard clinical care (Lord, 2019). The reason for this may be limited facilities as well as costly equipment (Majidpour et al., 2021; Valiente et al., 2014; Valiente et al., 2016). The survival rate for individuals receiving ototoxic treatment is increasing. Therefore, early identification, serial monitoring, and intervention with audiological assistance and treatment are of utmost importance, as this could lead to a better quality of life for these individuals (Lord, 2019). In some circumstances it is not possible to adjust an individual's treatment to prevent cochlear damage in the conventional frequencies. Early identification of damage and monitoring of these individual's hearing allows clinicians to counsel the patient and the family about ototoxicity that might have occurred. This will also ensure additional audiological treatment options that may have a positive impact on their quality of life (Lord, 2019).

Previous researchers who have reported on the clinical value of using EHF audiometry to monitor ototoxicity include Knight et al. (2007), who suggested that the assessment of EHFs in children during platinum chemotherapy may be a more reliable tool to detect cochlear damage in the early stages of ototoxicity than conventional screening audiometry. In accord with this, Abujamra et al. (2013) also found EHF audiometry to be more sensitive for the early identification of hearing loss in children and adolescents who are receiving cisplatin chemotherapy than conventional audiometry or DPOAE

testing. Therefore, it was concluded by these authors that EHF audiometry may be more useful in clinical practice for the monitoring of cochlear damage in these young patients (Abujamra et al., 2013). The research of Yu et al. (2014) indicated that EHF audiometry and DPOAE testing may be equally effective for monitoring early cochlear damage in individuals exposed to cisplatin-induced ototoxicity. Thus, it was concluded by Yu et al. (2014) that these two procedures supplement one another and should be used in conjunction during every cycle of chemotherapy to ensure early detection of cochlear damage.

The use of EHF audiometry to monitor early changes in the hearing ability of populations such as individuals exposed to noise, whether occupational or social, has also been suggested (Le Prell et al., 2013, Mehrparvar et al., 2014). Some researchers indicated that deterioration of hearing at EHFs is linked to noise exposure and may occur prior to the deterioration of hearing at the conventional frequencies (Le Prell et al., 2013). Therefore, EHF audiometry may be of use in the early detection of cochlear damage due to noise exposure (Valiente et al., 2016). Furthermore, monitoring changes in EHF thresholds may prove to be a practical procedure for identifying individuals who are susceptible to developing noise-induced hearing loss (NIHL) at conventional frequencies (Le Prell et al., 2013). Regular monitoring of hearing over time is crucial for determining the effectiveness of hearing conservation programmes and using EHF monitoring may be extremely useful for this purpose (Le Prell et al., 2013).

Various research studies have indicated that the use of EHF audiometry may be more reliable and sensitive for the early detection of NIHL than conventional audiometry and the acoustic trauma notch at 4000 Hz which is typically used as clinical indicator (Ahmed et al., 2001; Mehrparvar et al., 2014; Mehrparvar et al., 2011; Somma et al., 2008). However, the testing of EHF thresholds is currently not included in medical surveillance programmes, as its use for the early identification of NIHL in an industrial setting is still debated (Valiente et al., 2016). Not all researchers have confidence that EHF audiometry provides worthwhile additional information (Valiente et al., 2016). Balatsouras et al. (2005) investigated the use of EHF audiometry in participants with acoustic trauma. In contrast to the findings of previously mentioned studies, these researchers found no significant differences between noise exposed and non-noise

exposed participants in their EHF thresholds (above 12 500 Hz). Therefore, the researchers concluded that EHF audiometry was not useful as an early indicator for the identification and monitoring of NIHL (Balatsouras et al., 2005). In agreement with Balatsouras et al. (2005), another study assessing temporary threshold shifts in pop/rock musicians reported a significant threshold shift at the conventional frequencies of the participants, but no shift at the EHF-thresholds. Hence, they concluded that EHF audiometry from 9000 Hz to 14 000 Hz adds no information to the results for the early detection of NIHL (Schumuziger et al., 2007).

Longitudinal studies, which include serial monitoring of hearing thresholds by comparing the individuals own EHF thresholds over time, may prove to be clinically valuable for determining whether employees who are at risk of developing NIHL may be identified at an early stage. Changes in EHF thresholds over time may be a useful tool for identifying individuals who are susceptible to NIHL (Le Prell et al., 2013). It seems, then, that the use of EHF audiometry in diagnosing and monitoring different individuals exposed to excessive noise is still debateable. On the other hand, Ahmed et al. (2001) found that the variability of intra-participant EHF test results using EHFs is low in contrast to the higher inter-participant variability. EHF audiometry may thus be a more reliable procedure to monitor the hearing loss of an individual over time than conventional audiometry (Ahmed et al., 2001).

The potential of monitoring the hearing of individuals with diabetes mellitus (DM) using EHF audiometry has recently been considered (Vignesh et al., 2015). Type 2 DM is a metabolic disorder and the most common type of diabetes. This disorder may lead to dysfunction of various organs including the eyes, kidneys, nerves, heart, and blood vessels. Individuals with type 2 DM may also experience damage to the outer hair cells in the high-frequency regions of the cochlea (Vignesh et al., 2015). EHF audiometry may be valuable in the early identification of hearing loss in these individuals as well. A study by Vignesh et al. (2015) suggested that EHF audiometry should be included in the audiological test battery for monitoring purposes in these individuals. EHF audiometry can be used to identify cochlear damage due to certain systemic pathologies, which causes SNHL, at an early stage. Consequently, researchers have recommended that EHF audiometry should be included as standard

clinical practice with conventional audiometry for the evaluation of auditory functioning (Valiente et al., 2016).

Although the human auditory range extends to approximately 20 000 Hz and even though research recommends the inclusion of EHF audiometry for the early identification and monitoring of cochlear damage, the standard clinical procedure in the majority of clinical practices is still mostly limited to pure-tone testing up to 8000 Hz (Baiduc et al., 2013). Research is increasingly suggesting that assessment of the auditory system at EHFs may be advantageous for the early identification of chemically induced, noise-induced, and age-related hearing loss (Baiduc et al., 2013). Early identification of hearing loss and subsequent intervention are important and will increase the chance of preventing a hearing loss, especially before an individual's speech frequencies are affected (Mehrparvar et al., 2014; Valiente et al., 2016). As the interest in EHF audiometry is increasing, it is important to determine to what extent EHF audiometry may be used for the early identification and monitoring of cochlear damage, since the inclusion of EHF audiometry in standard audiological test protocols is still to be established (Lord, 2019).

To determine what has been documented regarding the use of EHF audiometry for the early identification and monitoring of hearing loss, a systematic review was conducted. This may benefit researchers by identifying, evaluating, and summarizing all the current research regarding early identification and monitoring of cochlear damage using EHF audiometry (Munn et al., 2018). A systematic review will allow for more reliable findings and conclusions, as a methodical review of the most important research findings in the field will minimise bias by including all relevant literature (Munn et al., 2018). The following research question was formulated prior to conducting the study: What is the potential value of EHF audiometry for early identification and monitoring of cochlear damage, as documented in literature?

2. METHOD

Chapter aim: *The aim of chapter two is to clarify aspects of the method and the procedures followed to select, process, and analyse the information about the benefits of EHF audiometry in early identification and monitoring of cochlear damage.*

The PRISMA-P checklist was used as a guideline for the systematic review (Shamseer et al., 2015). Following the checklist of PRISMA-P, this systematic review was registered in the Prospero database, registration number CRD42020200766.

2.1 Research aim

The main aim of the study was to systematically map the present evidence on the topic, to summarise the findings, and to determine the potential value of including EHF audiometry for the early identification and monitoring of cochlear damage.

2.2 Research design

In order to describe the value of EHF audiometry for the early identification and monitoring of cochlear damage, a systematic review of peer-reviewed literature was conducted. A systematic review refers to the process of systematically searching for research evidence from publications, to be able to assemble knowledge on a topic. The systematic review often adheres to a set of guidelines that regulate the manner in which the review is conducted (Grant & Bootht, 2009). The PRISMA-P checklist was used as a guideline for the current systematic review (Shamseer et al., 2015). This included a 26-item checklist which is divided into three main sections: administrative information, introduction, and methods. These guidelines and categories provided quality, validity, and reliability of reporting the relevant evidence (Shamseer et al., 2015).

2.3 Ethical considerations

Permission and ethical clearance to conduct the study was obtained from the Research Ethics Committee of the Faculty of Humanities, University of Pretoria; HUM055/0720 (Appendix A). This study entailed a systematic review of published

studies and required no involvement of human participants. Therefore, ethical considerations regarding human participants were not applicable.

The ethical aspects that were considered are as follows:

2.3.1 Plagiarism

The research study and the written report of the study were the original work of the researcher. All secondary material cited was carefully acknowledged and referenced according to the University of Pretoria's specifications using APA 7th edition manuscript format and referencing guidelines. The researcher adhered to the University of Pretoria policy on plagiarism (University of Pretoria, 2019).

2.3.2 Publication bias

Systematic reviews are prone to publication bias when reporting the results. It refers to the researchers only reporting on the positive findings and excluding information that might be negative. To reduce the incidence of publication bias, it is recommended that researchers utilise a review protocol. The quality of reviews may be improved through the use of the PRISMA-P checklist (Shamseer et al., 2015). To ensure that a large number of publications were included in the systematic review, multiple databases were utilised to ensure a comprehensive search for studies.

2.3.3 Reliability and validity

Reliability and validity are important in a research study to ensure trustworthiness. Reliability of a study implies that when the study is repeated using the same conditions, the measurements will be consistent. Validity of a study implies the accuracy with which an instrument will measure what it is expected to measure (Bannigan & Watson, 2009).

To ensure reliable and valid results for this study, the following procedures were followed:

- The publications were reviewed by the researcher to ensure that they met the inclusion and exclusion criteria and if there were any reservations, the supervisors also reviewed the publications.

- Multiple electronic databases were searched using different search strategies and key words and/or phrases to ensure that all relevant publications were identified.

2.4 Selection criteria for research material:

Research material that was accessed in this study included published studies on EHF audiometry and their use for the early identification and monitoring of cochlear damage. Specific criteria were determined before any articles were collected. The following inclusion and exclusion criteria were taken into consideration when research material was collected:

2.4.1 Inclusion criteria:

- Publications containing the keywords and phrases. This represented the main concept of the research topic and allowed the researcher to accurately identify relevant articles in the specific databases.
- The selected studies were restricted to studies published in English. There was no translator available to the researcher.
- All papers published between January 2010 and 11 August 2020 were included. This allowed for the inclusion of studies using more recently developed equipment for performing EHF audiometry.
- Studies involving human participants. Limiting studies to only human participants gave a better perspective of the human cochlear organ and functioning.
- Publications that were peer reviewed. Publications that are not peer reviewed increase the probability that bias may affect the results of the systematic review (Crowther et al., 2010)

2.4.2 Exclusion criteria:

- Publications that describe EHF audiometry, but do not primarily focus on early identification and monitoring of cochlear damage. This ensured that only studies reporting cochlear damage using EHF audiometry were included.
- Papers published outside the selected period of January 2010 to 11 August 2020.

- All duplicates and unrelated papers.
- Non-English publications.
- Animal studies.
- Publications that were not peer reviewed.
- All reviews, books, case studies, and posters were excluded.

2.5 Data collection procedure

The systematic review aimed to identify a large number of relevant publications that assisted in the answering of the research question. Four electronic databases were used in this study to search for the relevant publications, namely Academic Search Complete (Ebscohost), Medline (Ebscohost), Scopus, and PubMed. These databases were accessed through the University of Pretoria library services website, where the researcher performed a comprehensive search.

These databases were accessed on 11 August 2020, using a combination of key words and/or phrases that were identified from the research question. The researcher used a list of synonyms, different spellings, and appropriate abbreviations of the keywords that were compiled. The following keywords and/or phrases were identified from the research question and were utilised in the study: “Extended high frequency” OR EHF OR “Extended high frequency audiometry” OR “High frequency audiometry” AND “Early identification” OR “Early detection” OR Monitor/Monitoring AND “Hearing loss”. Additionally, demonstrated in Table 2.1 for each database there were limiters identified to increase the probability of eliminating the number of irrelevant studies during the search.

Table 2.1

Search strategies and results

Database	Search strategy	Identifiers	Limiters	Results
Scopus	All fields	“Extended high frequency” OR EHF OR “Extended high frequency audiometry” OR “High frequency audiometry” AND “Early	Year: 2010 to 2020, Document type: article or	298 articles

		identification" OR "Early detection" OR Monitor* AND "Hearing loss"	review, English language	
PubMed	All fields	"Extended high frequency" OR EHF OR "Extended high frequency audiometry" OR "High frequency audiometry" AND "Early identification" OR "Early detection" OR Monitor* AND "Hearing loss"	Year: 2010 to 2020, English language, humans	24 articles
MEDLINE	TX all text	"Extended high frequency" OR EHF OR "Extended high frequency audiometry" OR "High frequency audiometry" AND "Early identification" OR "Early detection" OR Monitor* AND "Hearing loss"	Year: 2010 to 2020, English language, humans	26 articles
Academic search complete	TX all text	"Extended high frequency" OR EHF OR "Extended high frequency audiometry" OR "High frequency audiometry" AND "Early identification" OR "Early detection" OR Monitor* AND "Hearing loss"	Year: 2010 to 2020, English language	160 articles

The first author reviewed the titles and abstracts of the identified publications using the keywords and/or phrases to exclude papers that did not meet the minimum inclusion criteria. If there were any reservations or ambiguities, the other two authors also reviewed the publications. Papers that did not meet the minimum predefined inclusion criteria were excluded using the Distiller Systematic Review (DSR), an online software programme (Evidence Partners, 2020). Some publications did not include an abstract, and in these cases the full article was reviewed. The full articles were only reviewed after all duplicated and unrelated publications had been excluded to determine whether the minimum inclusion criteria were met. A secondary search method was implemented to identify other related publications that met the inclusion criteria by manually reviewing the reference lists of all publications already identified during the primary search. The articles that were identified and selected from the

search were used to thoroughly analyse and categorize the information, and the data extracted from these studies were included in the systematic review.

The quality of the studies was determined by using the Newcastle-Ottawa Scale (NOS) quality assessment for cohort studies (Stang et al., 2010), as well as a modified version for cross-sectional studies (Herzog et al., 2013). The NOS contained three subcategories namely selection, comparability, and outcome. The quality was rated using the star system recommended by the NOS assessment. According to the NOS assessment, cohort studies may be awarded a star between zero and nine, and cross-sectional studies from zero to 10. The cohort and the cross-sectional studies were assessed according to a criterion that is demonstrated in Table 2.2.

Table 2.2

NOS quality assessment star system criteria

Cohort studies	Cross-sectional studies
Selection criteria (maximum 4 stars) a) representativeness b) non exposed cohort c) ascertainment of exposure d) outcome of interest.	Selection criteria (maximum five stars) a) representativeness b) sample size c) non-respondents d) ascertainment of the exposure.
Comparability (maximum two stars) a) was based on the controlled factors.	Comparability (maximum two stars) a) based on the controlled factors
Outcome (maximum three stars) a) assessment of outcome b) follow-up c) adequacy of follow-up.	Outcome (maximum three stars) a) assessment of the outcome b) appropriate statistical test.

2.6 Data analysis procedure

Data extraction was done by studying selected studies that were identified in the search according to the inclusion criteria. The DSR software programme (Evidence Partners, 2020) was used to organise all the results obtained from the searches in the different electronic databases. The software programme allowed screening of the titles

and abstracts, removing duplicates as well as reviewing of the full text of publications. Furthermore, the DSR software programme was utilised to tabulate, analyse, and categorize the information obtained in the publications. To avoid bias, the supervisors independently reviewed the data the researcher extracted. The extracted data was exported into a Microsoft Word document and a summarised table was compiled (Appendix B and Appendix C). The results were tabulated in such a manner that similarities and differences between the studies were emphasised.

The following variables were extracted from the articles:

- Author and year of publication.
- The study title
- The aim of the study
- The study design.
- The study population.
- The test parameters/equipment.
- The type of exposures causing cochlear damage.
- The conclusion of each study.
- The limitations and future research of each study.

Additionally, quantitative information was extracted by calculating the number and percentage of studies where results indicated whether EHF audiometry may be a valuable tool or may be a valuable tool in combination with other methods, or was not regarded as a valuable tool. A detailed description of the studies' results in each category were tabulated in Microsoft Word (Appendix D and Appendix E). Data was extracted under the following categories:

- Non-sequential analysis studies
- Sequential analysis studies
- Studies evaluated using prevalence of identified cochlear damage
- Studies evaluated using hearing threshold increase

3. ARTICLE

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EARLY IDENTIFICATION AND MONITORING OF COCHLEAR DAMAGE USING EXTENDED HIGH-FREQUENCY AUDIOMETRY: A SYSTEMATIC REVIEW

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Keywords: extended high-frequencies, extended high-frequency audiometry, cochlear damage, early identification, monitoring

3.1 Abstract:

Purpose: Extended high frequency (EHF) audiometry has been recommended for early identification and monitoring of cochlear damage, as the cochlear damage occurs at EHFs before the thresholds at conventionally tested frequencies (250 - 8000 Hz) are affected. Early detection and monitoring is thus important to reduce the progression of hearing loss. The present systematic review was conducted to investigate existing evidence regarding the potential value of EHF audiometry for early identification and monitoring of cochlear damage.

Method: The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist (PRISMA-P) was used as a guideline for the systematic review. Four electronic databases (Academic Search Complete, Medline, Scopus, and PubMed) were used to find relevant studies through keywords identified from the research question.

Results: Sixteen articles were compatible with the criteria and included cross-sectional and cohort studies, which were evaluated using the Newcastle-Ottawa scale

(NOS) for quality assessment. Despite the heterogeneity in the studies, it can be concluded that EHF audiometry was considered by seven studies (43.75%) to be a valuable procedure for early identification and monitoring of cochlear damage. Some studies suggested that the procedure is useful when combined with conventional audiometry (six studies – 37.5%) or distortion product otoacoustic emission (DPOAE) testing (two studies – 12.5%), or both procedures (one study – 6.25%). Due to the variety of equipment used to measure EHFs, no conclusion could be reached on preferred equipment. It is suggested that individuals should be tested with the same equipment over time for intra-monitoring of the EHFs to increase test-retest reliability. **Conclusions:** This systematic review demonstrated that EHF audiometry may be beneficial in the clinical assessment for early identification and monitoring of cochlear damage.

3.2 Introduction

According to the World Health Organisation (WHO), approximately 466 million people around the world have some type of disabling hearing loss (WHO, 2020). Sensorineural hearing loss (SNHL) is the most common type of hearing loss. It is reported to be the cause of more than 90% of hearing loss in adults (Eyvazzadeh, 2020). SNHL due to cochlear damage may result from various factors, including genetic anomalies, excessive or persistent noise exposure, aging, and exposure to ototoxic drugs (Wagner & Shin, 2019). Cochlear damage usually manifests as a high frequency hearing loss that steadily progresses towards the lower frequencies (Campbell & Le Prell, 2018; Mehrparvar et al., 2014; Vlaming et al., 2014). The damage caused to both the inner hair cells and the outer hair cells within the cochlea is permanent, since hair cells cannot be regenerated. Once the hair cells are

damaged, individuals will suffer from an irreversible hearing loss (Wagner & Shin, 2019). It is difficult to identify cochlear damage during the early stages of destruction, as 30 to 50% of these hair cells may be destroyed before any noticeable symptoms of hearing loss are reported (Daniel, 2007). The more severe the degree of high-frequency SNHL, however, the greater the effect will be on an individual's speech recognition abilities (Li et al., 2017). Although some of these individuals may already experience communication difficulties, they often delay seeking assistance (Vlaming et al., 2014). It is important that damage be detected as soon as possible, and appropriate measures be taken to reduce the progression of hearing loss, especially before an individual's speech frequencies are affected (Macca et al., 2015; Mehrparvar et al., 2014; Valiente et al., 2016).

The gold standard for assessing hearing sensitivity is pure-tone audiometry, conducted at frequencies of 250 Hz to 8000 Hz (Baiduc et al., 2013; Mehrparvar et al., 2014). Hair cell damage affecting hearing thresholds at frequencies higher than 8000 Hz may therefore not be detected by conventional audiometry (Ahmed et al., 2001). Additional equipment and procedures are required to identify deterioration of thresholds at an earlier stage. A recommended test procedure for the early detection and monitoring of individuals at risk for cochlear damage is EHF audiometry (Valiente et al., 2016). EHF audiometry or ultra-audiometry refers to the audiometric testing of thresholds at high frequencies of hearing that range from 10 000 to 20 000 Hz (Le Prell et al., 2013). It is hypothesised that EHF audiometry may be used as an early indicator of cochlear damage if a deterioration in the thresholds at frequencies higher than 8000 Hz can be detected, before deterioration is evident in the thresholds at standard frequencies (Ahmed et al., 2001; Valiente et al., 2016).

Research investigating the use of EHF audiometry for the early identification and monitoring of cochlear damage has increased recently. The value of using EHF audiometry in clinical practice as a monitoring tool has been reported in the case of individuals exposed to ototoxicity, as it is more sensitive and reliable in detecting initial ototoxic damage than conventional audiometry (Jacobs et al., 2012; Knight et al., 2007). Early detection of ototoxicity can lead to early intervention, which may halt the progression of hearing loss (Campbell & Le Prell, 2018). However, monitoring ototoxicity by means of EHF audiometry is not well established in standard clinical care (Lord, 2019).

The use of EHF audiometry to monitor early changes in the hearing ability of populations such as individuals exposed to noise, whether occupational or social, has also been suggested (Le Prell et al., 2013; Mehrparvar et al., 2014). Various research studies have indicated that the use of EHF audiometry may be more reliable and sensitive in the early detection of noise-induced hearing loss (NIHL) than conventional audiometry and the clinical 4000 Hz sign (Ahmed et al., 2001; Lord, 2019; Mehrparvar et al., 2011; Mehrparvar et al., 2014; Somma et al., 2008). On the other hand, some researchers who investigated the use of EHF audiometry in individuals exposed to noise reported no significant differences in the frequencies from 9000 Hz to 14 000 Hz. Hence, they concluded that EHF audiometry is not useful for the early identification and monitoring of cochlear damage (Balatsouras et al., 2005; Schmuziger et al., 2007). However, in longitudinal studies to determine whether employees who are at risk for developing NIHL may be identified at an early stage, serial monitoring of hearing thresholds by comparing the individual's EHF thresholds over time proved to be clinically valuable (Le Prell et al., 2013). Furthermore, Ahmed et al. (2001) found that the variability of intra-participant results in EHFs was low although the inter-

subject variation was large. EHF audiometry may thus be a more reliable test procedure than conventional audiometry to monitor the hearing loss within the individual over time (Ahmed et al., 2001).

The potential of using EHF audiometry to monitor the hearing of individuals with type 2 diabetes mellitus, who may experience damage to the outer hair cells in the high-frequency regions of the cochlea, has recently been considered (Vignesh et al., 2015). The conclusion was that EHF audiometry should be included in the audiological test battery for monitoring purposes in these individuals (Vignesh et al., 2015). Additionally, EHF audiometry may be used to identify certain systemic pathologies such as Fabry disease, genetic hearing loss, nasopharyngeal carcinoma treated with radiotherapy, and autoimmune hearing loss (Valiente et al., 2016). Therefore, it is recommended that EHF audiometry should be implemented as standard clinical practice with conventional audiometry to evaluate the entire auditory frequency range (Valiente et al., 2016). The standard clinical procedure is still mostly limited to pure tone testing up to 8000 Hz (Baiduc et al., 2013). This is despite the fact that the human auditory range extends to approximately 20 000 Hz, and that some researchers recommend the use of the results of EHF audiometry as an early indicator of as well as for monitoring cochlear damage (Baiduc et al., 2013). As the interest in EHF audiometry is increasing, it is important to determine to which extent this test procedure may be used for the early identification and monitoring of cochlear damage, as the clinical value of this procedure still has to be established (Lord, 2019).

The aim of the current study was to conduct a systematic review of literature to determine what has been documented regarding the use of EHF audiometry for the early identification and monitoring of hearing loss. The results of the review may

benefit researchers by identifying, evaluating, and summarizing current research regarding early identification and monitoring of cochlear damage using EHF audiometry (Munn et al., 2018). The following research question was formulated prior to conducting the study: What is the potential value of EHF audiometry for the early identification and monitoring of cochlear damage as documented in literature?

3.3 Materials and methods

A systematic review was conducted of peer-reviewed literature on the topic under investigation. The study was approved by the Research Ethics Committee of the Faculty of Humanities, University of Pretoria; HUM055/0720. The PRISMA-P checklist was used as a guideline for the systematic review (Shamseer et al., 2015). The study was registered on the Prospero database, registration number CRD42020200766. Four electronic databases were utilised in this study to search for the relevant publications, namely Academic Search Complete, Medline, Scopus, and PubMed. The search in the databases was conducted on August 11, 2020, and included all relevant reports published from January 2010 until this date.

The databases were accessed using a combination of the following keywords: "Extended high frequency" OR EHF OR "Extended high-frequency audiometry" OR "High-frequency audiometry" AND "Early identification" OR "Early detection" OR Monitor/Monitoring AND “Hearing loss”. The inclusion criteria included: research material that was published in English, from January 2010 to 11 August 2020, and involved human participants. Publications that were not peer-reviewed and described EHF audiometry without mentioning early identification and monitoring of cochlear damage in the title, aim, and/or keywords were excluded from the systematic review.

Any reviews, books, case reports, posters, and unrelated papers that did not answer the research question were also excluded.

The first author reviewed the title and abstracts of the publications identified using the keywords and/or phrases. If there were any uncertainties the other two authors also reviewed the publications. Papers that did not meet the minimum predefined inclusion criteria were excluded using Distiller Systematic Review software (Evidence Partners, Ottawa, Canada). If publications did not include an abstract, the full article was reviewed. After the duplicated and unrelated publications were excluded from the study, the full articles were reviewed to determine whether the minimum inclusion criteria were met. A secondary search method was implemented to identify other related publications that met the inclusion criteria by manually reviewing the reference lists of all publications already identified during the primary search. The articles that were identified and selected from the search were used to thoroughly analyse and categorise the data extracted from these studies.

The quality of the studies was determined by using the NOS quality assessment for cohort studies (Stang, 2010), as well as a modified version for cross-sectional studies (Herzog et al., 2013). The NOS contained three subcategories namely selection, comparability, and outcome. The quality was rated using the star system recommended by the NOS assessment. According to the NOS assessment cohort, studies may be awarded a star between zero and nine and cross-sectional studies from zero to 10. The cohort and the cross-sectional studies were assessed according to a criterion that is demonstrated in Table 3.1.

Table 3.1

NOS quality assessment star system criteria

Cohort studies	Cross-sectional studies
Selection criteria (maximum 4 stars)	Selection criteria (maximum five stars)
a) representativeness	a) representativeness
b) non exposed cohort	b) sample size
c) ascertainment of exposure	c) non-respondents
d) outcome of interest.	d) ascertainment of the exposure.
Comparability (maximum two stars)	Comparability (maximum two stars)
a) was based on the controlled factors.	a) based on the controlled factors
Outcome (maximum three stars)	Outcome (maximum three stars)
a) assessment of outcome	a) assessment of the outcome
b) follow-up	b) appropriate statistical test.
c) adequacy of follow-up.	

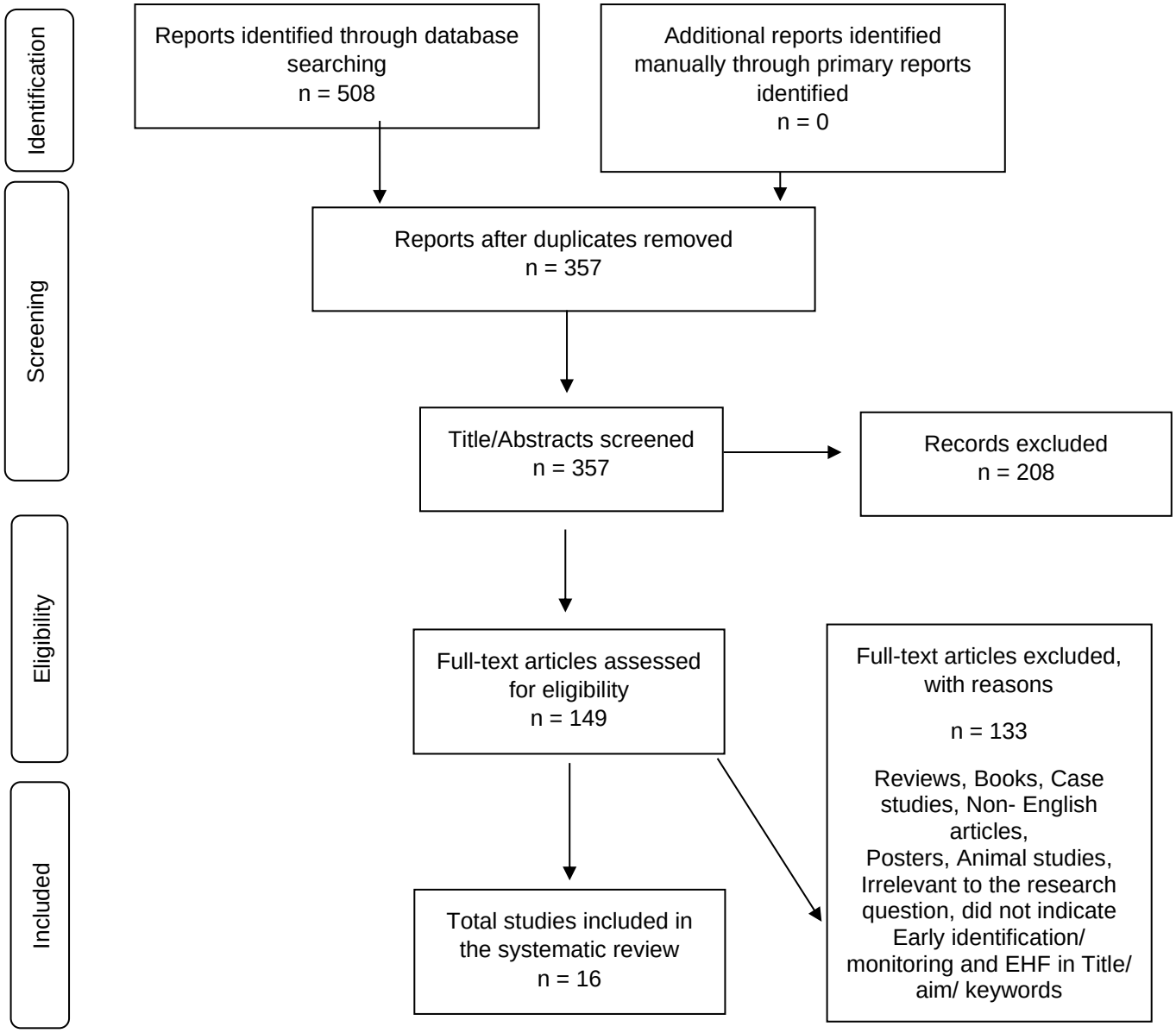
3.4 Results

Following the removal of 151 duplicates, 508 reports remained. The titles and abstracts of 357 reports were reviewed to determine their relevance to the aim of the study. Based on the exclusion criteria, 208 reports were removed. The 149 articles showing some applicability were reviewed in full text. A total of 16 articles were included in the final reports for this review as they could be directly linked to the aim of this study. During the secondary search through the reference list of the articles included in the primary search, no additional articles were identified that were not already included in the systematic review. It should be noted that some studies commenting on the clinical value of EHF audiometry were excluded, as it was not the primary aim of these studies to report on the potential of EHF audiometry for early identification and monitoring of cochlear damage. The systematic review consisted of

cohort studies as well as cross-sectional studies. Figure 3.1 demonstrates the PRISMA flow diagram with search results and procedural steps.

Figure 3.1

PRISMA flow diagram with search results and procedural steps



Note. PRISMA flow diagram. From *DistillerSR*, by Evidence Partners, 2020, retrieved from http://www.evidencepartners.com/products/distillersr-systematic-revview-software

Quality assessment

The NOS quality assessment was determined for all 16 studies. The results are indicated in Table 3.2. Four of the six cohort studies were rated to be of “good” quality (scored 7 to 9) and three of the studies received a score between 4 and 6, indicating that they were of “fair” quality. Five cross-sectional studies received a score between 9 and 10 classifying them as being “very good”. Four studies were rated to be of “good quality (scored 7 to 8) and one study was evaluated as “fair” (scored 5 to 6). None of the studies were excluded during the quality assessment.

Table 3.2

Quality assessment per the NOS assessment

First Author and year	Selection	Comparability	Outcome	Total
Riga et al. (2010)	3	2	3	Good (8)
Mehrparvar et al. (2011)	4	2	2	Good (8)
Buchler et al. (2012)	4	1	3	Good (8)
Abujamra et al. (2013)	3	0	3	Fair (6)
Luders et al. (2014)	3	1	2	Fair (6)
Macca et al. (2014)	4	2	3	Very good (9)
Mehrparvar et al. (2014)	4	2	3	Very good (9)
Yu et al. (2014)	3	0	2	Fair (5)
Vignesh et al. (2015)	4	2	3	Very good (9)
Gonzalez et al. (2017)	4	2	3	Very good (9)
Galarza-Delgado et al. (2018)	4	2	3	Very good (9)
Ma et al. (2018)	4	1	3	Good (8)
Vasconcelos et al. (2018)	3	1	3	Good (7)
Bayat et al. (2019)	3	1	3	Good (7)
Laffoon et al. (2019)	4	0	3	Good (7)
Li et al. (2019)	3	2	3	Good (8)

Table 3.3 summarises the characteristics of the included studies, according to a) first author and year of publication; b) design of the study; c) test equipment/parameters; and d) recommendations.

Table 3.3

Characteristics of included studies

FIRST AUTHOR AND YEAR	STUDY DESIGN	POPULATION	TEST EQUIPMENT/PARAMETERS	RECOMMENDATIONS
Riga, 2010	Prospective study, cohort study	NIHL	EHF's: 10000, 11 200, 12 500, 14 000, 16 000, 18 000 Hz Audiometer: Amplaid A321 Headphones: Sennheiser HDA 200	Extended high-frequency (EHF) audiometry may be useful (< 10 years exposed)
Mehrparvar, 2011	Historical, cohort study	NIHL	EHF's: 10 000, 12 000, 14 000, 16 000 Hz Audiometer: Interacoustic AC40 Headphones: Koss, R/80	EHF audiometry may be useful (more sensitive than conventional audiometry)
Buchler, 2012	Controlled prospective clinical study, cohort study	NIHL	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000, 18 000, 20 000 Hz Audiometer: GSI 61 Headphones: Sennheiser HDA200	EHF audiometry may be useful in conjunction with conventional audiometry
Abujamra, 2013	Transversal study, cross-sectional study	Ototoxicity	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Siemens Headphones: HDA 200	EHF audiometry may be useful (more sensitive than conventional audiometry and distortion product otoacoustic emission (DPOAE) testing

Luders, 2014	Retrospective observational cohort.	NIHL	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Madsen, model ITERA II Headphones: HDA 200	EHF audiometry may be a useful procedure in conjunction with conventional audiometry
Macca, 2014	Not indicated	NIHL	EHF's: 9000, 10 000, 11 000, 12 000, 13 000, 14 000, 15 000, 16 000, 17 000, 18 000Hz Audiometer: Labat Audiopack Headphones: Sennheiser HD 500	EHF audiometry may be useful in conjunction with conventional audiometry (individuals younger than 30 years old).
Mehrparvar, 2014	Prospective cross-sectional study	NIHL	EHF's: 10 000, 12 000, 14 000, 16 000 Hz Audiometer: AC 40 Headphones: R80	EHF audiometry may be useful (more sensitive than conventional audiometry and DPOAE testing)
Yu, 2014	Prospective study	Ototoxicity	EHF's: 9000, 11 200, 12 500, 14 000, 16 000, 18 000 and 20 000 Hz Audiometer: Interacoustic AC40	EHF audiometry may be useful in conjunction with DPOAE testing
Vignesh, 2015	Not indicated	Diabetes	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000Hz Audiometer: Inventis-piano Headphones: HD-200 transducer	EHF audiometry may be a useful (more sensitive than conventional audiometry)
Gonzalez, 2017	Comparative, cross-sectional study	Autoimmune disease	EHF's: 10 000, 12 000, 14 000 and 16 000 Hz Audiometer: Interacoustic AC40	EHF audiometry may be a useful procedure in conjunction with conventional audiometry.
Galarza-Delgado, 2018	Comparative cross-sectional study	Autoimmune disease	EHF's: 10 000, 12 000, 14 000, 16 000Hz Audiometer: Interacoustic AC40	EHF audiometry may be a useful procedure in conjunction with conventional audiometry.

Ma, 2018	Observational cross-sectional study	NIHL	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000, 18 000, 20 000 Hz Audiometer: Madsen model Conera Headphones Sennheiser HDA200	EHF audiometry may be useful (more sensitive than conventional audiometry)
Vasconcelos, 2018	Longitudinal prospective cohort study	Ototoxicity	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Madsen Itera II Headphones: TDH-39	EHF audiometry may be useful (more sensitive than conventional audiometry)
Bayat, 2019	Analytic cross-sectional study	Ototoxicity	EHF's: 10 000, 12 000, 14 000, 16 000hz Audiometer: Madsen Astera Headphones: Sennheiser HDA-200.	EHF audiometry may be useful (more sensitive than conventional audiometry)
Laffoon, 2019	Quantitative cross-sectional descriptive pilot study	NIHL	EHF's: 10 000, 12 500, 14 000, 16 000Hz Audiometer: Madsen Astera Earphones: ER-2 inserts	EHF audiometry may be useful in conjunction with conventional audiometry and DPOAE testing
Li, 2019	Not indicated	Diabetes	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Otometrics Conera	EHF audiometry may be useful in conjunction with DPOAE testing

Table 3.4 demonstrates the summary of the results, according to categories of a) sequential analysis, b) nonsequential analysis, c) sensitivity of EHF audiometry, and d) deterioration of EHF-thresholds. If a study concluded that EHF audiometry is more sensitive than another test procedure or did not report which procedure proved to be more beneficial than EHF audiometry, the study was categorised as useful. If the study reported that EHF audiometry may be useful as a supplementary tool to another test

procedure, it was categorised accordingly. A detailed description of the studies in each category is shown in Supplemental Material S1 and S2.

Table 3.4

Summary of results

	Nonsequential analysis	Sequential analysis	Studies combined	Sensitivity of EHF audiometry	Deterioration of EHF-thresholds
EHF audiometry as a useful procedure	Seven studies (43.75%)	-	Seven studies (43.75%)	Four studies (37.5%)	Seven studies (43.75%)
EHF audiometry in conjunction with conventional audiometry	Four studies (25%)	Two studies (12.5%)	Six studies (37.5%)	Two studies (12.5%)	Six studies (37.5%)
EHF audiometry in conjunction with DPOAE testing	One study (6.25%)	One study (6.25%)	Two studies (12.5%)	Two studies (12.5%)	One study (6.25%)
EHF audiometry in conjunction with conventional audiometry and DPOAE testing	One study (6.25%)	-	One study (6.25%)	One study (6.25%)	One study (6.25%)
Control group	11 studies (68.75%)	One study (6.25%)	-	Seven studies (43.75%)	12 studies (75%)
No control group	Two studies (12.5%)	Two studies (12.5%)	-	Two studies (12.5%)	Three studies (18.75%)
Total of studies	13 studies (81.25%)	Three studies (18.75%)	-	Nine studies (56.25%)	15 studies (93.75%)

During data extraction, it was found that some studies raised an additional factor regarding the influence that age has on EHFs. Five studies (31.25%) commented on the effect that age has on EHF audiometry and concluded that progressive hearing loss was found with an increase in age (Buchler et al., 2012; Laffoon et al., 2019, Ma

et al., 2018; Macca et al., 2015; Riga et al., 2010). One other study (6.25%) commented on the impact and reliability that age has on EHF audiometry and suggested EHF assessments in individuals older than five years (Abujamra et al., 2013).

3.5 Discussion

Several research projects have been conducted to demonstrate that EHF audiometry may be beneficial for early identification and monitoring of cochlear damage. Despite the recommendations of previous research, EHF audiometry is not yet being used as a routine clinical assessment in at-risk individuals (Valiente, 2016). As various research studies have been independently conducted, the present systematic review aimed to combine these studies and integrate their findings, to investigate the possibility of a collective conclusion regarding the clinical value of EHF audiometry for the early detection and monitoring of cochlear damage.

It is important to note that the studies were heterogeneous in nature regarding the type, intensity, and duration of exposure to a variety of factors that may cause cochlear damage. In the NIHL population, the type of noise exposure and the participants included occupational noise exposure, recreational firearm users, active-duty soldiers, civilian pilots, and music students. The treatment regime used for participants receiving ototoxic medication included cisplatin, amikacin, and methadone maintenance treatment. Participants in some studies were diagnosed with Primary Sjögren Syndrome and Rheumatoid Arthritis, while other studies investigated patients with type 2 diabetes mellitus. Another form of heterogeneity involved the diverse

equipment (audiometers and headphones) that was used for conventional audiometry. Different equipment was also used across the studies for determining EHF thresholds.

Furthermore, significant variations were noted in the methods used to determine cochlear damage. In some cases the participants were tested only once, while other researchers followed up with sequential testing. Authors also interpreted and reported the results differently. Some evaluated the sensitivity of EHF audiometry for identifying cochlear damage, others evaluated the possible deterioration in the individual's EHF thresholds. Such differences complicated the process of comparing the studies and formulating a conclusion with regard to the usefulness of EHF audiometry for the early identification and monitoring of cochlear damage. These differences might also have contributed to the diverse results reported in the studies (Gagnier et al., 2012). Despite the variations, all 16 studies concluded that EHF audiometry may be a useful tool for the early detection and monitoring of cochlear damage, either independently or in combination with another test procedure.

Nonsequential analysis

The majority of the studies (13 studies - 81.25%) tested participants only once. The study group was either compared with another study group or a control group. Seven of these studies (43.75%) agreed that EHF audiometry may be a useful test procedure in the early detection and monitoring of cochlear damage (Abujamra et al., 2013; Bayat et al., 2019; Ma et al., 2018; Mehrparvar et al., 2011; Mehrparvar et al., 2014; Riga et al., 2010; Vignesh et al., 2015). The remainder of the studies each reported different conclusions, although all the studies that used nonsequential analysis agreed that EHF audiometry is a valuable test procedure but more beneficial in combination with another procedure. Four studies (25%) concluded that EHF audiometry is more

valuable when used in combination with conventional audiometry (Galarza-Delgado et al., 2018; Gonzalez et al., 2017; Luders et al., 2014; Macca et al., 2018), one study (6.25%) recommended that EHF audiometry should be combined with DPOAE testing (Li et al., 2019), and one study (6.25%) suggested that all three test procedures should be used in combination for the early detection of cochlear damage (Laffoon et al., 2019).

Eight studies compared the results of EHF audiometry to the clinical value of using conventional audiometry (Galarza-Delgado et al., 2018; Gonzalez et al., 2017; Luders et al., 2014; Ma et al., 2018; Macca et al.,2015; Mehrparvar et al., 2011; Riga et al., 2010; Vignesh et al., 2015). These studies found poorer hearing thresholds in the EHF range of the study group than in the control group, as well as poorer hearing thresholds when comparing test results of the conventional frequencies between participant groups. EHF audiometry proved to be more sensitive than conventional audiometry for the early identification of cochlear damage, however, as the influence of cochlear damage was more predominant in the EHF thresholds. The researchers concluded that EHF audiometry may be a beneficial test procedure as it has the potential to identify cochlear damage much earlier than conventional audiometry (Ma et al., 2018; Mehrparvar et al., 2011; Riga et al., 2010; Vignesh et al., 2015). It should be noted that although the study of Riga et al. (2010) recommended EHF audiometry as a useful procedure, the study only reported the benefit of EHF audiometry in individuals exposed to cochlear damage for less than 10 years. In the study of Riga et al. (2010), conventional audiometry was found to be more effective than EHF audiometry in individuals exposed to cochlear damage for more than 10 years.

Two studies compared the hearing thresholds of a study group and a control group. Although poorer hearing thresholds were found for the study group in both conventional audiometry and EHF audiometry (Luders et al., 2014; Vignesh et al., 2015), EHF audiometry was found to be more sensitive for the early detection of cochlear damage. While Vignesh et al. (2015) recommended the use of EHF audiometry for the early detection of cochlear damage, Luders et al. (2014) recognised the potential of the combination of EHF audiometry and conventional audiometry. Contradictory to these results, Balatsouras et al. (2005) (whose study was not included in the systematic review) found inconsistent results when comparing the EHF thresholds of a study group to a control group and in some instances the control group obtained poorer thresholds than the study group with cochlear damage. Consequently, the study concluded that EHF audiometry provides no information additional to conventional audiometry. However, three other studies suggested that EHF audiometry may be beneficial in conjunction with conventional audiometry as both procedures showed poorer hearing thresholds for the study groups than for the control groups (Galarza-Delgado et al., 2018; Gonzalez et al., 2017; Macca et al.,2015).

The efficiency of EHF audiometry, conventional audiometry, and/or DPOAE testing as audiometric test procedure for identifying cochlear damage was compared in four studies (Abujamra et al., 2013; Baya et al., 2019; Li et al., 2019; Mehrparvar et al., 2014). Two of these studies concluded that EHF audiometry may be a useful procedure for the early identification of cochlear damage, as it proved to be a more sensitive procedure for this purpose than conventional audiometry and DPOAE testing (Abujamra et al., 2013; Mehrparvar et al., 2014). Laffoon et al. (2019) found that EHF audiometry may be more beneficial in combination with conventional audiometry and DPOAE testing. This was the only study that concluded that all three procedures

provided early evidence of cochlear damage and should therefore be used in combination (Laffoon et al., 2019).

Two studies that evaluated these three test procedures reported that only EHF audiometry and DPOAE testing proved to be sensitive procedures for the early identification of cochlear damage (Bayat et al., 2019; Li et al., 2019). Li et al. (2019) reported that EHF audiometry may be a valuable test procedure in combination with DPOAE testing, as using the two tests in combination improves the accuracy of early identification of cochlear damage. The results of a study by Bayat et al. (2019) confirmed the results of the study of Li et al. (2019) to a certain extent. Although DPOAE testing was found to be more sensitive in identifying cochlear damage, the study indicated that both EHF audiometry and DPOAE testing are more effective for the early detection of cochlear damage than conventional audiometry. The study did not specify, however, whether EHF audiometry and DPOAE testing should be used in combination, or which was the preferred procedure. EHF audiometry was simply categorised as a useful procedure for the early identification of cochlear damage (Bayat et al., 2019).

A previous study that was not included in the systematic review reported that DPOAE testing is the preferred procedure for early identification of cochlear damage as it is an objective test and does not require patients to respond (Dhooge et al., 2006). However, some researchers argue that DPOAE testing cannot assess the entire frequency range, which is necessary and important for the early identification of cochlear damage as the procedure was limited to conventional frequencies of 1000 Hz to 6000 Hz (Abujamra et al., 2013; Li et al., 2019). EHF audiometry may therefore be a more useful procedure for early detection of cochlear damage (Abujamra et al.,

2013; Li et al., 2019). The results of the current systematic review demonstrate that EHF audiometry may be regarded as the most useful procedure for the early identification of cochlear damage.

Sequential analysis

Three studies (18.75%) investigated the value of EHF audiometry by conducting a sequential analysis. Two studies (12.5%) investigated and compared EHF audiometry, DPOAE testing, and conventional audiometry as test procedures for the monitoring of cochlear damage (Buchler et al., 2012; Vasconcelos et al, 2018). Buchler et al. (2012) compared the participants' EHF-thresholds results to those of a control group as well as the participants' own EHF-thresholds over time, and reported temporary threshold shifts in the thresholds. The study concluded that EHF audiometry may be used in combination with conventional audiometry, as it remains the most reliable clinical procedure for monitoring cochlear damage (Buchler et al., 2012).

The study of Vasconcelos et al. (2018) confirmed these findings and found threshold shifts in the participant group at two- and six-months follow up assessments using both EHF audiometry and conventional audiometry (Vasconcelos et al., 2018). The study concluded that EHF audiometry was the most sensitive procedure for monitoring purposes and the detection of cochlear damage at two- and six-months intervals, although conventional audiometry was also sensitive in detecting threshold shifts at a six-month interval (Vasconcelos et al., 2018). Furthermore, the researchers reported that DPOAE testing was less conclusive and sensitive for the monitoring of cochlear damage. Both of these studies demonstrated that EHF audiometry has the potential

to be included in the clinical assessment in combination with conventional audiometry for the monitoring of cochlear damage (Buchler et al., 2012; Vasconcelos et al., 2018).

In addition, a previous study evaluating the test-retest reliability of EHF audiometry for periodic monitoring demonstrated that EHF audiometry may be regarded as reliable, as the hearing thresholds at the retest were within the American Speech-Language-Hearing Association criteria (ASHA 1994) for significant threshold shift (Frank et al., 2001). The evaluation of the test-retest reliability emphasised and confirmed the results of the previously discussed studies that EHF audiometry proved to be a reliable procedure for intra-individual monitoring and may improve the clinical value of this procedure for the monitoring of cochlear damage (Ahmed et al., 2001; Frank et al., 2001). Yu et al. (2014) reported on the sensitivity of identifying cochlear damage using EHF audiometry and DPOAE testing in combination. This study found the same sensitivity for both test procedures for identifying and monitoring cochlear damage, and therefore concluded that EHF audiometry may be a useful procedure to use in conjunction with DPOAE testing as the two procedures supplement each other during the monitoring of cochlear damage (Yu et al., 2014).

In the current systematic review, the various studies concluded that EHF audiometry may be useful for monitoring purposes when comparing an individual's hearing thresholds over time. Monitoring the patient's own thresholds over time will enable clinicians to effectively observe whether any threshold shifts occur. The patient, family, and medical team can then be counselled on either adjusting the harmful exposure or to make an informed decision with regard to the treatment that may follow. These studies also suggested that, although EHF audiometry may be a useful procedure, it

may be more beneficial to use the procedure in combination with conventional audiometry.

Sensitivity of EHF audiometry

Nine studies (56.25%) compared the sensitivity of EHF audiometry, conventional audiometry, and/or DPOAE testing for the early identification of cochlear damage. The studies included in the systematic review determined the sensitivity of the test procedures by evaluating the procedure's ability to identify cochlear damage at an earlier stage. Five studies investigated and compared all three test procedures (Abujamra et al., 2013; Bayat et al., 2019; Laffoon et al., 2019; Li et al., 2019; Mehrparvar et al., 2014). Mehrparvar et al. (2014) reported that EHF audiometry identified 69% of the participants with cochlear damage, and was therefore more sensitive in identifying cochlear damage than conventional audiometry (29%) and DPOAE testing (22% and 57% for low and high frequency DPOAE testing, respectively). In agreement, the study of Abujamra et al. (2013), found that EHF audiometry could identify 87% of patients with cochlear pathology while conventional audiometry could only identify 57% and DPOAE testing identified 64%. These two studies concluded that EHF audiometry proved to be the most sensitive test procedure to use for the identification of cochlear pathology. They regard EHF audiometry as a valuable test procedure to use for the early detection of cochlear damage (Abujamra et al., 2013; Mehrparvar et al., 2014).

The study of Li et al. (2019) determined the sensitivity of DPOAE testing in identifying cochlear damage to be 89.2% and that of EHF audiometry 63.1% (Li et al., 2019). This study does therefore not fully agree with the previous two studies. The study recommended the use of EHF audiometry and DPOAE testing in combination to

supplement each other, as these two procedures were more sensitive in identifying cochlear damage than conventional audiometry (Li et al., 2019). Furthermore, the study of Bayat et al. (2019) confirmed the results of the study of Li et al. (2019), as the study reported the sensitivity of identifying cochlear damage using EHF audiometry and DPOAE testing to be 40.74% and 51.85%, respectively (Bayat et al., 2019). Although DPOAE testing was found to be a more sensitive procedure, the study concluded that EHF audiometry is a clinical valuable procedure for the early identification of cochlear damage. It was not specified, however, if the two test procedures should be used in combination.

The study of Laffoon et al. (2019) reported on the sensitivity of various procedures in early identification of cochlear damage EHF audiometry identified 48.2% of participants with cochlear damage, whereas DPOAE testing and conventional audiometry identified 78.5% and 28.5% respectively. Even though the study found DPOAE testing to be more sensitive, the researchers recommended that in addition to conventional audiometry both EHF audiometry and DPOAE testing may be useful test procedures in combination for the early identification of cochlear damage (Laffoon et al., 2019). Laffoon et al. (2019) argued that although DPOAE testing was more sensitive, EHF audiometry covers higher frequency regions of the cochlea. The study of Yu et al. (2014) aimed to compare the sensitivity of EHF audiometry and DPOAE testing and reported that the two procedures were equally sensitive, as both procedures identified 40% of the participants with cochlear damage (Yu et al., 2014). Both these tests demonstrated the same sensitivity in identifying cochlear damage, yet the results were not always consistent for the same participant (Yu et al., 2014). This study confirmed the results of the study of Li et al. (2019) and recommended that

EHF audiometry and DPOAE testing should be used in combination to improve the accuracy for the monitoring and early detection of cochlear damage (Yu et al., 2014).

Three studies examined the identification of cochlear damage with EHF audiometry and conventional audiometry. One of the studies found EHF audiometry to be significantly more sensitive for the early identification of cochlear damage (94.8%) than conventional audiometry (74.6%), except for the age group from 50 to 59 years (Ma et al., 2018). The study consequently concluded that EHF audiometry may be a useful procedure for the early detection of cochlear damage for participants younger than 50 years of age. Two other studies also investigated the sensitivity of EHF audiometry and conventional audiometry for the early identification of cochlear damage and found that EHF audiometry was potentially a clinically valuable supplementary procedure in audiometric assessment (Gonzalez et al., 2017; Galarza-Delgado et al., 2018).

The study of Gonzalez et al. (2017) investigated the sensitivity of EHF audiometry (10 000 Hz to 16 000 Hz) and identified 95.2% of their participant group with cochlear damage using EHF audiometry compared to conventional audiometry covering the frequencies 4000 Hz to 8000 Hz. This latter procedure identified 55.6% and 60.3% of cochlear pathology in the right and left ears of their participants, respectively. The study also compared the sensitivity of high frequency testing to the lower conventional frequencies (500 Hz to 3000 Hz) and reported identifying 28.6% and 33.3% of the participants with cochlear damage using the lower frequencies only. The study of Galarza-Delgado et al. (2018) also confirmed that EHF audiometry may be useful in combination with conventional audiometry, although the study found EHF audiometry to be the most sensitive procedure for the early identification of cochlear damage.

Galarza-Delgado et al. (2018) investigated two separate groups of partcipants who were at risk of developing cochlear damage. The study reported the sensitivity of EHF audiometry in identifying cochlear damage in the first study group to be 94.9% compared to the sensitivity of conventional audiometry. Using the lower frequencies (500 Hz to 3000 Hz) the study identified 36.8% of participants with cochlear damage and using the higher frequencies of conventional audiometry (4000 Hz to 8000 Hz) the study identified 68.4% of participants. In the second study group, the sensitivity of EHF audiometry was found to be 100% compared to the conventional frequencies (500 Hz to 3000 Hz and 4000 Hz to 8000 Hz) with which respectively 60% and 70% of the partcipants with cochlear damage were identified.

With regard to the sensitivity of identifying cochlear damage using EHF audiometry, four studies (25%) found the procedure to be most sensitive and successful in identifying cochlear damage compared to the other procedures. However, the systematic review recognised that two other studies (12.5%) recommended that EHF audiometry may be useful in combination with conventional audiometry, two studies (12.5%) DPOAE testing, and one study (6.25%) recommended the combination of all three procedures. Therefore, the current systematic review demonstrated that EHF audiometry may be a beneficial procedure in a clinical assessment, although when available the procedure may be used in combination with conventional audiometry or DPOAE testing to increase sensitivity in the early detection of cochlear damage.

Deterioration of EHF-thresholds

The majority of the studies consulted in this systematic review (93.75%) investigated whether EHF audiometry may be a beneficial procedure for the early identification of cochlear damage by determining whether the EHF-thresholds deteriorated over time or in comparison to a control group. Four of these studies reported a deterioration in

the entire EHF-thresholds range (9000 Hz to 16 000 Hz - Abujamra et al., 2013; and 10 000 Hz to 16 000 Hz - Bayat et al., 2019; Gonzalez et al., 2017; Galarza-Delgado et al., 2018). Furthermore, three other studies also confirmed that the EHF-thresholds of the entire frequency range tested were affected by cochlear damage, except for the frequency of 16 000 Hz (Buchler et al., 2012; Li et al., 2019; Vignesh et al., 2015). The studies of Vignesh et al. (2015) and Li et al. (2019) determined the frequency range from 9 000 Hz to 14 000 Hz to be the most sensitive and valuable for the early detection and monitoring of cochlear damage, as the researchers found a significant difference in the results for these frequencies between the study and control group participants. However, Buchler et al. (2012) reported that frequencies from 11 000 to 14 000 Hz were the most sensitive when comparing the results of EHF audiometry of the study group with cochlear damage to that of the control group without cochlear damage.

An additional four studies highlighted 14 000 Hz and 16 000 Hz as specific frequencies to include for the early identification of cochlear damage. These frequencies were the most sensitive during EHF audiometry when assessing individuals who were at risk for cochlear damage (Laffoon et al., 2019; Ma et al., 2018; Mehrparvar et al., 2014; Riga et al., 2010). It should be noted that the study of Ma et al. (2018) only found frequencies 14 000 and 16 000 Hz to be significantly affected by cochlear damage in the age groups of 20 to 29 years and 30 to 39 years. The study of Mehrparvar et al. (2011) confirmed that 16 000 Hz was the most sensitive frequency to include for the early identification of cochlear damage. The study of Mehrparvar et al. (2011) was the only study that found 14 000 Hz not to be affected by cochlear damage in the participant group included in their study. The studies of Buchler et al. (2012) and Macca et al. (2015) reported that 14 000 Hz was the most important frequency to be

affected by cochlear damage. Although both these studies included 14 000 Hz as the most sensitive frequency, the study of Macca et al. (2015) identified 9000 Hz to 15 000 Hz as additional frequencies that were affected.

While the majority of the studies demonstrated that 14 000 Hz and 16 000 Hz were the most sensitive frequencies, two studies emphasised other EHFs that were most affected (Luders et al., 2014; Ma et al., 2018). The study of Luders et al. (2014) found only 9000 Hz in the right ears of participants to be significantly affected by cochlear damage. Although the researchers found poorer hearing thresholds in the participants of the study group with cochlear damage, no significant differences were found between the participant group with cochlear damage and to the control group without cochlear damage in their left ears at 9000 Hz, and both ears at 10 000 and 11 200 Hz. The reason for the differences in results may be that the study of Luders et al. (2014) used music students as participants and that the loudness and duration of exposure to music may not have exceeded the normative values to cause cochlear damage. However, the early detection of cochlear damage using EHF audiometry was not ruled out by Luders et al. (2014), as they hypothesised that longer years of music exposure may lead to different results being obtained in a follow-up study.

Furthermore, the study of Ma et al. (2018) identified other frequencies (11 200 Hz and 12 500 Hz for the 40 to 49 year old participants, and 10 000 and 11 200 Hz for the 50 to 59 year olds) as the most sensitive frequencies to be affected by NIHL. The study of Vasconcelos et al. (2018) evaluating the EHF thresholds of participants at risk of developing cochlear damage focused on temporary threshold shifts. Their results when conducting EHF audiometry for monitoring purposes demonstrated hearing threshold shifts at two- and six-months. At two months, there were EHF threshold

shifts in 50% and 60% in the right and left ears, respectively, of participants at risk for developing cochlear damage. The evaluation of EHF's at six months showed that there were hearing threshold shifts in both ears in 70% of participants (Vasconcelos et al., 2018).

Differences in EHF audiometry results between the different studies and participant groups may be due not only to the heterogeneity of the different population groups included in the different research projects, but also to different equipment and headphones used. Another factor contributing to differences in results between the different studies may have been the fact that although there are international standards for calibration of audiometric equipment in EHF's, these reference equivalent threshold sound pressure levels are limited to specific headphones (Valiente, Berrocal, et al., 2014). Despite the variations in the results of the studies, all the studies included in this systematic review concluded that EHF audiometry may be a potentially valuable. However, only seven studies (43.75%) agreed that EHF audiometry on its own may be useful for early identification and monitoring purposes while six studies (37.5%) recommended the use of EHF audiometry in combination with conventional audiometry. Furthermore, one study (6.25%) recommended the use of EHF audiometry in combination with DPOAE testing and another study (6.25%) recommended the combination with both conventional audiometry and DPOAE testing. These results suggest that EHF audiometry for early identification and monitoring of cochlear damage may be more beneficial when used in combination with conventional audiometry for optimal assessment of the frequency spectrum.

Effect of age on EHF audiometry

Six studies (37.5%) commented on the effect of age on the results of EHF audiometry. Five of these studies (31.25%) reported that progressive hearing loss and poorer hearing thresholds with an increase in age were revealed when using EHF audiometry (Buchler et al., 2012; Laffoon et al., 2019, Ma et al., 2018; Macca et al., 2015; Riga et al., 2010). Of these studies, it should be noted that Macca et al. (2015) concluded that EHF audiometry should be a useful procedure in the early detection of cochlear damage in individuals under the age of 30 years. Furthermore, the study of Ma et al. (2018) found that hearing thresholds of EHFs deteriorate with increasing age from 40 years onward, but especially from 50 years. Somma et al. (2008), whose study was not included in the systematic review, confirmed the research results of Ma et al. (2018) and suggested that EHF audiometry may be a useful procedure for the monitoring and early identification of cochlear damage in individuals younger than 40 years, as individuals' hearing abilities decrease with age. A more recent study confirmed these results. A noticeable deterioration in EHF thresholds was found from 30 years of age and more predominantly from 50 years of age (Wang et al., 2021). These results suggest an upper age limit for older individuals when assessing EHF thresholds. Age-related hearing loss develops initially at the highest frequencies and progresses towards the lower frequencies (Valiente et al., 2014).

The study of Abujamra et al. (2013) investigated paediatric participants and found no significant difference when comparing the hearing thresholds of the age groups older than five years and younger than five years, although the study highlighted that hearing thresholds are more reliably determined in participants older than five years (Abujamra et al., 2013). It has been reported that younger patients may struggle to concentrate and respond to subtle sounds, present difficulties with the placement of

earphones, and may experience fatigue as well as get distracted easily (Valiente et al., 2014). An additional study not included in the systematic review confirmed the reported difficulty of testing participants under the age of five years old (Hemmingsen et al., 2021). This study suggested that participants older than five years presented with better EHF thresholds than participants under the age of five years who may have limited cooperation skills.

Clinical implications

The studies included in the current systematic review all supported the use of EHF audiometry as a clinically valuable procedure for the early identification and monitoring of cochlear damage. Incorporating EHF audiometry in the clinical assessment of individuals at risk of developing cochlear damage may be a useful procedure for the early identification and monitoring of deteriorating hearing thresholds in the EHFs, and enable the audiologist to be proactive in decreasing such a risk. Clinicians should note that EHF audiometry may be particularly useful in younger individuals when assessing EHF-thresholds in individuals with NIHL, when monitoring ototoxicity, and in patients with diabetes or autoimmune diseases. Identification of risk at a younger age could limit cochlear damage, as hearing thresholds deteriorate with age especially from 40 years of age. Many studies investigating the use of EHF audiometry on participants at risk for developing cochlear damage reported the entire EHF-threshold range to be deteriorating. The majority (seven) of the studies included, however, determined that 14 000 Hz and/or 16 000 Hz were the most sensitive to cochlear damage, especially in participants with NIHL. Due to variation in equipment used to measure EHF's, no conclusion could be reached on preferred equipment. It is suggested that individuals

should be tested with the same equipment over time for intra-monitoring of EHFs to increase test-retest reliability.

Strengths and limitations of the study

The current systematic review presented with some strengths. The review was conducted in the light of the currently insufficient evidence to support the value of EHF audiometry in the early detection and monitoring of cochlear damage. The study attempted to summarize and review all evidence in the literature on early identification and monitoring of cochlear damage using EHF audiometry that was available from 2010 until the 11th of August 2021. This allowed the researchers to demonstrate the potential contribution of EHF audiometry to the clinical assessment of auditory functioning. Another strength that was identified is that the study used the PRISMA-P guidelines as a structure for the systematic review, which allowed reliable and valid reporting of the evidence. There were some limitations identified in the current study, such as the clinical heterogeneity that was present in the included studies. Consequently, it was difficult to conduct a meta-analysis due to the variety of outcomes that were not directly comparable. Furthermore, the studies that were published after the 11th of August 2021 or were not published in English were not included in this systematic review and therefore, some valuable contributions to the field of the study might have been excluded.

In conclusion, this systematic review has validated that EHF audiometry may be valuable for the clinical assessment of cochlear damage, although when available the procedure may be used in combination with conventional audiometry or DPOAE testing to increase the possibility of early detection of cochlear damage. For monitoring cochlear damage, the majority of the studies included in this systematic review

concluded that EHF audiometry may be more beneficial for intra-individual monitoring, as there are still no specific standard international norms available for EHF thresholds. By including EHF audiometry as part of the audiometric test battery in individuals at risk of cochlear damage, especially in younger individuals, practitioners will be able to identify and monitor cochlear damage earlier to prevent further deterioration of thresholds at conventional frequencies.

4. DISCUSSION AND CONCLUSION

Chapter aim: *The chapter aims to discuss the results and how the analysis of recent research studies through a systematic review may contribute to a clinician's role in early identification and monitoring of cochlear damage using EHF audiometry. The chapter also attempts to evaluate and highlight the clinical implications, identify strengths and limitations, and to make appropriate recommendations regarding future research.*

4.1 Summary of main findings

Several research projects have been conducted to demonstrate that EHF audiometry may be beneficial for the early identification and monitoring of cochlear damage. Despite previous research recommendations, EHF audiometry is not yet being used as a routine clinical assessment in at-risk individuals (Valiente, 2016). As various research studies have been independently conducted, the present systematic review aimed to combine these studies and integrate their findings to investigate the possibility of a collective conclusion regarding the clinical value of EHF audiometry for the early detection and monitoring of cochlear damage.

The first important factor to note in this systematic review is that the researchers included different types of exposure that cause cochlear damage and not just one specific exposure. The reason why the studies included in this study focused primarily on the early identification and monitoring of cochlear damage using EHF audiometry and not necessarily on only one specific pathology is due to the lack of publications a particular population group such as NIHL, ototoxicity, diabetes, and autoimmune diseases. However, this did not influence the current systematic review's aim, as it provided insight into the available literature and recommendations with regard to future research in this area. Through the collation of relevant evidence available using the predetermined criteria, the systematic review demonstrated what current literature has reported on the value of EHF audiometry in early identification and monitoring of cochlear damage.

The second important factor to note is that the studies included in this systematic review were heterogeneous in nature regarding the type of exposure, intensity, and duration of exposure to various factors that may cause cochlear damage. In the NIHL population, the type of noise exposure and the participants included occupational noise exposure, recreational firearm users, active-duty soldiers, civilian pilots, and music students. The majority (eight) of the studies included in this current study evaluated participants exposed to noise and at risk of developing NIHL. During the investigation, it was clear that 14 000 Hz and 16 000 Hz were the most sensitive and affected EHFs during noise exposure (Buchler et al., 2012; Laffoon et al., 2019; Riga et al., 2010; Ma et al., 2018; Macca et al., 2014; Mehrparvar et al., 2011; Mehrparvar et al., 2014. Riga et al. (2010) was one of the studies that found 14 000 Hz and 16 000 Hz to be the most sensitive for cochlear damage. Although the study highlighted that these two frequencies should be focused on during early identification and monitoring of cochlear damage, the study suggested that EHF audiometry may only be beneficial in individuals exposed to cochlear damage for less than 10 years. The study reported that conventional audiometry may be more effective than EHF audiometry in individuals exposed to cochlear damage for more than 10 years (Riga et al., 2010).

One study did, however, disagree with these findings. The study of Luders et al. (2014) found only 9000 Hz in the right ears of participants to be significantly affected by noise exposure. The differences in results may be that the study of Luders et al. (2014) used music students as participants and that the loudness and duration of exposure to music may not have exceeded the normative values of permissible noise exposure as found in industry. However, the early detection of cochlear damage using EHF audiometry was not ruled out by the study of Luders et al. (2014). They hypothesised that longer years of music exposure might lead to different results being obtained in a follow-up study as continuous exposure may lead to a greater hearing loss. It should also be noted that the study of Ma et al. (2018) only found frequencies 14 000 and 16 000 Hz to be significantly affected by cochlear damage in the age groups of 20 to 29 years and 30 to 39 years. The study of Ma et al. (2018) identified other frequencies (11 200 Hz and 12 500 Hz for the 40 to 49-year-old participants, and 10 000 and 11 200 Hz for the 50 to 59-year-olds) as the most sensitive frequencies to be affected by NIHL. Clinicians assessing and monitoring individuals exposed to noise may utilize EHF audiometry, as it can be beneficial for the early identification of cochlear damage

before the conventional frequencies are affected. Early detection and monitoring of cochlear damage using EHF audiometry in individuals exposed to noise may be beneficial as these individuals can be counselled on the long-term effect that noise exposure may have and the importance of using hearing protection prior to damage occurring at the most important speech frequencies. Clinicians can also focus on 14 000 Hz and 16 000 Hz as the majority of the studies demonstrated that these frequencies were the first to be affected during such exposure.

The treatment regime for participants receiving ototoxic medication included cisplatin, amikacin, and methadone maintenance treatment. Only four of the studies included in the systematic review investigated ototoxicity and how cochlear damage may either be detected early or monitored (Abujamra et al., 2013; Bayat et al., 2019; Vasconcelos et al., 2018; Yu et al., 2014). Using EHF audiometry to monitor ototoxicity in individuals has been proven to be effective. However, monitoring individuals exposed to ototoxicity using EHF audiometry is a non-standardised procedure, and one not well established in standard clinical care (Lord, 2019). All the studies included in the current systematic review agreed that EHF audiometry might be a useful procedure for the early detection and monitoring of cochlear damage. Significant variations were, however, noted in the methods used to determine cochlear damage, the participants were tested only once in some of the studies, while other researchers used sequential testing for monitoring purposes. The authors also interpreted and reported the results differently. Some evaluated the sensitivity of EHF audiometry for identifying cochlear damage; others evaluated the possible deterioration in the individual's EHF thresholds.

It was evident from this systematic review that the participants exposed to ototoxic medication, cochlear damage was present over the entire EHF range from 9000 Hz to 16 000 Hz (Abujamra et al., 2013; Bayat et al., 2019). For monitoring ototoxicity, the study of Vasconcelos et al. (2018) concluded that EHF audiometry was the most sensitive procedure when conducted at two- and six-months intervals. However, conventional audiometry was also sensitive in detecting threshold shifts at a six-month interval (Vasconcelos et al., 2018). Another study found that EHF audiometry was sensitive when monitoring participants exposed to ototoxic medication alongside DPOAE testing and recommended that both procedures should be used in

combination (Yu et al., 2014). However, the current systematic review suggests that EHF audiometry should be used in combination with conventional audiometry instead, as DPOAE testing cannot assess the entire frequency range, which is essential for the early identification of cochlear damage. Although the procedure has proven to be effective in the past, EHF audiometry may potentially be advantageous and should be used more regularly in patients exposed to ototoxic medication. By monitoring these patients using EHF audiometry, the clinician can identify cochlear damage in the EHFs earlier. After that, the patient, family, and medical team can then be counselled on either adjusting the harmful ototoxic medication to minimise further cochlear damage or making an informed decision concerning the treatment that may follow living with a hearing loss.

Participants in some studies were diagnosed with Primary Sjögren Syndrome and Rheumatoid Arthritis, while other studies investigated patients with type 2 DM. In these population groups, there is very little evidence that exists. Clinicians need to understand that these types of exposures also cause outer hair cell damage within the cochlea. In the type 2 DM population group, the studies of Vignesh et al. (2015) and Li et al. (2019) determined the frequency range from 9 000 Hz to 14 000 Hz to be the most sensitive and valuable for the early detection and monitoring of cochlear damage, as the researchers found a significant difference in the results for these frequencies between the study and control group participants. In the participants diagnosed with autoimmune diseases such as Primary Sjögren Syndrome and Rheumatoid Arthritis, the researchers suggested that EHF audiometry may be beneficial in combination with conventional audiometry as both procedures showed poorer hearing thresholds for the study groups than for the control groups (Galarza-Delgado et al., 2018; Gonzalez et al., 2017). These studies reported that by including EHF audiometry in a clinical assessment of patients diagnosed with type 2 DM and autoimmune diseases, clinicians might be able to identify cochlear damage before the conventional frequencies are affected. Long-term follow-up assessments should be considered for these individuals to monitor the changes in their EHF thresholds. More research studies should be conducted in these population groups to draw a more accurate conclusion and to demonstrate in longitudinal studies the impact and benefit that EHF audiometry has.

The third factor to note is another form of heterogeneity that involved diverse equipment (audiometers and headphones) used for conventional audiometry and different equipment that were also used across the studies for determining EHF thresholds. Only four of the 16 studies used similar audiometer (Interacoustic AC 40 audiometer) and only five of the studies used similar headphones (Sennheiser HAD 200). Due to the variety of equipment used to measure EHFs, no conclusion could be reached on the preferred equipment. However, when individuals are monitored within themselves using similar equipment as their previous assessment, the clinician can compare the results to determine if there were any threshold shifts present. Using similar equipment consistently during an individual's follow-up assessments may decrease the chance of inaccurate thresholds and increase test-retest reliability. In addition, a previous study evaluating the test-retest reliability of EHF audiometry for periodic monitoring demonstrated that EHF audiometry might be regarded as reliable, as the hearing thresholds at the retest were within the American Speech-Language-Hearing Association criteria (ASHA 1994) for significant threshold shift (Frank et al., 2001). The evaluation of the test-retest reliability emphasised and confirmed the results of this systematic review that EHF audiometry proved to be a reliable procedure for intra-individual monitoring and may improve the clinical value of this procedure for the monitoring of cochlear damage (Ahmed et al., 2001; Frank et al., 2001).

All of these elements causing heterogeneity in the systematic review complicated the process of comparing the studies and formulating a conclusion about the usefulness of EHF audiometry for the early identification and monitoring of cochlear damage. These differences might also have contributed to the diverse results reported in the studies (Gagnier et al., 2012). Differences in EHF audiometry results between the different studies and participant groups may be due, not only to the heterogeneity of the different population groups and the equipment included in the different research projects but also because there are no specific international standards for calibration of audiometric equipment in EHF's, the reference equivalent threshold sound pressure levels are limited to specific headphones (Valiente, Berrocal, et al., 2014). Despite the variations in the results of the studies, all the studies included in this systematic review concluded that EHF audiometry might be a potentially valuable clinical procedure for early identification and monitoring of cochlear damage. These studies demonstrated that including EHF audiometry as part of the standard clinical assessment either to be

used independently or in combination with conventional audiometry and/or DPOAE testing may be beneficial.

The final important factor to note is that age-related hearing loss develops initially at the highest frequencies and progresses towards the lower frequencies (Valiente et al., 2014). In the current systematic review, five studies (31.25%) revealed progressive hearing loss and poorer hearing thresholds with an increase in age when using EHF audiometry (Buchler et al., 2012; Laffoon et al., 2019, Ma et al., 2018; Macca et al., 2015; Riga et al., 2010). Both the studies of Macca et al. (2015) and Ma et al. (2018) concluded that EHF audiometry could be a useful procedure in the early detection of cochlear damage in individuals under the age of 30 years and 40 years, respectively, as individuals' hearing abilities decrease with age. A more recent study not included in the systematic review confirmed these results. A noticeable deterioration in EHF thresholds was found from 30 years of age and more prominently from 50 years of age (Wang et al., 2021). These results suggest that clinicians should be aware that age may be a factor during EHF audiometry and, therefore, an upper age limit of 30, especially 40 years is recommended when assessing the EHF thresholds of these individuals at risk of developing cochlear damage.

The study of Abujamra et al. (2013) investigated paediatric participants and found no significant difference when comparing the hearing thresholds age groups older than five years and younger than five years. However, the study highlighted that hearing thresholds are more reliably determined in participants older than five years (Abujamra et al., 2013). It has been reported that younger patients may struggle to concentrate and respond to subtle sounds, present difficulties with the placement of earphones, and may experience fatigue and get distracted easily (Valiente et al., 2014). An additional study not included in the systematic review confirmed the reported difficulty of testing participants under the age of five (Hemmingsen et al., 2021). This study suggested that participants older than five years presented with better EHF thresholds than participants under the age of five years who may have limited cooperation.

Focusing on a collective conclusion regarding the valuable use of EHF audiometry in early identification of cochlear damage, the current systematic review found seven studies (43.75%) to support EHF audiometry in isolation as a beneficial procedure (Abujamra et al., 2013; Bayat et al., 2019; Ma et al., 2018; Mehrparvar et al., 2011;

Mehrparvar et al., 2014; Riga et al., 2010; Vignesh et al., 2015). Following six studies (37.5%) that demonstrated EHF audiometry may be valuable in a clinical assessment in combination with conventional audiometry (Buchler et al., 2012; Galarza-Delgado et al., 2018; Gonzalez et al., 2017; Luders et al., 2014; Macca et al., 2018; Vasconcelos et al., 2018). Two studies (12.5%) recommended the combination of EHF audiometry and DPOAE testing (Li et al., 2019; Yu et al., 2014), and only one study (6.25%) recommended the combination of all three procedures (Laffoon et al., 2019). The systematic review suggests that clinicians may use EHF audiometry for early identification of cochlear damage and may be included in a clinical assessment for monitoring purposes to assess the entire frequency range from 250 Hz to 16 000 Hz. The study did not view DPOAE testing as a significant procedure compared to EHF audiometry as only three of the 16 studies recommended the combination of these procedures. As well as the fact that researchers argue that EHF audiometry can assess frequencies higher than DPOAE testing. This may allow a broader range of the frequency spectrum above 8 000 Hz to be considered, increasing the possibility of early detection of cochlear damage (Yu et al., 2014).

Previously researchers argued that EHF audiometry provided no additional information to assist conventional audiometry and was not a valuable procedure for early detection and monitoring of cochlear damage (Balatsouras et al., 2005; Schumziger et al., 2007). Recently, technology and clinical devices have become more advanced and are more sensitive concerning test-retest reliability in intra-individual monitoring (Majidpour et al., 2021; Somma et al., 2008). Therefore, the current systematic review's positive results demonstrated that EHF audiometry might be advantageous to include in a clinical assessment.

Combining the results of the different studies in the review, the studies investigating EHF audiometry that only tested the participants once and compared the results of the exposed group against a control group without exposure found seven studies (43.75%) to support the valuable use of EHF audiometry as an independent procedure for early identification of cochlear damage (Abujamra et al., 2013; Bayat et al., 2019; Ma et al., 2018; Mehrparvar et al., 2011; Mehrparvar et al., 2014; Riga et al., 2010; Vignesh et al., 2015). These research studies found EHF audiometry to be more sensitive in early detection of cochlear damage than the four studies (25%) that suggested the combination of conventional audiometry (Galarza-Delgado et al., 2018;

Gonzalez et al., 2017; Luders et al., 2014; Macca et al., 2018). One study (6.25%) recommended that EHF audiometry should be combined with DPOAE testing (Li et al., 2019), and one study (6.25%) suggested that all three test procedures should be used in combination for the early detection of cochlear damage (Laffoon et al., 2019). The results of the current systematic review demonstrate that EHF audiometry may be regarded as the most useful procedure for the early identification of cochlear damage. Individuals may be assessed or screened using EHF audiometry independently as it is less time-consuming when a patient cannot endure a longer evaluation time.

Two research studies (12.5%) that performed follow-up assessments on individuals at risk of developing cochlear damage demonstrated that EHF audiometry might be more useful with providing additional information to conventional audiometry (Buchler et al., 2012; Vasconcelos et al., 2018). Only one (6.25%) of the studies recommended EHF audiometry combined with DPOAE testing (Yu et al., 2014). In the current systematic review, the studies concluded that EHF audiometry might be useful for monitoring purposes when comparing an individual's hearing thresholds over time. Intra-monitoring of the patient's thresholds over time will enable clinicians to observe whether any thresholds shifts occurred effectively. These studies also suggested that, although EHF audiometry may be a useful procedure, it may be more beneficial to use the procedure in combination with conventional audiometry for optimal assessment of the frequency spectrum.

Concerning the sensitivity of EHF audiometry identifying cochlear damage, four studies (25%) found the procedure to be most sensitive and successful in identifying cochlear damage compared to the other procedures (Abujamra et al., 2013; Bayat et al., 209; Ma et al., 2018; Mehrparvar et al., 2014). However, the systematic review recognised that two other studies (12.5%) recommended that EHF audiometry may be useful in combination with conventional audiometry (Galarza-Delgado et al., 2018; Gonzalez et al., 2017), two studies (12.5%) DPOAE testing (Li et al., 2019; Yu et al., 2014), and one study (6.25%) recommended the combination of all three procedures (Laffoon et al., 2019). Therefore, the current systematic review demonstrated that EHF audiometry was the most beneficial procedure and may be included in a clinical assessment for early identification and monitoring of cochlear damage. Although,

when available, the procedure may be combined with conventional audiometry or DPOAE testing to increase sensitivity in the early detection of cochlear damage.

4.2 Clinical implications

The current systematic review supports audiologists to be more informed about the benefits of including EHF audiometry for early identification and monitoring of individuals at risk for cochlear damage. Incorporating EHF audiometry in the clinical assessment of individuals at risk of developing cochlear damage may be a valuable procedure for early identification and monitoring of deteriorating hearing thresholds in the EHFs and enabling the audiologist to be proactive in decreasing such a risk. Performing EHF audiometry may assist the clinician in counselling the individual to prevent hearing from decreasing to the conventional frequencies or to prepare the individual for specific difficulties that may arise with cochlear damage.

Clinicians should note that EHF audiometry may be particularly useful in younger individuals when assessing EHF thresholds in individuals with NIHL, monitoring ototoxicity, and in patients with diabetes or autoimmune diseases. Identification of risk at a younger age could limit cochlear damage, as hearing thresholds deteriorate with age, especially from 40 years of age. Many studies investigating the use of EHF audiometry on participants at risk for developing cochlear damage, such as individuals exposed to ototoxic medication or diagnosed with either type 2 DM or an autoimmune disease reported the entire EHF-threshold range to be deteriorating. However, the majority (seven) of the studies included, concluded that 14 000 Hz and 16 000 Hz were the most sensitive to cochlear damage, especially in participants with NIHL. When performing EHF audiometry on individuals exposed to NIHL, it may be beneficial to focus on the EHF threshold shifts at the frequencies of 14 000 Hz and 16 000 Hz for early identification and monitoring.

The studies included in the current systematic review all supported EHF audiometry as a clinically valuable procedure for early identification and monitoring of cochlear damage. EHF audiometry in an audiometric test battery may be more advantageous for the early detection of cochlear damage compared to conventional audiometry and

DPOAE testing. Although, when monitoring the EHF thresholds of these individuals at risk for cochlear damage, EHF audiometry may be more beneficial in combination with conventional audiometry as this procedure is still regarded as the gold standard of assessing for a hearing loss. As the studies included in the systematic review utilised many different types of equipment and there are still no specific international standard norms for EHF thresholds, EHF audiometry may be beneficial when monitoring individuals over time utilising similar equipment as the baseline audiometric assessment.

4.3 Critical evaluation

The strengths and limitations of the study were evaluated and indicated below:

4.3.1 Strengths of the study

The current systematic review presented with some strengths. The review was conducted in light of the currently insufficient evidence to support the value of EHF audiometry in the early detection and monitoring of cochlear damage. The study attempted to summarize and review all evidence in the literature on early identification and monitoring of cochlear damage that was available from 2010 until the 11th of August 2021. This allowed the researchers to demonstrate the potential contribution of EHF audiometry to the clinical assessment of auditory functioning. Another identified strength is that the study used the PRISMA-P guidelines as a structure for the systematic review, which allowed reliable and valid reporting of the evidence.

4.3.2 Limitations of the study

Some limitations were identified in the current study, such as the clinical heterogeneity present in the studies included. The studies included varied with regards to the type, intensity, and duration of exposure and different equipment that was used such as the audiometers and headphones. Consequently, it was difficult to describe and compare all the main concepts and conduct a meta-analysis due to the variety of outcomes that were not directly comparable. Furthermore, the studies that were not published in English or published after the 11th of August 2021 were not included in this systematic review and therefore, some valuable contributions to the field of the study might have been excluded.

4.4 Future research

The current systematic review included 16 studies that were heterogeneous in terms of study designs, population groups, exposure type and duration, and the equipment used. These differences may, however, be important in identifying which method will best aid future researchers in conducting their studies. In the future, studies may benefit more by defining and outlining the methodology. Therefore, including more studies using similar procedures may ensure that the results and data of the studies may be directly compared and combined to determine a definitive answer in the reliability and value of EHF audiometry. Ultimately, the same method across studies could enhance the reliability of EHF audiometry research in the early identification and monitoring of cochlear damage.

The lack of specific standard international norms of EHF-thresholds limits EHF audiometry's potential to identify and monitor cochlear damage in at-risk individuals. Therefore, future researchers should focus on and monitor an individual's EHF threshold within themselves, over time. These individuals should be tested with the same equipment at their follow-up assessment, as this may decrease the possibility of the equipment leading to inaccurate results. Moreover, it is suggested that larger sample sizes, control groups of the participants and longitudinal studies are needed to demonstrate EHF audiometry's long-term effect and potential in early detection and monitoring of cochlear damage. As age-related hearing loss develops initially at the highest frequencies and progresses towards the lower frequencies, the hearing thresholds decrease with an increase in age (Valiente et al., 2014). It is recommended that future studies focus on younger participants under the age of 50 years or researchers may group the participants in different age groups to demonstrate the effect that age has on the EHFs. Some of the current studies had limitations as they could not test frequencies above 16 000 Hz due to equipment limitations. It is suggested that future studies should focus on EHFs from 9 000 Hz to 16 000 Hz as most studies only tested participants up until 16 000 Hz.

Although the study provides promising evidence that EHF audiometry may be a useful procedure in assessing individuals at risk of cochlear damage, there is still a lack of evidence to draw a definite conclusion. Therefore, more research should be conducted on the value of EHF audiometry for the early identification and monitoring of cochlear damage. Furthermore, as there are limited studies on different types of cochlear

damage, more research of the same population groups are required so that the results of the studies can be directly compared to one another. When investigating populations such as individuals at risk for NIHL, the researchers may focus on 14 000 Hz and 16 000 Hz as the studies highlighted these two frequencies to be primarily affected during noise exposure.

4.5 Conclusion

This systematic review has validated that EHF audiometry may be beneficial in the clinical assessment of cochlear damage for early identification and monitoring. EHF audiometry is a sensitive procedure that can detect threshold shifts in frequencies from 9000 Hz to 16 000 Hz. The current study has proven that EHF audiometry may be beneficial in the early detection and monitoring of cochlear damage in individuals at risk, such as individuals exposed to noise, ototoxic medication, and patients diagnosed with type 2 DM and autoimmune diseases. Despite the heterogeneity of the different studies included, all studies agreed that EHF audiometry is a valuable procedure for the early detection and monitoring of cochlear damage, either independently or in combination with another test. These results suggest that EHF audiometry for early identification and monitoring of cochlear damage may be more beneficial when combined with conventional audiometry for optimal assessment of the frequency spectrum. By including EHF audiometry as part of the audiometric test battery, especially in younger individuals, practitioners may be able to identify cochlear damage earlier and monitor in an attempt to preserve the hearing of these individuals at risk.

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6. APPENDICES

APPENDIX A: ETHICAL CLEARANCE FORM

Faculty of Humanities
Fakulteit Geesteswetenskappe
Lefapha la Bomotho

Humanities 100

11 September 2020

Dear Miss N Troskie

Project Title:	Early identification and monitoring of cochlear damage using extended high- frequency audiometry: A systematic review
Researcher:	Miss N Troskie
Supervisor(s):	Prof ME Soer
	Prof L Pottas
Department:	Speech Language Path and Aud
Reference number:	16059523 (HUM055/0720)
Degree:	Masters

Thank you for the application that was submitted for ethical consideration.

The Research Ethics Committee notes that this is a literature-based study and no human subjects are involved.

The application has been **approved** on 27 August 2020 with the assumption that the document(s) are in the public domain. Data collection may therefore commence, along these guidelines.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. However, should the actual research depart significantly from the proposed research, a new research proposal and application for ethical clearance will have to be submitted for approval.

We wish you success with the project.

Sincerely,

Prof Innocent Pikirayi
Deputy Dean: Postgraduate Studies and Research Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: PGHumanities@up.ac.za

Fakulteit Geesteswetenskappe
Lefapha la Bomotho

Research Ethics Committee Members: Prof I Pikirayi (Deputy Dean); Prof KL Harris; Mr A Roos; Dr A-M de Beer; Dr A dos Santos; Ms KT Govinder Andrew; Dr P Guduza; Dr E Johnson; Prof D Maree; Mr A Mohamed; Dr I Naomé; Dr C Puttergill; Prof D Reyburn; Prof M Soer; Prof E Tajard; Prof V Thebe; Ms B Tsebe; Ms D Mokalapa

APPENDIX B: SUMMARY OF THE CHARACTERISTICS OF INCLUDED STUDIES

First author and year	Title	Aim	Study design	Study population
Riga, 2010	Screening protocols for the prevention of occupational noise-induced hearing loss: The role of conventional and extended high frequency audiometry may vary according to the years of employment	Identify the potential role of extended high-frequency (EHF) audiometry in screening protocols for early diagnosis of occupational noise-exposure	Prospective study, cohort study	Study group (SG): Industrial workers for >10 years SG: Industrial workers for 11 to 20 years SG: Industrial workers for 21 to 33 years
Mehrparvar, 2011	High-frequency audiometry: A means for early diagnosis of noise-induced hearing loss	Compare the hearing threshold and frequency of hearing loss in conventional and EHF audiometry in workers exposed to noise.	Historical, cohort study	SG: Textile workers Control group (CG): Workers from the same factories
Buchler, 2012	Extended frequency range hearing thresholds and otoacoustic emissions in acute acoustic trauma	Evaluate the value of EHF audiometry when monitoring acute acoustic trauma	Controlled prospective clinical study, cohort study	SG: Active-duty soldiers who experienced acute acoustic trauma CG: Active-duty soldiers who experienced no acute acoustic trauma
Abujamra, 2013	The use of high-frequency audiometry increases the diagnosis of asymptomatic hearing loss in paediatric patients treated with cisplatin–based chemotherapy	Evaluate paediatric patients being treated with cisplatin using EHF audiometry to determine if hearing damage could be detected at an earlier stage.	Transversal study, cross-sectional study	SG: Patients treated with cisplatin
Luders, 2014	Music students: conventional hearing thresholds and at high frequencies	Evaluate the hearing thresholds of music students and non-music students from 250 Hz to 16 000 Hz in order to determine if EHF audiometry is a useful tool for early detection of hearing loss.	Retrospective observational cohort.	SG: Music students CG: Non-music students
Macca, 2014	High-frequency hearing thresholds: effects of age, occupational ultrasound and noise exposure	Evaluate the effects of age, ultrasounds and noise on EHF's	Not indicated	SG: Participants exposed to noise CG: Participants without noise exposure
Mehrparvar, 2014	Conventional audiometry, extended high-frequency audiometry and DPOAEs for early diagnosis of NIHL	Compare three different tests for early detection of noise-induced hearing loss (NIHL)	Prospective cross-sectional study	SG: Participants exposed to noise CG: Participants without noise exposure
Yu, 2014	Comparison of the effectiveness of monitoring cisplatin-induced ototoxicity with extended high-frequency pure tone audiometry or distortion-product otoacoustic emission	The first aim of the study was to investigate which of EHF audiometry and distortion product otoacoustic emission (DPOAE) testing are more sensitive to detect cisplatin-induced ototoxicity.	Prospective study	SG: Chemotherapy patients with cisplatin treatment
Vignesh, 2015	Identifying early onset of hearing loss in young adults with diabetes mellitus type 2 using high-frequency audiometry	Establish EHF audiometry as a useful tool in early identifying hearing loss in type 2 diabetes mellitus (DM)	Not indicated	SG: Type 2 DM. CG: Health participants
Gonzalez, 2017	Extended high-frequency audiometry as early detection of hearing loss in primary Sjögren syndrome	Demonstrate the usefulness of EHF audiometry in the audiological assessment as a tool for early detection of hearing loss in patients with primary Sjögren syndrome.	Comparative, cross-sectional study	SG: Sjögren syndrome patients. CG: Healthy participants.

Galarza-Delgado, 2018	Early hearing loss detection in rheumatoid arthritis and primary Sjogren syndrome using extended high-frequency audiometry	Evaluate the hearing of rheumatoid arthritis and primary Sjogren syndrome patients and compare them with a healthy control group and with each other.	Comparative cross-sectional study	SG: Rheumatoid arthritis patients SG: Primary Sjogren syndrome patients CG: Healthy participants
Ma, 2018	Extended high-frequency audiometry (9–20 kHz) in civilian pilots	Investigating the usefulness of EHF audiometry to evaluate civilian pilots hearing status.	Observational cross-sectional study	SG: Civilian pilots CG: Healthy participants without noise exposure
Vasconcelos, 2018	Sequential analysis as a tool for detection of amikacin ototoxicity in the treatment of multidrug-resistant tuberculosis	Examine early detection of amikacin-induced ototoxicity in a population treated for multidrug-resistant tuberculosis (MDR-TB)	Longitudinal prospective cohort study	SG: MDR-TB patients
Bayat, 2019	Early diagnosis of hearing loss in patients under methadone maintenance treatment	Investigating the value of EHF audiometry in detecting early onset of hearing loss in methadone maintenance treatment patients and compare them with a group with similar age and gender	Analytic cross-sectional study	SG: Patients who received methadone maintenance treatment CG: Healthy participants
Laffoon, 2019	Conventional audiometry, extended high-frequency audiometry, and DPOAEs in youth recreational firearm users	Determine if EHF audiometry are useful as early indicators of cochlear damage from recreational firearm impulse noise exposure in youth firearm users.	Quantitative cross-sectional descriptive pilot study	SG: Youth recreational firearm users
Li, 2019	Early detection of hearing impairment in type 2 diabetic patients	Evaluate the application effects of EHF audiometry and DPOAE testing in early detection of hearing impairment in type 2 DM patients.	Not indicated	SG: Type 2 DM participants. CG: 60 healthy participants

APPENDIX C: SUMMARY OF THE EXTRACTED DATA

First author and year	Test parameters/ equipment	UNIVERSITEIT VAN PRETORIA UNIVERSITY OF PRETORIA YUNIBESITHI YA PRETORIA	Conclusion	Limitations and future research
Riga, 2010	EHF's: 10000, 11 200, 12 500, 14 000, 16 000, 18 000 Hz Audiometer: Amplaid A321 Headphones: Sennheiser HDA 200 Sound-proof booth	Noise exposure: 90 to 110 dBA Mean duration: 11.8 +/- 6.9 years	Hearing screening protocols could become more effective by focusing on different frequency ranges according to the work duration as well as by implementing extended high-frequency (EHF) audiometry in assessing workers that are exposed to noise <10 years.	Future research: Further research is required to conclude that EHF audiometry in screening protocols are a useful tool for early detection of NIHL mainly in workers with <10 years exposure.
Mehrparvar, 2011	EHF's: 10 000, 12 000, 14 000, 16 000 Hz Audiometer: Interacoustic AC40 Headphones: Kross, R/80 Sound-proof booth	SG: Mean continuous noise of 89.07 dBA, mean employment duration of 10.72 years CG: Mean noise exposure 75.60 dBA, mean employment duration of 9.59 years	EHF audiometry is more sensitive than conventional audiometry in early detection and may be useful in early diagnosis of noise-induced hearing loss (NIHL). Therefore, prevent hearing loss to occur in the lower frequencies particularly the speech frequencies.	Limitations: Could not assess frequencies 18 000 Hz and 20 000 Hz due to equipment limitations. The number of female participants were less than male participants.
Buchler, 2012	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000, 18 000, 20 000 Hz Audiometer: GSI 61 Headphones: Sennheiser HDA200 Sound-proof booth	Mean estimated distance from the acoustic trauma source: 1.3 m	Conventional audiometry is still the most important to monitor acute acoustic trauma. If possible, it should be complemented with EHF audiometry especially frequencies 11 000 to 14 000 Hz.	Not indicated
Abujamra, 2013	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Siemens Headphones: HDA 200	Mean dose of cisplatin received: 494.3 mg/m2 (range: 240 to 720 mg/2). Median time interval between the end of treatment and the assessment was 3 years (range: 3 months to 17 years)	EHF audiometry is more sensitive to detect hearing loss than conventional audiometry and DPOAE testing. EHF audiometry may be routinely used in clinical practice or research protocols to detect early cochlear damage in young patients.	Limitation: The small sample size of participants restricted the conclusion on the influence of certain risk factors such as age and the use of carboplatin or cranial radiotherapy exposure.
Luders, 2014	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Madsen, model ITERA II Headphones: HDA 200 Sound-proof booth	Musical practice varied from 1 to 41 years, with a mean of 11.17 years.	EHF audiometry demonstrated that periodic evaluation of EHF thresholds in music students may be a useful tool in early detection of hearing loss.	Not indicated
Macca, 2014	EHF's: 9000, 10 000, 11 000, 12 000, 13 000, 14 000, 15 000, 16 000, 17 000, 18 000Hz Audiometer: Labat Audiopack Headphones: Sennheiser HD 500 Sound proof-booth	Mean noise exposure: 13.17 +/- 8.02 years, > 80 dBA	In addition to conventional audiometry, EHF audiometry may be a useful tool for early detection of NIHL in young workers under the age of 30 years.	Limitation: The levels and time of ultrasound and noise exposure were gathered retrospectively from the management of the factories and was little documented.
Mehrparvar, 2014	EHF's: 10 000, 12 000, 14 000, 16 000 Hz Audiometer: AC 40 Headphones: R80 Sound- proof booth	SG: Mean noise exposure of 91.97+/- 4.15 dBA (time weighted average-8 hours), mean work duration of 10.76 +/- 5.52 years	EHF audiometry demonstrated to be the most sensitive and useful test for early detection of hearing loss in workers exposed to hazardous noise compare to conventional audiometry and distortion product	Limitations: Inherent limitations of all cross-sectional studies. Participants were all male therefore the results cannot be extrapolated to females. Could not assess frequencies 18 000 and

			otoacoustic emission (DPOAE) testing.	20 000 Hz due to equipment limitations Future research: Prospective studies are required to establish that a certain test will present with abnormal thresholds sooner than another test.
Yu, 2014	EHF's: 9000, 11 200, 12 500, 14 000, 16 000, 18 000 and 20 000 Hz Audiometer: Interacoustic AC40	Cycles of chemo therapy: 5 participants: 6 cycles 2 participants: 5 cycles 2 participants: 4 cycles 1 participant: 2 cycles	Both EHF audiometry and DPOAE testing displayed similar sensitivity in detecting ototoxicity but did not produce comparable results in all cases. Therefore, EHF audiometry and DPOAE testing complement one another and should be used simultaneously in every cycle of chemo therapy to ensure early detection of ototoxicity	Limitation: Small sample size of the population as not everyone completed the follow-up assessments. Future research: Greater sample size of participants are required to distinguish the usefulness of EHF audiometry in the monitoring of cisplatin-induced ototoxicity.
Gonzalez, 2017	EHF's: 10 000, 12 000, 14 000 and 16 000 Hz Audiometer: Interacustic AC40 Sound-proof booth	Degree of disease activity as classified by ESSPRI scale: 17(27.0%) participants- mild 26 (41.3%) participants- moderate 20 (31.7%) participants- severe	There is an association between Sjogren syndrome patients and sensorineural hearing loss (SNHL) in extended high frequencies. EHF audiometry demonstrated usefulness in assessment of these patients for early identification of hearing loss.	Future research: Larger group of participants is needed as well as long-term follow-up of patients after they have received sufficient control of the autoimmune disease. To support the conclusion, further investigation is needed between the association of primary Sjogren syndrome (PSS) and SNHL as a symptom.
Galarza-Delgado, 2018	EHF's: 10 000, 12 000, 14 000, 16 000Hz Audiometer: Interacoustic AC40 Sound- proof booth	Average dose of ototoxic medication: RA: 103 patients - methotrexate and folic acid (19.3 mg/week and 5 mg/day), 63 patients - chloroquine (101.4 mg/day), 37 patients – prednisone (6.3 mg/day). PSS: 22 patients - hydroxychloroquine (125 mg/day), 17 patients - methotrexate and folic acid (15 mg/week and 5 mg/day), 11 patients – prednisone (5 mg/day), and 2 patients – leflunomide (20 mg/day)	The study indicated that EHF's are affected initially and that SNHL has an association with autoimmune disease patients. Therefore, the study propose conducting audiometric studies within the routine protocol.	Limitation: The study only compared two autoimmune diseases. Future research: Further research should be conducted to completely understand the hearing behaviour of patients with autoimmune disease and identify potential audiological complications.
Ma, 2018	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000, 18 000, 20 000 Hz Audiometer: Madsen model Conera Headphones Sennheiser HDA200 Sound-proof booth.	Mean flight time per group: 20 to 29 years = 1381.1 h 30 to 39 years = 5868 h 40 to 49 years = 10 296 h 50 to 59 years = 18 163 h	EHF audiometry are more sensitive than conventional audiometry and may be useful in early detection of civilian pilots hearing.	Limitations: The study inherited the limitations of all cross-sectional studies All participants were male therefore cannot be extrapolated to females Future research: Prospective studies are needed to demonstrate that civilian pilots with worse hearing thresholds in EHFs are prone to hearing loss in conventional audiometry.
Vignesh, 2015	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000Hz	Minimum of 3 years duration with type 2 DM	EHF audiometry is an important tool for early identification of hearing loss compared to conventional	Not indicated

	Audiometer: Inventis-piano Headphones: HD-200 transducer Sound-proof booth.		audiometry. The study emphasis the use of EHF audiometry in a test battery for assessing type 2 DM and will allow for early identification and monitoring of these patients.	
Vasconcelos, 2018	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Madsen Itera II Headphones: TDH-39 Sound- proof booth.	Participants received amikacin for 6 months for the first time.	Over a 6-month period, amikacin- associated hearing threshold shifts were detected in the EHF's and it is possible to use EHF audiometry in health care to monitor these patients.	Limitations: The cognitive function of the participants was not systematically assessed. Treatment was not directly observed The serum levels of amikacin were not determined over the 6 months.
Bayat, 2019	EHF's: 10 000, 12 000, 14 000, 16 000hz Audiometer: Madsen Astera Headphones: Sennheiser HDA-200.	Methadone maintenance treatment (MMT) course consisted of a daily 30 mg methadone 7 days per week for 3 months.	EHF audiometry have the potential to detect changes earlier in the auditory function of MMT patients than conventional audiometry.	Limitation: EHF audiometry was not used for the pre-assessment of MMT hearing thresholds. Therefore, the causal association between MMT and hearing loss may not be certain. Further research: Case control studies with a greater sample size and pre- and post-MMT assessments are required to comprehend the exact mechanisms and effects of methadone on the hearing function.
Laffoon, 2019	EHF's: 10 000, 12 500, 14 000, 16 000Hz Audiometer: Madsen Astera Earphones: ER-2 inserts Sound-proof booth	Firearms was used on an average of 9.2 times per year and began shooting on an average of 7.6 years	In conjunction with conventional audiometry, EHF audiometry should be conducted up to 16 000 Hz in audiological protocols of youth firearm users to early identify, intervene and monitor for NIHL.	Limitations: Other noise exposure and general health that might cause cochlear damage was not investigated. The firearm noise exposure was not controlled in the days before the data collection. There was no control group for the study Future research: Future studies need to include a control group and expand on the study population. A longitudinal study design with exposure metrics would be valuable.
Li, 2019	EHF's: 9000, 10 000, 11 200, 12 500, 14 000, 16 000 Hz Audiometer: Otometrics Conera Sound-proof booth.	Two groups: Disease duration for > 10 years (36 participants) Disease duration < 10 years (29 participants)	Cochlear damage and high frequency hearing loss can occur in diabetic patients with normal hearing in the conventional frequencies. EHF audiometry are important for early detection of type 2 DM patients.	Future research: Further investigation is needed on the effect that diabetes has on the hearing of younger patients.

APPENDIX D: SUMMARY OF CALCULATED RESULTS

	Non-sequential analysis	Sequential analysis	Studies combined
EHF audiometry as a useful procedure	Seven studies (43.75%) Abujamra et al. (2013) Bayat et al. (2019) Ma et al. (2018) Mehrparvar et al. (2011) Mehrparvar et al. (2014) Riga et al. (2010) Vignesh et al. (2015)	-	Seven studies (43.75%) Abujamra et al. (2013) Bayat et al. (2019) Ma et al. (2018) Mehrparvar et al. (2011) Mehrparvar et al. (2014) Riga et al. (2010) Vignesh et al. (2015)
EHF audiometry in conjunction with conventional audiometry	Four studies (25%) Galarza-Delgado et al. (2018) Gonzalez et al. (2017) Luders et al. (2014) Macca et al. (2018)	Two studies (12.5%) Buchler et al. (2012) Vasconcelos et al. (2018)	Six studies (37.5%) Buchler et al. (2012) Galarza-Delgado et al. (2018) Gonzales et al. (2017) Luders et al. (2014) Macca et al. (2018) Vasconcelos et al. (2018)
EHF audiometry in conjunction with DPOAE-testing	One study (6.25%) Li et al. (2019)	One study (6.25%) Yu et al. (2014)	Two studies (12.5%) Li et al. (2019) Yu et al. (2014)
EHF audiometry in conjunction with conventional audiometry and DPOAE testing	One study (6.25%) Laffoon et al. (2019)	-	One study (6.25%) Laffoon et al. (2019)
Control groups	11 studies (68.75%) Bayat et al. (2019) Galarza-Delgado et al. (2018) Gonzalez et al. (2017) Laffoon et al. (2019) Li et al. (2019) Luders et al. (2014) Ma et al. (2018) Macca et al. (2015) Mehrparvar et al. (2011) Mehrparvar et al. (2014) Vignesh et al. (2015)	One study (6.25%) Buchler et al. (2012)	12 studies (75%) Buchler et al. (2012) Bayat et al. (2019) Galarza-Delgado et al. (2018) Gonzalez et al. (2017) Laffoon et al. (2019) Li et al. (2019) Luders et al. (2014) Ma et al. (2018) Macca et al. (2015) Mehrparvar et al. (2011) Mehrparvar et al. (2014) Vignesh et al. (2015)
No control groups	Two studies (12.5%) Abujamra et al. (2013) Riga et al. (2010)	Two studies (12.5%) Vasconcelos et al. (2018) Yu et al. (2014)	Four studies (25%) Abujamra et al. (2013) Riga et al. (2010) Vasconcelos et al. (2018) Yu et al. (2014)

Total of studies	**13 studies (81.25%)**	**Three studies (18.75%)**	-

APPENDIX E: SUMMARY OF CALCULATED RESULTS CONTINUE

	Sensitivity of EHF audiometry	Deterioration of EHF-thresholds
EHF audiometry as a useful procedure	Four studies (25%) Abujamra et al. (2013) Bayat et al. (2019) Ma et al. (2018) Mehrparvar et al. (2014)	Seven studies (43.75%) Abajumara et al. (2013) Bayat et al. (2019) Ma et al. (2018) Mehrparvar et al. (2011) Mehrparvar et al. (2014) Riga et al. (2010) Vignesh et al. (2015)
EHF audiometry in conjunction with conventional audiometry	Two studies (12.5%) Galarza-Delgado et al. (2018) Gonzalez et al. (2017)	Six studies (37.5%) Buchler et al. (2012) Galarza Delgado et al. (2018) Gonzales et al. (2017) Luders et al. (2014) Macca et al. (2018) Vasconcelos et al. (2018)
EHF audiometry in conjunction with DPOAE testing	Two studies (12.5%) Li et al. (2019) Yu et al. (2014)	One study (6.25%) Li et al. (2019)
EHF audiometry in conjunction with conventional audiometry and DPOAE testing	One study (6.25%) Laffoon et al. (2019)	One study (6.25%) Laffoon et al. (2019)
Control groups	Seven studies (43.75%) Bayat et al. (2019) Galarza-Delgado et al. (2018) Gonzalez et al. (2017) Laffoon et al. (2019) Li et al. (2019) Ma et al. (2018) Mehrparvar et al. (2014)	12 studies (75%) Buchler et al. (2012) Bayat et al. (2019) Galarza-Delgado et al. (2018) Gonzalez et al. (2017) Laffoon et al. (2019) Li et al. (2019) Luders et al. (2014) Ma et al. (2018) Macca et al. (2018) Mehrparvar et al. (2011) Mehrparvar et al. (2014) Vignesh et al. (2015)
No control groups	Two studies (12.5%) Abujamra et al. (2013) Yu et al. (2014)	Three studies (18.75%) Abujamra et al. (2013) Riga et al. (2010) Vasconcelos et al. (2018)

Total of studies	**Nine studies (56.25%)**	**15 studies (93.75%)**

APPENDIX F: PROOF OF SUBMISSION TO JOURNAL

Gmail Nadia Troskie <nadiatroskie2001@gmail.com>

Submission Confirmation for EARLY IDENTIFICATION AND MONITORING OF COCHLEAR DAMAGE USING EXTENDED HIGH-FREQUENCY AUDIOMETRY: A SYSTEMATIC REVIEW

AJA <em@editorialmanager.com> Sun, Dec 5, 2021 at 3:56 PM
Reply-To: AJA <aja@asha.org>
To: Nadia Troskie <nadiatroskie2001@gmail.com>

Dear Ms Troskie,

This message serves as confirmation that your submission entitled "EARLY IDENTIFICATION AND MONITORING OF COCHLEAR DAMAGE USING EXTENDED HIGH-FREQUENCY AUDIOMETRY: A SYSTEMATIC REVIEW" has been received by the American Journal of Audiology.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is https://www.editorialmanager.com/aja/.

The manuscript number is AJA-21-00258.

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