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The Epidemiology of Auditory Dysfunction in Type 2 Diabetic Adults in Africa: A Systematic Review and Meta-analysis

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DECLARATION

I, …***Achuma Fihla***…, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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CHAPTER ONE

Epidemiology of Auditory Dysfunction in Type 2 Diabetes Mellitus Adults in Africa:

A Systematic Review Study Protocol

1. Introduction

1.1. Background

Hearing loss is a condition that requires significant attention in less-developed regions of the world. Africa, in particular, has insignificant infrastructure and resources for early diagnosis and effective treatment. Hearing loss (defined as >35dB) is more common in Sub-Saharan Africa than in more affluent parts of the world. According to the World Health Organization, hearing loss prevalence estimates show 15.7% for those older than 15 years old in sub-Saharan Africa, compared to 4.9% of cases in high-income countries (1). Unfortunately, these prevalence results are met with disproportionate healthcare spending between low and middle (LMIC) and high-income countries. The global spend on treatment covers just 3% of the need in LMIC countries (1). However, the review that produced these results included only eleven studies (eight published and three unpublished), which went on to show very little existing evidence on health care spending in Africa. (2). This lack of data persists as many countries struggle to conduct extensive population-based surveys using standardised protocols and classification methods, which calls for more research to be executed in this field for an African population.

Similarly, financial restraint has also affected the treatment of diabetes in LMIC but, because of its exponential growth, more studies are implemented and published than ever before. WHO estimated 246 million people are living with DM at present, with an expected increase to 380 million people by the year 2025 (3). Reports have shown that low- and middle-income countries will suffer considerable consequences for the rise in incidence and that Africa will contribute to the rising global rates (4). The International Diabetes Federation (IDF) Atlas revealed that approximately

10.8 million individuals in Sub-Saharan Africa had DM in 2006, and that by 2025 it will rise to 18.7 million. This rate is increased by 80%, which has bypassed the worldwide predicted rise of 55% (4).

As DM grows to become more common in the general population, its impact on various organs of the body becomes more critical (5). Chronic complications of DM contribute to several changes that happen to the body in different periods of times, involving the nerves, skin, and lens (6). These complications disrupt an individual's quality of life and contribute to high rates of morbidity and mortality (7).

Diabetes is a metabolic disorder causing elevated blood sugar levels in the blood. It contributes to increased glycated haemoglobin deposits in vascular walls that lead to atherosclerosis (thickening of the basement membrane of the vessels). This constricting effect of diabetes is more pronounced in systems that require microvascular supply like the cochlea for energy and substrates. This constriction then leads to hearing loss, tinnitus, and even nerve damage as oxygen struggles to reach the inner ear's nerves (8). Hearing loss and tinnitus contribute to a decreased quality of life among those with the diagnoses (5).

Current epidemiological knowledge supports T2DM and its association with auditory disorders in both the young and older generation, proving that the occurrence of auditory disorder from a T2DM patient is independent of the pathophysiological changes likened to ageing (8). Most of the cross-sectional studies showed elevated hearing thresholds of participants diagnosed with T2DM, while some even reported the presence of otitis media and tinnitus (8). Prevalence studies, however, cannot account for temporality, and for this reason, cohort studies are used to attain incidence rates for the linear progression of auditory dysfunction in individuals with T2DM. There are, however, fewer incidence studies than prevalence studies, but the ones observed show a modestly increased risk of hearing impairment in people with T2DM compared to those without it (9).

Although these studies support the association between T2DM and the occurrence of auditory dysfunction, most of them are not investigated in an African population. In addition to African budget constraints, the literature gap creates a problem as lifestyle trends are different in the African context compared to the Western and European countries. This difference in lifestyle trends is due to higher-income countries being better suited to afford specific resources that low-middle-income countries would not sustain.

Evidence on this topic will inform the need for more epidemiology population-based studies assessing the association of auditory dysfunction in African people with T2DM. It will also facilitate the integration of audiological assessment in medical examinations of DM patients of all ages in Africa. Moreover, the robust knowledge focusing on the African context will assist in gaining the attention of policymakers to fund audiological screening programs. This knowledge will help in the early identification and treatment of hearing impairments in DM patient, further helping to decrease the double burden of infection on patients with DM. Early identification and management strategies for

hearing impairment in DM individuals are currently not included in the IDF guidelines. A study of this nature may warrant the inclusion of the methods mentioned above.

1.1.2. Aim of this paper

We are conducting this systematic review to determine the prevalence and incidence of T2DM related auditory dysfunction in African adults (aged 19 years and older) to provide robust epidemiological data within the African context. We anticipate this review will illuminate the growing prevalence of T2DM-related auditory dysfunctions, alert health professionals to the importance of screening T2DM patients for various auditory disorders, as well as for policymakers to prioritise early detection and treatment of hearing impairments.

1.1.3. Why is it important to do this review?

We anticipate that this review would provide a robust synthesis of epidemiological data to guide clinicians and researchers in their practice and further research. It will also potentially bring awareness to auditory dysfunction manifested in other highly prevalent chronic diseases. We found no information detailing the early identification and management of hearing impairment in DM patients in the IDF guidelines. We believed that meta-data showing an association between T2DM and the occurrence of auditory dysfunction may help facilitate the inclusion of hearing impairment management strategies for individuals with T2DM. It will also provide holistic and comprehensive care for patients diagnosed with T2DM in 160 countries that correspond with the IDF. The double burden of infection in people with DM will also reduce because early identification and hearing impairment management will prevent increased financial strain associated with late-stage identification of hearing.

1.1.4. Objective

We set out to provide an evidence-based estimate of the prevalence and incidence of T2DM-related hearing loss in African regions. Furthermore, we plan to compare audiometric thresholds of reported studies and factors influencing the prevalence, incidence, and severity of hearing loss. These factors will include the duration of T2DM effect on the onset of hearing loss and the relationship between

good versus poor glycaemic control on the occurrence and severity of T2DM in an African adult population.

1.1.5. Review question

The following research question guides this systematic review:

What is the prevalence and incidence of auditory dysfunction in adults clinically identified with type 2 diabetes mellitus aged 19 years and older in studies done on an African population?

1.2. Rationale

Several studies investigating the link between auditory disorders and DM have reported differing findings, with most of them assessing mixed populations of Type 1 and Type 2 DM in European and American people, and minimal research carried out on indigenous Africans with DM (10). There is a great need for robust evidence looking at the incidence and prevalence of diabetes-related auditory disorders in Africa. This information will bring awareness to the condition to improve identification and early treatment of ear and hearing impairments in people with T2DM. This study is unique because it focuses exclusively on the African continent. The data gathered on auditory disorders in people with T2DM will help develop policies and programmes focused on improving patient outcomes. The paper will also create a benchmark for comparing future patient outcomes and results to measure the success of the interventions.

1.3. Methodology and Analysis

1.3.1. Study Selection

All population-based study designs, cross-sectional studies and prospective or retrospective cohort studies that report the prevalence and incidence of auditory dysfunction in T2DM in an African population will be included.

1.3.2. Inclusion criteria

We included studies meeting the following inclusion criteria:

1. Include all cross-sectional and cohort studies examined on adults in Africa that report:

a. Adults from Africa 19 years and above as per WHO guidelines

b. Adults should be medically diagnosed or defined based on a measured fasting plasma glucose (FPG) specified by the WHO Criteria.

c. Published between the year January 1991 and January 2021 (11).

Authors were contacted via email for more information needed with the categorisation of articles.

1.3.2.1. Primary outcomes:

- Overall prevalence of auditory dysfunction in adults clinically diagnosed with T2DM in Africa.
- Prevalence of auditory dysfunction by African region.

1.3.2.2. Secondary outcome:

- Prevalence of auditory dysfunction according to the duration of T2DM.
- Prevalence of auditory dysfunction according to glycaemic control (good vs poor).

1.4. Search strategy for identification of relevant studies

1.4.1. Electronic databases

1. Electronic databases including PubMed/MEDLINE, EBSCO Host, Scopus, Web of Science.
2. Grey literature databases, e.g., Google scholar. Thesis and dissertation databases

1.4.2. Hand selection

1. A reference list of retrieved articles will be scanned for viable studies.
2. Notable authors of chosen studies will be contacted for more information on similar papers.

1.4.3. Search methods for identification of studies

Both published and unpublished studies were considered for inclusion in this study. A comprehensive search strategy with an African search filter was used to search for articles between 1991- 2021. Professional librarians from the University of Cape Town Health Sciences library were consulted for the expert design of the search strategy. Individual African countries and regional grouping names were used to identify studies that may have been indexed under local names. Both English and the specific country's native language were used in the search strategy for countries with both English and non- English names, while countries that had their name changed over the span of 1991-2021 had both their names included in the search strategy. Medical Search Terms (MeSH) terms were used when searching for studies on MEDLINE and PubMed. Rayyan QCRI systematic review web software was used to manage citations (12).

1.4.4. Study Selection

Three review authors (AF, AH and LP.) independently screened titles and abstracts of articles from electronic search outputs. The primary review author emailed study authors where clarification and essential details were missing. This step constituted the first stage of the review.

During the screening process, studies were marked as 'included' and 'excluded'. A meeting was scheduled to discuss which studies should be included or excluded from the 'pending' studies pile with

substantiated reasons for each decision. Full-text copies of studies that met the inclusion criteria were included and reviewed, and their details were drafted onto a data extraction form. Both reviewers agreed to the final number of studies included in the study. The search steps were documented on a PRISMA flow diagram. Conflicts between reviewers were resolved through discussion and involvement of a third reviewer if necessary.

1.4.5. Data extraction and management

Data was extracted by two independent authors (A.F & A.H). Discrepancies were resolved through discussion or by the involvement of the senior author, who made the final decision on what information should be included in the study. The data extraction form was pre- designed and piloted independently by two study authors using the same studies to assess comprehension. Data extracted form subheadings were adapted from the Joanna Briggs Institute Manual for prevalence studies https://wiki.jbi.global/display/MANUAL/Appendix+5.2%3A+Data+extraction+form+for+prevalence+studies. (Refer to Appendix 2).

The following information was retrieved:

- Study details: date of publication, study title, study design, study period and study purpose.
- Study population: which African country the study was conducted, the setting in which the research was conducted (e.g., community health facility or hospital), whether it was run in an urban or rural setting and how large the sample size was.
- The case definition reported in the study.
- The infected and uninfected individuals, namely, hearing loss or hearing impairment, ototoxicity, otitis media, and deafness.
- Type of audiometric test used, and average thresholds obtained.
- T2DM definition, good vs poor glucose control, average T2DM duration (years)
- The characteristic of the study population: age, sex, ethnicity and whether they have any comorbid diseases such as TB, HIV or hypertension.

After retrieval, the data was analysed and compared using Review Manager 5.4.1 software. If discrepancies arose during this process, they were resolved through discussions between the two reviewers and possibly involved a third reviewer if the matter was not resolved. Authors of studies deemed relevant for this review were contacted for missing information.

1.5. Quality appraisal of included studies

The Hoy et al., modified by Werfalli and colleagues' critical appraisal tool (13) (Appendix 3), was used to assess the prevalence studies' methodological quality in this paper. The quality of each study was assessed by grading the external and internal validity of each paper. The Risk of Bias criteria in the tool allocated four points for external validity and six points for internal validity. High risk of bias was marked as accumulated points between 0-5, moderate risk is 6-8 points, and low risk is >8. Authors independently assessed the risk of bias for each included study, and where there was disagreement, a third reviewer was consulted to resolve the dispute.

1.6. Data synthesis and analysis

1.6.1. Meta-analysis

Data was presented in text, tables, and graphs to illustrate the numerators and denominators of auditory disorders in Africans with T2DM. Data outcomes from similar studies were pooled together for analysis using a random-effects model where significant clinical and methodological heterogeneity existed between them. The pooled data for auditory disorders was presented as prevalence ratios with a 95% confidence interval (CI). Meta-analysis illustrating high heterogeneity were reported narratively.

1.6.2. Assessment of heterogeneity

Data was pooled to assess heterogeneity, first by visual inspection of the forest plots, and then followed by a Chi-squared test for heterogeneity. The significance level was set to 0.10, which is a p-value of <0.10, implying that studies do not share a standard effect size. The I(squared) (<25% low, 25%-50% as moderate and >75% high heterogeneity) statistics were used to estimate the percentage

of total variance across studies to assess the truth between-study differences. The studies' heterogeneity was evaluated using subgroups study-level characteristics, such as geographical region, rural/urban setting, duration of T2DM, good and poor glycaemic control. If there was a further explanation to be made, meta-regression was employed where necessary.

A sensitivity analysis was carried out to determine whether the study designs, study period or publication type of the removed study impacted the meta-analysis results.

1.7. Assessment of publication bias

Funnel plots were used to display the existence, if any, of publication bias. We used the estimators' distributional properties to formulate tests for the presence of publication bias and compare them with new methods of Begg (1994) and Egger (1997). The Duval and Tweedie' trim and fill methods were used alongside the Egger and Begg test to assess the robustness and magnitude of the publication problem (14).

1.8. Reporting of this review

This review was reported according to the preferred reporting items detailed in the PRISMA 2009 Checklist for systematic reviews and meta-analysis (15). The checklist contains a guideline for reporting systematic reviews of healthcare interventions and includes a PRISMA checklist.

1.9. Ethics and dissemination

This study did not require ethics approval since published material with non-identifiable data was be used. This study was the first to address and synthesise available studies reporting the epidemiology of auditory function in type 2 diabetes adults in the African context. Findings generated in this study will be used to inform the National Burden of Disease specialists of the incidence and prevalence and guide in health policy planning.

1.10. Logistics and timetable

Table 1: Schedule for completion of study (Estimate)

The expected timeline for the completion of this proposed study is summarised.

	June '20	July '20	Aug'20	Sep'20	DEC'21	JAN'21	FEB'21	FEB'21
Protocol andLit review	X	X	X					
Data management				X				
Data analysis					X	X		
Results							X	
Write-up								X

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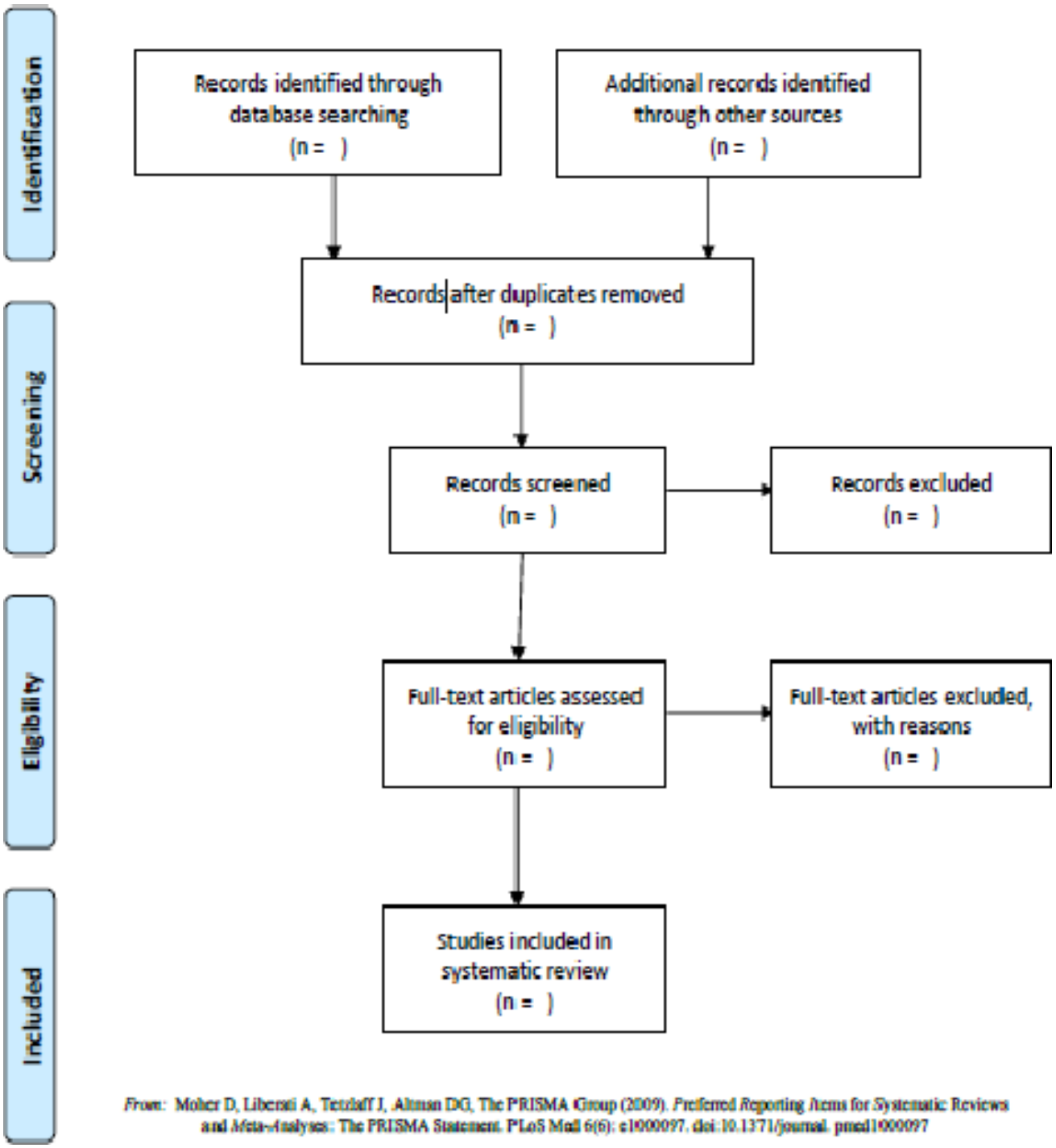
Appendix A: PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix B: Adapted Data Extraction Sheet

1. Study Information

Reviewer:

Checked by:

Study ID:

2. Citation Details

Authors:

Title of the study:

Journal:

Year:

Issue:

Study period:

3. Characteristics of Included Studies

Methods: Case definition:

Aim of the Study:

Study Design:

Year/timeframe for data collection:

643 Method of Assessment (PTA, ABR, OAE): Hearing Assessment classification:

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646 Condition Studied: Study definition used for T2DM:

647 Reported auditory dysfunction: PTA average (Left and Right ear): Comorbid diseases reported:

648

649

650 Participants: Population description:

651 No. of participants:

652 Abnormal/ T2DM (numerator/denominator): Age:

653 Sex:

654 Ethnicity:

655 Duration diagnosed with T2DM:

656 No. of abnormal results in good vs poor glycaemic control:

657

658 ABR means (waves I, III, V):

659

660 Setting: Inclusion criteria:

661 Exclusion criteria:

662 Subgroup reported:

663 Subgroup measured:

664 Rural or Urban:

665

666

667 4. Additional Information

Study author key conclusions:

Correspondence required for further study information:

693 # Appendix C: Quality Appraisal Tool

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Name of author (s): Year of publication: Study title:		
Risk of bias items	**Risk of bias levels**	**Points scored**
EXTERNAL VALIDITY		
1. Was the study's target population a close representation of the national population in relation to the variables, e.g., age, sex, occupation?	**Yes (LOW RISK)**: The study's target population was a close representation of the national populations.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population	1
2. Was the sampling frame a true or close representation of the target populations?	**Yes (LOW RISK)**: The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR was a census undertaken?	**Yes (LOW RISK)**: A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK)**: The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic	1

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CHAPTER TWO

Epidemiology of Auditory Dysfunction in Type 2 Diabetes Mellitus Adults in Africa:

Literature Review

2. Introduction

2.1. Background

Hearing impairment is a partial or complete inability to hear sounds. It is one of the major sensory disorders worldwide, affecting 466 million people globally, with 93% being adults (1). Hearing problems, when left untreated, may worsen and in severe cases, cause permanent damage to the hearing structures of the ear. Due to a lack of education on varying risk factors that affect hearing acuity, many people may unknowingly damage it, making it challenging to communicate with others without the assistance of a listening aid.

Hearing impairment is more common in sub-Saharan Africa than in more affluent parts of the world (2). WHO statistics show that hearing loss (defined as threshold >30dB) for adults above the age of 15-years old (1) were 15.7% in sub-Saharan Africa compared to the 4.9% prevalence rates in high-income countries. However, the estimates focusing on Africa are based on minimal data as the review only includes eleven studies (eight published and three unpublished). This shortage in literature is further propagated by the lack of relevant population-based surveys that use standardised protocols and classification methods (3), making it difficult to draw significant evidence to justify better healthcare resources and services for audiological conditions for the African context.

In addition to the limited data on hearing loss in Africa, its relation to Type 2 diabetes mellitus (T2DM) is an under-researched topic worldwide and much less investigated in Africa. Some studies have related the lack of research to a limited understanding of the cellular and molecular systems involved in hearing loss in people with diabetes mellitus (DM), while other studies attribute it to reduced access to cochlear tissue in humans for pathophysiological studies (4). Nevertheless, the available data, though scarce, does confirm a relationship between the presence of T2DM and the occurrence of hearing impairment (4, 5, 6, 7, 8).

With the growing interest in diabetes-related auditory dysfunction, it is not unexpected that increased research would initially reveal conflicting outcomes. For instance, several authors reported that the central nervous system was involved in auditory and vestibular issues in DM patients, while others proposed that DM accelerated the ageing process (9, 10). More recent population-based studies

investigating the association between T2DM and auditory dysfunction report their findings as outcomes of a slow, progressive, bilateral, high-frequency sensorineural hearing loss. Other studies analysing the mechanisms of the association of DM and hearing impairment produced results suggesting a combination of hyperglycaemia, oxidative stress due to microangiopathy, and auditory neuropathy (4). However, even with this knowledge, the topic is still far from complete elucidation.

This paper will provide an overview of human evidence of pathophysiological changes caused by T2DM and its effects on the auditory system. It will review prevalence and incidence data to assess the burden of disease in Africa. Trends contributing to disease impact between high- and low-income countries will be narratively discussed.

Findings discussed in the paper will help inform appropriate planning of policies and services of evidence-based advocacy for people with hearing impairment in low and middle-income countries. Results gathered will facilitate the integration of early detection and treatment of hearing disorders in T2DM patients with the hopes of possible integration of audiological screening in the medical treatment of T2DM patients.

2.2. Diabetes: Definition and Prevalence

2.2.1. Definition of Diabetes Mellitus

The World Health Organization (WHO) defines DM as a non-communicable disease (NCD) characterised by high glucose levels in the blood. The high glucose content can damage the heart, blood vessels, eyes, kidneys, and nerves (11). There are several types of diabetes mellitus, T2DM being the most common. T2DM, usually diagnosed in adults, manifests when the body becomes resistant to insulin or does not create enough insulin; this is in contrast to type 1 diabetes (T1DM), which occurs due to an absolute deficiency of insulin secretion (12).

2.2.2. Epidemiology of Type 2 Diabetes in Africa

Sub-Saharan Africa is not immune to the uprising of DM. In keeping with the WHO statistics mentioned above, T2DM is the predominant type of diabetes in the region, accounting for over 90% of cases (13)

T1DM constitutes the remainder. The reported cases add a significant burden on an already compromised health system due to high cases of infectious diseases such as malaria, tuberculosis and HIV in the continent (14).

2.2.3. Prevalence of T2DM

About 40 years ago, DM was a rare disease in the region. Low prevalence rates were evident in East and Western African countries (Ethiopia, Ghana, Lesotho, Uganda and Malawi between 1960 – mid-1985 presented a prevalence of <1%), while South Africa showed moderate prevalence rates, with cities and peri-urban areas having the highest occurrence of the disease (4%-8%). The high prevalence rates point to high obesity rates compared to other countries in the region (14, 15, 16). In countries such as Tanzania and Cameroon, the prevalence of DM is reported to increase six to ten-fold within 10 years. (17).

In 1995, the WHO estimated 135 million people living with DM globally and a projected increase to 154 million by 2000 (18). Estimates from the recent (International Diabetes Federation (IDF) Atlas of 2019 show that the current rates of infection is 463 million and will increase to 700 million by 2045 (19). Moreover, the 2019 IDF report showed that low to middle-income countries claim 79% of the world's diabetes cases. Within that rating, 19 million are adults between the ages of 20-79 living in African countries. This figure is estimated to rise to 47 million by 2045 (20). Each of these reports highlight that low to middle-income countries will claim the majority of the expected increase of DM cases, with the African continent contributing the largest proportion of cases to the rise (13, 21, 22).

2.3. Worldwide incidence and prevalence of T2DM related Hearing Impairment

2.3.1. Incidence of T2DM related auditory dysfunction

Although prevalence studies predominate most literature on the topic, there is a consensus of an increased risk of hearing impairment in people with DM than individuals without diabetes. One example of an incidence study is the Beaver Dam Study. The study recruited 1925 residents from the Beaver Dam to participate in a support study called the Epidemiology of Hearing loss Study (EHLS). Participants were aged between 43-84 years with normal hearing at baseline. Baseline hearing tests

were done between 1993 to 1995, followed by assessments in 1998-2000, 2003-2005, and 2009- 2010. Incident hearing impairment was defined as a pure-tone average (PTA) greater than 25dB at frequencies 500, 1000, 2000 and 4000Hz in either ear. The study showed an association between DM and slight elevation of risk of hearing impairment in age and sex-adjusted models. Although the risk was insignificant (HR = 1.26 [95% CI, 0.93-1.71]), a more significant risk was found in individuals with poorly controlled DM (HR=2.03 [95%CI, 1.01-4.08]) (23)

A more recent longitudinal study assessing 139 909 women from the Nurses' Health Study looked at the relationship between T2DM and the risk of self-reported incidence of hearing impairment. During the evaluation period (>2.4 million person-years of follow-up), subjects with T2DM for >8 years were found to have a higher risk of moderate or severe hearing impairment compared to participants that did not have T2DM in their multivariable-adjusted model (HR=1.16 [95% CI, 1.27]) (24).

The Blue Mountains Hearing Study sought to report the relationship between T2DM and the 5-year incidence and progression of hearing impairment. Hearing impairment was defined as a PTA above 25dB at 500, 1000, 2000 and 4000Hz in the better ear. T2DM was defined by physician-diagnosed reports stating a fasting blood glucose level of >= 7.0 mmol/L. After adjusting for multiple risk factors, results showed age-related hearing impairment in 50% of DM participants (n=210) compared to 38.2% of non-DM participants (n=1648), odds ratio (OR) 1.55 [95% CI 1.11-2.17]. After five years, hearing impairment appeared in 18.7% of subjects and 18.0% in those without DM (adjusted OR 1.01 [CI 0.54-1.91]). Participants that already had hearing impairment had threshold averages increased by >5dB. This progression was greater in participants with newly diagnosed DM (69.6%) than in those without DM (47.8%) over five years (adjusted OR 2.71 [CI 1.07-6.86]). (25). What stands out about the results of this study is that it observed a significant association between prevalent DM and hearing impairment but not incident DM and hearing impairment, which made the study not true to the intended study design.

Another study looked at the risk of sudden hearing impairment in DM individuals. A retrospective cohort study based on the Taiwan National Health insurance program (universal healthcare system covering 99% of the country's 23 million residents) assessed 26 566 newly diagnosed DM patients and 26 566 subjects without DM. These participants were selected from the claims made during 2000-2004. There were no significant differences between age, sex, or health care costs between the sample

group and all claimants. The sample group was extracted from the Longitudinal Health Insurance Database of 2000, which is a subset of the National Health Insurance Research Database containing all claim data from 1996 to 2009. Sudden sensorineural hearing loss was defined by the ICD-9 code (International Classification of Diseases, Ninth Revision, Clinical Modification). From 2000 to 2004, claims data were available for 26 566 people with DM meeting the criteria. An additional 26 566 non-DM subjects were recruited through random selection. Results showed a significant risk of sudden sensorineural hearing loss (SNHL) in the DM group compared to the non-DM group in two age groups: 35-49 and 50-64 years old. Incidence ratio for these groups were 2.09 (95% CI, 1.27-3.45) and 1.67(95% CI, 1.23-2.26) respectively. For people younger than 65, incidence rates did not show significant incidence rates for the DM group (26).

2.3.2. Prevalence data of T2DM related auditory dysfunction

Generally, epidemiological studies support the association between DM and hearing impairment. Most of the population-based studies that were found did not differentiate between T1DM and T2DM. However, attempts have been made to filter out studies only focusing on subjects with T2DM. We first examine the cross-sectional (prevalence) data.

A cross-sectional study carried out at a diabetes outpatient clinic in LAUTECH Teaching hospital (LTH) in Ogbomoso, Nigeria, assessed the patterns of otologic diseases and auditory acuity in T2DM patients. Ninety-seven consenting patients diagnosed with DM were recruited together with their age and sex-matched non-DM patients (90 subjects). Both groups were screened using otoscopy and pure-tone air and bone conduction audiometry. For audiometric testing, air conduction thresholds measured were 250, 500, 1000, 2000, 4000, 6000 and 8000Hz, while bone conduction was measured at 250, 500, 1000, 2000 and 4000Hz for each ear separately. Audiometry results showed hearing impairment in 21.5% (n= 21) T2DM candidates and 8.9% (n= 8) of controls (p=0.016). 5 out of 21 T2DM (23.8%) and 6 out of 10 controls (75.0%) presented with unilateral hearing impairment. Bilateral abnormal PTA results revealed a significantly higher proportion of T2DM patients than controls (p = <0.001). The most occurring type of hearing impairment was SNHL which was found to be significantly different (p= 0.012) from the 37.5% found in controls. The degree of hearing impairment common in T2DM patients was moderate hearing impairment found in 8 out of 21 participants (38.0%) and mild hearing impairment in controls (3 out of 8 = 37.5%), which were found to be statistically significant (p = 0.057).

(27). The most common occurring auditory disease associated with T2DM was otitis media with effusion (p= 0.027) (27).

A report looking at prevalence trends in US citizens between the ages of 25-69 years with and without DM found that the prevalence of hearing impairment in DM showed an increase from (28.5% [95% CI, 20.4%-36.6%] to 34.4% [95% CI, 29.1-39.7%]). Citizens without diabetics declined over time (from 24.4% [95% CI, 22.3-26.6%] to 22.3% [95% CI, 20.4-24.2%]), (28). Data from 1971-1973 and 1999-2004 cycles were used for this study. Estimates were adjusted for age, sex, race and educational level. Results illustrated in this study show that not only has the prevalence for hearing in T2DM is higher compared to those that do not have T2DM, but that those with DM have not had a reduction in hearing impairment prevalence since the 1970s (28).

Another Beaver Dam study similarly showed an association between T2DM and hearing impairment (29). The study analysed 3571 participants and found that people with T2DM were more likely to present with hearing impairment (59%) compared to controls (44%). Also, once participants with presbycusis-like audiometric results were excluded from the analysis, a significant association between T2DM and hearing impairment prevailed (OR = 1.41 [95% CI, 1.05-1.88, P= 0.02]) (29). However, the difference was not statistically significant when controlled for age.

Studies carried out outside of the US investigating the association of T2DM and hearing impairment have also proved an association. For instance, a Japanese study assessed middle-aged self-defence males through testing their hearing. Hearing impairment was defined as a PTA of >25dB in the worst ear at the following frequencies (500, 1000, 2000 and 4000 Hz). High frequencies (3000, 4000 and 6000Hz) were also evaluated. Participants were split into three groups; the first was impaired glucose tolerance (n=154), the second was a group of identified DM candidates (n= 103), and the third was non-diabetic candidates (n= 442). Results showed that T2DM was associated with hearing impairment (OR = 1.87 [95% CI, 1.20-2.91]), and significant threshold elevation was observed at 1000, 3000 and 8000Hz in people with DM compared to their non-diabetic controls. Furthermore, impaired glucose tolerance was not associated with an increased risk of hearing impairment (OR =1.16 [95% CI, 0.80-1.68]) (30).

Lastly, the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) examined hearing outcomes in 901 adults with DM (mean age: 57.4 years, +/- 9.0 years; n = 191) and without DM (51.2 years +/- 8.9, n= 710). Results showed a sign of low to mid-frequency hearing impairment (250-2000Hz) in persons with DM. However, no significant hearing impairment was found for age, sex, and hypertension-adjusted models (OR = 1.03 [95% CI, 0.56 – 1.92]). Furthermore, hearing thresholds were not affected by occupational noise exposure in the groups with and without DM. There was also no association between the length of diabetes and worsened hearing thresholds after adjusting for age, sex and hypertension (31).

2.4. History of T2DM related auditory dysfunction

In 1857, Jordao reported a case of hearing impairment associated with an emerging diabetic coma (32). Soon after, the invention of pure-tone audiometry made it possible to assess for auditory acuity of the inner ear in people with diabetes. Afterwards, researchers started reporting auditory acuity using audiometric test outcomes. The typical hearing impairment described by authors at that time was a progressive, bilateral, sensorineural deafness that occurred gradually. It mimicked presbycusis because it affected higher frequencies in older patients (32).

Papers looking at incidence rates between 1943- 1975 showed no consensus in the literature as varying authors quoted sensorineural hearing impairment incidence rates to be between 0 to 93% (32). In cases where authors disclosed their methodology for obtaining incidence rates, one of three options was used; two of the methods involved comparing hearing thresholds of diabetics to Johansen curves relating hearing levels of normal individuals to their ages (32). The second method compared the mean hearing level of diabetic participants with predicated hearing thresholds, while the third, unique to Friedman, involved calculated regression equations. Friedman then diagnosed subjects with z scores above 1.96 as having abnormal hearing (32). Subsequently, several authors reported additional factors that impact the hearing level of diabetic patients, such as duration of diabetes, sex, age, blood pressure, retinopathy, nephropathy and angiopathy (32).

As previously mentioned, not all authors agreed that DM could lead to hearing impairment. In 1981, a cross-sectional study carried out by Harner on 200 adults found no evidence of an increased prevalence of hearing among individuals with DM (33). Pure-tone audiometry was administered on

the participants using frequencies ranging from 250Hz to 8000Hz. The hearing prevalence results were compared to data from a population study of hearing prevalence from 12 years earlier. Harner's outcomes were made less valid because the results were not adjusted for decreased smoking prevalence and improved occupational hearing protection technology. Another study with a similar outcome investigated whether noise and DM together produce more hearing impairment than workers without DM. Participants (n= 28) with DM were sectioned into a high-noise (n= 15) and low-noise (n= 13) group. Results showed no difference in the higher threshold in the high-noise and low-noise exposed group compared to the non-exposed group of high and low noise (34). However, the results of this study are questionable as low participant numbers may reduce the power of the study and, as a result, miss the hearing difference between the DM group and their non-DM controls. Moreover, both Harner and Hodgson's research did not include the smoking history of the participants. Smoking is known to be a principal risk factor for hearing impairment.(35).

It is worth noting that most studies completed after the year 2000 found more positive reported associations between hearing impairment and DM. The development is a possible indication of increased awareness of potential confounders and a change in study designs over time. Hong, Buss and Thomas (2013) found that the change in study design may shift whether DM causes hearing impairment to focus on the pathology, prevalence, incidence, and progression of hearing impairment in people with diabetes. It can possibly raise the question of preventative measures that healthcare providers can use in reducing the risk of hearing for patients with DM (35).

2.5. Pathophysiology of T2DM

The exact aetiology of T2DM is not well-understood in literature due to the various findings in different research studies. Early investigators demonstrated that sustained neurodegeneration of cells caused by T2DM would lead to intercellular and extracellular processes that cause secondary disorders. These disorders include coronary artery disease, peripheral vascular disease, retinopathy, neuropathy and nephropathy, which the inner ear is sensitive to (36, 37, 38). Other studies provide evidence that T2DM is a multisystem disorder affecting the micro and macro-vascular system that cause vascular pathologies in the cochlea, resulting in auditory dysfunction (5, 39, 40). There is still yet to be an agreed-upon pathophysiological explanation of how T2DM affects the auditory system. The information presented below will explore the theories that existed in the past, and some current beliefs.

2.6. Anatomy and Physiology of the Human ear

2.6.1. Description of the anatomy of the cochlea and its mechanisms

The inner ear structures are designed to convert mechanical energy transmitted in the form of waves into neuronal impulses that can be interpreted as sound by the brain. In addition to hearing, inner ear structures also assist with postural balance and gaze fixation. The cochlear component assists with hearing, and the vestibular component assists with balance.

2.6.2. Mechanisms of auditory transduction

Auditory transduction is when the ear converts sound waves in the inner ear, changes them into nerve impulses in the cochlear component and later sends them to the brain to be interpreted as sound.

Sound waves enter the ear via the external auditory canal to reach the tympanic membrane (also referred to as the eardrum) (Figure 1). The tympanic membrane is a cone-shaped structure. It articulates with three tiny bones (or ossicles): the malleus, incus, and stapes, in the middle ear. (Figure 2a). The vibration of the tympanic membrane causes the ossicles in the middle ear to vibrate and pass information about frequency and amplitude to the footplate of the stapes, which moves in a piston-like motion that sends vibrations to another bony structure called the labyrinth. Due to the flexibility of the round window, the movement of the stapes allows for the displacement of the perilymph to allow sound vibrations to enter the bony labyrinth (41).

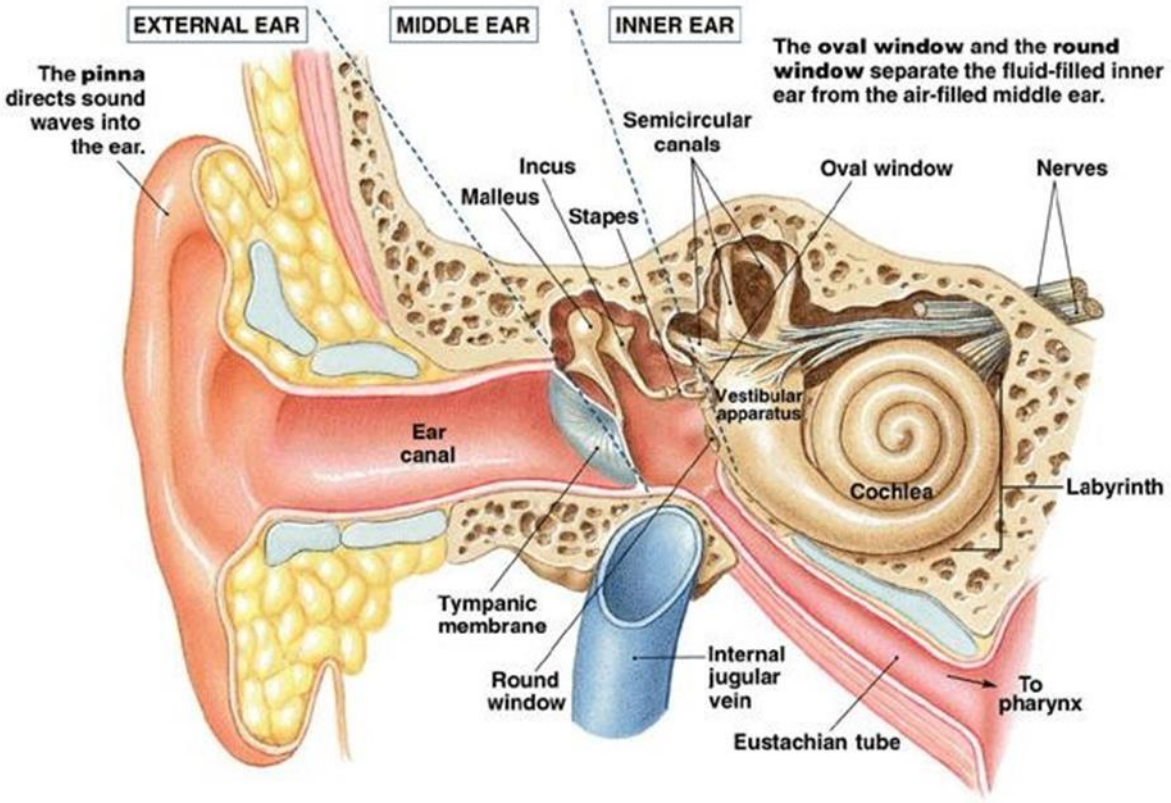

***Figure 1**: Illustration of external, middle and inner ear structures* (41). https://www.austincc.edu/apreview/PhysText/PNSafferentpt2.html#hearing

The portion of the spiral passage whereby vibrations ascend to the apex of the cochlear is called the scala vestibuli. The descending part of the passage is called the scala tympani. A third structure called the cochlear duct filled with endolymph is situated between these two structures. When viewed in cross-section, the membranes separating the two fluid-filled systems are visible (Figure 2a). They are the Reissner's membrane and the basilar membrane (Figure 2c). The membranes are flexible and will move with the vibrations scaling up the scala vestibuli. A specialised structure called the Organ of Corti is situated above the BM (41).

The basilar membrane is a specialised organ that responds to different sounds. Lower frequency sounds vibrate the BM closer to the apex, whereas higher frequency sounds will vibrate the base of the membrane (Figure 2d). The Organ of Corti converts these vibrations into nerve impulses and transports them via the brain's cochlear nerve to the brain to interpret it as sound.

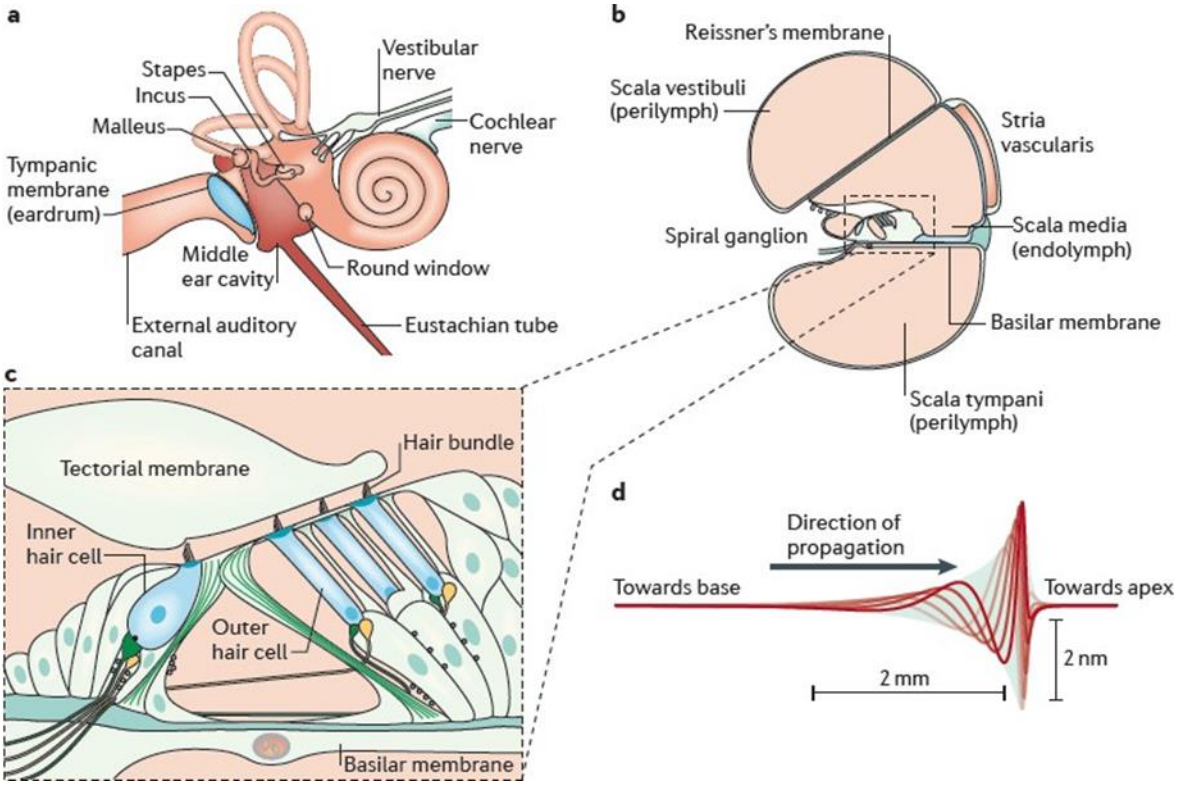

Figure 2: *Showing the cochlea and the organ of Corti* (41).

2.6.3. Diabetes and the Auditory system: Evidence from Human Pathophysiology

T2DM negatively affects the normal process of auditory transduction. The elevated blood glucose levels in DM result in increased deposits of glycated haemoglobin in the vascular walls. This increase in glycated haemoglobin deposits on endothelial walls results in abnormal growth of endothelial cells, leading to high blood lipid levels that inevitably trigger atherosclerosis (thickening of the base of blood vessels). The thickening of the vessels worsens over time and eventually disrupts body systems that need a free-flowing microvascular supply of blood (42), such as the cochlea. This disruption of blood flow to the cochlea causes issues in the disposal of metabolic waste to maintain homeostasis and the transportation of energy and substrates to sustain normal functioning (4). In addition to microvascular complications, DM is also believed to cause hyperglycemia-induced oxidative and nitrosative stress . This stress leads to endothelial dysfunction and DNA damage at a cellular level. (43). Research on the effects of DM on auditory dysfunction reports a multifactorial contribution of hyperglycaemia, oxidative stress that leads to cochlear microangiopathy and auditory neuropathy (44).

2.6.4. Auditory: Peripheral and central system pathophysiology

The effects of T2DM on the auditory system have also been observed by examining the peripheral auditory system of people with long-standing DM (6, 10, 45, 46, 47). Studies performed on human remains report many pathological mechanisms of the inner ear, such as thickened capillaries in the stria vascularis (6, 44), demyelination of the vestibulocochlear nerve, narrowed internal auditory artery, thickened basilar membrane and degeneration of inner and outer hair cells of the cochlea (48, 49, 50). Moreover, discoveries in other studies revealed degeneration of fibrocytes in the spiral ligament resulting in a loss of neurons to the spiral ligament. Other degenerative changes in the auditory brainstem pathway include; ischemia, sclerosis in the ventral and dorsal cochlear nuclei, inferior colliculus and medial geniculate body (47). These anomalies are found to occur independent of the normal processes of ageing (5, 45, 51).

Vascular abnormalities have also been found to affect cranial nerves resulting in malnourishment, progression of dysplasia (abnormal cells in tissues or organs with the probability of causing cancer), necrosis (death of cells in tissue or organ due to disease) of the nerve cell membrane and demyelination (52). This collection of abnormalities leads to reduced auditory conduction efficacy, which has been said to be a significant attribute to diabetes peripheral neuropathies (4).

The long-term presence of DM can also negatively affect auditory brainstem function. According to Konrad-Martin et al. (2010), Gupta et al. (2013) and Vaughan et al. (2007), abnormal Auditory Brainstem Responses (ABR) responses reported as prolonged peak, interpeak latencies and reduced peak amplitudes in individuals with T2DM. Latencies give us information about how electrical sound signals are transmitted through different parts of the auditory brainstem (53). Therefore, elongation of waves I, III and V in studies (54) and (55) signify a delay in the conduction of auditory signals in the brainstem of diabetic individuals. Auditory neuropathy is also reported to be responsible for degraded neural temporal coding in the upper brainstem, causing central auditory processing deficits. Audiometry shows higher interaural phase differences, poor frequency discrimination limens and increased gap detection (56).

2.6.5. Human Temporal Bone Studies

Histological studies are examining temporal bones belonging to individuals with DM show pathological changes in different cochlear cell types, especially in thick vascular regions of the stria vascularis, spiral ganglion, spiral ligament, and the basal turn of the cochlea (43). Various studies reveal different cell types in the cochlea show the same syndrome of histopathological changes. Differences in abnormalities, especially across the different cell types, exist. The theory behind the disparities is that other cochlear cells have different ways of transporting glucose and insulin, which causes them to have different susceptibilities to toxic effects of hyperglycemia (57).

2.7. Additional auditory disorder associated with DM

2.7.1. Tinnitus

Studies looking at the association between the presence of DM and the occurrence of tinnitus are relatively inconclusive. A study supporting the association compared 103 patients with T2DM (mean age 61.6, range 33-88 years) to 15,622 non-diabetics (mean age 55.1 years, range 26-98 years) (58). Results revealed that 80% of T2DM patients self-reported tinnitus while only 14% of non-T2DM patients reported experiencing tinnitus (58). Another study using data of 8,143 adults between the ages of 20-68 years from the National Health and Nutritional Examination Study (NHANES) of 1999-2002. Twenty-one percent reported tinnitus within the first year of the study, while 11.7% reported persistent tinnitus, which was defined to be experienced monthly or even more frequently (59). The study controlled for confounding variables such as age, sex, race/ethnicity, DM, noise exposure and smoking status. The study reported a strong correlation between DM and tinnitus. Other studies have not reported a strong association, and as a result, more population-based studies need to be carried out to clarify the relationship (8, 60).

2.7.2. Middle ear disorders

Individuals with DM are at increased susceptibility to infection due to elevated serum glucose levels that cause alterations in the diseased person's immune system. As a result, people with DM are at risk of developing malignant otitis externa (MOE) (8). MOE is a rare condition that can spread to adjacent bones. A study of MOE revealed that 90% of people with this condition had DM (61). Within that population, the infection is more common in older individuals with poor glucose control and those who wore hearing aids (62). The mortality for this MOE is as high as 50% (Deresinski, 1995). hrsth

2.8. Audiometric results for T2DM related hearing impairment

The typical diabetes-related hearing impairment found by several studies is a bilateral sensorineural hearing loss (63). It is characterised by a progressive hearing impairment that mainly affects high frequencies but shows a different configuration in low and medium frequencies. Moreover, some studies have even described diabetes as the cause for sudden unilateral hearing impairment (64, 65, 66). A study assessing the auditory acuity in forty-one T2DM participants and their age and sex-matched non-diabetic controls used pure-tone audiometry to find differences between the two groups (67). Results showed higher thresholds in the hyperglycemic age groups. Elevated thresholds were also observed in participants with poor control of their blood sugar levels (HbA1C > 8%) (9, 32, 65, 67, 68).

In contrast, a cross-sectional study of fifty people with diabetes (twenty-two of the people with diabetes were insulin-dependent) compared with age and sex-matched control group >60 years found no significant association between DM (69). The participants were assessed using pure-tone audiometry and tone decay as well as otological examinations. There was no significant difference between audiometric and speech testing results between the DM and control groups; in fact, they were all found to be normal. (69). More population-based data are needed to clarify this relationship.

2.9. Hearing loss as a function of age and diabetes mellitus

Ageing is the leading cause of sensorineural hearing loss in adults. Not only does it impair communication, but it severely diminishes an individual's quality of life, causing social withdrawal, psychological alienation, loss of confidence, and increased depression and anxiety (70). The internal ear structure undergoes different changes as we grow, and as a result, our hearing abilities may change in each age group.

A cross-sectional study involving 37,773 individuals (9,101 females and 28,672 males) who visited the Health Promotion Center for health screening from 2006 to 2012 conducted a hearing test examining 500, 1kHz, 2kHz, 3kHz, 4khz and 6kHz in a double walled sound booth. PTA results were determined by summing up the air conduction thresholds of the right and left ears at four frequencies (500, 1kHz, 2kHz and 4kHz) and dividing each frequency by two.

Average hearing thresholds were determined as mild (>= 26~40 dB), moderate (41~55 dB), moderately severe (56~70 dB) and severe (71~90 dB) based on the standards of ISO. Participants were split into age groups (20, 30, 40, 50, 60 and 70 year olds).

Results showed a significant increase in hearing loss prevalence with age being 1.6%, 1.8%, 4.6%. 14.0%, 30.8% and 49.2% respectively. Frequency-specific results showed abnormal thresholds at 6kHz for subjects in their twenties and thirties, at 4kHz-6kHz for subjects in forties and fifties, at 2-6kHz for subjects in their sixties and at 0.5kHz-6kHz for subjects in their seventies. Higher losses of hearing were observed in high frequencies, indicating that suggesting that age-related hearing loss starts relatively earlier in high frequencies. (71)

2.10. Discussion and Conclusion

Most studies reviewed in this study show an association between T2DM and hearing impairment in both the young and middle-aged population. This association further proves that auditory dysfunction in T2DM individuals is independent of the pathophysiological changes that come from ageing. It is likely that the effects of T2DM on the auditory system are easier to identify in the younger generation before the cumulative effects of ageing, noise exposure, ototoxic drugs, lifestyle and cardiometabolic risk factors that cause a discrepancy in the relationship.

Interpretation of the results found in the studies is made complicated by many factors. Most of the studies are cross-sectional, inhibiting conclusions on causality. However, incidence data from studies

(72, 73, 74) provide some support to the causal relationship between T2DM and auditory dysfunction. Furthermore, most studies do not explicitly state the type of DM, further inhibiting studies available for review.

Most of the studies on this topic are carried out in the Western and European context. Although it is beneficial for knowing the potential effects T2DM has on the human ear and infer it to other countries; it becomes a problem because lifestyle trends and limited access to resources due to budget constraints found in African countries will require their own tailored intervention programs different

from those of Western countries. Therefore, more studies looking at the association between diabetes and hearing impairment for the African context are needed.

Not all the studies are controlled for factors such as smoking, socioeconomic status, ototoxic medication, and medical comorbidities. Knowledge extracted from the studies mentioned show a limited amount of data looking at the reversal of auditory alterations caused by T2DM and an inconclusive relationship between T2DM and tinnitus (8).

There has also been some complication in noise exposure and ageing. Some authors reported that self-reported noise exposure isn't an explanation for the observed discrepancies between hearing impairment and people with T2DM compared to those without T2DM or in people with T2DM and employed in low and high-noise working spaces (34). Therefore, it is evident that ageing and noise exposure are partial explanations for the variance in auditory outcomes observed in people with T2DM. It, therefore, calls for more critical evaluations of these relationships.

In conclusion, there are enough meta-data findings available to support an association between T2DM and auditory dysfunction for other regions of the world, but scarce data to support an association for an African population. These findings necessitate the need for African-based research related to this topic. Knowledge gathered will facilitate the early identification and management of hearing and otologic disorders in people with DM. Moreover, high prevalence reports of T2DM-related auditory disorders found in young and older ages call for further investigation and inclusion in the International Diabetes Federation of Africa (IDF Africa). These inclusions will help facilitate the integration of audiological assessment in medical assessments of diabetic patients of all ages in Africa.

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CHAPTER THREE

The Epidemiology of Auditory dysfunction in Type 2 Diabetes Mellitus Adults in Africa:

Meta-analysis

Abstract

Background: There is a growing rate of diabetes related hearing loss (HL) worldwide. However, in under-developed countries, HL is still under-recognised as a complication of type 2 diabetes mellitus (T2DM). Although Africa presents a significant rise in T2DM every year, it is met with limited resources to assist its growing and ageing population.

Objectives: This systematic review and meta-analysis brings awareness to diabetes-related HL in the form of reliable medical evidence measuring the prevalence of T2DM-related HL in an African population.

Methods: Studies were screened using Rayyan QCRI. STATA software and the random-effects meta-analysis model was used to aggregate prevalence estimates with a 95% confidence interval. The Freeman Tukey Transformation was used to account for between study variability. The study protocol is published in PROSPERO international Register of Systematic Reviews (registration number CRD42021227801).

Results: We identified a total of 99 studies, 14 duplicates were removed and 67 were excluded. After full review only five studies were included for quantitative synthesis. All the studied were cross-sectional and used purposive sampling as their recruitment method.

Conclusions: Findings show most participants with T2DM experienced mild HL and slight delays in objective hearing assessments. Audiometric resources and qualified Audiologists are scarce in Africa. Therefore, the available evidence does not justify the added costs needed for routine audiometric assessments for patients with T2DM. However, it does serve to recommend prioritising further research regarding risk factors associated with developing auditory disorders in people with T2DM.

Keywords: auditory dysfunction, hearing loss, T2DM, prevalence, adults, Africa.

3.1. Introduction

Hearing loss (defined as >35 decibel (dB) (1) is a disabling disease more common in Sub-Saharan Africa compared to wealthier countries around the world. Hearing loss (HL) prevalence rates are estimated at 15.7% for people older than 15 years old in Sub-Saharan Africa compared to 4.9% in high-income countries. Although there is a higher number of cases of HL in low-middle-income countries, they are met with disproportionate health care spending, with health care treatment projections showing a mere 3% of the need in low-income countries (1).

Studies investigating diabetes mellitus (DM) have similarly reported financial restraint about the treatment of DM in African countries. WHO estimated 246 million to be living with DM with a projected rise to 380 million people by 2025 (2). Unfortunately, low, and middle-income countries will bear the brunt of this uprise. The International Diabetes Federation (IDF) Atlas approximated that 10.8million people in Sub-Saharan African had DM in 2006 and estimated an 18.7 million rise in cases by 2025. This increase of 80% bypasses the worldwide predicted rise of 55% (3)

Over the past 150 years, the causal relationship between diabetes duration and hearing loss occurrence has been investigated. Organisations like *The Audiology Project* and the *American Association of Diabetes Educators* dedicated to diabetes-related hearing loss research propose that DM causes elevated blood sugar levels in the blood, which contribute to an increase of glycated haemoglobin deposits in vascular walls, leading to atherosclerosis (thickening of the basement membrane of the vessels). This constricting effect is more pronounced in systems requiring microvascular supply, such as the cochlea for energy and substrates. This compression in the vascular system of the cochlea can potentially lead to hearing loss, tinnitus, and even nerve damage as oxygen struggles to reach nerves of the inner ear (4).

Recent epidemiological studies support the association of type 2 diabetes mellitus (T2DM) and auditory dysfunction for both the young and older generations, proving that the auditory disorder is independent of the pathophysiological changes coupled with ageing (4). Most cross-sectional studies showed elevated hearing thresholds of participants with T2DM, while others reported otitis media and tinnitus (4). There are significantly fewer studies presenting the linear progression of auditory dysfunction in people with T2DM. Still, those observed show a modestly increased risk of hearing impairment in people with T2DM compared to those without the diagnosis (5).

3.2. Aim:

Although there are studies investigating the association between T2DM and auditory dysfunction, most of them are not carried out on an African population. This creates a problem when attempting to advocate for resource allocation for audiology and diabetes interventions, as robust knowledge focusing on the African context can be used to gain policymakers' attention to fund intervention programs and help in early identification and treatment of hearing impairment in diabetic patients. This action can help decrease the double burden of infection on patients with DM. Currently, early identification and management strategies for hearing impairment in people with DM are not included in the International Diabetes Federation (IDF) guidelines. Therefore, a study of this manner, may warrant inclusion of the findings gathered in this study.

3.3. Methods

This study was registered in the PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO). The systematic review protocol was assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (6) (Appendix A, chapter 3) and provided the registration number CRD42021227801.

3.3.1. Literature search

In this study, we intended to identify prevalence and incidence studies that carried out their research on an African population between the year 1 January 1991, till 1 January 2021. We adapted this date range because WHO introduced a new grading system for hearing severity in 1991 (7, 8). The development of this grading system was necessary to allow worldwide gathering of prevalence data concerning hearing impairment and determine population factors that influence these prevalence results. Utilising this updated system for classifying hearing impairments will assist in providing up to date evidence-based comparison of the T2DM population groups for all regions identified for this study.

A comprehensive search for both published and unpublished studies was carried out by two authors (AF, AH and LP). A professional librarian assisted with formulating the research strategy. To identify studies exclusively done in Africa or on an African population, we used an African search filter alongside medical subject headings (MeSH) with a range of search terms for PubMed/MEDLINE,

EBSCOHost and Google Scholar. The African search filter consists of African country names and truncations like “east* Africa” to ensure studies indexed with regional instead of country-specific terms are retrieved (9). African names are both in English and other languages that countries may be identified in (i.e., “Ivory Coast” also specified as “Cote d’Ivoire”. In countries with more updated names, or names that have changed over the years, both their old and new names are included in the search (i.e., “Zaire” and “Democratic Republic of Congo” are both included” (Appendix B, chapter 3). We re-ran the search terms all the electronic databases on 09/05/2021 and found no additional studies.

Table 1: Electronic Search Strategy

Database	Search strategy	Results.
PubMed and MEDLINE	(((((Hearing Disorders OR hearing loss OR hearing impairment OR hearing disorder OR auditory disorder OR auditory disorders) OR ("Hearing Disorders"[Mesh])) OR ("Hearing Loss"[Mesh])) OR (deaf OR deafness)) AND ((type 2 diabetes OR type 2 diabetes mellitus OR T2DM OR NIDDM OR non-insulin dependent diabetes) OR ("Diabetes Mellitus, Type 2"[Mesh]))) AND ((Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe) OR ("Africa"[Mesh])	26
Scopus and EbscoHost	(TITLE-ABS-KEY (("Hearing Disorder*" OR "hearing loss" OR "hearing impairment" OR "auditory disorder*"))) AND (TITLE-ABS-KEY (("type 2 diabetes" OR "type 2 diabetes mellitus" OR t2dm OR niddm OR "non-insulin dependent diabetes"))) AND (TITLE-ABS-KEY (africa OR african OR algeria OR angola OR benin OR botswana OR "Burkina Faso" OR burundi OR "Cabo Verde" OR cameroon OR cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR chad OR comoros OR congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR djibouti OR egypt OR eritrea OR eswatini OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea- AND bissau OR "Ivory Coast" OR jamahiriya OR kenya OR lesotho OR liberia OR libya OR madagascar OR malawi OR mali OR mauritania OR mauritius OR mayotte OR morocco OR mozambique OR namibia OR niger OR nigeria OR principe OR reunion OR rwanda OR "Saint Helena" OR "Sao Tome" OR senegal OR seychelles OR "Sierra Leone" OR somalia OR "St Helena" OR sudan OR swaziland OR tanzania OR togo OR tunisia OR uganda OR "Western Sahara" OR zaire OR zambia OR zimbabwe))	4

Type of studies for inclusion: For a study to be included in this systematic review, it must be a cross-sectional or cohort study design to assess the prevalence and temporality of auditory dysfunction in T2DM adults. T2DM in adults aged 19 years and above had to be medically diagnosed or defined based on a measured fasting plasma glucose (FPG) specified by the WHO criteria (10). We ensured that studies included presented data to guarantee the calculation of prevalence. Studies were identified as meeting the inclusion criteria by ensuring their titles and abstracts were included for full-text review

by three reviewers (AF, AH and LP). Studies not meeting the inclusion criteria in the screening stage were excluded. Disagreements were discussed between reviewers until concurrence was reached.

Type of participants: This study intends to describe the prevalence of auditory dysfunction in clinically diagnosed T2DM adults in Africa.

Types of outcomes: Prevalence of Auditory dysfunction in adults with T2DM segregated by:

a) Overall prevalence of abnormal pure-tone average (PTA) in T2DM African population
b) Good versus poor glycaemic control
c) Age-specific prevalence of auditory dysfunction in T2DM population
d) African region-specific prevalence of auditory dysfunction.

3.3.2. Data Extraction and Management

AF and AH independently extracted data from the included studies according to the inclusion criteria. AF designed the data extraction form and independently piloted on three studies by team members AH and LP. After the pilot, the form was modified, and the three reviewers extracted data from the included studies and resolved disputes through discussion. The modified data extraction form is in *Appendix B, chapter 2*.

3.3.3. Selecting studies for inclusion

With the use of RAYYAN QCRI systematic review web application (https://rayyan.qcri.org/welcome) AF, AH and LP individually screened the titles and abstracts of all identified records from both the database searches and manual searches. The web application allowed for duplicate removal, blinding during the process of study selection, and easy pdf access to full articles and dissertations of studies included for the full review. Full-text studies eligible for inclusions were assessed and agreed upon by all three authors. The selection of studies process is documented on the PRISMA flow diagram displayed on *Figure 3, chapter 3*.

3.3.4. Quality appraisal of studies

The risk of bias assessment was conducted with the use of the Hoy et al criteria modified by Werfalli and colleagues (11) for each domain of the 9 included studies (12, 13, 14, 15, 16, 17, 18, 19, 20). The tool consists of 10 questions where each question is graded as either "yes" = "1 "and "no" = "0". We summated the points for each study, and the risk of bias was declared high risk if the points were between 0-5, moderate risk with 6-8 points and low risk > 8 points. One can locate the scoring form in *Appendix D, chapter 3.*

We assessed the risk of selection bias and attrition bias on Review Manager 5.4.1 according to the Cochrane guidelines (21). Three reviewers AF, AH and LP independently assessed the studies' quality and resolved conflicts by consensus.

3.3.5. Data synthesis and assessment of heterogeneity

Data were analysed using STATA 15.0 statistical software (22). Prevalence estimates for each study were re-calculated using the numerator and denominators for each included study (Table 1, chapter 3). The overall prevalence of eligible studies was calculated with the inclusion of a 95% confidence interval (CI), random-effects model and Freeman Tukey transformation to account for between-study variability. Due to the limited number of studies included in the meta-analysis, subgroup analysis was limited. We conducted a subgroup analysis by glycaemic control, and we narratively described results for objective hearing assessments and frequency-specific hearing level results. Although we initially intended to stratify by rural vs urban, none of the studies disclosed the type of area they conducted their studies in. Therefore, we were unable to carry out an analysis of this nature.

Heterogeneity between studies was assessed by analysing the chi-square tests and I2 statistic. An I^2 output of >50% was regarded as substantial heterogeneity (23).

Lastly, the assessment of the certainty of the evidence was carried using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool (https://www.gradeworkinggroup.org/#). Findings across the studies were judged as having high, moderate, low, or very low certainty of evidence. Certainty of the evidence lowers every time there is concern for risk of bias, inconsistency, indirectness, imprecision, and publication bias. High certainty means that carrying out more research on the subject matter is unlikely to change our confidence in the effect estimate. Moderate certainty represents a need for further or additional research in the subject matter. There is a possibility that it may impact the confidence of the effect estimate or may

even change the estimate. Lastly, a low certainty means that further research is highly likely to make a significant impact on our confidence in the estimate effect and is most likely to change the estimate, and very low states that we have very little confidence in the estimate effect and that the true effect is likely to be substantially different from the presented estimate effect (24, 25).

3.4. Results

3.4.1. Description of the studies and their design

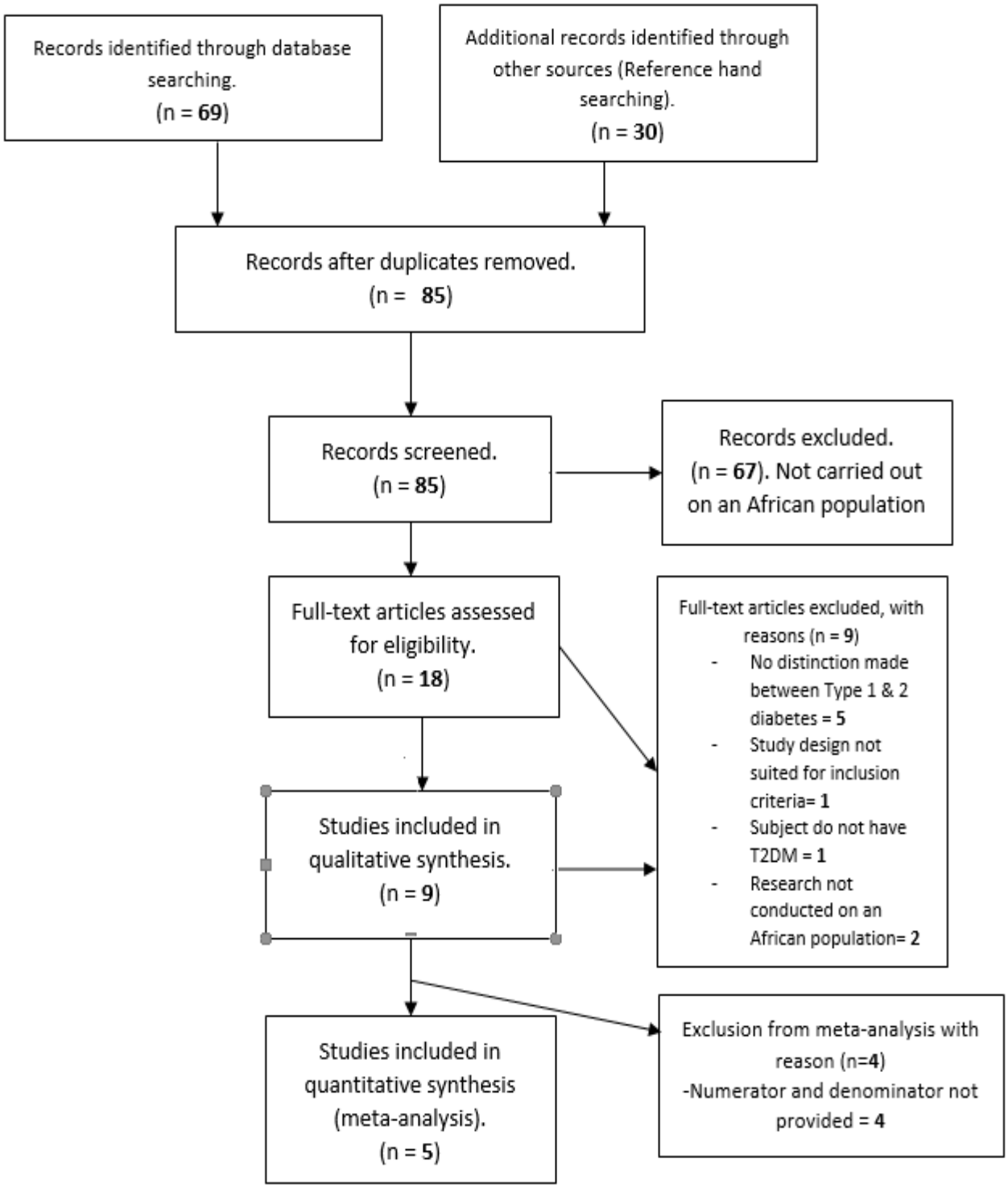
We identified sixty-nine records from searching four electronic databases, and thirty additional studies were included from screening the reference lists of studies included for full-text review. After screening the titles and abstracts and removing duplicate studies, we were left with 18 studies eligible for full-text review. Of these, only nine studies met the inclusion criteria and were included in the systematic review. The reason for excluding the other nine studies are found in *Figure 3, chapter 3*.

Of the nine included studies, five (56%) were published in peer-reviewed medical journals, the rest were master's theses completed in fulfilment of MA Audiology (22%) and Master's in Otorhinolaryngology (22%). Out of the 54 African countries, this study only managed to retrieve data from four (7%) African countries, which equates to 31% of the total African population (422 million of 1.341 billion) represented in this study. This review consists of three studies from South Africa, one from Egypt, four from Nigeria and one from Kenya *(Figure 1, chapter 3*). All the studies were cross-sectional and used purposive sampling as their recruitment method, with seven (77.8%) of the studies recruiting patients from local diabetes clinics *(table 2).*

Data extraction of applicable information was independently conducted by AF and SG. A third reviewer was included to mitigate any disagreements between the two reviewers. Study characteristics recorded included the country name, type of setting the study was conducted, the response rate, the case definition reported in the study, prevalence and incidence of auditory disorders (hearing loss, ototoxicity, otitis media, central auditory disorders, deafness), the type of diabetes and how it is defined in the study, and the characteristic of the study population (age, sex, ethnicity and whether they have any comorbid diseases).

Figure 2: PRISMA 2009 Flow Diagram search results

Flow diagram for study selection of studies looking at the effects of T2DM on hearing function



1606 ***Table 2: Summary of Study Characteristics***

1607 The table below compares common research methods and population sizes between the studies

1608 included for review in this study.

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Author	Country	Study Period	Study Design	T2DM Definition	Measures used to assess auditory functioning	Sex: F/M	Age specific	Population size: T2DM/Control
Adeba, 2015	Nigeria	-	Cross-sectional	WHO, 1991	PTA	T2DM=53/44 Control=50/40	58.9 µ age for T2DM group. 58.8 µ age for Control.	97/90
Idugboe, 2017	Nigeria	12 months	Cross-sectional	WHO, 1991	PTA	T2DM=35/35 Control=35/35	31 – 64	70/70
Kruger, 2018	South Africa	12 months	Cross-sectional	WHO, 1991	Interacoustics Eclipse AEP system	T2DM=18/12 Control= 18/12	37 – 57	30/30
Lasisa, 2003	Nigeria	-	Cross-sectional	WHO, 1991	PTA	ALL= 137/103	13 – 90	80/160
Minnaar, 2017	South Africa	12 months	Cross-sectional	WHO, 1991	Kuduwave (PTA)	T2DM = 16/12 Control = 16/12	43 - 55	28/28
Noha, 2015	Egypt	-	Cross-sectional	-	PTA, BAEP, OAEs: TEOAE & DPOAE	T2DM= 18/14 Control= 18/12	32 – 70	32/30
Okwiri, 2016	Kenya	17 months	Cross-sectional	WHO, 1991	PTA, ABR	ALL= 43/35	22 – 55	78 (ALL)
Ologe, 2005	Nigeria	-	Cross-sectional	-	PTA	T2DM=40/16 Control=34/18	56.95 µ age for T2DM group. 53.27 µ age for control group	56/52
Van der Westhuizen, 2019	South Africa	-	Cross-sectional	-	PTA	-	23 – 60	32/32

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Table 3: Excluded studies with reasons

List of studies excluded after full-text assessment. The table below describes the reasons for excluding these studies.

Author	Reasons for exclusion
El-Hini et al, 2019	No distinction made between Type 1 and Type 2 Diabetes
Hlayisi et al, 2017	
Hlayisi et al, 2019	
Ogundiran et al, 2012	
Finsterer et al, 2017	Study type is not included cohort or cross-sectional study
Sanju et al, 2016	
Gorwara et al, 2016	Participants are not inhabitants in Africa
Shamshirgaran et al, 2019	
Ologe FE et al, 2005	Participants not => 18 years

3.4.2. Quality of methodology

Risk of bias assessment: We used the Hoy et al, modified by Werfalli and colleagues Critical Appraisal Checklist for Studies Reporting Prevalence to assess the methodological quality of the included full-text articles (8). The review was carried out by two reviewers (AF and AH). Four studies scored risk of bias score of eight (2, 3, 4, 5, 6), and five studies scored a risk of bias score of nine (12, 13, 27, 14, 15). Because all the studies included for full review used purposive sampling, the risk of bias question three was marked as "N/A" for "not applicable" on the use of random allocation. Question 10 posed the question of whether an appropriate use of the numerator and denominator was conducted, however, as mentioned before, some of studies did not provide numerator and denominator values (2, 3, 4, 5, 6) and therefore the note "NP" meaning "not provided" was made on the critical appraisal form. Taking the exceptions into consideration, all the included studies scored a low risk of bias. (Appendix C, Chapter 3).

Publication bias assessment: According to the Cochrane Recommendations on testing for funnel plot asymmetry https://training.cochrane.org/handbook/current research should only carry out this assessment when there are at least ten studies included for meta-analysis. When there are fewer studies, the power of the tests will be too low to distinguish chance from real asymmetry. For this reason, we could not conduct this test.

Heterogeneity: The overall synthesis showing a prevalence of hearing loss in an African population depicted a significantly high heterogeneity (I^2=94.5%, p = 0.000). We carried out a heterogeneity assessment by temporarily removing the Adeba (2015) study (I^2= 89.9%, p = 0.00). After observing a high heterogeneity even after removing the Adeba (2015) study, we temporarily removed the Okwiri (2016) and the Noha (2015) study in addition to the Adeba (2015) study and found that the heterogeneity significantly decreased to I^2 0.00%, p = 0.00. The high heterogeneity levels could be owed to the following:

A. Physiological noise (breathing, heartbeat of the patient), psychological factors (level of concentration of the patient, how they perceive the instruction of the examiner), the method of stimulus presentation (duration of tone presentation and the length of the interval) contribute a 5-10dB difference on obtained thresholds (28). Physical attributions like differences in the model and calibration of the machine, the position of the transducer when placed in the ears of a patient and the effects of ambient noise on the results can cause a combined uncertainty level of 4.9dB. Research further states that, even though a single clinician takes all the necessary precautions to avoid an uncertainty contribution, they can still end up with a 4.9dB uncertainty level. These contributions can all affect the accuracy and reliability of the test results causing an internal and external variability of audiometric results between patients.
B. Individuals belonging to different communities are exposed to different factors in their environment that can potentially affect their hearing threshold levels. Individuals living closer to noise polluted areas or working with heavy and loud machinery such as drills and explosives stand a greater risk of acquiring noise-induced hearing loss. Ototoxic medications such as aminoglycosides, antibiotics and some cancer treatment drugs can negatively affect an individual's hearing (28).
C. Internal variability attributed to years of diabetes diagnosis and glycaemic control status in participants can influence hearing thresholds (29).

Missing Data: Some of the authors in this study needed to be contacted for additional data. We contacted the following authors for information:

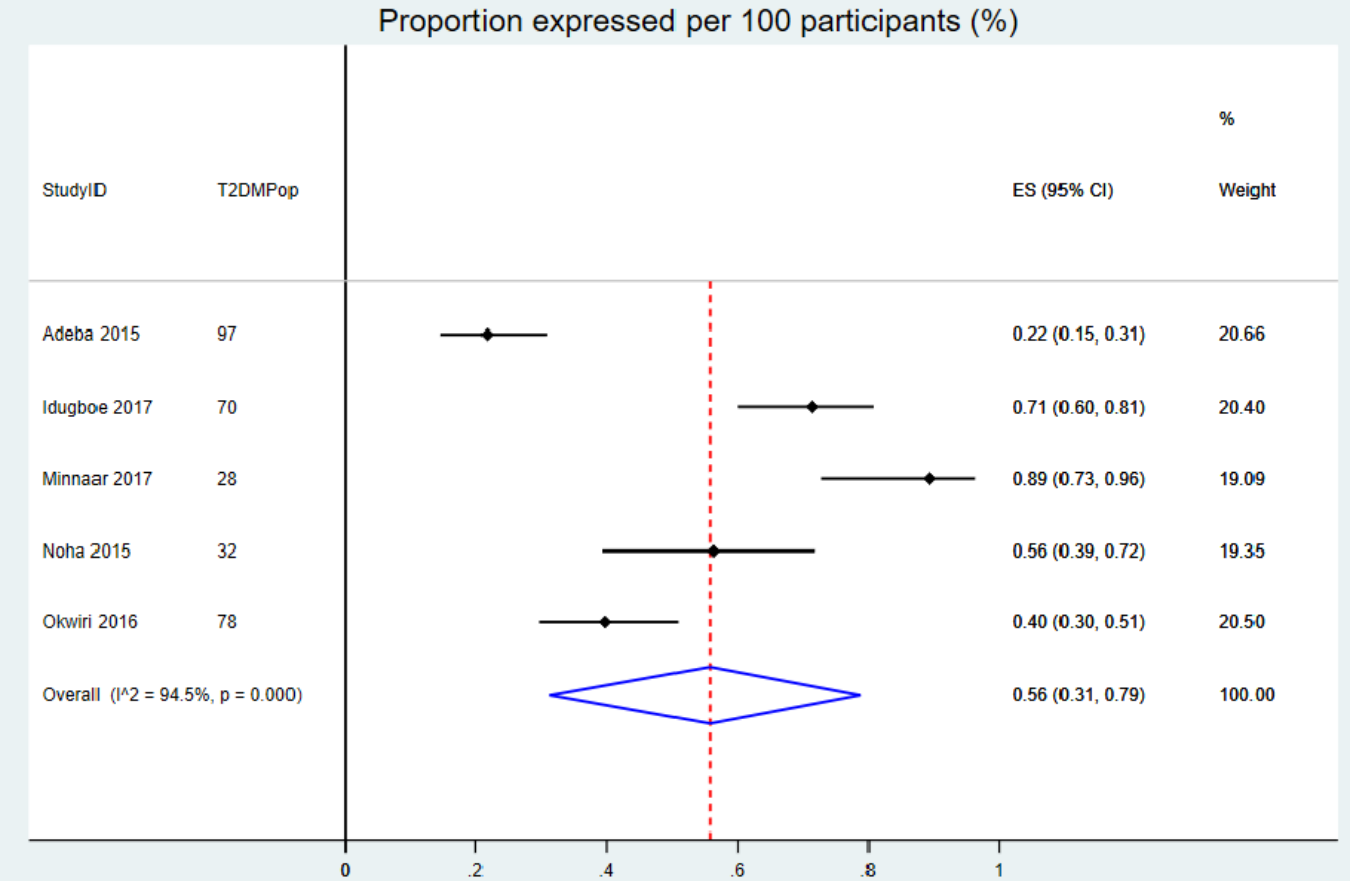
a. Lasisi et al (16): provided frequency-specific mean dB thresholds and listed the number of participants that fell into either the mild, moderate, severe, or profound level of hearing. The results were presented as that of both the T1DM and T2DM participants. In addition, results for tinnitus, sensorineural hearing loss (SNHL), labyrinthitis, Meniere's disease and poor versus good glycaemic control averages were reported as percentages. These represented both the T1DM and T2DM groups in the study. On the 31 January 2021, we emailed the study author to provide stratified numerator and denominator data for both groups in the study, but no response was received.
b. Ologe et al (19) presented frequency-specific hearing level for the T2DM and control group. The author presented these figures as mean hearing levels (dB) and standard deviations for each left and right ear frequency. We contacted the author on the 31 January 2021 to offer us the total number of participants detected to have hearing loss amongst the T2DM and control groups. The author has not responded to the request, which resulted in the study not being added for meta-analysis.
c. P300 event potentials reflect information about memory and attention associated with internal cognitive processes, affecting auditory processing. The study detailing this information is the only one identified in the African context, resulting in it not being included for a meta-analysis (18). In addition, the author did not provide numerator and denominator figures for participants with normal and abnormal P300 event potentials. The results are therefore reported narratively in the results section.

3.5. Data Synthesis:

3.5.1 Overall synthesis

The overall prevalence of hearing loss in a T2DM African population is 0.56 (95% CI, 0.31 to 0.79). The test for heterogeneity shows an I2 = 94.5% for (5 studies, n= 305). *(Figure 3)*.

Figure 3: The overall prevalence of hearing loss in a T2DM African population.



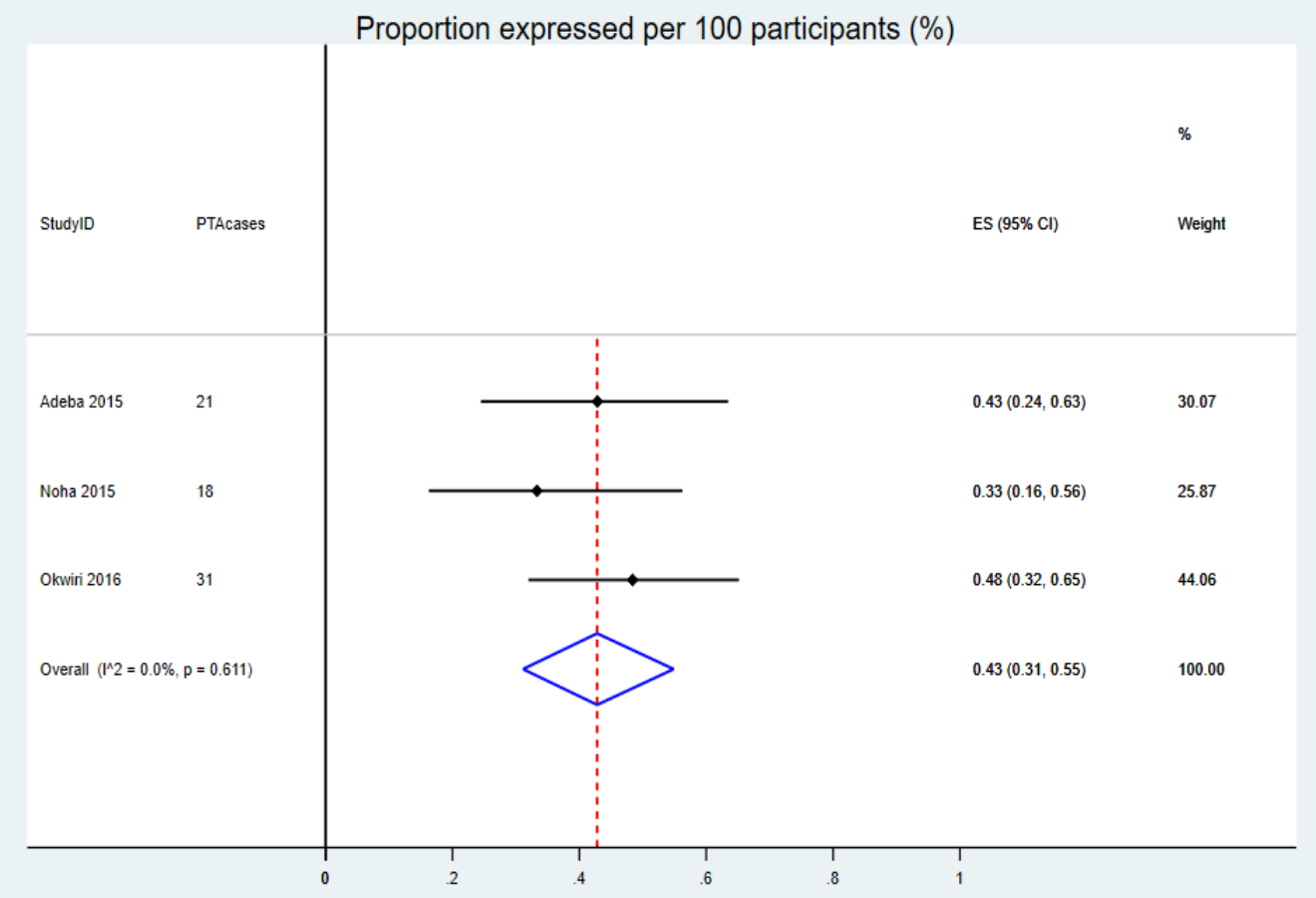
NB: T2DMPop = T2DM population

Five studies overall provided a prevalence of abnormal PTAs among African participants with T2DM. Results illustrate a 56% prevalence of hearing loss in adults with T2DM. The definition we used for abnormal PTA was a pure tone average greater than or equal to 25dB at frequencies 500Hz, 1000Hz, 2000Hz & 4000Hz. The test for heterogeneity shows an I2 of 94.5% for all the five studies. Because this result is above 75%, it tells us that there is considerable variability between the studies included for this analysis.

3.5.2. Glycaemic control analysis

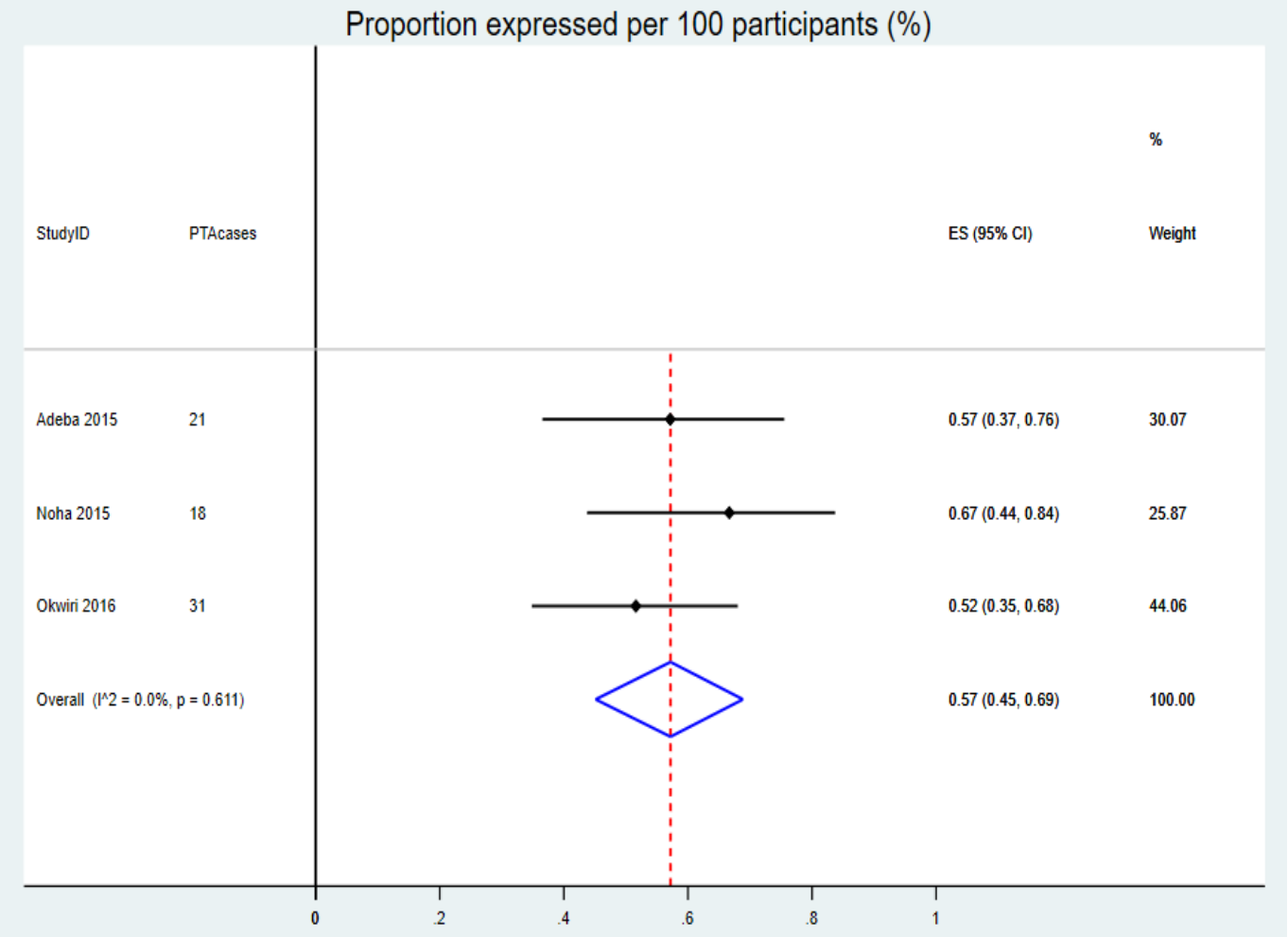
An analysis was conducted to assess the pooled prevalence estimate for good versus poor glycaemic control in participants with clinically diagnosed hearing loss. The forest plots reveal: 0.43 (95% CI, 0.31 to 0.55) (3 studies, n= 70) in the good glycaemic control group versus 0.57 (95% CI, 0.45 to 0.69) (3 studies, n= 70) in the poor glycaemic control group.

Figure 4: The prevalence rate of good glycaemic control in African participants clinically identified with hearing loss



NB: PTAcases = abnormal pure-tone audiometry cases.

Figure 5: The prevalence rate of poor glycaemic control in African participants clinically identified with hearing loss.



NB: PTAcases = abnormal pure-tone audiometry cases.

We assessed the pooled prevalence estimate for good versus poor glycaemic control in participants with clinically diagnosed hearing loss. Forest plot results revealed a 44% prevalence of individuals with hearing loss amongst those with good glycaemic control between three studies, while that of poor glycaemic control reveals a prevalence of 57% of participants presenting with a hearing loss between three studies. Both good and poor glycaemic control heterogeneity show an I^2 result of below 40%, meaning that there is very little to no variance between the three studies included for the analysis.

All the studies used the ADA (2017) and Society for Endocrinology, Metabolism and Diabetes of South Africa (EMDSA) of 2016 guideline recommendation of an average of 80-130mg/dL fasting glucose level

for good glycaemic control and an average of => 130mg/dL regarded as poor glycaemic control. The results above indicate a pooled prevalence of 43% for good glycaemic controlled participants, while those with poor glycaemic control have a 57% pooled prevalence for hearing loss.

3.5.3. Objective Hearing tests analysis.

Table 4: Mean differences of absolute and interpeak latencies across included studies

Absolute and Interpeak Latency mean differences							
Author/year	**Country**	**WAVE I**	**WAVE III**	**WAVE V**	**I-III**	**III-V**	**I-V**
Kruger, 2018	South Africa	1.60/0.22	3.85/0.28	5.73/0.43	2.25/0.27	1.91/0.24	4.15/0.43
Okwiri, 2016	Nigeria	0.67/0.26	2.88/0.40	4.63/0.61	2.21/0.40	1.74/0.34	3.65/0.58
Noha, 2015	Egypt	1.6/0.2	3.75/0.15	5.6/0.25	2.1/0.2	1.8/0.2	3.95/0.25

An Auditory Brainstem Responses (ABR) analysis could not be carried out by studies (12) (17) and (20) which conducted objective assessments on their participants because they did not provide participant proportions for their results. However, on observation of the mean differences in the absolute latencies (Wave I, III and V) showed that two (7, 5) out of the three studies exhibited delayed latencies for all three waves, while the Okwiri (2016) study showed normal absolute latencies for its participants with T2DM (27).

P300 mean amplitude for the T2DM group presented (μ = 12.10, SD = 3.70), and non-diabetic group presented with (μ = 15.08, SD = 2.82). There was a statistically significant effect of glucose on amplitude (p= 0.013). For every 1 mmol/L increase in glucose resulted in a – 0.27 amplitude decreased in the diabetic group for both ears.

3.5.4. Frequency specific hearing level comparison diabetic and non-diabetic groups

Table 5: Frequency-specific hearing mean differences in diabetics and their matched control groups (mean, standard deviation).

Frequency-specific hearing mean values for T2DM and control group									
		500Hz (m, sd)		**1000Hz (m, sd)**		**2000Hz (m, sd)**		**4000Hz (m, sd)**	
Author,year	**Country**	**T2DM**	**Control**	**T2DM**	**Control**	**T2DM**	**Control**	**T2DM**	**Control**
Minnaar, 2017	South Africa	29.2dB (14.1)	26.6dB (11.7)	26.8dB (17)	23.8dB (14.5	24.1dB (15.7)	21.9dB (13.5)	18.7dB (16.5)	19dB (17.55)
Idugboe, 2017	Nigeria	28.5dB (10.7)	23.1dB (14.2)	32dB (11.9)	22.4dB (9.5)	33.5dB (23.2)	21.5dB (10)	42.1dB (15.5)	24.4dB (11.4)
Ologe, 2005	Nigeria	30.5dB (17.45)	19dB (12.55)	30.4dB (18.15)	19.85dB (13.15)	32.6dB (18.9)	21.05dB (12.85)	37.7dB (20.35)	23.6dB (14.85)

We could not conduct a meta-analysis for frequency-specific hearing levels of 500Hz, 1000Hz, 2000Hz and 4000Hz because studies (19), (13) and (15) did not provide participant proportion for all four frequencies. However, there was no hearing loss exhibited for diabetic and non-diabetic participants in the low (500Hz) and mid (1000Hz) frequency on observation of the mean differences presented for each frequency. In the higher frequencies (2000Hz and 4000Hz), we observed mild hearing loss in studies (19) and (13) while their matched non-diabetic participants exhibited no hearing loss. The study by Minnaar, (2017) (15) presented normal hearing levels for both the diabetic and non-diabetic group.

3.6. Literature Review Findings

3.6.1. Age

Diabetes and hearing loss are common problems brought about by ageing. While T2DM has been associated with hearing loss, a causal link is difficult to establish. Most of the studies reviewed in this study show an association between T2DM and hearing impairment in both the young and middle-aged population, proving that auditory impairments caused by T2DM, are independent of the

pathophysiological changes that come from ageing. We realised that the effects of T2DM on the auditory system are easier to identify in the younger generation before the cumulative effects of ageing, noise exposure, ototoxic drugs, lifestyle and cardiometabolic that cause a discrepancy in the relationship.

Out of the studies we decided on including in this review, none of them presented age specific prevalence results related to auditory functioning for an African population. However, there was a study that carried out this investigation on a Western population aged between 20 years to 70 years of age. The results showed that as the years progressed, the more prevalent the hearing loss became. Results showed a prevalence of 4.49%, 2.97%, 0.00% and 0.00% for mild, moderate, moderately severe and severe HL respectively for individuals in their thirties. 5.87%, 1.89%, 0.38% and 0.00% respectively for individuals in their forties. 12.69%, 5.57%, 0.46% and 1.39% respectively for individuals in their fifties. 14.79%, 11.83%, 0.59% and 2.96% respectively for individuals in their sixties. Lastly, 24.59%, 14.75%, 3.28% and 3.28% respectively for individuals in their seventies. The study compared the results of subjects without DM with those that do and found that there was a greater prevalence of hearing loss in those with DM than those without (17.3% vs 6.5%, $p<0.05$). Higher frequency loss was observed in both the subjects with DM and those without, but a greater degree of high frequency hearing loss was found in those with DM, suggesting that DM can worsen higher frequency loss in individuals due to its degenerative effects.

3.6.2. Glycaemic control

Whether hearing loss is with diabetes independent of glycaemic control has not been established. A few studies have shown that hearing impairment in individuals with T2DM is expedited by poor glycaemic control. This is due to a prolonged collection of glycation of the outer hair cells associated with poor glycaemic control in individuals with T2DM. This is not a definite explanation as there some studies that have not identified a significant association between these two phenomena (29). The mechanisms of glycation are a result of an on-going research on animal models, which are limited by their hospital-based nature. The confounders and other co-morbidities of the studies were not controlled, therefore bigger epidemiological studied experimented on human subjects are necessary for full elucidation of this subject.

3.6.3. African region specific and Overall Prevalence.

Although we had set out to investigate the prevalence of diabetes related hearing loss within different regions of Africa, this study only managed to retrieve data from only four out of the 54 African countries, namely, South Africa, Egypt, Nigeria and Kenya (Figure 1, Chapter 3).

Prevalence results of hearing loss in individuals with T2DM were 22%, 40%, 56%, 71% and 89% for Nigeria, Kenya, Egypt, Nigeria and South Africa respectively. Most these studies do not provide a significant impact of T2DM on the auditory system and there are no prospective studies to prove the potential causality of T2DM on the auditory system.

There are reportedly more studies looking at the effects of T2DM on the auditory system carried out on a Western and European individuals. Although there is some merit in knowing the effects of T2DM on auditory functioning in other populations to allow inference of data to the less developed countries, lifestyle trends and limited access to resources due to budget constraints will require their own tailored intervention programs different from those of the Western and European nations

3.7. Discussion:

3.7.1. Summary of main results

This study reviews research on an African population using a comprehensive search strategy across several electronic databases and grey literature sites without enforcing a language or publication-type barrier. Our main aim for this systematic review was to determine the prevalence of abnormal hearing responses on an African population with T2DM as well as present it for adults over the age of 65 and under 65. Unfortunately, we could not present this analysis because all the study participants included for this review were below the age of 60 years of age. Furthermore, we were unable to pool data and present it as per region as stipulated in the protocol as there were only four (Egypt, Kenya, Nigeria and South Africa) out of the 54 African countries presented. Three out of the four countries were represented by one study each (Egypt, Kenya and South Africa), while Nigeria had four studies included (see Figure 1, chapter 3). We could not pool area setting data as studies included for this review did not disclose the type of area they sampled their participants from. We pooled data for good versus poor glycaemic control. Furthermore, we conducted an overall analysis of hearing loss within an African population with T2DM. We narratively reported objective hearing assessment and frequency-specific hearing level data on account of missing numerator and denominator information.

3.7.2. Overall application of evidence

Pooled calculation of the prevalence of hearing loss in an African population with T2DM was found to be 56%. Although this meta-analysis does not explicitly show the degree of hearing loss, all these studies used the same criterion to diagnose HL as a PTA greater than 25dB. Therefore, it would be safer to infer that people with T2DM are more likely to have a hearing threshold above 25dB. On observation of the frequency-specific hearing level table, most PTA thresholds were found to be below 30dB in the low frequency (500Hz) for two out of the three included studies (13, 15). The hearing levels decreased from the mid-to-higher frequency levels for two out of the three studies (13, 19). This suggests that hearing loss may not significantly impact the quality of life of people with T2DM, but great caution should be taken to avoid conditions that may superimpose on hearing structures and worsen the mild degree of hearing loss.

Additionally, the frequency-specific hearing level table reveals that higher frequencies present with greater hearing thresholds for the Omoregie (2017) and Ologe (2005) studies (13) (19). These studies assessed participants of an older diabetic population. This information concurs with evidence shown by several studies stating hearing loss is more dominant in higher frequencies (30, 31, 32), and further solidifies evidence of an original study by Taylor et al (33) who discovered that the configuration of diabetes-related hearing loss mimicked that of presbycusis. Presbycusis usually occurs as people gradually grow older and are most likely to begin at 65 years (34). As ageing occurs, a person starts to lose sensory cells at the basal turn of the cochlea resulting in higher-frequency hearing loss (35, 36). Unfortunately, we were unable to ascertain the cause of the higher frequency loss for most of the studies as all the participants across the studies were below the age of 65, and hearing thresholds were not stratified according to age groups in most of the studies included. In either case, high-frequency hearing loss cases often have trouble understanding speech, and when left untreated, can worsen and negatively impact an individual's quality-of-life.

Objective tests analysis

Analysis of mean differences of the absolute and interpeak latencies of the three studies in (*table 2, chapter 3*) show us that most of the studies reveal longer latencies for their T2DM population when compared to normative values published by the University of Cape Town (UCT), Audiology Department (26). These results are in accordance with Durmus's study (37) who found prolonged absolute latencies, and Gupta (42) who found waves III and V to be prolonged but equal in wave I for the diabetes and control group. Latencies give us information about the speed electrical sound signals

are transmitted through different parts of the auditory brainstem (38). Therefore, elongation of waves I, III and V in studies (12) and (20) signifies a delay in the conduction of auditory signals within the brainstem of diabetic individuals. The Okwiri (2016) study showed faster conduction for waves III and V, but delayed transmission for wave I (17).

Interpeak latencies (IPL) for most of the studies were delayed. IPL's for waves I-III and III-V were delayed for studies (12) and (17) but normal for (20), when compared to normative data. These findings justify findings by Bansal (2006) (39), which declaring neuronal development is prominent among people with diabetes complications. Therefore, it is expected for neurons in the brainstem to show significant changes in the diabetic groups compared to normative data.

P300 event potentials were assessed on normal hearing participants clinically diagnosed with T2DM. This assessment gives us information about the processing of memory and attention mechanisms which are dependent on internal cognitive processing (40). The latency (marked by 240-400ms) indicates the speed of processing, while amplitude (marked by 8-15 µV) indicates attention ability (41, 42). P300 neural generators are the hippocampus, thalamus, inferior parietal lobe, temporal lobe, dorsolateral prefrontal cortex, cingulate cortex, and amygdala (40, 41, 42). A study by Sadeghi (43) stated that the hippocampus can be affected by T2DM and decrease auditory information processing speed. This finding is concurrent with the results of the van der Westhuizen study (18) reporting a significant decrease in P300 amplitude (12.10 µV, SD = 3.70) and an increase in latency (352.56ms, SD= 36.36) in adults. The latency results for this study agree with previous studies showing an average of 314.8 to 405.6ms, but higher than amplitude results, which demonstrate 1.98 µV for the de Freitas Alvarenga (2005) study and 3.15 µV for the Manjeet (2013) study (44) (45). The significance of this assessment is to gather information on the subclinical effects T2DM may or may not invoke in adults tested normal for behavioural audiometric testing.

Glycaemic control analysis

Glycaemic control refers to the typical levels of blood sugar (glucose) in a person with DM. For sub-group analysis, we split the hearing results between good and poor glycaemic control, which are categories based on the ADA guideline recommendation of 2017 (46). Good glycaemic control is defined as an average fasting blood glucose level of 80-130mg/dL, while a poor glycaemic control is an average fasting blood glucose level of >130mg/dL (46). Prevalence data for glycaemic control indicate a pooled prevalence of 43% for good glycaemic controlled participants, while those with poor glycaemic control show a pooled prevalence of 57% of hearing loss. These results coincide with the

Beaver Dam Study that found a significant risk of hearing loss in individuals with poorly controlled DM (47). Unfortunately, we did not have enough studies to pool data for objective hearing tests, but one study expressed ABR results for good and poor glycaemic control participants (20). Participants with poor glycaemic control presented slightly delayed latencies across all waves, while participants of good glycaemic control presented a slight delay in wave III. These findings concur with three studies that found that the presence of high glucose levels in the blood create free radicals which over time cause excessive production of reactive oxygen species that lead to neuronal cell death, causing a delay in ABR potentials (48, 49, 50). It further states that delayed ABR latencies can be prevented or reversed through the treatment of antioxidants. These antioxidants reverse the effect of diabetes on nerve conduction velocities and improve auditory neural signal transfer in the brainstem (50). Further research on this matter will better our understanding of diabetes induced pathogenesis of hearing loss.

3.7.3. Limitations:

There are a few potential limitations that could be sources of bias in this meta-analysis:

- We included both the PTA and ABR results, which pose the risk of being configure differently. Although the PTA audiometers results were presented according to the 4- tone PTA average, they may vary regarding calibration and the model of the machine. In addition, the PTA and ABR tests provide different results as one assesses behavioural hearing perception and the other evaluates retrocochlear pathways of hearing, respectively.

- We observed some heterogeneity in the results of the included studies. The variance can be attributed to the small number of studies included, different sample sizes, populations, proportions of diabetes and control groups, and hearing loss prevalence in the control groups across included papers.

- Realising a causal relationship between T2DM and hearing loss or any other auditory disorder is a complex deed as we have no record of the participants hearing acuity before T2DM diagnosis. Thus, conducting a prospective study is required to establish the linear progression of hearing function in people with T2DM and compare them to their matched controls.

- Internal variability such as glycaemic control levels and years of diagnosis within people with diabetes can influence hearing thresholds. That is why randomising participants into experiment and control groups for prospective observation can be effective in assessing the effects of these covariables.

- Lastly, different population groups come from different countries and different environments. Even though they are age-matched with their experimental groups, we remain uncertain of potential aggravators in the environment that can influence the effects of T2DM on the auditory system.

3.7.4. Strengths

This systematic review is the first of its kind to assess the prevalence of auditory dysfunction in people living in Africa diagnosed with T2DM. Its main strength is the method it undertook to retrieve viable studies for review and synthesis. Firstly, we utilised the skills of a professional librarian to formulate a comprehensive search strategy for different electronic databases to retrieve as many studies related to the topic as possible. In addition, using an African search filter, no language and publication restriction ensured that we got the maximum number of studies available for review. As suggested by the PRISMA guidelines of 2020 we have carried out a methodological quality appraisal on each study's individual study. We enforced a 1999 publication date limit to ensure that the method of hearing assessment for all the studies included reflects the updated WHO hearing loss definition. This ensures that hearing acuity results from all the studies are standardised to that of the updated WHO definition.

3.7.5. Conclusion and Recommendations:

The results of this meta-analysis show an overall prevalence of 56% for hearing loss in an adult T2DM population. Many of the participants were found to present with mild hearing loss which was more prevalent in the higher frequencies (2kHz – 4kHz). These results are compatible with most studies assessing the prevalence of auditory dysfunction in T2DM participants.

The ABR absolute wave latencies I, II and V are slightly longer when compared to normative adult data, which is equivalent to studies that found slower latencies within the T2DM groups. Our findings show that most participants with T2DM experienced mild hearing loss and slight delays in their objective hearing assessments. Africa is a poorly resourced continent. Audiometric resources and qualified audiologists are scarce. Therefore, the available evidence we currently have does not justify the added costs needed for routine audiometric assessments for patients with T2DM. However, this paper does serve to recommend prioritising further research regarding risk factors associated with developing auditory disorders in people with T2DM. In addition, in honour of there being a positive risk for developing hearing loss, adapting low-cost methods for patient and clinician education would help patients and health practitioners be aware of added complications related to T2DM diagnosis.

3.8. Ethics and Dissemination

This study did not require ethical clearance as we utilised secondary data that is accessible to the public. The study protocol was submitted to the UCT and reviewed by the Faculty of Health Science Human Research Ethics Committee (reference number: HREC/REF 264/2021). The waiver is located in *Appendix C, chapter 3*.

3.9. Funding

No funding was needed for the carry through of this systematic review.

3.10. Contributions

All authors of the study were responsible for formulating the structure of the protocol. AF designed the study, conducted the literature search, and formulated the data extraction sheet. AF, AH and LP screened for eligible studies to be included for the study and extracted the relevant information for data analysis and synthesis. AF synthesised the data and wrote the final draft of the paper. AH provided critical guidance on the analysis and LP guided the direction of the study. All authors proof-read the 3 parts of the paper and approved the final version.

3.11. Declaration of interests

We declare that there are no competing interests to the creation of this study.

3.12. Acknowledgements

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2157 Appendix A: PRISMA Checklist 2009

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Appendix B: Descriptive Search Strategy

PUBMED/MEDLINE/SCOPUS/EBSCOHOST

PubMed – Achuma 15 Feb 2021. Rerun on 09 May 2021 (26 results)

#13

Search: (((((Hearing Disorders OR hearing loss OR hearing impairment OR hearing disorder OR auditory disorder OR auditory disorders) OR ("Hearing Disorders"[Mesh])) OR ("Hearing Loss"[Mesh])) OR (deaf OR deafness)) AND ((type 2 diabetes OR type 2 diabetes mellitus OR T2DM OR NIDDM OR non-insulin dependent diabetes) OR ("Diabetes Mellitus, Type 2"[Mesh]))) AND ((Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe) OR ("Africa"[Mesh])

26 02:15:53

#12

Search: (Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe) OR ("Africa"[Mesh])

904,761 02:15:40

#11

Search: "Africa"[Mesh] Sort by: Most Recent

274,396 02:15:27

#10

Search: Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe

904,761 02:15:05

#9

Search: ((((Hearing Disorders OR hearing loss OR hearing impairment OR hearing disorder OR auditory disorder OR auditory disorders) OR ("Hearing Disorders"[Mesh])) OR ("Hearing Loss"[Mesh])) OR (deaf OR deafness)) AND ((type 2 diabetes OR type 2 diabetes mellitus OR T2DM OR NIDDM OR non-insulin dependent diabetes) OR ("Diabetes Mellitus, Type 2"[Mesh]))

537 02:13:59

#8

Search: (type 2 diabetes OR type 2 diabetes mellitus OR T2DM OR NIDDM OR non-insulin dependent diabetes) OR ("Diabetes Mellitus, Type 2"[Mesh])

195,791 02:13:42

#7

Search: (((Hearing Disorders OR hearing loss OR hearing impairment OR hearing disorder OR auditory disorder OR auditory disorders) OR ("Hearing Disorders"[Mesh])) OR ("Hearing Loss"[Mesh])) OR (deaf OR deafness)

141,686 02:13:31

#6

Search: "Diabetes Mellitus, Type 2"[Mesh] Sort by: Most Recent

137,111 02:13:04

#5

Search: type 2 diabetes OR type 2 diabetes mellitus OR T2DM OR NIDDM OR non-insulin dependent diabetes

195,791 02:12:38

#4

Search: deaf OR deafness

47,935 02:10:18

#3

Search: "Hearing Loss"[Mesh] Sort by: Most Recent

70,299 02:10:04

#2

Search: "Hearing Disorders"[Mesh] Sort by: Most Recent

88,243 02:09:22

#1

Search: Hearing Disorders OR hearing loss OR hearing impairment OR hearing disorder OR auditory disorder OR auditory disorders

132,687

Ebsco

Attached

Scopus

4

(TITLE-ABS-KEY (("Hearing Disorder*" OR "hearing loss" OR "hearing impairment" OR "auditory disorder*"))) AND (TITLE-ABS-KEY (("type 2 diabetes" OR "type 2 diabetes mellitus" OR t2dm OR niddm OR "non-insulin dependent diabetes"))) AND (TITLE-ABS-KEY (africa OR african OR algeria OR angola OR benin OR botswana OR "Burkina Faso" OR burundi OR "Cabo Verde" OR cameroon

OR cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR chad OR comoros OR congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR djibouti OR egypt OR eritrea OR eswatini OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea- AND bissau OR "Ivory Coast" OR jamahiriya OR kenya OR lesotho OR liberia OR libya OR madagascar OR malawi OR mali OR mauritania OR mauritius OR mayotte OR morocco OR mozambique OR namibia OR niger OR nigeria OR principe OR reunion OR rwanda OR "Saint Helena" OR "Sao Tome" OR senegal OR seychelles OR "Sierra Leone" OR somalia OR "St Helena" OR sudan OR swaziland OR tanzania OR togo OR tunisia OR uganda OR "Western Sahara" OR zaire OR zambia OR zimbabwe))

3 document results

3

TITLE-ABS-KEY (africa OR african OR algeria OR angola OR benin OR botswana OR "Burkina Faso" OR burundi OR "Cabo Verde" OR cameroon OR cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR chad OR comoros OR congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR djibouti OR egypt OR eritrea OR eswatini OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea- AND bissau OR "Ivory Coast" OR jamahiriya OR kenya OR lesotho OR liberia OR libya OR madagascar OR malawi OR mali OR mauritania OR mauritius OR mayotte OR morocco OR mozambique OR namibia OR niger OR nigeria OR principe OR reunion OR rwanda OR "Saint Helena" OR "Sao Tome" OR senegal OR seychelles OR "Sierra Leone" OR somalia OR "St Helena" OR sudan OR swaziland OR tanzania OR togo OR tunisia OR uganda OR "Western Sahara" OR zaire OR zambia OR zimbabwe)

148,871 document results

2

TITLE-ABS-KEY (("type 2 diabetes" OR "type 2 diabetes mellitus" OR t2dm OR niddm OR "non-insulin dependent diabetes"))

256,372 document results

1

TITLE-ABS-KEY (("Hearing Disorder*" OR "hearing loss" OR "hearing impairment" OR "auditory disorder*"))

137,377 document results

- Manual searches were carried out for Google Scholar and the OpenUCT Theses and Dissertations web browser.

Appendix C: Human Research Ethics Waiver

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

26 April 2021

HREC/REF 264/2021

A/Prof M Engel
Department of Medicine
J46.43-, OMB
Email: mark.engel@uct.ac.za
Student: fhlach001@myuct.ac.za

Dear A/Prof Engel

PROJECT TITLE: THE EPIDEMIOLOGY OF AUDITORY DYSFUNCTION IN TYPE 2 DIABETES MELLITUS ADULTS IN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a systematic review.

As the systematic review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: "*Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research.*"

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledge that the Master's Candidate, Miss Achuma Fihla, IS also involved in this project.

Yours sincerely

pp UBurges)

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Appendix D: Critical Appraisal Checklist

Hoy et al. Critical Appraisal Checklist for Studies Reporting Prevalence (11)

Reviewer: Achuma Fihla

Date: 11 May 2021

HOY ET AL., QUALITY ASSESSMENT CRITERIA FOR PREVALENCE STUDIES									
	Author/Date								
Questions	Minnaar. D., 2017	Noha. M. et al., 2015	Kruger.L., 2018	Lasisi. O.A., 2003	Okwiri. N., 2016	Adebola. S. O., 2015	Van der Westhuizen., 2019	Idugboe.O.J., 2017	Ologe.F.E., 2005
External Validity									
Risk of Bias 1	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 2	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Risk of Bias 4	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Internal Validity									
Risk of Bias 5	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 6	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 7	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 8	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 9	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Risk of Bias 10	LOW	NP	LOW	NP	LOW	LOW	NP	LOW	NP
QUALITY OF METHODOLOGY (no. of points):	9	8	9	8	9	9	8	9	8