Spring 2022

# Associations Between Atherogenic Markers and Hearing Loss: National Health and Nutrition Examination Survey: 2011-2012, 2015-2016

Anna Anya Rombakh
*Central Washington University*, rombakhanya@hotmail.com

# ASSOCIATIONS BETWEEN ATHEROGENIC MARKERS AND HEARING LOSS: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY: 2011-2012, 2015-2016

---

A Thesis

Presented to

The Graduate Faculty

Central Washington University

---

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

Nutrition

---

by

Anna Rombakh

June 2022

CENTRAL WASHINGTON UNIVERSITY

Graduate Studies

We hereby approve the thesis of

Anna Rombakh

Candidate for the degree of Master of Science

APPROVED FOR THE GRADUATE FACULTY

_____ _____
Dr. David Gee, Committee Chair

_____ _____
Dr. Amie Wojtyna

_____ _____
Dr. Nicole Stendell-Hollis

_____ _____
Dean of Graduate Studies

ABSTRACT

# ASSOCIATIONS BETWEEN ATHEROGENIC MARKERS AND HEARING LOSS: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY: 2011-2012, 2015-2016

Anna Rombakh

June 2022

**Importance** Hearing loss (HL) is a major public health problem that has been previously found to be associated with abnormal atherogenic markers.

**Objective** To investigate the associations between such atherogenic markers and the degree of HL using continuous NHANES data from cycle years 2011-2012 and 2015-2016.

**Design, Study, and Participants** This observational study used data from two National Health and Nutrition Examination Survey (NHANES) cycle years 2011-2012 and 2015-2016. NHANES continuously conducts data collection via home interviews and physical exams completed in their Mobile Examination Centers. NHANES participants ages 20-69 who partook in audiometry, anthropometric and laboratory testing were included. Data was analyzed from 2011-2012 and 2015-2016 cycle years.

**Exposures** Substantial hearing loss was defined as a HL degree of moderate (41-55dB) or higher at any frequency.

**Main Outcomes and Measures** Risk of hypercholesterolemia was defined as $\geq 240$ mg/dL, hypoalphalipoproteinemia or low levels of high-density lipoprotein cholesterol as

≤ 40 mg/dL for males and ≤ 50 mg/dL for females, elevated low-density lipoprotein cholesterol as ≥ 160 mg/dL, hypertriglyceridemia was defined as ≥ 175 mg/dL, elevated levels of Apolipoprotein B as ≥ 130 mg/dL and elevated non-high-density lipoprotein cholesterol as ≥ 190 mg/dL. Associations between abnormal atherogenic markers and substantial HL were determined in adjusted multivariate logistic regression models, t-tests and chi-square analysis.

**Results** Among 8955 participants there were significant associations between gender, age, BMI and race/ethnicity and substantial hearing loss ($p<.0001$). No significant differences were identified between people with normal and substantial hearing loss in regards to mean concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B cholesterol (ApoB). Significant differences were identified between prevalence of triglycerides and substantial hearing loss ($p<.0001$). Multivariate logistic regression models found that after adjusting for covariates there was no significant association between having hypertriglyceridemia and substantial hearing loss (OR 1.2, 95% CI, 0.8-1.8).

**Conclusions and Relevance** This study's results showed no association between atherosclerosis markers and degree of hearing loss. However, due to conflicting findings of several studies on this topic, further research should be done to determine if lipid markers can affect hearing loss.

ACKNOWLEDGMENTS

Thank you Dr. David Gee, Dr. Amie Wojtyna, and Dr. Nicole Stendell-Hollis for your consistent help and support throughout the CWU Nutrition graduate program.

TABLE OF CONTENTS

LIST OF TABLES

# CHAPTER 1

## INTRODUCTION

In 2019, hearing loss (HL) affected an estimated 1.5 billion of the global population, contributing to the third most common cause of years of living with disability (YLDs).[1] HL is commonly believed to be caused by noise exposure or aging, but still largely remains a major public health problem with an unclear etiology. HL in midlife has also been estimated to be associated with 9% of dementia cases, increasing an individual's level of cognitive impairment and leading to social isolation.[2,3]

HL can be caused by damage or dysfunction of the peripheral and/or central auditory system from the external ear to the cerebral auditory cortex. HL type can be categorized as sensorineural (cochlear or spiral ganglion impairment), conductive (outer or inner ear impairment) or mixed.[4] Mechanisms currently under investigation for HL includes development of reactive oxygen species (ROS) and oxidative stress possibly caused by antioxidant imbalances,[5,6] and the "lipid hypothesis". The current possible explanation for the "lipid hypothesis" is that as atherosclerosis markers such as total serum cholesterol elevate, blood viscosity will increase contributing to atherosclerosis of arteries such as the internal auditory artery (IAA). The IAA is responsible for supplying blood to the cochlea, auditory nerve, and the stria vascularis (SV) which is located at the wall of the cochlea.[7] When blood supply to the SV is constricted, vital nutrients are unable to be supplied to hair cells, also known as stereocilia, leading to the irreversible damage of hair cells and diminished hearing sensitivity.[8] This type of damage has been seen in numerous studies in individuals with cardiovascular disease, diabetes, chronic kidney disease and in individuals with dyslipidemia.[9-13] Similarly, an observational study

utilizing data from the National Health and Nutrition Examination Survey (NHANES) examining the relationship between risk factors of hearing loss and diabetes identified that individuals with low high-density lipoprotein and elevated total cholesterol where more likely to be hearing impaired.[9]

The original study on this lipid hypothesis investigated hearing levels of members of the southeast Sudan tribe, known as the Mabaans. Living in a noise-free environment, researchers Rosen and colleagues sought out to research the possible associations between vascular changes such as blood pressure, cholesterol and hearing loss compared to healthy adults living in the United States. Rosen et al., identified that there was a positive inverse relationship with better hearing being associated with lowered cholesterol levels. They also concluded that although noise exposure is an obvious and large component in hearing loss, other factors such as nutrition, vascular changes, stress, climate, and genetic factors play a more significant role then previously known at the time. This inspired many to continue examining the relationship of blood lipids and hearing loss.[14]

In an experimental study done in 1997, Nguyen and Brownell identified that lipidosis of the inner ear may be a mechanism of vascular changes affecting hearing. Nguyen identified in guinea pig cochlea that cholesterol has varied distributions among outer stereocilia membranes, and when cholesterol is integrated in such cells, lateral wall stiffness increases, possibly contributing to hearing impairment.[15] Therefore, the purpose of this observational study was to investigate the associations between such atherogenic markers and the degree of hearing loss using continuous NHANES data from cycle years 2011-2012 and 2015-2016.

# LITERATURE REVIEW

## Hearing Loss
### *Prevalence and Mechanisms*

As of 2019, 1.57 billion people experienced hearing loss (HL) globally.[1] Accounting for 20.3% of the global population, those experiencing HL are inconvenienced with economic burden, social isolation, cognitive impairment, and depression or anxiety.[2-4] According to the Global Burden of Disease Study 2019, the number of individuals with moderate to complete hearing loss has increased by 79.1% since 1990.[1] This rapid increase of HL prevalence is concerning according to the World Health Organization (WHO), yet it is not getting the proper awareness by public health officials and society.[16]Although one may speculate that this rapid increase can be attributed to the expeditious aging population (>60 years), which is projected to double by 2050.[17] HL has also been studied to be correlated with disorders such as dementia in older adults,[3] speech and language developmental delays in children,[18] and diseases such as diabetes, hypertension, chronic kidney disease and cardiovascular disease.[13]

There are various types of HL, which can be classified as either conductive (damage of outer or middle ear), sensorineural (impairment in the cochlea or spiral ganglion) or mixed (both conductive and sensorineural). The peripheral auditory system which is responsible for converting sound energy into neural signals, is comprised of the outer, middle, and inner ear (cochlea). The hair cells (also known as stereocilia) of the cochlea are supplied nerve signals by the neurons of the spiral ganglion, which are signaled centrally to the auditory nuclei of the brain stem via the auditory nerve. Mammalian cochlea stereocilia are vulnerable to irreversible damage from various

stressors, and are not regenerated, therefore when damage to the hair cells is present, it is permanent.[19]

Auditory testing is commonly performed using pure tone air conduction audiometry (PTA). This type of audiometry testing examines sensitivity of hearing by presenting an individual with pure tone signals to each ear through earphones at varied intensity.[20] Hearing threshold is determined by the softest sound an individual can hear at each frequency 50 percent of the time, using frequencies vital to human communication[14]. Sensitivity of PTA testing has been set at 92 percent, with a specificity of 94 percent in diagnosing sensorineural hearing loss.[21,22]

HL causes are multifactorial, ranging from aging processes, genetics, noise, and environmental exposures, or idiopathic. Sex differences have also been reported for HL, with males being more likely to experience HL compared to women. This can be accredited to men being more likely to work in occupations exposed to workplace noise, according to a Canadian study.[23] As previously mentioned, chronic diseases have been examined for their correlations with HL, with cardiovascular disease risk factors being a focus of literature since 1965, when the original study was published by Rosen and Olin on the possible association of HL and elevated serum cholesterol and blood pressure.[14,24]

## Associations with Hearing Loss

### *Dyslipidemia*

Recently, chronic diseases have been examined in literature for their association with HL. Dyslipidemia is a known risk factor for cardiovascular disease and can be defined as elevated atherogenic markers such as total serum cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides, apolipoprotein B (ApoB) or low levels of

high-density lipoprotein cholesterol (HDL-C). However, recent studies have also made claims that non-high density lipoprotein (non-HDL-C) may be a better atherogenic marker to include when analyzing for risk of cardiovascular disease.[25-27] Non-HDL-C is calculated by subtracting HDL-C from TC and does not require a fasted blood sample. It also encompasses LDL-C and very low lipoprotein cholesterol (VLDL-C), therefore including all apolipoprotein B lipoproteins,[19] LDL-C, an important pro-atherogenic lipoprotein, inhabits cholesteryl ester and TG inside the particle, and apolipoproteins on the surface. The main transporter of TG is VLDL-C, and when lipolysis of this particle occurs, LDL-C is created.[27] LDL-C is considered vital in CVD risk assessment, as it is responsible for cholesterol transport to tissues which accumulates in the plasma. When the cholesterol component of LDL-C is deposited in the endothelium of the arteries, development of atherosclerosis occurs. ApoB, a primary apolipoprotein of LDL-C, has also been found to be related to cardiovascular disease risk when elevated. HDL-C, the smallest lipoprotein found in plasma, plays an influential role in reverse cholesterol transport, a system in the body that reverses atherosclerosis processes. Therefore, low levels of HDL-C are at as a large component of cardiovascular disease risk.[28]

Dyslipidemia is currently on the rise in the United States, with current prevalence at 49.2% and increasing with age.[27] Dyslipidemia and its relationship with HL is controversial, as many studies have conflicting findings. Researchers Rosen and Olin in 1965, identified that there was a positive inverse relationship with better hearing and lowered serum cholesterol levels.[24] Lee and researchers also identified that elevated TC and TG levels were significantly associated with an increased prevalence of sensorineural hearing loss.[29] Elevated TG levels were identified as possible risk factors for hearing loss

caused by noise exposure in a study done by Chang et al.,[26] yet Gold and researchers did not identify a significant association in their study done in 1989,[25] Related results were found in a study done by Helzner et al., where the association between cardiovascular disease (CVD) and risk factors with age-related hearing loss (presbycusis) were assessed in a population of black and white older adults.[8] This cross-sectional cohort study recruited 2,049 healthy adults to undergo pure-tone audiometry testing as well as CVD history and risk factors. Helzner and researchers found that elevated levels of TG and high BMI (especially among women) were significantly associated with diminished auditory function. On the contrary, researchers in a Norway study found, surprisingly, that elevated levels of HDL-C and lowered levels of LDL-C and TC had protective effects on hearing.[30] Marlow et al., also found that when assessing the relationship between hearing impairment and undiagnosed diseases such as hyperlipidemia, there was no significant difference between adults with hearing impairment and adults with usual hearing.[13]

As previously mentioned, recently non-HDL-C has been studied as a better marker for cardiovascular disease then other atherogenic markers. In a recent study evaluating the association of non-HDL-C and risk of sensorineural hearing loss using Korean Health and Nutrition Examination Survey (KNHANES), researchers identified that elevated non-HDL-C was significantly associated with an increased risk, possibly making non-HDL-C a valuable tool in predicting  sensorineural hearing loss risk.[31] Similarly, researchers Ballesteros and colleagues evaluated genetic and acquired risk factors of individuals dealing with sudden sensorineural hearing loss and if there was a correlation with cardiovascular risk factors. They found that there was a positive

association between abnormal lipid profiles and increased risk of sensorineural hearing loss, yet researchers concluded that multi-causality should be further researched in risk of sensorineural hearing loss.[32]

### *Dyslipidemia and Hearing Loss Mechanisms*

Possible explanations for arteriosclerotic changes being involved in hearing loss has been explained by multiple theories. The current possible explanation is that as atherosclerosis markers such as TC elevate, blood viscosity will increase contributing to atherosclerosis of arteries such as the internal auditory artery (IAA). The IAA is responsible for supplying blood to the cochlea, auditory nerve and the stria vascularis (SV) which is located at the wall of the cochlea.[8]When blood supply to the SV is constricted, vital nutrients are unable to be supplied to stereocilia, leading to the irreversible damage of stereocilia and diminished hearing sensitivity.[25] As previously mentioned, several studies have identified correlations with hypertriglyceridemia with an increased risk of having hearing loss. This can be perhaps explained by an experimental study done by Skeggs et al., in which it was identified that isolated enrichment of triglycerides adequately activates the alteration of cholesterol removal and delivery mechanisms, possibly leading to a diminished function of the endothelium[33] and reduced microcirculation of the cochlea.

### *BMI and Hearing Loss*

Several studies have emphasized that elevated BMI or obesity may be correlated with an increased risk of hearing loss.[34] Due to obesity already having numerous co-morbidities including hypertension, cardiovascular disease, diabetes, and dyslipidemia

that have also been associated with increased risk of hearing loss, many researchers have aimed to examine if such relationships exist with hearing loss as well.[35]

In a retrospective longitudinal study utilizing data from the Nurses' Health Study II, researchers examined associations of elevated BMI, waist circumference, physical activity, and self-reported hearing loss in women. They identified that women with an elevated BMI are at an increased risk of hearing loss.[36] Similarly in a cross-sectional and longitudinal prospective study, researchers in Korea identified that higher levels of TC, TG, and BMI were significantly associated with an increased risk of sensorineural hearing loss.[29] However, in a retrospective cohort study done in Taiwan, researchers did not identify any significant association with sensorineural hearing loss diagnosis.[37]

Positive inverse relationships have also been identified in many studies researching the associations of cardiovascular risk factors and elevated BMI. In a recent cross-sectional study conducted in Australia, researchers aimed to assess relationships between hearing loss and cardiovascular risk factors using data from a larger community-based population study. Tan et al., found that obesity, elevated TC, and lowered HDL-C were all associated with an increased prevalence of hearing loss.[38] On the contrary, Sharagorodsky and researchers examined cardiovascular risk factors and incident hearing loss in men, and identified that a history of elevated cholesterol was associated independently to risk of hearing loss, yet elevated BMI was not found to be associated with hearing loss risk.[39] Similarly, researchers Lohi and colleagues, researched the relationship of hearing impairment and cardiovascular disease, and did not identify a significant association between cardiovascular disease and hearing loss in the cross-sectional study. However, elevated BMI was identified as more common in men with

hearing loss.[40] The linear relationship of elevated BMI and hearing loss, seems to be supported by many studies, although due to elevated BMI being also associated with many other confounding factors such as cardiovascular disease risk, hypertension, and diabetes, it's vital for further research to be done to better understand if elevated BMI is independently responsible for hearing loss risk.

### *Elevated BMI and Hearing Loss Mechanisms*

Proposed mechanisms behind elevated BMI or obesity and hearing impairment are not fully understood in literature, nevertheless there are several possible explanations. Researchers have proposed that lifestyle factors such as lack of physical activity and overconsumption of specific foods such as foods high in trans-fat and saturated fat, leads to increased risk of cardiovascular disease contributing to hearing loss risk. This outcome was examined in a longitudinal cohort study evaluating associations between healthy dietary patterns and risk of hearing loss in women. Researchers identified that in fact when women had followed the DASH diet, they had a lowered risk of hearing loss.[41]

Another proposed mechanism identified in the relationship between obesity and hearing loss is lowered levels of adiponectin, an anti-inflammatory adipokine associated with obesity and other metabolic disorders. Adiponectin is also involved in the regulation of insulin sensitivity, metabolism, and atherosclerosis. When elevated, adiponectin has been linked to an inverse relationship with high-frequency hearing loss, implying that low levels may lead to hearing impairment.[42] This relationship was proven in two experimental animal studies conducted on mice. The first study, conducted by Wu et al., aimed to observe the function of adiponectin in hearing loss by examining genotypes associated with polymorphisms of the adiponectin gene. Researchers recruited Han

Chinese volunteers aged 40-80 years to establish a cohort for research on adiponectin genotypes. In addition, these researchers also studied mature mice to confirm the role of adiponectin in hearing loss in this study's experiment. Wu et al., identified that the adiponectin genotypes show effects on hearing levels when plasma adiponectin levels fluctuate, and this finding was further established in mice cochlea.[43] Similarly, a study done by Tanigawa et al., was one of the first to show the relationship of adiponectin deficiency and hearing loss in mice. These researchers identified that when mice were supplemented with adiponectin, hearing loss was prevented, and multivariate logistic regression analysis indicated that adiponectin was indeed an independent factor in predicting hearing loss in mice.[44]

*Race/Ethnicity*

Observational studies analyzing associations between race/ethnicity and hearing loss have identified that there is a 60-70% decreased odds of noise-induced hearing loss amongst non-Hispanic blacks compared to non-Hispanic whites.[45-47] In a study examining the relationship between risk factors for hearing loss amongst those with diabetes utilizing NHANES data, it was identified that even though non-Hispanic blacks and Mexican Americans were more likely to have diabetes compared to other racial groups, they had a lower prevalence of hearing loss.[9] One epidemiological study proposed that this may be related to skin color and melanocytes. Melanocytes in the cochlea, which produce melanin have been studied to act protective against free radicals, resulting in less hearing impairment.[48] Nevertheless, it is vital for more research to be done on the subject of mechanisms behind the differences in hearing impairment amongst race/ethnicities.

## Age-Related Hearing Loss

Hearing loss is often thought of as an inevitable outcome of aging, yet age-related hearing loss (AHL) or presbycusis is a multifactorial degenerative disorder that is not yet fully understood. AHL has high prevalence among older adults, effecting an estimated 50% of those years 70 and over, to a degree that affects their daily life.[45] As previously mentioned, HL has been found to be related to many secondary outcomes such as increased morbidity, economic burden, social isolation, dementia and depression or anxiety.[2-4] AHL can be defined as hearing loss that is unexplainable by known otologic diseases, ototoxins, or genetic factors.[49] Several studies have proposed that AHL is multicausal, an outcome of acquired (e.g. hereditary) or external factors (e.g. noise, injury) impacting the inner year over decades of time, leading to hearing impairment.[50]

### *Age-Related Hearing Loss Mechanisms*

AHL or Presbycusis develops in the inner ear, and due to the location of the inner ear being deep within the temporal bone, medical professionals are unable to complete a biopsy while the individual is alive. Histology of tissues within the inner ear after death have shown that AHL is associated with deterioration of the SV, and less associated with damage of the stereocilia,[51] which was also confirmed in studies with aging gerbils.[52,53]

Correspondingly, another proposed mechanism for AHL, reactive oxygen species (ROS), have been studied to play a large part in the decline of cochlear cells within the aging process. ROS, a biproduct from the mitochondrial metabolism throughout the generation of ATP are potentially damaging to cell components.[6] This oxidative damage accrues, leading to tissue damage with aging.[54] To control for damage of the ROS, an

antioxidant system is in place, in which antioxidant scavengers, and enzymes, including superoxide dismutase, catalase, and glutathione peroxidase (Gpx).[55] Studies have shown that Gpx activity is accelerated in the SV of cochlea in older rats, confirming hypotheses that AHL is most likely associated with the deterioration of the SV. [56]

## Noise-Related Hearing Loss

Noise-related HL, like other types of hearing loss has a complex etiology and not one known independent cause. Known as a type of sensorineural hearing loss, noise-induced HL is correlated with an exposure of noise for prolonged periods of time. In 2017, WHO estimated that 1.1 billion young people between ages 12-35, will experience hearing loss due to an over exposure to noise.[16] It has been hypothesized that any sound over 85 dB can increase the likelihood of developing noise-induced hearing loss, which can be a result of work-related (e.g. construction) or recreational noise exposure (e.g. music festivals).[57] Progressive hearing loss is a common symptom of noise-related hearing loss, with moderate and temporary exposure leading to recovery after hours or days.[58] Similarly to other hearing loss, noise-induced HL can be explained by oxidative stress damage from ROS, inflammation in the cochlea, or genetic/hereditary factors.[59]

## National Health and Nutrition Examination Survey

The National Health and Nutrition Examination Survey (NHANES), developed in the 1960s, was originally piloted as a series of surveys focusing on diverse populations and/or health topics in the United States. This eventually developed into a continuous program with evolving health focuses, used to better assess the current health and nutritional status of individuals residing in the US. This vital data is acquired through interviews and physical examinations and examines a nationally representative sample of

an estimated 5,000 US residents each year. NHANES' at-home interview portion of data collection includes questions about socioeconomic state, nutritional status, medical history, and demographics. Physical examination involves examination of medical, dental, physiological and laboratory measurements completed in their Mobile Examination Center (MEC). To increase reliability of data, NHANES oversamples individuals of Mexican-American, non-Hispanic Asian, non-Hispanic Black, and non-Hispanic White ethnicity over the age of 60 years. Individuals participating in NHANES are all given a specific sample weight, representative of the United States civilian non-institutionalized Census populace. NHANES does not represent the population of those institutionalized, which includes those residing in nursing homes, hospitals, military, or incarceration/correctional facilities. NHANES is an incredible tool that is utilized by several governmental, research, academic and healthcare institutions. Examples of NHANES data use being involved in endeavors includes pediatric growth charts being consistently adapted for new reference standards, and blood lead data being involved in governmental policy change for eliminating lead from gasoline, certain foods, and aluminum cans available in the US.[60]

REFERENCES


1. Haile LM, Kamenov K, Briant PS, et al. Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019. *The Lancet*. 2021;397(10278):996-1009. doi:10.1016/S0140-6736(21)00516-X

2. Griffiths TD, Lad M, Kumar S, et al. How Can Hearing Loss Cause Dementia? *Neuron*. 2020;108(3):401-412. doi:10.1016/j.neuron.2020.08.003

3. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734. doi:10.1016/S0140-6736(17)31363-6

4. Cunningham LL, Tucci DL. Hearing Loss in Adults. *N Engl J Med*. 2017;377(25):2465-2473. doi:10.1056/NEJMra1616601

5. Al-Benna S, Hamilton CA, McClure JD, et al. Low-Density Lipoprotein Cholesterol Determines Oxidative Stress and Endothelial Dysfunction in Saphenous Veins From Patients With Coronary Artery Disease. *ATVB*. 2006;26(1):218-223. doi:10.1161/01.ATV.0000193626.22269.45

6. Böttger EC, Schacht J. The mitochondrion: a perpetrator of acquired hearing loss. *Hear Res*. 2013;303:12-19. doi:10.1016/j.heares.2013.01.006

7. Oron Y, Elgart K, Marom T, Roth Y. Cardiovascular Risk Factors as Causes for Hearing Impairment. *Audiol Neurotol*. 2014;19(4):256-260. doi:10.1159/000363215

8. Helzner EP, Patel AS, Pratt S, et al. Hearing Sensitivity in Older Adults: Associations with Cardiovascular Risk Factors in the Health, Aging and Body Composition Study: Hearing Sensitivity and CVD. *J Am Soc Geriatr Dent*. 2011;59(6):972-979. doi:10.1111/j.1532-5415.2011.03444.x

9. Bainbridge KE, Hoffman HJ, Cowie CC. Risk Factors for Hearing Impairment Among U.S. Adults With Diabetes: National Health and Nutrition Examination Survey 1999-2004. *Diabetes Care*. 2011;34(7):1540-1545. doi:10.2337/dc10-2161

10. Deepika P, Rajeshwary A, Usha S, Goutham MK, Raghav S. Does dyslipidemia worsen the hearing level in diabetics? *J Otol*. 2017;12(4):198-201. doi:10.1016/j.joto.2017.07.003

11. Deal JA, Reed NS, Kravetz AD, et al. Incident Hearing Loss and Comorbidity: A

Longitudinal Administrative Claims Study. *JAMA Otolaryngol Head Neck Surg*. 2019;145(1):36. doi:10.1001/jamaoto.2018.2876

12. Nash SD, Cruickshanks KJ, Klein R, et al. The prevalence of hearing impairment and associated risk factors: the Beaver Dam Offspring Study. *Arch Otolaryngol Head Neck Surg*. 2011;137(5):432-439. doi:10.1001/archoto.2011.15

13. Marlow NM, Malaty J, Jo A, et al. Hearing Impairment and Undiagnosed Disease: The Potential Role of Clinical Recommendations. *JSLHR*. 2017;60(1):231-237. doi:10.1044/2016_JSLHR-H-15-0373

14. Rosen S, Plester D, El-Mofty A, Rosen HV. Relation of Hearing Loss to Cardiovascular Disease. *Trans Am Acad Ophthalmol Otolaryngol*. 1964;68:433-444.

15. Nguyen TVN, Brownell WE. Contribution of membrane cholesterol to outer hair cell lateral wall stiffness. *Otolaryngol Head Neck Surg*. 1998;119(1):14-20. doi:10.1016/S0194-5998(98)70167-6

16. Chadha S, Cieza A. Promoting global action on hearing loss: World hearing day. *Int J Audiol*. 2017;56(3):145-147. doi:10.1080/14992027.2017.1291264

17. Bureau UC. 65 and Older Population Grows Rapidly as Baby Boomers Age. Census.gov. Accessed April 8, 2022. https://www.census.gov/newsroom/press-releases/2020/65-older-population-grows.html

18. Wake M, Hughes EK, Poulakis Z, Collins C, Rickards FW. Outcomes of Children with Mild-Profound Congenital Hearing Loss at 7 to 8 Years: A Population Study. *Ear & Hearing*. 2004;25(1):1-8. doi:10.1097/01.AUD.0000111262.12219.2F

19. Cunningham LL, Tucci DL. Hearing Loss in Adults. *N Engl J Med*. 2017;377(25):2465-2473. doi:10.1056/NEJMra1616601

20. NHANES 2009-2010: Audiometry Data Documentation, Codebook, and Frequencies. Accessed April 7, 2022. https://wwwn.cdc.gov/nchs/nhanes/2009-2010/AUX_F.htm

21. Frank T, Petersen DR. Accuracy of a 40 dB HL Audioscope™ and Audiometer Screening for Adults: *Ear and Hearing*. 1987;8(3):180-183. doi:10.1097/00003446-198706000-00009
22. Walker JJ, Cleveland LM, Davis JL, Seales JS. Audiometry screening and interpretation. *Am Fam Physician*. 2013;87(1):41-47.

23. Feder K, Michaud D, McNamee J, Fitzpatrick E, Davies H, Leroux T. Prevalence of Hazardous Occupational Noise Exposure, Hearing Loss, and Hearing Protection Usage Among a Representative Sample of Working Canadians. *J Occup Environ Med*. 2017;59(1). https://journals.lww.com/joem/Fulltext/2017/01000/Prevalence_of_Hazardous_Occupational_Noise.15.aspx

24. Rosen S, Olin P. Hearing Loss and Coronary Heart Disease. *Arch Otolaryngol-Head and Neck Surg*.1965;82(3):236243.doi:10.1001/archotol.1965.00760010238004

25. Gold S, Haran I, Attias J, Shapira I, Shahar A. Biochemical and Cardiovascular Measures in Subjects with Noise-Induced Hearing Loss: *J Occup Environ Med.*1989;31(11):933-937. doi:10.1097/00043764-198911000-00018

26. Chang NC, Yu ML, Ho KY, Ho CK. Hyperlipidemia in noise-induced hearing loss. *Otolaryngol Head Neck Surg*. 2007;137(4):603-606. doi:10.1016/j.otohns.2007.04.022

27. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics—2021 Update: A Report From the American Heart Association. *Circ*. 2021;143(8). doi:10.1161/CIR.0000000000000950

28. Michos E, Subedi BH, Joshi PH, Jones SR, Martin SS, Blaha MJ. Current guidelines for high-density lipoprotein cholesterol in therapy and future directions. *VHRM*. Published online April 2014:205. doi:10.2147/VHRM.S45648

29. Lee JS, Kim DH, Lee HJ, et al. Lipid Profiles and Obesity as Potential Risk Factors of Sudden Sensorineural Hearing Loss. Cheng XW, ed. *PLoS ONE*. 2015;10(4):e0122496. doi:10.1371/journal.pone.0122496

30. Engdahl B, Aarhus L, Lie A, Tambs K. Cardiovascular risk factors and hearing loss: The HUNT study. *Int J Audiol.*2015;54(12):958-966.

31. Wang S, Ye Q, Pan Y. Serum non-high-density lipoprotein cholesterol is associated with the risk of sudden sensorineural hearing loss. *Medicine*. 2020;99(7):e19175. doi:10.1097/MD.0000000000019175

32. Ballesteros F, Alobid I, Tassies D, et al. Is There an Overlap between Sudden Neurosensorial Hearing Loss and Cardiovascular Risk Factors? *Audiol Neurotol*. 2009;14(3):139-145. doi:10.1159/000171475

33. Skeggs JW, Morton RE. LDL and HDL enriched in triglyceride promote abnormal cholesterol transport. *J Lipid Res*. 2002;43(8):1264-1274.

doi:10.1194/jlr.M100431-JLR200

34. Yang JR, Hidayat K, Chen CL, Li YH, Xu JY, Qin LQ. Body mass index, waist circumference, and risk of hearing loss: a meta-analysis and systematic review of observational study. *Environ Health Prev Med*. 2020;25(1):25. doi:10.1186/s12199-020-00862-9

35. Apovian CM. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care*. 2016;22(7 Suppl):s176-s185.

36. Curhan SG, Eavey R, Wang M, Stampfer MJ, Curhan GC. Body Mass Index, Waist Circumference, Physical Activity, and Risk of Hearing Loss in Women. *Am J Med Open*. 2013;126(12):1142.e1-1142.e8. doi:10.1016/j.amjmed.2013.04.026

37. Hwang JH. Role of Obesity on the Prognosis of Sudden Sensorineural Hearing Loss in Adults. *Otolaryngol Head Neck Surg*. 2015;153(2):251-256. doi:10.1177/0194599815584599

38. Tan HE, Lan NSR, Knuiman MW, et al. Associations between cardiovascular disease and its risk factors with hearing loss-A cross-sectional analysis. *Clin Otolaryngol*. 2018;43(1):172-181.

39. Shargorodsky J, Curhan SG, Eavey R, Curhan GC. A prospective study of cardiovascular risk factors and incident hearing loss in men. *Laryngoscope*. 2010;120(9):1887-1891. doi:10.1002/lary.21039

40. Lohi V, Hannula S, Ohtonen P, Sorri M, Mäki-Torkko E. Hearing impairment among adults: The impact of cardiovascular diseases and cardiovascular risk factors. *Int J Audiol*. 2015;54(4):265-273. doi:10.3109/14992027.2014.974112

41. Curhan SG, Wang M, Eavey RD, Stampfer MJ, Curhan GC. Adherence to Healthful Dietary Patterns Is Associated with Lower Risk of Hearing Loss in Women. *J Nutr.*2018;148(6):944-951. doi:10.1093/jn/nxy058

42. Hwang JH, Hsu CJ, Liu TC, Yang WS. Association of plasma adiponectin levels with hearing thresholds in adults: Plasma adiponectin and hearing thresholds. *Clin Endocrinol*. 2011;75(5):614-620. doi:10.1111/j.1365-2265.2011.04090.x

43. Wu CC, Tsai CH, Lu YC, et al. Contribution of adiponectin and its type 1 receptor to age-related hearing impairment. *Nuerobiol Aging*. 2015;36(6):2085-2093. doi:10.1016/j.neurobiolaging.2015.02.030

44. Tanigawa T, Shibata R, Ouchi N, et al. Adiponectin deficiency exacerbates age-related hearing impairment. *Cell Death Dis*. 2014;5(4):e1189-e1189.

doi:10.1038/cddis.2014.140
45. Agrawal Y. Prevalence of Hearing Loss and Differences by Demographic Characteristics Among US Adults Data From the National Health and Nutrition Examination Survey, 1999-2004. *Arch Intern Med*. 2008;168(14):1522. doi:10.1001/archinte.168.14.1522

46. Lin FR, Maas P, Chien W, Carey JP, Ferrucci L, Thorpe R. Association of Skin Color, Race/Ethnicity, and Hearing Loss Among Adults in the USA. *JARO*. 2012;13(1):109-117. doi:10.1007/s10162-011-0298-8

47. Helzner EP, Cauley JA, Pratt SR, et al. Race and Sex Differences in Age-Related Hearing Loss: The Health, Aging and Body Composition Study: Health ABC: Hearing Loss Risk Factors. *J Am Geriatr Soc*. 2005;53(12):2119-2127. doi:10.1111/j.1532-5415.2005.00525.x

48. Lin FR, Maas P, Chien W, Carey JP, Ferrucci L, Thorpe R. Association of Skin Color, Race/Ethnicity, and Hearing Loss Among Adults in the USA. *JARO*. 2012;13(1):109-117. doi:10.1007/s10162-011-0298-8

49. Goman AM, Lin FR. Hearing loss in older adults - From epidemiological insights to national initiatives. *Hear Res.*2018;369:29-32. doi:10.1016/j.heares.2018.03.031

50. Ohlemiller KK. Mechanisms and genes in human strial presbycusis from animal models. *Brain Res*. 2009;1277:70-83. doi:10.1016/j.brainres.2009.02.079

51. Shuknecht HF, Watanuki K, Takahashi T, et al. Atrophy of the Stria Vascularis, A Common Cause For Hearing Loss. *Laryngoscope*. 1974;84(10):1777-1821. doi:10.1288/00005537-197410000-00012

52. Dubno JR, Eckert MA, Lee FS, Matthews LJ, Schmiedt RA. Classifying Human Audiometric Phenotypes of Age-Related Hearing Loss from Animal Models. *JARO*. 2013;14(5):687-701. doi:10.1007/s10162-013-0396-x

53. Schulte BA, Schmiedt RA. Lateral wall Na, K-ATPase and endocochlear potentials decline with age in quiet-reared gerbils. *Hear Res*. 1992;61(1-2):35-46. doi:10.1016/0378-5955(92)90034-K

54. Balaban RS, Nemoto S, Finkel T. Mitochondria, Oxidants, and Aging. *Cell*. 2005;120(4):483-495. doi:10.1016/j.cell.2005.02.001

55. Yamasoba T, Lin FR, Someya S, Kashio A, Sakamoto T, Kondo K. Current concepts in age-related hearing loss: Epidemiology and mechanistic pathways. *Hear Res*. 2013;303:30-38. doi:10.1016/j.heares.2013.01.021

56. Coling D, Chen S, Chi LH, Jamesdaniel S, Henderson D. Age-related changes in antioxidant enzymes related to hydrogen peroxide metabolism in rat inner ear. *Nuerosci Lett*. 2009;464(1):22-25. doi:10.1016/j.neulet.2009.08.015

57. Ding T, Yan A, Liu K. What is noise-induced hearing loss? *Br J Hosp Med*. 2019;80(9):525-529. doi:10.12968/hmed.2019.80.9.525

58. Shi L, Liu K, Wang H, et al. Noise induced reversible changes of cochlear ribbon synapses contribute to temporary hearing loss in mice. *Acta Oto-Laryngologica*. 2015;135(11):1093-1102. doi:10.3109/00016489.2015.1061699

59. Kurabi A, Keithley EM, Housley GD, Ryan AF, Wong ACY. Cellular mechanisms of noise-induced hearing loss. *Hear Res*. 2017;349:129-137. doi:10.1016/j.heares.2016.11.013

60. NHANES - About the National Health and Nutrition Examination Survey. Published January 8, 2020. Accessed April 18, 2022.

# CHAPTER III

# JOURNAL ARTICLE

ABSTRACT

ASSOCIATIONS BETWEEN ATHEROGENIC MARKERS AND HEARING LOSS: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY: 2011-2012, 2015-2016

Anna Rombakh

June 2022

**Importance** Hearing loss (HL) is a major public health problem that has been previously found to be associated with abnormal atherogenic markers.

**Objective** To investigate the associations between such atherogenic markers and the degree of HL using continuous NHANES data from cycle years 2011-2012 and 2015-2016.

**Design, Study, and Participants** This observational study used data from two National Health and Nutrition Examination Survey (NHANES) cycle years 2011-2012 and 2015-2016. NHANES continuously conducts data collection via home interviews and physical exams completed in their Mobile Examination Centers. NHANES participants ages 20-69 who partook in audiometry, anthropometric and laboratory testing were included. Data was analyzed from 2011-2012 and 2015-2016 cycle years.

**Exposures** Substantial hearing loss was defined as as a HL degree of moderate (41-55dB) or higher at any frequency.

**Main Outcomes and Measures** Risk of hypercholesterolemia was defined as $\geq 240$ mg/dL, hypoalphalipoproteinemia or low levels of high-density lipoprotein cholesterol as

≤ 40 mg/dL for males and ≤ 50 mg/dL for females, elevated low-density lipoprotein cholesterol as ≥ 160 mg/dL, hypertriglyceridemia was defined as ≥ 175 mg/dL, elevated levels of Apolipoprotein B as ≥ 130 mg/dL and elevated non-high-density lipoprotein cholesterol as ≥ 190 mg/dL. Associations between abnormal atherogenic markers and substantial HL were determined in adjusted multivariate logistic regression models.

**Results** Among 8955 participants there were significant associations between gender, age, BMI and race/ethnicity and substantial hearing loss ($p < .0001$). No significant differences were identified between people with normal and substantial hearing loss in regards to mean concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B cholesterol (ApoB). Significant differences were identified between prevalence of triglycerides and substantial hearing loss ($p < .0001$). Multivariate logistic regression models found that after adjusting for covariates there was no significant association between having hypertriglyceridemia and substantial hearing loss (OR 1.2, 95% CI, 0.8-1.8).

**Conclusions and Relevance** This study's results showed no association between atherosclerosis markers and degree of hearing loss. However, due to conflicting findings of several studies on this topic, further research should be done to determine if lipid markers can affect hearing loss.

# INTRODUCTION

In 2019, hearing loss (HL) affected an estimated 1.5 billion of the global population, contributing to the third most common cause of years of living with disability (YLDs).[1] HL is commonly believed to be caused by noise exposure or aging, but still largely remains a major public health problem with an unclear etiology. HL in midlife has also been estimated to be associated with 9% of dementia cases, increasing an individual's level of cognitive impairment and leading to social isolation.[2,3]

HL can be caused by damage or dysfunction of the peripheral and/or central auditory system from the external ear to the cerebral auditory cortex. HL type can be categorized as sensorineural (cochlear or spiral ganglion impairment), conductive (outer or inner ear impairment) or mixed.[4] Mechanisms currently under investigation for HL includes development of reactive oxygen species (ROS) and oxidative stress possibly caused by antioxidant imbalances,[5,6] and the "lipid hypothesis". The current possible explanation for the "lipid hypothesis" is that as atherosclerosis markers such as total serum cholesterol elevate, blood viscosity will increase contributing to atherosclerosis of arteries such as the internal auditory artery (IAA). The IAA is responsible for supplying blood to the cochlea, auditory nerve, and the stria vascularis (SV) which is located at the wall of the cochlea,[7] When blood supply to the SV is constricted, vital nutrients are unable to be supplied to hair cells, also known as stereocilia, leading to the irreversible damage of hair cells and diminished hearing sensitivity.[8] This type of damage has been seen in numerous studies in individuals with cardiovascular disease, diabetes, chronic kidney disease and in individuals with dyslipidemia.[9-13] Similarly, an observational study utilizing data from the National Health and Nutrition Examination Survey (NHANES)

examining the relationship between risk factors of HL and diabetes identified that individuals with low high-density lipoprotein and elevated total cholesterol where more likely to be hearing impaired.[9]

The original study on this lipid hypothesis investigated hearing levels of members of the southeast Sudan tribe, known as the Mabaans. Living in a noise-free environment, researchers Rosen and colleagues sought out to research the possible associations between vascular changes such as blood pressure and HL compared to healthy adults living in the United States. Rosen et al., identified that there was a positive inverse relationship with better hearing being associated with lowered cholesterol levels. They also concluded that although noise exposure is an obvious and large component in HL, other factors such as nutrition, vascular changes, stress, climate, and genetic factors play a more significant role then previously known at the time. This inspired many to continue examining the relationship of blood lipids and HL.[14]

In an experimental study done in 1997, Nguyen and Brownell identified that lipidosis of the inner ear may be a mechanism of vascular changes affecting hearing. Nguyen identified in guinea pig cochlea that hearing impairment can be attributed to the varied blood cholesterol dispersals in the stereocilia tissues. When blood cholesterol is integrated in stereocilia cells, lateral wall stiffness increases, contributing to hearing impairment.[15] Therefore, the purpose of this observational study was to investigate the associations between such atherogenic markers and the degree of HL using continuous NHANES data from cycle years 2011-2012 and 2015-2016.

# METHODS

*Study Population*

This study used data from the National Health and Nutrition Examination Survey (NHANES)[16]. NHANES, a cross sectional health study managed by the National Centers for Health Statistics and is intended to assess the health status of individuals residing in the United States. NHANES continuously conducts data collection via home interviews and physical exams completed in their Mobile Examination Centers. This study utilized data from cycle years 2011-2012 and 2015-2016 (most recent audiometry data available).

Participants in this study included individuals 20-69 years of age (audiometry testing was only completed on those 20-69 years of age) who partook in both home interviews and physical examinations from NHANES. Male and female participants were included. Pregnant or lactating females were excluded from this study in addition to those who did not receive audiometry testing.

*Design and Procedures*

This study analyzed audiometry examination data from pure tone air conduction audiometry testing. Pure-tone audiometry signals were played to each ear at varying intensities until the threshold at which the participant was just able to perceive the tone were identified. Air conduction hearing thresholds in decibels hearing level (dB HL) were obtained for each ear at 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000Hz by trained audiometric technicians in NHANES Mobile Examination Centers.

Degree of HL was defined according to the American Speech Language Hearing Association (ASHA) guidelines[17]. Degree of HL at any frequency was categorized the ASHA with the following thresholds: normal hearing -10-15 dB, slight HL 16-25 dB,

mild HL 26-40 dB, moderate HL 41-55 dB, moderately severe HL 56-70 dB, Severe HL 71-90 dB, and Profound HL >91 dB. Substantial HL was defined in this study as a HL degree of moderate (41-55dB) or higher at any frequency.

Data was examined to observe the relationship between risk of abnormal blood lipid values and degree of HL. Risk of hypercholesterolemia was defined as $\geq 240$ mg/dL, hypoalphalipoproteinemia or low levels of high-density lipoprotein cholesterol as $\leq 40$ mg/dL for males and $\leq 50$ mg/dL for females, elevated low-density lipoprotein cholesterol as $\geq 160$ mg/dL, hypertriglyceridemia was defined as $\geq 175$ mg/dL, elevated levels of Apolipoprotein B as $\geq 130$ mg/dL and elevated non-high-density lipoprotein cholesterol as $\geq 190$ mg/dL[18]. The methodology used to determine these laboratory values can be found on the NHANES webpage[16]. The following data was also collected during the in-home interview or in the NHANES mobile examination center: race/ethnicity, gender, age, weight, and body mass index (BMI).

*Statistical Analysis*

Data analysis was performed using the Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Descriptive statistics were used to summarize characteristics such as mean and standard error. Chi-square analysis was used to establish significant differences in prevalence of hearing loss and abnormal blood lipids. Logistic regression models were used to establish odds ratios along with crude and adjusted models (adjusted for confounding due to age, gender, BMI, or ethnicity). T-test analyses were run to identify significant differences in the mean values of age, BMI, or blood lipid concentrations between those with normal hearing and those with substantial HL. Statistical significance was determined if p-value $<0.05$.

# RESULTS

Descriptive statistics of those with normal hearing and those with substantial HL are shown in Table 1. Those with substantial HL were significantly older (mean = 56 years) compared to those with normal hearing (mean = 41 years) (Table 1, $p$ <.0001). Of females, 11% had substantial HL, while 24% of men had substantial HL ($p$ < .0001). There were significant differences found in the prevalence of substantial HL with race/ethnicity, with 20% of NH-Whites with substantial HL ($p$ < .0001), NH-Blacks (11%), Mexican-Americans (13%), NH-Asians (13%) and other including multi-racial ethnicity (16%). Body mass index (BMI) significantly higher for those with substantial HL compared to normal hearing with an average BMI of 30 for those with substantial HL (mean = 30.0) and for those with normal hearing (mean = 28.9, $p$ < .0001).

**Table 1. Descriptive Statistics of Normal Hearing and Substantial Hearing Loss Subjects. (± SEM)**

| | N | Normal Hearing | Substantial Hearing Loss | p-value* |
|---|---|---|---|---|
| **Total** | **8955** | **82.3%** | **17.7%** | |
| **Gender (%)** | | | | |
| **Female** | **4555** | **88.7 ± 0.9** | **11.3 ± 0.9** | |
| **Male** | **4400** | **75.8 ± 1.4** | **24.3 ± 1.4** | **< .0001** |
| **Age (years)** | | **41.1 ± 0.4** | **56.0 ± 0.4** | **< .0001** |
| **Race/Ethnicity (%)** | | | | |
| **Non-Hispanic Whites** | **2785** | **79.8 ± 1.3** | **20.2 ± 1.3** | |
| **Non-Hispanic Blacks** | **2221** | **89.0 ± 0.7** | **11.0 ± 0.7** | |
| **Mexican-Americans** | **1300** | **86.6 ± 1.2** | **13.4 ± 1.2** | |
| **Non-Hispanic Asians** | **1256** | **87.3 ± 2.0** | **12.7 ± 2.0** | |
| **Other** | **1393** | **83.8 ± 1.8** | **16.2 ± 1.7** | **< .0001** |
| **Body Mass Index ($kg/m^2$)** | | **28.9 ± 0.2** | **30.0 ± 0.3** | **< .0001** |
| **Atherogenic Markers** | | | | |
| **Total cholesterol (mg/dl)** | **3800** | **193.2 ± 1.0** | **191.0 ± 1.9** | **.4352** |
| **LDL-cholesterol (mg/dl)** | **3740** | **115.4 ± 0.8** | **111.4 ± 1.6** | **.1227** |
| **Non-HDL cholesterol (mg/dl)** | **3800** | **138.5 ± 1.0** | **138.6 ± 2.1** | **.2824** |
| **Apolipoprotein B (mg/dl)** | **3798** | **91.5 ± 0.7** | **93.1 ± 1.3** | **.6714** |
| **HDL cholesterol (mg/dl)** | **3800** | **54.7 ± 0.5** | **52.5 ± 1.2** | **.6175** |
| **Triglycerides (mg/dl)** | **3798** | **116.7 ± 2.1** | **141.0 ± 7.8** | **< .0001** |

No significant differences were found between normal and substantial HL in regard to mean concentrations of total serum cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (Non-HDL-C), Apolipoprotein B (ApoB) , and high-density lipoprotein cholesterol (HDL-C) when analyzing prevalence of dyslipidemia (Table 2). In contrast, mean triglyceride concentrations were 20.8% higher in individuals with substantial HL in contrast to individuals with normal hearing ($p < .0001$).

Similarly, there was no significant difference when analyzing prevalence of dyslipidemia in normal hearing and substantial HL between elevated TC (12.4% vs. 11.3%), elevated LDL-C (10.1% vs. 7.7%), elevated non-HDL-C (10.9% vs. 12.3%), elevated ApoB (7.7% vs 7.2%), and low HDL-C (33.0% vs. 33.8%). However, prevalence of hypertriglyceridemia was significantly higher in those with substantial HL compared to those with normal hearing (22.4% vs. 14.5%) (Table 2).

**Table 2. Prevalence of Dyslipidemia in Normal Hearing and Significant Hearing Loss Subjects.**

| | N | Normal Hearing (% ± SEM) | N | Substantial Hearing Loss (% ± SEM) | p-value |
|---|---|---|---|---|---|
| **Total** | **7401** | | **1554** | | |
| **Total Cholesterol (>240 mg/dl)** | **833** | **12.4 ± 0.7** | **195** | **11.3 ± 1.2** | **.4352** |
| **LDL Cholesterol (>160 mg/dl)** | **314** | **10.1 ± 0.9** | **70** | **7.7 ± 1.3** | **.1227** |
| **Non-HDL Cholesterol (> 190 mg/dl)** | **782** | **10.9 ± 0.6** | **201** | **12.3 ± 1.4** | **.2824** |
| **Apolipoprotein B (> 130 mg/dl)** | **245** | **7.7 ± 0.7** | **63** | **7.2 ± 1.2** | **.6714** |
| **HDL-cholesterol (< 40 mg/dl for males) (< 50 mg/dl for females)** | **2645** | **33.0 ± 1.0** | **577** | **33.8 ± 2.0** | **.6175** |
| **Triglycerides (> 175 mg/dl)** | **458** | **14.5 ± .9** | **145** | **22.4 ± 2.6** | **< .0001** |

Simple logistic regression analysis of hypertriglyceridemia prevalence among those with substantial HL showed that compared to young adults (20-39 years), middle-aged adults (39-60 years) have a 2.4-fold (95% CI, 1.9-3.1, OR=2.4) increased odds of having hypertriglyceridemia (Table 3). In contrast, older adults (60+ years) have a 1.8-fold (95% CI, 1.2-2.8, OR=1.8) increased odds when compared to young adults. Logistic regression analysis of hypertriglyceridemia prevalence and BMI category showed that when compared to normal weight, overweight individuals were at a 3.4-fold (95% CI,

2.4-4.6, OR=3.4) increased odds of having hypertriglyceridemia. Not surprisingly, obese individuals were at a 5.0-fold (95% CI 3.7-6.4, OR=5.0) increased odds of having hypertriglyceridemia when compared to those of a normal BMI. When compared to NH-Blacks (lowest prevalence of substantial HL), NH-Whites were at a 2.6 fold (95% CI, 2.0-3.4, OR=2.6) increased odds, while Mexican-Americans were at a 3.0 (95% CI, 2.0-4.7, OR=3.0) increased odds, NH-Asians were at a 2.3 (95% CI, 1.6-3.3, OR=2.3) increased odds and other including multi-racial having 2.5 fold (95% CI,1.6-3.7, OR=2.5) increased odds of hypertriglyceridemia. Lastly, logistic regression analysis indicated that there was a 70% (OR 1.7, 95% CI, 1.3-2.3) greater odds of having hypertriglyceridemia in those with substantial HL when not adjusting for age, BMI, gender, or race/ethnicity (Table 3).

**Table 3. Simple Logistic Regression Analysis of Hypertriglyceridemia and Individual Co-variates.**
**(Crude Model)**

| | **Hypertriglyceridemia Odds Ratio (95% CI)** |
|---|---|
| **Age Group (ref = 20-39 years)** | |
| **39-60 years** | **2.4 (1.9-3.1) **** |
| **60+ years** | **1.8 (1.2-2.8) **** |
| **Gender (ref = Female)** | |
| **Male** | **1.8 (1.5-2.2)**** |
| **BMI (ref = Normal (18.5-24.5kg/m$^2$))** | |
| **Underweight (18.5kg/m$^2$)** | **1.0 (0.5-2.2)** |
| **Overweight (25-29.9kg/m$^{2)}$** | **3.4 (2.4-4.6)**** |
| **Obese (30+kg/m$^2$)** | **5.0 (3.7-6.4)**** |
| **Race/Ethnicity (ref = NH Black)** | |
| **NH White** | **2.7 (2.0-3.4)**** |
| **Mexican-Americans** | **3.0 (2.0-4.7)**** |
| **NH Asians** | **2.3 (1.6-3.3)**** |
| **Other including Multi-Racial** | **2.5 (1.6-3.7)**** |
| **Substantial Hearing Loss vs. Normal Hearing (ref= Normal Hearing)** | **1.7 (1.3-2.3)**** |

Multivariate logistic regression analysis was conducted to examine the

relationship between hypertriglyceridemia with the covariates of age group, sex, BMI category, race/ethnicity, and HL. (Table 4) Using this model, middle-aged adults still had a significant 2.2-fold (95% CI, 1.7-2.9) increased odds of having hypertriglyceridemia compared to young adults. However, older adults' odds of hypertriglyceridemia decreased to a non-significant 1.5 fold (95% CI, 0.9-2.4) compared to 1.8 when unadjusted. The odds of hypertriglyceridemia in men in this multivariate model was still significantly greater in women (OR = 1.7, 95% CI, 1.3-2.2). The odds-ratio for hypertriglyceridemia in overweight individuals decreased from 3.4 to 3.2 (95% CI, 2.3-4.4) odds when compared to normal weight individuals. There was no change for obese individuals when compared to normal weight (OR 5.0, 95% CI, 3.6-6.8). There was no significant change when analyzing race/ethnicity, except for NH Asians increased odds from 2.3 to 4.2 (2.8-6.4) odds. When adjusting for the other covariates, the odds-ratio for hypertriglyceridemia was no longer significant in those with substantial HL compared to those with normal hearing (OR 1.2, 95% CI, 0.8-1.8).

**Table 4. Multivariate Regression Analysis of Hypertriglyceridemia and Degree of Hearing Loss (Adjusted Model)**

| | Hypertriglyceridemia Odds Ratio (95% CI) |
|---|---|
| **Age Group (ref = 20-39 years)** | |
| **39-60 years** | **2.2 (1.7-2.9) **** |
| **60+ years** | **1.5 (0.9-2.4)** |
| **Gender (ref = Female)** | |
| **Male** | **1.7 (1.3-2.2)**** |
| **BMI (ref = Normal (18.5-24.5kg/m$^2$))** | |
| **Underweight (18.5kg/m$^2$)** | **1.2 (0.5-2.5)** |
| **Overweight (25-29.9kg/m$^{2)}$** | **3.2 (2.3-4.4)**** |
| **Obese (30+kg/m$^2$)** | **5.0 (3.6-6.8)**** |
| **Race/Ethnicity (ref = NH Black)** | |
| **NH White** | **2.6 (2.0-3.5) **** |
| **Mexican-Americans** | **3.1 (2.0-4.7)**** |
| **NH Asians** | **4.2 (2.8-6.4)**** |
| **Other-Including Multi-Racial** | **2.6 (2.0-3.5)**** |
| **Substantial Hearing Loss vs. Normal Hearing (ref= Normal Hearing)** | **1.2 (0.8-1.8)** |

## DISCUSSION

This study revealed that elevated atherogenic markers were not associated with substantial HL, except for elevated triglyceride levels. However, when the results were adjusted for covariates of age, race/ethnicity, body mass index, and gender, hypertriglyceridemia was no longer significantly associated with substantial HL. The present study is one of several studies evaluating the relationship between blood lipid markers and HL, thereby adding to the literature on this controversial topic.

The pioneers in this research topic, Rosen et al., published the original article in 1965 on the possible association between dyslipidemia and HL.[19] They studied the hearing levels of the remote Mabaan tribe (southeast Sudan), who resided in a reduced noise environment compared to a control group of healthy adults in the United States. They identified that there was a positive inverse relationship with better hearing being

associated with lowered blood cholesterol levels. They also concluded that although noise exposure is an obvious and large component in HL, other factors such as nutrition, vascular changes, stress, climate, and genetic factors play a more significant role then previously known at the time. Although the current study did not analyze nutrition, stress, climate, or genetic factors, it was identified that age, BMI, gender, and race/ethnicity were significantly associated with a higher odds of having hypertriglyceridemia, which was discovered to be associated with substantial HL in the unadjusted model. In fact, those with substantial HL had a 20.8% higher triglyceride mean concentration than those with normal hearing levels.

Atherogenic markers examined in this present study can be used to determine risk for cardiovascular disease (CVD). The large Nord-Trøndelag HL study (NTHLS), a large population-based cohort study (n=31,547), Norwegians residing in the county of Nord-Trøndelag were recruited to participate in pure-tone audiometry testing and questionnaires.[20] The NTHLS study also examined the association between CVD risk factors and HL. Those researchers concluded that although associations between HL and risk factors was present, the results were unexpected. Surprisingly to these researchers it was also identified that as HDL-C levels, LDL-C and TC increased, HL prevalence decreased, indicating a possible protective effect of elevated blood lipids on HL.[20] Consequently, elevated atherogenic markers may not be the main culprit of diminished auditory function.

In 2011, Helzner et al., assessed the association between CVD and risk factors with age-related HL (presbycusis) in a population of older black and white black and adults.[8] This cross-sectional cohort study recruited 2,049 healthy adults to undergo pure-

tone audiometry testing as well as establishing their CVD history and CVD risk factors. Similarly, to the results of our study, Helzner and researchers found that elevated levels of triglycerides and high BMI (especially among women) were significantly associated with diminished auditory function. Consistent with Helzner et al. and our study's results, a European population based multi-national study analyzing risk factors for presbycusis, identified that a higher BMI was associated with diminished hearing sensitivity.[21]

Mechanisms behind elevated BMI and increased risk of HL are not yet widely understood in literature.[22] Multiple studies have identified associations between elevated BMI and higher prevalence of HL. Possible mechanisms include poor lifestyle choices such as overconsumption of foods associated with increased risk of CVD, obesity and diabetes[23] and decreased levels of plasma adiponectin. Low levels of plasma adiponectin, an anti-inflammatory adipokine has been associated with obesity,[24] and involved in the regulation of insulin sensitivity, metabolism and atherosclerosis.[25] When elevated, adiponectin has been linked to an inverse relationship with high-frequency HL, implying that low levels may lead to HL.[26] This relationship was proven in two experimental animal studies conducted on mice.[27,28]

The first study, conducted by Wu et al., aimed to observe the function of adiponectin in HL by examining genotypes associated with polymorphisms of the adiponectin gene. Researchers recruited middle to older adult Han Chinese to form a cohort for research on adiponectin genotypes, as well as mature mice utilized to confirm hypotheses in this study's experiment. Wu et al., identified that the adiponectin genotypes show effects on hearing levels when plasma adiponectin levels fluctuate, and this finding was further established in mice cochlea.[27] Similarly, a study done by Tanigawa et al., was

one of the first to show the relationship of adiponectin deficiency and HL in mice. Tanigawa and researchers supplemented adiponectin to hyperlipidemic apolipoprotein E-knockout (APN-KO) mice and compared hearing threshold to wild-type mice (control). Researchers identified that when APN-KO mice were supplemented with adiponectin, HL was prevented, and multivariate logistic regression analysis indicated that adiponectin was indeed an independent factor in predicting HL in mice.[28]

In the large Framingham study, researchers Gates et al., identified comparable results to this study, in which no significant association was found between hearing levels and triglyceride and total cholesterol levels in all genders after adjusting for covariates such as age. Interestingly, they also identified that in women, there was a significant inverse relationship with HDL levels and low frequency HL.[29] Researchers Suzuki and colleagues similarly identified no significant association between the impact of serum lipid levels on hearing function between triglyceride and total cholesterol levels.[30] Marlow et al., found that when assessing the relationship between HL and undetected diseases such as hyperlipidemia, there was no significant difference between adults with HL and adults with normal hearing.[13]

Results of this present study indicated that those with substantial hearing loss were significantly older and more likely to be males, which may confound the relationship between hypertriglyceridemia and HL. Hypertriglyceridemia has been associated with being more likely to be elevated in males than in females, and in those of an older age, as observed in an NHANES study monitoring CVD risk factors.[31] Similar findings were identified in a 2006 study, in which Evans and researchers examined the association with dyslipidemia and diminished auditory function. In this

cross-sectional study, researchers found similar findings that older males were significantly associated with HL.[32] In a Japanese study evaluating the relationship between dyslipidemia, diabetes, hypertension risk factors and hearing impairment also identified that incidence of HL was elevated in men (31.5% vs 20.8%) and having two or more risk factors for cardiovascular disease were found to be positively correlated with hearing impairment (for males).[33] In an large cohort study examining subclinical atherosclerosis' associations with hearing impairment, researchers found that risk of HL was amplified for those whom are older, men and high BMI. Subclinical atherosclerosis, evaluated by carotid artery intima media thickness and plaque, was also identified to be associated with a 15% elevated risk of HL during a five year follow up.[34] Males may be more likely to have hearing loss as a recent study done in Canada indicated that men had a significantly higher likelihood to have exposure to hazardous occupational noise.[35] However, when associations between hyperlipidemia and noise-related HL were examined by Demir et al., no significant relationship was identified.[36] Nevertheless, after adjustment to covariates, it is evident that it may be more vital to look at anthropometrics, gender, and race/ethnicity when examining this association.

STRENGTHS AND LIMITATIONS

This present study's strengths included large sample size and utilization of current guidelines on blood cholesterol management for examination of prevalence and odds ratios. Limitations of this study included a small number of cycle years used due to lack of audiometry examination data available in recent years of NHANES. As with any observational study only associations and not causation can be established. Lastly, prior

research evaluating HL mentioned in this study, had varying thresholds for determining degree of HL, proving it difficult to make concrete correlations.

## CONCLUSIONS AND APPLICATIONS

This study's results showed no association between atherosclerosis markers and degree of hearing loss. While the prevalence of hypertriglyceridemia was greater in those with hearing loss, after adjusting for age, sex, race/ethnicity and elevated BMI, the odds of hypertriglyceridemia were not significantly greater in those with substantial hearing loss compared to those with normal hearing. However, due to conflicting findings of several studies on this topic, further research should be done to determine if lipid markers can affect hearing loss.

REFERENCES


1. Haile LM, Kamenov K, Briant PS, et al. Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019. *The Lancet*. 2021;397(10278):996-1009. doi:10.1016/S0140-6736(21)00516-X

2. Griffiths TD, Lad M, Kumar S, et al. How Can Hearing Loss Cause Dementia? *Neuron*. 2020;108(3):401-412. doi:10.1016/j.neuron.2020.08.003

3. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734. doi:10.1016/S0140-6736(17)31363-6

4. Cunningham LL, Tucci DL. Hearing Loss in Adults. *N Engl J Med*. 2017;377(25):2465-2473. doi:10.1056/NEJMra1616601

5. Al-Benna S, Hamilton CA, McClure JD, et al. Low-Density Lipoprotein Cholesterol Determines Oxidative Stress and Endothelial Dysfunction in Saphenous Veins From Patients With Coronary Artery Disease. *ATVB*. 2006;26(1):218-223. doi:10.1161/01.ATV.0000193626.22269.45

6. Böttger EC, Schacht J. The mitochondrion: a perpetrator of acquired hearing loss. *Hear Res*. 2013;303:12-19. doi:10.1016/j.heares.2013.01.006

7. Oron Y, Elgart K, Marom T, Roth Y. Cardiovascular Risk Factors as Causes for Hearing Impairment. *Audiol Neurotol*. 2014;19(4):256-260. doi:10.1159/000363215

8. Helzner EP, Patel AS, Pratt S, et al. Hearing Sensitivity in Older Adults: Associations with Cardiovascular Risk Factors in the Health, Aging and Body Composition Study: Hearing Sensitivity and CVD. *J Am Soc Geriatr Dent*. 2011;59(6):972-979. doi:10.1111/j.1532-5415.2011.03444.x

9. Bainbridge KE, Hoffman HJ, Cowie CC. Risk Factors for Hearing Impairment Among U.S. Adults With Diabetes: National Health and Nutrition Examination Survey 1999-2004. *Diabetes Care*. 2011;34(7):1540-1545. doi:10.2337/dc10-2161

10. Deepika P, Rajeshwary A, Usha S, Goutham MK, Raghav S. Does dyslipidemia worsen the hearing level in diabetics? *J Otol*. 2017;12(4):198-201. doi:10.1016/j.joto.2017.07.003

11. Deal JA, Reed NS, Kravetz AD, et al. Incident Hearing Loss and Comorbidity: A Longitudinal Administrative Claims Study. *JAMA Otolaryngol Head Neck Surg*.

2019;145(1):36. doi:10.1001/jamaoto.2018.2876

12. Nash SD, Cruickshanks KJ, Klein R, et al. The prevalence of hearing impairment and associated risk factors: the Beaver Dam Offspring Study. *Arch Otolaryngol Head Neck Surg*. 2011;137(5):432-439. doi:10.1001/archoto.2011.15

13. Marlow NM, Malaty J, Jo A, et al. Hearing Impairment and Undiagnosed Disease: The Potential Role of Clinical Recommendations. *JSLHR*. 2017;60(1):231-237. doi:10.1044/2016_JSLHR-H-15-0373

14. Rosen S, Plester D, El-Mofty A, Rosen HV. Relation of Hearing Loss to Cardiovascular Disease. *Trans Am Acad Ophthalmol Otolaryngol*. 1964;68:433-444.

15. Nguyen TVN, Brownell WE. Contribution of membrane cholesterol to outer hair cell lateral wall stiffness. *Otolaryngol Head Neck Surg*. 1998;119(1):14-20. doi:10.1016/S0194-5998(98)70167-6

16. NHANES - About the National Health and Nutrition Examination Survey. Published January 8, 2020. Accessed March 28, 2022.

17. Clark JG. Uses and abuses of hearing loss classification. *ASHA*. 1981;23(7):493-500.

18. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;139(25). doi:10.1161/CIR.0000000000000625

19. Rosen S, Plester D, El-Mofty A, Rosen HV. Relation of Hearing Loss to Cardiovascular Disease. *Trans Am Acad Ophthalmol Otolaryngol*. 1964;68:433-444.

20. Engdahl B, Aarhus L, Lie A, Tambs K. Cardiovascular risk factors and hearing loss: The HUNT study.*Int J Audiol*. 2015;54(12):958-966.

21. Fransen E, Topsakal V, Hendrickx JJ, et al. Occupational Noise, Smoking, and a High Body Mass Index are Risk Factors for Age-related Hearing Impairment and Moderate Alcohol Consumption is Protective: A European Population-based Multicenter Study. *JARO*. 2008;9(3):264-276.

22. Yang JR, Hidayat K, Chen CL, Li YH, Xu JY, Qin LQ. Body mass index, waist circumference, and risk of hearing loss: a meta-analysis and systematic review of

observational study. *Environ Health Prev Med*. 2020;25(1):25.

23. Mozaffarian D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. *Circulation*. 2016;133(2):187-225.

24. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in Obesity and Type 2 Diabetes: Close Association with Insulin Resistance and Hyperinsulinemia. *J Clin Endocrinol Metab.* 2001;86(5):1930-1935.

25. Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: More Than Just Another Fat Cell Hormone? *Diabetes Care*. 2003;26(8):2442-2450.

26. Hwang JH, Hsu CJ, Liu TC, Yang WS. Association of plasma adiponectin levels with hearing thresholds in adults: Plasma adiponectin and hearing thresholds. *Clin Endocrinol*. 2011;75(5):614-620.

27. Wu CC, Tsai CH, Lu YC, et al. Contribution of adiponectin and its type 1 receptor to age-related hearing impairment. *Neurobiol Aging*. 2015;36(6):2085-2093.

28. Tanigawa T, Shibata R, Ouchi N, et al. Adiponectin deficiency exacerbates age-related hearing impairment. *Cell Death Dis*. 2014;5(4):e1189-e1189.

29. Gates GA, Cobb JL, D'Agostino RB, et al. The Relation of Hearing in the Elderly to the Presence of Cardiovascular Disease and Cardiovascular Risk Factors. *Arch Otolaryngol Head Neck Surg.* 1993; 119:156–161. [PubMed: 8427676]

30. Suzuki K, Kaneko M, Murai K. Influence of Serum Lipids on Auditory Function. *Laryngoscope*. 2000;110(10):1736-1738.

31. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2011;123(20):2292-2333. doi:10.1161/CIR.0b013e3182160726

32. Evans MB, Tonini R, Shope CD, et al. Dyslipidemia and Auditory Function. *Otol Neurotol*. 2006;27(5):609-614.

33. Hara K, Okada M, Takagi D, et al. Association between hypertension, dyslipidemia, and diabetes and prevalence of hearing impairment in Japan. *Hypertens Res*. 2020;43(9):963-968.

34. Fischer ME, Schubert CR, Nondahl DM, et al. Subclinical atherosclerosis and increased risk of hearing impairment. *Atherosclerosis*. 2015;238(2):344-349.

35. Feder K, Michaud D, McNamee J, Fitzpatrick E, Davies H, Leroux T. Prevalence of Hazardous Occupational Noise Exposure, Hearing Loss, and Hearing Protection Usage Among a Representative Sample of Working Canadians. *J Occup Environ Med.* 2017;59(1).

36. Demir MG, Aydin S. The Effect of the Cholesterol Levels on Noise-Induced Hearing Loss. *Int Arch Otorhinolaryngol*. 2018;22(1):19-22.